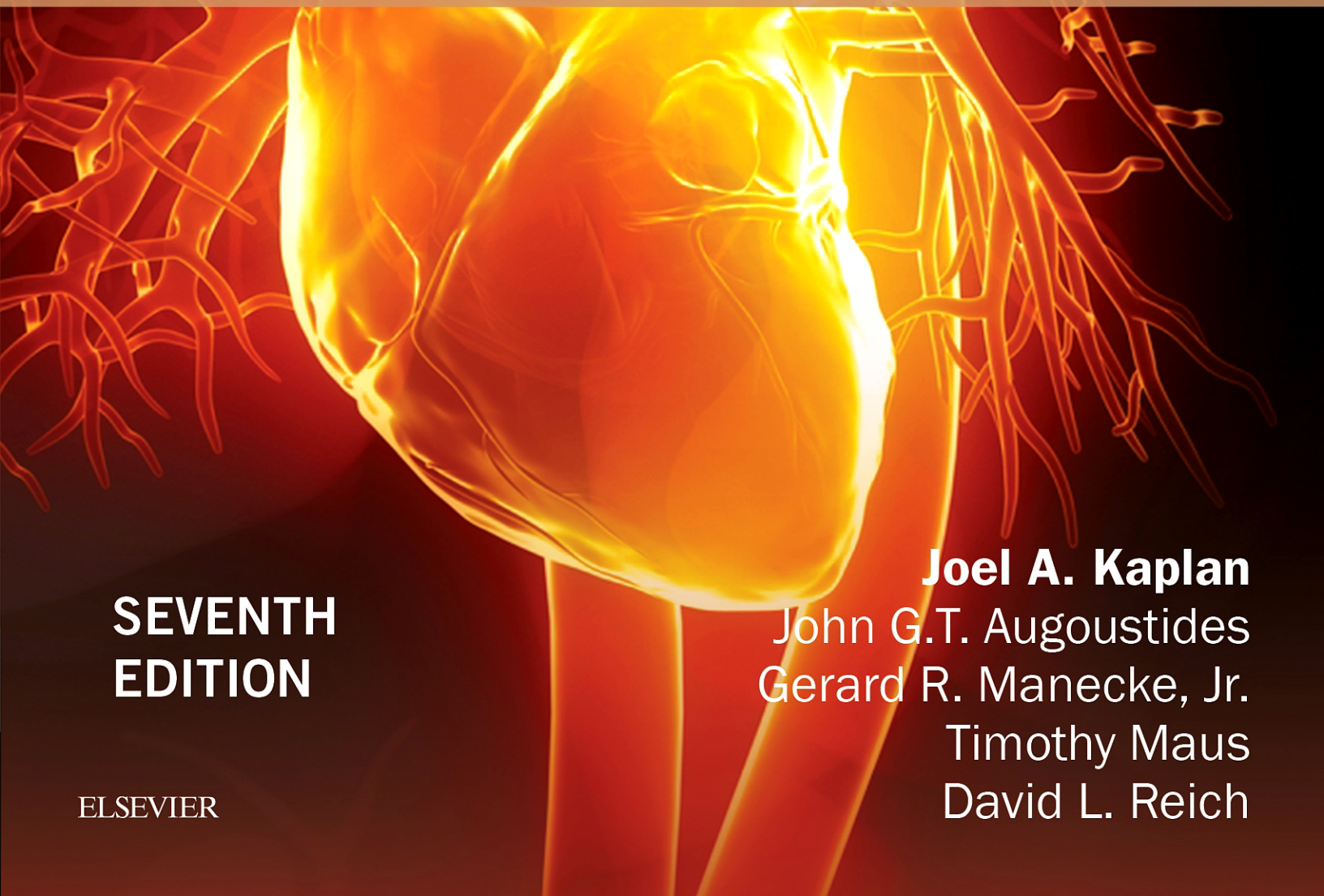
KAPLAN'S CARDIAC ANESTHESIA

FOR CARDIAC AND NONCARDIAC SURGERY



SEVENTH EDITION

Joel A. Kaplan
John G.T. Augoustides
Gerard R. Manecke, Jr.
Timothy Maus
David L. Reich

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Seventh Edition

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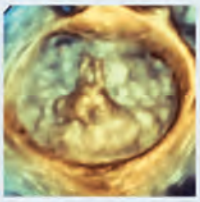

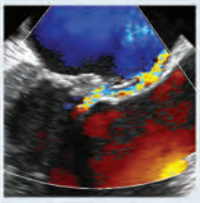

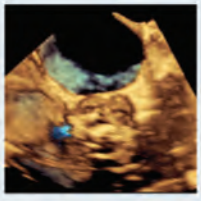

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DEDICATION

To my loving wife, Norma, on the occasion of our fiftieth wedding anniversary

Joel A. Kaplan, MD, CPE, FACC

To our families and loved ones for their support and understanding

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PREFACE

The seventh edition of *Kaplan's Cardiac Anesthesia* has been written to further enhance the perioperative management of the patient with cardiac disease undergoing either cardiac or noncardiac surgery. The first edition was published in 1979 during the early years of modern cardiac surgery when our focus was primarily on anesthetizing cardiac surgical patients. Continued advances in the care of patients with heart disease have expanded the role of cardiac anesthesiologists into preoperative evaluation, advanced cardiac imaging and other monitoring devices, postoperative critical care, and pain management. Today, we are also being asked to care for or help "rescue" the sickest cardiac patients undergoing noncardiac surgery and to participate as a member of the cardiac care team by performing procedures in locations distant from cardiac operating rooms. This edition focuses on the current issues associated with advanced cardiopulmonary assist devices, procedures in hybrid operating rooms, and new anticoagulants and coagulants, as well as being members of the heart team deciding on the best options for our sick patients.

This edition is subtitled "For Cardiac and Noncardiac Surgery" to emphasize the expanded role of all anesthesiologists in the perioperative medical care of high-risk cardiac patients undergoing all types of procedures. Ten chapters have been added as the final section of this book and deal specifically with these patients, the complex care and procedures they require, and the techniques used to reduce the incidence of major adverse cardiac events. This contrasts with only one chapter in the first edition that pointed out that some cardiac patients undergoing noncardiac surgery could be just as sick or sicker than those having cardiac surgery and that their cardiovascular complications could carry a high mortality rate after noncardiac surgery. That chapter, from 1979, stated that "the anesthesiologist should be experienced in modern cardiac anesthesia skills…able to insert the monitoring devices, interpret the data, utilize new pharmacotherapy, and understand the patient's basic pathophysiology." Certainly this is even more important today, with patients presenting for noncardiac surgery and having drug-eluting stents, multiple antiplatelet drugs, ventricular assist devices, multiple drugs for end-stage heart failure, and implanted electrical devices that produce cardiac resynchronization therapy. These advanced levels of cardiac care, no longer rare, are seen routinely in noncardiac surgery performed in operating rooms, outlying areas of the hospital, and even in outpatient surgical settings. In addition, many patients undergoing vascular or thoracic surgery, some cardiac patients with complicated obstetric problems, and many other noncardiac surgical patients may have significant cardiovascular issues requiring that all anesthesiologists have the skills needed (eg, basic cardiac echocardiography) to diagnose and treat these perioperative problems so as to reduce complications.

The content of the seventh edition ranges from the basic sciences to translational medicine and the latest evidence-based clinical care of the sickest and most complex cardiac patients. To maintain its place as the standard reference textbook in the field, this edition has been completely revised, expanded, and updated to reflect the ongoing changes in cardiovascular care, especially the rapid growth and use of new monitoring techniques, minimally invasive cardiac surgical procedures performed with or without cardiopulmonary bypass, advances in postoperative care, and renewed emphasis on patient safety and reductions in postoperative complications. Significant contributions to the text have been made by leading experts in anesthesiology, cardiology, cardiac surgery, and critical care medicine from around the world. The emphasis throughout the book is on using the latest scientific developments to guide proper therapeutic interventions in the perioperative period. In addition, some chapters include expert guidelines published by leading national and international scientific specialty organizations.

Due to the success of the educational aids used in the previous edition, the Key Points of each chapter appear first in the chapter and Teaching Boxes are highlighted with many of the important take-home messages. The content of the book is enhanced by full-color presentations of the text, multicolor echo and Doppler images, cine clips, and supplementary video material on the ExpertConsult website that accompanies the print version of the text. The website also will be used to update the book on a regular basis as new material appears before the next edition.

In preparing this edition, I have been helped enormously by the four associate editors. They have helped recruit new authors, worked with them on timely production and coordination of their chapters, and expanded the educational opportunities with unique contributions. Dr. Augoustides serves as the liason editor between the book and the *Journal of Cardiothoracic and Vascular Anesthesia,* providing updates on the book's website from new material (eg, new oral anticoagulants) appearing in the journal, as well as selected highlights of the previous year in cardiothoracic and vascular anesthesia. Dr. Maus serves as the editor of the *Transesophageal Echocardiography Video Atlas* (ie, 2D and 3D views, Doppler, and hemodynamic videos) and the Pathologic View Library (eg, perivalvular leaks, aortic dissection, and obstructive cardiomyopathy) found on the book's website. This allows the reader of the book to move seamlessly from the text to the echocardiography video supplementary material. Using the ExpertConsult. Inkling platform, the interested reader can further expand his or her reading on advanced echocardiography by moving to the companion textbook entitled *Perioperative Transesophageal Echocardiography* and edited by Dr. Reich. Finally, Dr. Manecke has coordinated the noncardiac surgery section of the book and introduced the new concepts of goal-directed therapy, enhanced recovery from anesthesia, and the perioperative anesthetic/surgical home for cardiac patients. As we transition from volume-based practices by independent experts to value-based care by a team of experts, these new approaches will allow us as cardiac anesthesiologists to position ourselves as participants in the entire episode of care and the success of the entire team.

Kaplan's Cardiac Anesthesia was written by acknowledged experts in each specific area or related specialties. It is the most authoritative and up-to-date collection of material in the field. Each chapter aims to provide the scientific foundation of the subject matter, the clinical basis for practice, and (when available) outcome information. All of the chapters have been coordinated in an effort to maximize their clinical utility. Whenever possible, material has been integrated from anesthesiology, critical care medicine, cardiology, cardiac surgery, physiology, and pharmacology to present a complete clinical picture. Thus this edition should continue to serve as the definitive text for cardiac anesthesia residents, fellows, faculty, practitioners, cardiologists, cardiac surgeons, intensivists, and others interested in the management of the patient with cardiac disease for either cardiac or noncardiac surgery.

This edition should further facilitate the application of the techniques and procedures that have been learned in the cardiac surgical operating rooms to cardiac patients undergoing noncardiac surgery. These patients compose a much larger group than those undergoing cardiac surgery, and they are often sicker and at higher risk because their underlying cardiac disease is not being corrected by the operative procedure. All of our learning and experience dealing with cardiac surgery should be used to improve the outcomes of these noncardiac surgical patients. It is our overall experience and skill demonstrated while caring for the sickest cardiac patients undergoing new and innovative operations that led J. Willis Hurst, MD, one of the world's leading cardiologists, to state in his Foreword to the first edition of this book that "this cardiologist views the modern cardiac anesthesiologist

with awe." If he thought we were good in 1979, he must be amazed to see our care today guided by the latest monitoring techniques in patients who never would have been operated on in the past.

The editors gratefully acknowledge the contributions made by the authors of each of the chapters. They are the dedicated experts who have made the field of cardiac anesthesia what it is today and are the teachers of our young colleagues practicing anesthesiology around the world. This book would not have been possible without their hard work and expertise.

Joel A. Kaplan, MD, CPE, FACC
Editor

A Textbook for All Anesthesiologists

Patients with cardiac disease undergoing noncardiac surgery should be evaluated … and managed … in a similar manner to patients having cardiac surgery. In order to be able to care for these sick patients … the anesthesiologist and his assistants should be experienced in modern cardiac anesthesia skills. The anesthesiologist must be able to insert monitoring devices … interpret the ECG, utilize the new pharmacotherapy, and understand the patients basic pathophysiology.

Joel A. Kaplan and Ronald W. Dunbar
Cardiac Anesthesia, 1979

The first textbook on anesthesia for surgery of the heart was written by Kenneth K. Keown, who provided anesthesia for Charles Bailey (first successful mitral commisurotomy in 1948), and was published in 1956. This single-author text was 109 pages and had 115 references. Although many different textbooks on this subspecialty have appeared since then, the earliest and now longest and most up to date is this one edited by Joel A. Kaplan, which first appeared in 1979. It is justifiably regarded as the definitive standard reference textbook of cardiac anesthesia.

I first became acquainted with Dr. Kaplan during my second decade as a cardiac surgeon at the University of Washington when I heard him speak at a cardiac surgical meeting extolling and reviewing the role cardiac anesthesiologists can play in improving the outcomes of our patients. Shortly thereafter a team consisting of a cardiac anesthesiologist, a perfusionist, and me were sent by our chairmen to see how the experts in the eastern United States practiced cardiac surgery, and one of those sites was Emory University, where Dr. Kaplan practiced. A few years later as an anesthesia resident and then as a cardiac anesthesia fellow, the first edition of his textbook was a major resource for us, as documented by the profuse highlighting and underlining of text in that book (which still sits in my bookshelf), and then guided our initiation of the cardiac anesthesia program at the University of Kentucky more than 30 years ago.

Cardiac Anesthesia has made many contributions to the practice of anesthesia, cardiovascular medicine, and critical care. The first edition emphasized the importance of a firm understanding of cardiovascular and pulmonary physiology and pharmacology and the interaction of drugs on these two systems. *Cardiac Anesthesia* introduced routine monitoring of electrocardiography (ECG) and invasive monitoring of arterial, central venous, and pulmonary artery pressure, venous saturations, and cardiac output. It identified the discrepancy between central venous pressure and left atrial pressure by introducing the direct measurement of left atrial pressure and the subsequent use of monitoring of pulmonary artery occlusion (wedge) pressure. *Cardiac Anesthesia* also introduced the use of ECG to detect perioperative myocardial ischemia (eg, V_5 lead) and the treatment of it with intravenous nitroglycerin.

Cardiac anesthesiologists have revolutionized the evaluation and perioperative management of cardiac patients undergoing cardiac and noncardiac surgery. They were instrumental in the adoption of monitoring of arterial blood gases, the development of the surgical intensive care unit (ICU), and the incorporation of advanced respiratory and hemodynamic monitoring and management (including aggressive pharmacologic therapy with inotropes and others vasoactive drugs) in the ICU and the noncardiac operating room. Cardiac anesthesiologists collaborated with the American Heart Association/American College of Cardiology in developing various guidelines for management of such patients. They called attention to the frequent occurrence and adverse consequences of perioperative myocardial ischemia during noncardiac surgery. They initiated the use of invasive monitoring—first with the pulmonary artery catheter (PAC) and then with transesophageal echocardiography (TEE)—in the perioperative management of cardiac patients and the participation of anesthesiologists in their management in postsurgical ICUs. They introduced narcotic anesthesia (Lowenstein, Stanley) for these patients and the use of newer pharmacologic agents to treat severe heart failure, hypertension, and arrhythmias. Cardiac anesthesiologists were responsible for introducing TEE to cardiology practice in the United States and since that time have collaborated closely in the application of echocardiography to cardiac care, education, and certification.

Perhaps the greatest contribution has been the recognition very early in the history of cardiac surgery of the importance of a team (surgeon, anesthesiologist, perfusionist, nurse) in the successful management of patients. This concept has now been embedded as an important component of enhanced recovery after surgery and the perioperative surgical/anesthesia home. The Society of Cardiovascular Anesthesiologists has been a leader in improving the functioning of these teams and its safety implications, as discussed in the new chapter on patient safety and avoiding errors. All of this has led to the dramatic improvement of the care of patients with cardiac disease, those undergoing not only cardiac surgery but also noncardiac surgery and nonsurgical care, and likely has contributed to the dramatic improvement in outcomes of these sick patients over the last 40 years.

The first edition of this textbook emphasized the importance of a firm knowledge of the physiology, pharmacology, and pathophysiology of cardiac disease and the importance of management guided by detailed hemodynamic monitoring, including the use of the PAC. Subsequent editions reflected advances in cardiac surgery and anesthesia over the last 4 decades. The second edition (1987) introduced echocardiography, cardiac transplantation, circulatory assistance beyond intraaortic balloon pumping, and central nervous system monitoring and devoted more attention to myocardial protection and postoperative care. The third edition (1993) added chapters on noncardiac surgery in patients with cardiac disease and more on echocardiography (including color flow) and devoted more attention to coagulation and bleeding, central nervous system dysfunction, and the importance of outcome studies after cardiac and noncardiac surgery in patients with heart diseases. The fourth edition (1999) included new chapters on systemic inflammatory response and practice management. The fifth edition (2006) provided chapters that discussed the history of cardiac surgery and anesthesia and predictions of future developments, as well as chapters on molecular cardiovascular medicine, minimally invasive cardiac surgery, and surgical approaches to heart failure, including more advanced ventricular assist devices, pain management, strategies to reduce medical errors, and training in cardiac anesthesia. The sixth edition (2011) subtitled, "The Echo Era," emphasized the maturation of echocardiography and integrated its use into various other chapters throughout that edition.

The present edition advances a theme from the first edition of this text, as reflected in the quote at the start of this forward: the application of the principles of cardiac anesthesia to the management of patients

with cardiac disease outside of the cardiac surgery operating room. Many of its chapters provide essential information, but most relevant are those in the last section, which cover the everyday issues of patients with coronary stents, implantable electronic devices, and implantable ventricular assist devices; the benefits of the use of echocardiography outside the cardiac surgery rooms; and what can be done postoperatively to decrease the incidence of major adverse cardiac events and mortality following noncardiac surgery. I believe that this new edition points out that nearly every site where anesthesiologists practice is potentially a "heart room" and therefore, nearly all anesthesiologists must become cardiac anesthesiologists.

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VIDEO CONTENTS

1 Assessment of Cardiac Risk and the Cardiology Consultation[1]

MANISH BANSAL, MD, DNB CARDIOLOGY, FACC, FASE | VALENTIN FUSTER, MD, PhD, MACC | JAGAT NARULA, MD, PhD, MACC | PARTHO P. SENGUPTA, MD, DM, FACC, FASE

KEY POINTS

1. Perioperative cardiac morbidity is multifactorial, and understanding the predictive risk factors helps define the risk for individual patients.
2. Assessment of myocardial injury is based on the integration of information from myocardial imaging (eg, echocardiography), electrocardiography (ECG), and serum biomarkers, with significant variability in the diagnosis depending on the criteria selected.
3. Multivariate modeling has been used to develop risk indices that focus on preoperative variables, intraoperative variables, or both.
4. Key predictors of perioperative risk are dependent on the type of cardiac operation and the outcome of interest.
5. New risk models have become available for valvular heart surgery and for combined coronary and valvular cardiac procedures.
6. For patients undergoing noncardiac surgery, the objectives and approach to cardiac evaluation are entirely different. The nature of the noncardiac surgery and the urgency of the surgical procedure are the primary determinants of the extent of cardiac evaluation in these patients.
7. For most patients undergoing noncardiac surgery, preoperative coronary revascularization is not required unless the patient presents with an unstable cardiac condition or has significant myocardial ischemia and the noncardiac surgery is not urgent.

In the early 1980s, coronary artery bypass graft surgery (CABG) was characterized by operative mortality rates in the range of 1% to 2%. Over the ensuing years, urgent and emergent operations and "redo" procedures became common, and greater morbidity and mortality rates were observed. Percutaneous coronary interventions (PCIs) absorbed low-risk patients from the surgery pool, with the net result that the operative mortality rate increased to the range of 5% to 6%. The trend toward PCI has continued, with trials demonstrating the safety of stenting even in left main coronary artery disease (CAD).[1–3] This demographic shift has led governmental health oversight agencies to ask for justification of the observed increase in CABG mortality, often prompting a time-consuming and expensive chart review to identify the differences in patient populations that led to the greater morbidity. Even with this information, however, it has been difficult to *objectively* determine the impact of these new and compelling factors on mortality. The impetus for the development of a risk-adjusted outcome assessment and appropriate risk adjustment scoring system was the need to compare adult cardiac surgery results in different institutions and to benchmark the observed complication rates.[4] With the recent passage of health care reform legislation and interest in controlling health care expenditures, there is increased interest in public reporting of perioperative outcomes with optimal risk adjustment.

The first risk-scoring scheme for cardiac surgery was introduced by Paiement and colleagues at the Montreal Heart Institute in 1983.[5] Since then, many preoperative cardiac surgery risk indices have been developed. The patient characteristics that affected the probability of specific adverse outcomes were identified and weighed, and the resultant risk indices have been used to adjust for case-mix differences among surgeons and centers where performance profiles have been compiled. In addition to comparisons among centers, the preoperative cardiac risk indices have been used to counsel patients and their families in resource planning, to identify high-risk groups for special care or research, to determine cost-effectiveness, to determine effectiveness of interventions, to improve provider practice, and to assess costs related to severity of disease.[6,7]

In contrast, the objectives of cardiac evaluation in a patient undergoing noncardiac surgery are entirely different. In contrast to patients undergoing cardiac surgery, for whom extensive cardiac evaluation is part of the workup, the cardiac status of patients undergoing noncardiac surgery is often unknown (see Chapter 43). In such patients, the benefit of performing cardiac assessment with its inherent time and resource implications needs to be weighed against the impact such information could have on perioperative planning and the potential risks associated with any delay in the noncardiac surgery. The main goal in this setting is to identify a high-risk group of patients who would benefit from either noninvasive or invasive cardiac evaluation and appropriate perioperative medical management or interventional therapy (see Chapters 2 and 3).

Sources of Perioperative Myocardial Injury in Cardiac Surgery

Myocardial injury, manifested as transient cardiac contractile dysfunction ("stunning") or acute myocardial infarction (AMI) or both, is the most frequent complication after cardiac surgery and the most important cause of hospital complications and death. Furthermore, patients who experience a perioperative myocardial infarction (MI) have a poor long-term prognosis; only 51% of such patients remain free from adverse cardiac events after 2 years, compared with 96% of patients without perioperative MI.[8]

It is important to understand the pathogenesis of this morbidity and mortality to clarify the determinants of perioperative risk. This is particularly important with respect to cardiac outcomes because the definition of *cardiac morbidity* represents a continuum rather than

[1]The editors and the publisher would like to thank Drs. Jiri Horak, Emile R. Mohler, and Lee A. Fleisher for contributing a chapter on this topic to the prior edition of this work. It has served as the foundation for the current chapter.

BOX 1.1 DETERMINATIONS OF PERIOPERATIVE MYOCARDIAL INJURY

Disruption of blood flow
Reperfusion of ischemic myocardium
Adverse systemic effects of cardiopulmonary bypass

a discrete event. This understanding can help target the biologically significant risk factors and interventions that may decrease irreversible myocardial necrosis.

Myocardial necrosis is the result of progressive pathologic ischemic changes that start to occur in the myocardium within minutes after interruption of its blood flow (eg, during cardiac surgery) (Box 1.1). The duration of the interruption of blood flow, either partial or complete, determines the extent of myocardial necrosis, and both the duration of the period of aortic cross-clamping (AXC) and the duration of cardiopulmonary bypass (CPB) have consistently been shown to be the main determinants of postoperative outcomes. In a study with an average follow-up of 10 years after complex cardiac surgery, Khuri[9] observed a direct relation between the lowest mean myocardial pH recorded during or after the period of AXC and long-term patient survival. Patients who experienced acidosis (pH <6.5) had decreased survival compared with those who did not. Because myocardial acidosis reflects both myocardial ischemia and poor myocardial protection during CPB, this study demonstrated the relation of the adequacy of intraoperative myocardial protection to long-term outcome (see Chapters 3, 7, 20, and 31).

Reperfusion of Ischemic Myocardium

Surgical interventions requiring interruption of blood flow to the heart must be followed by restoration of perfusion. Numerous experimental studies have provided compelling evidence that reperfusion, although essential for tissue and organ survival, is not without risk because of the potential extension of cell damage as a result of reperfusion itself. Myocardial ischemia of limited duration (<20 min) that is followed by reperfusion leads to functional recovery without evidence of structural injury or biochemical evidence of tissue injury.[10,11] However, reperfusion of cardiac tissue that has been subjected to an extended period of ischemia results in a phenomenon known as *myocardial reperfusion injury.*[12–14] Thus, a paradox exists in that tissue viability can be maintained only if reperfusion is instituted within a reasonable period, but doing so risks extending the injury beyond that caused by the ischemic insult itself. This finding is supported by the observation that ventricular fibrillation was prominent when regionally ischemic canine hearts were subjected to reperfusion.[15] Jennings and associates[16] reported adverse structural and electrophysiologic changes associated with reperfusion of the ischemic canine heart, and Hearse[17] introduced the concept of an oxygen paradox based on cardiac muscle enzyme release and alterations in ultrastructure when isolated hearts were reoxygenated after a period of hypoxic perfusion.

Myocardial reperfusion injury is defined as the death of myocytes, which were alive at the time of reperfusion, as a direct result of one or more events initiated by reperfusion. Myocardial cell damage results from restoration of blood flow to the previously ischemic heart and extends the region of irreversible injury beyond that caused by the ischemic insult alone. The cellular damage that results from reperfusion can be reversible or irreversible, depending on the duration of the ischemic insult. If reperfusion is initiated within 20 minutes after the onset of ischemia, the resulting myocardial injury is reversible and is characterized functionally by depressed myocardial contractility, which eventually recovers completely. Myocardial tissue necrosis is not detectable in the previously ischemic region, although functional impairment of contractility may persist for a variable period, a phenomenon known as *myocardial stunning.* Initiation of reperfusion after longer than 20 minutes, however, results in escalating degrees of irreversible myocardial injury or cellular necrosis. The extent of tissue necrosis that develops during reperfusion is directly related to the duration of the ischemic event. Tissue necrosis originates in the subendocardial region of the ischemic myocardium and extends to the subepicardial region of the area at risk; this is often referred to as the *wavefront phenomenon.* The cell death that occurs during reperfusion can be characterized microscopically by explosive swelling, which includes disruption of the tissue lattice, contraction bands, mitochondrial swelling, and calcium phosphate deposition within mitochondria.[15]

The magnitude of reperfusion injury is directly related to the magnitude of the ischemic injury that precedes it. In its most severe form, it manifests as a "no-reflow" phenomenon. In cardiac surgery, prevention of myocardial injury after release of the AXC, including prevention of no-reflow, is directly dependent on the adequacy of myocardial protection during the period of AXC. The combination of ischemic and reperfusion injury is probably the most frequent and most serious type of injury leading to poor outcomes in cardiac surgery today (see Chapters 2, 3, 7, 13–16, 20, and 31).

Basic science investigations (in mouse, human, and porcine hearts) have implicated acidosis as a primary trigger of apoptosis. Acidosis, reoxygenation, and reperfusion—but not hypoxia (or ischemia) alone—are strong stimuli for programmed cell death, and cardiac apoptosis has been demonstrated to lead to heart failure.[18,19] This suggests that apoptotic changes might be triggered in the course of a cardiac operation, initiating an injurious cascade of adverse clinical events that manifest late in the postoperative course.

Based on the previous discussion, it is clear that a significant portion of perioperative cardiac morbidity is related primarily to intraoperative factors. However, preoperative risk factors also influence ischemic and reperfusion injury.

Adverse Systemic Effects of Cardiopulmonary Bypass

In addition to the effects of disruption and restoration of myocardial blood flow, cardiac morbidity may result from systemic insults due to CPB circuit-induced contact activation. Inflammation in cardiac surgical patients is produced by complex humoral and cellular interactions, including activation, generation, or expression of thrombin, complement, cytokines, neutrophils, adhesion molecules, mast cells, and multiple inflammatory mediators.[20] Because of the redundancy of the inflammatory cascades, profound amplification occurs to produce multiorgan system dysfunction that can manifest as coagulopathy, respiratory failure, myocardial dysfunction, renal insufficiency, and neurocognitive defects. Coagulation and inflammation also are linked closely through networks of both humoral and cellular components, including tissue factor and proteases of the clotting and fibrinolytic cascades. Vascular endothelial cells mediate inflammation and the cross-talk between coagulation and inflammation. Surgery alone activates specific hemostatic responses, immune mechanisms, and inflammatory responses mediated by the release of various cytokines and chemokines (see Chapters 9, and 31–35). This complex inflammatory reaction can lead to death from nonischemic causes and suggests that preoperative risk factors may not predict morbidity. The ability to risk-adjust populations is critical for the study of interventions that may influence these responses to CPB.

Assessment of Perioperative Myocardial Injury in Cardiac Surgery

The current clinical armamentarium is devoid of a means by which perioperative cardiac injury can be reliably monitored in real time, and this has led to the use of indicators of AMI after the event occurs. There is a lack of consensus regarding how to measure myocardial injury in cardiac surgery because of the continuum of cardiac injury. Electrocardiographic changes, biomarker elevations, and measures

BOX 1.2 ASSESSMENT OF PERIOPERATIVE MYOCARDIAL INJURY

Assessment of cardiac function
- Echocardiography

Nuclear imaging

Electrocardiography
- Q waves
- ST-T wave changes

Serum biomarkers
- Myoglobin
- Creatine kinase
- CK-MB isoenzyme
- Troponin
- Lactate dehydrogenase

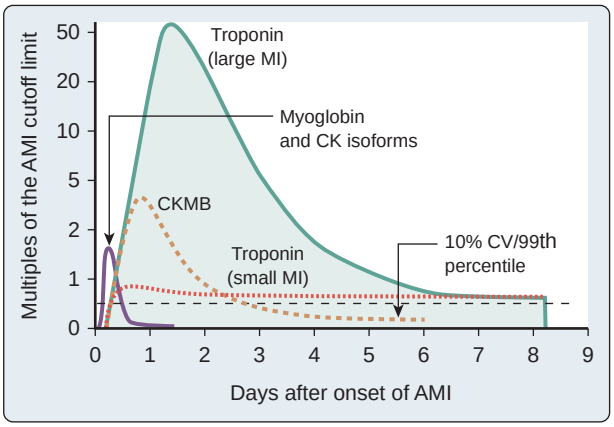


Fig. 1.1 Time course of the appearance of various markers in the blood after acute myocardial infarction *(AMI)*. Shown are the time concentrations/activity curves for myoglobin and creatine kinase *(CK)* isoforms, troponin after large and small infarctions, and CKMB. Note that with cardiac troponin some patients have a second peak in addition. *CKMB,* Creatine kinase, myocardial bound; *CV,* coefficient of variation. *(From Jaffe AS, Babuin L, Apple FS: Biomarkers in acute cardiac disease: the present and the future.* J Am Coll Cardiol. *2006;48[1]:1–11.)*

of cardiac function have all been used (Box 1.2), but all assessment modalities are affected by the direct myocardial trauma of surgery. In 2000, the American College of Cardiology/European Society of Cardiology (ACC/ESC) published a definition of MI that included a characteristic rise and fall in blood concentrations of cardiac troponins or creatine kinase (CK)-MB, or both, in the context of a coronary intervention; other modalities are less sensitive and specific (Fig. 1.1).[21]

The Joint ESC/ACC Foundation (ACCF)/American Heart Association (AHA)/World Heart Federation Task Force published a new Universal Definition of Myocardial Infarction in 2007[22] and revised it in 2012.[23] According to this most recent version of the definition, MI can be diagnosed based on detection of a rise and fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischemia in the form of any of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block), development of pathologic Q waves on ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (RWMA). Because CABG itself is associated with cardiac trauma resulting in an increase in the serum levels of cardiac enzymes, an arbitrary cutoff level for elevation of cardiac biomarker values of more than 10 times the 99th percentile of the upper reference limit has been recommended for diagnosing MI during the immediate period after cardiac surgery. However, this threshold is more robust for diagnosing MI after an isolated on-pump CABG; cardiac biomarker release is typically considerably higher after combined valve replacement and CABG and considerably lower after an off-pump CABG.[24]

Assessment of Cardiac Function

Cardiac contractile dysfunction is the most prominent feature of myocardial injury, despite the fact that there are no perfect measures of postoperative cardiac function. The need for inotropic support, low cardiac output (CO) diagnosed with the use of CO measurement technologies, and assessment of abnormal ventricular function by transesophageal echocardiography (TEE) are practical intraoperative options for evaluation of cardiac contractility. Use of inotropic support and CO measurements are not reliable measures, however, because they depend on loading conditions and interpractitioner variability. Failure to wean from CPB, in the absence of systemic factors such as hyperkalemia and acidosis, is the best evidence of intraoperative myocardial injury or cardiac dysfunction, but it also may be multifactorial and therefore is a less robust outcome measure.

Because RWMAs on TEE follow the onset of ischemia within 10 to 15 seconds, echocardiography can be a sensitive and rapid monitor for cardiac ischemia/injury.[25] An irreversible RWMA indicates irreversible myocardial necrosis (see Chapters 12–16). The importance of echocardiographic assessment of cardiac function is further enhanced by its value as a predictor of long-term survival.[26] For patients undergoing CABG, a postoperative decrease in left ventricular (LV) ejection fraction (LVEF) compared with the preoperative baseline predicts decreased long-term survival.[27]

Nevertheless, the use of echocardiography for detecting postoperative LV systolic dysfunction has some challenges. Echocardiographic and Doppler systems have the limitation of being sensitive to alterations in loading conditions, similar need for inotropic support and CO determinations,[28] and the interpretation of TEE images is also operator dependent.[29] Additionally, myocardial stunning (postischemic transient ventricular dysfunction) is a common cause of new postoperative RWMAs, and the resulting wall motion abnormalities and LV systolic dysfunction are often transient. However, the appearance of a new LV RWMA in the postoperative period, whether caused by irreversible AMI or by reversible myocardial stunning, is an indication of some form of inadequate myocardial protection during the intraoperative period and therefore is of interest for assessment of the need for new interventions. At the same time, there are nonischemic causes of RWMAs, such as conduction abnormalities, ventricular pacing, and myocarditis, that confound the use of this measure for assessment of ischemic morbidity.

Electrocardiography Monitoring

The presence of new persistent Q waves of at least 0.03-s duration, broadening of preexisting Q waves, or new QS deflections on the postoperative ECG have been considered evidence of perioperative AMI.[30] However, new Q waves also may be caused by unmasking of an old MI and therefore are not indicative of a new AMI. Crescenzi and colleagues[31] demonstrated that the presence of a new Q wave together with high levels of biomarkers was strongly associated with postoperative cardiac events, whereas the isolated appearance of a new Q wave had no impact on postoperative cardiac outcome. Additionally, new Q waves may actually disappear over time.[32] Signs of non–Q-wave MI, such as ST-T wave changes, are even less reliable signs of AMI after cardiac surgery in the absence of biochemical evidence. ST-segment changes are less specific for perioperative MI because they can also be caused by changes in body position, hypothermia, transient conduction abnormalities, pericarditis, and electrolyte imbalances (see Chapter 12).

Serum Biochemical Markers to Detect Myocardial Injury

Serum biomarkers have become the primary means of assessing the presence and extent of AMI after cardiac surgery. Serum biomarkers that are indicative of myocardial damage include the following (with postinsult peak time given in parentheses): myoglobin (4 h), total CK (16 h), CK-MB isoenzyme (24 h), troponins I and T (24 h), and lactate dehydrogenase (LDH) (76 h). CK-MB isoenzyme has been used most widely, but studies have suggested that troponin I is the most sensitive and most specific marker for depicting myocardial ischemia and infarction.[33–37] Accordingly, cardiac troponin I is the current biomarker of choice for diagnosing myocardial injury.[23]

Numerous studies have demonstrated the value of cardiac biomarkers in predicting short- and long-term outcomes in patients undergoing cardiac surgery. For example, Klatte and coworkers reported on the implications of CK-MB level in 2918 high-risk CABG patients enrolled in a clinical trial of an antiischemic agent.[38] They calculated the postoperative peak CK-MB ratio (ie, the peak CK-MB value divided by the upper limit of normal for the laboratory test) for each patient. The unadjusted 6-month mortality rates were 3.4%, 5.8%, 7.8%, and 20.2% for patients with CK-MB ratios of less than 5, between 5 and 10, between 10 and 20, and greater than 20, respectively.[38] The relation remained statistically significant after adjustment for LVEF, congestive heart failure (CHF), cerebrovascular disease, peripheral vascular disease, cardiac arrhythmias, and the method of cardioplegia delivery.

In the Arterial Revascularization Therapies Study (ARTS), 496 patients with multivessel coronary artery disease undergoing CABG were evaluated by CK-MB testing after surgery and at 30 days and 1 year of follow-up.[39] Patients with increased cardiac enzyme levels after CABG were at increased risk for both death and repeat AMI within the first 30 days. CK-MB increase also was independently related to late adverse outcome. Other studies have similarly documented the prognostic value of cardiac troponin I. Increased cardiac-specific troponin I or T after CABG has been associated with a cardiac cause of death and with major postoperative complications within 2 years after CABG.[40,41]

A few new biomarkers of perioperative cardiac injury or ischemia are under development. Brain natriuretic peptide (BNP) can be detected in the early stages of ischemia and decreases shortly after ischemic insult, allowing better detection of reinjury.[42] BNP concentrations after CABG in patients who experienced cardiac events within 2 years after surgery were significantly greater than those in patients free of cardiac events.[43] Soluble CD40 ligand (sCD40L) is another early biomarker of myocardial ischemia,[44] and CPB causes an increase in the concentration of plasma sCD40L. A corresponding decrease in platelet CD40L suggests that this prothrombotic and proinflammatory protein is derived primarily from platelets and may contribute to the thrombotic and inflammatory complications associated with CPB.[45] Future research will be required to determine how these biomarkers may be used to assess outcome after cardiac surgery.

Variability in Diagnosis of Perioperative Myocardial Infarction

The variability in diagnosis of perioperative AMI was studied by Jain and colleagues,[46] who evaluated data from 566 patients at 20 clinical sites. Twenty-five percent of the patients met Q-wave, CK-MB, or autopsy criteria for AMI. Among them, 19% had increased CK-MB concentrations and ECG changes. Four percent met either Q-wave plus CK-MB or autopsy criteria. Multicenter data collection showed a substantial variation in the incidence of AMI and an overall incidence rate of up to 25%. The determination of perioperative AMI was highly variable depending on the definitions used.

Clinicians are still searching for a gold standard approach to diagnose perioperative AMI. Perioperative myocardial necrosis or injury ranges from mild to severe and can have an ischemic or nonischemic origin in patients undergoing cardiac surgery. Perioperative ECG changes, including Q waves, and new RWMAs on TEE are less reliable than in the nonperioperative arena. As mentioned earlier, troponin I or T is currently the best indicator of myocardial damage after cardiac surgery.

Cardiac Risk Assessment and Cardiac Risk Stratification Models in Patients Undergoing Cardiac Surgery

In defining important risk factors and developing risk indices, each of the studies has used different primary outcomes. Postoperative mortality remains the most definitive outcome that is reflective of patient injury in the perioperative period. Death can be cardiac and noncardiac related, and if cardiac related, it may be ischemic or nonischemic in origin. Postoperative mortality rate is reported as either the in-hospital rate or the 30-day rate. The latter represents a more standardized definition, although it is more difficult to capture because of the difficulty inherent in assessing death rates of discharged patients who may die at home or another facility. Risk-adjusted postoperative mortality models permit assessment of the comparative efficacy of various techniques in preventing myocardial damage, but they do not provide information that is useful in preventing the injury in real time.[47] The postoperative mortality rate also has been used as a comparative measure of quality of cardiac surgical care.[48,49]

Postoperative morbidity includes AMI and reversible events such as CHF and need for inotropic support. The problems of using AMI as an outcome of interest were described earlier. Because resource utilization has become such an important financial consideration for hospitals, the length of stay in the intensive care unit (ICU) increasingly has been used as a factor in the development of risk indices (see Chapters 37 and 38).

Predictors of Perioperative and Postoperative Morbidity and Mortality

Clinical and angiographic predictors of operative mortality were initially defined from the results of the Coronary Artery Surgery Study (CASS).[50,51] A total of 6630 patients underwent isolated CABG between 1975 and 1978. Women had a significantly greater mortality rate than men; mortality increased with advancing age in men, but this was not a significant factor in women. Increasing severity of angina, manifestations of heart failure, and number and extent of coronary artery stenoses all correlated with greater mortality, whereas LVEF was not a predictor. Urgency of surgery was a strong predictor of outcome, and those patients requiring emergency surgery in the presence of a 90% left main coronary artery stenosis sustained a 40% mortality rate.

A risk-scoring scheme for cardiac surgery (CABG and valve) was introduced by Paiement and associates[5] at the Montreal Heart Institute in 1983. Eight risk factors were identified: (1) poor LV function, (2) CHF, (3) unstable angina or recent MI (within 6 wk), (4) age greater than 65 years, (5) severe obesity (body mass index >30 kg/m^2), (6) reoperation, (7) emergency surgery, and (8) other significant or uncontrolled systemic disturbances. The investigators identified three classes of patients: those with none of the listed risk factors (normal), those presenting with one risk factor (increased risk), and those with more than one factor (high risk). In a study of 500 consecutive patients undergoing cardiac surgery, it was found that operative mortality increased with increasing risk score (confirming the scoring system).

zzzOne of the most commonly used scoring systems for CABG was developed by Parsonnet and colleagues[52] (Table 1.1). Fourteen risk factors were identified for in-hospital or 30-day mortality after univariate regression analysis of 3500 consecutive operations. An additive model was constructed and prospectively evaluated in 1332 cardiac procedures. Five categories of risk were identified with increasing mortality rates, complication rates, and length of stay at the Newark Beth Israel Medical Center. The Parsonnet Index frequently is used as a benchmark for comparisons among institutions. However, it was created earlier than the other models and may not be representative

TABLE 1.1 Components of the Additive Model

Risk Factor	*Assigned Weight*
Female sex	1
Morbid obesity (≥1.5 × ideal weight)	3
Diabetes (unspecified type)	3
Hypertension (systolic BP >140 mm Hg)	3
Ejection fraction (%):	
Good >50)	0
Fair (30–49)	2
Poor (<30)	4
Age (y):	
70–74	7
75–79	12
≥80	20
Reoperation	
First	5
Second	10
Preoperative IABP	2
Left ventricular aneurysm	5
Emergency surgery after PTCA or catheterization complications	10
Dialysis dependency (PD or Hemo)	10
Catastrophic states (eg, acute structural defect, cardiogenic shock, acute renal failure)[a]	10–50[b]
Other rare circumstances (eg, paraplegia, pacemaker dependency, congenital HD in adult, severe asthma)[a]	2–10[b]
Valve surgery	
Mitral	5
PA pressure ≥60 mm Hg	8
Aortic	5
Pressure gradient >120 mm Hg	7
CABG at the time of valve surgery	2

[a]On the actual worksheet, these risk factors require justification.
[b]Values were predictive of increased risk for operative mortality in univariate analysis.
BP, Blood pressure; *CABG,* coronary artery bypass graft; *HD,* heart disease; *Hemo,* hemodialysis; *IABP,* intraaortic balloon pump; *PA,* pulmonary artery; *PD,* peritoneal dialysis; *PTCA,* percutaneous transluminal coronary angioplasty.
From Parsonnet V, Dean D, Bernstein A. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation.* 1989;79:I3, by permission.

TABLE 1.2 Risk Model Results

Variable	*Odds Ratio*
Age (in 10-y increments)	1.640
Female sex	1.157
Race other than white	1.249
Ejection fraction	0.988
Diabetes	1.188
Renal failure	1.533
Serum creatinine (if renal failure is present)	1.080
Dialysis dependence (if renal failure is present)	1.381
Pulmonary hypertension	1.185
Cerebrovascular accident timing	1.198
Chronic obstructive pulmonary disease	1.296
Peripheral vascular disease	1.487
Cerebrovascular disease	1.244
Acute evolving, extending myocardial infarction	1.282
Myocardial infarction timing	1.117
Cardiogenic shock	2.211
Use of diuretics	1.122
Hemodynamic instability	1.747
Triple-vessel disease	1.155
Left main disease >50%	1.119
Preoperative intraaortic balloon pump	1.480
Status	
Urgent or emergent	1.189
Emergent salvage	3.654
First reoperation	2.738
Multiple reoperations	4.282
Arrhythmias	1.099
Body surface area	0.488
Obesity	1.242
New York Heart Association class IV	1.098
Use of steroids	1.214
Congestive heart failure	1.191
PTCA within 6 h of surgery	1.332
Angiographic accident with hemodynamic instability	1.203
Use of digitalis	1.168
Use of intravenous nitrates	1.088

PTCA, Percutaneous transluminal coronary angioplasty.
From Shroyer AL, Plomondon ME, Grover FL, et al: The 1996 coronary artery bypass risk model: the Society of Thoracic Surgeons Adult Cardiac National Database. *Ann Thorac Surg.* 1999;67:1205, by permission of Society of Thoracic Surgeons.

of the current practice of CABG. Since publication of the Parsonnet model, numerous technical advances now in routine use have diminished CABG mortality rates.

Bernstein and Parsonnet[53] simplified the risk-adjusted scoring system in 2000 to provide a handy tool in preoperative discussions with patients and their families and for preoperative risk calculation and stratification. The authors developed a logistic regression model, in which 47 potential risk factors were considered, and a method requiring only simple addition and graphic interpretation was designed for relatively easy approximation of the estimated risk. The final estimates provided by the simplified model correlated well with the observed mortality (Fig. 1.2).

The Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database (NCD) represents the most robust source of data for calculating risk-adjusted scoring systems. Established in 1989, the database included 892 participating hospitals in 2008 and has continued to grow. This provider-supported database, one of the largest in the world, allows participants to benchmark their risk-adjusted results against regional and national standards. New patient data are brought into the STS database on a semiannual basis. These new data are analyzed, modeled, and tested using a variety of statistical algorithms.

Since 1990, when more complete data collection was achieved, risk stratification models have been developed for both CABG and valve replacement surgery. Models developed in 1995 and 1996 were shown to have good predictive value[54,55] (Table 1.2 and Fig. 1.3). In 1999, the STS analyzed the database for valve replacement with and without CABG to determine trends in risk stratification. Between 1986 and 1995, 86,580 patients were analyzed. The model evaluated the influence of 51 preoperative variables on operative mortality by univariate and multivariate analyses for the overall population and for each subset. After the significant risk factors were determined by univariate analysis, a standard logistic regression analysis was performed using the training-set population to develop a formal model. The test-set population then was used to determine the validity of the model. The preoperative risk factors associated with greatest operative mortality rates were salvage status, renal failure (dialysis dependent and nondialysis dependent), emergent status, multiple reoperations, and New York Heart Association class IV status. The multivariate logistic regression analysis identified 30 independent preoperative risk factors among the six valvular models that represented isolated valvular surgery or valvular surgery in combination with CABG. The addition of CABG increased the mortality rate significantly for all age groups and for all subset models.[56]

There are currently three general STS risk models: CABG, valve (aortic or mitral), and valve plus CABG. These three models comprise seven specific, precisely defined procedures: the CABG model refers to an isolated CABG; the valve model includes isolated aortic or mitral valve replacement and mitral valve repair; and the valve plus CABG model includes aortic valve replacement with CABG, mitral valve replacement with CABG, and mitral valve repair with CABG. Besides operative mortality, these models were developed for eight additional end points: reoperation, permanent stroke, renal failure, deep sternal wound infection, prolonged (>24 h) ventilation, composite major

CARDIAC SURGERY:
PREOPERATIVE RISK-ESTIMATION WORKSHEET
(not intended for retrospective risk stratification)

Newark Beth Isreal Medical Center
Division of Surgical Research

Patient's Name:
Patient Number:
Date:

INSTRUCTIONS:

Step 1. Fill in the blanks for existing risk factors, using the scores provided. (Note: Scores shown are in arbitrary units, and are not, by themselves, estimates of percent risk.)

Step 2. Add the scores to obtain a total score. (Include common risk factors on this side of the page and less common risk factors on the other side.)

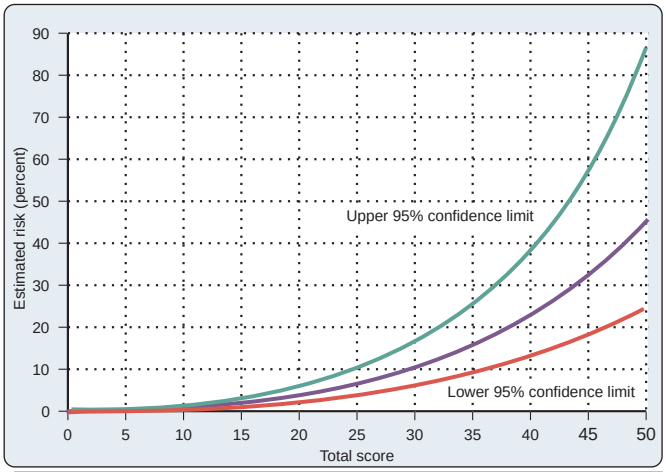
Step 3. See reverse side to interpret the total score.

RISK FACTOR	*SCORING (APPROXIMATE SYSTEM 97)*		*VALUE*
Female gender		6	6
Age	70–75 76–79 80+	2.5 7 11	7
Congestive failure		2.5	
COPD, severe		6	
Diabetes		3	
Ejection fraction	30–42% <30%	6.5 8	
Hypertension	Over 140/90, or history of hypertension, or currently taking anti-hypertension medication	3	3
Left-main disease	Left-main stenosis is 50%	2.5	
Morbid obesity	Over 1.5 times ideal weight	1	1
Preoperative IABP	IABP present at time of surgery	4	
Reoperation	First reoperation Second or subsequent reoperation	10 20	
One valve, aortic	Procedure proposed	0	
One valve, mitral	Procedure proposed	4.5	
Valve + ACB	Combination valve procedure and ACB proposed	6	
Special conditions	*(see reverse side)*		
		TOTAL SCORE:	17

(See reverse side for risk estimation.)

RISK VALUES FOR SPECIAL CONDITIONS

Cardiac	
Cardiogenic shock (urinary output <10 cc/hr)	12
Endocarditis, active	5.5
Endocarditis, treated	0
LV aneurysm resected	1.5
One valve, incuspid: procedure proposed	5
Pacemaker dependency	0
Transmural acute MI within 48 hr	4
Ventricular septal defect, acute	12
Ventricular tachycardia, ventricular fibrillation, aborted sudden death	1
Pulmonary	
Asthma	1
Endotracheal tube, preoperative	4
Idiopathic thrombocytopenic purpura	12
Pulmonary hypertension (mean pressure >30)	11
Hepato-renal	
Cirrhosis	12.5
Dialysis dependency	13.5
Renal failure, acute or chronic	3.5
Vascular	
Abdominal aortic aneurysm, asymptomatic	0.5
Cartoid disease (bilateral or 100% unilateral occlusion)	2
Peripheral vascular disease, severe	3.5
Miscellaneous	
Blood products refused	11
Severe neurologic disorder (healed CVA, paraplegia, muscular dystrophy, hemiparesis)	5
PTCA or cathaterization failure	5.5
Substance abuse	4.5



Use the total score to read the estimated preoperative-risk range from this plot, which shows the estimated risk of mortality together with 95% confidence limits.

Fig. 1.2 Preoperative Risk-Estimation Worksheet. *(From Bernstein AD, Parsonnet V. Bedside estimation of risk as an aid for decision-making in cardiac surgery.* Ann Thorac Surg. *2000;69:823, by permission from the Society of Thoracic Surgeons.)*

morbidity or mortality, prolonged length of stay (>14 days), and short length of stay (<6 days and alive).[57–59] These models are updated every few years and are calibrated annually to provide an immediate and accurate tool for regional and national benchmarking, and they have been proposed for public reporting. The calibration of the risk factors is based on the ratio between observed and expected results (O/E ratio), and calibration factors are updated quarterly. The expected mortality (E) is calibrated to obtain a national O/E ratio.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is another widely used model for cardiac operative risk evaluation. It was constructed from an analysis of 19,030 patients undergoing a diverse group of cardiac surgical procedures from 128 centers across Europe[60,61] (Tables 1.3 and 1.4). The following risk factors were associated with increased mortality: age, female sex, elevated serum creatinine level, extracardiac arteriopathy, chronic airway disease, severe neurologic dysfunction, previous cardiac surgery, recent MI, reduced LVEF, chronic CHF, pulmonary hypertension, active endocarditis, unstable angina, procedure urgency, critical preoperative condition, ventricular septal rupture, noncoronary surgery, and thoracic aortic surgery. For a given individual, each of these risk factors is assigned a score, and the sum total of these is used to predict surgical risk. In 2003, a more sophisticated, logistic version of EuroSCORE was released to permit more accurate risk assessment in individuals deemed to be at very high risk.[62]

The additive EuroSCORE has been used widely and validated across various centers in Europe and around the world, making it a primary tool for risk stratification in cardiac surgery.[63–74] Although its accuracy has been well established for CABG and isolated valve procedures, its predictive ability in combined CABG and valve procedures has been less well studied. Karthik and associates[65] showed that, in patients undergoing combined procedures, the additive EuroSCORE significantly underpredicted the risk when compared with the observed mortality. The logistic EuroSCORE[62] performed better in this setting.

In 2011, the EuroSCORE was recalibrated to keep up with new evidence. The revised EuroSCORE, known as EuroSCORE II,[75] permits more accurate risk estimation yet preserves the powerful discrimination of the original model. The EuroSCORE II is currently the recommended model for assessment of cardiac surgical risk. It can be accessed online (www.euroscore.org/calc.html) or downloaded as a Smartphone application.

Many other investigators have developed risk assessment models using data representing different populations and different surgical

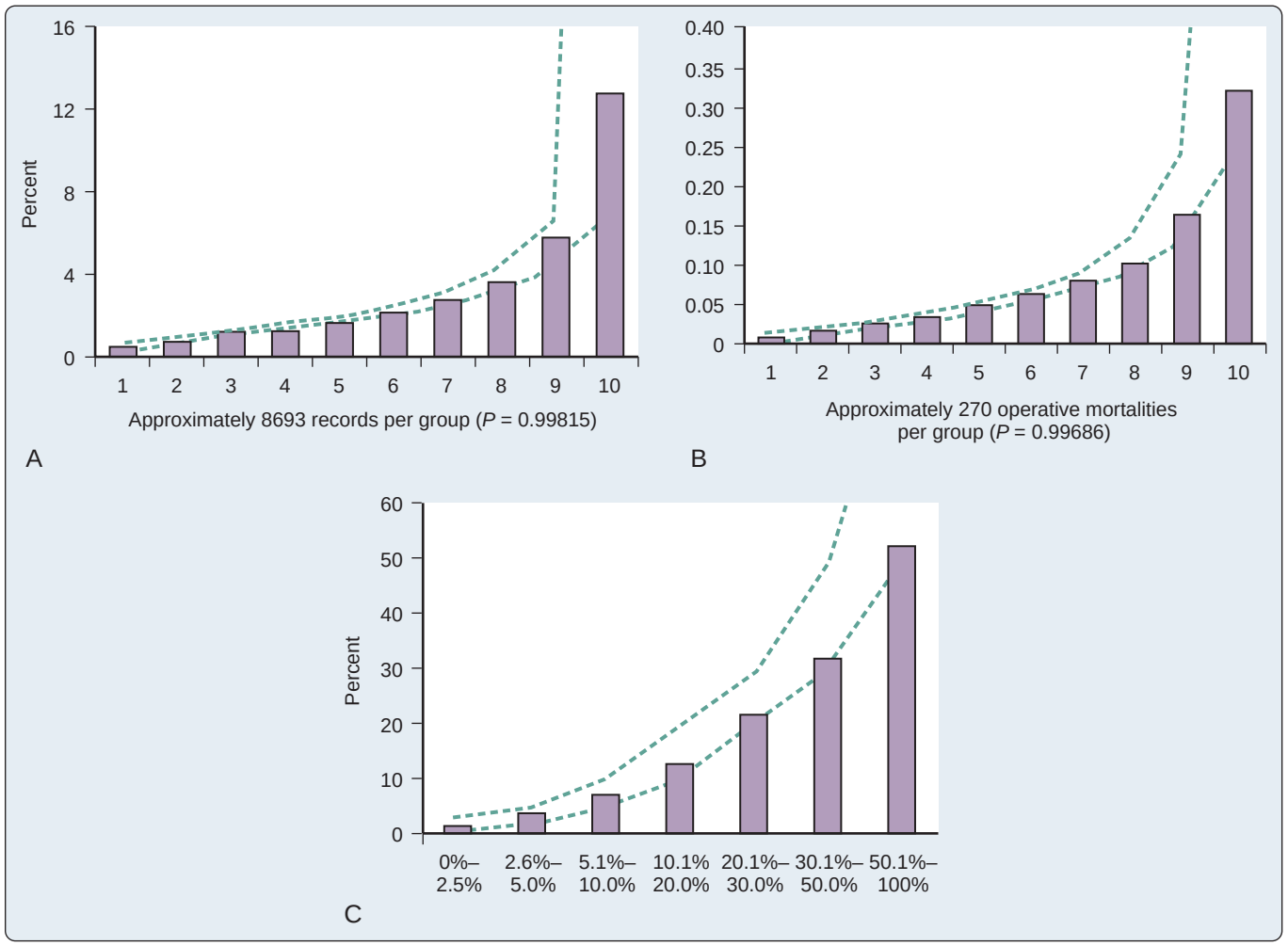


Fig. 1.3 After the predicted risk for each patient in the test set was determined, the patient records were arranged sequentially in order of predicted risk. The population was divided into 10 groups with an equal number of records in each group (A), 10 groups with an equal number of deaths in each group (B), or 7 groups by clinically relevant risk category (C). The predicted mortality rate was compared with the actual mortality for each of the groups. *Dashed lines* represent the range of predicted mortality for a group of patients; *bars* represent actual mortality for that group. *(From Shroyer AL, Plomondon ME, Grover FL, et al. The 1996 coronary artery bypass risk model: the Society of Thoracic Surgeons Adult Cardiac National Database.* Ann Thorac Surg. *1999;67:1205, by permission of the Society of Thoracic Surgeons.)*

practices.[76–84] Hannan and colleagues[82] evaluated predictors of mortality after valve surgery using data from 14,190 patients in New York state. A total of 18 independent risk factors were identified in the six models of differing combinations of valve surgery and CABG. Shock and dialysis-dependent renal failure were among the most significant risk factors in all models. The risk factors and odds ratios are shown in Tables 1.5–1.7. They also studied which risk factors were associated with early readmission (≤30 d) after CABG. Of the 16,325 total patients, 2111 (12.9%) were readmitted within 30 days for reasons related to CABG. Eleven risk factors were found to be independently associated with greater readmission rates: older age, female sex, African American race, greater body surface area, previous AMI within 1 week, and six comorbidities. After controlling for these preoperative patient-level risk factors, two provider characteristics (annual surgeon CABG volume <100 and hospital risk-adjusted mortality rate in the highest decile) and two postoperative factors (discharge to nursing home or rehabilitation/acute care facility and length of stay during index CABG admission ≥5 d) also were related to greater readmission rates.

Dupuis and associates[84] attempted to simplify the approach to evaluating the risk of cardiac surgical procedures in a manner similar to the original American Society of Anesthesiologists (ASA) physical status classification. They developed a score that uses a simple categorization of five classes plus an emergency status (Table 1.8). The Cardiac Anesthesia Risk Evaluation (CARE) score model collected data from 1996 to 1999 and included 3548 patients to predict both in-hospital mortality and a diverse group of major morbidities. It combined clinical judgment and the recognition of three risk factors previously identified by multifactorial risk indices: comorbid conditions categorized as controlled or uncontrolled, the complexity of the surgery, and the urgency of the procedure. The CARE score demonstrated predictive characteristics similar or superior to those of the more complex indices. The development of these several excellent risk models for cardiac valve surgery provides a powerful new tool to improve patient care, select procedures, counsel patients, and compare outcomes (see Chapter 21).

Consistency Among Risk Indices

Many different variables have been found to be associated with the increased risk during cardiac surgery, but only a few have consistently

TABLE 1.3 Risk Factors, Definitions, and Weights (Score)

Risk Factors	*Definition*	*Score*
Patient-Related Factors		
Age	Per 5 y or part thereof over 60 y	1
Sex	Female	1
Chronic pulmonary disease	Long-term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	One or more of the following: claudication; carotid occlusion or >50% stenosis; previous or planned intervention on the abdominal aorta, limb arteries, or carotids	2
Neurologic dysfunction	Disease severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	3
Serum creatinine	>200 µmol/L before surgery	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	One or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anesthesia room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria <10 mL/h)	3
Cardiac-Related Factors		
Unstable angina	Rest angina requiring IV nitrates until arrival in the anesthesia room	2
Left ventricular dysfunction	Moderate or LVEF 30–50% Poor or LVEF <30% Recent myocardial infarct (<90 d)	1 3 2
Pulmonary hypertension	Systolic pulmonary artery pressure >60 mm Hg	2
Surgery-Related Factors		
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of the ascending aorta, arch, or descending aorta	3
Postinfarct septal rupture		4

CABG, Coronary artery bypass graft surgery; *LVEF,* left ventricular ejection fraction.
From Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16:9.

TABLE 1.4 Application of EuroSCORE Scoring System

			95% Confidence Limits for Mortality	
EuroSCORE	*Patients (N)*	*Deaths (N)*	*Observed*	*Expected*
0–2 (low risk)	4529	36 (0.8%)	0.56–1.10	1.27–1.29
3–5 (medium risk)	5977	182 (3.0%)	2.62–3.51	2.90–2.94
≥6 (high risk)	4293	480 (11.2%)	10.25–12.16	10.93–11.54
Total	14,799	698 (4.7%)	4.37–5.06	4.72–4.95

EuroSCORE, European System for Cardiac Operative Risk Evaluation.
From Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg.* 1999;16:9, by permission.

BOX 1.3 COMMON VARIABLES ASSOCIATED WITH INCREASED RISK FOR CARDIAC SURGERY

Age
Female sex
Left ventricular function
Body habitus
Reoperation
Type of surgery
Urgency of surgery

BOX 1.4 MEDICAL CONDITIONS ASSOCIATED WITH INCREASED RISK

Renal dysfunction
Diabetes (inconsistent)
Recent acute coronary syndrome

been found to be major risk factors across multiple and very diverse study settings. Age, female sex, LV function, body habitus, reoperation, type of surgery, and urgency of surgery were among the variables consistently present in most of the models (Box 1.3).

Although a variety of investigators have found various comorbid diseases to be significant risk factors, no diseases have been shown to be consistent risk factors, with the possible exception of renal dysfunction and diabetes. These two comorbidities were shown to be important risk factors in a majority of the studies (Box 1.4).

Applicability of Risk Indices to a Given Population

It is critical to appreciate how these indices were created so as to understand how best to apply a given risk index to a specific patient or population. The application of these risk models to a specific population must be done with caution and after careful study. One issue is that the profile of patients undergoing cardiac surgery is constantly changing, and patients who previously would not have been included in the development data set because they were not considered surgical candidates are now undergoing surgery. Therefore, the models require continuous updating and revision. In addition, cardiac surgery itself is changing with the increasing use of off-pump and less invasive procedures, and this may alter the influence of preexisting conditions.

One critical factor in the choice of model for a given practice is to understand the clinical goals used in the original development process. Additionally, despite extensive research and widespread use of risk models in cardiac surgery, there are methodologic problems. The extent of the details in the reports varies greatly. Different conclusions can be reached depending on the risk model used. Processes critical to the development of risk models are shown in Fig. 1.4.

The underlying assumption in the development of any risk index is that specific factors (eg, disease history, physical findings, laboratory data, nature of surgery) cannot be modified with respect to their influence on outcome. For example, the urgency of the planned surgical procedure and the baseline comorbidities cannot be changed. However, the models themselves depend on the appropriate selection

TABLE 1.5 Significant Independent Risk Factors for in-Hospital Mortality: Aortic Valve Surgery With or Without CABG

	Isolated Aortic Valve Replacement (C = 0.809)		Aortic Valvuloplasty or Valve Replacement Plus CABG (C = 0.727)	
Risk Factor	*OR*	*95% CI for OR*	*OR*	*95% CI for OR*
Age ≥55 y	1.06	1.04–1.08	1.04	1.02–1.06
Hemodynamic instability	3.97	1.85–8.51	NS	
Shock	8.68	2.76–27.33	9.09	3.82–21.62
CHF in same admission	2.26	1.54–3.30	NS	
Extensively calcified ascending aorta	1.96	1.22–3.15	1.56	1.16–2.08
Diabetes	2.52	1.67–3.81	NS	
Dialysis-dependent renal failure	5.51	2.58–11.73	3.17	1.70–5.90
Pulmonary artery systolic pressure ≥50 mm Hg	2.35	1.61–3.41	2.28	1.75–2.96
Body surface area	NS		0.28	0.16–0.50
Previous cardiac operation	NS		2.13	1.54–2.96
Renal failure, no dialysis	NS		2.36	1.32–4.21
Aortoiliac disease	NS		1.88	1.26–2.82

C, C statistic; *CABG,* coronary artery bypass graft; *CHF,* congestive heart failure; *CI,* confidence interval; *NS,* not significant; *OR,* odds ratio.
From Hannan EL, Racz MJ, Jones RH, et al. Predictors of mortality for patients undergoing cardiac valve replacements in New York State. *Ann Thorac Surg.* 2000;70:1212, by permission of the Society of Thoracic Surgeons.

TABLE 1.6 Significant Independent Risk Factors for in-Hospital Mortality: Mitral Valve Surgery With or Without CABG

	Isolated Mitral Valve Replacement (C = 0.823)		Mitral Valve Replacement Plus CABG (C = 0.718)	
Risk Factor	*OR*	*95% CI for OR*	*OR*	*95% CI for OR*
Age ≥55 y	1.08	1.06–1.11	1.07	1.05–1.09
Carotid disease	2.98	1.65–5.39	1.81	1.21–2.70
Shock	9.17	4.17–20.16	5.29	3.03–9.22
CHF in same admission	3.03	2.01–4.56	NS	
Dialysis-dependent renal failure	5.07	1.98–12.97	NS	
Endocarditis	4.28	2.49–7.36	NS	
Ejection fraction <30%	NS	1.76	1.23–2.51	
Hemodynamic instability	NS	3.40	2.16–5.36	
Extensively calcified ascending aorta	NA	1.94	1.27–2.96	

C, C statistic; *CABG,* Coronary artery bypass graft surgery; *CHF,* congestive heart failure; *CI,* confidence interval; *NA,* not available; *NS,* not significant; *OR,* odds ratio.
From Hannan EL, Racz MJ, Jones RH, et al. Predictors of mortality for patients undergoing cardiac valve replacements in New York state. *Ann Thorac Surg.* 2000;70:1212, by permission of the Society of Thoracic Surgeons.

TABLE 1.7 Significant Independent Risk Factors for in-Hospital Mortality: Surgery on Multiple Valves With or Without CABG

	Multiple Valvuloplasty or Valve Replacement (C = 0.764)		Multiple Valvuloplasty or Valve Replacement Plus CABG (C = 0.750)	
Risk Factor	*OR*	*95% CI for OR*	*OR*	*95% CI for OR*
Age ≥55 y	1.05	1.03–1.07	1.05	1.10–1.08
Aortoiliac disease	3.55	1.17–10.72	4.63	2.12–10.10
CHF in same admission	2.18	1.44–3.29	NS	
Malignant ventricular arrhythmia	2.62	1.19–5.78	NS	
Extensively calcified ascending aorta	2.13	1.13–4.00	NS	
Diabetes	1.87	1.13–3.10	2.49	1.46–4.24
Renal failure without dialysis	3.55	1.88–6.72	NS	
Dialysis-dependent renal failure	9.37	4.10–21.40	NS	
Female sex	NS	1.95	1.20–3.18	
Hemodynamic instability	NS	3.65	1.50–8.86	
Shock	NS	50.19	6.08–414.44	
Hepatic failure	NS	8.21	1.84–36.66	
Endocarditis	NS	4.70	1.59–13.87	

C, C statistic; *CABG,* Coronary artery bypass graft surgery; *CHF,* congestive heart failure; *CI,* confidence interval; *NA,* not available; *NS,* not significant; *OR,* odds ratio.
From Hannan EL, Racz MJ, Jones RH, et al. Predictors of mortality for patients undergoing cardiac valve replacements in New York state. *Ann Thorac Surg.* 2000;70:1212, by permission of the Society of Thoracic Surgeons.

of baseline variables or risk factors to study, and their prevalence in the population of interest is critical for them to affect outcome. For example, referral patterns to a given institution may result in an absence of certain patient populations, in which case some risk factors may not appear in the model or their influence may be different than in the population on which the model was based. Also, the use of multivariate logistic regression may eliminate biologically important risk factors that are not present in sufficient numbers to achieve statistical significance.

In developing a risk index, it is important to validate the model and to benchmark it against other known means of assessing risks. It is important to determine whether the index predicts morbidity,

TABLE 1.8 Cardiac Anesthesia Risk Evaluation (CARE) Score

1 = Patient with stable cardiac disease and no other medical problem (a noncomplex surgery is undertaken)
2 = Patient with stable cardiac disease and one or more controlled medical problems[a] (a noncomplex surgery is undertaken)
3 = Patient with any uncontrolled medical problem[b] or any patient in whom a complex surgery is undertaken[c]
4 = Patient with any uncontrolled medical problem *and* in whom a complex surgery is undertaken
5 = Patient with chronic or advanced cardiac disease for whom cardiac surgery is undertaken as a last hope to save or improve life
E = Emergency: surgery as soon as diagnosis is made and operating room is available

[a]Examples: controlled hypertension, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, controlled systemic diseases, others as judged by clinicians

[b]Examples: unstable angina treated with intravenous heparin or nitroglycerin, preoperative intraaortic balloon pump, heart failure with pulmonary or peripheral edema, uncontrolled hypertension, renal insufficiency (creatinine level >140 µmol/L), debilitating systemic diseases, others as judged by clinicians

[c]Examples: reoperation, combined valve and coronary artery surgery, multiple valve surgery, left ventricular aneurysmectomy, repair of ventricular septal defect after myocardial infarction, coronary artery bypass of diffuse or heavily calcified vessels, others as judged by clinicians

From Dupuis JY, Wang F, Nathan H, et al. The cardiac anesthesia risk evaluation score: a clinically useful predictor of mortality and morbidity after cardiac surgery. *Anesthesiology.* 2001;94:194, by permission.

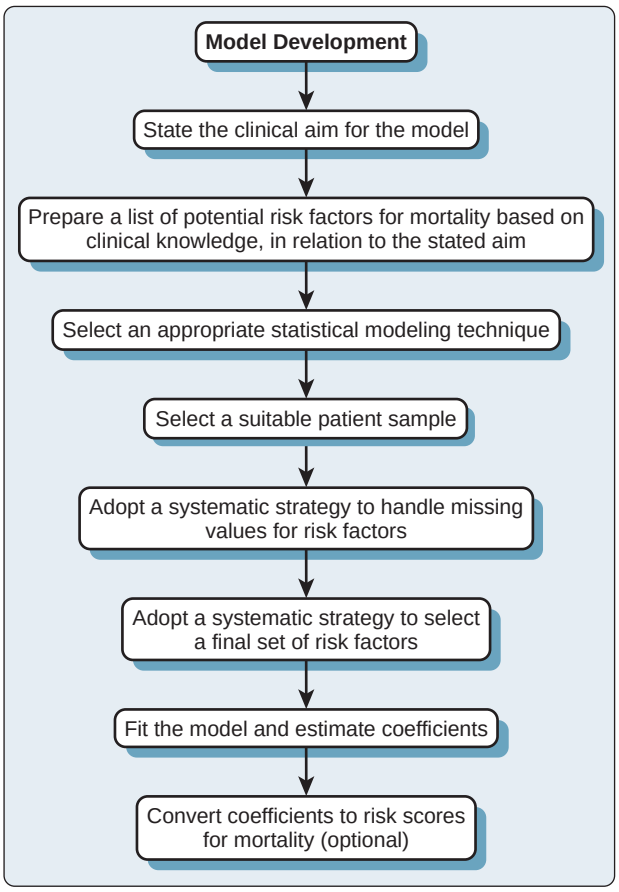


Fig. 1.4 Risk model development. *(From Omar RZ, Ambler G, Royston P, et al. Cardiac surgery risk modeling for mortality: a review of current practice and suggestions for improvement.* Ann Thorac Surg. *2004;77:2232, by permission of the Society of Thoracic Surgeons.)*

mortality, or both. Typically, a model's performance is first evaluated on its goodness of fit to the developmental data (*validation*). Alternatively, the original data can be split and the model can be built on half of the data and validated on the other half. Because this method reduces the total number of patients and outcomes available to create the model, it is best suited to situations in which data on tens of thousands of patients are available. This internal validation does not provide the practitioner with information on the generalizability of the model. External validation on a large, completely independent test data set is the best approach to satisfying this requirement.

Calibration refers to a model's ability to predict mortality accurately. Numerous tests can be applied, the most common being the Hosmer-Lemeshow test. If the *P* value from a Hosmer-Lemeshow test is greater than .05, the current practice of investigators is to claim that the model predicts mortality accurately.

Discrimination is the ability of a model to distinguish patients who die from those who survive. The area under the receiver operating characteristic (ROC) curve is the common method of assessing this facet of the model. In brief, the test is determined by evaluating all possible pairs of patients, determining whether the predicted probability of death should ideally be greater for the patient who died than for the one who survived. The ROC area is the percentage of pairs for which this is true, graphed as the sensitivity versus 1 – the specificity. The current practice in cardiac surgery is to conclude that a model discriminates well if the ROC area is greater than .7. If predictions are used to identify surgical centers or surgeons with unexpectedly high or low rates, achieving a high ROC area alone is not adequate, but good calibration is also critical. A poorly calibrated model may indicate that large numbers of institutions or surgeons have excessively high or low rates of mortality, when in fact the fault lies with the model, not the clinical performance. If predictions are used to stratify patients according to disease severity, to compare treatments, or to decide questions of patient management, both calibration and discrimination are important aspects to consider.

A key problem in the development of cardiac surgery risk stratification models is the evolving practice of surgery. New procedures or variations on older procedures may affect perioperative risk yet not be accounted for in the data used to develop the model. Despite these limitations, the calibrated and validated risk model remains the most objective tool currently available. Clinicians need to understand the specific model they are using, its strengths and weaknesses, to appropriately apply the model in academic research, patient counseling, benchmarking, and management of resources.

Specific Risk Conditions

Renal Dysfunction

Renal dysfunction has been shown to be an important risk factor for surgical mortality in patients undergoing cardiac surgery.[85–87] However, the spectrum of what constitutes renal dysfunction is broad, with some models defining it as increased creatinine levels and others defining it as dialysis dependency.

The Northern New England Cardiovascular Study Group reported a 12.2% in-hospital mortality rate after CABG in patients on chronic dialysis versus a 3.0% mortality rate in patients not on dialysis.[88] However, the incidence of dialysis dependency in the cardiac surgical population is sufficiently low (eg, 0.5% in New York state) that it may not enter into many of the models developed.

Acute kidney injury (AKI) after cardiac surgery carries significant morbidity and mortality. Patients who developed severe renal dysfunction (defined as a glomerular filtration rate [GFR] of <30 mL/min) after CABG had a mortality rate of almost 10%, compared with 1% for patients with normal renal function.[89] Poor outcomes associated with perioperative AKI have led to development of predictive models of AKI to identify patients at risk. One of these models predicts the need for renal replacement therapy (RRT) after cardiac surgery. Wijeysundera and coworkers[90] retrospectively studied a cohort of 20,131 cardiac surgery patients at two hospitals in Ontario, Canada. The multivariate preoperative predictors of RRT were estimated GFR, diabetes mellitus requiring medication, LVEF status (ie, ≤40%), previous cardiac surgery, procedure other than CABG, urgency of surgery (ie, nonelective case), and preoperative use of an intraaortic balloon pump (IABP).

An estimated GFR of 30 mL/min or less was assigned 2 points; a GFR of 31 to 60 mL/min and each of the other components were assigned 1 point each. Among the 53% of patients with low risk scores (≤1 point), the risk for RRT was 0.4%; among the 6% of patients with high-risk scores (≥4 points), it was 10%. Another group developed a robust prediction rule to assist clinicians in identifying patients with normal or near-normal preoperative renal function who are at high risk for development of severe renal insufficiency.[91] In a multivariate model, the preoperative patient characteristics most strongly associated with postoperative severe renal insufficiency included age, sex, white blood cell count greater than 12,000/μL, prior CABG, CHF, peripheral vascular disease, diabetes, hypertension, and preoperative IABP.

A major issue with respect to the development of indices to predict perioperative renal failure is that the pathophysiology of perioperative AKI includes inflammatory, nephrotoxic, and hemodynamic insults. This multifactorial nature of AKI might be one of the reasons that a limited single-strategy approach has not been successful.[92] Contrast agents used for angiography before cardiac surgery represent one of the modifiable nephrotoxic factors. Delaying cardiac surgery beyond 24 hours after the exposure and minimizing the contrast agent load can decrease the incidence of AKI in elective cardiac surgery cases.[93]

Uniformity of AKI definition, achieved by using the RIFLE criteria (risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage kidney disease), has improved risk stratification models, and use of early biomarkers of AKI should provide additional tools to design clinical trials addressing this important issue.[94,95]

Diabetes

The association between diabetes mellitus and mortality in cardiac surgery has been inconsistent; some studies support the association, but others do not.[96–103] Several randomized trials have evaluated outcome with CABG versus PCI in patients with diabetes. In the Coronary Artery Revascularization in Diabetes (CARDia) trial,[104] a total of 510 patients who had diabetes with multivessel or complex single-vessel CAD from 24 centers were randomized to PCI plus stenting (and routine abciximab) or CABG. After 1 year, the composite rate of death, MI, and stroke was 10.5% in the CABG group and 13.0% in the PCI group (hazard ratio [HR], 1.25; 95% confidence interval [CI], 0.75 to 2.09; $P = .39$); the all-cause mortality rates were 3.2% and 3.2%, respectively; and the rates of death, MI, stroke, or repeat revascularization were 11.3% and 19.3% (HR, 1.77; 95% CI, 1.11 to 2.82; $P = .02$), respectively.

In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 2368 patients with both type 2 diabetes and heart disease were randomly assigned to undergo either prompt revascularization along with intensive medical therapy or intensive medical therapy alone, and to undergo either insulin-sensitization or insulin-provision therapy. After a mean follow-up interval of 5.3 years, all-cause mortality, cardiac mortality, MI, and other end points were assessed.[105] The mortality rates did not differ between prompt revascularization versus intensive medical therapy alone or between the two insulin strategies. However, patients in the CABG stratum had significantly fewer MI events with prompt revascularization, and their composite end point of MI plus cardiac death was significantly reduced with insulin-sensitization therapy. The researchers concluded that for patients similar to those in the PCI group, intensive medical therapy alone was an excellent first-line strategy, but for patients with more extensive CAD, similar to those enrolled in the CABG stratum, prompt CABG (in the absence of contraindications), intensive medical therapy, and insulin-sensitization therapy appeared to be a preferred strategy to reduce the incidence of MI.[106]

More recent studies have directly compared CABG with PCI in diabetic patients with multivessel CAD. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1900 diabetic subjects to either PCI or CABG. After 5 years of follow-up, CABG was shown to result in lower rates of death and MI, although the stroke rate was higher in the CABG group.[107] A metaanalysis including eight studies comparing CABG with PCI in diabetic subjects reaffirmed the superiority of CABG in these patients.[108]

Acute Coronary Syndrome

Patients with a recent episode of any non–ST-segment elevation acute coronary syndrome before CABG have greater rates of operative morbidity and mortality than do patients with stable coronary syndromes.[109] However, the American College of Cardiology Foundation, in collaboration with numerous other societies, has published appropriate use criteria for coronary revascularization.[110] Because there are numerous class A recommendations for revascularization, many patients come to the operating room directly after coronary angiography or after attempted stent placement with antiplatelet agents. There is evidence to suggest that it is beneficial to delay CABG for 3 to 7 days in selected stable patients with contraindications to PCI who have experienced ST-elevation myocardial infarction (STEMI) or non–ST-elevation myocardial infarction (NSTEMI).[111] In addition, patients with a hemodynamically significant right ventricular MI should be allowed a period of time for the injured ventricle to recover.[112]

Assessment of Cardiac Risk in Patients Undergoing Noncardiac Surgery

The approach to preoperative cardiac risk assessment and stratification in patients undergoing noncardiac surgery is distinct from that in patients undergoing cardiac surgery. In the latter group, extensive cardiac evaluation is part of the routine preoperative workup, and the patient undergoes corrective therapy for the underlying disease. In contrast, although the presence of a cardiac illness is an added, and often powerful, risk factor for perioperative morbidity and mortality in patients undergoing a noncardiac surgery, the underlying cardiac status in most cases is either inadequately known or not known at all. This necessitates some form of cardiac evaluation in these patients. However, several factors need to be taken into consideration, including overall functional status of the patient, the surgical risk entailed by the proposed noncardiac surgery, the urgency of the noncardiac surgery and the potential risk associated with any delay, the availability of necessary resources for cardiac evaluation, and the impact that the information derived from cardiac evaluation is likely to have on perioperative planning and management (see Chapter 43).

Stepwise Approach to Cardiac Risk Assessment in Patients Undergoing Noncardiac Surgery

Both the ACC/AHA and the ESC recommend a stepwise approach to cardiac risk assessment in patients undergoing a noncardiac surgery (Fig. 1.5).[113,114] Their approaches are based on similar principles and are almost identical.

Step 1: Determine the Urgency of the Noncardiac Surgery

If the noncardiac surgery is emergent (ie, one in which life or limb will be threatened if the surgery is not performed promptly, typically within 6 h), no further cardiac evaluation is warranted in most instances. The clinical risk factors should be assessed, and knowledge about preexisting cardiac illness, if available, should be incorporated to help determine the surgical strategy and optimize perioperative monitoring and management.

Step 2: Identify Any Unstable Cardiac Condition

If the surgery is not emergent, then it should be determined whether the patient has any unstable cardiac condition (Box 1.5). If the patient is diagnosed as having an unstable cardiac condition, a multidisciplinary approach is required, including the patient, the family, and all stakeholders in the patient's caregiver team. A decision needs to be reached about how to stabilize the underlying cardiac condition,

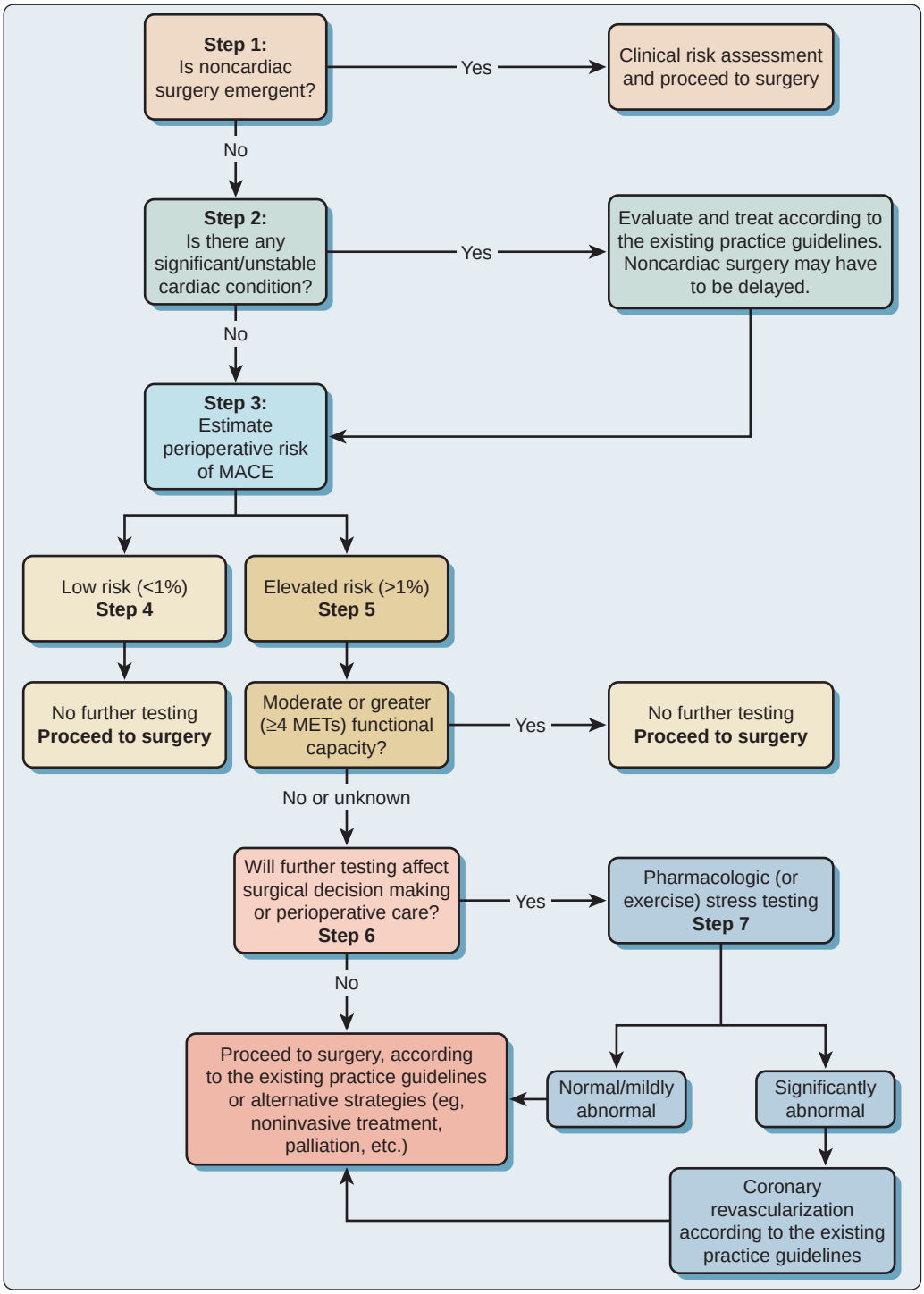
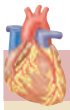


Fig. 1.5 Stepwise approach to perioperative cardiac risk assessment in patients undergoing noncardiac surgery. *MACE*, Major adverse cardiovascular event; *MET*, metabolic equivalent. (*Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines.* J Am Coll Cardiol. *2014;64:e77–e137; Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management. The Joint Task Force on Non-cardiac Surgery: Cardiovascular Assessment and Management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA).* Eur Heart J. *2014;35:2383–2431.*)



BOX 1.5 UNSTABLE CARDIAC CONDITIONS

Acute coronary event
Recent myocardial infarction with residual myocardial ischemia
Acute heart failure
Significant cardiac arrhythmias
Symptomatic valvular heart disease

keeping in mind the priority of cardiac versus noncardiac interventions, the risks involved in either approach, and the impact of cardiac treatment (eg, use of antiplatelet or anticoagulant agents) on the subsequent noncardiac surgery. Depending on the outcome of this discussion, patients may either proceed for cardiac intervention if the index surgical procedure can be delayed or proceed directly to the noncardiac surgery with optimal medical therapy if the delay is incompatible.

Step 3: Assess Cardiac Risk of the Noncardiac Surgery

In patients who do not have an unstable heart disease, the next step is to assess the cardiac risk involved in the proposed noncardiac surgery. There are a number of methods to derive this risk estimate, but the most practical approach is to use risk scores or algorithms. The most validated risk indices for this purpose are the Revised Cardiac Risk Index (RCRI)[115] and the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) surgical risk calculator (http://www.surgicalriskcalculator.com)[116] (Table 1.9). The RCRI considers six major risk factors, each of which is assigned a score of 1. Patients who have a score of 0 or 1 are expected to have a low risk of major adverse cardiac events (MACE), whereas those with a score of 2 or higher are likely to have an elevated risk. Although the RCRI is simple to use and has been validated in populations outside the original cohort, it does not provide surgery-specific cardiac risk estimates, and it also tends to underestimate risk in patients undergoing major vascular surgery.[117] The NSQIP surgical risk calculator, which is based on the data derived from more than 1 million surgeries, provides more comprehensive assessment of the surgery-specific risk of a number of clinical outcomes, including MACE and death, and is the preferred approach for this purpose.[116] However, it is more complex to use, requires a Web-based calculator, and has not been validated in populations outside the original cohort.

Based on the anticipated cardiac risk, the surgical interventions can be broadly divided into three groups based on the estimated 30-day rate of cardiac events (ie, cardiac death and MI): low risk (<1%), intermediate risk (1–5%), and high risk (>5%).

Step 4: If the patient Has a Low Cardiac Risk

If the patient is estimated to have a low perioperative risk of an adverse cardiac event, no further cardiac evaluation is required, and the patient may proceed with the planned surgery. However, appropriate guideline-recommended risk-reduction pharmacotherapies should be instituted depending on the clinical condition of the patient.[113,114] Initiation of a beta-blocker regimen may be considered before surgery in patients with known CAD or myocardial ischemia. Treatment should ideally be initiated at least 2 days (and up to 30 days) before surgery, starting with a low dose and gradually titrating the dose to achieve a resting heart rate between 60 and 70 bpm with a systolic blood pressure greater than100 mm Hg. In most patients with atherosclerotic vascular disease, particularly those undergoing vascular surgery, initiation of statin therapy should be strongly considered. In addition, in patients who have heart failure due to LV systolic dysfunction, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should also be considered before surgery. However, care should be taken to avoid hypotension during the perioperative period. A decision also needs to be reached about discontinuation of antiplatelet and/or anticoagulant agents in those who are already receiving these therapies, and alternative therapies, if any, should be recommended as appropriate.

TABLE 1.9 Risk Factors in Commonly Used Models for Assessment of Cardiac Risk in Patients Undergoing Noncardiac Surgery

Risk Factor	*Revised Cardiac Risk Index*	*American College of Surgeons NSQIP Surgical Risk Calculator*
Ischemic heart disease	Yes	Yes (previous cardiac event)
Cerebrovascular disease	Yes (history of cerebrovascular accident or transient ischemic attack)	No
Type of surgery	Yes (intrathoracic, intraabdominal, or suprainguinal vascular surgery)	Yes (uses Current Procedural Terminology codes)
Renal dysfunction	Yes (creatinine ≥2 mg/dL)	Yes (acute renal failure, need for dialysis)
Diabetes mellitus	Yes (insulin-dependent diabetes mellitus)	Yes
Heart failure	Yes	Yes
Age	No	Yes
Sex	No	Yes
Hypertension	No	Yes
Body mass index	No	Yes
Dyspnea	No	Yes
Smoker	No	Yes
COPD	No	Yes
Functional status	No	Yes
Physical status		Yes (uses ASA Physical Status classification system)
Wound class	No	Yes
Ascites	No	Yes
Systemic sepsis	No	Yes
Ventilator dependency	No	Yes
Disseminated cancer	No	Yes
Steroid use	No	Yes
Emergency surgery	No	Yes

ASA, American Society of Anesthesiologists; *COPD,* chronic obstructive pulmonary disease; *NSQIP,* National Surgical Quality Improvement Program.

Step 5: If the Patient Has an Elevated Cardiac Risk

In patients who are estimated to have an elevated risk of MACE, an assessment of functional capacity is required. Functional capacity is usually expressed in terms of metabolic equivalents (METs) and classified as excellent (>10 METs), good (7–10 METs), moderate (4–6 METs), poor (<4 METs), or unknown.

If the patient has not had a recent exercise test, functional status can usually be estimated from activities of daily living (Fig. 1.6) or, more formally, by using an activity scale such as the Duke Activity Status Index[118] or the Specific Activity Scale.[119] Examples of activities associated with greater than 4 METs include climbing two flights of stairs, walking up a hill, running a short distance, walking on level ground at 4 mph, and performing heavy work around the house. If the patient is able to easily perform 4 METs or more physical activity, he or she can proceed to the planned noncardiac surgery without the need for any further cardiac evaluation.

Step 6: If the Patient Has Poor or Unknown Functional Capacity

In patients with elevated cardiac risk whose functional capacity is poor or unknown, one must determine whether further testing will affect patient decision making (eg, a decision to perform the original surgery or willingness to undergo a cardiac intervention might change depending on the results of the test) or perioperative care. If it will, stress

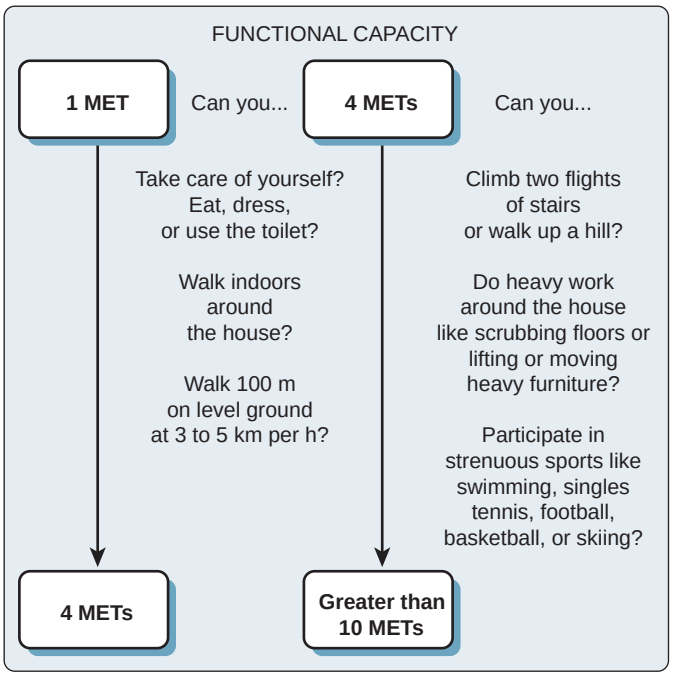


Fig. 1.6 Estimated energy requirements for various activities during daily life. *km per h*, kilometers per hour; *MET*, metabolic equivalent. *(Data from Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index).* Am J Cardiol. *1989;64:651–654. and Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association.* Circulation. *2001;104:1694–1740.)*

testing should be performed, and if the stress test result is normal, the patient can proceed to noncardiac surgery according to the guideline-directed medical therapy (GDMT). However, if the stress test result is abnormal, then depending on the extent of the abnormality, coronary angiography and revascularization should be considered. The patient can then proceed to surgery with GDMT or explore alternative, less invasive or noninvasive therapeutic options for the underlying noncardiac illness.

Although there are no randomized trials on the use of preoperative stress testing, a large number of single-site studies and their metaanalyses have demonstrated its clinical utility in the preoperative evaluation of patients undergoing noncardiac surgery.[120–124] These studies have shown that a normal stress test result has a very high negative predictive value for perioperative cardiac events, whereas the presence of moderate-to-large areas of myocardial ischemia is associated with increased risk of perioperative MI and/or death. In contrast, the presence of RWMAs (unless extensive) on rest imaging has little predictive value.

Most data on the impact of inducible myocardial ischemia on perioperative outcomes are based on pharmacologic stress testing.[120–124] Therefore, it remains the modality of choice in these patients, more so because many are not able to perform adequate exercise. However, in patients who are able to exercise adequately, it seems reasonable that exercise stress testing, when combined with echocardiography or myocardial perfusion scintigraphy, would perform similarly to pharmacologic stress testing.[125–127] Exercise-induced electrocardiographic changes alone are not as predictive and cannot be relied on.[125–128]

There are no randomized trials comparing different imaging modalities (eg, echocardiography vs myocardial perfusion imaging) for predictive accuracy as part of preoperative pharmacologic stress testing. However, a retrospective metaanalysis comparing thallium imaging with stress echocardiography in patients scheduled for elective noncardiac surgery showed that a moderate-to-large defect (present in 14% of the population) detected by either method predicted postoperative cardiac events, with stress echocardiography being slightly superior.[120] Given the lack of adequate evidence, it is recommended that the choice of imaging modality should be guided by the available local expertise in performing pharmacologic stress testing.

Step 7: If Testing Is Unlikely to Affect Decision Making or Care

If a patient with elevated cardiac risk has poor or unknown functional capacity but stress testing is unlikely to affect decision making or care, it is reasonable to proceed to surgery according to the GDMT or to consider alternative, less invasive or noninvasive therapeutic options for the underlying noncardiac illness.

Role of Handheld and Pocket Ultrasound

As outlined earlier, the current guidelines do not recommend routine cardiac imaging in most patients undergoing noncardiac surgery if the surgery is emergent or if the patient is physically active and does not have any overt manifestations of a cardiac illness. These recommendations are based on the assumptions that clinical evaluation is generally sufficient to identify most of the clinically relevant cardiac conditions, that the necessary resources required for cardiac imaging may not be readily available, and that in most instances recognition of a cardiac lesion during preoperative testing would not lead to a cardiac intervention. However, each of these assumptions has an important caveat.

Although a good physical examination remains an integral component of any form of medical assessment and cannot be substituted because of the wealth of information it provides, it has its limitations. It is subjective; it depends heavily on the clinical skills of the examining physician; and even with the most experienced clinicians, it has a diagnostic accuracy that is, at best, suboptimal.[129] There are several cardiac conditions that may be inherently silent (eg, asymptomatic LV systolic dysfunction) and cannot be recognized based on clinical evaluation alone. Further, accurate assessment of lesion severity on clinical examination, even for valvular lesions, remains challenging, especially when the patient has a combination of cardiac lesions. Handheld and pocket ultrasound devices offer an attractive option in these circumstances. Numerous studies have demonstrated that the addition of a screening, bedside echocardiographic examination to clinical assessment significantly increases diagnostic accuracy, reduces unwarranted diagnostic and treatment referrals, facilitates optimal use of health care resources, and is cost-effective[129–133] (see Chapter 46).

The current generation of pocket ultrasound devices offer two-dimensional and color Doppler imaging but lack spectral Doppler. Still, the image quality is usually excellent, which allows a diagnostic accuracy comparable to that achieved with full-scale echocardiography equipment.[131,134–136] At the same time, limited functionalities available on these devices serve to simply their use by physicians. Studies have shown that physicians can quickly be trained in the use of pocket ultrasound devices for rapid screening of patients to recognize major cardiac abnormalities.[137] When required, bedside imaging can also be combined with remote, Web-based interpretation to enhance the diagnostic accuracy of the screening echocardiographic examination and to ensure quality control.[137,138]

Although it is true that a cardiac lesion recognized at the time of preoperative evaluation in patients scheduled to undergo a noncardiac surgery does not necessarily require immediate cardiac intervention, studies have demonstrated that the presence of unrecognized LV systolic dysfunction or valvular heart disease is associated with worse outcomes.[115,137–141] For example, Flu and colleagues studied the value of preoperative echocardiography in 1005 consecutive patients undergoing elective vascular surgery at a single center.[139] LV dysfunction (LVEF <50%) was present in 50% of the patients, 80% of whom were asymptomatic.[58] The 30-day cardiovascular event rate was highest in patients with symptomatic HF (49%), followed by those with asymptomatic systolic LV dysfunction (23%), asymptomatic diastolic LV dysfunction (18%), and normal LV function (10%).

BOX 1.6 HANDHELD OR POCKET ULTRASOUND FOR CARDIAC EVALUATION

Enhances diagnostic accuracy of clinical examination
Can be combined with remote interpretation of acquired images to ensure optimum diagnostic accuracy
Allows recognition of major cardiac lesions
Provides information that may have incremental value in optimizing perioperative outcomes of patients undergoing a noncardiac surgery
Is simple to use and easy to incorporate into the preoperative evaluation
Has been shown to be cost-effective compared with physical examination alone

Bedside echocardiographic examination using a handheld or pocket ultrasound device can have great incremental value in these circumstances (Box 1.6). It permits easy and prompt recognition of significant cardiac lesions, and such information provides the operating team an opportunity to incorporate measures to optimize perioperative outcomes. For example, a less invasive surgical approach can be adopted, regional anesthesia can be used preferentially in certain circumstances, greater caution can be exercised with regard to perioperative fluid and hemodynamic monitoring and management, appropriate cardiac pharmacotherapies can be instituted if circumstances allow; and, importantly, the patient and family can be alerted about the possibility of a cardiac event during the perioperative period. In a recent study of patients undergoing cataract surgery in a community setting, pocket echocardiography allowed recognition of a major cardiac lesion in 14.2% of those patients considered to be free of any major cardiac illness based on clinical examination alone. Of these, roughly one-fourth (3.3% of the entire study population) had cardiac lesions deemed prohibitive for cataract surgery in an unmonitored setting. As a result, these surgeries were rescheduled to be performed later in a hospital under more intensive monitoring.[137] Although this study does not imply that every patient undergoing noncardiac surgery needs to have an echocardiographic examination, it does show that the availability of handheld and pocket ultrasound devices permits easy incorporation of an echocardiographic examination in the preoperative evaluation and may help optimize cardiac outcomes.

Conclusions

Preoperative cardiac risk assessment and stratification of patients undergoing cardiac or noncardiac surgery are pivotal in optimizing perioperative outcomes. In cardiac surgery patients, the main goal of cardiac risk assessment, from the anesthesiologist's perspective, is to provide risk-adjusted mortality rates for preoperative counseling of the patient and family and to identify the group at high risk for a perioperative cardiac event. Based on individual risk factors, perioperative care can be modified to improve the patient's outcome. Various complex or simplified risk-adjusted morbidity and mortality models can serve as tools for facilitating perioperative risk assessment. However, even a well-calibrated model with good discrimination has to be used with caution when applied to individual counseling. First, it is difficult for any model to predict morbidity or mortality, which occur with a low incidence. Second, it has to be clear that the scoring system provides only the probability of death or a major complication and that the individual patient and family members may have difficulty understanding how an adverse outcome could have occurred if the predicted incidence was low in their understanding preoperatively.

In contrast, the underlying cardiac status of noncardiac surgical patients is often unknown or inadequately known. The main goal in this setting is to define an optimal cardiac evaluation strategy considering various patient-related and surgery-related factors and, based on the findings of such evaluation, to provide recommendations for optimal perioperative management to achieve the best possible outcomes. In most such patients, noninvasive cardiac evaluation with optimization of cardiac medications and care to minimize hemodynamic perturbations during the perioperative period are all that is required to ensure cardiac safety. Invasive cardiac evaluation and coronary revascularization usually are not required unless the patient presents with an unstable cardiac condition or has significant myocardial ischemia and the noncardiac surgery is not urgent.

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2 Cardiovascular Imaging

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KEY POINTS

1. Echocardiography is the most widely used modality for cardiac imaging in almost any form of cardiac disease.
2. Echocardiography is noninvasive, safe, readily available, and portable, and it has the ability to provide vast amounts of information about cardiac structure and function. Additionally, echocardiography is the only modality available for imaging during the intraoperative period.
3. A combination of transthoracic and transesophageal imaging permits comprehensive evaluation of most cardiac pathologies. The advent of three-dimensional transesophageal echocardiography has further enhanced the utility of this modality, especially in the evaluation of mitral valve disease.
4. Stress echocardiography is helpful in the assessment of inducible myocardial ischemia, myocardial viability, and certain valve disorders.
5. Myocardial perfusion imaging can be performed using SPECT or PET and is useful in the evaluation of myocardial ischemia and viability.
6. Cardiac computed tomography and cardiac magnetic resonance are increasingly used when there are conflicting results or when further information is required in the preoperative phase of care.
7. Cardiac magnetic resonance is the gold standard for quantitative assessment of ventricular volumes, ejection fraction, and mass. It is also able to evaluate ventricular and valvular function, atherosclerosis, and plaque composition.
8. Computed tomographic aortography is the best modality for the evaluation of aortic aneurysms and dissections. Additionally, computed tomographic coronary angiography offers an alternative to invasive coronary angiography for excluding significant coronary artery disease in patients undergoing noncoronary surgery.

Imaging is fundamental to perioperative evaluation and management of patients undergoing cardiac surgery. Even for those presenting with a noncardiac illness, cardiac imaging is often required to supplement the preoperative evaluation.

For many years, cardiac catheterization and nuclear imaging were the only modalities available for clinical use. The introduction of echocardiography in the early 1970s heralded a revolution in the field of cardiovascular imaging, and echocardiography soon surpassed all other modalities to become the cornerstone of cardiac imaging. Because of its noninvasive nature, safety, easy availability, portability, repeatability, and capacity to provide vast amounts of clinically relevant information, echocardiography has remained the most useful modality for cardiac imaging.

The last several decades have witnessed yet another explosion in imaging techniques with the evolution of cardiac computed tomography (CCT), cardiac magnetic resonance (CMR), and positron emission tomography (PET) as routine clinical evaluation tools. In the field of perioperative evaluation, these alternative imaging modalities have complemented more than supplemented traditional imaging. This chapter provides a brief overview of the roles of these different imaging modalities in the evaluation and management of various cardiac conditions.

Echocardiography

Transthoracic echocardiography (TTE) is required in all patients scheduled for cardiac surgery and is often the basis for surgical decision making itself. In contrast to the nonsurgical setting, in which TTE is usually sufficient to provide most of the information needed to meet the clinical objectives, transesophageal echocardiography (TEE) is also frequently required for patients for whom surgery is being considered. Preoperatively, TEE helps provide information that is critical for surgical planning (eg, valve repair vs valve replacement, coronary artery bypass surgery alone or with concomitant mitral valve repair). During the intraoperative period, TEE is the only modality available for cardiac imaging. In the immediate postoperative period, TEE is often called for because the presence of tissue edema, surgical dressings, and drains and the reduced ability to change the patient's position render transthoracic imaging extremely challenging.

Assessment of Left Ventricular Systolic Function

Left ventricular (LV) systolic function is one of the most important predictors of outcome in all cardiac conditions, and almost all therapeutic decisions in these patients are influenced by the status of LV systolic function. For cardiac anesthesiologists, preoperative knowledge of LV systolic dysfunction is crucial for anticipating and preparing for perioperative complications, whereas subsequent assessments are required for diagnosing and managing the cause of hemodynamic instability. Patients with LV systolic dysfunction who undergo coronary artery bypass graft surgery (CABG) are known to require more inotropic support after cardiopulmonary bypass (CPB).[1,2] Additionally, systolic dysfunction is a reliable prognosticator for surgical mortality.[3–5]

LV ejection fraction (LVEF) is the simplest and the most widely used measure of global LV systolic function. A number of echocardiographic methods are currently available for estimation of LVEF, but the biplane modified Simpson method is the most accurate and is also the method recommended by the American Society of Echocardiography (ASE).[6] In practice, however, LVEF is often estimated semiquantitatively by visual inspection alone, and this technique has been shown to have a reasonably high degree of accuracy when performed by an experienced echocardiographer.[7,8]

The Simpson method considers the LV cavity as a stack of disks of equal height; LV volume is calculated by summing the volumes of all the disks (Fig. 2.1). This is accomplished by manually tracing the LV

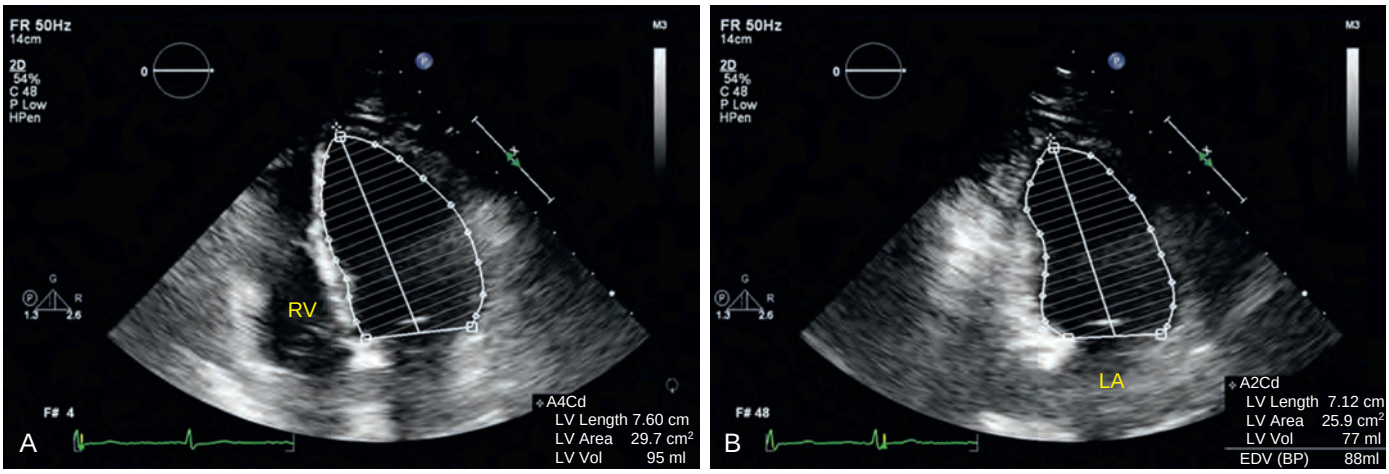

Fig. 2.1 Measurement of left ventricular volumes and ejection fraction using the Simpson summation-of-disks method. A, Apical four-chamber view in end-diastole. B, Same view in end-systole. *LA*, Left atrium; *RV*, right ventricle.

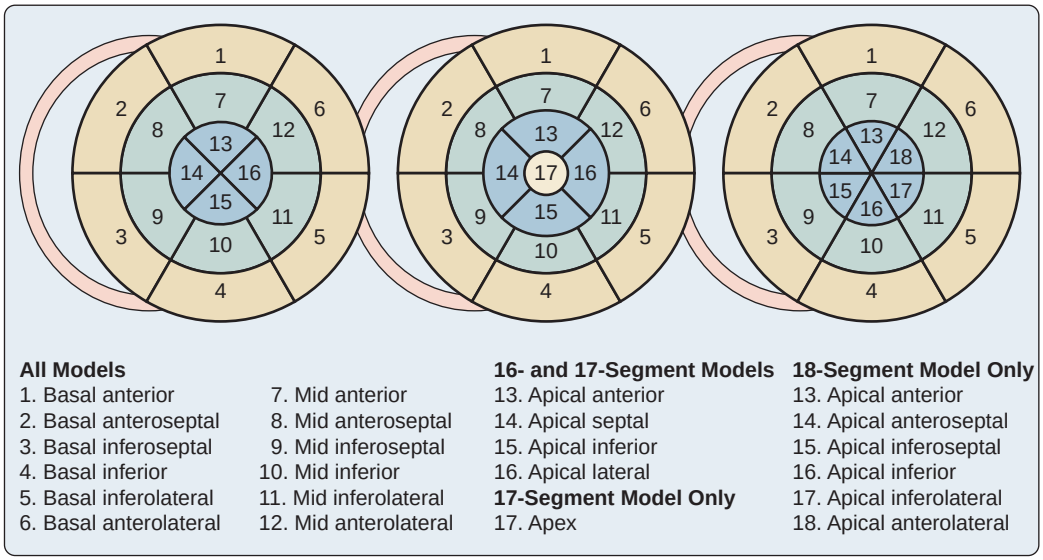

Fig. 2.2 Schematic diagram of the various left ventricular segmentation models: the 16-segment model *(left)*, the 17-segment model *(center)*, and the 18-segment model *(right)*. *(With permission from Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr. *2015;28:1–39 e14.)*

endocardial border in the apical four- and two-chamber views, both at end-diastole and at end-systole. These data are then processed by the internal software of the equipment to provide LV volumes and LVEF. The main advantage of this method is that it remains applicable even when the ventricle is distorted, but its accuracy depends heavily on adequate visualization of the blood-endocardial interface. Currently, harmonic imaging is routinely used to improve endocardial border recognition, and in difficult cases LV cavity contrast can also be used.

Three-dimensional echocardiography (3DE) is the most accurate method for estimation of LVEF by echocardiography.[6] Unlike the two-dimensional (2D) methods, it does not make any assumptions about LV cavity shape and therefore is not influenced by the LV geometry. However, it requires considerable expertise, it has lower temporal resolution, and, as with 2D methods, its accuracy is dependent on image quality. For LVEF estimation by 3DE, a full volume dataset that includes the entire left ventricle is acquired. The image is then analyzed, either online or offline, using quantitation software. The endocardial border is semiautomatically identified in the end-diastolic and the end-systolic frames and adjusted manually to correct for any errors introduced by automatic border recognition. The software then calculates LV volumes and LVEF.

Regional Left Ventricular Systolic Function

In cardiac patients, assessment of regional LV systolic function has considerable clinical relevance. Coronary artery disease (CAD) is the prototype cardiac illness that affects the left ventricle regionally, and the presence of regional LV systolic dysfunction is virtually diagnostic of underlying CAD. The assessment of regional LV systolic function also provides an estimate of the overall extent of myocardial damage, permits recognition of the affected coronary arteries, and facilitates assessment of myocardial viability and inducible myocardial ischemia.

During echocardiography, LV regional function assessment is performed by visual inspection of the extent of *wall thickening* in each myocardial segment. The ventricle is traditionally divided into 16 segments, as recommended by the ASE (Fig. 2.2). A 17-segment model, with the apical cap being the 17th segment, has been proposed for use

when the objective of the examination is to compare the findings with those of nuclear imaging or radiology (CCT or CMR).[6]

Depending on the extent of wall thickening, the wall motion can be classified as normal, hypokinetic, akinetic, or dyskinetic, or it can be formally scored as 1 (normal), 2 (hypokinetic), 3 (akinetic), or 4 (dyskinetic/aneurysmal). Averaging the scores of all the evaluated segments provides a wall motion score index, which can be used as a surrogate for global LVEF. In the assessment of regional wall motion, distinction must be made between actual wall thickening and endocardial motion, which is affected by tethering effects from adjacent myocardial segments and by the translational movement of the heart. The inferior and posterior LV segments are often classified erroneously as hypokinetic by less experienced clinicians who do not appreciate that wall thickening is the gold standard for assessing regional LV function.

Role of Speckle-Tracking Echocardiography

Although LVEF is the most validated measure of LV systolic function, it is operator dependent, load dependent, and relatively insensitive to subtle changes in myocardial contractile function. Additionally, it represents an oversimplification of LV myocardial deformation, which is a complex, multidimensional process. Speckle-tracking echocardiography (STE) offers a potential solution to some of these limitations and serves to complement the information conveyed by assessments of LVEF.[9,10]

STE is a gray-scale–based technique that measures myocardial deformation using frame-by-frame tracking of the acoustic "speckles" present within the gray-scale ultrasound image.[10] The magnitude of the myocardial deformation is expressed as strain, which is the percentage change in length of the myocardial segment. The rate at which this deformation occurs is expressed as the strain rate, which has the unit of sec^{-1}. For clinical purposes, LV myocardial strain is measured in three principal directions: longitudinal, radial, and circumferential. Additionally, LV rotation and twist around the long axis can be measured. The longitudinal strain is derived from the apical four-chamber, two-chamber, and long-axis images; short-axis images are used for estimating radial strain, circumferential strain, rotation, and twist (Fig. 2.3).

Currently, it is feasible to measure global longitudinal strain, which is the average of peak longitudinal strain of all LV myocardial segments, with a high degree of reproducibility that is sufficient for regular clinical use. Accordingly, the ASE recommends measuring global longitudinal strain, along with LVEF, as an estimate of global LV systolic function.[6] The main clinical application of global longitudinal strain is in early recognition of subclinical LV systolic dysfunction in various clinical situations, such as patients receiving potentially cardiotoxic cancer chemotherapies and patients with valvular heart disease and cardiomyopathy. Other components of strain (ie, radial, circumferential) and segmental strain are currently not ready for regular clinical use.

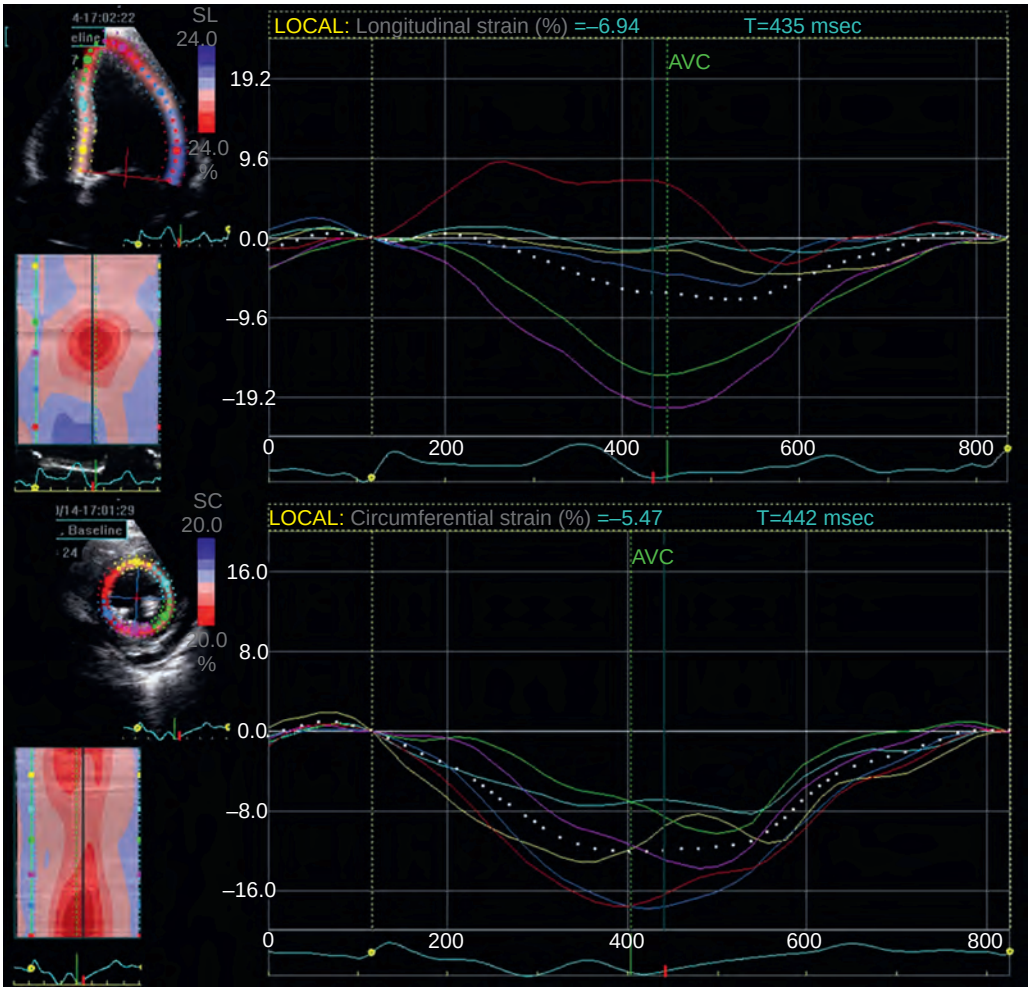

Fig. 2.3 Speckle-tracking echocardiography–based measurement of left ventricular longitudinal strain *(upper panel)* and circumferential strain *(lower panel)*. Colored traces depict segmental strain for corresponding myocardial segments. The dotted white line depicts the average of the six segments visualized in the particular view. *AVC*, Aortic valve closure.

The initial experience with STE has shown great promise; however, because it is a gray-scale–based technique, it is highly dependent on image quality. Additionally, a major limitation of STE at present is intervendor variability, which precludes comparison among measurements obtained on different STE platforms.[11,12] A joint ASE and European Association of Cardiovascular Imaging (EACVI) task force, in collaboration with industry partners, is working toward standardization of all elements involved in STE technology to minimize, and possibly eliminate, this vendor dependence.[12]

Assessment of Left Ventricular Diastolic Function

Abnormalities of LV diastolic function are common in patients undergoing cardiac surgery and have diagnostic and prognostic relevance.[13] Diastolic dysfunction during and after CABG is associated with greater time on CPB and with greater inotropic support up to 12 hours postoperatively.[14] This may be due to deterioration of diastolic dysfunction after CABG, which may persist for several hours.[15–17] Diastolic dysfunction increases the risk of perioperative morbidity and mortality.[18] Assessment of LV diastolic dysfunction permits a more accurate estimation of LV filling pressure (LVFP), information that is crucial to optimal management of critically ill patients. Goal-directed therapy using intravenous fluids, diuretics, vasopressors, and vasodilators requires knowledge of the LVFP.

Echocardiography is currently the best modality for assessing LV diastolic function in clinical practice. Several echocardiographic measures of LV diastolic function are available.[19] The examination usually begins with interrogation of the mitral inflow pattern and measurement of mitral annular velocities. The specific mitral inflow measurements include the mitral inflow early diastolic (E) and late diastolic (A) velocities, the ratio of the two (E/A), and the deceleration time of the E wave (dtE). Mitral annular early diastolic velocity (e′) is measured using tissue Doppler imaging. The ratio of mitral E to e′. (E/e′) provides an accurate and relatively load-independent measure of LVFP. Left atrial (LA) volume and tricuspid regurgitation (TR) jet velocity (a surrogate for pulmonary artery systolic pressure) are other useful measurements. Integrating all this information provides a quick assessment of LV diastolic function in most patients. When required, additional information can be obtained by evaluating pulmonary vein flow patterns, mitral inflow propagation velocity, isovolumic relaxation time, and so on. The ASE has recently published guidelines outlining a stepwise approach to assessment of LV diastolic function and estimation of LVFP or LA pressure in patients with and without LV systolic dysfunction (Fig. 2.4).[19a]

Right Heart Evaluation

Dysfunction of the right side of the heart, in the absence of congenital heart disease, is most often secondary to left heart pathologies, especially MV disease and severe LV systolic dysfunction. Additionally, obstructive airway disease and pulmonary thromboembolism are common in cardiac surgical patients. Primary right heart pathology is encountered less frequently and includes right ventricular (RV) myocardial infarction and organic tricuspid valve disease.

Unlike the left ventricle, the right ventricle has complex anatomy. The RV inflow portion, main body, and outflow tract (RVOT) do not lie in the same anatomic plane, rendering it impossible to image the entire right ventricle from one echocardiographic window. Accordingly, different acoustic windows must be used, including the RV inflow view, the RV outflow view, the RV-focused apical four-chamber view, and the subcostal view. Abnormalities of RV size and shape and global and regional contractility are qualitatively assessed, and various RV and right atrial (RA) dimensions are obtained from these windows[20] (Table 2.1). Additionally, tricuspid valve function, the presence of any intracardiac masses, and so on can be evaluated.

Because of the complex shape of the right ventricle, the RV ejection fraction generally cannot be measured by echocardiography. As a result, RV systolic function is indirectly assessed using alternative parameters, such as M-mode–derived tricuspid annular plane systolic excursion, tricuspid annular systolic velocity on tissue Doppler imaging, RV cavity fractional area change on 2D echocardiography, and myocardial performance index obtained from pulsed-wave Doppler or tissue Doppler imaging[20] (see Table 2.1). Additionally, RV free wall longitudinal strain can be measured with the use of STE.[6] Although it has now become feasible to measure RV ejection fraction by 3DE, the method is cumbersome and not yet ready for regular clinical use.[6]

In contrast, the assessment of RV diastolic function is simpler than that of LV diastolic function. The easy accessibility of the inferior vena cava (IVC) for imaging permits direct estimation of RA pressure, which in the absence of any tricuspid inflow obstruction is the same as RV filling pressure (RVFP).[20] If the IVC is normal in size (≤21 mm) and collapses by more than 50% on deep inspiration, the RA pressure is considered to be normal (ie, ~3 mm Hg; range, 0–5 mm Hg).

TABLE 2.1 Echocardiographic Measures of Right Ventricular Size and Systolic Function

Measurement	*Transthoracic Echocardiographic View*	*Normal Value*
RV Size		
RV basal diameter	RV focused apical four-chamber view	25–41 mm
RV mid-diameter	RV focused apical four-chamber view	19–35 mm
RV longitudinal diameter	RV focused apical four-chamber view	59–83 mm
RV outflow tract proximal	Parasternal long-axis view	21–35 mm
RV outflow tract distal	Parasternal short-axis view	17–27 mm
RV free wall thickness	Subcostal view	1–5 mm
RV Systolic Function		
Fractional area change	RV focused apical four-chamber view	≥35%
Tricuspid annular plane systolic excursion	Apical four-chamber view (providing best alignment of ultrasound beam with annulus motion)	>16 mm
Tricuspid annular peak systolic velocity	Apical four-chamber view (providing best alignment of ultrasound beam with annulus motion)	>10 cm/s
Pulsed Doppler myocardial performance index	A combination of parasternal short-axis view and apical four-chamber view	≤0.43
Tissue Doppler myocardial performance index	Apical four-chamber view (providing best alignment of ultrasound beam with annulus motion)	≤0.54
RV ejection fraction by 3DE	Full volume dataset from apical window	≥45%
RV free wall strain	RV focused apical four-chamber view	–20% or more

3DE, Three-dimensional echocardiography; *RV*, right ventricular.

From Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39 e14; Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.* 2010;23:685–713; quiz 786–788.

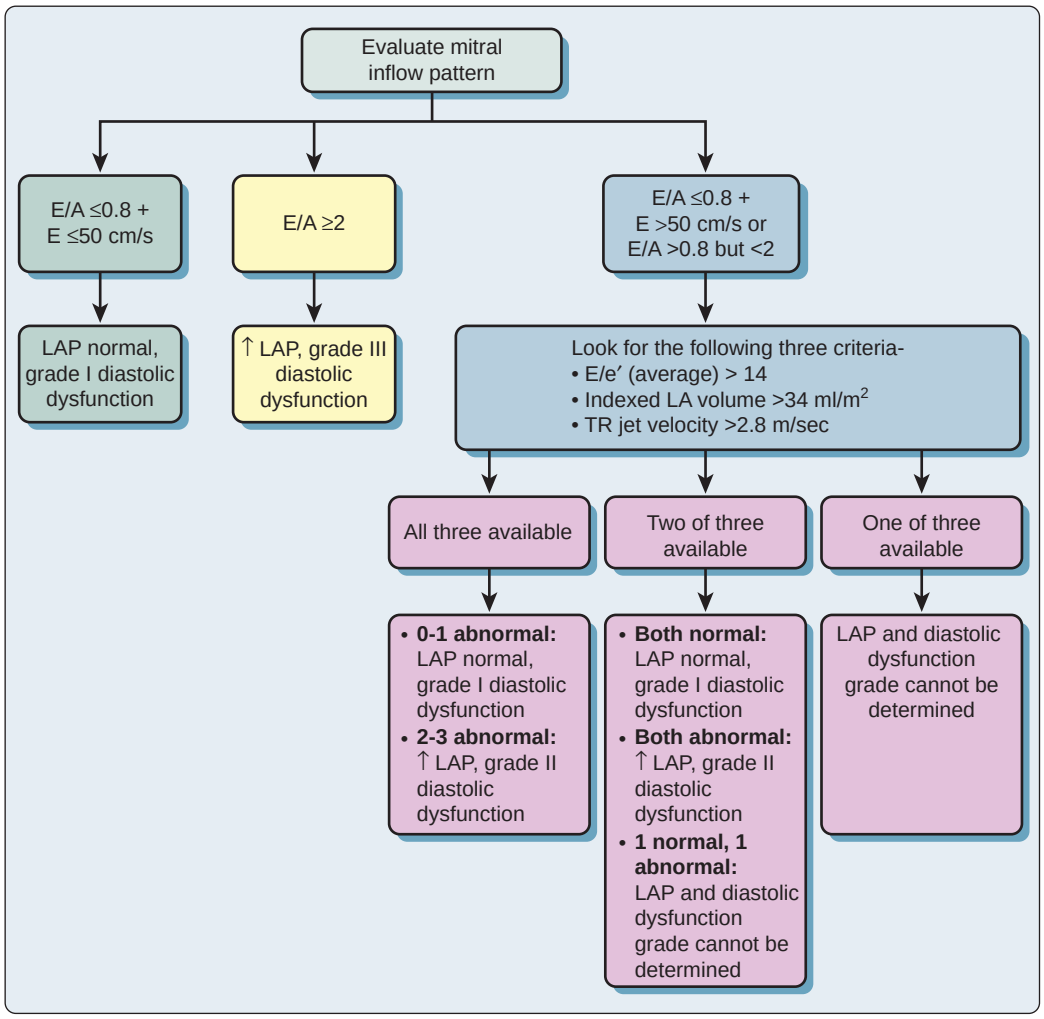

Fig. 2.4 Algorithm for echocardiographic estimation of left atrial pressure and grading left ventricular diastolic function in patients with myocardial disease but with or without left ventricular systolic dysfunction. *A,* Mitral inflow late diastolic velocity; *E,* mitral inflow early diastolic velocity; *e′,* mitral annular early diastolic velocity; *LA,* left atrial; *LAP,* left atrial pressure; *TR,* tricuspid regurgitation. *(Modified from: Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr. *2016;29:277–314.)*

However, a dilated IVC (>21 mm) that collapses by less than 50% on inspiration indicates significantly elevated RA pressure (~15 mm Hg; range, 10–20 mm Hg). When IVC size and collapsibility are discrepant with one another, the RA pressure is assumed to be in the intermediate range (~8 mm Hg; range, 5–10 mm Hg). In such cases, additional parameters can be obtained to more accurately define the RA pressure, such as tricuspid inflow E/A and E/e′ ratios, E-wave deceleration time, and hepatic vein flow pattern. Because both IVC size and collapsibility are affected by positive-pressure ventilation, this approach cannot be used for estimating RA pressure in patients who are mechanically ventilated, which is quite common in the perioperative setting. Interrogation of the hepatic vein flow pattern can provide valuable information about RA pressure in this setting.

RV systolic pressure and pulmonary vascular resistance can also be estimated by echocardiography (see later discussion).

Assessment of Valve Lesions

Valvular heart disease is the second most common primary indication, after CAD, for cardiac surgery. Valve lesions also frequently coexist in patients undergoing surgery for other cardiac and noncardiac indications.

Echocardiography is currently the best modality available for evaluation of valvular heart disease. A combination of TTE and TEE permits comprehensive assessment of valve anatomy and function and provides all the relevant information required to determine the need for and type of valve intervention. Additionally, intraoperative TEE is useful in assessing the adequacy of valve surgery and in recognizing any surgery-related complications (eg, LV outflow tract obstruction, paravalvular regurgitation).

Mitral Valve Lesions

Rheumatic heart disease is, by far, the most common cause of mitral stenosis (MS), even in developed nations. Mitral annular calcification, which is common in elderly persons and in those undergoing hemodialysis, can also produce mitral inflow obstruction, although mitral regurgitation (MR) is more frequent.

In patients with rheumatic MS, echocardiography typically reveals mitral leaflet thickening with doming of the anterior mitral leaflet, restriction of posterior mitral leaflet motion, and variable amounts

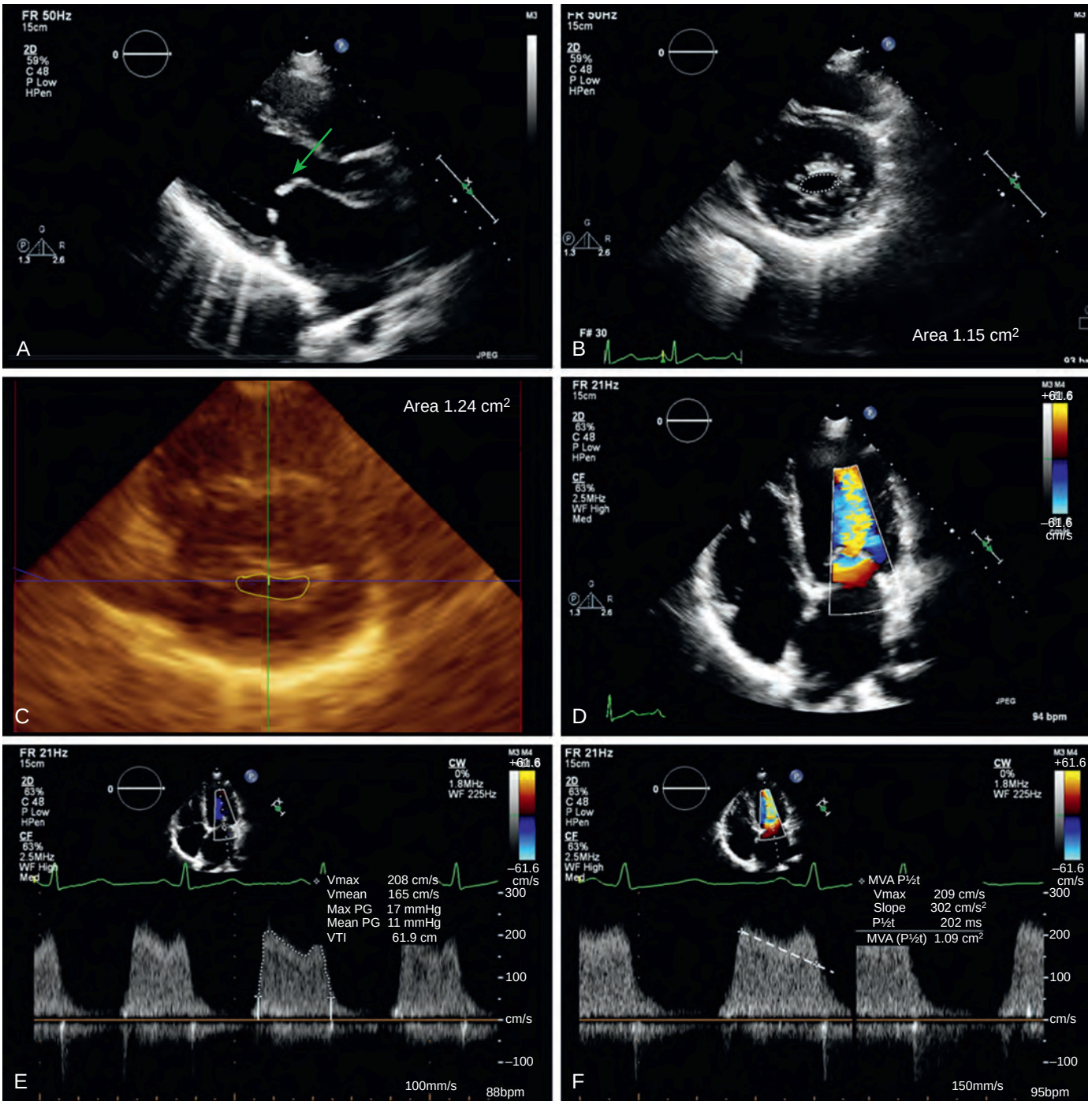

Fig. 2.5 Typical echocardiographic findings in a patient with rheumatic mitral stenosis. A, Parasternal long-axis view demonstrates restricted mitral leaflet opening with doming of anterior mitral leaflet *(arrow)*. Estimation of mitral valve area by planimetry from the parasternal short-axis view using two-dimensional (B) and three-dimensional (C) echocardiography is shown. D, Apical four-chamber view with color Doppler shows turbulent forward blood flow jet through the narrowed mitral orifice. Continuous wave Doppler is shown for estimation of transmitral gradients (E) and mitral valve area (F) by the pressure half-time method.

of leaflet calcification, fusion, and calcification of commissures. Thickening, shortening, and calcification of the subvalvular apparatus are also typically present (Fig. 2.5). These abnormalities can be formally graded with one of the various scoring systems available.[21–25] The severity of MS can be determined by measuring the transmitral gradient or by estimating the MV area, using either planimetry or the pressure half-time method[26] (Table 2.2; see Fig. 2.5). Of these, MV planimetry is the most accurate method (unless the predominant obstruction is at the level of chordae) because it is not influenced by heart rate and hemodynamics. However, its accuracy depends on gray-scale image quality and on ensuring that the measurement is performed exactly at the tips of the MV leaflets. 3DE is the best modality for this purpose because it allows the operator to optimally position the imaging plane for planimetry.[27,28] In addition to assessment of MV

TABLE 2.2 Echocardiographic Criteria for Severity of Mitral Valve Lesions

Parameter	*Mild*	*Moderate*	*Severe*
Mitral Stenosis			
Specific Findings			
Mitral valve area (cm^2)	>1.5	1.0–1.5	<1.0
Supportive Findings			
Mitral valve mean gradient (mm Hg)[a]	<5	5–10	>10
Pulmonary artery systolic pressure (mm Hg)	<30	30–50	>50
Mitral Regurgitation			
Structural Parameters			
Left atrial size	Normal[b]	Normal or dilated	Usually dilated[c]
Left ventricular size	Normal[b]	Normal or dilated	Usually dilated[c]
Mitral valve apparatus	Normal or abnormal	Normal or abnormal	Abnormal
Doppler Parameters			
Color flow jet area (cm^2)[d]	Small, central jet (usually <4 cm^2, or <20% of left atrial area)	Variable	Large central jet (usually >10 cm^2, or >40% of left atrial area) or variable-size wall-hugging jet in left atrium
Mitral inflow (pulsed wave)	A-wave dominance[e]	Variable	E wave dominance (E usually >1.2 m/s)[e]
Jet density (continuous wave)	Incomplete or faint	Dense	Dense
Jet contour (continuous wave)	Parabolic	Usually parabolic	Early peaking triangular
Pulmonary vein flow	Systolic dominance[f]	Systolic blunting[f]	Systolic flow reversal[g]
Quantitative Parameters[h]			
Vena contracta width (cm)	<0.3	0.3–0.69	≥0.7
Regurgitant volume (mL/beat)[i]	<30	30–44 (mild to moderate) 45–59 (moderate to severe)	≥60
Regurgitant fraction (%)	<30	30–39 (mild to moderate) 40–49 (moderate to severe)	≥50
Effective regurgitant orifice area (cm^2)[j]	<0.20	0.20–0.29 (mild to moderate) 0.30–0.39 (moderate to severe)	≥0.40

[a]At heart rates between 60 and 80 beats/minute.
[b]Unless there are other causes of left atrial or left ventricular dilatation.
[c]Acute mitral regurgitation is an exception.
[d]At a Nyquist limit of 50 to 60 cm/s.
[e]Usually in patients older than 50 years of age or in conditions of impaired relaxation, in the absence of mitral stenosis or other causes of elevated left atrial pressure.
[f]Unless other reasons for systolic blunting (eg, atrial fibrillation, elevated left atrial pressure) are present.
[g]Pulmonary venous systolic flow reversal is specific but not sensitive for severe mitral regurgitation.
[h]Quantitative parameters can help subclassify the moderate regurgitation group into mild-to-moderate and moderate-to-severe subgroups, as shown.
[i]For functional mitral regurgitation due to left ventricular systolic dysfunction, ≥30 mL is used as the cutoff point for defining severity.
[j]For functional mitral regurgitation due to left ventricular systolic dysfunction, ≥0.20 cm^2 is used as the cutoff point for defining severity.
From Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1–23; quiz 101–102; Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

morphology and MS severity, echocardiography aids in the evaluation of concomitant valve lesions, if any, and in detection of LA or LA appendage thromboses.

In comparison to MS, MR is a more complex entity with a multitude of etiologies and pathogenic mechanisms. MR can be organic, caused by direct pathologic involvement of one or more components of the MV apparatus; examples include rheumatic heart disease, degenerative diseases, systemic inflammatory diseases, infective endocarditis, ischemic heart disease (chordal or papillary muscle rupture), and congenital malformations (Fig. 2.6). Alternatively, MR can be of functional origin: The MV apparatus itself is normal, but leaflet coaptation during systole is impaired as a result of regional or global dilatation and dysfunction of the LV. Functional MR is common in patients with LV systolic dysfunction undergoing CABG and is an independent predictor of morbidity and mortality in these patients.[29–31]

TEE provides excellent visualization of the MV because of its proximity to the transducer. The exact pathology, the extent of the pathology, mitral annulus size, and papillary muscle and chordal geometry can all be delineated in great detail. Additionally, in patients with functional MR, tenting height, tenting area, and coaptation length can be assessed. When available, 3D TEE provides incremental information regarding MV pathology. One major advantage of 3D TEE is that it provides the "surgeon's view" of the MV, facilitating easy appreciation of the MV pathology preoperatively (Fig. 2.7).

For assessment of MR severity, a number of measures combining 2D and Doppler data are available, as outlined in Table 2.2.[32] Lower thresholds are used for defining the severity of functional MR compared with organic MR.[33]

Aortic Valve Lesions

Senile degeneration, bicuspid aortic valve (AV) disease, and rheumatic heart disease are the most common causes of aortic stenosis (AS). The same conditions can also result in aortic regurgitation (AR). AR can also result from aortic root pathologies, infective endocarditis, systemic inflammatory diseases, and other causes.

The echocardiographic assessment of AV lesions is based on principles similar to those for MV lesions (Table 2.3).[26,32] Compared with the MV, however, adequate visualization of the AV is often difficult, even on TEE. Inability to align the Doppler beam with the direction of blood flow in the conventional TEE views offers further challenges to the assessment of AS severity. Deep transgastric views are required to measure the AS gradient with TEE, but they may not always result in a satisfactory evaluation. An additional challenge in the assessment of AS severity is the frequent occurrence of inappropriately low transaortic gradients despite a significantly reduced AV area.[26,33–35] This discrepancy is common in the setting of LV systolic dysfunction. Dobutamine echocardiography may help in further evaluation of these patients, as described later. However, a paradoxically low gradient may also be seen in the presence of a normal LVEF. The exact pathogenesis underlying this entity, its prognostic significance, and the optimum management strategies remain debatable.[33–35]

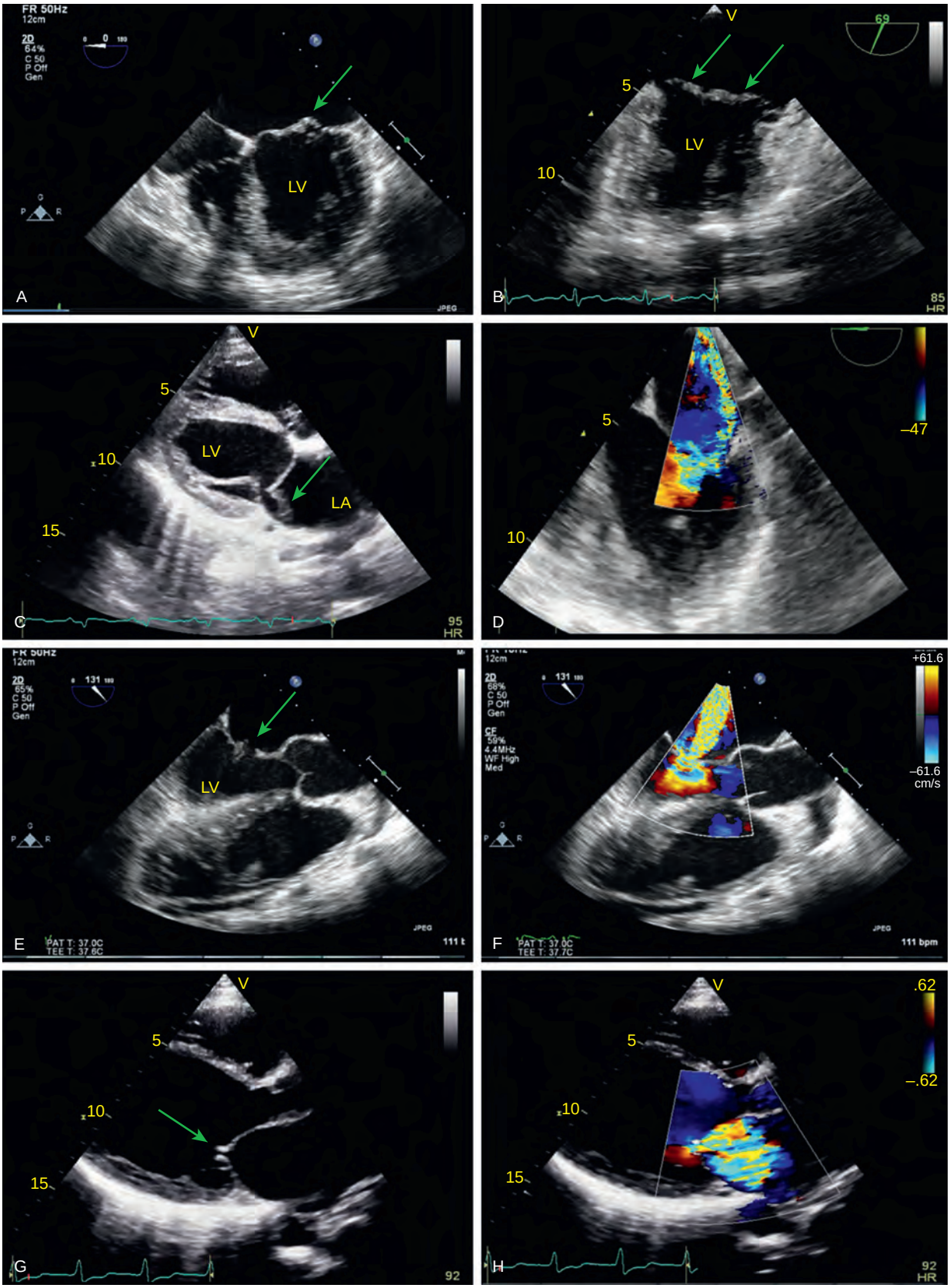

Fig. 2.6 Illustrative examples of mitral regurgitation from various causes. A and B, Bileaflet mitral valve prolapse (*arrows*). C and D, Papillary muscle rupture secondary to acute myocardial infarction. The torn papillary muscle is seen prolapsing into the left atrium (C, *arrow*), resulting in posteriorly directed severe mitral regurgitation (D). E and F, Infective endocarditis with perforation of the anterior mitral leaflet (E, *arrow*) results in severe mitral regurgitation through the perforation (F); G and H, Functional severe mitral regurgitation secondary to left ventricular systolic dysfunction and dilatation. Mitral valve leaflets are markedly tented resulting in noncoaptation (*arrow* in G). *LA*, Left atrium; *LV*, left ventricle.

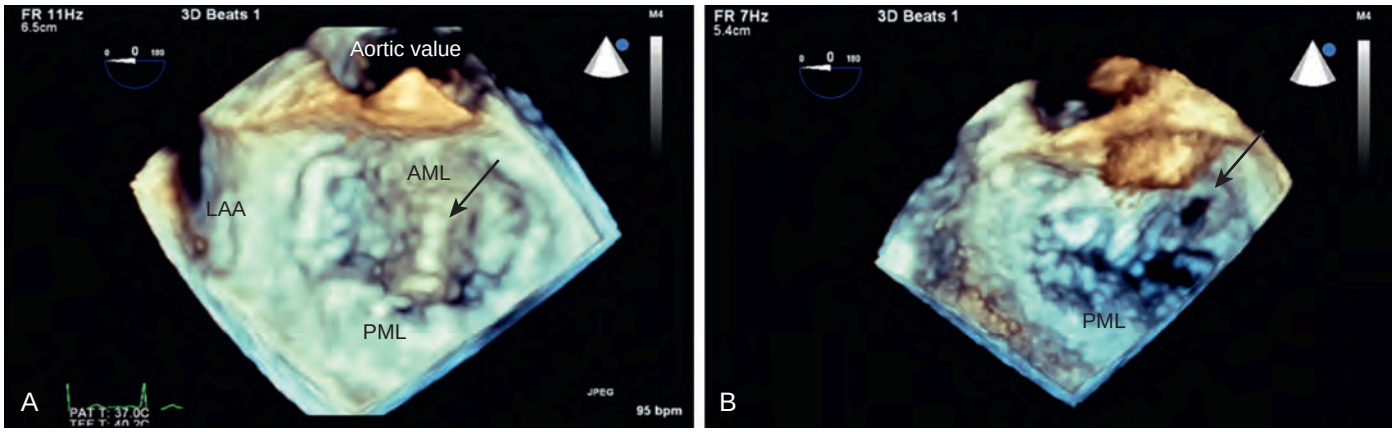

Fig. 2.7 Three-dimensional transesophageal echocardiography shows the mitral valve from the left atrial aspect, with the aortic valve in the 12 o'clock position (the "surgeon's view"). A, Prolapse of the A2 scallop of the anterior mitral leaflet *(arrow)*. B, Perforation in the A3 scallop of the anterior mitral leaflet *(arrow)*. *AML*, Anterior mitral leaflet; *LAA*, left atrial appendage; *PML*, posterior mitral leaflet.

TABLE 2.3 Echocardiographic Criteria for Severity of Aortic Valve Lesions

Parameter	*Mild*	*Moderate*	*Severe*
Aortic Stenosis			
Aortic jet peak velocity (m/s)	2.6–2.9	3.0–4.0	>4.0
Aortic valve mean gradient (mm Hg)[a]	<20	20–40	>40
Aortic valve area (cm^2)	>1.5	1.0–1.5	<1.0
Indexed aortic valve area (cm^2/m^2)	>0.85	0.60–0.85	<0.60
Velocity ratio	>0.50	0.25–0.50	<0.25
Aortic Regurgitation			
Structural Parameters			
Left ventricular size	Normal[b]	Normal or dilated	Usually dilated[c]
Aortic leaflets	Normal or abnormal	Normal or abnormal	Abnormal/ flail, or wide coaptation defect
Doppler Parameters			
Jet width in LVOT (color flow)[d]	Small in central jets	Intermediate	Large in central jets; variable in eccentric jets
Jet density (continuous wave)	Incomplete or faint	Dense	Dense
Jet deceleration rate (continuous wave) (pressure half-time, ms)[c]	Slow, >500	Medium, 500–200	Steep, <200
Diastolic flow reversal in descending aorta (pulsed wave)	Brief, early diastolic reversal	Intermediate	Prominent holodiastolic reversal
Quantitative Parameters[f]			
Vena contracta width (cm)[d]	<0.3	0.3–0.60	≥0.6
Jet width/LVOT width ratio (%)[d]	<25	25–45 (mild to moderate) 46–64 (moderate to severe)	≥65
Jet CSA/LVOT CSA ratio (%)[d]	<5	5–20 (mild to moderate) 21–59 (moderate to severe)	≥60
Regurgitant volume (mL/beat)	<30	30–44 (mild to moderate) 45–59 (moderate to severe)	≥60
Regurgitant fraction (%)	<30	30–39 (mild to moderate) 40–49 (moderate to severe)	≥50
Effective regurgitant orifice area (cm^2)	<0.10	0.10–0.19 (mild to moderate) 0.20–0.29 (moderate to severe)	≥0.30

CSA, Cross-sectional area; *LVOT*, left ventricular outflow tract.
[a]At heart rates between 60 and 80 beats/minute.
[b]Unless there are other causes of left ventricular dilatation
[c]Acute aortic regurgitation is an exception.
[d]At a Nyquist limit of 50 to 60 cm/s.
[e]Pressure half-time is shortened with increasing left ventricular diastolic pressure and vasodilator therapy and may be lengthened with chronic adaptation to severe aortic regurgitation.
[f]Quantitative parameters can help subclassify the moderate regurgitation group into mild-to-moderate and moderate-to-severe subgroups, as shown.
From Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1–23; quiz 101–102; Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

Other Valve Lesions

Functional TR is another common valve lesion encountered in the surgical setting. Any condition resulting in severe pulmonary hypertension can cause TR. In cardiac patients, the most common causes are severe LV systolic dysfunction and significant MV disease. Significant TR in the absence of pulmonary hypertension occurs much less frequently and may be a consequence of previous RV myocardial infarction, atrial septal defect, or direct organic involvement of tricuspid valve leaflets in rheumatic heart disease, carcinoid disease, trauma, infective endocarditis, or the Ebstein anomaly. Organic, significant TR usually requires surgical correction, but the optimum management strategy for functional TR remains controversial. Although correction of the primary

pathology can often lead to partial or complete resolution of TR, it is less likely to regress, and may even progress, if tricuspid annulus dilation is present. In patients undergoing MV surgery, a maximum tricuspid annulus diameter greater than 4 cm (or >21 mm/m^2) on preoperative echocardiography is generally considered to indicate the need for surgical correction of TR at the time of MV surgery.[33,36–37]

Tricuspid valve pathology is best imaged by TTE and TEE, but on occasion the patient may have poor TTE windows, or the TEE study may be insufficient. Morphology of the valve, size of the annulus, TR gradient, status of RV systolic function, and RA pressure are the important data that need to be obtained from echocardiography.

Tricuspid stenosis is very rare and is usually congenital, associated with carcinoid tumor, or rheumatic in origin. Significant pulmonary regurgitation is also rare and typically occurs secondary to pulmonary hypertension or previous repair of congenital pulmonary stenosis. Pulmonary stenosis, however, is not uncommon. It is almost always congenital in origin and usually occurs as an isolated valvular, subvalvular, or supravalvular stenosis. The pulmonic valve is not well visualized on either TTE or TEE, especially in adults, but the transpulmonary gradient can be estimated in most patients.

Apart from native valve disease, patients can present with a wide variety of prosthetic heart valve (PHV)-related complications. Although echocardiography remains the primary modality for the evaluation of PHV function, adequate visualization of mechanical prosthetic valves, especially prosthetic AVs, is difficult because of acoustic shadowing and other artifacts caused by prosthetic materials. Mitral PHVs, however, can be imaged reasonably well, especially with TEE. The mobility of occluders, thickening of the leaflets in cases of tissue valves, valve dehiscence, paraprosthetic leaks, and presence of pannus, thrombus, or vegetation can be diagnosed effectively. Additionally, a reasonable amount of hemodynamic information can be obtained and can be corroborated with the anatomic findings to ascertain the actual mechanisms and severity of PHV malfunction.

Infective endocarditis is another common indication for valve surgery in patients with either native or prosthetic valves. It can be a life-threatening disease, with mortality rates reported to be as high as 40%.[38] The diagnosis is usually based on visualization of vegetations by echocardiography, which is the primary modality for diagnosing infective endocarditis. In severe cases, valve perforations, paravalvular abscesses, and PHV dehiscence can also be seen. With current-generation technologies, the sensitivity of TTE for detection of native valve endocarditis is in the range of 82% to 89%, and the specificity is 70% to 90%.[38–41] For prosthetic valve endocarditis, however, the sensitivity of TTE is rather poor (<50%). TEE is clearly the imaging modality of choice for infective endocarditis. For native valve endocarditis, TEE has a sensitivity of 90% to 100% and a specificity greater than 90%. Even for prosthetic valve endocarditis, TEE is highly accurate, with sensitivity in the range of 80% to 90% and specificity greater than 90%.[38–44]

Hemodynamic Assessment

Although invasive hemodynamic monitoring is routine in patients undergoing cardiac surgery, echocardiography offers an excellent alternative if invasive monitoring is not feasible. Typically, echocardiography is the best option for hemodynamic assessment during the preoperative period, or in the late postoperative period after discharge from the intensive care unit, and also in noncardiac surgery. An added advantage of echocardiography is that it allows hemodynamic data to be directly correlated with cardiac anatomy and function. Vast amounts of hemodynamic information can be obtained from echocardiography, including intracardiac pressures, cardiac output, and vascular resistance.

Intracardiac Pressures

A wide range of intracardiac pressures can be derived using the simplified Bernoulli equation, which states that the pressure gradient (ΔP) driving a blood flow jet within the cardiovascular system is equal to $4v^2$, where v is the peak jet velocity. If the pressure within the upstream or downstream chamber is known, the pressure in the other chamber can be calculated by measuring the peak jet velocity between the two chambers. The most common application of this formula is in estimation of RV systolic pressure or pulmonary artery systolic pressure from a TR jet. The RV systolic pressure is derived by adding mean RA pressure (estimated from IVC measurements as described earlier or from jugular venous observations with head elevation) to the peak TR jet gradient. In the absence of any RVOT obstruction, RV systolic pressure is identical to the pulmonary artery systolic pressure. The same principle can be applied for estimating other intracardiac pressures using other jets (eg, pulmonary artery end-diastolic pressure from a pulmonary regurgitant jet, RV systolic pressure from the jet crossing a ventricular septal defect, LA pressure from the mitral regurgitation jet).

A number of equations are also available for the estimation of peak systolic and mean pulmonary pressure from RVOT acceleration time and from pulmonary regurgitation jet velocity.[45–48] However, these formulas involve certain assumptions, and their accuracy is affected by several hemodynamic factors.

Cardiac Output and Vascular Resistance

During echocardiography, flow through any cardiac structure can easily be estimated by multiplying the cross-sectional area of the structure by the velocity-time integral (VTI) of the blood flow through that structure. This provides stroke volume, which is then multiplied by the heart rate to calculate cardiac output (CO).

In clinical practice, LV outflow tract (LVOT) is the site most commonly used for measurement of CO (Fig. 2.8). LVOT is easy to visualize, it is almost circular in shape, and its size does not change much during the cardiac cycle. Additionally, the blood flow through the LVOT is mostly laminar, which minimizes the chance of inadvertently sampling velocities that are not truly representative of the actual blood flow at that point. The LVOT diameter is measured from the parasternal or TEE long-axis view and the VTI from the apical five-chamber or TEE deep transgastric view (using pulsed-wave Doppler ultrasonography). Precision should be maintained while obtaining these measurements, because any errors will become magnified when the calculations are performed.[49]

There are several circumstances in which the CO measured at the LVOT may not be accurate or representative of true CO, including significant LVOT obstruction and AR. In such cases, the measurements can be performed at the MV or at the RVOT, provided there is no significant MR or intracardiac shunt, respectively.

Once the CO has been determined, systemic vascular resistance (SVR) can be estimated using the principle of Ohm's law, which states that the resistance across any vascular circuit is equal to the pressure gradient across the circuit divided by the flow:

$$\text{SVR} = (\text{Mean aortic pressure} - \text{Mean RA pressure}) / \text{Systemic blood flow}$$

Mean systemic blood pressure is used as a surrogate for mean aortic pressure; all the other values can be obtained by echocardiography, as described earlier. When the pressure gradient is measured in mm Hg and CO in L/min, the derived vascular resistance is described in Wood units, which can be converted to metric units (dynes·s·cm^{-5}) by multiplying by 80.

Although a similar equation can be applied for the estimation of pulmonary vascular resistance (PVR), it is generally not used because of the difficulties in obtaining transpulmonary gradients by echocardiography. An alternate, simpler method has been proposed for measuring the PVR (in Wood units); it relies on the TR jet velocity (in m/s) and the RVOT-VTI (in cm):

$$\text{PVR} = (\text{Peak TR velocity} / \text{RVOT} - \text{VTI}) \times 10 + 0.16$$

Pericardial Diseases

Bleeding into the pericardial space is a common occurrence during the immediate postoperative period after cardiac surgery and an important

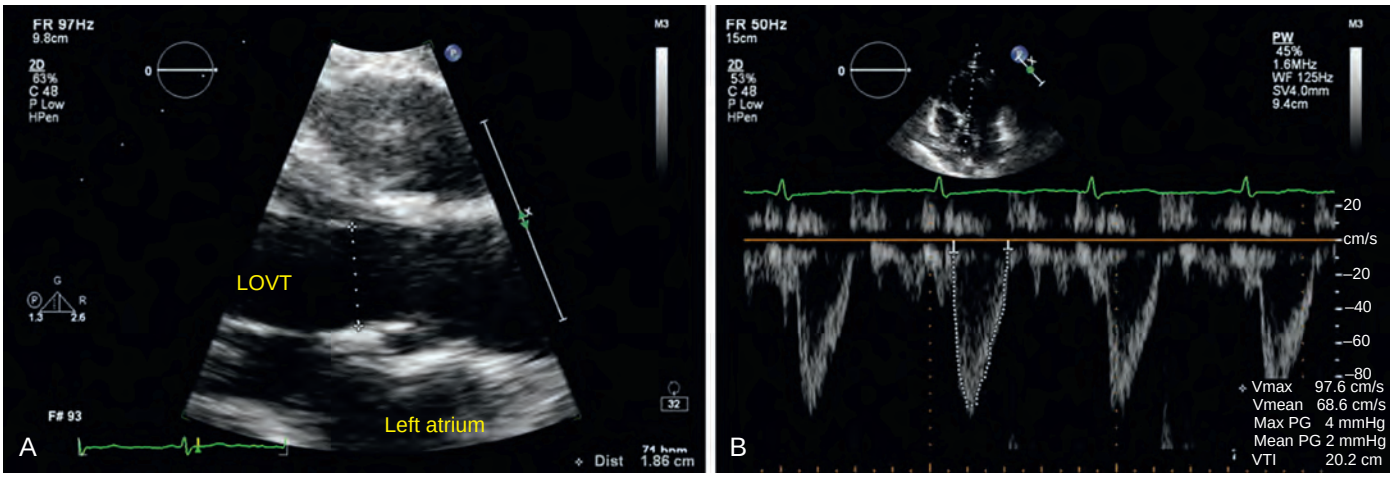

Fig. 2.8 Echocardiographic estimation of cardiac output at the left ventricular outflow tract (LVOT). A, LVOT diameter is measured from the parasternal long-axis view in midsystole. B, Measurement of the LVOT velocity-time integral (VTI) using pulsed-wave Doppler ultrasonography in apical five-chamber view. See text for details.

cause of hemodynamic compromise in this setting. Pericardial effusions can also occur secondary to a number of cardiac and noncardiac conditions; for example, it can occur as an immune reaction after myocardial infarction or cardiac surgery. Echocardiography not only allows detection and quantification of pericardial collections but also permits assessment of the hemodynamic significance of the phenomenon.

The pericardial fluid or blood collection can be circumferential or localized, and it usually appears as an echolucent space outside the heart. When bleeding is the cause, however, the fluid is more echogenic, and even frank clots may be seen. Additionally, fibrinous bands, septa, and pericardial echogenic deposits are commonly visualized in cases of exudative effusions. When a pericardial collection is localized posterior to the LV, it can be difficult to distinguish from a pleural collection. Extension of the collection posterior to the descending thoracic aorta suggests a pleural origin, rather than pericardial.

When a pericardial effusion is visualized, an important clinical question is whether there is any evidence of cardiac tamponade. Evidence of diastolic RA and RV collapse, a restrictive-type mitral inflow pattern with significant respiratory variation in mitral and tricuspid inflow velocities, and a dilated, noncollapsing IVC indicate the presence of cardiac tamponade (Fig. 2.9). The size of the effusion itself is not a reliable indicator because the rapidity of fluid accumulation is more important than the actual quantity of fluid in the causation of cardiac tamponade.

Apart from pericardial collections, constrictive pericarditis is another common pericardial pathology and is itself an indication for cardiac surgery. In patients with suspected chronic constrictive pericarditis, pericardial thickening and calcification may be visualized on echocardiography. More often, however, it is the hemodynamic abnormalities that draw attention to the possibility of constriction physiology. The echocardiographic findings suggestive of constriction include (1) exaggerated ventricular interdependence, as evidenced by septal bounce, deviation of septal position with respiration, and significant respiratory variation in mitral and tricuspid inflow velocities; (2) a restrictive-type mitral inflow pattern with a relatively preserved or exaggerated mitral e′ (known as annulus paradoxus) or a medial mitral e′ that is taller than the lateral e′ (known as annulus reversus); and (3) a dilated, noncollapsing IVC. In uncertain cases, assessment of myocardial strain and torsion abnormalities may provide further clues to help reach an accurate diagnosis.[50–51]

In patients with various pericardial pathologies, echocardiography helps not only in diagnostic evaluation but also in guiding therapeutic interventions (eg, pericardiocentesis, pericardiectomy) and in assessing the adequacy of those procedures.

Diseases of the Aorta

Aortic aneurysm and aortic dissection are commonly encountered cardiac pathologies. Despite advances in endovascular repair, surgery remains the primary treatment modality for most patients. Although CCT is the modality of choice for imaging the aorta, echocardiography is a good modality for initial evaluation, especially in acutely ill or hemodynamically unstable patients.

Ascending aortic aneurysms usually occur because of cystic medial degeneration; they frequently involve the aortic root and cause AR. These aneurysms are more common in patients with hypertension, bicuspid AV, or connective tissue diseases such as Marfan or Ehlers-Danlos syndrome (see Chapter 23).[52] In contrast, descending aortic aneurysms are mostly caused by atherosclerosis and are associated with the same risk factors as for CAD. Among descending aortic aneurysms, abdominal aneurysms are more common than thoracic aortic aneurysms.

Although TTE can provide clear visualization of the aortic root and the proximal segment of the ascending aorta, imaging of the arch and the descending thoracic aorta is usually challenging. In contrast, TEE can image the entire length of the descending thoracic aorta, in addition to aortic root and the proximal segment of ascending aorta, but the aortic arch, especially the proximal portion, is not visualized because of the interposition of the left main bronchus in the path of the ultrasound beam. An aortic aneurysm appears as a localized dilatation of a segment of the aorta to more than 1.5 times its normal size. Echocardiography can be used to measure both the width and the longitudinal extent of the aneurysm, as well as its relationship to major anatomic landmarks. Additionally, mural thrombi are frequently seen, especially in large aneurysms.

Ascending aortic dissection is a true cardiac surgical emergency that needs to be diagnosed urgently and treated surgically. In aortic dissections, there is a tear in the intima that forms a communication with the aortic true lumen. The media is exposed to blood flow, and a false lumen typically forms. The dissection extends in either an anterograde or a retrograde fashion, often involving the branch arteries.[53] Aortic dissections most commonly originate in one of two locations that experience greatest stress: the ascending aorta just above the sinuses of Valsalva (65%) or the descending aorta just distal to the subclavian artery (20%). Other, less common sites include the aortic arch (10%) and the abdominal aorta (5%).

Echocardiography is an excellent modality for the initial assessment of patients with aortic dissection, particularly those with proximal aortic dissection. TTE has a sensitivity of 77% to 80% and a specificity of 93% to 96% for the diagnosis of proximal aortic

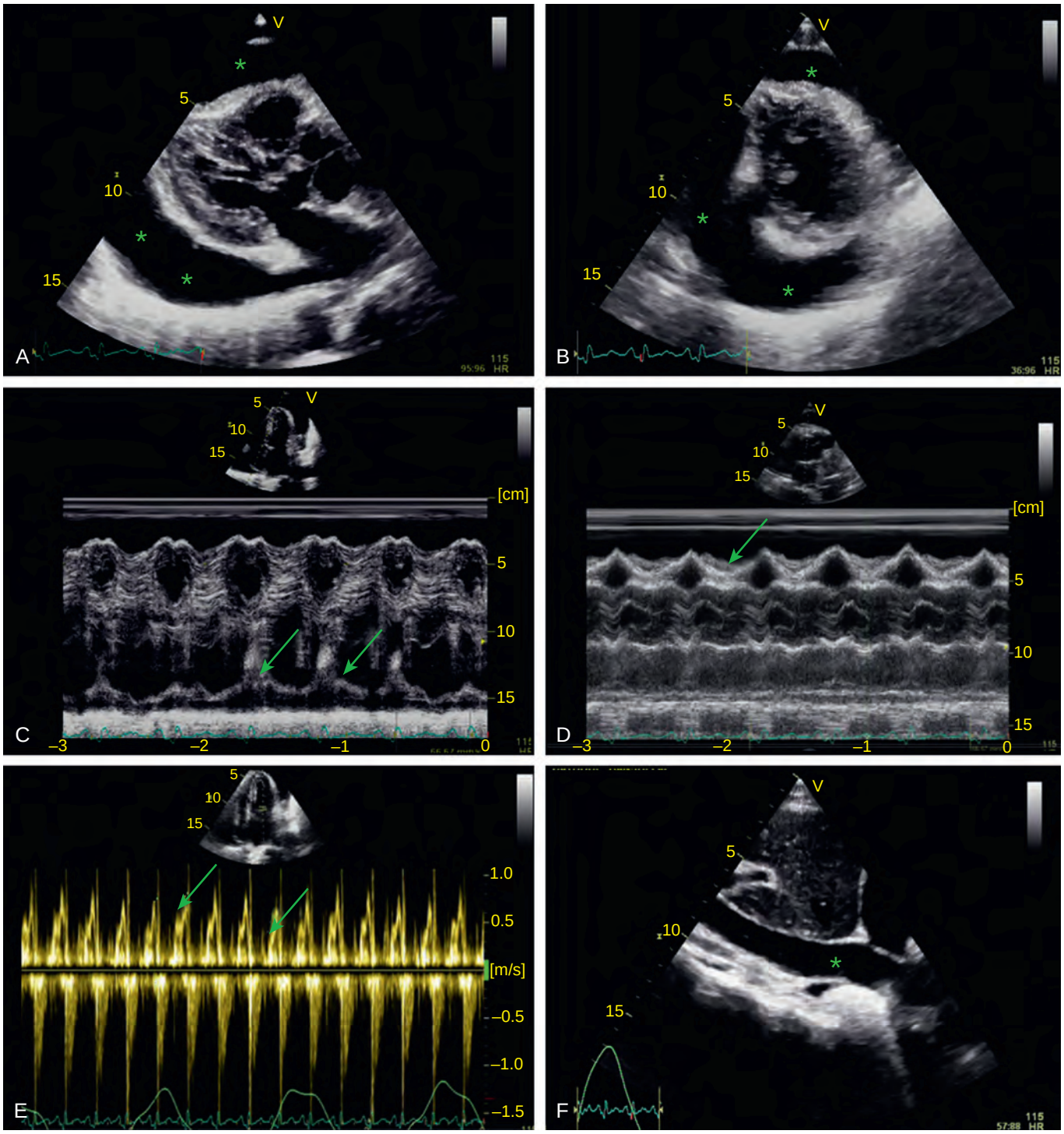

Fig. 2.9 A patient with cardiac tamponade. Parasternal long-axis view (A) and short-axis view (B) show a large circumferential pericardial effusion *(asterisks)*. C, Late diastolic right atrial collapse *(arrows)*. D, Early diastolic right ventricular collapse *(arrow)*. E, Significant respiratory variation in mitral inflow velocities *(arrows)*. F, Dilated inferior vena cava *(asterisk)* suggestive of elevated right heart filling pressure.

dissection, whereas the sensitivity and specificity of TEE in this application are 98% and 95%, respectively.[54,55] The sensitivity of TTE for detecting distal aortic dissection is much lower, for the reasons mentioned earlier, but TEE can diagnose most dissections involving the descending thoracic aorta. TEE can also demonstrate intimal tears in most cases, and it permits recognition of true and false lumina. Additionally, both TTE and TEE are helpful in defining the mechanism of AR if present, in assessing the underlying primary AV pathology if present, and in recognizing pericardial extension of the dissection (Fig. 2.10).

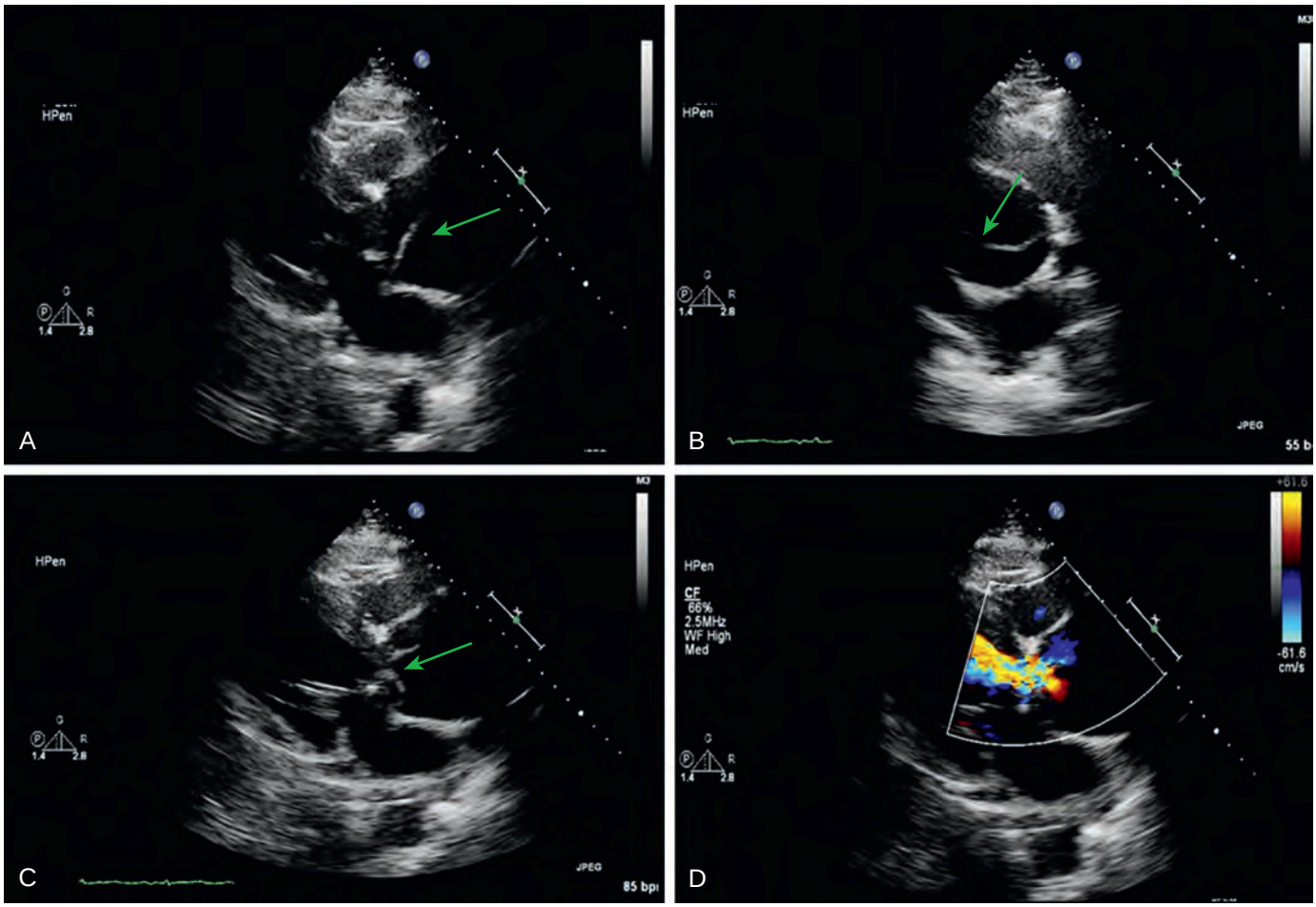

Fig. 2.10 An illustrative example of proximal aortic dissection. Dissection flap *(arrow)* is seen in the ascending aorta in the long-axis view (A) and in the short-axis view (B). The dissection flap is prolapsing though the aortic valve orifice (C, *arrow*), resulting in severe aortic regurgitation (D).

Miscellaneous Disorders

Echocardiography is also useful in providing surgically relevant information about patients undergoing cardiac surgery for various structural lesions such as hypertrophic cardiomyopathy or intracardiac masses. In patients with hypertrophic cardiomyopathy who are undergoing septal myectomy, echocardiography delineates the extent of septal hypertrophy, the site of maximum thickness, the presence of any papillary muscle abnormalities, and the presence, severity, and mechanism of MR, all of which are helpful in planning the surgical procedure.

Stress Echocardiography

Inclusion of a hemodynamic stressor at the time of imaging greatly expands the diagnostic realm of echocardiography. Inducible myocardial ischemia and myocardial viability can be assessed, the patient's symptoms can be corroborated, and the hemodynamic significance of valve lesions can be better assessed if there is ambiguity.

Myocardial Ischemia

Assessment of the presence, extent, and severity of myocardial ischemia is the most common indication for performing stress echocardiography. During stress echocardiography, inducible ischemia is diagnosed by the development of new wall motion abnormalities, which may manifest as delayed thickening, reduced thickening, or no thickening at all.

Patients can be stressed by exercise or by the use of pharmacologic agents.[56] In patients who are physically active, exercise is the preferred modality because it is physiologic, allows symptom correlation, and permits assessment of functional capacity, which itself is a powerful prognostic marker. Exercise is most often done on a treadmill or, less commonly, on a bicycle ergometer.[57] Compared with bicycle ergometry, treadmill exercise typically results in greater workload during the stress test. However, the lower workload achieved during bicycle ergometry is compensated by the ability to image during the exercise itself, so the two modalities have equivalent diagnostic accuracy.[58]

Pharmacologic stress testing is a negative prognosticator in itself because patients who are not able to achieve sufficient physical activity to perform an exercise stress test have a greater incidence of cardiovascular disease and other comorbidities. Pharmacologic stress testing can be performed using either dobutamine, which is a chronotropic/inotropic agent, or a vasodilator such as dipyridamole or adenosine. Atropine is often combined with pharmacologic stress testing to increase the sensitivity of the test.[59–62]

If the patient has an implanted pacemaker and a pacemaker-dependent rhythm, pacing stress echocardiography can be performed using an external programmer to sequentially increase the heart rate. It is usually combined with dobutamine infusion to simultaneously augment contractility.

Regardless of the stress modality, the imaging protocols are almost identical.[56] Representative gray-scale images (typically the parasternal long-axis, midventricular short-axis, apical four-chamber, and apical

two-chamber views) are acquired at baseline and at, or immediately after, peak stress. Bicycle exercise and pharmacologic agents also allow acquisition of low-stress and recovery images. Hemodynamic data (eg, LVFP, TR, MR) are also captured at baseline and at peak stress. The gray-scale images are analyzed for any inducible wall motion abnormalities with the use of a digitized, quad-screen display format to allow side-by-side comparisons.

The accuracy of stress echocardiography for detection of inducible ischemia has been examined in numerous studies. In a large metaanalysis, the average sensitivity and specificity of exercise echocardiography were found to be 83% and 84%, respectively.[63] These values were 80% and 85%, respectively, for dobutamine echocardiography; 71% and 92% for dipyridamole echocardiography; and 68% and 81% for adenosine stress echocardiography.[63] A number of factors that influence the accuracy of stress echocardiography, including the adequacy of stress, delayed imaging after stress, the extent of CAD, the coronary vessel or vessels affected, use of beta-blockers and other antianginal agents, preexisting wall motion abnormalities, previous CABG, the presence of concomitant conduction abnormalities, and the acoustic quality of the gray-scale images. Additionally, the technical expertise of the personnel involved in image acquisition and interpretation greatly influences the diagnostic accuracy of this modality.[56,64,65]

Myocardial Viability

In patients with significant LV systolic dysfunction, the presence of myocardial viability is a good prognostic marker and is associated with greater likelihood of functional recovery after revascularization.[66–70] Accordingly, myocardial viability is often assessed in these patients to determine the need for, and to choose the mode of, revascularization.

Although reduced end-diastolic wall thickness (<6 mm) has been reported to have high negative predictive value for the presence of myocardial viability,[71] the converse is not true. For this reason, dobutamine echocardiography is the primary echocardiographic modality used for the assessment of myocardial viability in clinical practice. The dobutamine infusion is started at a low dose (typically 2.5–5 μg/kg per minute), and the dose is doubled every 3 minutes to a maximum of 40 μg/kg per minute. At low doses (up to 10 μg/kg per minute), dobutamine augments cardiac contractility without any appreciable increase in myocardial oxygen demand. However, when the dose is increased further, there is a progressive increase in heart rate and myocardial oxygen demand. As a result, a dysfunctional but viable segment that is underperfused (ie, a *hibernating* segment) will improve at low doses but worsen again at peak doses. This biphasic response is considered to be the hallmark of myocardial viability and is the most accurate predictor of functional recovery after revascularization.[72] In contrast, when a myocardial segment is dysfunctional but well perfused (i.e., *stunned* myocardium), it will demonstrate a sustained improvement in contractility at both low and peak doses (uniphasic response). Such a segment is likely to improve with time without the need for any revascularization. If there is no improvement in contractility with a low dose, lack of myocardial viability is indicated, and the likelihood of functional recovery is very low. In a metaanalysis comparing various modalities for assessment of myocardial viability, dobutamine echocardiography was reported to have a sensitivity of 84% and a specificity of 81% for predicting functional recovery after revascularization.[73]

An important limitation of stress echocardiography, when used for evaluation of CAD, is the subjectivity of assessment. All interpretation with this modality is based on visual analysis of wall motion. Quantitative techniques such as tissue velocity imaging and strain imaging have been explored to minimize this subjectivity and to improve the diagnostic accuracy of stress echocardiography. The results indicate that the use of tissue velocity and strain as adjuncts to wall motion analysis can indeed enhance the accuracy of stress echocardiography for evaluation of myocardial ischemia and viability.[74–79] Due to several technical limitations, however, the role of these techniques is limited at present.

Valve Lesions

Although valve lesions are typically evaluated at rest only, stress echocardiography may be required in certain situations. For patients who have significant valve disease but are asymptomatic, exercise stress echocardiography can be performed to assess symptoms and to determine overall functional capacity. Development of symptoms at low levels of stress, especially if accompanied by evidence of hemodynamic compromise (eg, fall in blood pressure, significant increase in pulmonary artery systolic pressure), may indicate the need for valve surgery.[33]

A specific indication for stress echocardiography is in the evaluation of low-gradient severe AS in the presence of LV systolic dysfunction.[26] The AS may be truly severe and the gradients spuriously low due to LV systolic dysfunction. Alternatively, the AS may not be severe, with the reduced valve area being a function of inadequate opening force (pseudo-severe AS). Low-dose dobutamine echocardiography (maximum dose, 10–20 μg/kg per minute) can help make this distinction. In the former situation, an increase in LV contractility with dobutamine infusion significantly increases the transaortic gradient without a concomitant increase in valve area. In these cases, LV systolic dysfunction is likely to be secondary to severe AS and can be expected to improve after AV replacement. In contrast, if the AS is not truly severe, dobutamine infusion augments valve opening such that the valve area increases but the gradients do not increase much. In such patients, LV systolic dysfunction is not related to AS, and AV replacement may not be helpful. On occasion, a patient may have fairly advanced LV systolic dysfunction with no contractile reserve, which precludes making the distinction between severe AS and pseudo-severe AS. Patients in this subgroup have high associated surgical mortality rates and poor long-term outcomes, although valve replacement may still improve LV function and outcome in selected individuals.[80]

Stress echocardiography may also have a role in the evaluation of functional MR. An exercise-induced increase in the MR effective regurgitation orifice by greater than 13 mm^2 has been shown to be an independent predictor of mortality and hospital admission for heart failure in patients with chronic ischemic LV systolic dysfunction and functional MR.[81]

Myocardial Nuclear Scintigraphy

Myocardial nuclear scintigraphy is the most widely used modality for assessment of myocardial ischemia and viability, at least in the preoperative setting. There are two main forms of myocardial nuclear imaging, single-photon emission computed tomography (SPECT) and positron emission tomography (PET). Both use the principles of radioactive decay to evaluate the myocardium and its blood supply.

The radionuclides that are used in SPECT are technetium 99m (^{99m}Tc) and thallium 201 (^{201}Tl). ^{99m}Tc is a large radionuclide that emits a single photon or gamma ray per radioactive decay event, with a half-life of 6 hours. The energy of the emitted photon is 140,000 electron volts (140 keV). ^{201}Tl is less commonly used and decays by electron capture. It has a much longer half-life (73 hours), and the energy emitted is between 69 and 83 keV. To obtain images, the gamma rays that are released from the body must be captured and modified by a detector (gamma camera). The standard camera is composed of a collimator, scintillating crystals, and photomultiplier tubes. When a radionuclide emits gamma rays, it does so in all directions. A collimator made of lead that has small, elongated holes is used as a filter to accept only those gamma rays traveling from the target organ toward the camera. Once the selected gamma rays have reached the scintillating crystals, they are converted to visible light and then to electrical signals by the photomultiplier tubes. These signals are processed by a computer to form images. Myocardial regions that are infarcted or ischemic after stress have relatively decreased tracer uptake and therefore decreased signal (counts) in the processed images.

Although PET also uses radioisotopes to produce images, the actual process of image formation is quite distinct from that of SPECT. The most common radioisotopes used for cardiac evaluation by PET

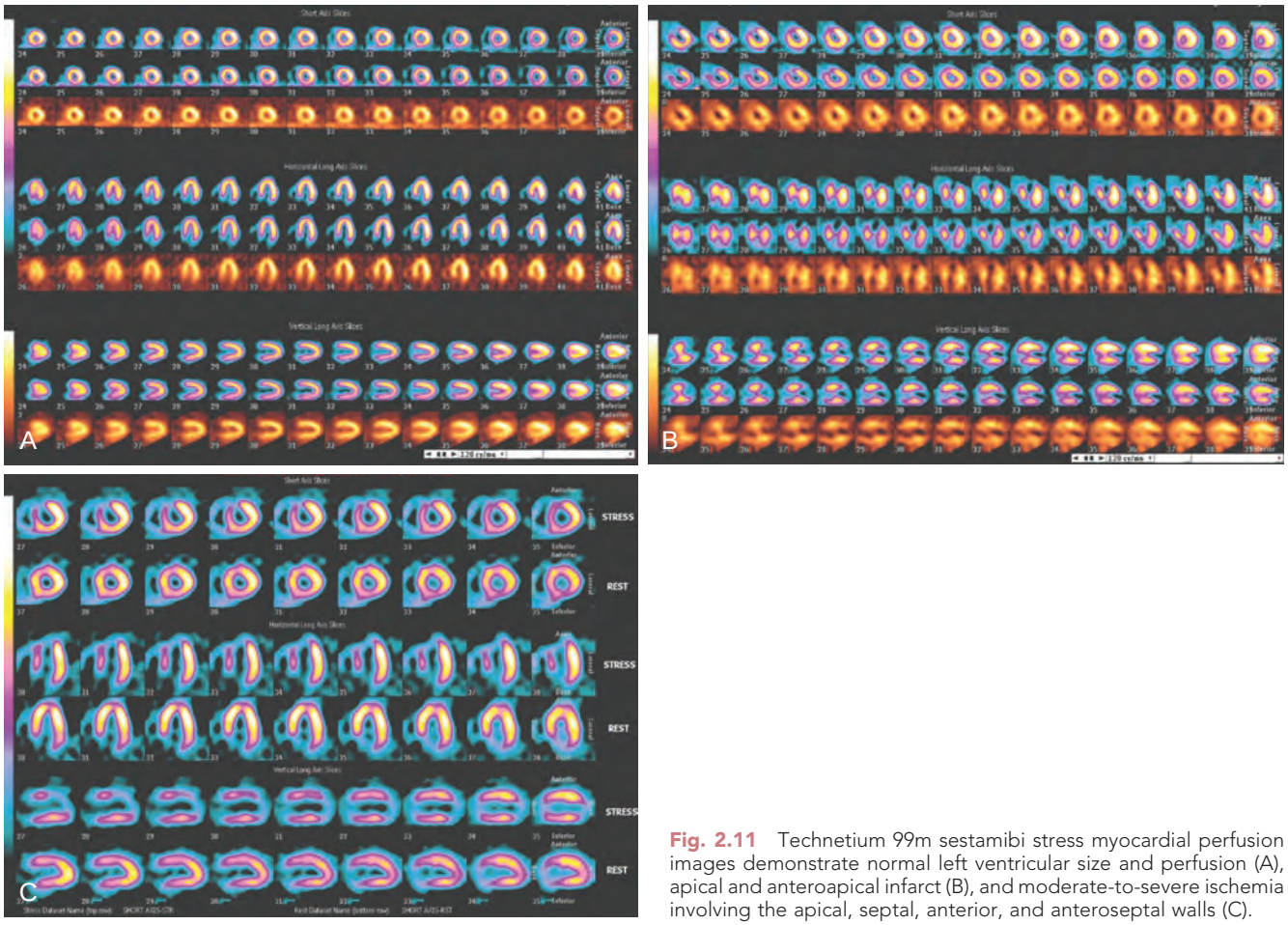

Fig. 2.11 Technetium 99m sestamibi stress myocardial perfusion images demonstrate normal left ventricular size and perfusion (A), apical and anteroapical infarct (B), and moderate-to-severe ischemia involving the apical, septal, anterior, and anteroseptal walls (C).

imaging are rubidium 82, *N*-ammonia 13, and fluorine 18 (^{18}F). ^{18}F is a much smaller radionuclide than ^{99m}Tc. It emits a positron (β^+) antiparticle. This ionized antiparticle travels until it interacts with an electron. The electron and the positron are antiparticles of each other, meaning that they have the same mass but are opposite in charge. When they encounter each other, both particles disintegrate and are converted into energy in the form of two photons, each with the same energy (511 keV), traveling in opposite directions. This phenomenon, known as *pair annihilation*, is used to create the images in PET. PET cameras also differ from SPECT cameras in that they capture only incoming photons that travel in opposite directions and arrive at a circular detector around the body at precisely the same time. PET detectors have much higher sensitivity than SPECT cameras because they do not require a collimator. As in SPECT, PET cameras use scintillating crystals and photomultiplier tubes. PET systems have been combined with CT and magnetic resonance imaging (MRI) systems to simultaneously display PET metabolic images and the corresponding anatomic information.

Detection of myocardial ischemia is the most common indication for performing myocardial perfusion imaging. Either SPECT or PET can be used for this purpose, which is based on assessments of LV myocardial uptake of the radioisotope at rest and after stress. Myocardial uptake is reduced after stress in myocardial regions where significant coronary artery stenosis is present. ^{99m}Tc is the radioisotope most commonly used for this purpose. It must be injected when peak heart rate is reached, and the patient must continue exercising (or the pharmacologic stress must be continued) for at least 1 minute afterward to allow sufficient time for the radioisotope to circulate through the myocardium. The images are displayed in three LV orientations (short-axis, horizontal long-axis, and vertical long-axis) for proper LV wall-segment analysis. The stress images are exhibited directly above the corresponding rest images so that normal myocardium can be differentiated from ischemic myocardium (Fig. 2.11).

PET scanners have inherently less attenuation and higher resolution than those used in SPECT, making PET the more desirable modality.[82] Pharmacologic stressors are usually used in PET myocardial perfusion tests because of the very short half-life of PET radioisotopes. The sensitivity and specificity of SPECT for detection of obstructive CAD are 91% and 72%, respectively; use of PET improves the specificity to 90%.[82] Normal findings on SPECT imply that the probability of experiencing a cardiac event is less than 1% per year, and a normal result on rubidium 82 (^{82}Rb) PET indicates a probability of less than 0.4% per year.

For viability assessment with SPECT imaging, ^{201}Tl is used more frequently, taking advantage of this isotope's long half-life (73 hours). Thallium uptake is dependent on several physiologic factors, including blood flow and sarcolemmal intercellular integrity. The time required for uptake is short in normal myocardium, but 24 hours may be needed in hibernating myocardium that still has metabolic activity. Patients are injected with thallium radioisotope and imaged the same day for baseline studies. After 24 hours, new images are obtained without any further injection. The baseline images and 24-hour images are compared. Defects that are present at baseline but filled in at 24 hours represent viability (Fig. 2.12). Technetium radioisotopes also can be used under different protocols for the evaluation of viable myocardium.

PET imaging is more sensitive than SPECT, and it is considered by many experts to be the gold standard for assessment of viability. PET has the ability to identify the presence of preserved metabolic activity in areas of decreased perfusion when 18-fluorodeoxyglucose (FDG) is used. PET imaging uses both FDG and either rubidium or

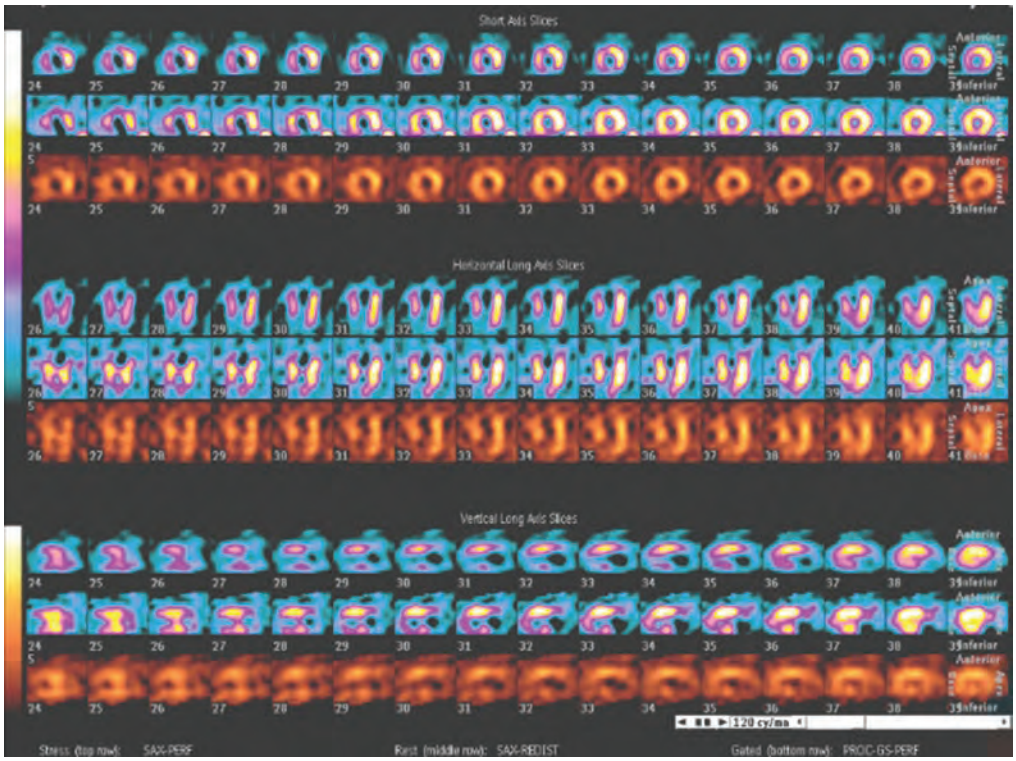

Fig. 2.12 Thallium rest-redistribution scan demonstrates hibernating myocardium involving the apical-basal anteroseptum, midbasal inferior, midbasal inferoseptum, and midbasal inferolateral wall segments. There is infarction of the apex, inferoapical, and apical-lateral wall segments.

ammonia radioisotopes for quantification of energy utilization by the myocardium and for evaluation of patterns of blood flow. Areas with reduced blood flow and reduced FDG uptake are considered to represent scar and infarction. Areas with reduced blood flow and normal FDG uptake are considered viable.[83] A metaanalysis of more than 750 patients demonstrated a sensitivity of 92% and a specificity of 63% for regional functional recovery with this method; the positive and negative predictive values were 74% and 87%, respectively.[84]

Nuclear scintigraphic methods, including both SPECT and PET myocardial perfusion imaging, can also be used to evaluate global and segmental LV systolic function. This is achieved by implementing ECG gating during data acquisition. Most often, eight frames or phases are acquired per cardiac cycle. Gated images can be acquired both at rest and after stress. However, rest images typically involve a lower radiation dose, so the images may be noisy; for this reason, most institutions perform gated imaging on the post-stress images. Accurate LV systolic analysis is limited with this technique in the circumstance of stress-induced ischemia, in which myocardial stunning can transiently reduce the LVEF. Another limitation of ECG-gated SPECT or PET is arrhythmias, specifically frequent premature ventricular contractions or atrial fibrillation. Assessment of LV function also may be inaccurate in patients with extensive myocardial infarction: Because there is absence of isotope in the scar regions, the endocardial border cannot be defined.

An alternative technique is gated blood pool scanning (also known as multiple-gated acquisition, or MUGA). In this technique, the cardiac blood pool is imaged with high resolution during the cardiac cycle. Ventricular function and various temporal parameters can be measured.[85] There is good correlation between echocardiography and MUGA for the evaluation of LVEF, and in fact, MUGA has demonstrated better intraobserver and interobserver reproducibility compared with echocardiography.[86] Nuclear imaging can also be used for assessment of LV diastolic function, but it is much less useful than echocardiography for that purpose. At least 16 phases of the cardiac cycle need to be acquired to evaluate diastolic dysfunction using SPECT. The two main parameters that can be measured by SPECT are LV peak filling rate and time to peak filling rate.

Myocardial infarction causes denervation of the scar, and subsequent interruption of sympathetic nerves induces denervation of adjacent viable myocardium.[87,88] Sympathetic nerves are very sensitive to ischemia and usually become dysfunctional after repeated episodes of ischemia that do not result in irreversible myocyte injury.[89,90] Matsunari and associates[91] demonstrated that the area of denervation is larger than the area of scar and corresponds to the area at risk for ischemia. Additionally, Bulow and coworkers[92] showed that denervation of myocytes can occur in the absence of previous infarction. Myocyte sympathetic innervation can be measured by PET using carbon 11 (^{11}C)-labeled hydroxyephedrine (HED). This is compared with PET resting perfusion images to determine the area of the scar. Areas of normal resting perfusion and reduced HED retention indicate viable myocardium.

SPECT imaging of myocardial uptake of iodine 123 (^{123}I)-labeled metaiodobenzylguanidine (*m*IBG), which is an analog of the sympathetic neurotransmitter norepinephrine, provides an assessment of β-receptor density. Reduced ^{123}I-*m*IBG uptake is associated with adverse outcomes in patients with heart failure and has been proposed as a marker of response to treatment.[93]

Cardiac Computed Tomography

CCT has grown significantly in clinical use since the advent, in the early 2000s, of multidetector CT (MDCT) scanners with submillimeter resolution that allow evaluation of the coronary anatomy. The x-ray tube produces beams that traverse the patient and are received by a detector array on the opposite side of the scanner. The tube and detector arrays are coupled to each other and rotate around the patient at a velocity of 250 to 500 microseconds per rotation. In 1999, the first MDCT scanner used for coronary imaging had four rows of

detectors and a scanning coverage of 2 cm per rotation. Breath-holds on the order of 10 to 20 seconds were required to cover the entire heart. Artifacts produced by the patient's respiration and heart rate variability rendered many studies nondiagnostic for the assessment of coronary stenosis. With today's advanced technology, 256-slice systems are standard, and 320-slice systems with 16 cm of coverage are able to capture the entire heart in one heartbeat and rotation.

CCT uses ionizing radiation for the production of images. Concern about excessive medical radiation exposure has been raised. Although several techniques, such as prospective ECG-gated acquisition, may be implemented to reduce the radiation dose,[94–96] a risk-benefit assessment must be done for the selection of patients who have appropriate indications for CCT.

Coronary angiography is currently one of the most common indications for performing CCT. The patient's heart rate must be lowered to less than 65 beats/minute to achieve adequate results when imaging the coronary arteries. This usually requires the administration of oral or intravenous beta-blockers. After the scan has been completed, images are reconstructed at various points of the cardiac cycle and analyzed on a computer workstation. Cardiac CT angiography (CCTA) has been well studied for the diagnosis of CAD in patients without known ischemic heart disease, demonstrating a sensitivity of 94% and a negative predictive value of 99%.[97] It is being increasingly employed to exclude obstructive CAD before valve surgery in patients with low-to-intermediate pretest probability to avoid invasive testing. In one study of CCTA for this purpose, researchers performed conventional coronary angiography and 64-slice MDCT in 50 patients (mean age, 54 y) who were about to undergo valve replacement for AR. CCTA demonstrated a sensitivity of 100%, a specificity of 95%, and a negative predictive value of 100%. Additionally, it was determined that use of CCTA could have allowed 70% of the patients to avoid invasive catheterization.[98] Two further studies used preoperative 16- and 64-slice CCTA in patients with AS. The mean ages of the patients were 68 and 70 years, respectively. In each study, both the sensitivity and the negative predictive value were 100% for detection of significant stenosis.[99,100] These studies showed that preoperative coronary evaluation with CCTA is safe and accurate. It is important that only patients with no known CAD or those with low-to-intermediate risk be referred for CCTA. In general, patients with degenerative AS are older and have greater risk for CAD. Patients who undergo valve surgery for MR because of MV prolapse are usually younger and are excellent candidates for CCTA.

CT aortography is the imaging modality of choice for evaluation of aortic pathologies such as aortic aneurysms and nonemergency dissections. Imaging protocols used for evaluation of the aorta are similar to those used for CCTA. It is important to have the scan gated to the patient's ECG because the ascending aorta moves significantly during the cardiac cycle. Nongated scans have inherent motion artifacts that can be confused with a dissection. Use of prospective ECG gating also minimizes radiation exposure. Visualization of the aortic root and coronary arteries is crucial because ascending aortic dissections can involve the ostia of the coronary arteries.

Once the images are acquired by specialized CT workstations, the aorta is evaluated and measured. The aorta is lined up in multiple orthogonal views to measure the true short axis throughout the length of the aorta. The excellent spatial and contrast resolution of this modality is useful for the evaluation of dissection. Entry points of dissection, intimal flap location, false lumen, extension into branch arteries, and the abdominal aortic circulation are easily visualized.

Although echocardiography is the gold standard for imaging valvular disease, advanced imaging with CCT or CMR may be required if TTE and TEE are technically difficult or if there are discrepancies in the findings. CMR offers more functional data than CCT, but CCT may be used if further anatomic information about a valve is required. For evaluating prosthetic valves, CCT is usually superior to CMR because of metallic artifact from the valve, which is visualized on CMR (see Chapter 21).

Valvular calcification is common in patients presenting with AS, particularly senile degenerative AS. CCT can accurately quantify AV calcification and can help assess the severity of AS. An AV calcium score of 1100 or greater has 93% sensitivity and an 82% specificity for severe AS.[101] Additionally, contrast-enhanced CCT allows for excellent visualization of the AV morphology and accurately differentiates between bicuspid and tricuspid AVs[102] (Fig. 2.13). Aortic valve planimetry can also be performed. AV areas measured by CCT have been demonstrated to have a strong correlation with valve areas and transvalvular gradients obtained by echocardiography.[103–107]

CCT also can be used for the evaluation of AR. CCT can elucidate the potential mechanism of AR, including inadequate leaflet coaptation during diastole, leaflet prolapse, cusp perforation, and interposition of an intimal flap in cases of type A aortic dissection. Regurgitant orifice areas measured by CCT have an excellent correlation with AR severity parameters, including vena contracta width and the regurgitant jet/LVOT height ratio obtained by TTE.[108,109]

In patients with MS, ECG-gated, contrast-enhanced CCT can permit assessment of MV morphology in a manner analogous to echocardiography.[110,111] Calcium scoring of the MV is also possible but has lower reproducibility than for the AV.[112] The degree of MV calcification correlates significantly with the severity of MS seen on TTE.[113] MV areas obtained by planimetry also correlate significantly with MS data obtained by TTE.[114]

CCT can accurately diagnose MV prolapse by evaluating cine loops of the MV, and the exact scallops that are prolapsing can be identified. Severity of MR can be assessed by planimetry of the regurgitant orifice, which has been shown to correlate with TEE.[115] Additionally, the presence of calcification of the MV annulus and leaflets can help determine whether the valve can be repaired or needs to be replaced.

CCT can also be used to evaluate tricuspid and pulmonary valve (PV) pathologies. For evaluation of the PV, CCT may be superior to echocardiography; adequate visualization of the PV on echocardiography is usually difficult.

CCT is an excellent modality for the evaluation of PHVs. It has the ability to clearly depict the mechanical prosthesis and to detect any abnormality, including valve thrombosis. This is done by using retrospective scanning and acquiring the entire cardiac cycle to play cine loops and visualize the leaflets through systole and diastole. The mechanical valves that are used currently consist of two disks that open symmetrically (Fig. 2.14). In one study, the valve function of the two-disk prosthesis, including opening and closing angles, was evaluated by CCT and compared with findings from fluoroscopy and echocardiography. CCT correlated significantly with both echocardiographic imaging modalities for these valves.[116] The role of CT in the assessment of bioprosthetic valves is similar because the metallic artifacts often preclude adequate assessment by echocardiography.

CCT is excellent for the diagnosis of paravalvular abscesses. The abscesses appear as paravalvular fluid-filled collections on CCT and are imaged by acquiring a delayed scan approximately 1 minute after contrast is administered. The contrast agent is retained within the abscess even after it washes out of the circulation[117] (Fig. 2.15). A study comparing MDCT with intraoperative TEE for the detection of suspected infective endocarditis and abscesses demonstrated excellent correlation. CCT correctly identified 96% of patients with valvular vegetations and 100% of patients with abscess. Additionally, CCT performed better than TEE in the characterization of abscesses.[118]

CCT, with its excellent spatial and temporal resolution, can also facilitate an accurate assessment of LV function.[119–121] CCT uses actual 3D volumes to calculate LV systolic function. Retrospective scanning is used for functional analysis because the entire cardiac cycle (both systole and diastole) must be acquired. The raw data set is then reconstructed in cardiac phase intervals of 10%, from 0% (early systole) to 90% (late diastole), to derive functional information. Advanced computer workstations allow cine images to be reconstructed and displayed in multiple planes. Segmental wall motion analysis can also be performed using the 17-segment model recommended by the American

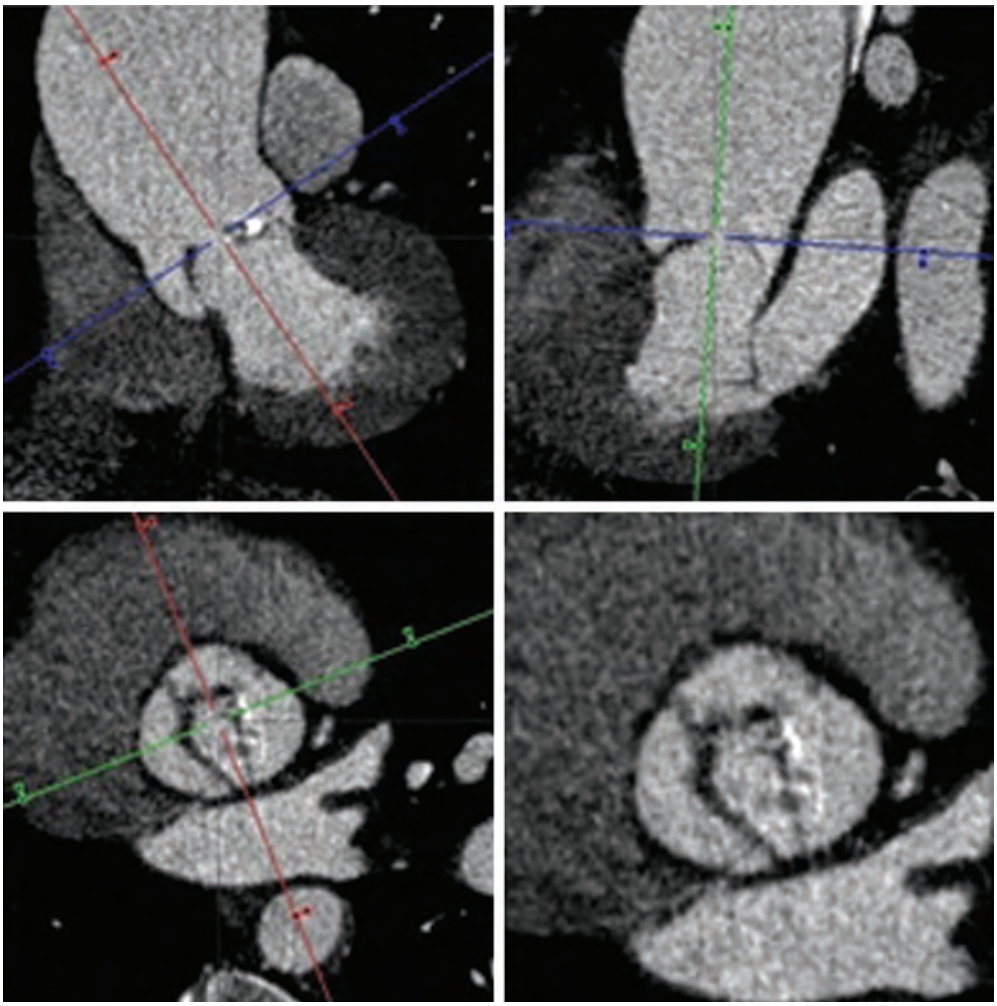

Fig. 2.13 Computed tomographic angiography. (A and B) Orthogonal radiographs display the ascending aortic aneurysm. (C and D) The bicuspid aortic valve (BAV) in short-axis view for evaluation of the valve area by planimetry.

College of Cardiology/American Heart Association.[122] The main limitation to using CCT for LV systolic function assessment is the radiation exposure. Because retrospective ECG gating is required to image the entire cardiac cycle, radiation exposure is relatively high. In comparison, CCT studies performed for other indications require prospective ECG gating and expose the patient to radiation during only 10% to 15% of the cardiac cycle. Therefore, to reduce radiation exposure, LV functional information is not acquired in most clinical scenarios.

Finally, CT is also the test of choice for the diagnosis of pulmonary embolism (Fig. 2.16). MDCT pulmonary angiography has a sensitivity of 83% and a specificity of 96% for the detection of acute pulmonary embolism. Inclusion of a lower-extremity CT venogram has been demonstrated to increase the sensitivity and specificity for pulmonary embolism diagnosis to 90% and 95%, respectively, but at the cost of a much higher level of ionizing radiation exposure.[123] CT pulmonary angiography has largely replaced nuclear ventilation/perfusion imaging (also known as lung scintigraphy or $\dot{V}/\dot{Q}$ scanning) for the diagnosis of pulmonary embolism. The latter has limited use in patients with chronic lung disease, and a high number of $\dot{V}/\dot{Q}$ scans (>72%) are found to have intermediate probability, indicating a 20% to 80% likelihood of pulmonary embolism. However, if CT pulmonary angiography cannot be performed because of increased creatinine level, $\dot{V}/\dot{Q}$ scanning may be used as an alternative (see Chapter 26).

CTA can evaluate signs of pulmonary hypertension by analyzing RV function, RV and RA volumes, RV hypertrophy, enlargement of proximal pulmonary vessels, and pruning of distal ones. ECG-gated CTA is required to assess RV function and volumes.

Cardiovascular Magnetic Resonance Imaging

CMR is a robust and versatile imaging modality. It has the ability to evaluate multiple elements of cardiac status, including function, morphology, flow, tissue characteristics, perfusion, angiography, and metabolism. It can do this because of its unique ability to distinguish morphology without the use of any ionizing radiation by taking advantage of the influence of magnetic fields on the abundance of hydrogen atoms in the human body. Multicontrast CMR uses the intrinsic molecular properties of tissues and three types of contrast: the longitudinal (T1) and transverse (T2) relaxation times in different tissues after an initial radiofrequency pulse, and the concentration of protons in different tissues in the form of water and macromolecules (ie, proton density). These parameters are measured under various pulse sequence protocols to provide information on the structural relationships and processes of interest (eg, tumors, changes in blood flow, metabolism of tissues).

T1-weighted images highlight lipid content; fat depositions appear bright or hyperintense. T2-weighted imaging is used for evaluation of edema[124] and fibrous tissue,[125] both of which appear hyperintense. In dynamic contrast-enhanced CMR, the paramagnetic contrast agent

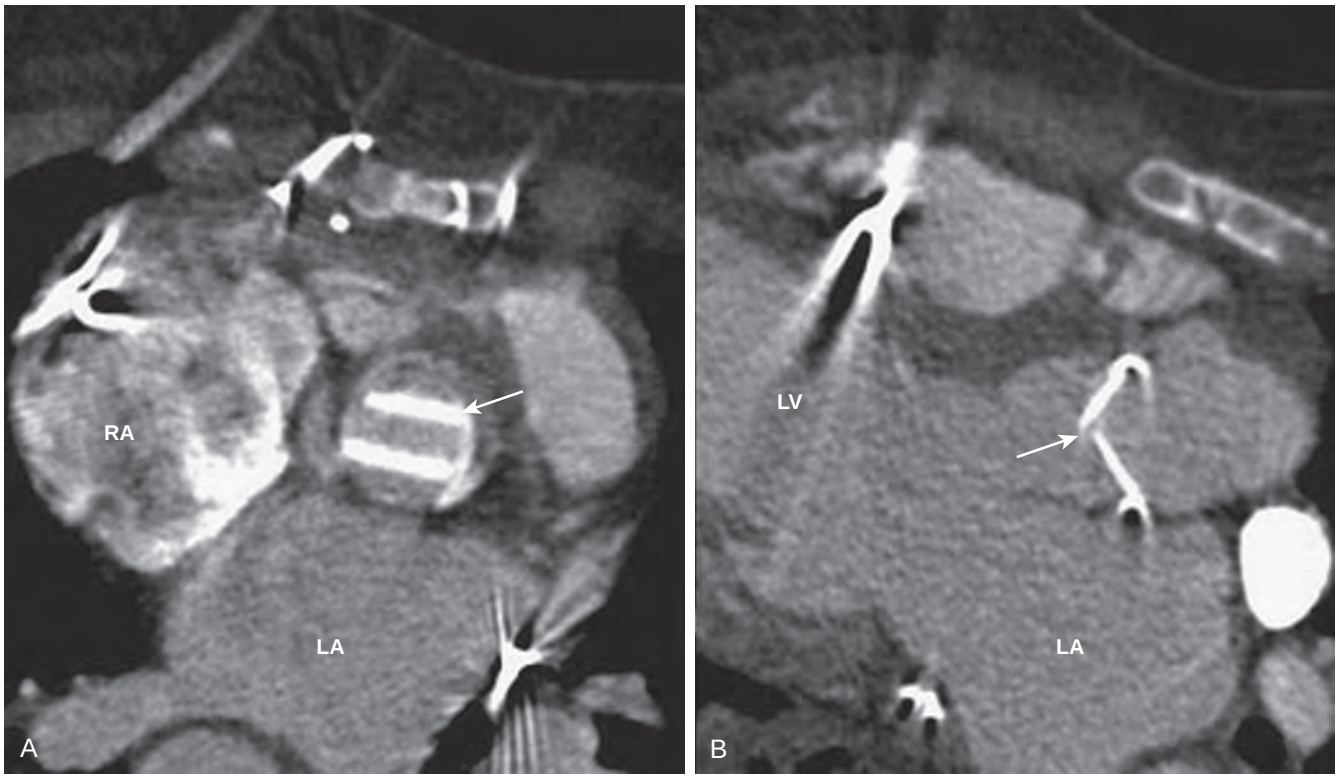

Fig. 2.14 Computed tomography angiography of an aortic mechanical valve *(arrow)* in short-axis view (A) and three-chamber view (B). *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium.

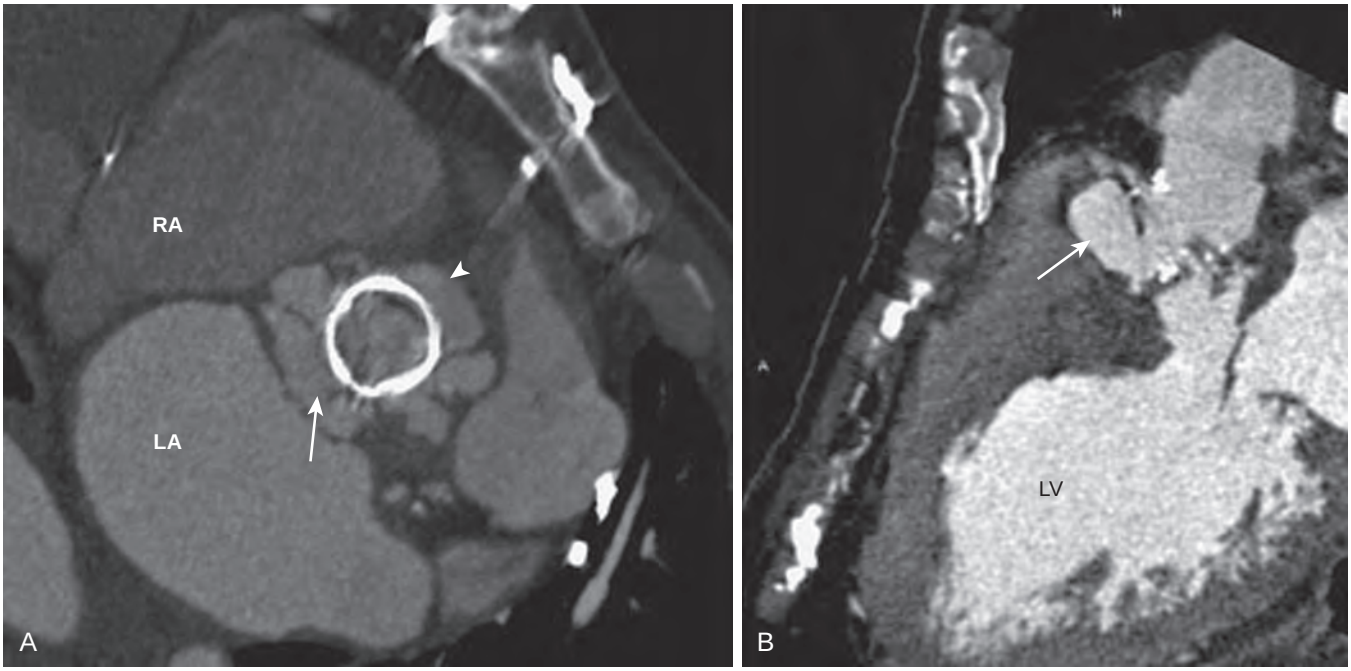

Fig. 2.15 Computed tomography angiography of a bioprosthetic aortic valve *(arrowhead)* with a paravalvular abscess *(arrow)* in the short-axis view (A) and the three-chamber view (B). *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium.

gadolinium is used to enhance the magnetization (T1) of protons in nearby water and create a stronger signal. Additionally, gadolinium contrast permeates through the intercellular space in necrotic or fibrotic myocardium, enabling myocardial scar detection on late gadolinium enhancement.

CMR is considered the gold standard for the quantitative assessment of biventricular volumes, ejection fraction, and mass while also offering excellent reproducibility.[126] CMR has good spatial and temporal resolution, allowing for cine imaging. Typically, a stack of 10 to 14 contiguous 2D slices is acquired and used for LV functional analysis.[127]

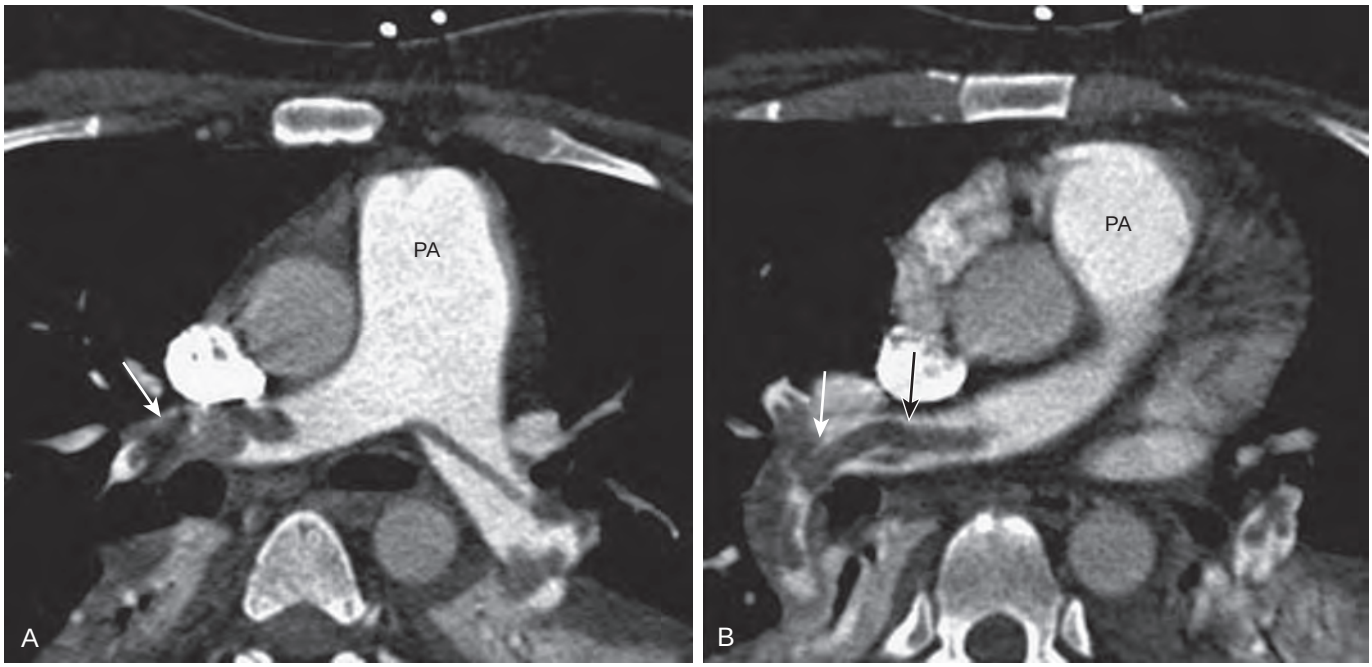

Fig. 2.16 A and B, Computed tomography angiography shows large pulmonary emboli *(arrows)* at two different axial scan levels. *PA,* Pulmonary artery.

The acquisition of each of these images usually requires a breath-hold of at least 10 to 20 seconds. At a computer workstation, the endocardial and epicardial contours of the LV can be traced manually in each short-axis slice at the points of maximal and minimal ventricular dimensions. The software then calculates the volume of the ventricular cavity per slice as the product of the area enclosed within the endocardial contour multiplied by slice thickness. The data are then combined to calculate LV volumes and LVEF. Additionally, cine images may be acquired in the four-, three-, and two-chamber views for LV segmental wall analysis (Fig. 2.17).

Velocity-encoded (phase-contrast) cine-CMR is capable of measuring intraventricular blood flow accurately and can quantify MV and pulmonary vein flows, which are hemodynamic parameters of diastolic function. In patients with amyloidosis, echocardiography and velocity-encoded cine imaging have been shown to correlate significantly in estimations of pulmonary vein systole/diastole ratios, LV filling E/A ratio, and E-wave deceleration time, all of which are diastolic functional indices.[128] In addition to measuring blood flow and velocity through the MV and pulmonary vein, CMR tagging is able to measure myocardial velocities of the walls and the MV, similar to strain rate and tissue Doppler measurements in echocardiography. CMR delayed-enhancement imaging also is used for diagnosis of diastolic dysfunction. The presence and severity of fibrosis on delayed-enhancement imaging correlate significantly with the severity of diastolic dysfunction.[129]

CMR can also be used for perfusion imaging by evaluating the first pass of gadolinium contrast through the myocardium. ECG-gated images are acquired using three LV short-axis slices (base, middle, and apical) and, possibly, a four-chamber image depending on the heart rate. As the contrast agent is injected, it is tracked through the right side of the heart and, subsequently, through the LV cavity and LV myocardium. The assessment of perfusion requires imaging over several consecutive heartbeats, during which time the contrast bolus completes its first pass through the myocardium. Imaging must be completed within a single breath-hold. For stress imaging, first-pass perfusion images are acquired at rest and then again during adenosine or dobutamine infusion. The same three- or four-slice positions are used for both rest and stress images for comparison. Perfusion defects appear as areas of delayed and/or decreased myocardial enhancement and are interpreted visually.

The accuracy of stress MRI perfusion has been validated in several trials. In one trial, which evaluated 147 consecutive women with chest pain or other symptoms suggestive of CAD, MRI perfusion was compared with invasive angiography. The stress perfusion MRI had a sensitivity, specificity, and accuracy of 84%, 88%, and 87%, respectively.[130] Another study comparing stress perfusion MRI with invasive angiography examined 102 subjects. Stress MRI demonstrated a sensitivity of 88% and a specificity of 82% for the diagnosis of significant flow-limiting stenosis.[131] A negative MRI perfusion stress test also confers significant prognostic information: Patients with a normal result have a 3-year event-free survival rate of 99.2%.[132]

CMR has emerged as the gold standard for evaluation of myocardial scarring. Late gadolinium enhancement is used as the marker of myocardial scarring. Gadolinium contrast is injected intravenously, and imaging is performed 5 to 10 minutes later. Gadolinium tends to accumulate extracellularly; however, in normal myocardium, there is insufficient space for gadolinium deposition. In the setting of chronic scar, the volume of gadolinium distribution increases because of an enlarged interstitium in the presence of extensive fibrosis.[133] Hence, normal or viable myocardium appears as nulled or dark, whereas scar appears bright (Fig. 2.18). The advantage of delayed-enhancement imaging is that it allows for assessment of the transmural extent of the scar. The images are analyzed visually, and the thickness of scarring compared with wall thickness is quantified by percentage (ie, none, 1–25%, 26–50%, 51–75%, or 75–100%). A wall segment is considered to be viable and has a high probability of functional recovery if the scar thickness is no more than 50% of the wall thickness.[134] Acquiring LV short-axis images identical to those used for functional assessment allows for side-by-side comparisons of function and delayed-enhancement evaluation.

CMR, like CCT, allows for excellent evaluation of valvular morphology, but it also has advantages over CCT in that blood-flow analysis is feasible and there is no ionizing radiation exposure. CMR allows for differentiation between bicuspid and tricuspid AVs using cine imaging. AS severity can be quantified by using phase-encoded imaging. Similarly to echocardiography, phase-encoded imaging

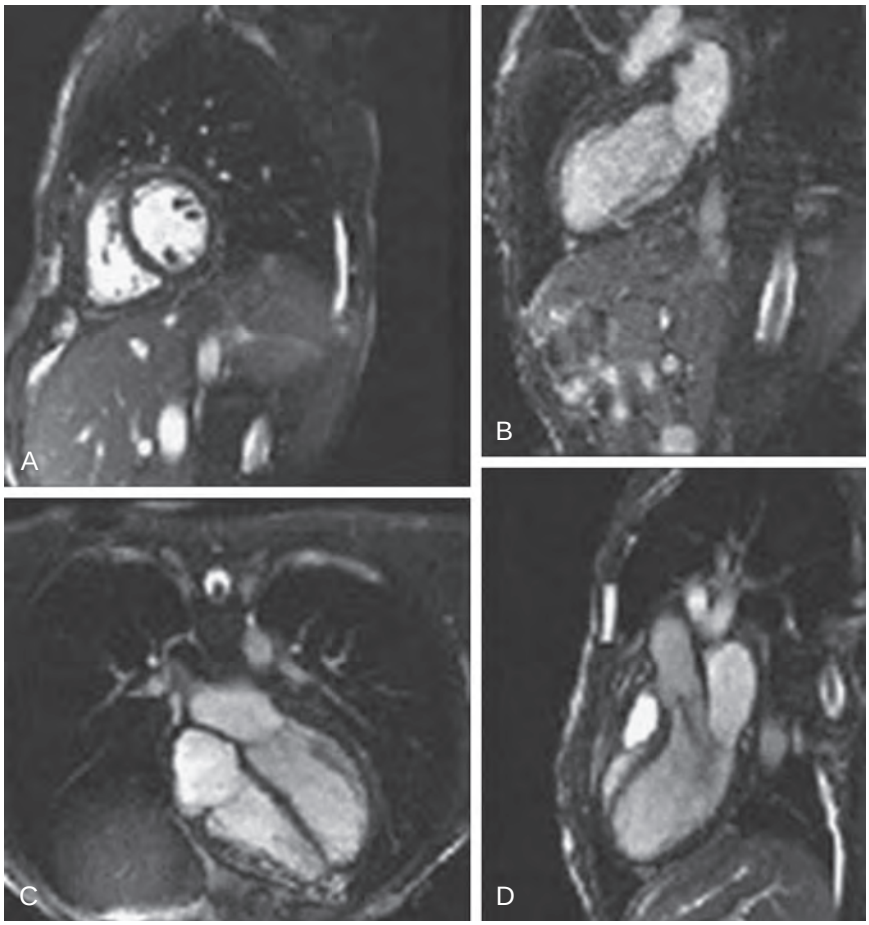

Fig. 2.17 Cardiac magnetic resonance demonstrates short-axis (A), two-chamber (B), four-chamber (C), and three-chamber (D) views.

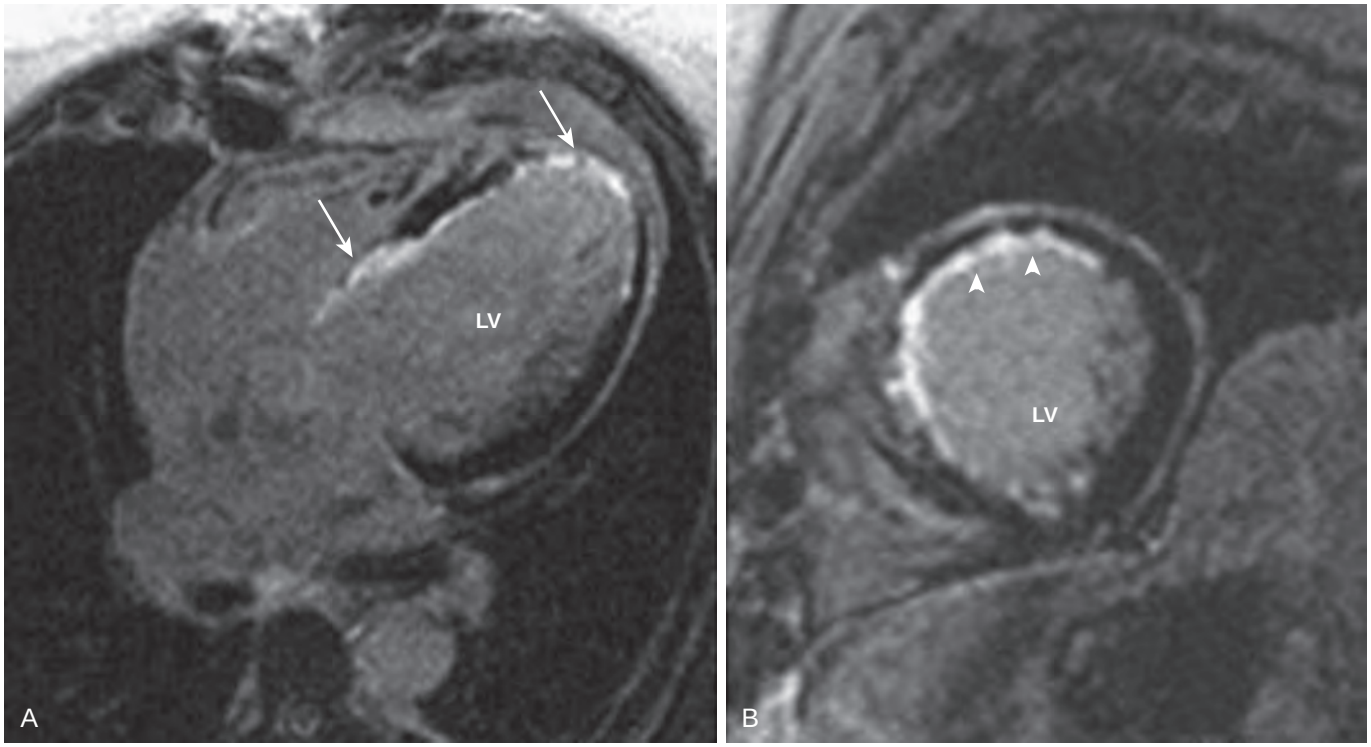

Fig. 2.18 Cardiac magnetic resonance demonstrates delayed-enhancement imaging. A, Four-chamber view with transmural scars *(arrows)* appearing bright in the septum and apex. B, Short-axis view showing partial scar with viability *(arrowheads)* of the anterior wall. *LV*, Left ventricle.

allows for the measurement of velocities through the AV, which can be used to derive mean and peak AV gradients. The effective AV area can also be obtained by measuring the LVOT area and using the continuity equation.[135] Alternatively, AV area can be derived by direct planimetry of the AV using cine images.[136]

CMR phase-encoded imaging can be used additionally for the evaluation of AR. Images are acquired just above the AV, and the velocity and volume of blood per heartbeat are measured in the forward and reverse directions. This allows for measurement of the exact amount of blood exiting the AV, as well as the amount of blood that regurgitates back through the valve. From this, the regurgitant volume and the regurgitant fraction can be determined.

CMR allows for excellent morphologic evaluation of the MV, TV, and PV, and functional assessments can be performed simultaneously with the use of phase-contrast imaging. PHV structure and gradients can also be assessed in the same manner.

CMR is also an excellent tool for the evaluation of aortic aneurysms and dissections. It has no ionizing radiation exposure and is therefore ideal for serial evaluations of the aorta. Similar to CCT, CMR is also ECG gated to compensate for cardiac movement. So-called black-blood imaging provides excellent morphologic information regarding the aortic wall, whereas bright- blood cine sequences provide an alternative anatomic assessment. Delayed-enhancement imaging can also be used to aid in the diagnosis of false lumen thrombosis. 3D images can be acquired and transferred to a workstation for evaluation and measurements, similar to CTA analysis.

CMR is the gold standard for RV functional analysis; however, 64-slice MDCT has been found to have excellent correlation with CMR for RV function and RV volume measurements.[137] Phase-contrast imaging of the pulmonary arteries can be used to evaluate the severity of pulmonary hypertension. This is performed by measuring the velocity of blood in the pulmonary arteries and the elasticity of these vessels.

CMR also can evaluate atherosclerosis[138] in large vessels and is capable of imaging morphology and distinguishing among the various elements of atherosclerotic plaque composition, including fibrous tissue, lipid core, calcification, and hemorrhage.[139]

Invasive Coronary Angiography

Conventional (i.e., invasive) coronary angiography remains the gold standard for evaluation of coronary anatomy and the anatomic extent and severity of CAD. No coronary revascularization procedure can be performed without prior invasive coronary angiography. Additionally, coronary angiography is required to exclude significant CAD in many patients undergoing noncoronary surgery. The indications for coronary angiography before a cardiac surgical procedure include age greater than 40 years for men, postmenopausal status for women, symptoms suggestive of coronary ischemia, LV systolic dysfunction, and the presence of one or more major cardiovascular risk factors.[33] Although CCTA is an alternative in these patients when the pretest probability of CAD is relatively low, conventional coronary angiography is often preferred because of its superior accuracy, its feasibility regardless of heart rate and rhythm, the need for a smaller amount of contrast agent, and noninterference from calcium present in the coronary arteries or the AV.

Vascular Imaging

Atherosclerosis is a generalized disorder and tends to involve multiple vascular beds concurrently. Accordingly, evaluation of noncoronary vascular beds is often required in patients undergoing CABG. Additionally, vascular imaging is required for the evaluation of various nonatherosclerotic disorders, such as deep vein thrombosis, peripheral venous insufficiency, or systemic embolism from an intracardiac mass or thrombus.

Vascular ultrasonography, CTA, and magnetic resonance angiography (MRA) are the primary modalities used for vascular imaging. Typically, ultrasonography is used as the initial screening test, particularly for vessels that are easily accessible to ultrasound imaging. CTA and MRA are used subsequently to further delineate the anatomic extent, severity, and other characteristics of the vascular lesions.

Carotid Artery Stenosis

Stroke is a severely debilitating disease, and extracranial atherosclerotic disease, specifically carotid artery stenosis, is the major cause. Atherosclerotic plaques most often form in the proximal internal carotid artery; however, the common carotid artery is also involved at times. In patients who have had a carotid endarterectomy, the distal common carotid artery is a frequent location for plaque formation. Usually stroke occurs as the first symptom of the disease, and often a carotid bruit is the only sign that can be detected on physical examination. The two main predictors for stroke are previous symptoms (ie, transient ischemic attack or recent stroke) and severity of the stenotic lesions.[140] For this reason, diagnosis is critical for the prevention of stroke. Several imaging modalities can be used for diagnosis. CTA has excellent spatial and contrast resolution for plaque detection and morphology. It is able to detect plaque anywhere in the carotid circulation, and it is used to define the vascular anatomy proximal and distal to a stenotic plaque.

CT, however, is not used as the initial screening test. Vascular ultrasound is easily accessible and can be brought to the patient's bedside. It is inexpensive, risk free, and excellent for the evaluation of carotid anatomy and flow dynamics. B-mode ultrasound is used for the anatomic definition of the arteries; the severity of plaques is evaluated by Doppler ultrasound, which measures the velocity and pressure gradients across lesions. Doppler imaging has limitations, however. It can give false measurements, and anything that decreases the velocity of the blood from the heart to the carotid arteries can interfere with accurate estimation of carotid stenosis. Most commonly, severe LV dysfunction, valvular heart disease, and aortic disease are the problems. Highly calcified plaques also may cause an ultrasound artifact that can interfere with accurate assessment.

MRA is another tool for carotid artery assessment. It is more expensive than the other modalities but is relatively safe and provides detailed information on the anatomy and plaque morphology. Black-blood imaging is a magnetic resonance sequence in which blood appears black and vessel walls are enhanced to highlight and define plaque morphology. Angiography can be performed without gadolinium contrast by using a time-of-flight sequence, which provides high-intensity signals for flowing blood. Additionally, phase contrast imaging can provide information on blood flow velocity pressure across stenotic lesions. In general, CT and MRI are used only in cases in which vascular ultrasonography is limited or the patient requires carotid endarterectomy for carotid artery stenosis.

Renal Artery Stenosis

Renal artery stenosis (RAS) is one of the most common causes of secondary hypertension. It can result from atherosclerosis, fibromuscular dysplasia, or certain systemic disorders. Atherosclerosis is responsible for approximately 90% of all RAS cases.[141,142] Fibromuscular dysplasia is the most common cause in young and middle-aged women, and it is responsible for 10% of all cases. Atherosclerotic RAS is associated with risk factors similar to those for CAD. The clinical presentation can be related to renal or extrarenal complications. Renovascular hypertension induced by RAS can cause renal damage, renal atrophy, and increased creatinine levels. Extrarenal effects range from angina and myocardial infarction to hypertension-induced stroke and flash pulmonary edema.

The initial diagnostic tool is vascular ultrasonography. Renal artery anatomy and flow velocities can be accurately analyzed with the use of B-mode and Doppler ultrasound. Ultrasonography is also a good tool to monitor the renal artery after percutaneous or surgical intervention. Common limitations of ultrasonography for visualization of

renal arteries are patient obesity and gas in the gastrointestinal tract, which affect 15% to 20% of all studies. Additionally, mild stenosis and accessory renal arteries may be completely missed.

CTA of the renal arteries has the same advantages as in coronary evaluation. Data can be reconstructed and visualized on workstations that allow 2D analysis of the renal arteries in any desired plane. One of the main disadvantages is that patients with RAS often have abnormal renal function, in which case iodine contrast is contraindicated.

MRA is an excellent tool for the diagnosis of RAS. With multicontrast and contrast-enhanced magnetic resonance, the sensitivity and specificity for the diagnosis of RAS are 100% and 99%, respectively.[143–150] Anatomic and perfusion evaluations of the kidneys can be performed simultaneously.

Peripheral Arterial Disease

Peripheral arterial disease (PAD) simply means noncoronary atherosclerosis. However, cerebrovascular and renovascular diseases are generally considered separate entities, and the term *PAD* is usually reserved for lower extremity disease.

Because atherosclerosis is a systemic disease, PAD is highly prevalent in patients with CAD, and vice versa. A history of cigarette smoking has a particularly strong association with PAD, conferring a two to three times greater risk for PAD than for CAD.[151] Eighty percent of all patients with PAD are active smokers or have smoked cigarettes in the past.[152,153] In the PARTNERS study, almost 7000 patients were evaluated for the prevalence of PAD using ankle-brachial index as the diagnostic modality. The study included subjects older than 70 years of age and subjects between the ages of 50 and 69 with either a history of tobacco smoking or diabetes. PAD was found in 29% of this population.[154] PAD most often is asymptomatic, with a relatively small percentage of patients experiencing intermittent claudication.[155–157]

Vascular ultrasound is typically the first modality used once PAD has been diagnosed or suspected clinically. It has very high sensitivity and specificity (90% and 95%, respectively) for detection of greater than 50% stenosis from the iliac artery to the popliteal artery.

CTA and MRA are the preferred modalities when percutaneous or surgical intervention is planned. CTA, because of its excellent spatial resolution, has a sensitivity greater than 92.9% and a specificity greater than 96.2% for detection of obstructions greater than 50%.[158,159] MRA also is accurate for the detection of PAD (Fig. 2.19). Its sensitivity and specificity are between 90% and 100% for detection of greater than 50% stenosis when compared with conventional angiography.[160] Compared with CTA, MRA demonstrates greater interobserver agreement.[161,162]

Peripheral Venous Thrombosis and Venous Insufficiency

Venous thromboembolism is a life-threatening complication that commonly occurs in patients undergoing cardiac and major noncardiac surgeries. In the United States, 2.5 million cases of deep vein thrombosis (DVT) occur annually, and it is estimated that approximately 25% of all untreated DVTs embolize and cause pulmonary embolism. Conversely, almost 80% of the cases of pulmonary embolism result from lower extremity DVTs. Vascular ultrasonography is the imaging modality of choice for the diagnosis of DVT. Its sensitivity and specificity for the detection of proximal lower extremity DVTs are 90.6% and 94.6%, respectively.[138,163] MDCT, which is the test of choice for diagnosis of pulmonary embolism, can also be used to perform a lower extremity CT venogram. Although this use enhances the diagnostic accuracy, it is accompanied by a much higher level of exposure to ionizing radiation[123] (see Chapter 26).

Chronic venous insufficiency occurs more often with increasing age and also has a greater incidence in women than in men. Common clinical symptoms include limb pain, swelling, stasis skin changes, itching, restless legs, nocturnal leg cramps, and ulceration. Most cases of deep venous disease have either a nonthrombotic or a postthrombotic cause. Both types can involve reflux, obstruction, or both.

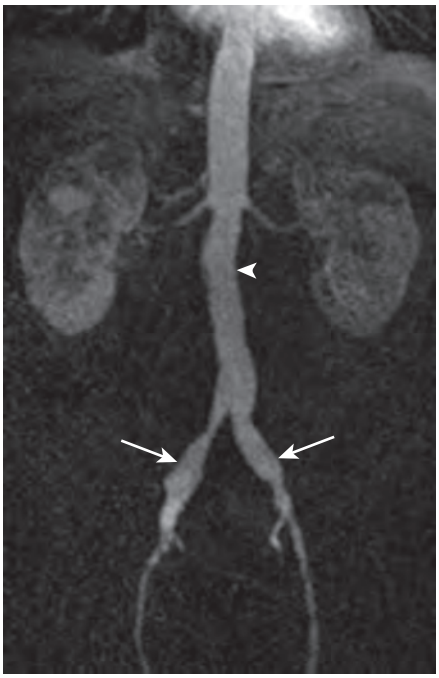

Fig. 2.19 Magnetic resonance angiography demonstrates the abdominal aorta *(arrowhead)* and common iliac arteries *(arrows)* with severe atherosclerosis.

Vascular inflammation, occurring most notably by way of several cytokine mechanisms, causes tissue damage and results in chronic venous insufficiency.[164] Vascular ultrasound is commonly used to diagnose venous insufficiency in the lower limbs, and it can accurately detect the site and severity of venous reflux, incompetent venous perforators, and obstructive changes resulting from previous DVT.

Summary

At least some form of cardiac imaging is essential at almost every step in the management of patients undergoing cardiac surgery. Echocardiography, because of its unmatched attributes, remains the preferred modality for this purpose. Invasive coronary angiography, nuclear scintigraphy, CCT, and CMR are other excellent modalities that are employed for specific clinical indications or when the information obtained from echocardiography is insufficient or equivocal. It is important for anesthesiologists to understand the advantages and limitations of all these imaging modalities and to use them to complement one another. For the overall benefit of the patient, the clinician must take into account the accuracy, cost, and time required for each modality, as well as potential radiation exposures (the long-term effects of which are still not clearly understood).

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3

Cardiac Catheterization Laboratory: Diagnostic and Therapeutic Procedures in the Adult Patient

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KEY POINTS

1. The cardiac catheterization laboratory has evolved from a purely diagnostic facility to a therapeutic one in which many facets of cardiovascular disease can be effectively modified or treated. Despite improvements in equipment, the quality of the procedure depends on well-trained and experienced physicians with proper certification, adequate procedural volume, and personnel committed to the continuous quality improvement process.
2. Guidelines for diagnostic cardiac catheterization have established indications, contraindications, and criteria to identify high-risk patients. Careful evaluation of the patient before the procedure is critical to minimize risks.
3. Interventional cardiology began in the late 1970s as balloon angioplasty, with a success rate of 80% and emergent coronary artery bypass graft surgery (CABG) rates of 3% to 5%. Although current success rates exceed 95%, with CABG rates of less than 1%, failed percutaneous coronary intervention (PCI) presents a challenge for the anesthesiologist because of hemodynamic problems, concomitant medications, and the underlying cardiac disease.
4. Since the introduction of drug-eluting stents (DESs), acute closure due to coronary dissection has diminished significantly, and restenosis rates have fallen precipitously.
5. The first-generation DESs (Cypher, Cordis, Miami Lakes, FL, and Taxus, Boston Scientific, Marlborough, MA) were extremely effective at reducing in-stent restenosis when compared with bare metal stents (BMSs). However, DESs have demonstrated higher rates of late stent thrombosis (LST), especially in the setting of premature discontinuation of dual antiplatelet therapy. Second-generation DESs (Xience, Abbott Vascular, Abbott Park, IL, and Resolute, Medtronic, Minneapolis, MN) have LST rates comparable to those of BMSs and therefore are the preferred stent type.
6. As a treatment strategy for patients with acute myocardial infarction, primary PCI is preferred to the administration of thrombolytic therapy because of its higher rates of infarct artery patency and TIMI grade 3 flow and lower rates of recurrent ischemia, reinfarction, intracranial hemorrhage, and death.
7. In the United States, increasing numbers of diagnostic coronary angiograms and PCIs are performed from a transradial approach because of lower vascular complication rates and patient preference for this approach compared with the more traditional transfemoral approach.
8. In multivessel coronary artery disease, an angiographic SYNTAX score should be calculated to assist with decision making regarding percutaneous versus surgical revascularization. A multidisciplinary heart team meeting (including a cardiologist, a cardiovascular surgeon, and, occasionally, an anesthesiologist) should then convene to discuss and optimize patient care by providing an individualized treatment recommendation.
9. Extensive thrombus, heavy calcification, degenerated saphenous vein graft, and chronic total occlusion present specific challenges in PCI. Various specialty devices have been developed to address these problems and have had varying degrees of success.
10. Acute thrombotic PCI complications can usually be overcome with more aggressive antithrombotic and antiplatelet pharmacotherapy. These medications can complicate the management of an unstable patient who requires transfer for bailout CABG. Appropriate understanding of the pharmacokinetics is essential for the cardiac anesthesiologist.
11. The reach of the interventional cardiologist has extended beyond coronary vessels to include closure of congenital defects and percutaneous treatment of valvular disease. These complex procedures are more likely to require general anesthesia but also can be effectively managed with monitored anesthesia care or regional anesthesia techniques.

The cardiac catheterization laboratory (CCL) began as a diagnostic unit. In the 1980s, percutaneous transluminal coronary angioplasty (PTCA) started the gradual shift to therapeutic procedures. Concomitantly, noninvasive modalities of echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) improved, and in some cases obviated, the need for diagnostic catheterization studies. Some experts predicted the imminent demise of diagnostic cardiac catheterization studies.[1,2] The promise of PTCA led to various atherectomy and aspiration devices and stents, with or without drug elution. The evolution of the CCL has continued, with many laboratories commonly performing procedures for the diagnosis and treatment of peripheral and cerebral vascular disease.[3] In addition, there has been an expansion of the treatment of noncoronary forms of cardiac disease in the CCL. Closure devices for patent foramen ovale (PFO), atrial septal defect (ASD), and ventricular septal defect (VSD) are emerging as alternatives to cardiac surgery. Many high-risk patients with valvular disease are now being treated with percutaneous valve repair and replacement, decreasing the incidence of balloon valvuloplasty. A variety of devices for circulatory support are available for implantation by percutaneous methods. To accommodate these new procedures, hybrid laboratories have been created to allow a team of cardiologists, cardiac surgeons, and anesthesiologists to safely perform these new percutaneous techniques (see Chapter 27).

The first cardiac catheterization was performed in 1929 by Dr. Werner Forssman, a surgical resident in the Auguste Viktoria Hospital at Eberswald, near Berlin, in an attempt to identify a safer route to administer epinephrine directly into the heart during intraoperative cardiac arrests. Forssmann asked a colleague to place a catheter in his arm. The catheter was successfully passed to his axilla, at which time Forssmann, under radioscopic guidance and using a mirror, advanced the catheter into his own right atrium (RA). Forssmann subsequently practiced in a small town in the Rhine Valley, but eventually he shared the Nobel Prize in 1956 for this procedure.[4]

The world quickly acknowledged Forssmann's accomplishments[5] with right-sided heart catheterization (RHC); in 1930, Klein[5a] employed RHC to measure cardiac output (CO) using the Fick method. In 1941, André Cournand published his work on RHC in the *Proceedings of the Society of Experimental Biology and Medicine*.[5b] Dexter and colleagues first reported cardiac catheterization in the pediatric population in 1947, and they were the first to document correlation between the pulmonary capillary wedge pressure (PCWP) and left atrial pressure (LAP).[5c] Zimmerman[5d] and Limon-Lason and Bouchard[5e] first performed arterial retrograde heart catheterization in 1950, and Seldinger[5f] developed his percutaneous approach in 1953. Ross[6] and Cope developed transseptal catheterization in 1959. The first coronary angiogram was inadvertently performed by Mason Sones in October 1958. While performing angiography of the aorta, the catheter moved during placement of the x-ray equipment, and Dr. Sones injected 50 mL of contrast into the patient's right coronary artery (RCA). Expecting cardiac arrest from this amount of contrast and with no external defibrillator available, Sones jumped to his feet and grabbed a scalpel to perform a thoracotomy. Fortunately, asystole lasted only 5 seconds, the patient awoke perplexed by the commotion, and this incident led to the birth of selective coronary angiography.[7]

Diagnostic catheterization led to interventional therapy in 1977, when Andreas Gruentzig performed the first PTCA.[6a] Refinements in both diagnostic and interventional equipment occurred over the next 15 to 20 years, but the focus remained on coronary artery disease (CAD). More recently, cardiologists have expanded into the diagnosis and treatment of peripheral vascular disease and treatment of structural heart disease. Currently, several transcatheter heart valves have been approved by the US Food and Drug Administration (FDA) and are available for the treatment of aortic stenosis. Transapically inserted heart valves are being developed for the treatment of mitral valve (MV) disease and percutaneously deliverable clips for mitral regurgitation (MR).

Hybrid coronary artery bypass procedures are performed in some institutions, with internal mammary artery grafting to the left anterior descending (LAD) coronary artery via a limited incision, with or without robotic guidance, and with percutaneous treatment of other vessels.[8] Many newer CCLs feature access, ventilation, and lighting designed for these multidisciplinary procedures. Because anesthesiologists will work in these suites, it seems intuitive that they should participate in their design.

This brief historical background serves as an introduction to the discussion of diagnostic and therapeutic procedures in the adult CCL.[9] The reader must realize the dynamic nature of this field. In the past, up to 5% of percutaneous coronary interventions (PCIs) failed, but most centers now report procedural failure rates of less than 1%. Simultaneously, the impact on the anesthesiologist has changed. The high complication rates of years past required holding an operating room (OR) open for all PCIs, but complication rates are now so low that some procedures are performed at hospitals without on-site surgical backup. Despite the lower rate of adverse events, the anesthesiologist is occasionally confronted with a patient who is in need of emergent surgical revascularization. The anesthesiologist may find the information in this chapter useful in planning the preoperative management of these cardiac or noncardiac surgical procedures based on diagnostic information obtained in the CCL. When anesthesia is required for procedures in the hybrid laboratory or the CCL, this chapter will help the anesthesiologist, in collaboration with the cardiology and cardiac surgery team, to provide safe anesthesia care for these challenging patients.

Catheterization Laboratory Facilities: Radiation Safety and Image Acquisition

Room Setup, Design, and Equipment

The setup and design for the hybrid cardiac catheterization OR is covered separately in Chapter 27. This section reviews the importance of radiation safety to prevent the adverse effects of radiation, including dermal necrosis and cellular mutation, that lead to brain, skin, and thyroid cancers; birth defects; and infertility.[10] For the individual laboratory, the monitoring suite is separated from the x-ray imaging equipment by leaded glass and lead-lined walls. Voice communication from the central area is maintained to coordinate tasks performed centrally (eg, monitoring and recording data, determining the activated coagulation time [ACT]), thereby minimizing staff radiation exposure.[11] A representative CCL is shown in Fig. 3.1.

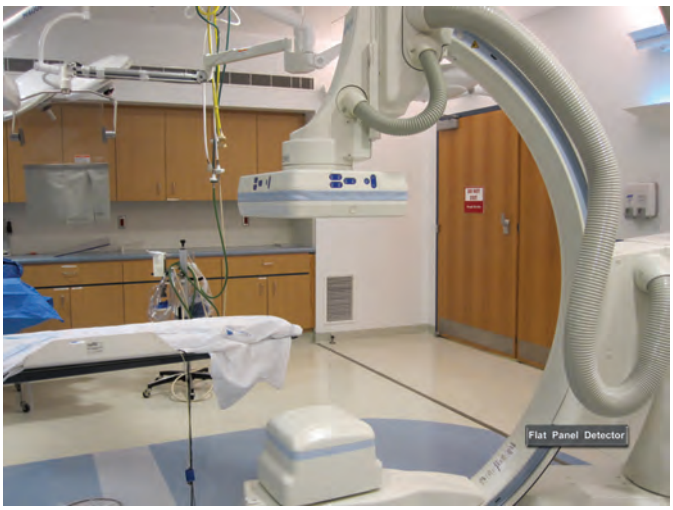


Fig. 3.1 A representative cardiac catheterization laboratory. The x-ray tube is located below the table, and the flat-panel detector is located above the table, both mounted on a C arm. Shielding, image monitors, and emergency equipment can also be seen.

Radiation Safety

Radiation safety must be considered in all aspects of the CCL, from room design to everyday practice.[12] Lead-lined walls, lead-glass partitions, and mobile lead shielding, including aprons and thyroid shields, are useful in limiting the daily exposure of personnel.

A thermoluminescent film badge, also known as a dosimeter, must be worn at all times by any persons exposed to the x-ray equipment, and levels must be monitored regularly. In the past, anesthesiologists responding to emergencies in the CCL were exposed to radiation only briefly and infrequently, if at all. With the requirement for the presence of an anesthesiologist in many of the newer multidisciplinary procedures, the inclusion of anesthesiologists in formal monitoring programs may be appropriate. Radiation levels should not exceed 5 rem (0.05 Sv) per calendar year, 1.25 rem (0.0125 Sv) per calendar quarter, or approximately 100 mrem (0.001 Sv) per week.[13] Operator and staff radiation exposures have been assessed for years, but only recently has the issue of radiation toxicity to the patient gained attention. With long PCI and electrophysiology procedures, radiation injury to the patient and the need to monitor dose delivery to the patient are now appreciated.[14] Contemporary equipment estimates and records patient radiation doses. Lead aprons and thyroid shields are mandatory for all personnel in the procedure suite. Although they are cumbersome, these shields protect the reproductive glands and about 80% of the active bone marrow.[12] Eye shielding also should be considered for those working in close proximity to the x-ray source.[15]

It is not within the scope of this chapter to cover all aspects of radiation safety in cardiovascular imaging. For a more complete review of this topic, the reader is referred to a consensus document published in 2014 by the American College of Cardiology (ACC), American Heart Association (AHA), Heart Rhythm Society, and Society for Cardiovascular Angiography and Interventions (SCAI).[16]

Nevertheless, several features of radiation safety require a brief review. The duration of the procedure increases the exposure. Cine imaging (ie, making a permanent recording) requires about 10 times the radiation exposure of fluoroscopy. Although newer equipment may narrow this ratio and provide a permanent recording of the fluoroscopic images, limiting cine imaging is a way to decrease exposure. Proximity to the x-ray tube, which is usually situated below the patient, is directly related to exposure. The bulk of the radiation exposure to medical personnel is the result of scattered x-rays coming from the patient. When working in an environment where x-rays are in use, clinicians should always remember a simple rule: The amount of radiation exposure is related to the square of the distance from the source. No body part should ever be placed in the imaging field when fluoroscopy or cine imaging is being performed. Finally, the cardiologist can decrease x-ray scatter, and thereby decrease personnel exposure, by placing the imaging equipment as close to the patient as possible.[17]

The anesthesiologist should recognize x-ray use in the CCL and take appropriate precautions. For multidisciplinary procedures, this requires some attention to the location of equipment and the use of portable shields. Most lead aprons have openings in the back and protect best when the wearer is facing the source of the x-rays. Emergent situations, such as when the anesthesiologist is asked to resuscitate a critically ill patient during a procedure, may require the cardiologist to use fluoroscopic imaging while the anesthesiologist is within feet of the x-ray tube or even straddling it. Aprons and thyroid shields are clearly necessary to protect the anesthesiologist while at the head of the patient, and a lead thickness of 0.5 mm will stop 96% of the x-ray beam scatter.[12] The use of x-rays can almost always be interrupted to protect personnel, although needed patient care may require the interruptions to be brief. A collaborative effort between the cardiologist and the anesthesiologist is necessary, and communication is essential. The goal of the anesthesiologist should be to treat the patient while protecting oneself and others from excessive radiation exposure.[16]

Filmless Imaging and Flat-Panel Technology

Essentially all modern laboratories use filmless or digital recording. Radiation is needed to generate an image, and recordings are made at various frequencies (frames per second). The best image quality for film is obtained with frame rates greater than 30 per second. Digital imaging decreases radiation exposure in the CCL by allowing for image acquisition at lower frame rates (ie, 15 frames/second) while still maintaining excellent image quality. Cost savings have been achieved by elimination of the need to purchase, process, and store film. Film imaging was an analog technique, and a single recording was made. Copies rarely were made because of the cost and degradation of image quality. If films were loaned, lost, or misplaced, the study could not be reviewed. With the current digital technologies, images are archived on a central server and can be viewed at remote workstations.[18] An unlimited number of copies can be made at low cost and with no loss of image quality.

The evolution of angiographic recording has extended beyond recording formats. Charged-couple device cameras and flat-panel detectors are now ubiquitous in modern laboratories.[19] X-rays are generated from below the patient by the x-ray tube, pass through the patient, and are captured by the detector. In this system, the x-rays are both acquired and digitally processed by the flat panel.[16] The flat panel is above the patient (analogous to the image intensifier). This current generation of imaging in the CCL delivers improved image quality because the dynamic range of the image (ie, the number of shades of gray) is improved. This type of system has the potential to decrease radiation exposure by providing immediate feedback to the x-ray generator. In laboratories designed for peripheral vascular work, including many of the hybrid ones, the flat panel above the patient can be quite large and may limit access to the patient's face.

Facility Caseload

All catheterization facilities must maintain appropriate patient volume to ensure competence. ACC/AHA guidelines previously recommended that a minimum of 300 adult diagnostic cases be performed to provide adequate care,[13] including a minimum of 200 PCIs.[20–22] However, a 2012 update set no diagnostic minimums and recommended at least 75 PCIs per year. If the individual physician's annual volume is less than 75 cases, a quality assurance committee should perform an annual review of 15% of cases (randomly chosen) to ensure continued quality.[13] Facilities performing PCIs without in-house surgical backup are becoming more prevalent.[23–25] National guidelines now support the performance of both elective and emergent PCI in centers without cardiac surgical capabilities, giving elective PCI a class IIb rating and primary PCI a class IIa rating.[25–27] Although emergent coronary artery bypass graft surgery (CABG) is infrequent in the stent era, a well-established agreement must be in place with an on-site surgical hospital to minimize treatment delays when emergent CABG is required.

Primary PCI for acute myocardial infarction (AMI) is the accepted standard treatment for patients who are in cardiogenic shock, those who have contraindications to thrombolytic therapy, and those who have not responded to thrombolytic therapy. It is the preferred therapy for patients who present late in the course of an infarction, and it is probably the optimal treatment for all myocardial infarctions (MIs), provided that it can be performed in a timely manner.[26–28]

Although minimum volumes are recommended, no regulatory controls currently exist. In a study of volume-outcome relationships published for New York state, a clear inverse relation was identified between CCL caseload and rates of procedural mortality and CABG.[29] In a nationwide study of Medicare patients, low-volume centers had a 30-day mortality rate of 4.2%, whereas in high-volume centers the mortality rate was 2.7%.[30] However, other reports suggest that activity level is an incomplete surrogate for quality. In other words, high-volume operators and hospitals are not necessarily of high quality, and low-volume operators and hospitals are not necessarily of low quality. Centers of excellence, based on physician and facility quality

and the spectrum of overall services provided, may well be the model for cardiovascular care in the future.[31]

Patient Selection for Catheterization

Indications for Cardiac Catheterization in the Adult Patient

Box 3.1 lists indications for cardiac catheterization. The major indication is for the detection of CAD; the remaining indications are focused on hemodynamic assessment to evaluate valvular heart disease, pulmonary hypertension, and cardiomyopathies.[32] With respect to CAD, approximately 20% of the adult population studied will be found to have normal coronary arteries.[13] This reflects limitations in the specificity of the clinical criteria and noninvasive tests used to select patients for catheterization (see Chapters 1 and 2). Despite continued improvements in noninvasive assessment, coronary angiography is currently considered the gold standard for diagnosing and defining the extent of CAD. With advances in MRI and multislice CT scanning, the next decade may well see a further evolution of the CCL to an interventional suite with fewer diagnostic responsibilities.[1]

Patient Evaluation Before Cardiac Catheterization

Diagnostic cardiac catheterization in the 21st century universally is considered an outpatient procedure except for the high-risk patient. Therefore, the precatheterization evaluation is essential for quality patient care. Evaluation before cardiac catheterization includes diagnostic tests that are necessary to identify high-risk patients. An electrocardiogram (ECG) must be obtained for all patients shortly before catheterization. Necessary laboratory studies before catheterization include an appropriate coagulation profile (prothrombin time [PT], partial thromboplastin time [PTT], and platelet count), hemoglobin, and hematocrit. Electrolytes are obtained together with baseline blood urea nitrogen and creatinine (Cr) values to assess renal function. Recent guidelines express a preference for estimation of the glomerular filtration rate (GFR) using accepted formulas, and many clinical laboratories now report this value routinely.[32a] Urinalysis and chest radiography may provide useful information but are no longer routinely obtained by all operators. Prior catheterization reports should be available. If the patient had prior PCI or CABG surgery, anatomic information concerning stent or bypass placement also must be available.

The precatheterization history is important to determine the risk profile for the patient, including previous exposure to contrast dye and the reaction to it, if any. If a true contrast reaction (eg, rash, breathing difficulties, angioedema) occurred with prior contrast exposure, premedication with glucocorticoids and diphenhydramine is required before the patient arrives at the CCL. Nonionic contrast dyes can be administered to patients with a history of anaphylactoid reactions to the ionic contrast dyes. Diabetes mellitus (DM), preexisting chronic kidney disease (CKD), and heart failure are widely accepted risk factors for contrast-induced nephropathy (CIN). A Cr level greater than 1.5 mg/dL, particularly in a patient with DM, or a GFR of less than 60 mL/min should prompt special precautions.[33] If the patient has stage IV CKD with a GFR of less than 30 mL/min, the study may need to be canceled or delayed. Nephrotoxicity is dependent on the amount of dye reaching the renal arteries and can be reduced by hydrating the patient before the procedure, avoiding high-osmolar contrast dyes and nephrotoxic medications (eg, nonsteroidal antiinflammatory drugs), limiting the amount of dye administered, and maintaining an interval of 72 hours between exposures if multiple studies are required.[34] These measures may reduce the risk of transient worsening of renal dysfunction and the need for permanent renal replacement therapy.[12] In patients at risk for nephrotoxicity, validated equations are used to calculate the maximal allowable contrast dose for any given procedure.[35]

A review of the noninvasive cardiac evaluation before cardiac catheterization allows the cardiologist to formulate objectives for the procedure. In patients with hypotension and severely impaired functional capacity on exercise stress testing, left main coronary artery (LM) lesions or high-grade proximal LAD stenoses should be suspected. Knowing the location of perfusion or wall-motion abnormalities in a particular coronary distribution, the cardiologist must specifically identify or exclude coronary lesions in these areas during the procedure. In patients with echocardiographic evidence of a left ventricular

BOX 3.1 INDICATIONS FOR DIAGNOSTIC CATHETERIZATION IN THE ADULT PATIENT

Coronary Artery Disease
Symptoms
Unstable angina
Postinfarction angina
Angina refractory to medications
Typical chest pain with negative diagnostic testing
History of sudden death

Diagnostic Testing
Strongly positive exercise tolerance test
Early positive, ischemia in ≥5 leads, hypotension, ischemia present for ≥6 min of recovery
Positive exercise testing after myocardial infarction
Strongly positive nuclear myocardial perfusion test
Increased lung uptake or ventricular dilation after stress
Large single or multiple areas of ischemic myocardium
Strongly positive stress echocardiographic study
Decrease in overall ejection fraction or ventricular dilation with stress
Large single area or multiple or large areas of new wall motion abnormalities

Valvular Disease
Symptoms
Aortic stenosis with syncope, chest pain, or congestive heart failure
Aortic insufficiency with progressive heart failure
Mitral insufficiency or stenosis with progressive congestive heart failure symptoms
Acute orthopnea/pulmonary edema after infarction with suspected acute mitral insufficiency

Diagnostic Testing
Progressive resting left ventricular dysfunction with regurgitant lesion
Decreasing left ventricular function and/or chamber dilation with exercise

Adult Congenital Heart Disease
Atrial Septal Defect
Age >50 y with evidence of coronary artery disease
Septum primum or sinus venosus defect

Ventricular Septal Defect
Catheterization for definition of coronary anatomy
Coarctation of the aorta
Detection of collaterals
Coronary arteriography if increased age and/or risk factors are present

Other
Acute myocardial infarction therapy—consider primary percutaneous coronary intervention
Mechanical complication after infarction
Malignant cardiac arrhythmias
Cardiac transplantation
Pretransplantation donor evaluation
Posttransplantation annual coronary artery graft rejection evaluation
Unexplained congestive heart failure
Research studies with institutional review board review and patient consent

(LV) thrombus or left-sided endocarditis, left ventriculography may not be performed.

Patient medications may need to be altered in preparation for a heart catheterization. On the morning of the catheterization, antianginal and antihypertensive medications are routinely continued, whereas diuretic therapy is withheld. Diabetic patients are scheduled early, if possible, because the procedure requires NPO status. No short-acting insulin is given, and half of the long-acting insulin dose is usually administered. Patients on oral anticoagulation should stop warfarin (Coumadin) for 48 to 72 hours before catheterization to target an international normalized ratio (INR) of 1.8 or less if femoral artery access is used. Radial artery access is considered an option without discontinuation of warfarin.[36] For patients who are managed with non–vitamin K antagonist novel oral anticoagulant (NOAC) therapy, the dose may need to be withheld for 24 to 48 hours depending on renal function and the bleeding risk of the procedure.[37,38] In patients who are anticoagulated because of mechanical prosthetic valves, the best management may be intravenous (IV) heparin before and after the procedure, when the warfarin effect is not therapeutic.[39] Low-molecular-weight heparins (LMWHs) are used in this setting, but this use is controversial. LMWHs vary in their duration of action, and their effect cannot be monitored through use of the activated PTT. Special dosing is required for certain patient groups including the elderly, those with an elevated body mass index, and those with CKD.[40] The differing pharmacokinetics need to be considered, particularly with regard to hemostasis at the vascular access site. IV heparin is routinely discontinued 1 to 2 hours before catheterization, except in patients with unstable angina. Therapy with aspirin or P2Y12 platelet inhibitors or both is almost always continued for patients with angina for those with prior CABG.[41]

Contraindications, High-Risk Patients, and Postcatheterization Care

Despite advances in facilities, equipment, techniques, and personnel, the precatheterization evaluation must identify those patients who are at increased risk for complications. In a modern facility with an experienced staff, the only absolute contraindication is refusal by a competent patient or an incompetent patient's inability to provide informed consent. Relative contraindications are listed in Box 3.2; the primary operator is responsible for this assessment.[13]

Box 3.3 lists criteria for identifying high-risk patients before catheterization. Procedural alterations may be based on this assessment, such as avoidance of crossing an aortic valve or performing ventriculography.[42] In any case, the determination as to whether a patient is a candidate for catheterization must be based on risk versus benefit for each individual patient.

With the increased emphasis on outpatient procedures in medicine today, outpatient diagnostic catheterization is becoming the standard of care for stable patients. Unstable and postinfarction patients are already hospitalized, and catheterization usually is performed before discharge. Planned PCI usually requires hospital admission; however, same-day discharge in carefully selected patients is gaining momentum because it appears to be safe, especially when radial artery access has been used.[43] Even when outpatient catheterization is planned, assessment of the patient after catheterization is required. Some patients, particularly those with LM CAD, critical aortic stenosis, uncontrolled hypertension, significant LV dysfunction with congestive heart failure, or significant postprocedural complications such as a large femoral access site hematoma, will require hospital admission.[13]

In addition to the high-risk cardiac patient, patients with renal insufficiency may require overnight hydration before and after catheterization. Patients on chronic anticoagulation with warfarin require measurement of their coagulation status and may require heparinization before and/or after the procedure. Day-of-procedure ambulation and discharge are planned for patients undergoing outpatient catheterization.[34] Radial artery catheterization is increasing in popularity and is associated with a reduction of vascular complications.[36,44] For a variety of reasons, the sheaths used for radial access are not suitable for long-term monitoring purposes and should be removed at the conclusion of the procedure. For patients undergoing catheterization via the percutaneous femoral approach, the use of smaller catheters (4 Fr) for the arterial puncture may hasten ambulation.[45] Alternatively, a variety of vascular closure devices are approved for use.[46] Vascular closure devices differ in the material that is used and are classified as active or passive approximators of the arteriotomy. The most commonly used device, Angio-Seal (St. Jude Medical, Plymouth, MN), uses an intraluminal anchor made of bioabsorbable material. However, it is recommended that the treated vessel not be used for repeat arterial access for up to 3 months, to permit absorption of the anchor and limit the risk for embolization. Protocols for early ambulation may permit the patient to be out of bed 2 to 4 hours after hemostasis, or even earlier if a closure device is used.[46]

BOX 3.2 RELATIVE CONTRAINDICATIONS TO DIAGNOSTIC CARDIAC CATHETERIZATION

1. Uncontrolled ventricular irritability: the risk for ventricular tachycardia/fibrillation during catheterization is increased if ventricular irritability is uncontrolled
2. Uncorrected hypokalemia or digitalis toxicity
3. Uncorrected hypertension: predisposes to myocardial ischemia and/or heart failure during angiography
4. Intercurrent febrile illness
5. Decompensated heart failure, especially acute pulmonary edema
6. Anticoagulation state; international normalized ratio (INR) >1.8, femoral approach
7. Severe allergy to radiographic contrast agent
8. Severe renal insufficiency and/or anuria, unless dialysis is planned to remove fluid and radiographic contrast load

Modified from Baim DS, Grossman W. *Cardiac Catheterization, Angiography, and Intervention* (6th ed.). Philadelphia: Lippincott Williams & Wilkins; 2000.

BOX 3.3 IDENTIFICATION OF THE HIGH-RISK PATIENT FOR CATHETERIZATION

Age
- Infant: <1 y old
- Elderly: >70 y old

Functional class
- Mortality ↑ 10-fold for class IV patients compared with I and II

Severity of coronary obstruction
- Mortality ↑ 10-fold for left main disease compared with one- or two-vessel disease

Valvular heart disease as an independent lesion
- Greater risk when associated with coronary artery disease

Left ventricular dysfunction
- Mortality ↑ 10-fold in patients with low ejection fraction (<30%)

Severe noncardiac disease
Renal insufficiency
Insulin-requiring diabetes
Advanced peripheral and cerebral vascular disease
Severe pulmonary insufficiency

Modified from Baim DS, Grossman W. *Cardiac Catheterization, Angiography, and Intervention* (6th ed.). Philadelphia: Lippincott Williams & Wilkins, 2000; from Mahrer PR, Young C, Magnusson PT. Efficacy and safety of outpatient cardiac catheterization. *Cathet Cardiovasc Diagn.* 1987;13:304.

Cardiac Catheterization Procedures

Whether the procedure is elective or emergent, diagnostic or interventional, coronary or peripheral, certain basic components are relatively constant in all circumstances. Variations depend on the specific situation and are discussed later in this chapter.

Patient Preparation

All patients receive a thorough explanation of the procedure, often including pamphlets and videos. A full explanation of the technique and potential risks minimizes patient anxiety and is similar to the preoperative anesthesia visit. It is important for the cardiologist to meet the patient before the study. This relaxes the patient while allowing the physician to become better acquainted with the patient, aiding in the decision-making process. Although some laboratories allow the patient to have a clear liquid breakfast up to 2 to 3 hours before the procedure, outpatients are routinely asked to have no oral intake for 8 hours before the procedure, except for oral medications.

Patients with previous allergic reactions to iodinated contrast agents require adequate prophylaxis.[44] Greenberger and colleagues[47] studied 857 patients who had a prior allergic reaction to contrast media. In this study, 50 mg of prednisone was administered 13 hours, 7 hours, and 1 hour before the procedure. Diphenhydramine (50 mg intramuscularly) also was administered 1 hour before the procedure. No severe anaphylactic reactions occurred, and the overall incidence of urticarial reactions in known high-risk patients was 10%. The use of nonionic contrast agents may further decrease reactions in patients with known contrast allergies.[48] The administration of histamine H_2 blockers (eg, 300 mg cimetidine) is less well studied.[48] For patients undergoing emergent cardiac catheterization who have known contrast allergies, 200 mg of hydrocortisone is administered intravenously immediately and repeated every 4 hours until the procedure is completed. Diphenhydramine (50 mg IV) is recommended 1 hour before the procedure.[48]

CIN is defined as an increase in serum Cr concentration of more than 0.5 mg/dL, or 25% above baseline level, within 48 hours.[34] Although it is infrequent, occurring in fewer than 5% of PCIs, when it does occur its impact on patient morbidity and mortality is significant.[49] Total contrast doses of less than 4 mL/kg are recommended for patients with normal renal function, and lower doses are recommended for those with preexisting renal dysfunction (Cr >1.5), particularly diabetic patients.[34] A study of more than 8000 patients undergoing PCI identified eight risk factors for CIN: hypotension, intraaortic balloon pump (IABP), congestive heart failure, CKD, DM, age older than 75 years, anemia, and contrast volume.[50] It is essential that the patient at high risk be identified and properly treated. In addition, renal function should be monitored for at least 48 hours in patients at high risk for CIN, particularly if surgery or other interventions are planned.

Several methods have been used to decrease renal toxicity from contrast agents. The two most important measures are minimizing contrast dose and providing adequate hydration, either with 0.9% saline at a rate of 1 mL/kg per hour for 12 hours before and after the procedure, if tolerated,[34] or with isotonic sodium bicarbonate. Currently, there are various protocols for the infusion of isotonic sodium bicarbonate, which can be prepared by combining 150 mL of $NaHCO_3$ with 850 mL of sterile H_2O.[51–54] Low-osmolar contrast agents are the standard of care, and despite initial interest in isoosmolar contrast agents, findings in later studies have been mixed.[55,56] *N*-Acetylcysteine (Mucomyst) showed initial promise, but extensive subsequent studies failed to show reductions in CIN, and it is not currently recommended.[56–58] Ultrafiltration dialysis has been beneficial in small studies.[58]

Patient Monitoring and Sedation

Standard limb leads with one chest lead are used for ECG monitoring during cardiac catheterization. One inferior and one anterior ECG lead are monitored during diagnostic catheterization. During an interventional procedure, two ECG leads are monitored in the same coronary artery distribution as the vessel undergoing PCI. Radiolucent ECG leads permit monitoring without interfering with angiographic data.

Sedation in the CCL, from preprocedural administration or from IV administration during the procedure, may lead to hypoventilation and hypoxemia. The administration of midazolam, 1 to 5 mg intravenously, with fentanyl, 25 to 100 μg, is common practice. For older patients, or if there is a risk of respiratory compromise, a dexmedetomidine infusion starting at 0.2 to 1 μg/kg per hour after a loading dose of 0.25 to 0.5 μg/kg per hour over 10 minutes can be helpful because it provides sedation and analgesia without affecting respirations. Institutional guidelines for conscious sedation typically govern these practices. Light to moderate sedation is beneficial to the patient, particularly for angiographic imaging and interventional procedures. Sedation is critical for patients who undergo a radial artery approach; conscious sedation has been shown to reduce the incidence of radial artery spasm, which, when severe, may force the operator to adopt a transfemoral approach to complete the procedure. Deep sedation, in addition to its widely recognized potential to cause respiratory difficulties, poses distinct problems in the CCL. Deep sedation often requires supplemental oxygen, which complicates the interpretation of oximetry data and may alter hemodynamics.

Sparse data exist regarding the effect of sedation on hemodynamic variables and respiratory parameters in the CCL. One study examined the cardiorespiratory effects of diazepam sedation and flumazenil reversal of sedation in patients in the CCL.[59] A sleep-inducing dose of diazepam that was administered intravenously in the CCL produced only slight decreases in mean arterial pressure, PCWP, and LV end-diastolic pressure (LVEDP), with no significant changes in intermittently sampled arterial blood gases. Flumazenil rapidly reversed the sedative effects without significant alterations in hemodynamic or respiratory variables.

More complex interventions have resulted in longer procedures. Although hospitals require conscious sedation policies, individual variation in the type and degree of sedation is common. General anesthesia is rarely required for coronary procedures, but it is frequently used for percutaneous valve procedures (eg, transcatheter aortic valve, MV replacement), ASD closure, and aortic endografts. Advancements in intracardiac echocardiography have decreased the need for intubation and transesophageal echocardiography (TEE) in certain patients and procedures.[60] Pediatric procedures require general anesthesia more commonly than those in adults. As the frequency of noncoronary procedures increases, the presence of an anesthesiologist in the CCL will be required more often.

Left-Sided Heart Catheterization

Catheterization Site and Anticoagulation

Left-sided heart catheterization (LHC) traditionally has been performed by means of a brachial or femoral artery approach. In the 1950s, the brachial approach was first introduced, using a cutdown with brachial arteriotomy. The brachial arteriotomy is often time-consuming, can seldom be performed more than three times in the same patient, and has greater complication rates. This led operators to adopt the femoral approach, which became almost universally accepted. The percutaneous radial artery approach was later developed to improve patient comfort and reduce vascular complications, but its use remained relatively stagnant for more than 10 years. Currently, only a small percentage of procedures are performed via the radial approach in the United States, but that number is increasing rapidly. Over the most recently reported 6-year time period, there was a 13-fold increase in radial artery PCI, with wide geographic variation.[43,61] This approach may be preferred in patients with significant lower extremity peripheral artery disease, recent (<6 months) femoral or abdominal aortic surgery, significant hypertension, coagulopathy, morbid obesity, advanced age, female sex, or an initial cardiac presentation of an acute coronary syndrome (ACS).

The placement of an intraarterial sheath into the radial artery is similar to the placement of devices into any other artery except that the artery has a much smaller caliber and is prone to spasm. Some operators recommend performance of an Allen or a Barbeau test before the procedure to assess for adequate contralateral blood flow into the hand from the ulnar artery.[62] This is an area of controversy because the fundamental question is whether the result of either test is predictive of hand ischemia when radial artery occlusion occurs. Case series of patients with abnormal collateral flow from an absent or diminutive ulnar artery who underwent radial artery harvesting for use as bypass conduits have reported no postoperative hand ischemia.[63] Therefore, because of the lack of outcome data demonstrating the predictive value of testing for dual circulation, some operators have moved away from the routine use of such tests.[64]

Because of the unique characteristics of the radial artery, special dedicated hydrophilic sheaths and access kits are routinely used when gaining access into this arterial bed. Once access has been achieved, to reduce the incidence of radial artery occlusion, intraarterial medications including some combination of nitroglycerin (NTG), a calcium channel blocker (verapamil, diltiazem, or nicardipine), and lidocaine are administered. Most of the time, this combination is physician specific, but at times the patient's hemodynamic status dictates the medical regimen. For example, verapamil and diltiazem should be avoided in the setting of bradycardia, and NTG and nicardipine may be avoided in the setting of hypotension. In addition, the patient who is undergoing a diagnostic heart catheterization from the radial approach requires the use of parenteral anticoagulation with either unfractionated heparin (UFH) or bivalirudin, which have been shown to decrease the rate of radial artery occlusion.[65] The recommended regimen is intraarterial or IV UFH at a dose of at least 500 units/kg or 5000 units. In those patients with heparin-induced thrombocytopenia, the recommendation is to use a bivalirudin bolus dose of 0.75 mg/kg.[66,67]

The development of dedicated catheters for engagement of the coronary arteries when using a radial artery approach has greatly reduced the procedure time. In addition, advances in the management of sheath removal have improved the rates of radial artery occlusion. The current recommendation is to remove the sheath immediately after completion of the procedure and to place a hemostatic compression device, which prevents hematoma formation at the access site but allows for patency of the vessel. Patency of the radial artery can be assessed by evaluating for a radial artery pulse just distal to the compression device.[68] This technique has been called patent hemostasis. When it is used properly, the rates of radial artery occlusion are on the order of 1% to 5%.[64]

There are relatively few contraindications to performing a radial artery procedure: patients who require support devices or other devices that are not compatible with sheaths smaller than 7 Fr, patients with known congenital or noncongenital vascular anomalies of the upper limb, patients who require dialysis fistulas, patients who require use of the radial artery as a conduit for CABG surgery, and patients with known peripheral vaso-occlusive disease, including thromboangiitis obliterans (Buerger disease) and Raynaud disease.

The main advantage of the radial artery approach is that it minimizes vascular complications in patients presenting with ACS, because many of these patients are treated with aggressive anticoagulant and antiplatelet therapy before vascular access is attempted. The RIVAL and RIFLE-STEACS trials both demonstrated lower vascular complication rates and evidence to suggest an overall mortality benefit for the radial approach compared with a transfemoral approach.[69,70] As the adoption of the radial approach continues to increase worldwide, it is important for anesthesiologists to appreciate the unique features of access and hemostasis with this approach compared with the more traditional transfemoral approach.

The percutaneous femoral artery approach is performed using catheters that allow for operator ease and speed of performance. The landmarks for the percutaneous femoral approach are illustrated in Fig. 3.2. The percutaneous approach uses the Seldinger technique or modifications thereof with a Cook needle, which does not have

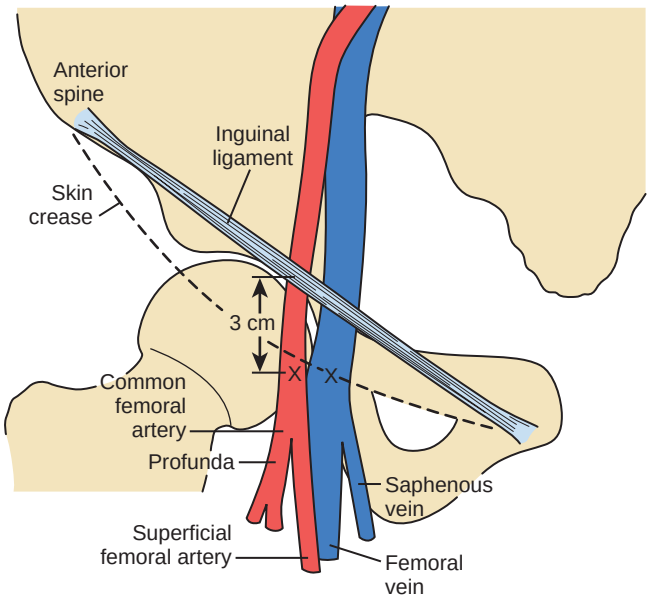


Fig. 3.2 Relevant anatomy for percutaneous catheterization of the femoral artery and vein. The right femoral artery and vein run underneath the inguinal ligament, which connects the anterior-superior iliac spine and the pubic tubercle. The arterial puncture should be made approximately 1.5 to 2 fingerbreadths (3 cm) below the inguinal ligament and directly over the femoral artery pulsation. The venous puncture should be made at the same level but approximately 1 fingerbreadth medial to the arterial position. *X*, Puncture site. *(From Baim DS, Grossman W. Percutaneous approach. In: Grossman W, ed.* Cardiac Catheterization and Angiography *[3rd ed.]. Philadelphia: Lea & Febiger; 1986:60.)*

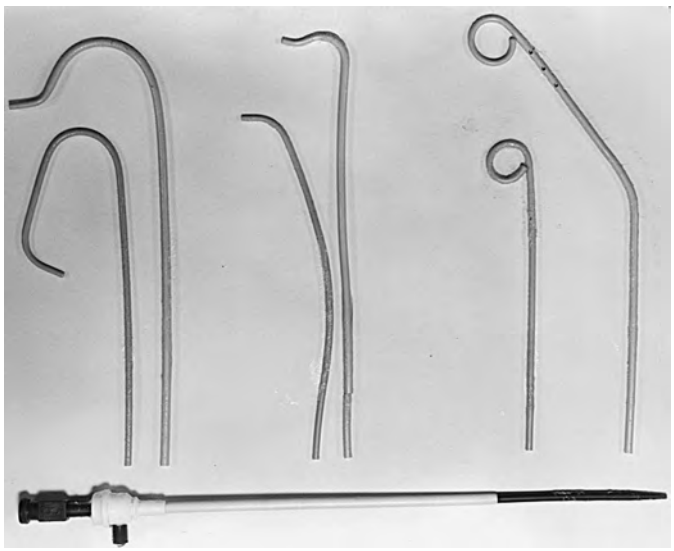


Fig. 3.3 Femoral artery catheters and sheath. *Left,* Standard left coronary artery catheters. *Middle,* Standard right coronary artery catheters. *Right,* Standard ventricular pigtail catheters. *Bottom,* Femoral artery sheath.

an internal obturator. Once the wire is successfully inserted into the vessel, standard sheaths (4 to 8 Fr) are placed in the femoral artery. Through these sheaths, separate coronary artery catheters are inserted to perform left and then right coronary cineangiography, and left ventriculography is performed with the use of a pigtail catheter. These standard catheters and a sheath are illustrated in Fig. 3.3.

In patients with synthetic grafts in the femoral area, arterial access is possible after the grafts are a few months old, and complication rates are similar to those seen in patients with native vessels. An additional

problem may be encountered with aortofemoral grafts. If the native iliac system or distal aorta is occluded, it can be a challenge to advance the catheters through the bypass conduit, and a radial approach should be strongly considered.

At the completion of catheterization via the femoral approach, a closure device may be inserted. If so, femoral arteriography typically is performed via the sheath to assess the adequacy for use of the device. If hemostasis will be obtained with manual compression, the patient is returned to the preprocedure/postprocedure holding area for sheath removal. If an RHC is performed, arterial and venous sheaths should be removed separately to avoid the formation of an atrioventricular (AV) fistula.[71] Pressure is then applied manually or by a compression device. The duration of bed rest depends on the size of the sheath.[72] Closure devices provide for more rapid hemostasis after the procedure, allowing for earlier ambulation and discharge. However, complication rates have not decreased with use of these devices.[73] Closure devices include collagen plugs placed within the artery, which require avoidance of the site for repeat puncture for 3 months, external arterial or subcutaneous plugs that do not hinder repeat access, and suture devices that perform percutaneous arteriotomy closure.[46]

Once hemostasis has been achieved, access site checks and distal pulse assessments should be performed on a regular basis. Sandbag placement is seldom used. In most outpatient diagnostic studies, patients are ambulatory and ready to be discharged 2 to 4 hours after the procedure.[45,72]

In contemporary practice, routine anticoagulation for diagnostic procedures from the femoral approach often is omitted because of the limited arterial access times, unproven need for anticoagulation, and risks for reversing anticoagulation and/or potential delay in sheath removal. If a sheath is to be left in place for longer than 30 to 60 minutes (ie, to confer about management or to transfer a patient), then anticoagulation is recommended. Heparinization is used routinely during brachial or radial catheterization to prevent thrombosis of the smaller arm arteries that may be obstructed by the sheath, as discussed earlier.

Contrast Agents

Adverse reactions have been the major disadvantage of the ionic contrast agents since their introduction for urinary tract visualization in 1923.[48] Contrast agents used for cardiovascular imaging are divided into two groups according to whether they dissociate into ionic particles in solution (ionic media) or do not dissociate (nonionic media). The ionic agents were the first group developed, with sodium diatrizoate and iothalamate anions as the iodine carriers. Commercially available agents using meglumine and sodium salts of diatrizoic acid include Renografin, Hypaque, and Angiovist. In 1975, Shehadi[74] reported on a prospective survey of 30 university hospitals in the United States, Canada, Europe, and Australia, involving 112,003 patients, in which ionic contrast agents were used for cardiovascular diagnosis. The overall rate of adverse reactions was 5.65%, with 0.02% of patients having severe reactions, including death in eight patients.

The next generation of contrast agents began to impact clinical practice in the 1980s. These agents, listed in Table 3.1, are predominantly monomeric, nonionic agents with the exception of the two dimers: ioxaglate (ionic) and iodixanol (nonionic). These agents, particularly the nonionic dimer iodixanol, have lower osmolarity and potentially lower systemic toxicity.[51]

Several areas must be discussed when comparing ionic and nonionic contrast agents. First, the ECG effects (transient heart block, QT and QRS prolongation), depression of LV contractility, and systemic hypotension from peripheral vasodilation are more pronounced with the ionic agents but statistically only marginally different from the effects of the nonionic compounds.[75] The hemodynamic effects of the nonionic dimer, iodixanol, were compared with those of the nonionic monomer, iohexol, in 48 patients; although both agents caused an increase in LVEDP, the increase was significantly less in the iodixanol group.[76] In addition, iodine content may vary among agents, resulting in variations in opacification. In patients who have had previous anaphylactoid reactions to iodinated contrast, nonionic contrast decreases the incidence of an anaphylactoid reaction with repeat contrast exposure.[47,51] Finally, the nonionic agents and dimers are more expensive than the ionic agents. When these agents were first introduced, this difference was large and slowed the adoption of the newer agents. Current price differences are less dramatic, and nonionic agents are used in most laboratories.[51]

TABLE 3.1 Nonionic and Dimeric Contrast Agents

Product[a]	*Type of Contrast Agent*	*Concentration (mg/mL)*	*Osmolality (mOsm/kg water)*
Monomers			
Iohexol (Omnipaque)	Nonionic LOCM	350	844
Iopamidol (Isovue)	Nonionic LOCM	370	796
Ioxilan (Oxilan)	Nonionic LOCM	350	695
Iopromide (Ultravist)	Nonionic LOCM	370	774
Ioversol (Optiray)	Nonionic LOCM	350	792
Dimers			
Iodixanol (Visipaque)	Nonionic IOCM	320	290
Ioxaglate (Hexabrix)	Ionic LOCM	320	600

[a]Omnipaque and Visipaque are registered trademarks of Nycomed, Zurich, Switzerland. Isovue is a registered trademark of Bracco Diagnostics, Princeton, NJ. Oxilan and Hexabrix are registered trademarks of Guerbet, Villepinte, France. Ultravist is a registered trademark of Berlex Laboratories, Wayne, NJ. Optiray is a registered trademark of Mallinckrodt Medical, St. Louis, MO.

IOCM, Iso-osmolar contrast media; *LOCM*, low-osmolality contrast media.

Both ionic and nonionic agents have anticoagulant and antiplatelet effects, these being more pronounced with ionic agents. A comparison of the nonionic agents iohexol (monomer) and iodixanol (dimer) with the ionic dimer, ioxaglate, demonstrated a clear distinction, with the in vivo antiplatelet effect of the ionic agent 65% greater than that of the nonionic agents.[77] Regardless of the agent used, these differences are unlikely to be important for diagnostic procedures. Although minute thrombi may form when blood and nonionic contrast remain in a syringe, clinical sequelae have not been reported.[78]

Patients with impaired renal function (Cr >1.5 mg/dL; GFR <60 mL/minute), particularly if they are diabetic, have an increased risk of renal impairment after contrast administration.[34] The effects of contrast agents on the kidneys are more pronounced when larger volumes are delivered near the renal arteries. Therefore, the choice of contrast is most important with arteriography of the renal arteries or the abdominal aorta. Abdominal arteriography can be done with digital subtraction techniques and the intraarterial injection of gaseous carbon dioxide, avoiding the use of any iodinated contrast.

Two large, multicenter trials have compared ionic and nonionic agents in patients undergoing cardiovascular diagnostic imaging.[79,80] One involved 109,546 patients in Australia, and the other involved 337,647 patients in Japan. These studies demonstrated severe adverse reactions in 0.9% and 0.25% those patients exposed to ionic agents, respectively, whereas the rates of severe adverse reactions in patients exposed to nonionic agents were 0.02% and 0.04%, respectively. For intervention procedures, one trial compared the iso-osmolar nonionic dimer, iodixanol, with the ionic dimer, ioxaglate, in 856 PCI patients at high risk and reported a 45% reduction in major adverse cardiac events (MACEs) in the iodixanol group.[81] Iodixanol (Visipaque) has also been compared with low-osmolar contrast agents in attempts to limit nephrotoxicity, with mixed results.[82]

Minimizing the use of contrast is the surest way to limit nephrotoxicity. For patients at greatest risk, this might require that procedures be staged; for instance, a diagnostic study may be performed on one day and an interventional procedure at a later date. An additional concern is that iodinated contrast is administered frequently for other purposes, such as CT. If staging of procedures or repeat contrast administration is required, delaying these additional studies for 72 hours or until renal dysfunction has recovered is recommended.[37]

Right-Sided Heart Catheterization

Indications

The Cournand catheter initially was used to measure right-sided heart pressures but required fluoroscopic guidance for placement. The Cournand catheter permitted the measurement of CO by the Fick method. Clinical applications of right-sided hemodynamic monitoring changed greatly in 1970 with the development of the flow-directed, balloon-tipped, pulmonary artery catheter (PAC) by Swan and Ganz. This balloon flotation catheter allowed the clinician to measure pulmonary artery (PA) and wedge pressures without fluoroscopic guidance. It also incorporated a thermistor, making repeated measurements of CO feasible. With this development, the PAC left the CCL and entered both the OR and the intensive care unit.[83]

In the CCL, RHC is performed for diagnostic purposes. The routine use of RHC during standard LHC was studied by Hill and associates.[84] Two hundred patients referred for LHC for suspected CAD also underwent RHC. This resulted in an additional 6 minutes of procedure time and 90 seconds of fluoroscopy time. Abnormalities were detected in 35% of the patients; however, management was altered in only 1.5% of the patients. With this in mind, routine RHC cannot be recommended. Box 3.4 outlines acceptable indications for RHC during LHC.

CO measurements during RHC using the thermodilution technique allow for a further assessment of ventricular function.[85] This obviously is helpful in the setting of an AMI to identify high-risk groups and to measure the effects of cardiac medications.[86,87] Measurement of CO can differentiate high-output failure states (eg, hyperthyroidism, Paget disease, beriberi, anemia, AV malformations, AV fistula) from those occurring secondary to a low CO. In patients with congenital heart disease, RHC allows for measurement of oxygen saturation in various cardiac chambers and calculation of intracardiac shunting. In patients with ASD, the right-sided heart catheter passes through the defect into the left atrium (LA), allowing for complete saturation and pressure measurements. The thermodilution technique cannot be used to measure CO in the setting of intracardiac shunting; in such cases, the Fick method must be used. With significant tricuspid regurgitation or a very low CO, the Fick method provides a more accurate measurement of CO and is preferred. Pharmacologic therapy for pulmonary hypertension has become more effective, and RHC is used to confirm the diagnosis of pulmonary *arterial* hypertension (PAH) and differentiate it from pulmonary *venous* hypertension. Knowledge of the response of PAH to nitric oxide, adenosine, or a vasodilator is helpful for the cardiologist to determine optimal therapy, so these agents are occasionally administered during an RHC.[88,89]

Procedure

The brachial, femoral, and internal jugular venous approaches are the approaches most commonly used for RHC in the CCL. The brachial approach for RHC may be done percutaneously or by means of a venotomy. One pitfall in the brachial approach is identification of the proper vein for insertion. The basilic and brachial veins are preferable, whereas the cephalic vein on the radial aspect of the arm is tortuous in the axilla and should be avoided for catheter insertion. When the left brachial (or left internal jugular) approach is considered, the operator must be aware of the possibility of an anomalous left-sided superior vena cava (SVC) that empties into the coronary sinus, hindering catheter passage into the right ventricle (RV). Whenever the peripheral arm veins are entered, the catheter or sheath must be moist and inserted quickly to decrease venous spasm.

The femoral approach for PAC insertion is performed under fluoroscopic guidance using one of two approaches. The catheter can be advanced against the lateral wall of the atrium, creating a loop in the RA, after which the balloon is inflated and advanced across the tricuspid and pulmonic valves to the PCWP position. Or, the catheter can be passed from the RA into the RV; with clockwise rotation and balloon inflation, the catheter then enters the pulmonary outflow tract and is advanced into the PA and PCWP positions.

Shunt Calculations

Although it is common to obtain oxygen saturation values from the PA during RHC, a complete oxygen saturation assessment is required in patients with suspected left-to-right shunts. In the adult population, ASDs and postinfarction VSDs are the most common left-to-right shunts requiring identification. In these patients, 0.5 to 1.0 mL of blood is obtained from the following locations: the SVC and the inferior vena cava (IVC); high, middle, and low portions of the RA; the right ventricular apex and outflow tract; and the main PA (rarely, right and left PA). These saturations are obtained on entry with the PAC, and repeat sampling is dune during pullback if the data are ambiguous. The samples must be obtained in close temporal proximity to avoid systemic factors affecting oxygen saturation (eg, hypoventilation). A step-up in saturation identifies the level at which the shunt is occurring. Right-to-left shunts are suspected when the arterial blood is not fully saturated even with maximal oxygen supplementation; this must be differentiated from intrapulmonary shunting.

Pulmonic and systemic flows are calculated as modifications of the Fick equation for CO determination.[90] The Fick equation states that the cardiac output can be calculated as the oxygen consumption divided by the arteriovenous oxygen difference.[90] It is important that measurements be made during steady-state conditions. The $\dot{Q}_p/\dot{Q}_s$ ratio is calculated for patients with left-to-right shunting by the following equation:

$$\dot{Q}_p/\dot{Q}_s = (Sa_{O_2} - S\bar{v}_{O_2})/(Spv_{O_2} - Spa_{O_2})$$

where $\dot{Q}_p$ is pulmonary flow, $\dot{Q}_s$ is systemic flow, Sa_{O_2} is systemic arterial oxygen saturation, $S\bar{v}_{O_2}$ is mixed venous oxygen saturation, Spv_{O_2} is pulmonary venous oxygen saturation, and Spa_{O_2} is PA oxygen saturation. The pulmonary and systemic flows are measured in L/minute and the oxygen saturations in mL/L.

In the presence of an RA step-up, an estimated resting $S\bar{v}_{O_2}$ sample is obtained by the following weighted average:

$$S\bar{v}_{O_2} = [3 \times (\text{SVC saturation}) + 1 \times (\text{IVC saturation})] \div 4$$

Saturation values are measured in high and low regions of the SVC and IVC and are normally the same. If anomalous pulmonary venous drainage is present, regional differences in saturation in either the SVC or the IVC may occur. Calculation of the $\dot{Q}_p/\dot{Q}_s$ ratio does not require measurement of oxygen consumption (mL/minute), and it can be calculated with any stable level of oxygen supplementation. However, calculation of the absolute values of pulmonary and systemic flow does require this measurement, which can be complicated if supplemental oxygen is required.

Correction of the defect is required if the $\dot{Q}_p/\dot{Q}_s$ ratio is greater than 2 but is unnecessary if it is less than 1.5. Ratios between 1.5 and 2.0 require additional confirmatory evidence and clinical assessment before a decision to intervene can be made.

BOX 3.4 INDICATIONS FOR DIAGNOSTIC RIGHT-SIDED HEART CATHETERIZATION DURING LEFT-SIDED HEART CATHETERIZATION

- Significant valvular pathology
- Suspected intracardiac shunting
- Acute infarct—differentiation of free wall versus septal rupture
- Evaluation of right- and/or left-sided heart failure
- Evaluation of pulmonary hypertension
- Severe pulmonary disease
- Evaluation of pericardial disease
- Constrictive pericarditis
- Restrictive cardiomyopathy
- Pericardial effusion
- Pretransplantation assessment of pulmonary vascular resistance and response to vasodilators

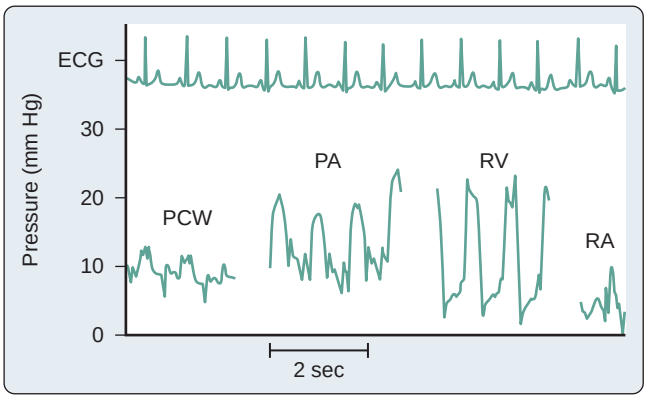


Fig. 3.4 A pullback tracing obtained using a pulmonary artery catheter from the pulmonary capillary wedge *(PCW)* position, to the pulmonary artery *(PA)*, right ventricle *(RV)*, and right atrium *(RA)*. *ECG*, Electrocardiogram.

The following example demonstrates the calculation of left-to-right shunting in a patient with an ASD given the following oxygen saturation values: IVC = 68%; SVC = 60%; mid-RA = 77%; mid-RV = 77%; $SpaO_2$ = 77%; and SaO_2 = 92%.

$$S\bar{v}O_2 = [3(60) + 68] \div 4 = 62$$

$$\dot{Q}_p/\dot{Q}_s = (92 - 62)/(92 - 77) = 30/15 = 2$$

Significant bidirectional or right-to-left shunting is unusual in adult patients. These shunts occur in the setting of congenital heart disease, typically after the development of pulmonary arterial disease. As more children with corrected or partially corrected congenital heart disease reach adulthood, the likelihood of encountering an adult with a complicated shunt will increase. These encounters may be additionally complicated by the development of adult cardiology problems, mainly CAD. However, about 25% of the population has a PFO, and right-to-left shunting through the PFO with systemic oxygen desaturation can occur if the RA pressures become increased. This may occur after pulmonary embolism or after an RV infarction, among other causes.

Calculation of bidirectional shunting involves determination of the effective blood flow ($\dot{Q}_{eff}$). $\dot{Q}_{eff}$ represents the flow if no right-to-left or left-to-right shunting existed.[90] Right-to-left shunting is equal to $\dot{Q}_s - \dot{Q}_{eff}$, and left-to-right shunting is equal to $\dot{Q}_p - \dot{Q}_{eff}$. The following formulas are derived from the Fick equation for CO:

$$\dot{Q}_s = O_2 consumption/SaO_2 - S\bar{v}O_2$$

$$\dot{Q}_p = O_2 consumption/SpvO_2 - SpaO_2$$

$$\dot{Q}_{eff} = O_2 consumption/SpvO_2 - S\bar{v}O_2$$

Right-sided heart pressure may be obtained either on entry or on pullback (Fig. 3.4). Catheter placement via the femoral approach may be time-consuming, with expedited passage necessary to prevent catheter softening. For this reason, pressure measurements often are obtained during catheter pullback to ensure temporal proximity. As with all invasive procedures, complications can occur with RHC, so risks and benefits must be assessed in advance[91] (see Chapter 13). If general anesthesia is required, the fraction of inspired oxygen (FIO_2) is reduced to approximately 25% or lower when checking the saturations in different chambers of the heart. Higher FIO_2 during the procedure may change the pulmonary vascular resistance measurements.

Endomyocardial Biopsy

Endomyocardial biopsy is the only reliable method to detect rejection in the transplanted heart. However, its role in the management of other cardiovascular diseases in adult and pediatric patients remains controversial. In 2007, the ACC/AHA/European Society of Cardiology published recommendations on endomyocardial biopsy.[92] The preferred approach is through the internal jugular vein (in the United States) or the femoral vein (in Europe), with subclavian and even brachial approaches also used. Complications are infrequent and are related to the access site (in 2% of patients), arrhythmia or conduction abnormalities (1–2%), or perforation (0.5%). Death, a rare event, is related to perforation. Histologic evaluation of the tissue is the purpose of the procedure, and it must be done by experienced pathologists to justify the risks.

Indications are controversial, but most groups agree that important information can be obtained in the setting of new-onset heart failure (<2 weeks) and also for those patients who have had heart failure for 2 weeks to 3 months without response to therapy.[92] Other potential indications include unexplained restrictive cardiomyopathy, anthracycline cardiomyopathy, suspected cardiac tumor, unexplained arrhythmias, and heart failure associated with hypertrophic cardiomyopathy (HCM), but these are less clear. A complete review of potential scenarios can be found in the 2007 scientific statement.[92]

Diagnostic Catheterization Complications

Although adult diagnostic catheterization with selective coronary cineangiography has been performed since the late 1950s, complication rates were not monitored until 1979, when the SCAI established the first registry to prospectively follow the performance of participating laboratories. In 1982, the first publication from this registry reported complication rates from a study population of more than 50,000 patients.[93] This was updated in 1989 with a report on 222,553 patients who underwent selective coronary arteriography between 1984 and 1987.[94] Similar complication rates were noted in the two reports. Complications are related to multiple factors, but severity of disease is important. Mortality rates are low. Complications are specific for RHC and LHC (Box 3.5). The registry reported incidences of major complications as follows: death, 0.1%; MI, 0.06%; cerebrovascular accident, 0.07%; arrhythmia, 0.47%; contrast reaction, 0.23%; and vascular complications, 0.46%.[94] Infectious complications are infrequent, although they may be underreported. Guidelines for infection control are based more on extrapolation from OR studies than on randomized control data from the CCL.[95] Although advances in technology have been made, similar complication rates persist, most likely because of the higher risk status of patients undergoing catheterization today.[13] The current registries for identifying complications are focused primarily on percutaneous interventions. In addition to institutional and regional databases such as those of the Cleveland Clinic and Northern New England, the ACC maintains the National Cardiovascular Data Registry (NCDR).

Vascular complications from the percutaneous femoral approach occur in fewer than 1% of diagnostic procedures, with the most common being pseudoaneurysm.[46] This risk is greater for obese patients, in whom compression is more difficult. Therapy for pseudoaneurysm is either ultrasound-directed thrombin injection or surgical repair. In patients with aortic regurgitation (AR), an increased incidence of femoral arteriovenous fistulas is seen because of the widened pulse pressure.[71] Many small arteriovenous fistulas will close spontaneously. If the fistula is large or is associated with high output (rare) or with edema of the affected leg, surgical correction is indicated. Thrombosis of the femoral artery occurs rarely, and underlying atherosclerotic disease usually is severe. Emergent restoration of flow is essential, with a surgical approach used at some hospitals and a percutaneous approach at others.

Arrhythmogenic complications during LHC are more frequent with ionic contrast than with nonionic contrast, and they occur during coronary injection. Surprisingly, the presence of the catheter in the left ventricle rarely causes a sustained arrhythmia. Early contrast media containing potassium produced ventricular fibrillation during coronary arteriography. However, current contrast materials are potassium free and contain added calcium. As a result, the incidence rate of significant ventricular arrhythmias is 0.47%.[94]

BOX 3.5 COMPLICATIONS OF DIAGNOSTIC CATHETERIZATION

Left-Sided Heart Catheterization

Cardiac Complications

Death
Myocardial infarction
Ventricular fibrillation
Ventricular tachycardia
Cardiac perforation

Noncardiac Complications

Stroke
Peripheral embolization
Air
Thrombus
Cholesterol
Vascular surgical repair
Pseudoaneurysm
Arteriovenous fistula
Embolectomy
Repair of brachial arteriotomy
Evacuation of hematomas
Contrast-related complications
Renal insufficiency
Anaphylaxis

Right-Sided Heart Catheterization

Cardiac Complications

Conduction abnormality
RBBB
Complete heart block (RBBB superimposed on LBBB)
Arrhythmias
Valvular damage
Perforation

Noncardiac Complications

Pulmonary artery rupture
Pulmonary infarction
Balloon rupture
Paradoxic (systemic) air embolus

LBBB, Left bundle branch block; *RBBB*, right bundle branch block.

Anaphylactoid reactions has occurred in approximately 5% to 8% of cases when nonionic contrast agents were used. The definition of reaction severity and the differential diagnosis for severe reactions are listed in Table 3.2. Severe hypersensitivity reactions manifest as urticaria and pruritus, bronchospasm, hypotension, laryngeal edema, and cardiovascular collapse. The three most common risk factors for an acute reaction are a history of asthma, a prior reaction to dye, and atopy.

The treatment of the reaction depends on the patient's symptoms. For urticaria without symptoms, the dye injection is stopped and the patient is reassured. If the patient is symptomatic, 25 to 50 mg of diphenhydramine (Benedryl) along with 100 mg of hydrocortisone can be administered; if the reaction is severe, the treatment is 0.1 to 0.3 mg of subcutaneous (SC) or intramuscular (IM) epinephrine. For facial or laryngeal edema, the treatment is oxygen and 0.1 to 0.3 mg of SC or IM epinephrine or, if the patient is hypotensive, 0.1 mg of IV epinephrine up to 1 mg. If respiratory distress is present, the patient should be intubated. For bronchospasm, oxygen and β_2-agonist inhalers should be administered; if the patient is unresponsive, 0.1 to 0.3 mg of epinephrine SC or IM should be given. Consider intubation if the oxygen saturation is low despite treatment.

For anaphylactoid reactions, resuscitation includes airway management and cardiovascular support. Oxygen should be administered, and intubation should be considered if the patient is hypoxic despite oxygen. The circulation should be supported with boluses of isotonic Ringer lactate or normal saline solution. If there is no response, IV epinephrine should be administered 0.1 mg at a time to a maximum of 1 mg. Hydrocortisone, diphenhydramine, and H_2 antagonists may be administered, but these are secondary treatments.[47]

TABLE 3.2 Contrast-Induced Anaphylactoid Reactions

Severity Classification		
Minor	*Moderate*	*Severe*
Urticaria (limited)	Urticaria (diffuse)	Cardiovascular shock
Pruritus	Angioedema	Respiratory arrest
Erythema	Laryngeal edema	Cardiac arrest
	Bronchospasm	

Differential Diagnosis (Severe Reactions)	
Cardiac	*Noncardiac*
Vasovagal reaction	Hypovolemia
Cardiogenic shock	Dehydration
Right ventricular infarction	Blood loss—gastrointestinal, vascular, external
Cardiac tamponade	Drug-related causes
Cardiac rupture	Narcotic, benzodiazepine, protamine
Bezold-Jarisch reflex	Sepsis

Adapted from Goss J, Chambers C, Heupler F, et al. Systemic anaphylactoid reactions to iodinated contrast media during cardiac catheterization procedures. *Cathet Cardiovasc Diagn.* 1995;34:99.

Cholesterol embolization can occur after catheter manipulation, and it has been described after cardiac catheterization.[96] Although the femoral approach can be used in patients with unrepaired abdominal aortic aneurysms, an increased incidence of cholesterol embolization syndrome may occur in this population.[97] Cholesterol embolization produces arterial occlusion of the small vessels by cholesterol crystals and results in a serious clinical presentation including livedo reticularis, acrocyanosis of the lower extremities, renal insufficiency, and accelerated hypertension. The clinical course is variable; the condition does not respond to anticoagulation, and it can potentially lead to an insidious development of progressive renal failure, accelerating hypertension, and a fatal outcome.[98]

Valvular Pathology

The number of patients presenting with valvular heart disease (VHD) in developed countries is growing, primarily because of the increasing age of the population. In 2014, the ACC/AHA published updated practice guidelines for the management of VHD.[99] These guidelines cover the invasive and noninvasive evaluation of valvular problems and the therapeutic approaches. Despite these guidelines, a number of patients are referred for intervention too late in the course of their disease or are not referred at all, either of which results in poor long-term outcomes. On the other hand, intervention in the asymptomatic patient requires expertise in evaluation and noninvasive imaging assessment. The following discussion focuses on valve pathology as a dominant problem. Some patients have mixed valve disease, but there is a paucity of data on the natural history of such coexistent conditions (see Chapter 21).

Stenotic Lesions

The transvalvular gradient and transvalvular flow must be quantified to assess the severity of stenotic lesions. Hydraulic principles state that as valvular stenosis worsens, the valve orifice produces progressively greater resistance to flow, resulting in a pressure drop (pressure gradient) across the valve. At any given stenotic orifice size, greater flow across the orifice yields a greater pressure gradient. Both the CO and the heart rate (HR) determine flow.

Gorlin and Gorlin[100] derived a formula from fluid physics to relate valve area to blood flow and blood velocity:

$$\text{Valve area} \propto \text{Blood flow} \div \text{Blood velocity}$$

In general, as a valve orifice becomes increasingly stenotic, the velocity of flow must progressively increase if total flow across the valve is to be maintained. Flow velocity can be measured by the Doppler principle to estimate valve area; however, in the CCL, this is not as practical as measuring blood *pressures* on either side of the valve.

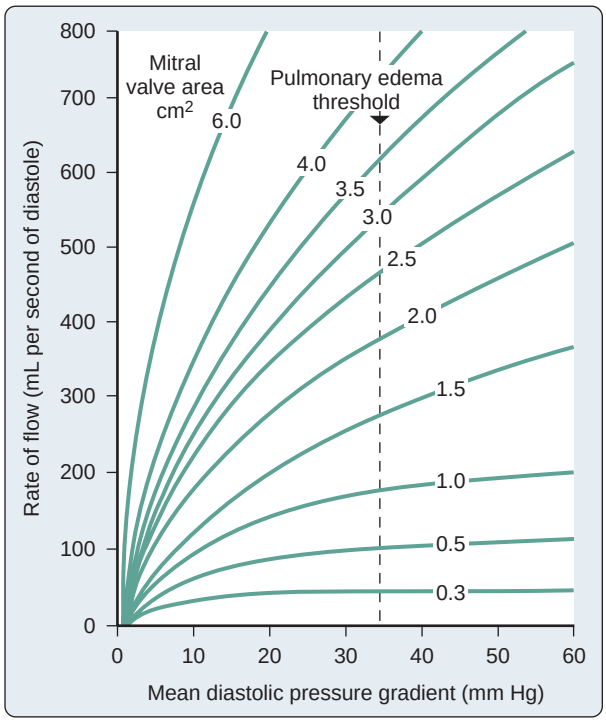


Fig. 3.5 Rate of flow in diastole versus mean pressure gradient for several degrees of mitral stenosis. The pressure gradient is directly proportional to the square of the flow rate. Therefore, as the degree of stenosis progresses, modest increases in flow (eg, with light exercise) will require large increases in the pressure gradient. As an example, a cardiac output of 5.2 L/minute, heart rate of 60 beats/minute, and diastolic filling time of 0.5 second produce a 200 mL/second flow during diastole. With mild mitral stenosis (valve area = 2.0 cm^2), the required pressure gradient remains small (<10 mm Hg), but with severe stenosis (valve area <1.0 cm^2), the resultant gradient is high enough to exceed the threshold for pulmonary edema. *(From Wallace AG. Pathophysiology of cardiovascular disease. In: Smith LH Jr, Thier SO, eds.* Pathophysiology: The Biological Principles of Disease. The International Textbook of Medicine, *Vol. 1. Philadelphia: Saunders; 1981:1192.)*

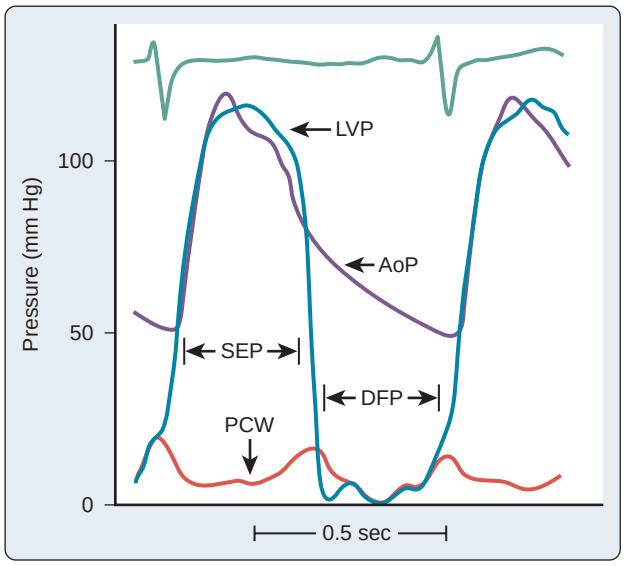


Fig. 3.6 Simultaneous left ventricular pressure *(LVP)*, aortic pressure *(AoP)*, and pulmonary capillary wedge *(PCW)* (ie, left atrial) pressure waveforms. The systolic ejection period *(SEP)* is defined as the period during which the aortic valve is open (extending from the point at which LVP crosses over AoP at the beginning of systole to the point at which AoP crosses over LVP near the end of systole) and forward blood flow is present in the aorta. The diastolic filling period *(DFP)* is the length between the initial PCWP and LV crossover in early diastole to the point of end diastole (peak of R wave). *(Modified from Grossman W, Baim DS, eds.* Cardiac Catheterization, Angiography, and Intervention *[4th ed.]. Philadelphia: Lea & Febiger; 1991:153.)*

As described by Gorlin and Gorlin,[100] the velocity of blood flow is related to the square root of the pressure drop (P) across the valve. Stated another way, for any given orifice size, the transvalvular pressure gradient is a function of the square of the transvalvular flow rate:

$$P_1 - P_2 \propto (\text{Blood velocity})^2$$

For example, with mitral stenosis (MS), as the valve area progressively decreases, modest increases in the rate of flow across the valve cause progressively larger increases in the pressure gradient across the valve (Fig. 3.5).

The actual time of the cardiac cycle during which flow occurs must be known to complete the calculation. For semilunar valves (aortic and pulmonic), flow occurs during the systolic ejection period (SEP)—that is, during ventricular contraction while the aortic valve is open. For AV valves (mitral and tricuspid), flow occurs during the diastolic filling period (DFP), while the MV is open (Fig. 3.6). The HR determines the duration of the SEP or DFP over an entire minute. Also present in the Gorlin formula is a coefficient that quantifies the conversion of potential energy (pressure energy) to kinetic energy (velocity). This term also contains an empirically derived factor that accounts for the difference between calculated and measured valve areas at the time of surgery or postmortem examination.

The final Gorlin formula then becomes

$$\text{Valve area} = \text{CO} \div [(\text{DFP or SEP})(\text{HR})]/44.3 \cdot \text{C} \cdot (P_1 - P_2)^{1/2}$$

where CO is cardiac output (mL/min), DFP or SEP is diastolic filling period or systolic ejection period in seconds per beat, HR is heart rate in beats per minute, C is the orifice constant (aortic, 1.0; mitral, 0.85; tricuspid, 0.7), and $P_1 - P_2$ is the mean pressure difference across the orifice as determined by computer-assisted analysis or area blanketing. The 44.3 coefficient is derived from the energy calculation.

Aortic Stenosis

The normal adult aortic valve area is 2.6 to 3.5 cm^2, which corresponds to a normal aortic valve index of 2.0 cm^2/m^2. As the valve area decreases to a range of 1.5 to 2.0 cm^2 (or a valve index of 1.0 cm^2/m^2), the major hemodynamic finding is a rise in the LV systolic pressure, which is increased to maintain a normal aortic systolic pressure. An elevation in LVEDP also may be observed, which is merely a reflection of the decrease in compliance of the hypertrophied ventricle (see Chapter 21).

As the stenosis becomes moderate and the valve area decreases to 1.0 to 1.5 cm^2 or a valve index of 0.6 to 0.9 cm^2/m^2, symptoms can occur. The left ventricle exhibits a more rounded appearance at its peak systolic pressure, and there is a progressive increase in the LVEDP. As the left ventricle hypertrophies, its filling becomes more dependent on the contraction of the LA; this is reflected as an augmented A wave on the ventricular tracing. At that point, the increased LA pressure makes atrial fibrillation (AF) more likely, and the decreased compliance of the left ventricle makes it poorly tolerated. Widening of the systolic pressure gradient from the left ventricle to the aorta, a decrease in the rate of rise of the upstroke of the aortic pressure tracing, and a delay in the time to peak aortic pressure (*pulsus parvus et tardus*) also are seen (Fig. 3.7).

In the case of severe AS, with a valve area of less than 1.0 cm^2 and a valve area index of less than 0.5 cm^2/m^2, a decrease in systolic function of the left ventricle can occur. Increases in PA pressure, PCWP, and right atrial pressure also are observed. These latter changes often are accompanied by symptoms of congestive heart failure.

In some patients, the mean aortic valve gradient does not correlate with low aortic valve area, and the patient is categorized as having low-flow, low-gradient (LF/LG) AS with either preserved or

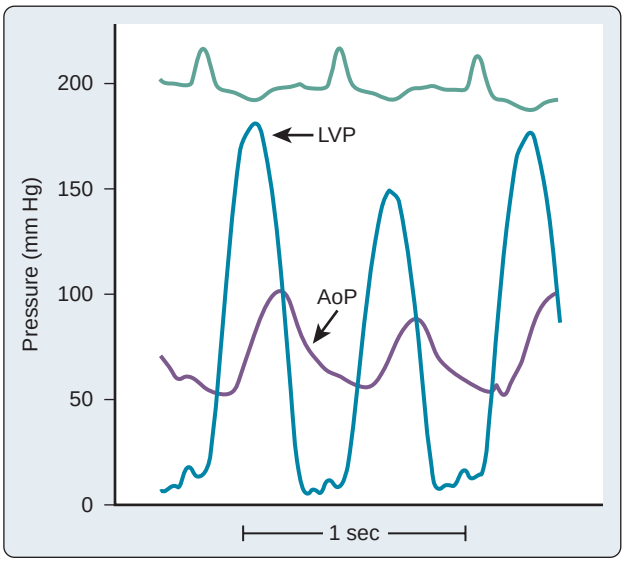


Fig. 3.7 Left ventricular pressure *(LVP)* and aortic pressure *(AoP)* waveforms in a patient with aortic stenosis. Of note are the large pressure gradient from left ventricle to aorta at peak systolic pressure, the delay to onset of the aortic upstroke, and the decrease in the rate of rise of the aortic pressure. End-diastolic pressure is still normal at this stage of the disease.

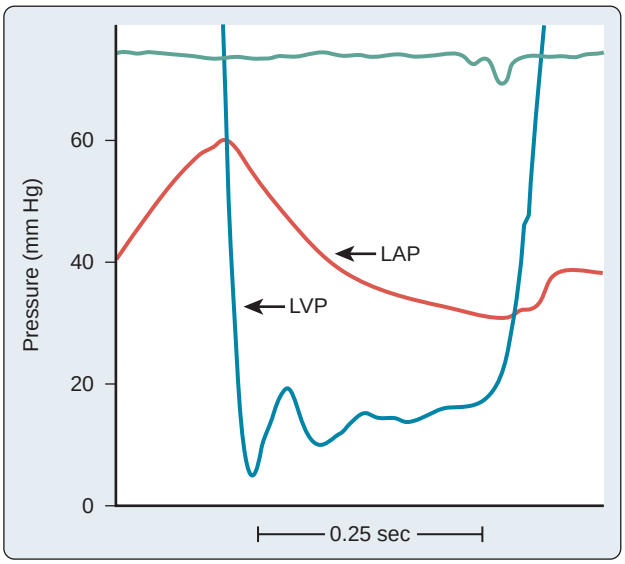


Fig. 3.8 Mitral stenosis, with pressures measured at catheterization. Notice the gradient during diastole between the left atrial *(LAP)* and the left ventricular *(LVP)* pressures and the increase in the LAP.

reduced LV function. Determining optimal therapy and the timing of intervention for patients with LF/LG AS presents unique challenges. Among those patients with classic LF/LG AS with reduced ejection fraction (EF), dobutamine infusions administered in the CCL or in the echocardiography laboratory may help to identify those who will benefit from aortic valve replacement (AVR).[101] For patients who have paradoxical LF/LG AS with preserved LV function, a careful assessment must ensue because the published data are limited and conflicting with respect to the benefit of surgical valve replacement.[102,103] Quite often, these patients need multimodality imaging, including cardiac magnetic resonance (CMR) along with calcium scoring of the aortic valve, to assist with determination of the severity of the disease process.[104,105] Further studies are needed to determine which patients with paradoxical LF/LG AS can benefit from AVR and which type of AVR (surgical vs transcatheter) should be used (see Chapters 21 and 27).

Mitral Stenosis

In normal adults, the MV orifice is 4 to 6 cm^2. Mild MS is considered to be present when the MV orifice is reduced to less than 2.0 cm^2. In this condition, the typical hemodynamic finding is an elevation in either LAP or PCWP. An increase in LAP tends to maintain normal flow across the valve. With an MV orifice of less than 1.0 cm^2, considered to be critical MS, a much larger LA-to-LV gradient is required to maintain reasonable flow across the valve (Fig. 3.8). An increase in LAP during diastole leads to early opening and a slightly delayed closure of the MV (Fig. 3.9). It is easy to understand why a slow HR in the presence of MS is preferred, because a maximal DFP is necessary to maintain reasonable flow and sustain CO across the MV. Another hemodynamic hallmark in patients with MS is the reduced increase in LV pressure during early diastole. Normally, a fairly rapid increase is seen during the DFP, but the slope of this pressure increase is delayed in the presence of severe MS. Elevations in right-sided heart pressures are common in severe MS; with severe long-standing MS, the PA pressure can reach or exceed the systemic arterial pressure. Atrial remodeling in MS is characterized by LA enlargement, loss of myocardium, and scarring, which produces widespread conduction abnormalities and is associated with a higher incidence of AF.

Doppler echocardiography has reduced the importance of performing a catheterization to evaluate valvular disease (see Chapters 14, 15, and 21). However, in stenoses of borderline severity, data from the CCL is still important for clinical decision making. Performance of exercise or administration of inotropic agents increases the CO. In addition to confirmation of inotropic reserve, this increase in output increases the flow across the valves and increases the gradient exponentially. When both the gradient across the valve and the CO are low, augmentation of flow can help to distinguish severe stenosis with reversible ventricular failure from mild stenosis with irreversible ventricular failure.

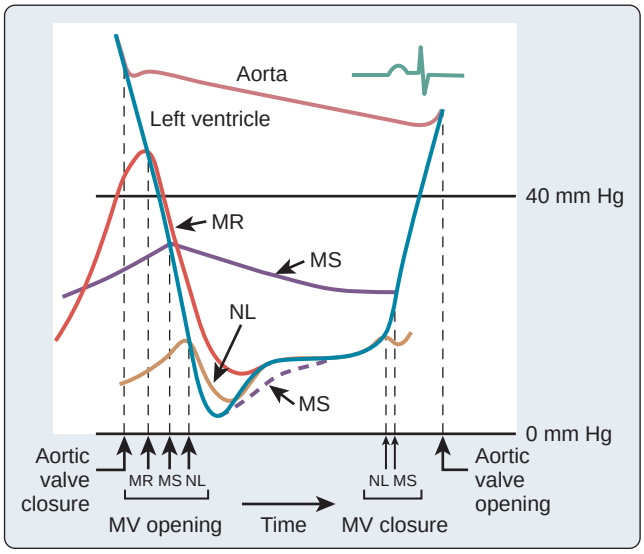


Fig. 3.9 Idealized diagram summarizes mitral valve disorders, concentrating on the diastolic filling period. In mitral stenosis *(MS)*, the increase in left atrial pressure *(solid purple line)* versus normal atrial pressure *(gold line)* causes early mitral valve *(MV)* opening and a slight delay in MV closure. Left ventricular rapid filling is delayed, which delays the increase of ventricular pressure *(dotted purple line)* compared with that seen during normal diastole *(gold line)*. In mitral regurgitation *(MR)*, the left atrial pressure *(red line)* has a large V wave, because the atrium fills with blood from the pulmonary veins and with blood regurgitating through the MV, causing the MV to open early. *NL*, Normal. *(From Braunwald E. Valvular heart disease. In: Braunwald E, ed.* Heart Disease: A Textbook of Cardiovascular Medicine *[3rd ed.]. Philadelphia: Saunders; 1988:1024.)*

Regurgitant Lesions

The severity of valve regurgitation or incompetence is quantified angiographically. However, several hallmark changes occur in the presence of regurgitant lesions. The aortic valve and the MV are discussed as examples here (see Chapters 14, 15, 16, and 21).

Aortic Regurgitation

Acute AR or aortic insufficiency is uncommon unless there is aortic dissection, sudden failure of a valve prosthesis, or native valve destruction in the setting of bacterial endocarditis. In the presence of acute AR, there are sudden increases in end-systolic and end-diastolic volumes and pressures. The normal ventricle is suddenly faced with an increased load and generates greater pressure. During relaxation, because the ventricle is filling with blood from the aorta, there is a delay in the isovolumic pressure decline, accompanied by rapid increases in ventricular diastolic pressures, both because of continued valve regurgitation. The wide pulse pressure, a characteristic sign of chronic AR, may not be seen in the acute setting. In addition, the dicrotic notch, which usually occurs with aortic valve closure, is absent in severe AR. A condition called *pulsus bisferiens,* a common finding in the presence of AR, is caused by the tidal-wave effect as regurgitant blood entering the ventricle during early diastole causes a reflected pressure wave that is seen in the aorta. In the PCWP tracing, an accentuated V wave commonly is seen in the presence of AR, presumably reflecting the decreased compliance of the ventricles.

Chronic AR can be caused by aortic root dilation, bicuspid valves, rheumatic fever, failing prostheses, endocarditis, Marfan syndrome, and other conditions. With chronic AR, the left ventricle dilates and becomes more compliant; this leads to a lower LVEDP than in acute AR. End-diastolic pressure may even be in the normal range until terminal failure is present. The systolic arterial pressure increases, and the diastolic pressure decreases; the former is caused by the greater ventricular pressures generated and the latter by continued runoff from the arterial system into the ventricle (Fig. 3.10). AR imposes both a pressure load and a volume load on the left ventricle. Accordingly, the mass of the left ventricle can increase markedly if the condition is chronic.

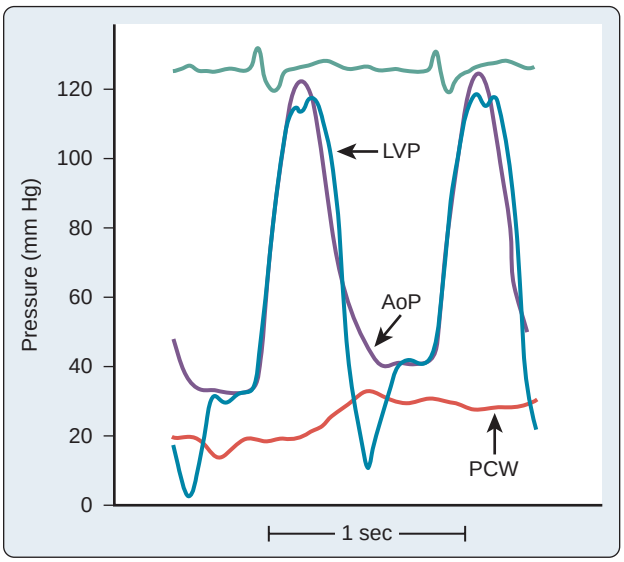


Fig. 3.10 Aortic regurgitation. Simultaneous aortic *(AoP)*, left ventricular *(LVP)*, and pulmonary wedge *(PCW)* pressures demonstrate a wide aortic pulse pressure with absence of the dicrotic notch, a rapid increase in LVP during early diastole caused by regurgitation, and increased PCW, reflective of increased left ventricular end-diastolic pressure. *(Modified from Grossman W, Baim DS. Profiles in valvular heart disease. In: Grossman W, ed.* Cardiac Catheterization, Angiography, and Intervention *[4th ed.]. Philadelphia: Lea & Febiger; 1991:575.)*

Mitral Regurgitation

MR can be either acute or chronic in nature. Acute MR usually occurs secondary to a condition such as acute ischemia that leads to dysfunction of the papillary muscles of the MV or frank rupture of the chordae tendineae or papillary muscles after a significant MI. Rupture of the chordae tendineae can occur in the setting of endocarditis or spontaneously and can cause acute MR (Fig. 3.11). In this instance, it is not uncommon to see an enormously large V wave in the PCWP or LAP tracing as ventricular blood freely flows back into a small, normal, and therefore noncompliant LA. This also is accompanied by acute increases in PA pressure and right atrial pressure, which can lead to significant clinical signs and symptoms of heart failure.

In the setting of chronic MR, the LA can become quite large, nonfunctional, and compliant. Therefore, a significant regurgitant fraction can exist in the presence of a minimal V wave on the pressure tracing.

Prosthetic Valves

The assessment of the function of a bioprosthetic valve is similar to the assessment of a native valve. However, the assessment of a mechanical prosthesis differs in several regards. First, patients with mechanical prostheses require chronic anticoagulation, and this typically needs to be interrupted for the catheterization procedure. Second, mechanical valves should not be crossed with catheters or wires because doing so could cause sudden and severe valvular regurgitation. Finally, the leaflets of a mechanical prosthesis are (slightly) radioopaque, and leaflet motion can be assessed by fluoroscopy. The normal angles of opening and closing are specific to each valve model, size, and location, and these values are available from the manufacturer. Restricted mobility implies that pannus or thrombus has covered one or more leaflets. Similarly, instability of a mechanical prosthesis usually can be detected by fluoroscopy. Echocardiography also is used to evaluate prosthetic valves (see Chapters 14–17). However, transthoracic studies do not reliably view prosthetic mitral leaflets, and fluoroscopy can be repeated serially with little risk or inconvenience to the patient.

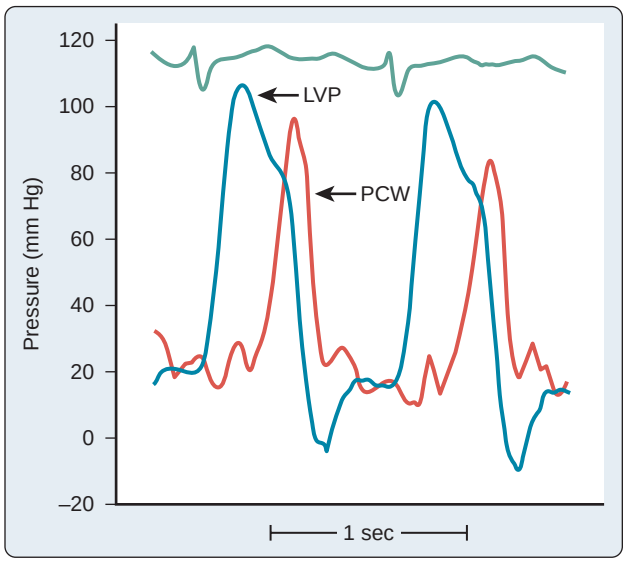
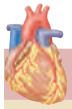


Fig. 3.11 Acute mitral regurgitation caused by chordae tendineae rupture. Simultaneous measurement of left ventricular pressure *(LVP)* and pulmonary wedge *(PCW)* pressure demonstrates a large V wave caused by severe regurgitation into a normal-sized left atrium. Notice that the V wave is delayed temporally. This delay is caused by the time required for the pressure wave to travel through the compliant pulmonary venous and capillary beds to the pulmonary artery catheter. *(Modified from Grossman W, Baim DS. Profiles in valvular heart disease. In: Grossman W, ed.* Cardiac Catheterization, Angiography, and Intervention *[4th ed.]. Philadelphia: Lea & Febiger; 1991:564.)*



BOX 3.6 ANGIOGRAPHY

Coronary anatomy
- Left anterior descending coronary artery with diagonal and septal branches
- Circumflex artery with marginal branches
- Right coronary artery with conus, sinoatrial nodal, AV nodal, and right ventricular branches
- Dominant circulation (posterior descending): 10% circumflex; 90% right coronary artery

Coronary collaterals
Coronary anomaly
Ventriculography/aortography
EF calculation
Valvular regurgitation

AV, Atrioventricular; *EF*, ejection fraction.

Angiography

Ventriculography

Ejection Fraction Determination

Ventriculography routinely is performed in the single-plane 30-degree right anterior oblique (RAO) or biplane 60-degree left anterior oblique (LAO) and 30-degree RAO projections using 20 to 45 mL of contrast with injection rates of 10 to 15 mL/second (Box 3.6). Complete opacification of the ventricle without inducing ventricular extrasystoles is necessary for accurate assessment during ventriculography. Premature contractions not only alter the interpretation of MR but result in a false increase in the EF.

The EF is a global assessment of ventricular function. It is calculated as follows:

$$EF = [EDV - ESV]/EDV = SV/EDV$$

where EF is ejection fraction, EDV is end-diastolic volume, ESV is end-systolic volume, and SV is stroke volume.

The primary clinical method for calculating ventricular volumes to determine the EF uses the area-length method described by Dodge and coworkers in 1960.[106] Before calculation, visual identification is needed to identify the outer margin of the ventricular silhouette for end-systole and end-diastole in both RAO and LAO projections. The ventricle is approximated as an ellipsoid to facilitate volume calculations (Fig. 3.12). Biplane ventriculography is used to define the major (L) and minor (M and N) axes, following the standard geometric formula for the area (A) of an ellipsoid[107]:

$$A_{rao} = \pi(L_{rao}/2)(M/2)$$
$$A_{lao} = \pi(L_{lao}/2)(N/2)$$

The volume (V) is calculated as follows:

$$V = [8/3\pi][A_{rao}(A_{lao}/L_{min})]$$

where L_{min} is the shorter of L_{rao} and L_{lao}.

Single-plane calculation in the 30-degree RAO projection assumes that M = N and that L is the true long axis. Using the ellipsoid volume calculation, V = π/6 LMN, and substituting 4A/πL for M and N, the following formula is obtained:

$$V = (8A^2/3\pi L)$$

Calculation of EF does not require correction for magnification, but measurement of dimensions or calculation of volumes does. Such correction can be made using a calibrated grid imaged after cineangiography, or the part of the catheter that is in the ventricle can be used for calibration. Catheters with precise calibration markings are available. Contemporary software permits calibration that is based on the heights of the table and the detector. Mathematical equations for ventricular volume overestimate the true volume; regression equations

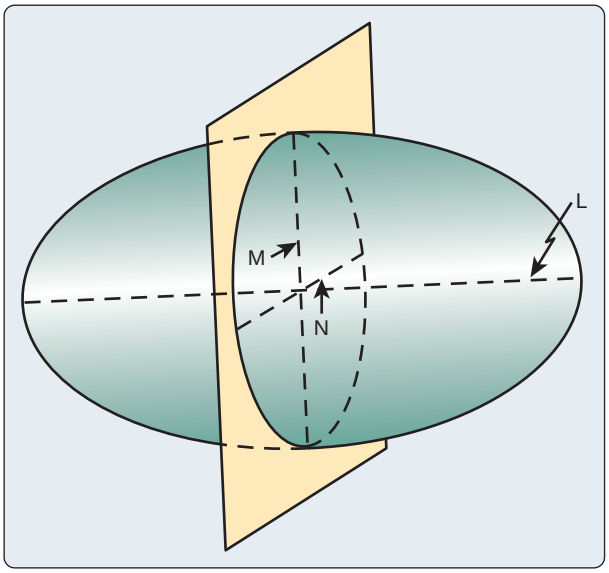


Fig. 3.12 Ellipsoid used as reference diagram for the left ventricle. The long axis *(L)* and the short axes (*M* and *N*) are shown. *(From Fifer MA, Grossman W. Measurement of ventricular volumes, ejection fraction, mass, and wall stress. In: Grossman W, ed.* Cardiac Catheterization and Angiography *[3rd ed.]. Philadelphia: Lea & Febiger; 1986:284.)*

are used to correct for this.[107] This method, or a variation of it, has been incorporated into software on most modern systems.

There are problems with the use of EF as a measure of ventricular function. EFs calculated by various techniques (eg, echocardiography, ventriculography, gated blood pool scanning) may not be identical because of the mathematical modeling involved. When single-plane ventriculography is used to calculate the EF, dysfunction of a nonvisualized segment (eg, the lateral wall in an RAO ventriculogram) and global function may be overestimated. Most importantly, the EF is a load-dependent measure of ventricular function. Changes in preload, afterload, and contractility can significantly alter the EF determination. Therefore, the EF can vary over time without any change in the myocardium if the loading conditions or the inotropic conditions change. Identification of a load-independent measure of LV function has been the quest of many cardiologists over the years. The best approximation requires pressure-volume analysis under various loading conditions to generate a series of curves. Although pressure-volume curve analysis is not used in routine clinical practice, it provides assessment of the systolic and diastolic properties of the ventricle and has been a valuable research tool (see Chapters 6 and 13). In addition to EF calculations, ventriculography allows for estimation of wall stress and LV mass.

Abnormalities in Regional Wall Motion

Segmental wall motion abnormalities are defined in both RAO and LAO projections. A grading scale of 0 to 5 may be used to identify hypokinesis (decreased motion), akinesis (no motion), and dyskinesis (paradoxic or aneurysmal motion). The values are as follows: 0 = normal; 1 = mild hypokinesis; 2 = moderate hypokinesis; 3 = severe hypokinesis; 4 = akinesis; 5 = dyskinesis (aneurysmal). Each wall segment is identified as outlined in Fig. 3.13 for both the LAO and the RAO projection. These segments correspond roughly to vascular territories.

Other details occasionally can be learned from the ventriculogram. Filling defects, particularly in akinetic or dyskinetic segments, can be seen and are suggestive of intracavitary thrombus. VSDs can be detected and localized. Obliteration of the LV cavity or outflow tract during systole suggests intracavitary obstruction, as seen in HCM.

Assessment of Mitral Regurgitation

A qualitative assessment of the degree of MR can be made with LV angiography. This technique depends on proper catheter placement

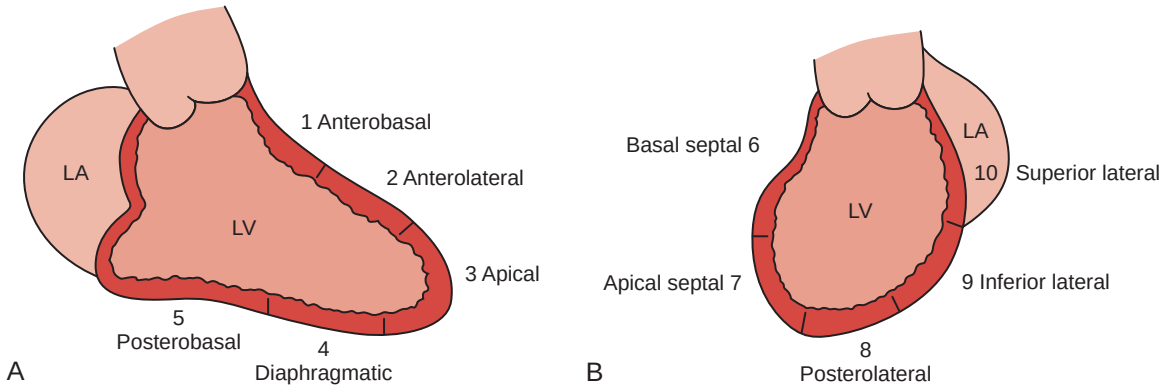


Fig. 3.13 Terminology for left ventricular segments. (A) Terminology for left ventricular segments 1 through 5 analyzed from the right anterior oblique ventriculogram. (B) Terminology for left ventricular segments 6 through 10 analyzed from the left anterior oblique ventriculogram. *LA*, Left atrium; *LV*, left ventricle. *(From Killip T, Principal Investigators of CASS and their Associates. National Heart, Lung, and Blood Institute Coronary Artery Surgery Study.* Circulation. *1981;63[suppl I]:1.)*

outside the mitral apparatus in the setting of no ventricular ectopy. The assessment is, by convention, done on a scale of 1+ to 4+, with 1+ being mild MR and 4+ being severe MR. As defined by ventriculography, 1+ regurgitation is that in which the contrast material clears from the LA with each beat, never causing complete opacification of the LA. Moderate or 2+ MR is present when the opacification does not clear with one beat, leading to complete opacification of the LA after several beats. In 3+ MR (moderately severe), the LA becomes completely opacified and equal in opacification to the left ventricle after several beats. In 4+ MR, the LA densely opacifies with one beat, and the contrast refluxes into the pulmonary veins.

By combining data from left ventriculography and RHC, a more quantitative assessment of MR can be made by calculating the regurgitant fraction. The EDV and ESV are measured, and the difference between them is the total LV stroke volume. The total stroke volume calculated from angiography can be quite high, but in the setting of significant MR, a significant portion of this volume is ejected backward into the LA. The forward stroke volume (FSV) must be calculated from a measurement of forward CO by the Fick or thermodilution method:

$$FSV = CO/HR$$

The regurgitant stroke volume (RSV) then can be calculated by subtracting the FSV from the total stroke volume (TSV):

$$RSV = TSV - FSV$$

The regurgitant fraction (RF) is the RSV divided by the TSV:

$$RF = RSV/TSV$$

An RF of less than 20% is considered mild, 20% to 40% is considered moderate, 40% to 60% is considered moderately severe, and greater than 60% is considered severe MR.

Aortography

The primary indication for aortography performed in the CCL is to delineate the extent of AR. Secondary indications include defining supravalvular lesions and determining the origins of saphenous vein grafts (SVGs). Studies to differentiate proximal and distal dissections may be performed in the CCL. However, TEE, MRI, and CT scanning with contrast are more commonly used to make this diagnosis.[108]

Similar to MR, AR is graded 1+ to 4+ based on the degree of contrast dye present in the LV chamber during aortography. As with MR, assessment of AR is dependent on proper catheter placement free of the valve leaflets but not too high in the ascending aorta. In mild (1+) AR, there is transient filling of the LV cavity by contrast dye that clears after each systolic beat; in moderate (2+) AR, a small amount of contrast dye is regurgitated into the left ventricle and is present throughout the subsequent systolic beat; in moderately severe (3+) AR, a significant amount of contrast dye is present in the left ventricle throughout systole, but not at the intensity of that in the aorta; in severe (4+) AR, contrast dye is present in the left ventricle consistent with the intensity of that in the aorta, with rapid ventricular opacification and delayed clearance after aortic injection.

Coronary Arteriography

Description of Coronary Anatomy

The LM bifurcates into the circumflex (Cx) and LAD arteries and is variable in length (Fig. 3.14). Occasionally, the Cx and LAD arise from separate ostia or the LM trifurcates, creating a middle branch, the ramus intermedius, which supplies the high lateral wall of the left ventricle. Both septal perforators and diagonal branch vessels arise from the LAD, which is described as having proximal, middle, and distal portions based on the location of these branch vessels. The proximal LAD is the portion located before the first septal and first diagonal branch; the middle LAD is between the first and second septal and diagonal branches; and the distal LAD is beyond the major septal and large diagonal vessels. The distal LAD provides the apical blood supply in two-thirds of patients, whereas the distal RCA supplies the apex in the remaining one-third (see Chapters 7 and 20).

The Cx artery is located in the AV groove and is angiographically identified by its location next to the coronary sinus. The latter is seen as a large structure that opacifies during delayed venous filling after left coronary injections. Marginal branches arise from the Cx artery and are the vessels in this coronary artery system usually bypassed. The Cx in the AV groove is often not surgically approachable.

The dominance of a coronary system is defined by the origin of the posterior descending artery (PDA), through which septal perforators supply the inferior one-third of the ventricular septum. The origin of the AV nodal artery often is near the origin of the PDA. In 85% to 90% of patients, the PDA originates from the RCA. In the remaining 10% to 15%, the PDA arises from the Cx artery. Codominance, or a contribution from both the Cx and the RCA, can occur and is defined when septal perforators from both vessels arise and supply the posteroinferior aspect of the left ventricle. Surgical bypass of this region can be difficult when this anatomy exists.

Coronary Anomalies

The coronary anomalies most frequently encountered during coronary angiography are listed in Box 3.7. Anomalous coronary origins are seldom of clinical or surgical significance but potentially make coronary angiography more time-consuming. Rarely, anomalous coronary arteries arising from the opposite cusp and traversing between the PA and the aorta produce vessel compression and ischemia. The Bland–Garland–White syndrome occurs when the LAD arises from the PA. Although most patients present early in life, young adults

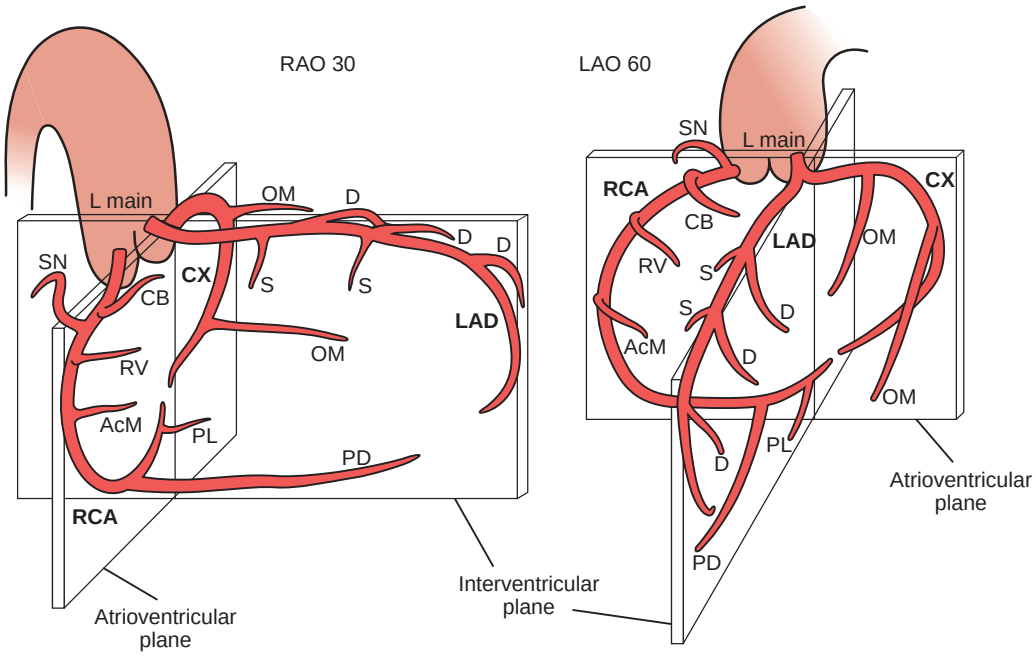
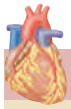


Fig. 3.14 Representation of coronary anatomy relative to the interventricular and atrioventricular valve planes. Coronary branches are indicated as follows: *AcM*, acute marginal; *CB*, conus branch; *CX*, circumflex; *D*, diagonal; *L main*, left main; *LAD*, left anterior descending; *OM*, obtuse marginal; *PD*, posterior descending; *PL*, posterolateral left ventricular; *RCA*, right coronary; *RV*, right ventricular; *S*, septal perforator; and *SN*, sinus node branch. *LAO*, Left anterior oblique; *RAO*, right anterior oblique. *(From Baim DS, Grossman W. Coronary angiography. In: Grossman W, Baim DS, eds.* Cardiac Catheterization, Angiography, and Intervention *[4th ed.]. Philadelphia: Lea & Febiger; 1991:200.)*



BOX 3.7 CORONARY ANOMALIES

Anomalous Coronary Origin
Left main coronary artery from right sinus of Valsalva separately or with right coronary artery
Circumflex artery as a separate origin off right cusp or with common origin with right coronary artery
Right coronary artery as a separate vessel from left cusp with a separate ostium or having a common ostium with the circumflex branch

Coronary Artery From Pulmonary Artery
Left coronary artery (Bland–Garland–White syndrome)
Right coronary artery

Fistula Formation From Normal Coronary Origin
Coronary branch vessels drain directly into right ventricle, pulmonary artery, coronary sinus, superior vena cava, pulmonary vein

with this syndrome also may present with sudden cardiac death or ischemic cardiomyopathy.[109] Fistulas between a coronary artery and a heart chamber (coronary-cameral fistulas) are not uncommon; most are small and of no clinical significance.[110]

A variety of classification systems have been proposed for coronary anomalies. Some systems try distinguishing significant anomalies from minor ones, whereas others consider all anomalies anatomically, independent of clinical or hemodynamic repercussions.[111] The reported incidence of coronary anomalies varies. The life-threatening anomalies, particularly an anomalous origin of the LM from the right sinus, often are diagnosed at autopsy.[111]

Assessing the Degree of Stenosis

By convention, the severity of a coronary stenosis is quantified as *percentage diameter reduction*. Multiple views of each vessel are recorded, and the worst narrowing is used to make clinical decisions. Diameter reductions can be used to estimate area reductions; for instance, if the narrowing were circumferential, 50% and 70% diameter reductions would result in 75% and 91% cross-sectional area reductions, respectively. Using the reduction in diameter as a measure of lesion severity is difficult if diffuse CAD creates difficulty in defining the "normal" coronary diameter. This is particularly true in patients with insulin-dependent DM and in individuals with severe lipid disorders. In addition, the use of percentage diameter reduction does not account for the length of the stenosis.

Qualitative estimates of percentage of diameter reduction are highly variable among different observers and are not reflective of coronary flow. Using a Doppler velocity probe, White and colleagues[112] demonstrated that lesion severity was underestimated in the overwhelming majority of vessels with more than 60% stenosis. However, when visual interpretation is required for clinical decision making, rather than for research purposes, there may be a systematic bias toward overestimation of lesion severity. Quantitative coronary angiography was developed to overcome the pitfalls of qualitative visual interpretation of lumen reductions. Although the technique was cumbersome in its early iterations, most contemporary imaging systems include a usable quantification program.[113] Even with quantification, however, the limitations of angiography remain.[114] This is especially true in LM disease: Patients with an equivocal stenosis by angiography can often be mistakenly categorized unless a functional assessment of the stenosis is performed.[115] Without this physiologic lesion assessment, mischaracterization of the lesion severity can lead to faulty individual decision making about the need for revascularization.

Accurate interpretation of coronary angiograms and quantitation are possible only when high-quality images are obtained. Contrast

injections must be forceful to fully opacify the artery, and pressure tracings must be closely observed to prevent coronary artery dissection. When smaller catheters are used, smaller syringes or power injection may be required for adequate coronary opacification. Branch vessels must clearly be separated with the use of cranial and caudal angulations. Periodic assessment of image quality is required to ensure that the imaging equipment is functioning properly.[16]

Intravascular ultrasound (IVUS) is an imaging modality that uses a miniature transducer in the lumen of the artery to generate a two-dimensional, cross-sectional image of the vessel. Although electronic (phased-array) transducers exist, most intracoronary systems use mechanical rotation to provide 360-degree imaging. This rotation introduces the potential for artifacts that must be recognized as such. Refinements to these systems permit a transducer diameter of about 1 mm with an imaging frequency of 40 megahertz (MHz) for coronary arteries. However, the transducer is placed into the coronary (or peripheral) artery over a 0.014-inch guidewire. Therefore, it entails greater risk than angiography, and anticoagulation is mandatory. The transducer is placed distally in the vessel, and a mechanical system is used to withdraw the transducer at a controlled rate, typically 0.5 mm/second, while a recording is made. Software permits reconstruction of serial cross-sectional images into longitudinal views, and volumetric analysis is possible. Both the lumen and the vessel wall can be imaged. The apposition of stent struts can be confirmed, and small dissections can be seen. Wall constituents such as calcium and pooled lipids can be identified, allowing a "virtual histology" analysis.

IVUS has been a critical research tool over the years. For instance, early stent implantation was associated with a high risk for subacute thrombosis that seemed refractory to anticoagulants. IVUS identified incomplete expansion of many stents with the existing deployment techniques and incomplete apposition of the struts to the vessel wall. Deployment techniques were modified to include higher pressures and larger balloon diameters, and the incidence of subacute thrombosis subsequently receded. The volumetric measurements made possible by IVUS are sufficiently reproducible to gauge the effects of medication on the progression of atherosclerotic plaque. IVUS is used clinically in selected situations. In a study comparing IVUS findings with quantitative angiography, the plaque burden at maximal obstruction frequently was underestimated by quantitative angiography.[114] IVUS is useful in evaluating equivocal lesions of the LM, ostial stenoses, and vessels overlapping angiographically, and it is superior to angiography in early detection of the diffuse, immune-mediated arteriopathy of cardiac transplantation allografts.[116,117] As an adjunct to PCI, IVUS has been used to assess the adequacy of stent deployment, the extent of vessel calcification, and the presence of edge dissections.[118] IVUS reports contain information on diameter reductions and area reductions, which translate to angiographic values. However, an important value in the IVUS report is the minimal luminal area (MLA). Generally, an MLA of less than 4.0 mm^2 in a proximal coronary vessel correlates with an ischemic response during perfusion imaging, and an MLA of less than 6.0 mm^2 in the LM correlates with ischemia. Finally, IVUS can be used to ensure optimal stent sizing and deployment. Similar equipment exists for peripheral vessels, although the role of IVUS in the periphery remains to be delineated.

A newer imaging modality in the CCL, one that produces images similar to those obtained with IVUS, is optical coherence tomography (OCT). The fundamental difference is the use of light rather than ultrasound for the production of high-resolution intracoronary images. The coronary OCT light source uses a bandwidth in the near-infrared spectrum with central wavelengths ranging from 1250 to 1350 nm. At these wavelengths, tissue penetration is limited to 1 to 3 mm, compared with 4 to 8 mm achieved by IVUS.[119] The image is formed by backscattering of light from the vessel wall. With higher resolution, OCT demonstrates higher sensitivity in the detection of stent malapposition, neointimal hyperplasia, and intrastent tissue protrusion, but it is less valuable for imaging plaque size or determining tissue characteristics (Fig. 3.15).[120] Therefore, the main advantage of OCT is to optimize stent deployment. With continued refinements, this imaging modality will likely become more widely used. At the present time, it remains largely a research tool.

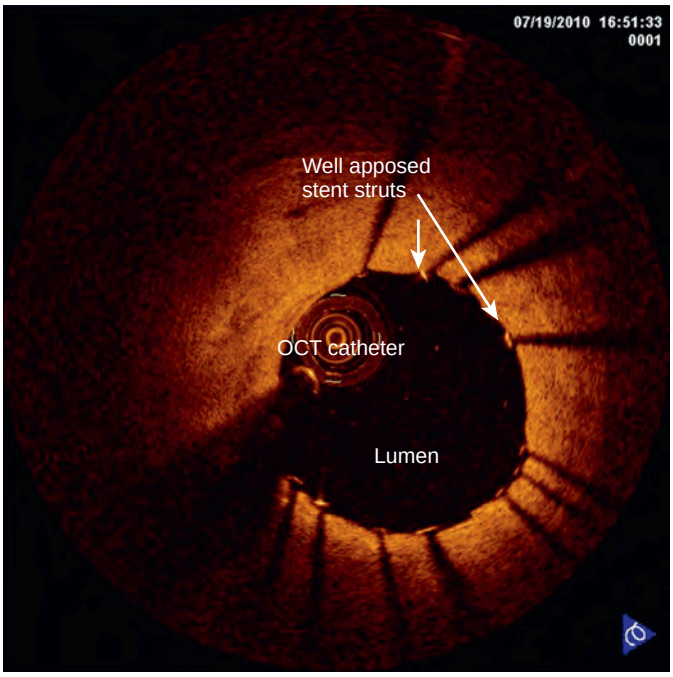


Fig. 3.15 A coronary artery and stent struts after deployment as visualized by optical coherence tomography (OCT).

Anatomic information is usually used to guide management decisions. However, revascularization may offer no advantage over medical therapy when it is guided by anatomic data.[121] This finding has prompted renewed interest in the physiologic assessment of coronary stenoses.[122] One method uses a Doppler probe that is incorporated into a standard, 0.014-inch angioplasty wire (Volcano Therapeutics, San Diego, CA). The Doppler probe is placed distal to the coronary stenosis, and the baseline velocity is recorded. An intracoronary (or IV) agent is administered to produce maximal coronary dilation, and the velocity is recorded again. A normal response is about a fourfold increase in velocity, but for clinical use a value of twofold is used. The stability of velocity recordings varies, and accurate readings require careful placement of the probe into the middle of the vessel. These concerns have limited use of the Doppler wire in clinical practice. An alternative is the Pressure Wire (St. Jude Medical, St. Paul, MN), which incorporates a micromanometer into a standard angioplasty wire. Again, the micromanometer is placed distal to the stenosis, and maximal coronary dilation is induced by administration of an intracoronary or IV vasodilator. The ratio of the distal pressure to the aortic pressure (measured at the tip of the guiding catheter) is calculated at peak vasodilation and is termed the *fractional flow reserve* (FFR). Correlation with nuclear stress testing has been good for both techniques. For instance, an FFR of less than 0.75 after adenosine vasodilation predicts an abnormal nuclear perfusion scan result. This can aid in the assessment of an angiographically borderline stenosis. Clinical outcomes have been good for those patients with a higher ratios.[123,124] Moreover, when PCI is guided by pressure-wire measurements, as opposed to angiography alone, fewer stents are implanted and clinical outcomes are superior.[125–127]

Coronary Collaterals

Common angiographically defined coronary collaterals are described in Box 3.8. Although they are present at birth, these vessels become functional and enlarge only if an area of myocardium becomes hypoperfused by the primary coronary supply.[128] Angiographic identification of collateral circulation requires both knowledge of the potential

BOX 3.8 COLLATERAL VESSELS

Left Anterior Descending Coronary Artery (LAD)
Right-to-Left
Conus to proximal LAD
Right ventricular branch to mid-LAD
Posterior descending septal branches at midvessel and apex

Left-to-Left
Septal to septal within LAD
Circumflex-OM to mid-distal LAD

Circumflex Artery (Cx)
Right-to-Left
Posterior descending artery to septal perforator
Posterior lateral branch to OM

Left-to-Left
Cx to Cx in AV groove (left atrial circumflex)
OM to OM
LAD to OM via septal perforators

Right Coronary (RCA)
Right-to-Right
Kugels—proximal RCA to AV nodal artery
RV branch to RV branch
RV branch to posterior descending
Conus to posterior lateral

Left-to-Right
Proximal middle and distal septal perforators from distal LAD
OM to posterior lateral
OM to AV nodal
AV groove Cx to posterior lateral

AV, Atrioventricular; *OM*, obtuse marginal; *RV*, right ventricular.

BOX 3.9 INTERVENTIONAL CARDIOLOGY TIMELINE

1977 Percutaneous transluminal coronary angioplasty (PTCA)
1991 Directional atherectomy
1993 Rotational atherectomy
1994 Stents with extensive antithrombotic regimen
1995 Abciximab approved
1996 Simplified antiplatelet regimen after stenting
2001 Distal protection
2003 Drug-eluting stents (DES)
2008 Second-generation DES
2010 Percutaneous pulmonary valve approved
2011 Transcatheter aortic valve replacement (TAVR) approved
2012 MitraClip approved
2015 Impella approved

collateral sources and prolonged imaging to allow for coronary collateral opacification.

The increased flow from the collateral vessels may be sufficient to prevent ongoing ischemia. A main coronary or branch vessel must be reduced in luminal diameter by 80% to 90% to recruit collaterals for an ischemic area. Clinical studies suggest that collateral flow can double within 24 hours during an episode of acute ischemia.[129] However, collateral vessels require time to develop, and only well-developed collaterals respond to NTG. The RCA is a better collateralized vessel than the LM. Areas that are supplied by good collaterals are less likely to be dyskinetic or akinetic.

Interventional Cardiology: Percutaneous Coronary Intervention

A timeline of important events in the history of PCI is presented in (Box 3.9). Catheter-based interventions were initially pioneered by Andreas Gruentzig in 1977 as PTCA, and they have expanded dramatically beyond the balloon to include a variety of PCIs.[130] The use of PCI in the United States has grown considerably since the early 1980s; however, the annual volume of PCI procedures peaked in 2006 and has steadily declined since then. Numerous factors have contributed to this reduction in procedural volume, including a reduction in restenosis by drug-eluting stents (DESs), a greater emphasis on medical therapy for the treatment of stable CAD, enhanced primary and secondary prevention efforts, a reduction in the incidence of ST-segment elevation myocardial infarction (STEMI), the increasing use of parameters such as FFR to better evaluate lesion severity, and the development and application of appropriate use criteria.[23]

The discussion of interventional cardiology is divided into two parts. The first part consists of a general discussion of issues that relate to all catheter-based interventions, including indications, operator experience, equipment and procedures, restenosis, and complications. Anticoagulation and controversial issues in interventional cardiology also are reviewed. The second part is a discussion of the various catheter-based systems for PCI, beginning with the first one, PTCA, and including devices in development. With this review, the cardiac anesthesiologist may better understand the current practice and future direction of interventional cardiology.

General Topics for All Interventional Devices

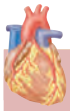
Indications

Throughout the history of PCI, technology and operator expertise have continually advanced. The interventionalist now has the capability to approach places in the coronary tree that were previously inaccessible. This is reflected in the expanded role for PCI. Although PCI was first restricted to patients with single-vessel disease and normal ventricular function who had a discrete, noncalcified lesion in the proximal vessel, it now is performed as preferred therapy in many groups of patients, including selected patients with unprotected LM stenosis (ie, no bypass grafts).[131] The most recently published guidelines state that LM PCI is a reasonable alternative to CABG in patients who have anatomic conditions associated with good procedural and longer-term outcomes and who are at increased risk for surgery.[23]

Box 3.10 provides a summary of current clinical indications for PCI. Primary PCI is the standard of care for patients with STEMI with or without cardiogenic shock.[28,132] Although PCI was initially reserved for patients who were considered suitable candidates for CABG, it is now routinely performed in patients who are not candidates for CABG in both emergent and nonemergent settings.[23] In considering both the indications and the appropriateness of PCI, the physician must review the patient's history, including functional class, treadmill results with or without perfusion data, and wall motion assessment analysis. Noninvasive demonstration of ischemia, either before the procedure or with an intraprocedural physiologic assessment, avoids inappropriate procedures prompted by the significant interobserver variability in visual assessment of percent diameter reduction that occurs even among experienced angiographers.[121,133–135]

Absolute contraindications are few. For unprotected LM stenosis in a patient who is a surgical candidate, has diffusely diseased native vessels, or has a single remaining conduit for myocardial circulation, a PCI approach is used only after the case has been considered by the heart team.[23] Several series of unprotected LM PCI procedures have been published, and this topic is in evolution.[131,136] Although the procedural risk is low, most of these procedures are performed in patients who are not ideal operative candidates (see later discussion). Multivessel PCI frequently is performed and remains a reasonable alternative to CABG in selected patients.[134] However, CABG remains the preferred therapy for many patients, particularly those with DM.[137]

In addition to indications and contraindications, there is the concept of appropriateness. The SCAI, The Society of Thoracic Surgeons (STS), the American Academy of Thoracic Surgeons (AATS), the ACC, and the AHA published a consensus document on coronary revascularization in 2009, followed by an update in 2012.[138,139] These documents attempted to identify the appropriate therapy for various patient scenarios, based on presentation, anatomy, medications, and results of noninvasive and invasive testing. For each scenario, revascularization is considered appropriate, inappropriate, or uncertain. Although this consensus approach is far from all-inclusive and does not replace the physician's judgment in regard to an individual patient, these documents provide an overview of the potential appropriateness of medical therapy, PCI, and CABG.



BOX 3.10 CLINICAL INDICATIONS FOR PERCUTANEOUS TRANSLUMINAL CORONARY INTERVENTIONAL PROCEDURES

Cardiac Symptoms
- Unstable angina pectoris or non–ST-segment elevation myocardial infarction (NSTEMI)
- Angina refractory to antianginal medications
- Angina after myocardial infarction
- Sudden cardiac death

Diagnostic Testing
- Early positive exercise tolerance testing
- Positive exercise tolerance test despite maximal antianginal therapy
- Large areas of ischemic myocardium on perfusion or wall motion studies
- Positive preoperative dipyridamole or adenosine perfusion study
- Electrophysiologic studies suggestive of arrhythmia related to ischemia

Acute Myocardial Infarction
- Cardiogenic shock
- Unsuccessful thrombolytic therapy in unstable patient with large areas of myocardium at risk
- Contraindication to thrombolytic therapy
- Cerebral vascular event
- Intracranial neoplasm
- Uncontrollable hypertension
- Major surgery <14 days previously
- Potential for uncontrolled hemorrhage
- Probably preferred for all cases of ST-segment elevation acute myocardial infarction (STEMI)

Equipment and Procedure

Although the femoral artery is still the most commonly used access site, the radial artery has seen increased adoption, as discussed earlier. Despite numerous advances, all PCIs still involve sequential placement of the following: a guiding catheter in the ostium of the vessel, a guiding wire across the lesion and into the distal vessel, and one or more devices of choice at the lesion site. Routine central venous access is not required and increases access site complications. Its use is reserved for situations in which peripheral venous access is limited, temporary pacing may be required, or hemodynamic monitoring may be helpful.

Guiding catheters are available in multiple shapes and sizes for coronary and graft access, device support, and radial artery entry.[23,130] Guidewires offer flexible tips for placement into tortuous vessels and stiffer shafts to provide support for the newer devices during passage within the vessel. Separate guidewire placement within branch vessels may be required for coronary lesions at vessel bifurcations (Fig. 3.16; see Videos 3-1 and 3-2). In selecting the appropriate device for a particular lesion, IVUS or OCT may be used to determine the size of the vessel and the composition of the lesion.[135,140,141]

While a device is present in a coronary artery, blood flow is impeded to a varying degree. In vessels that supply large amounts of myocardium (eg, proximal LAD), prolonged obstruction of flow is poorly tolerated. However, when only smaller areas of myocardium are jeopardized or the distal vessel is well collateralized, longer occlusion times are possible. Distal protection devices, which involve balloon occlusion, may result in loss of flow down the vessel for up to 5 minutes. However, with current technology, occlusion times seldom exceed 1 minute.

The performance of PCI immediately after a diagnostic procedure is known as an ad hoc intervention. This strategy is obviously preferred in emergent situations and has become the default paradigm in stable CAD as well. It is more convenient for the patient and more cost-effective from a payer standpoint. However, it has been suggested that ad hoc PCI may be performed too frequently in situations in which a procedural pause would be preferable for additional informed consent or for consideration of alternative revascularization strategies.[142] Ad hoc PCI requires careful preparation because the patient and family must understand not only the risks and benefits of the diagnostic procedure but also those of various revascularization strategies. Informed consent is required for all potential procedures before sedation is given. The cardiologist must carefully assess each clinical situation and must have a collegial relationship with his or her surgical colleagues to expedite heart team discussions in cases of complex CAD. In general, ad hoc PCI is appropriate for symptom relief in patients who are receiving optimal antianginal therapy, have symptoms limiting their quality of life, and have evidence of ischemia in the target artery by stress testing or FFR. Among those with stable ischemic heart disease,

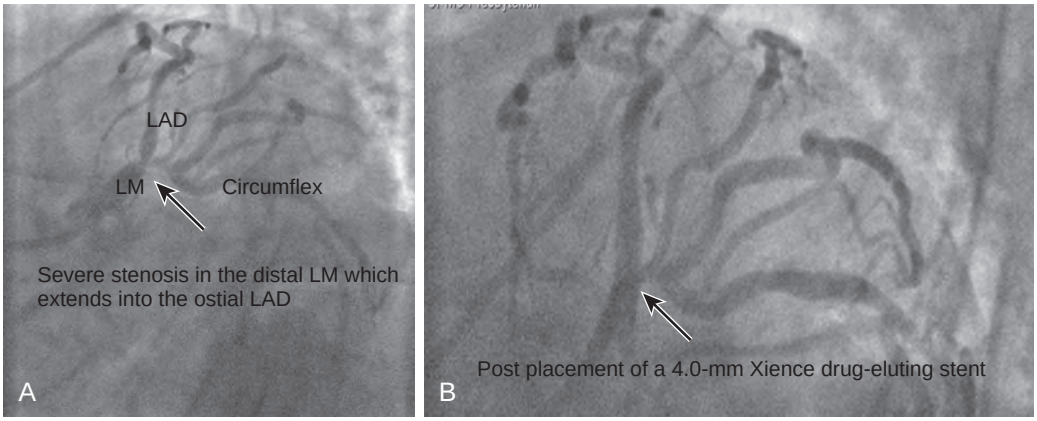


Fig. 3.16 (A) Severe stenosis in the distal left main coronary artery *(LM)* which extends into the ostial left anterior descending coronary artery *(LAD)*. (B) Image obtained after placement of a 4.0-mm Xience drug-eluting stent.

it is most appropriate to proceed with ad hoc PCI when the patient is symptomatic with large areas of myocardium at risk. Ad hoc PCI may be inappropriate if complications have occurred during the diagnostic catheterization, excessive radiation or contrast was used, or a heart team approach is indicated to identify the best strategy for treatment of complex coronary disease.

Antiischemic medications may permit longer periods of vessel occlusion before signs and symptoms of ischemia become limiting.[143] This additional time could permit the completion of a complex case or allow the use of distal protection devices. Most centers use either intracoronary or IV NTG at some point during the procedure to treat or prevent coronary spasm. Intracoronary calcium channel blockers frequently are used to treat vasospasm and the "no-reflow" phenomenon.[144] The latter term describes an absence of flow in a coronary vessel when there is no epicardial obstruction. No-reflow is associated with a variety of adverse outcomes; it is seen when acutely occluded vessels are opened during an MI or when PCI is performed in old SVGs. The cause is believed to be microvascular obstruction from embolic debris or microvascular spasm or both. Intracoronary calcium antagonists may help to restore normal flow, and nicardipine is preferred for its relative lack of hemodynamic and conduction effects.[145] Nitroprusside and adenosine have also been used effectively. Continuous NTG infusions are rarely necessary after PCI unless symptoms or signs of ongoing ischemia are detected.

After the PCI procedure, the patient is transferred to the appropriate unit for the level of care required. The STEMI patient is admitted to the cardiac care unit, the inpatient with ACS often returns to the previous level of care, and the outpatient returns to the equivalent of a preprocedure/postprocedure holding area. As the field of interventional cardiology has changed since the 1970s, so has care of the patient after PCI.[146] Multiple factors enter into the location and duration of post-PCI care. Hospitals must work with physicians and patients to create the appropriate pathways to provide quality patient care.

Restenosis

Once PTCA/PCI became an established therapeutic option for treatment of CAD, two major limitations were realized: acute closure and restenosis. The use of stents and antiplatelet therapy significantly decreased the incidence of acute closure. Before stents were available, restenosis occurred in 30% to 40% of PTCA procedures. With stent use, this figure decreased to about 20%. However, restenosis remained the Achilles heel of intracoronary intervention until the advent of the DES.

Restenosis usually occurs within the first 6 months after an intervention and has three major mechanisms: vessel recoil, negative remodeling, and neointimal hyperplasia.[147] Vessel recoil is caused by the elastic tissue in the vessel and occurs early after balloon dilation. It is no longer a significant contributor to restenosis because metal stents are almost 100% effective in preventing recoil.[148] Negative remodeling refers to late narrowing of the external elastic lamina and adjacent tissue, which accounted for up to 75% of lumen loss in the past.[147] This process also is prevented by metal stents and no longer contributes to restenosis. Neointimal hyperplasia is the major component of in-stent restenosis (ISR) in the current era. Neointimal hyperplasia is more pronounced in the diabetic patient, which explains the increased incidence of restenosis in this population.[149] DESs limit neointimal hyperplasia and have dramatically reduced the frequency of ISR.[150,151]

Establishing the true rate of restenosis requires a uniform definition. Clinical restenosis is defined as recurrence of angina or a positive stress test that results in a repeat procedure. Angiographic restenosis is defined at repeat catheterization and occurs at a greater rate than clinical restenosis. To be classified as a restenotic lesion at follow-up catheterization, there must be a reduction in luminal diameter at least 50% visually, with a decrease of 0.72 mm quantitatively from the post-PTCA result.[152] IVUS can measure the cross-sectional area and may be used in assessing restenosis.[147] Because restenosis usually occurs within 6 to 12 months after intervention, symptoms occurring after the first year more commonly represent progression of atherosclerotic disease.[152]

Several clinical factors have been linked to restenosis. These include cigarette smoking, DM, male sex, absence of prior infarction, and unstable angina. Of these, only DM has consistently shown a statistically significant association with restenosis.[152] Lesion characteristics proven to predict restenosis are lesion location, baseline stenosis diameter and length, post-PTCA stenosis severity, and adjacent artery diameter.[153] In the stent era, the major predictors of restenosis are the presence or absence of DM, lesion length, and stent diameter.

Medical therapy to decrease restenosis has been challenging.[154] Aspirin decreases the risk for acute occlusion but does not significantly decrease the risk for restenosis. The use of cilostazol to prevent ISR has shown promise in the limited clinical trials available.[155] Vascular brachytherapy has been useful to treat ISR, but results for prophylactic treatment have been disappointing.[156,157]

The major gains in combating restenosis have been in the area of stenting.[158] Intracoronary stents maximize the increase in lumen area during the PCI procedure and decrease late lumen loss by preventing recoil and negative remodeling. However, neointimal hyperplasia is enhanced because of a foreign body–like reaction to the stent. Different stent designs and strut thicknesses lead to different restenosis rates.[159,160] Systemic administration of antiproliferative drugs decreases restenosis but causes significant systemic side effects. DESs that use a polymer to attach the antiproliferative drug to the stent have shown the best results to date for decreasing restenosis.[150,151,161]

In the days of balloon angioplasty, the risk for acute vessel closure was 5% to 10%, but these events occurred almost exclusively in the CCL or within the first 24 hours after the procedure. Acute closure was related to dissection, thrombosis, or both. Emergent bypass surgery was frequently necessary to salvage myocardium. Bare metal stents (BMSs) reduced the incidence of acute closure dramatically but introduced a less common phenomenon, stent thrombosis.[162] Stent thrombosis is a rare circumstance, but when it is encountered, it frequently results in a large MI or death. In 2007, the Academic Research Consortium put forth a new standard definition in order to make it possible to compare the true rates of stent thrombosis across different trials and registries. By this definition, early stent thrombosis is defined as an event that occurs within 30 days after the index stent insertion, and late stent thrombosis (LST) is one that occurs between 30 and 360 days after insertion. Very late stent thrombosis is that which occurs after 1 year.[163] In addition to the timing of the event, the definition is also subdivided into definite, probable, and possible stent thrombosis. Adequate stent deployment and thienopyridine therapy reduce the frequently of early stent thrombosis to about 1%.

Important lessons were learned when stent placement was accompanied by brachytherapy. LST was recognized as an important problem and appeared to be caused by delayed coverage of the stent struts. As a result, prolonged use of thienopyridines became imperative because it reduces the likelihood of LST.[164]

In anticipation of a similar situation, namely delayed stent coverage by neointima, the clinical trials of DESs incorporated prolonged thienopyridine therapy. In these trials of predominantly low-risk patients treated with a 3- to 6-month course of thienopyridines, the risk for stent thrombosis was identical to that seen with BMSs, at least out to 1 year.[165] However, case reports and registry reports began to describe LST. Pathologic reports described incomplete tissue coverage of DESs at late time points.[166] In response to this information, the FDA convened a panel to evaluate the problem in December 2006. Several specialty organizations responded by recommending that the course of clopidogrel be extended to 1 year after implantation of a DES if no contraindications exist.[167,168]

Although all DESs have the same general components, they differ with respect to the stent platform, the polymer coating, and the antirestenotic drug type embedded in the polymer. With the advent of second-generation DESs, which use different polymers and different drug elution types, there has been a considerable decline in the rates of LST.[169] This change in technology has reinvigorated the debate about

the optimal duration of dual antiplatelet therapy (DAPT) after DES placement. Randomized published trials have suggested that 6 months of DAPT appears equivalent to longer durations of DAPT.[170] However, another DAPT trial showed improved outcomes in those treated with a combination of aspirin and clopidogrel for 30 months compared with the traditional 12 months.[171] These findings will most likely result in modifications to the current guidelines. Most practicing cardiologists are now attempting to individualize the duration of DAPT by taking into account the type of stent placed, the complexity of the lesion, the patient's bleeding risk, other medical comorbidities, and the need for long-term warfarin or NOAC therapy. Discontinuation of antiplatelet therapy should be approached with caution, and long-term single antiplatelet therapy with aspirin is recommended indefinitely (see Chapters 35 and 44).

Anticoagulation

Thrombosis is a major component of ACS and of acute complications during PCI; its management is continually evolving.[172,173] Proper anticoagulation regimens are essential to limit bleeding complications and thrombotic complications, both of which negatively impact prognosis.[174] This is most important with interventional procedures, in which the guiding catheter, wire, and device in the coronary artery serve as nidi for thrombus. In addition, catheter-based interventions disrupt the vessel wall, exposing thrombogenic substances to the blood. Table 3.3 summarizes current antiplatelet regimens in patients receiving stents (see Chapters 35 and 44).

The primary pathway for clot formation during PCI has proved to be platelet mediated. This has prompted a focus on aggressive antiplatelet therapy. Aspirin was developed in the late 19th century and subsequently was found to block platelet activation by irreversible acetylation of cyclooxygenase. It remains the foundation of antiplatelet therapy for PCI patients. When administered at least 24 hours (and preferably up to 72 hours) before the intervention in doses of 81 to 1500 mg, aspirin decreases thrombotic complications.[172] Aspirin resistance and combination therapy with nonsteroidal antiinflammatory drugs are controversial.[175] Cilostazol, a phosphodiesterase inhibitor with antiplatelet effects, has been used in peripheral vascular disease; data on the use of cilostazol after coronary intervention remain inconclusive.[176]

Clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor block the adenosine diphosphate (ADP) receptor P2Y12 on platelets. Initially, ticlopidine was the thienopyridine used after PCI. However, side effects, including dyspepsia, neutropenia, and a small but clinically significant incidence of thrombotic thrombocytopenic purpura, led to its replacement by clopidogrel, which has a lower incidence of these events.[177,178] Clopidogrel (Plavix) has been shown to be beneficial in patients with ACS for up to 9 months of therapy, both with and without PCI.[179] A 1-month course of clopidogrel is standard therapy after implantation of a BMS for stable disease. An extended course of therapy is used when BMSs are implanted for ACS.[180] At least 1 year of clopidogrel therapy is recommended when a DES is implanted for any indication.[167] Because clopidogrel and prasugrel are prodrugs, their onset of action is slow unless a loading dose is used. A loading dose of 300 or 600 mg is typically administered.[181] The relative efficacy and safety of clopidogrel have been established in men and women, although the variability in individual responsiveness has raised concern.[182,183] Resistance to an antiplatelet drug is a pharmacodynamic phenomenon in which there is no significant reduction from baseline in platelet function after treatment. Despite the variability of platelet reactivity, the most recently updated ACC guidelines do not recommend routine platelet testing in those with stable or unstable coronary syndromes.[23] The 2012 update to the STS guideline on use of antiplatelet drugs in patients undergoing cardiac surgery stated that preoperative point-of-care platelet testing to assess bleeding risk and, ultimately, the timing of surgery may be useful after treatment with usual doses of antiplatelet drugs.[184]

Prasugrel (Effient), like clopidogrel and ticlopidine, is a third-generation thienopyridine prodrug that is converted into an irreversible antagonist of the ADP P2Y12 receptor. However, its onset of action is faster and less variable. When compared with clopidogrel in patients with ACS, prasugrel reduced ischemic complications (ie, nonfatal MI, need for urgent revascularization, and stent thrombosis) but caused more bleeding complications. An unfavorable risk/benefit ratio was identified for three groups: age 75 years or older, body weight less than 60 kg, and a history of stroke or transient ischemic attack. Major bleeding related to CABG was significantly greater with prasugrel (13%, vs 3% with clopidogrel), which is why surgery in patients taking prasugrel should be delayed to permit recovery of platelet function.[185]

Ticagrelor (Brilinta) is a newer, nonthienopyridine inhibitor of the P2Y12 receptor. Unlike the other drugs in its class, binding to the P2Y12 receptor is reversible. It has a much faster onset of action than clopidogrel and has been assigned to a new chemical class of antiplatelet agents, the cyclopentyltriazolopyrimidines. Its safety and effectiveness was documented in the PLATO trial, which involved 18,000 patients presenting with an ACS. There was an overall 2% absolute risk reduction in the composite end point of death, recurrent MI, or cerebrovascular accident with ticagrelor compared with clopidogrel.[186]

TABLE 3.3 Anticoagulation in the Catheterization Laboratory

Medication	*Dose*	*Mechanism of Action*	*Half-Life*	*Monitoring*
Antiplatelet Medications				
Aspirin	75–325 mg	Acetylates cyclooxygenase	3 h	Platelet function assays
Clopidogrel	300–600 mg loading dose 75 mg daily	Irreversibly binds to P2Y12 platelet receptor	6 h	Platelet function assays
Prasugrel	300 mg loading dose 5–10 mg daily	Irreversibly binds to P2Y12 platelet receptor	7 h	Platelet function assays
Ticagrelor	300 mg loading dose 90 mg bid daily	Irreversibly binds to P2Y12 platelet receptor	7 h	Platelet function assays
Glycoprotein IIb/IIIa Inhibitors				
Abciximab	0.25 mg/kg bolus 0.125 μg/kg per min infusion	Monoclonal antibody GPIIb/IIIa platelet receptor inhibition	30 min	Platelet function assays
Eptifibitide	180 μg/kg bolus 2 μg/kg per min infusion	Cyclic heptapeptide GPIIb/IIIa platelet receptor inhibition	2.5 h	Platelet function assays
Tirofiban	25 μ/kg bolus 0.15 μg/kg per min infusion	Nonpeptide GPIIb/IIIa platelet receptor inhibition	2 h	Platelet function assays
Anticoagulants				
Heparin	70–100 U/kg bolus	Indirect inhibitor of thrombin	Dose-dependent, ~1 h	Activated clotting time (ACT), partial thromboplastin time (PTT)
Enoxaprin	0.5–0.75 mg/kg bolus	Inhibitor of factor Xa	4 h	Anti-Xa levels
Bivalirudin	0.75 mg/kg bolus 1.75 mg/kg per h infusion	Direct thrombin inhibitor	25 min	ACT

Another important finding suggested a potential negative interaction between ticagrelor and high-dose aspirin. Therefore, the current recommendations suggest that patients maintain their daily dose of aspirin at 100 mg or less when used in conjunction with ticagrelor for the treatment of ACS, including those patients who undergo stenting.

Cangrelor is another ADP inhibitor that is unique in its delivery form as an IV agent. Advantages of cangrelor, which might improve clinical outcomes over other antiplatelet agents, are its rapid onset of action and rapid return of platelet function after cessation. Cangrelor (Kangrelor) was approved for clinical use by the FDA in late 2015.[187]

Several additional issues should be highlighted regarding antiplatelet therapy. Thienopyridine therapy for ACS patients has been shown to reduce cardiac events, but concerns have been raised about bleeding should CABG be necessary. The consistency and magnitude of this observation have not been sufficient to limit its use in these situations.[188] Management of patients undergoing invasive or noncardiac surgical procedures on DAPT is complicated and requires consideration of all options (see Chapter 44). The risks associated with drug discontinuation (stent thrombosis, MI, death) must be weighed against the risks of continuation of the drugs (bleeding) and the risks of cancellation or deferral of the procedure.[189] All antiplatelet and anticoagulant medications increase the risk for bleeding, and DAPT increases the risk more than single therapy does. The ACC, the American College of Gastroenterology, and the AHA published a Clinical Expert Consensus Document in 2008. This document recommended therapy with a proton pump inhibitor (PPI) for virtually all patients receiving DAPT.[190] More recently, observational data suggested that the combination of clopidogrel and a PPI was associated with a greater rate of ischemic events, and ex vivo studies showed that the combination was associated with less inhibition of platelet function than clopidogrel alone. This led to an FDA warning about the combination in 2009, which was followed by the performance of a randomized trial. The conclusions were that among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. In addition, there was no apparent cardiovascular interaction between clopidogrel and omeprazole.[191]

Another clinical conundrum involves combining antiplatelet and anticoagulant therapy in patients with concomitant coronary vascular disease and a high CHA_2DS_2-VASc atrial arrhythmia score,[32a] a combination that has been shown to increase an individual's bleeding risk.[192,193] When confronted with this scenario, many physicians avoid triple therapy with warfarin, aspirin, and a thienopyridine. Published data have shown a reduction in bleeding with double therapy (clopidogrel plus warfarin) compared with triple therapy.[194] Depending on the type of stent used and the time course of treatment, the regimen may also consist of warfarin plus acetylsalicylic acid, which produces an even lower bleeding rate.[192] Overall, the optimal treatment for these patients requires careful consideration of the indications for each therapy as the risks and benefits of combination therapy are weighed.

UFH has been used since the inception of PTCA, with the dose regimen undergoing significant evolution over time. Initially, high doses were used to prevent abrupt closure of the vessel. With experience and the introduction of stents, the dosing has evolved into a weight-based regimen (70–100 U/kg) that is routine and endorsed by the guidelines.[23] The ACT is monitored to guide additional heparin therapy. Protamine is not routinely used, and the femoral sheaths are removed once the ACT is 150 seconds or less. If a transradial approach is used, the sheath is removed immediately after the procedure and a transradial band is placed to apply hemostatic pressure while allowing for adequate perfusion to the affected hand (patent hemostasis). Limitations of UFH include a variable antithrombotic effect requiring frequent ACT measurements, inability to inhibit clot-bound thrombin, and concerns regarding heparin-induced thrombocytopenia syndrome. These limitations have led to the search for a replacement for UFH.[195]

As an alternative to heparin, direct thrombin inhibitors have been investigated in the setting of PCI. The synthetic compound bivalirudin (Angiomax; The Medicines Company, Parsippany, NJ) is the best studied of these agents (see Chapter 35). The advantage of direct thrombin inhibitors is the direct dose response and the shorter half-life, which leads to a lower incidence of bleeding complications. The Bivalirudin Angioplasty Trial randomized 2161 patients and supported the hypothesis that bivalirudin reduces ischemic complications marginally but reduces bleeding dramatically during PCI, compared with UFH.[196] The REPLACE-2 trial randomized 6010 patients undergoing PCI (primarily stenting) to bivalirudin or UFH with glycoprotein IIb/IIIa (GPIIb/IIIa) inhibition.[197] MACEs were similar between the two groups, but major bleeding was significantly less in the bivalirudin group. The ACUITY trial studied 13,819 patients with ACS undergoing PCI, comparing bivalirudin alone with either UFH or enoxaparin and a GPIIb/IIIa inhibitor (GPI). One-year results showed no difference in composite ischemia or mortality among the three groups.[198] The HORIZONS-AMI trial randomized 3602 STEMI patients undergoing PCI to bivalirudin or UFH with a GPI. The bivalirudin group had fewer clinical events, lower mortality rates (cardiac and total), and less major bleeding at 1 year.[199] As a result of these studies, bivalirudin has become the most widely used antithrombin agent for ACS patients. However, newer data have questioned the superiority of bivalirudin over UFH alone with lower dosing and selective use of GPIs. The recently published HEAT-PPCI trial showed no difference in bleeding rates but higher rates of definite stent thrombosis in the bivalirudin arm, and this finding has prompted many operators to reconsider UFH as the first-line antithrombin agent.[200]

Argatroban, another direct thrombin inhibitor, is also approved for use during PCI, although fewer data are available. The direct thrombin inhibitors are easier to use but more expensive than UFH; they are similar in cost to the combination of UFH and a GPI. There currently is no known agent to reverse the effects of these new compounds (see Chapter 35). In patients with normal renal function, coagulation can be expected to return to normal in about 2 hours.

LMWHs are obtained by depolymerization of standard UFH. LMWHs were developed to overcome the limitations of UFH.[201] Enoxaparin (Lovenox) has been studied extensively in patients with ACS. Overall, enoxaparin use leads to a slight reduction in the occurrence of MI when compared with UFH and has a similar side-effect profile.[202] The NICE trials were registries of patients treated with enoxaparin instead of UFH during PCI.[203] In addition, the SYNERGY trial was a randomized comparison of enoxaparin and UFH in patients with an ACS for whom early catheterization was planned; about half of both groups underwent PCI.[204] Based on these and smaller trials, enoxaparin and UFH seem to be associated with similar rates of cardiac events and bleeding complications when used during PCI. Therefore, most interventionalists are comfortable with the use of enoxaparin for ACS and the management of patients receiving enoxaparin in the periprocedural period. However, UFH offers several advantages for the patient who arrives in the CCL without prior antithrombin therapy: a shorter half-life, which facilitates sheath removal; the ability to easily monitor the drug's effect by measuring the ACT; and the ability to reverse the effect of UFH with protamine.

The OASIS 5 trial studied 20,078 patients with ACS who were randomized to enoxaparin or fondaparinux. Fondaparinux is a synthetic pentasaccharide that is thought to bind to the high-affinity binding site of the anticoagulant factor, antithrombin III, increasing the anticoagulant activity of antithrombin III 1000-fold. In patients receiving fondaparinux plus either GPIs or thienopyridines, bleeding was reduced and net clinical outcomes were improved compared with enoxaparin. Although fondaparinux was found to be safe and effective in a few trials, it was associated with an increased risk of guide catheter–related thrombosis in patients who underwent PCI.[205] Because of this potential harmful complication, fondaparinux was given a class III recommendation (harmful therapy) in the updated STEMI guidelines for patients being treated with primary PCI.[29]

Arterial thrombi are rich in platelets. Prevention of these thrombi is complicated by the fact that platelets aggregate in response to many stimuli. Aspirin inhibits only one of these pathways. The final common aggregation pathway is the GPIIb/IIIa receptor on the platelet surface. Fibrinogen can bind to two GPIIb/IIIa receptors on separate platelets to permit aggregation. Several compounds have been developed to target this receptor. The chimeric monoclonal antibody, abciximab (ReoPro) was the first GPI (GPIIb/IIIa inhibitor) approved. Abciximab is given as a bolus followed by a 12-hour infusion. Bleeding times increase to more than 30 minutes, and ex vivo platelet aggregation is almost abolished. The platelet binding of this compound essentially is irreversible, and more than 48 hours is required for normal platelet function to return. During the clinical trials of this agent, patients requiring emergency CABG experienced no significant increase in adverse events with platelet transfusions used to restore normal platelet function. In the EPIC study of high-risk PCI patients, abciximab reduced early ischemic complications by 35% and late events by 26%, with an increase in vascular complications.[206] In the EPILOG study, a similar benefit in lower-risk interventional patients was seen.[207] In addition, fewer vascular complications occurred when adjunctive heparin was used in lower doses, and vascular access site management improved. Abciximab is more expensive than the other GPIs, and its repeated use may lead to thrombocytopenia.[208]

The other GPI compounds, eptifibatide (Integrilin) and tirofiban (Aggrastat), are not antibodies but rather synthetic agents that bind reversibly to the GPIIb/IIIa receptor. Both have half-lives of approximately 1.5 hours in patients with normal renal function; normal hemostasis returns within 6 hours after cessation of the medication.[209] Standard doses lead to very high plasma concentrations of these medicines, so a platelet transfusion is less effective in correcting the hemostatic defect with these agents compared with abciximab. Studies have shown that eptifibatide plus UFH is superior to UFH alone in stable patients undergoing PCI, abciximab plus UFH is superior to UFH alone, and abciximab is superior to tirofiban in more unstable patients undergoing PCI.[210,211] GPIs have not proved beneficial in SVG interventions.[212]

Currently, the choice of GPI for patients undergoing PCI is controversial because the reduction in ischemic complications is almost offset by the increased bleeding complications. Presently, there are four general indications for GPI use: (1) patients with a non–ST-segment elevation myocardial infarction (NSTEMI) undergoing PCI, particularly if they have not been adequately preloaded with a thienopyridine; (2) patients with thrombotic complications or large side-branch closure during any PCI; (3) selected patients with STEMI, particularly those not preloaded with a thienopyridine in the emergency department and those with a large thrombus burden visualized on angiography; and (4) patients undergoing ad hoc PCI for stable or unstable CAD who are not adequately preloaded with a thienopyridine.[213,214] Several oral GPIs have been used in clinical trials, but the results were disappointing for reasons that remain unclear.[215]

Thrombolytic therapy has been used for the treatment of STEMI since the 1980s. Although some of the early studies used intracoronary administration of thrombolytics, the need for a CCL precluded widespread adoption, and IV administration of thrombolytics became standard treatment for STEMI. Several agents have been used, including streptokinase, anistreplase, alteplase, reteplase, and tenecteplase.[216] Alteplase, reteplase, and tenecteplase are recombinant variations of tissue plasminogen activator and are specific for fibrin (as opposed to fibrinogen). They differ primarily in their half-lives, a difference that affects the dosing regimens. Since the early 1990s, emergent or primary PCI has evolved as an alternative, and often this treatment is preferable to use of IV thrombolytics. With both therapies, time to treatment correlates with myocardial salvage and clinical outcome.[217] In the setting of planned primary PCI, use of adjunctive thrombolytic agents (classified as facilitated PCI) has not proved beneficial and may be detrimental.[28,218] In patients with unsuccessful thrombolytic therapy, rescue PCI is beneficial but not without risk, whereas repeat thrombolysis is ineffective.[28,219]

Outcomes: Success and Complications

An important component of an interventional cardiology program is quality assessment. This is not just a score card of complications; it is a process in which risk-adjusted outcomes are compared with national standards and the results are used to identify avenues for improvement.[220,221] Tracking of outcome data has been a feature of interventional cardiology since its beginning and has contributed to the rapid developments in the field. The history of interventional cardiology has been marked by an increase in success rates with a simultaneous decrease in adverse events. This reflects both significant technologic advancement and increased operator skill, both of which were facilitated by the systematic collection of outcomes data. PCI once was considered successful if the luminal narrowing was reduced to less than 50% residual stenosis.[222] In current practice with stent placement, a residual stenosis greater than 20% is seldom accepted, and excellent stent expansion without edge dissection is required before termination of the procedure.[223] The initial National Heart, Lung, and Blood Institute (NHLBI) PTCA registry from 1979 to 1983 reported a success rate of 61% and a major coronary event rate of 13.6%. The 1985 to 1986 NHLBI registry reported a success rate of 78%, with a 4.3% incidence of AMI and a 3.4% incidence of emergency CABG.[218] In the current stent era, success rates are greater than 95% and emergent surgery rates are less than 1% in laboratories performing more than 400 PCIs annually.[224]

The ACC developed the NCDR in the 1990s. Currently, more than 1000 CCLs in the United States participate. Participation in NCDR is voluntary and requires a dedicated employee at each facility for data entry. Outcomes for both diagnostic and interventional procedures are tabulated, adjusted for baseline risk, and provided to the participating facility. Results from an ACC NCDR publication are listed in Table 3.4.

Recent plateaus in the rates of success and complications reflect not only the maturity of the field and changes in demographics but also the scope of practice of PCI. As older patients with more comorbidities undergo PCI, further statistical improvements will be harder to achieve, but risk-adjusted outcomes must be studied. From and colleagues[225] looked at a 19-year experience with PCI in 138 patients 90 years of age or older. There was a high technical success rate and a relatively low morbidity and mortality rate when the patients were properly selected. Patients with chronic total occlusions (>3 months) have also been studied. In an era of increased technical advances, these patients have seen improved procedural success, long-term vessel patency, and survival outcomes.[226] The Occluded Artery Trial (OAT) entered 2201 patients more than 3 days after MI with vessel occlusion, followed them for longer than 3 years, and demonstrated no benefit across various risk categories when PCI was performed.[227] Continued attention to outcomes data will help to identify the limits of PCI.

The incidence of procedure-related MI is controversial and depends on the definition of MI (eg, new Q waves, total creatine kinase [CK] increase, CK-isoform elevation, troponin elevation).[228] Increased CK levels occur in approximately 15% of catheter-based interventional procedures, with significant increases (threefold baseline) present in

TABLE 3.4 Morbidity and Mortality for Percutaneous Coronary Intervention

Complication	*Outcome (%)*
Dissection	5
Abrupt closure	1.9
Successful reopening	41
Angiographic success	94.5
Postintervention myocardial infarction	0.4
Coronary artery bypass graft surgery	1.9
Death	1.4
Clinical success	92.2
No adverse events	96.5

From Anderson HV, Shaw R, Brindis RG, et al. A contemporary overview of percutaneous coronary interventions. The American College of Cardiology–National Cardiovascular Data Registry (ACC-NCDR). J Am Coll Cardiol. 2002;39:1096.

TABLE 3.5 Lesion-Specific Characteristics of Type A, B, and C Coronary Lesions[a]

Type A Lesions (Least Complex)	
Discrete (<10 mm length)	Little or no calcification
Concentric	Less than totally occlusive
Readily accessible	Nonostial in location
Nonangulated segment, <45 degrees	No major branch involvement
Smooth contour	Absence of thrombus
Type B Lesions (Intermediate)	
Tubular (10–20 mm in length)	Moderate to heavy calcification
Eccentric	Total occlusions <3 mo old
Moderate tortuosity of proximal segment	Ostial in location
Moderately angulated, >45 segment degrees, <90 degrees	Bifurcation lesions requiring double guidewires
Irregular contour	Some thrombus present
Type C Lesions (Most Complex)	
Diffuse (>2 cm in length)	Total occlusions >3 mo old
Excessive tortuosity of proximal segment	Inability to protect major side branches
Extremely angulated segments >90 degrees	Degenerated vein grafts with friable lesions

[a]American Heart Association/American College of Cardiology classification of lesion type.

From Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous transluminal angioplasty. *J Am Coll Cardiol.* 1993;22:2033.

8%.[228] These figures are even greater for interventions in SVGs and with some devices. For years, routine enzymatic assessment of interventional procedural infarctions has been performed at the discretion of the operator. Some studies have suggested that long-term outcome is adversely related to even small periprocedural increases in troponin values ("infarctlets").[229] These increases are reduced by GPIs. Stone and coworkers[230] published data from 7143 PCI patients. In their study, CK-MB isoenzyme increases of more than eight times the upper limit of normal were predictive of death in the subsequent 2-year follow-up. However, smaller enzyme increases, including a threefold increase of enzymes seen in 17.9% of patients, proved to have no impact on survival.[230]

In 1988 (revised in 1993), the ACC/AHA task force developed a lesion morphology classification in an attempt to correlate the complexity of lesions with outcomes. This anatomic characterization of lesion complexity is outlined in Table 3.5. However, as operators have gained experience and equipment has improved, complication rates have decreased across all subsets. A 1998 study of more than 1000 consecutive lesions identified success rates for A, B1, and B2 lesions as approximately equal (95% to 96%), with only C lesions having success rates lower than 90% (88%).[231] B1 lesions are characterized as containing one of the characteristics in Table 3.5, and B2 lesions are characterized as containing two of the characteristics in Table 3.5. The Mayo Clinic devised a risk score for PCI and compared it with the ACC/AHA criteria in 5064 PCIs. They found that the ACC/AHA criteria better predicted success, whereas complications were better predicted with the Mayo classification.[232]

Bleeding complications related to PCI have been studied extensively because they are associated with prolonged hospitalization, increased hospital costs, patient dissatisfaction, morbidity, and 1-year mortality.[233,234] Various anticoagulation regimens to maximize efficacy and minimize bleeding have been studied and were discussed earlier. At present, bleeding avoidance strategies are strongly recommended and encompass procedural (radial artery approach, fluoroscopy-guided femoral approach), pharmacologic (low-dose heparin, shorter GPI infusions, bivalirudin), and technologic (vascular closure devices) strategies.[235]

Iatrogenic pericardial effusion and tamponade are infrequent complications of PCI and may be life-threatening if a large perforation occurs or a small perforation goes unrecognized. Because this is most commonly an acute event, relatively small amounts of blood can result in hemodynamic compromise. The incidence of these events during PCI varies and commonly is reported as occurring in 1% of cases or fewer. However, this complication is dependent on the guidewire and interventional devices, with hydrophilic wires and atherectomy catheters more likely to be involved. Tamponade can also occur in non-PCI procedures such as AF ablation, pacemaker placement, valvuloplasty, use of percutaneous closure devices, and percutaneous valve replacement. Prompt recognition of tamponade is required after PCI or other cardiac procedures and can be facilitated with emergent echocardiography. Pericardiocentesis is life-saving and should be performed without delay.[236]

Intimal dissection was a significant issue in the prestent era, occurring in up to 10% of all PTCAs. Propagation of an intimal dissection is the leading cause of vessel occlusion during an intervention. It is normally initiated by arterial disruption by the PCI device, but it also may be caused by the guiding catheter or wire. Stenting significantly reduces these events by approximating the intimal dissection flap and reestablishing flow down the true lumen.

Bifurcation lesions have become a significant area of interest in the stent era. Side-branch occlusion caused by displacement of plaque from the primary vessel lesion occurs in 1% to 20% of patients, and bifurcation lesions often require attention to both the primary and secondary branch vessels. Various techniques have been used to protect the side branch, ranging from primary vessel stenting with balloon dilation of the branch vessel through the stent strut to various types of branch-vessel stenting. The "crush" technique involves stenting of both the primary and the branch vessel; the initial success rates are excellent, but side-branch restenosis may be a problem.[237] The bifurcation stent technique most widely practiced currently, based on clinical outcomes for non-LM coronary lesions, is treatment of the main branch with provisional stenting of the side branch.[238] In other words, the main vessel is stented, and if adequate flow is maintained in the side branch, no further treatment is rendered (Fig. 3.17).

Recognition of high-risk lesions and patient characteristics allows the cardiologist to better predict which patients are at increased risk for catheter-based interventional therapy.[161] In current interventional practice, when a high-risk patient is identified, the cardiologist should share this information with the surgeon and anesthesiologist so that patient care is not compromised in the event of an emergency.

Operating Room Backup

When PTCA was introduced, all patients were considered candidates for CABG. The physician learning curve in the early 1980s was considered to be 25 to 50 cases; increased complications were seen during these initial cases.[20,21,130] All PCI procedures had immediate OR availability, and often the anesthesiologist was present in the CCL. In the 1990s, OR backup was necessary less often. Perfusion catheter technology had developed to allow for longer inflation times with less ischemia.[239] Over time, the need for emergency surgery declined dramatically as a result of more experienced operators, improved techniques, better stents, and improved antiplatelet and anticoagulation regimens.[240] Because the incidence of emergent CABG has been reduced to 0.2% of PCI procedures, more institutions are beginning to perform PCI despite lack of cardiac surgery facilities on site. The main reasons are to provide timely access for primary PCI in patients with STEMI and to provide care to patients who do not want to travel. In 1911, the AHA, the American College of Cardiology Foundation (ACCF), and the SCAI updated their recommendations for PCI without surgical backup[22] (Table 3.6). Although many coronary lesions can be treated at stand-alone PCI centers, the 2014 SCAI/ACC/AHA guidelines state that intervention should be avoided in patients with specific coronary lesions (Box 3.11) and that transfer for emergency CABG must occur when there is high-grade LM or three-vessel disease with clinical or hemodynamic instability after a successful or unsuccessful PCI attempt in an occluded vessel or if there is a failed or unstable PCI result and ongoing ischemia with IABP support.[241] Transfer agreements with established oversight hospitals with on-site cardiac surgery capability are required; minimal requirements for operators and institutions must be met, and a comprehensive quality assurance program must be in place.[24]

Infrequently, high-risk interventional cases still may require a cardiac OR on immediate standby. This may occur in an emergent

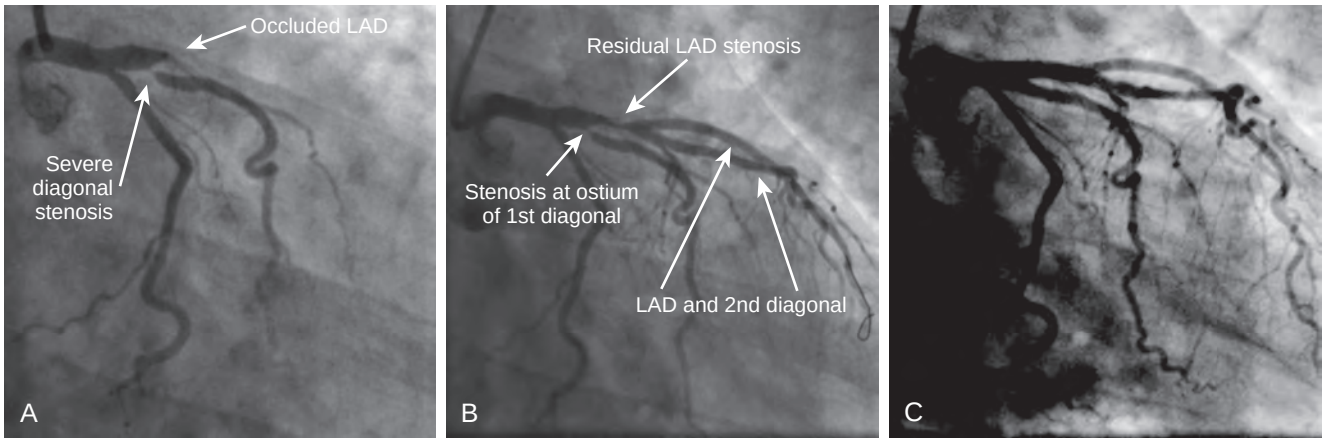


Fig. 3.17 Primary percutaneous coronary intervention for an anterior ST-elevation acute myocardial infarction (STEMI). (A) Complete occlusion of the left anterior descending artery *(LAD)* and high-grade stenosis of the first diagonal. (B) After thrombectomy. Antegrade flow is restored in the LAD and a second diagonal, but severe stenosis persists in the LAD. (C), After stenting of the LAD and first diagonal.

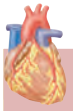
TABLE 3.6 Recommendations for Percutaneous Coronary Intervention (PCI) Without Surgical Backup

Primary PCI is reasonable in hospitals without on-site surgery provided that appropriate planning for program development has been accomplished.	Class IIa Level of Evidence B
Elective PCI might be considered in hospitals without on-site cardiac surgery provided that appropriate planning for program development has been accomplished and rigorous clinical and angiographic criteria are used for proper patient selection.	Class IIb Level of Evidence B
Primary or elective PCI should not be performed in hospitals without on-site cardiac surgery capabilities without a proven plan for rapid transport to a cardiac surgery operating room in a nearby hospital or without appropriate hemodynamic support capability for transfer.	Class III Level of Evidence C

From Levine GN, Piates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *J Am Coll Cardiol.* 2011;58:e44.

situation in which a patient with STEMI requires assistive support during primary PCI[242] or, more electively, when a patient is identified as being at high risk but is not a candidate for a hybrid laboratory or no such facility is available.[8] A preoperative anesthetic evaluation that allows for assessment of the overall medical condition, past anesthetic history, current drug therapy, and allergic history as well as a physical examination concentrating on airway management considerations is reserved for these high-risk cases.

Regardless of the location of the interventional procedure, when an emergency CABG is necessary, it is essential either to have an OR with a basic cardiac setup ready to go or to have the cardiology and surgery teams provide enough lead time to adequately prepare an OR. A basic cardiac setup includes the essential equipment to perform a CABG and an anesthesia setup with emergency medications such as heparin, epinephrine, vasopressin, and norepinephrine available to support the circulation until the patient is placed on cardiopulmonary bypass (CPB), as well as invasive monitors such as TEE and transducers to measure arterial blood pressure, central venous pressure, and pulmonary artery pressures and resuscitative devices including defibrillators and pacemakers. These patients are often critically ill, with ongoing myocardial injury and circulatory collapse. Time is critical to limit the damage and prevent death. Therefore, the sooner the anesthesiologist, staff, and OR personnel are aware of an arriving patient in this perilous condition, the better for all involved. In addition, because this situation occurs infrequently, cooperation among the interventionalist, the surgeon, and the anesthesiologist is essential for optimal patient care in this critically ill population.



BOX 3.11 CHARACTERISTICS THAT MAKE PERCUTANEOUS CORONARY INTERVENTION INAPPROPRIATE IN STAND-ALONE CENTERS

Avoid Treatment

- >50% Stenosis of the LM proximal to the infarct-related lesion, especially if the area in jeopardy is small and the overall LV function is not severely impaired
- Long, calcified, or severely angulated target lesions at high risk for PCI failure
- Lesions in areas other than the infarct artery unless they appear to be flow limiting in patients with hemodynamic instability or ongoing symptoms
- Lesions with TIMI flow grade 3 in patients with LM or three-vessel disease if CABG is more likely to be a superior revascularization strategy
- Culprit lesions in more distal branches that jeopardize only a modest amount of myocardium if there is more proximal disease that could be worsened by attempted intervention
- Chronic total occlusion

Transfer for Emergency CABG

- High-grade LM or three-vessel disease with clinical or hemodynamic instability after successful or unsuccessful PCI attempt in an occluded vessel, preferably with IABP support
- Failed or unstable PCI result and ongoing ischemia, with IABP support

CABG, Coronary artery bypass graft surgery; *IABP*, intraaortic balloon pump; *LM*, left main coronary artery; *LV*, left ventricular; *PCI*, percutaneous coronary intervention; *TIMI*, Thrombolysis in Myocardial Infarction grading system.
Modified from Dehmer GJ, Blankenship JC, Cilingiroglu M, et al. SCAI/ACC/AHA expert consensus document: 2014 Update on percutaneous coronary intervention without on-site backup. *Catheter Cardiovasc Interv.* 2014;84:169.

General Management for Failed Percutaneous Coronary Intervention

The main causes of PCI failure are coronary dissection, suboptimal lumen enlargement, no-reflow, and coronary artery perforation.[243] Levi and colleagues[244] reviewed PCIs in STEMI patients from 2001 to 2010 and found that the incidence of primary PCI failure was 5.4%. Independent predictors of primary PCI failure included age greater than 65 years, female sex, unfavorable preprocedural Thrombolysis in Myocardial Infarction (TIMI) grade, presence of vessel calcifications,

and operational factors including nighttime interventions and PCI performed during the first years of the study. Failed reperfusion increased the risks of 30-day, 6-month, and 1-year mortality.

Most PCI failures result from suboptimal lumen enlargement or no-reflow, and most are treated conservatively. Patients undergo repeat PCI, and in most cases flow is restored. If a significant area of myocardium is at risk, these patients can undergo an elective CABG. Of the 5% of patients who present to the OR for emergency CABG, 75% (6.2% of all failures) have coronary artery dissection and the remainder have a mechanical obstruction that produces hemodynamic instability.[243] In such instances, myocardial ischemia or infarction ensues, depending on the degree of collateralization.[245]

In preparation for the OR, a perfusion catheter, pacemaker, and/or PAC may be inserted in the CCL, depending on patient stability, OR availability, and patient assessment by the cardiologist, cardiothoracic surgeon, and anesthesiologist. Although these procedures are intended to better stabilize the patient, this is achieved at the expense of ischemic time. An IABP or one of the newer support devices may be placed. Although these devices can reduce the myocardial oxygen requirements, myocardial necrosis still will occur in the absence of coronary or collateral blood flow. The anesthesiologist should examine the vascular sheaths that are in place and determine which ones are venous and which arterial. He or she should also review any inotropic, vasoactive, and anticoagulant medications that have been administered and determine whether blood products are available (Box 3.12).

In the OR, anesthetic management depends on the hemodynamic instability of the patient. Hemodynamically stable patients can have a controlled induction and intubation with placement of invasive monitors including intraarterial and central venous catheters. If heart failure is anticipated after CPB, placement of a PAC with $S\bar{v}O_2$ and continuous CO measurements will be beneficial, especially if ventricular assist device placement is anticipated. A TEE is also beneficial in these patients. *Because these patients usually have received significant anticoagulation with heparin and occasionally with GPIs, attempts at catheter placement should not be undertaken when direct pressure cannot be applied to a vessel.* The most experienced individual should perform these procedures.

Patients who arrive in cardiogenic shock may require preinduction inotropic support to prevent cardiovascular collapse during induction and intubation. As with all heart failure patients, it is important to remember that these patients have a slower circulatory time and IV inductions will be slower; they also are more susceptible to the hemodynamic effects of the inhalation agents. For induction, medications that provide the most stable hemodynamics should be used.

The worst scenario is the patient who arrives in the OR in profound circulatory shock or in full cardiopulmonary arrest. In these patients, CPB should be established as quickly as possible, and it is important to have IV heparin prepared to anticoagulate the patient before bypass. No attempt to establish access for monitoring should be made if it would delay the start of surgery. The only real requirement to start a case such as this is to have good IV access, a five-lead ECG, airway control, a functioning blood pressure cuff, arterial access from the PCI procedure, and, if available, TEE. Preinduction inotropic support is required for these patients. If large doses of vasoactive medications were administered during the prebypass period, the patient may become severely hypertensive once on CPB, requiring the use of vasodilators.

In many cases of emergency surgery, the cardiologist has placed femoral artery sheaths for access during the PCI. *These should not be removed,* again because of heparin (or bivalirudin) and GPI therapy during the PCI. A femoral artery sheath provides extremely accurate pressure measurements that closely reflect central aortic pressure. Also, a PAC may have been placed in the CCL, and this can be adapted for use in the OR.

Several surgical series have looked for associations with mortality in patients who present for emergency CABG after failed PCI. Complete occlusion, urgent PCI, and multivessel disease have all been associated with an increased mortality.[246] In addition, long delays lead to increased morbidity and mortality. The paradigm shift in cardiovascular medicine toward PCI will be negatively impacted if significant numbers of serious complications occur because of prolonged delays in arranging emergent cardiac surgical care for the infrequent occurrence of failed PCI.[247,248] As the frequency of PCI at institutions with no on-site cardiac surgery facility increases, cooperation among specialties and facilities will be required to ensure that timely transfer can be arranged after a failed PCI. Important time will be lost unless formal arrangements are in place ahead of time.[24]

BOX 3.12 PREPARATION OF THE PATIENT FOR SURGERY AFTER FAILED INTERVENTION

- Perform usual preoperative evaluation for an emergent procedure.
- Inventory vascular access sites (eg, pulmonary artery catheter, intraarterial balloon pump)
- Defer removal of sheaths.
- Review medicines administered.
  - Boluses may linger even if infusion is stopped (eg, abciximab).
  - Check medicines that have been administered before arrival at the catheterization laboratory (eg, enoxaparin, clopidogrel).
- Confirm availability of blood products.

Support Devices for High-Risk Angioplasty

As devices and techniques in the CCL become more sophisticated, interventional cardiologists are expanding their practice to address more complex lesions and more high-risk patients who are deemed unsuitable candidates for surgical repair. Although there is no consensus on the definition of a high-risk PCI, a patient is considered to be at high risk when there is a combination of adverse clinical, anatomic, and hemodynamic factors that, when combined, will significantly increase the risk of periprocedural major adverse cardiac and cerebral events (MACCE) (Box 3.13).[249] These patients are at higher risk for hemodynamic compromise from either LV failure, arrhythmias, ischemia-reperfusion injury, or distal embolization of atherogenic material leading to cardiogenic shock or malignant arrhythmias.[250]

Percutaneous mechanical circulatory devices (MCS) can provide a bridge by maintaining coronary perfusion pressure, supporting the right or left ventricle, and reducing myocardial workload, allowing the cardiologist time to complete the intervention. Another beneficial effect of MCS is to augment mean arterial pressure and CO, allowing vasopressor and inotropic support to be decreased or discontinued. The four mechanical circulatory devices that can be placed percutaneously in the CCL are the IABP, the Impella (Abiomed, Danvers, MA), the TandemHeart (CardiacAssist, Pittsburgh, PA), and extracorporeal membranous oxygenation (ECMO) (see Chapter 28).

The IABP acts as an MCS because it augments diastolic pressure and myocardial perfusion by inflating when the aortic valve is closed, which increases the coronary pressure gradient from the aorta to the coronary circulation, and by deflating at the beginning of isovolumic contraction and immediately before the onset of systole, which creates a dead space in the thoracic aorta, reducing afterload and promoting forward flow[251] (Fig. 3.18). The net result is a reduction in LVEDP and LV volume, wall tension, myocardial work, and oxygen demand with preserved or increased stroke volume, EF, and CO.[252] The effectiveness of the IABP depends on the size of the balloon in proportion to the aorta. The larger the balloon, the more blood is displaced. This is the most commonly used MCS because it is ubiquitous, it is easy to insert, and it is available in a variety of catheter and balloon sizes, allowing for maximum diastolic augmentation while minimizing vascular complications.

The disadvantages of the IABP include the following: (1) it can provide only a limited increase in CO (about 0.3 to 0.5 L/minute)

BOX 3.13 CLINICAL, ANATOMIC, AND HEMODYNAMIC CRITERIA USED TO IDENTIFY HIGH-RISK PERCUTANEOUS CORONARY INTERVENTIONS

1. Clinical
   a. Cardiogenic shock within 12 h or at the start of coronary intervention
   b. Left ventricular systolic dysfunction on presentation with EF <30–40%
   c. Killip class II-IV on presentation or congestive heart failure
   d. Coronary intervention after resuscitated cardiac arrest within 24 h
   e. STEMI
   f. Acute coronary syndrome complicated by unstable hemodynamics, dysrhythmia, or refractory angina
   g. Mechanical complications of acute myocardial infarction
   h. Age >70–80 y
   i. History of cerebrovascular disease, diabetes, renal dysfunction, or chronic lung disease
2. Anatomic
   a. Intervention in an unprotected left main coronary artery or left main equivalent
   b. Multivessel disease
   c. Distal left main bifurcation intervention
   d. Previous CABG including intervention in a graft, particularly a degenerated graft
   e. Last remaining coronary conduit
   f. Duke Myocardial Jeopardy score >8/12
   g. Target vessel providing a collateral supply to an occluded second vessel that supplies >40% of the left ventricular myocardium
   h. SYNTAX score >33
3. Hemodynamic
   a. Cardiac index <2.2 L/min per square meter
   b. PCWP >15 mm Hg
   c. Mean pulmonary artery pressure >50 mm Hg

CABG, Coronary artery bypass graft surgery; *EF*, ejection fraction; *PCWP*, pulmonary capillary wedge pressure; *STEMI*, ST-segment elevation myocardial infarction.

From Myat A, Patel N, Tehrani S, et al. Percutaneous circulatory assist devices for high-risk coronary intervention. *J Am Coll Cardiol Cardiovasc Interv*. 2015;8:229.

and requires some native CO; (2) it relies on synchronization with the cardiac cycle to function and may not be reliable with dysrhythmias; and (3) its function is adversely affected by any increase in aortic compliance, reduction in systemic vascular resistance, or higher HR. Complications include balloon displacement, rupture, leak, or entrapment; thrombus formation in the pressure line or catheter; aortic dissection or rupture; lower limb ischemia; hemolysis; and bleeding at the insertion site. Absolute contraindications for IABP placement include aortic insufficiency, aortic dissection, and aortic stents.

The Impella is an axial flow left ventricular assist device (LVAD) that is positioned across the aortic valve under fluoroscopic or echocardiographic guidance; it is approved by the FDA for use in the CCL. The LVAD aspirates blood from the left ventricle and delivers it to the ascending aorta. It has a pigtail conformation that stabilizes it in the left ventricle while preventing the pump from adhering to the myocardium (Fig. 3.19). This results in LV unloading, reducing end-diastolic wall stress while improving diastolic compliance, aortic and intracoronary pressures, and coronary flow reserve and decreasing coronary

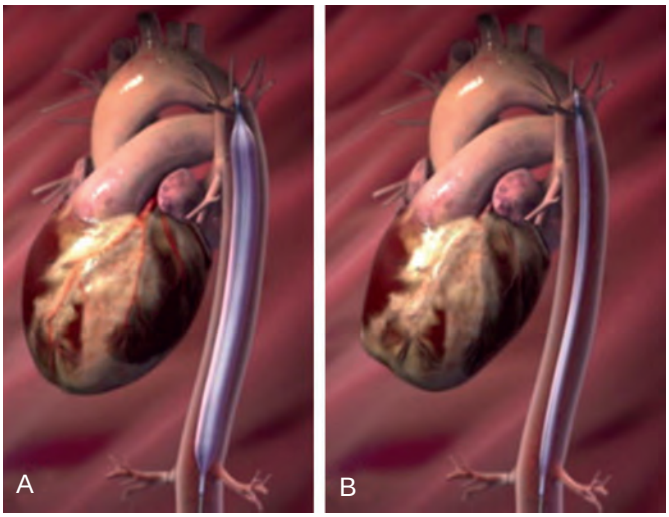


Fig. 3.18 Intraaortic balloon pump. (A) Balloon inflation during diastole increases aortic diastolic pressure and augments coronary perfusion pressure. (B) Balloon deflation during systole decreases systemic vascular resistance and assists with forward flow. *(From deWaha S, Desch S, Eitel I, et al. Intra-aortic balloon counterpulsation: basic principles and clinical evidence.* Vascul Pharmacol. *2014;60:52.)*

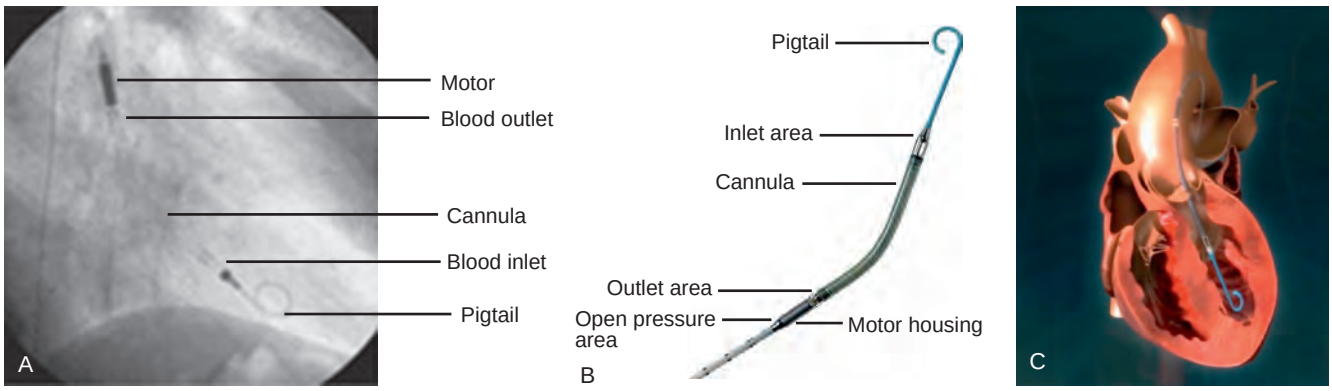


Fig. 3.19 The Impella left ventricular assist device. (A) The Impella in place inside the heart. (B) The Impella device, showing the pigtail, the inlet area where blood from the left ventricle enters the device, the cannula, the outlet area where blood is injected to the aorta, and the pump. *(From Kunai S, Kini AS. Percutaneous left ventricular support devices.* Cardiol Clin. *2010;28:169.) (C). The position of the Impella in the left ventricle. (From Myat A, Patel N, Tehrani S, et al. Percutaneous circulatory assist devices for high-risk coronary intervention.* J Am Coll Cardiol Cardiovasc Interv, *2015;8:229.)*

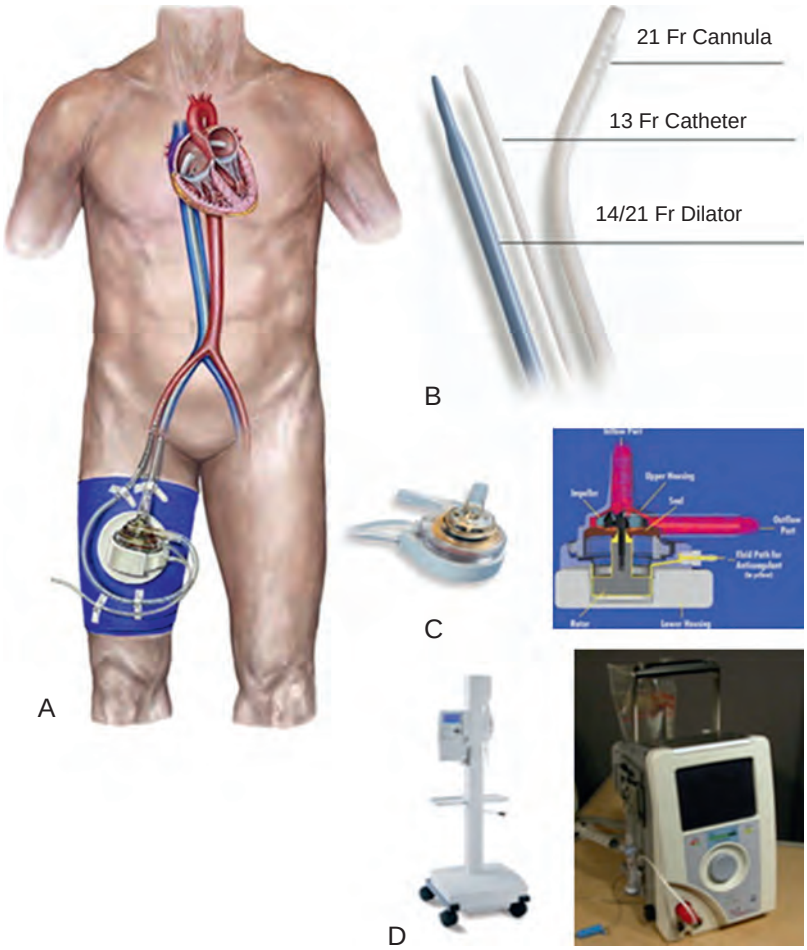


Fig. 3.20 TandemHeart left ventricular assist device. (A) TandemHeart cannula placement in the femoral artery and left atrium via a transseptal puncture. (B) The TandemHeart cannulas. (C) A closeup view of the pump. (D) The TandemHeart pump and console. *(From Kunai S, Kini AS. Percutaneous left ventricular support devices.* Cardiol Clin. *2010;28:169.)*

microvascular resistance. These effects may allow for recovery of hibernating or stunned myocardium. The Impella may also provide a bridge to a surgical procedure (eg, CABG, placement of a more permanent LVAD) or to cardiac transplantation. The Impella pump comes in three sizes: 2.5, 3.8, and 5.0 L/minute. Although the 5.0 L/minute pump can provide total CO, its implantation requires a surgical cutdown of the femoral or axillary artery. The 3.8 L/minute pump was developed to increase the amount of support without requiring a surgical cutdown.

The advantages of the Impella are that it can augment the CO by 2.5 to 3.8 L/minute, it can be used to support the circulation for up to 7 days, and it does not require a stable cardiac rhythm, CO, or blood pressure signal for optimal function, although it does require adequate LV filling.[253] The disadvantages include the following: (1) it has limited availability; (2) it requires large catheters for implantation, increasing the risk of vascular complications; (3) it provides nonpulsatile flow; (4) there is a risk of displacement of the inflow cannula into the aorta; (5) it produces hemolysis and decreased CO; and (6) there is insufficient flow to the periphery in patients weighing more than 100 kg. Compared with the IABP, the Impella has a higher risk of limb ischemia, hemolysis, and bleeding at the insertion site. The Impella is contraindicated in patients with preexisting aortic valve disease or an LV mural thrombus.

The TandemHeart is a centrifugal-flow LVAD in which the inflow cannula is inserted via the femoral vein up the IVC and RA and into the LA through a transseptal puncture; the outflow cannula is inserted into the femoral artery and positioned at the aortic bifurcation, providing flows of up to 5 L/minute (Fig. 3.20). In patients with cardiogenic shock, the TandemHeart can improve the cardiac index and mean arterial pressure and reduce filling pressures including PA pressure, PCWP, and central venous pressure, thus decreasing myocardial workload and demand.[254–257] The advantages of the TandemHeart are that it can augment CO for up to 14 days and, like the Impella, it does not require a stable cardiac rhythm, blood pressure signal, or CO for optimal function. The disadvantages include limited availability, a requirement for expertise in transseptal puncture, the fact that implantation cannot occur during cardiopulmonary resuscitation, hypoxemia due to shunting if the left atrial cannula slips back into the RA, a prolonged implantation time, and the use of large cannulas, which increases the risk of vascular compromise, hemolysis, and limb ischemia. Because the Impella 3.8 L/minute pump can maintain an almost equivalent flow rate with less risk of vascular compromise, the use of the TandemHeart may be limited.

Venoarterial ECMO is a modified CPB circuit that provides a continuous nonpulsatile CO. Venoarterial ECMO can be initiated percutaneously, via cannulation of the femoral artery and vein, or centrally, via the aorta and the SVC/IVC (Fig. 3.21). ECMO removes carbon dioxide from and adds oxygen to venous blood via an artificial membrane, bypassing the pulmonary circulation.[258] It is the only MCS that can oxygenate the blood, and it can support the circulation for several weeks. Unlike the percutaneous LVADs and IABP, ECMO can increase LV afterload and wall stress, increasing myocardial oxygen demand. Initiating ECMO is resource intensive and requires technical skills and

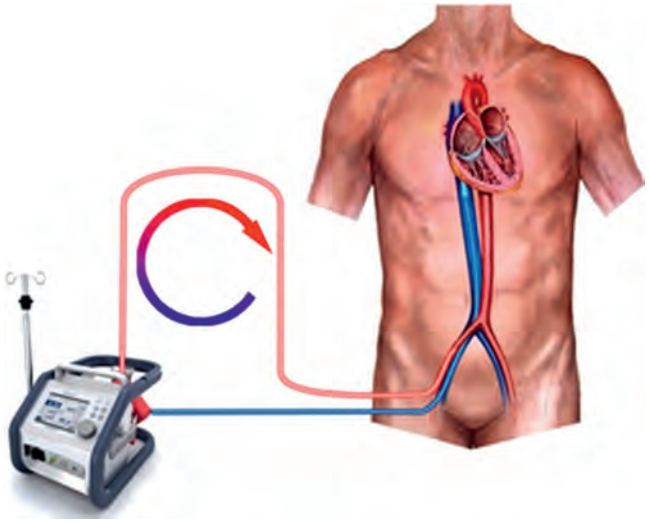


Fig. 3.21 Femoral venoarterial ECMO. *(From Myat A, Patel N, Tehrani S, et al. Percutaneous circulatory assist devices for high-risk coronary intervention.* J Am Coll Cardiol Cardiovasc Interv. *2015;8:229.)*

a team including surgeons, anesthesiologists, and perfusionists. The ECMO system is composed of a venous reservoir, an external centrifugal blood pump, a membrane oxygenator, and a rewarming heparin-coated system. Systemic anticoagulation with heparin is required to achieve an ACT between 150 and 180 seconds.[258] Disadvantages of ECMO that are not seen with the other MCS include relative lung ischemia, overventilation producing tissue alkalosis, poor perfusion to the coronary and cerebral vessels, pulmonary hypertension, and possible requirement for use of an IABP and/or inotropic agents to maintain contractility and thereby avoid LV stasis, distention, and intraventricular thrombus formation. Complications of ECMO include vascular injury, limb ischemia, and increased risk of hemorrhage due to reduced platelet count, hemolysis, consumptive coagulopathy, and systemic heparinization, which may result in intrathoracic, abdominal, or retroperitoneal hemorrhage.

A few studies have been performed to determine where MCS belongs in the care of high-risk patients undergoing PCI. The majority of studies compared the IABP with conventional medical management, and a few compared the LVADs with IABP. The Balloon Pump–Assisted Coronary Intervention Study-1 (BCIS-1) was the first prospective, open, multicenter, randomized controlled trial (RCT) designed to determine whether elective IABP insertion before high-risk PCI reduces MACCE at 28 days.[259] The study found similar rates of MACCE in both treatment arms and no significant difference between them in the secondary end points of 6-month mortality and overall rate of bleeding. This study was flawed because there was crossover in the use of IABP in the medically managed group in patients with higher BCIS-1 Jeopardy scores, suggesting the need for standby MCS in extremely high-risk patients.[259] The 5-year all-cause mortality data from the BCIS-1 study demonstrated a significant mortality advantage with elective IABP insertion, even in the crossover group.[260]

The CRISP-AMI trial was a prospective multicenter RCT with the goal of determining whether prophylactic IABP insertion within 6 hours after the onset of chest pain and planned primary PCI for STEMI in patients without cardiogenic shock could reduce the mean infarct size as measured by cardiac MRI.[261] As in the BCIS-1 trial, the operators had the option of placing an IABP in the primary PCI group for persistent hypotension, cardiogenic shock, malignant arrhythmias, or AMI complications. Although there was no difference in the end points of LV mean EF and ESV, major bleeding, transfusion, or major vascular complications at 30 days and no difference in mortality, recurrent MI, or new or worsening heart failure at 6 months, 8.5% of patients receiving standard care crossed over to the IABP group, supporting the idea that standby MCS is needed for high-risk patients. There was a significant difference between the groups in the time to death, cardiogenic shock, or new or worsening heart failure, which was longer in patients who were randomized in the PCI-IABP group. In the majority of metaanalyses comparing outcomes for prophylactic IABP versus medical management (except for patients in cardiogenic shock), the use of prophylactic IABP in high-risk or STEMI patients is not recommended.[262–264]

The studies comparing percutaneous LVADs for high-risk PCI complicated by cardiogenic shock include the IMPRESS in Severe Shock trial, currently underway, which will compare the Impella 3.8 L/minute LVAD with IABP in patients with AMI complicated by cardiogenic shock who are awaiting primary PCI.[249] In small registries and single-center studies, the Impella improved the cardiac index, but this did not result in a survival advantage. The ISAR-SHOCK trial randomized 25 patients with AMI complicated by cardiogenic shock to IABP or the Impella implanted after revascularization. Although the Impella significantly augmented the cardiac index, it did not improve 30-day mortality, and there was a trend toward greater transfusion requirements.[265] A similar study comparing the TandemHeart and IABP in patients revascularized for AMI complicated by cardiogenic shock[266] and a metaanalysis comparing the Impella and TandemHeart with IABP[267] had similar conclusions. Although the LVADs improved hemodynamic and metabolic variables, they did not confer a survival advantage compared with the IABP and were associated with higher rates of complications, including hemolysis and limb ischemia. Because of selection bias and interhospital differences in the definition of cardiogenic shock, it is difficult to determine which MCS should be used and whether it should be initiated electively, before the procedure, as standby, for rescue, or after the procedure.

No RCTs or metaanalyses are available for ECMO. Current guidelines are derived by expert consensus based on evidence from single-center observational studies and case reports.[249]

Controversies in Interventional Cardiology

Percutaneous Coronary Intervention Versus Optimal Medical Therapy in Stable Coronary Artery Disease

Ischemic heart disease (IHD) remains a major public health problem nationally and internationally. It is estimated that 1 in 3 adults in the United States has some form of cardiovascular disease; more than 17 million have CAD, and almost 10 million have angina pectoris. CAD remains the leading cause of death in men and women worldwide. The costs of caring for patients with IHD are enormous, estimated at $156 billion in the United States for both direct and indirect costs in 2008. More than one-half of direct costs are related to hospitalization. In 2003, the Medicare program alone paid $12.2 billion for hospitalizations due to IHD.

Early revascularization in STEMI patients has been well validated to improve mortality.[268] In addition, early percutaneous revascularization has been shown to improve survival and to reduce the incidence of death or nonfatal MI compared with aggressive medical therapy alone in the management of non–ST-elevation ACS.[269] However, the role of PCI in the management of stable CAD remains controversial. In the most recently published guidelines on stable angina, the goals of care are to minimize the likelihood of death while maximizing the health and function of the patient. How exactly to achieve these well-stated goals remains at the heart of the controversy. The guidelines recommend complementary and overlapping strategies, beginning with education about the etiology, treatment options, and prognosis of IHD and support for active participation of patients in their treatment decisions. It is also necessary to identify and treat conditions that contribute to, worsen, or complicate IHD and to effectively modify risk factors for IHD by both pharmacologic and nonpharmacologic means. Use of an evidenced-based approach to improve patients' health status and survival, with attention to avoiding drug interactions and side effects, is also strongly encouraged. Finally, use of revascularization by PCI or CABG is appropriate when there is clear evidence of the potential to improve patients' health status and survival.[270]

Having clear evidence of overall benefit compared with potential risks is the ideal situation in which to offer revascularization to patients with stable IHD. In a minority of cases, this balance is absent, as evidenced by NCDR data suggesting that approximately 10% to 12% of PCIs could be considered inappropriate because of a lack of perceived benefit.[271] Several beliefs influence patients and physicians to choose revascularization when the likelihood of benefit is less than the potential risks of the procedure. An ingrained preference for action (ie, revascularization) over perceived inaction (ie, medical therapy alone) likely influences the decision making of both patients and physicians in many cases.[272] Moreover, some health care professionals are unduly pessimistic about survival with conservative medical therapy and inaccurately optimistic about the survival benefits of revascularization procedures.[273] Finally, some patients believe mistakenly that PCI has the potential to prevent AMI and prolong survival.

On the other side of the argument, the well-publicized COURAGE trial touting clinical equipoise between optimal medical therapy (OMT) and OMT plus PCI in patients with stable CAD has been criticized.[274] Although this landmark clinical trial appears to have been effective in changing management of low-risk stable CAD to include an initial trial of OMT,[121] some salient points need to be addressed. The study population was a highly selected group of patients; only 6.3% of the more than 36,000 patients screened were randomized. Compliance with OMT was exemplary in this trial, with compliance rates for aspirin, statins, and β-blockers all greater than 90%. In addition, blood pressure was under better control than in the general population and national health data sets; 65% of participants had a systolic blood pressure of less than 130 mm Hg).[275] For these reasons, it is unclear whether similar results can be achieved in everyday medical care outside a clinical trial. From the PCI arm, only 3% of patients received a DES, which explains why more than 20% of PCI-treated patients in this trial underwent an additional revascularization procedure at a median of 10 months of follow-up. Finally, there was a higher than expected crossover rate from the OMT group to the OMT-PCI arm (32%). Many interventionalists now believe that the COURAGE trial confirms earlier data sets suggesting that many highly motivated individuals with low-risk anatomy fare well with OMT as an initial strategy; however, when OMT is combined with PCI, quality of life is improved because of a reduction in the prevalence of angina pectoris.[276–278]

The most recently published PCI guideline recognizes the benefits of PCI in stable CAD as a means to reduce angina pectoris. PCI is given a class IIa indication to improve angina symptoms in patients with unacceptable angina for whom OMT cannot be implemented because of medication contraindications, adverse effects, or patient preferences.[22] The debate over the "best" treatment strategy will undoubtedly continue, but the evidence appears relatively clear. An initial strategy of OMT is reasonable, but in patients with high risk factors or continued symptoms, early angiography is warranted, with revascularization as directed by the angiographic and clinical findings.

Percutaneous Coronary Intervention Versus Surgical Revascularization in Complex Coronary Artery Disease

The choices available for treatment of multivessel CAD are PCI, CABG, and medical therapy. In the 1970s, CABG was compared with medical therapy in several randomized trials. A survival benefit for CABG was seen in only a few subgroups, such as those with LM disease and those with three-vessel disease and impaired LV function. Both CABG and medical therapy have improved since that time, but few recent comparisons have been made.

In the mid-1980s, when PCI consisted only of balloon PTCA, the first comparisons of catheter intervention versus CABG were begun. By the early to mid-1990s, nine RCTs had been published comparing PTCA with CABG in patients with significant CAD. Only the BARI trial was statistically appropriate for assessing mortality.[279] These trials are summarized in Fig. 3.22. These studies concluded that there were similarities between the two approaches with respect to relief of angina and 5-year mortality. Costs were initially lower in the PCI group, but by 5 years costs had converged because of the need for repeat PCI precipitated by restenosis in 20% to 40% of the PCI group.[280] The only clear difference between PCI and CABG for patients with multivessel disease in the BARI trial occurred in the subset of patients with DM.[279] In a subgroup analysis, both insulin-dependent and non–insulin-dependent diabetic patients with multivessel disease had a lower 5-year mortality rate with CABG (19.4%) than with PCI (34.5%).[281]

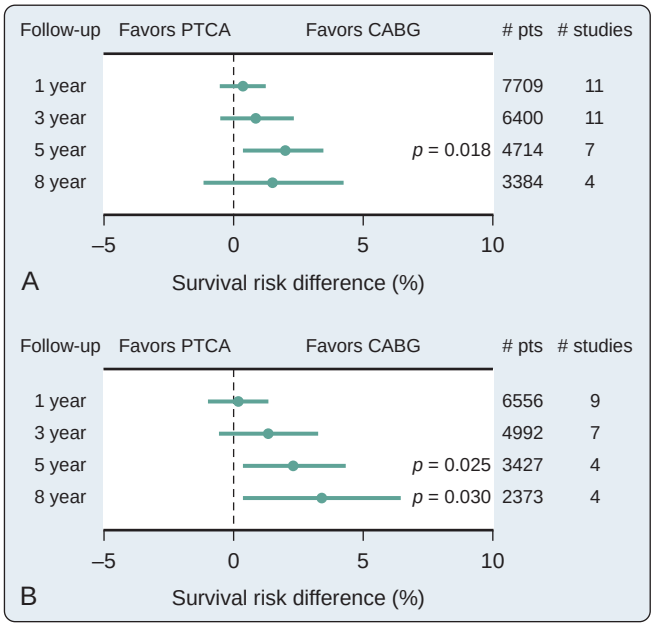


Fig. 3.22 Randomized trials of coronary artery bypass graft surgery *(CABG)* versus percutaneous coronary angioplasty *(PTCA)* in patients with multivessel coronary disease show risk differences for all-cause mortality in years 1, 3, 5, and 8 after initial revascularization. (A) All trials. (B) Multivessel trials. *(Redrawn from Hoffman SN, TenBrook JA, Wolf MP, et al. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes.* J Am Coll Cardiol. *2003;41:1293. Copyright 2003, with permission from The American College of Cardiology Foundation.)*

Regretfully, these trials were outdated by the time of their publication. For patients undergoing PCI, stents had become the norm. Use of stents produced a significant decrease in emergent CABG because of the reduced rate of acute closure and a decrease in repeat procedures because of less restenosis.[152] For patients undergoing CABG, off-pump coronary artery bypass became more common during this time period, with its potential to decrease complications.[282] In addition, the importance of arterial grafting, with its favorable impact on long-term graft patency, was recognized.[283]

To address the changes in PCI and CABG therapy, four more randomized trials were undertaken, and these are included in Fig. 3.22. The results of the newer studies were similar to the results of the earlier ones. In the Arterial Revascularization Therapy Study (ARTS), patients with DM had poorer outcomes with PCI, with rates of MACCE greater than 50% at 5 years. Overall, there was no difference in the rates of mortality, cerebrovascular accident, or MI between the groups at 5 years, but there was a higher MACCE rate in the stenting arm, which was driven by a higher rate of repeat revascularization because BMSs were utilized.[284]

The well-known Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial randomized 1800 patients with three-vessel CAD and/or LM stenosis to either CABG or PCI with paclitaxel-eluting stents with the intention of obtaining complete revascularization. Patients were eligible regardless of clinical presentation on the condition that the angiograms were reviewed by both a cardiologist and a cardiac surgeon and complete

revascularization was believed feasible by both techniques. After 1 year, 17.8% of the PCI patients and 12.4% of the CABG patients had experienced a MACCE ($P = .002$). Although this difference was driven primarily by a greater need for repeat revascularization in the PCI group, the rate of death was nonsignificantly greater in the PCI group, at 4.4%, compared with 3.5% in the CABG group. The rate of stroke was significantly greater in the CABG group, 2.2%, versus 0.6% in the PCI group ($P = .003$).[285] The 5-year published data showed that outcomes were stratified based on the calculation of a SYNTAX score, which is an angiographically calculated score that takes into account the burden and location of CAD. For patients with low SYNTAX scores, including those with isolated LM disease, PCI appeared to be an acceptable alternative to CABG. However, in those with intermediate- to high-risk SYNTAX scores, CABG appeared superior mainly because of lower MACCE rates and lower repeat revascularization rates.[286]

A metaanalysis of six major clinical trials that compared PCI with CABG for multivessel CAD revealed an unequivocal reduction in long-term mortality and MI in addition to reductions in repeat revascularizations favoring CABG. These findings were consistent in diabetics and nondiabetics.[287] As with the debate about PCI versus OMT, there will continue to be heated discussions regarding the optimal therapy for patients with multivessel CAD. Perhaps the most important lesson from these trials is the requirement to form and maintain a heart team consisting of cardiovascular surgeons, cardiologists, and anesthesiologists so that complex cases involving difficult anatomy and medical comorbidities can be discussed in an open format. When multidisciplinary care is delivered, outcomes are improved.[288]

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft Surgery for Left Main Coronary Artery Disease

Of all patients undergoing coronary angiography, approximately 4% are found to have LM CAD.[289] CABG has long been considered to be the gold standard revascularization method for patients with LM disease because it confers a survival benefit when compared with medical therapy. The data to support this statement comes from RCT subgroup analyses performed 3 decades ago on 91 patients with LM CAD in the Veterans Administration Cooperative Study.[290] A metaanalysis of these trials demonstrated a 66% reduction in relative risk and mortality with CABG, with the benefit extending to 10 years.[291] Since these studies were completed, there have been improvements in medical therapy including the use of acetylsalicylic acid, lipid-lowering therapy (3-hydroxy-3-methyl-glutaryl–coenzyme A [HMG CoA] reductase inhibitors), and angiotensin-converting enzyme inhibitors, along with improvements in surgical technique with the use of left internal mammary artery grafting.[292] For this reason, many have argued for updated comparisons of LM CAD treatments, especially because interventional cardiologists have been steadily expanding the application of coronary stenting to include patients with increasingly complex lesions, such as LM disease.[293]

The majority of studies comparing PCI with CABG for LM stenting have been single-center studies, and in all but one the patient populations were not randomized, so the potential bias in patient selection may confound interpretation of the results.[294–296] In addition, the only published randomized study, the Prospective Randomized Study of Unprotected Left Main Stenting Versus Bypass Surgery (LE MANS study), was small, consisting of approximately 50 patients in each treatment group.[297] Because of the limited strength of published data, LM PCI was previously considered a class III or class IIb recommendation in the US guidelines. More recently, in a significantly larger RCT using DESs, the composite end point of death, MI, or stroke at 2 years occurred in 4.4% of patients treated with PCI and 4.7% of patients treated with CABG. However, ischemia-driven target-vessel revascularization was more often required in those patients treated with PCI (9.0% vs 4.2%).[298] The publication of the results of the SYNTAX LM prespecified subgroup, which included 705 patients, contributed significantly to the data.[299] This landmark study concluded that patients with LM disease who underwent revascularization with PCI had safety and efficacy outcomes comparable to those achieved with CABG at 1 year. The recently published 5-year outcomes from this study suggested that PCI-treated patients had a lower stroke rate but a higher revascularization rate than CABG-treated patients; there was no significant difference in mortality (12.8% vs 14.6% with PCI and CABG, respectively, $P = .53$).[300]

TABLE 3.7 Recommendations for Percutaneous Coronary Intervention in Left Main Coronary Artery Disease

PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant (≥50% stenosis) unprotected left main CAD with 1. Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome: a. Low SYNTAX score ≤22 b. Ostial or trunk left main CAD 2. Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS predicted risk of operative mortality ≥5%)	Level of Evidence B
PCI to improve survival is reasonable in patients with UA/NSTEMI when an unprotected left main coronary artery is the culprit lesion and the patient is not a candidate for CABG.	Level of Evidence B
PCI to improve survival is reasonable in patients with acute STEMI when an unprotected unprotected left main coronary artery is the culprit lesion, distal coronary flow is <TIMI grade 3, and PCI can be performed more rapidly and more safely than CABG.	Level of Evidence C

CABG, Coronary artery bypass graft surgery; *CAD,* coronary artery disease; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment elevation myocardial infarction; *STS,* The Society of Thoracic Surgeons; *UA,* unstable angina; *TIMI,* Thrombolysis in Myocardial Infarction score.

From Levine GN, Piates ER, Blankenship JC, et al. ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *J Am Coll Cardiol.* 2011;58:e44.

The results from these three RCTs suggest (but do not definitively prove) that major clinical outcomes in *selected* patients with LM CAD are similar with CABG and with PCI at 1- to 5-year follow-up, but repeat revascularization rates are higher after PCI than after CABG. The extent of disease should be accounted for when choosing between surgery and PCI. Patients with high SYNTAX scores seemed to benefit more from surgery than those in the lower tertiles. The most recently published PCI guidelines now give PCI a class IIa indication for LM PCI, as outlined in Table 3.7.[22]

In conclusion, the physician must weigh the data, discuss the case within the confines of a dedicated heart team, and then explain the advantages and disadvantages of both techniques to the individual patient. CABG offers a more complete revascularization, with survival advantages in selected groups and a decreased need for repeat procedures.[285,292] The disadvantages of CABG are the higher early mortality risk, longer hospitalization and recovery times, higher initial expense, morbidity associated with leg incisions, increased risk for stroke, and limited durability of venous grafts. The cost of DESs may negate the initial cost advantage of PCI if multiple stents are used. In the future, the balance of acceptance will continue to shift among medical therapy, percutaneous revascularization, and surgical revascularization as more RCTs are completed (see Chapters 1, 2, 20, and 44).

Specific Interventional Devices

Interventional Diagnostic Devices

Percutaneous Transluminal Coronary Angioplasty

PTCA is an important component of the interventional procedure because it provides the opening for stents to be implanted. The mechanism by which balloon inflation leads to vessel patency must be understood to better understand balloon angioplasty. Although four mechanisms have been described to explain the efficacy of this procedure (ie, plaque splitting, stretching of the arterial wall, plaque

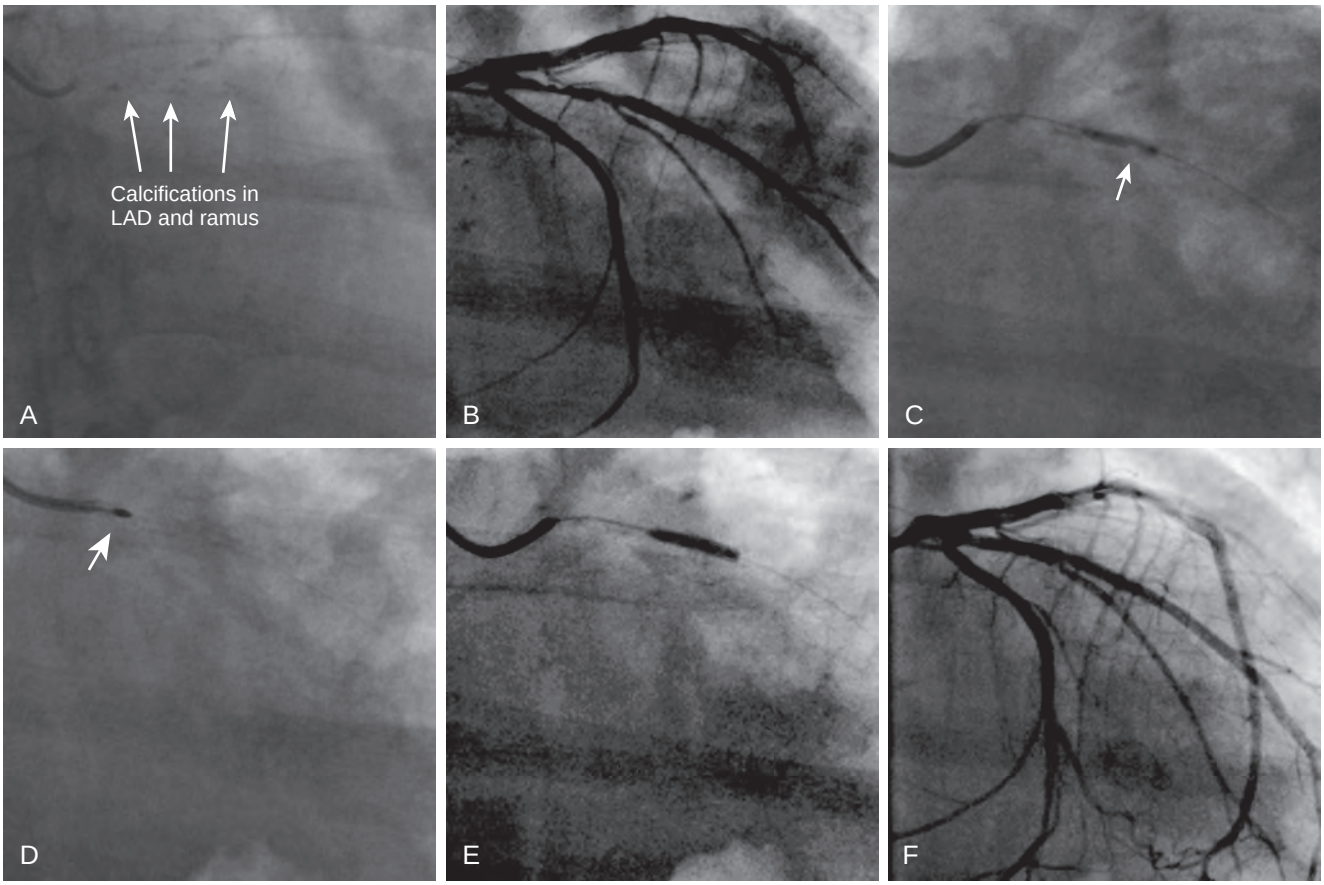


Fig. 3.23 Rotational coronary atherectomy. (A) Fluoroscopy shows calcification of the ramus intermedius. (B) Angiography shows a severe stenosis. (C) Percutaneous transluminal coronary angioplasty balloon *(arrow)* cannot be expanded. (D) A 1.5-mm rotational atherectomy burr *(arrow)* is advanced at 140,000 rpm. (E) Balloon expands fully after rotational atherectomy. (F) Final result after stent placement. *LAD,* Left anterior descending coronary artery.

compression, and plaque desquamation), the primary mechanism is *discrete* intimal dissection, which results in plaque compression into the media. Desquamation and distal embolization of superficial plaque components have been observed; however, experimental studies demonstrate these to be minor contributors to the procedure's efficacy.[130] Propagation of the intimal dissection is the primary cause of vessel occlusion during angioplasty (see Fig. 3.17).

Although the mechanism of balloon angioplasty has not changed, equipment and operator expertise have improved to the point that procedural success rates now exceed 90%.[224] These advances allow for the treatment of sicker patients and more complex coronary lesions while success rates continue to improve and complication rates decrease.[301]

Atherectomy Devices: Directional and Rotational

Atherectomy devices are designed to remove some amount of plaque or other material from an atherosclerotic vessel. Directional coronary atherectomy was the first nonballoon technology to gain FDA approval, in 1991. In this technique, tissue was removed from the coronary artery, debulking the area of stenosis. Although tissue removal is an attractive concept, application of directional coronary atherectomy was limited. Trials comparing this technique with PTCA did not show improved angiographic restenosis rates, and greater rates of acute complications were seen with directional coronary atherectomy.[302–304]

The FDA approved rotational coronary atherectomy in 1993. The Rotablator catheter (Boston Scientific Corp., Marlborough, MA) is designed to differentially remove nonelastic tissue with the use of a diamond-studded burr rotating at 140,000 to 160,000 rpm. Rotational artherectomy is designed to alter lesion compliance, particularly in heavily calcified vessels, and it is often used before balloon dilation to permit full expansion of the vessel.[305] The ablated material is emulsified into 5-μm particles, which pass through the distal capillary bed. Heavily calcified lesions commonly are chosen for rotational atherectomy (Fig. 3.23). In addition, restenotic (in-stent), bifurcation, ostial, and nondilatable lesions are candidates for the Rotablator.[306] Contraindications to the Rotablator include tortuous anatomy, poor ventricular function, thrombus, poor runoff, and lesions within SVGs.[307]

The main limitation of rotational atherectomy is the no-reflow phenomenon.[144] This effect is thought to be secondary to particle load. It is associated with myocardial ischemia and occasionally with infarction. Hemodynamic problems can occur, particularly in patients with depressed LV function. The frequency of no-reflow has been reduced by shorter, slower ablation passes and the addition of vasodilators to the flush solution.[307] In heavily calcified vessels, rotational atherectomy may be the only procedure that can change the compliance of an artery and permit complete expansion of balloons and stents. However, rotational atherectomy is more cumbersome and time-consuming than balloon dilation. It is rarely used alone, and stent placement usually is necessary to achieve an adequate result. Therefore, although rotational atherectomy is available in most interventional laboratories, it is a niche item primarily relegated to vessels with significant calcification.

Cutting Balloon

Vessel wall damage during interventional procedures is considered to be the initiating factor for neointimal proliferation, which ultimately can lead to restenosis. All interventional technologies damage the

vessel wall to some degree. In an attempt to decrease intimal injury, the cutting balloon (Flextome, Boston Scientific) was introduced, based on the concept of microsurgical dilation. Whereas standard balloon PCI dilates haphazardly and can severely injure the arterial wall, the cutting balloon permits vessel expansion with lower pressure and less wall injury, reducing the stimulus for restenosis.

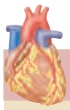
This device is a noncompliant balloon with three or four blades, depending on balloon size. These blades are 10 to 15 mm long and 0.25 mm in diameter and are attached to the balloon by a proprietary bond-to-bond manufacturing process. Once inflated, the balloon introduces the blades into the coronary intima, producing a series of tiny longitudinal incisions before balloon dilation occurs. These microscopic cuts permit less traumatic vessel expansion. The safety and efficacy of this technique have been validated; however, no benefit was found when the cutting balloon was compared with PTCA in a large group of patients. The cutting balloon is currently used to decrease plaque shift in bifurcating lesions, to change artery compliance, and to treat ISR.[308]

A newer cutting balloon technology is the Angiosculpt scoring balloon (Spectranetics, Freemont, CA), which use three 0.005-inch cylindrical nitinol wires as the scoring device. Nonrandomized data suggest improved stent expansion, less geographic miss owing to less slippage of the balloon, and less vessel trauma compared with traditional PTCA or primary stent placement.[309,310] The device is currently FDA approved to treat ISR, complex type C coronary lesions, and bifurcation lesions.

Intracoronary Stents

The introduction of intracoronary stents has had a larger impact on the practice of interventional cardiology than any other development.[311]

The use of intracoronary stents exploded during the mid-1990s[312] (Box 3.14). In April of 1993, the Gianturco-Roubin flex stent (Cook, Bloomington, IN), a coiled balloon-expandable stent, was approved by the FDA for treatment of acute closure after PCI. Use of the Gianturco-Roubin stent was limited by difficulties with its delivery and high rates of restenosis. The first stent to receive widespread clinical application was the Palmaz-Schatz tubular slotted stent (Johnson & Johnson, New Brunswick, NJ), which was approved for treatment of de novo coronary stenosis in 1994.[313] Throughout the 1990s, multiple stents were introduced with improved support, greater flexibility, and thinner struts, resulting in improved delivery and decreased rates of restenosis (Fig. 3.24).[159,160]



BOX 3.14 STENTS

- Antiplatelet therapy after stent placement: indefinite aspirin therapy plus
  - BMS: clopidogrel 4 wk for patients without ACS, 12 mo with ACS
  - DES: clopidogrel 12 mo
- With BMS, thienopyridines reduce subacute thrombosis from 3% to <1%.
- DES have never been tested without clopidogrel.
- A concern with first-generation DES is delay in endothelial coverage of the stent.
- With clopidogrel, subacute and late thrombosis rates for DES and BMS are identical.
- Very late thrombosis rates are greater with first-generation DES.
- Late stent thrombosis rates with second-generation DES are similar to those with BMS.
- Options for elective surgery in patients with stents:
  - Delay surgery until clopidogrel regimen is completed: recommended
  - Perform surgery during clopidogrel therapy: accept bleeding risk

ACS, Acute coronary syndromes; *BMS*, bare metal stents; *DES*, drug-eluting stents.

The major limitations of catheter-based interventions previously had been acute vessel closure and restenosis. Stents offered an option for stabilizing intimal dissections while limiting late lumen loss, major components of acute closure, and restenosis. Clinical trials demonstrated the ability of stents to not only salvage a failed PTCA, thus avoiding emergent CABG (see Fig. 3.17), but also reduce restenosis.[159,314] Multiple studies documented the benefit of stenting compared with PTCA alone in a variety of circumstances, including long lesions, vein grafts, chronic occlusions, and the thrombotic occlusions of AMI. Only in small vessels did stenting not demonstrate a restenosis benefit when compared with balloon angioplasty.[315] Clinical restenosis rates declined from 30% to 40% with PTCA to less than 20% with BMSs.[313]

Stent technology improved in incremental fashion. Modifications in coil geometry, alterations in the articulation sites, and the use of meshlike stents offered minor advantages.[158] Various metals (eg, tantalum, nitinol) were used, and various coatings (eg, heparin, polymers, even human cells) were applied.[159] In addition, the delivery systems used to implant stents were decreased in size.[160] Stent procedures, once requiring 9-Fr guiding catheters, can now be performed through 5- to 6-Fr catheters.

With the realization that restenosis involves poorly regulated cellular proliferation, researchers focused on medicines with antiproliferative effects. Many of these medicines were toxic when given systemically—a tolerable situation in oncology but not for a relatively benign condition such as restenosis. For such medicines, local delivery was attractive, and the stent provided a vehicle.

Rapamycin, a macrolide antibiotic, is a natural fermentation product produced by *Streptomyces hygroscopicus*, which was originally isolated in a soil sample from Rapa Nui (Easter Island).[316] Initially investigated as an antifungal agent, it was soon discovered to have potent immunosuppressant activities, making it unacceptable as an antibiotic but attractive for prevention of transplant rejection. Rapamycin (also called sirolimus) works through inhibition of a protein kinase called the mammalian target of rapamycin (mTOR), a mechanism that is distinct from those of other classes of immunosuppressants. Because mTOR is central to cellular proliferation as well as immune responses, this agent was an inspired choice for a stent coating. A metal stent does not hold drugs well and permits little control over their release. These limitations required that polymers be developed to attach a drug to the stent and to allow the drug to slowly diffuse into the wall of the blood vessel while eliciting no inflammatory response.[317] The development of DESs would not have been possible without these (proprietary) polymers. This led to the true revolution in PCI, which began with the approval in April 2003 of the first DES,[223] the Cypher (Johnson & Johnson/Cordis, Bridgewater, NJ). Use of the Cypher ceased in 2011.

A European trial randomized 238 patients to receive either a sirolimus-eluting stent or a BMS. Remarkably, there was no restenosis in the group that received the DES.[318] A larger American trial randomized 1058 patients to a sirolimus-eluting stent or a BMS. At 9 months, restenosis rates were 8.9% in the DES group and 36.3% in the BMS group, with no difference in adverse events. Clinically driven repeat procedures were required in 3.9% and 16.6% of the two groups,[318] respectively. This benefit was sustained, if not slightly improved, at 12 months.[319] Although these stents were initially approved only for de novo lesions in native vessels of stable patients, similar benefits have been shown in every clinical scenario that has been studied.[320–324]

The next first-generation DES to receive FDA approval, in March 2004, was the Taxus stent (Boston Scientific). The Taxus stent uses a polymer coating to deliver paclitaxel, a drug that also has many uses in oncology. Paclitaxel is a lipophilic molecule derived from the Pacific yew tree, *Taxus brevifolia*. It interferes with microtubular function, affecting mitosis and extracellular secretion and thereby interrupting the restenotic process at multiple levels.[325] The Taxus IV study randomized 1314 patients to the Taxus stent or a BMS. Angiographic restenosis was 26.6% in the BMS group and only 7.9% in the Taxus

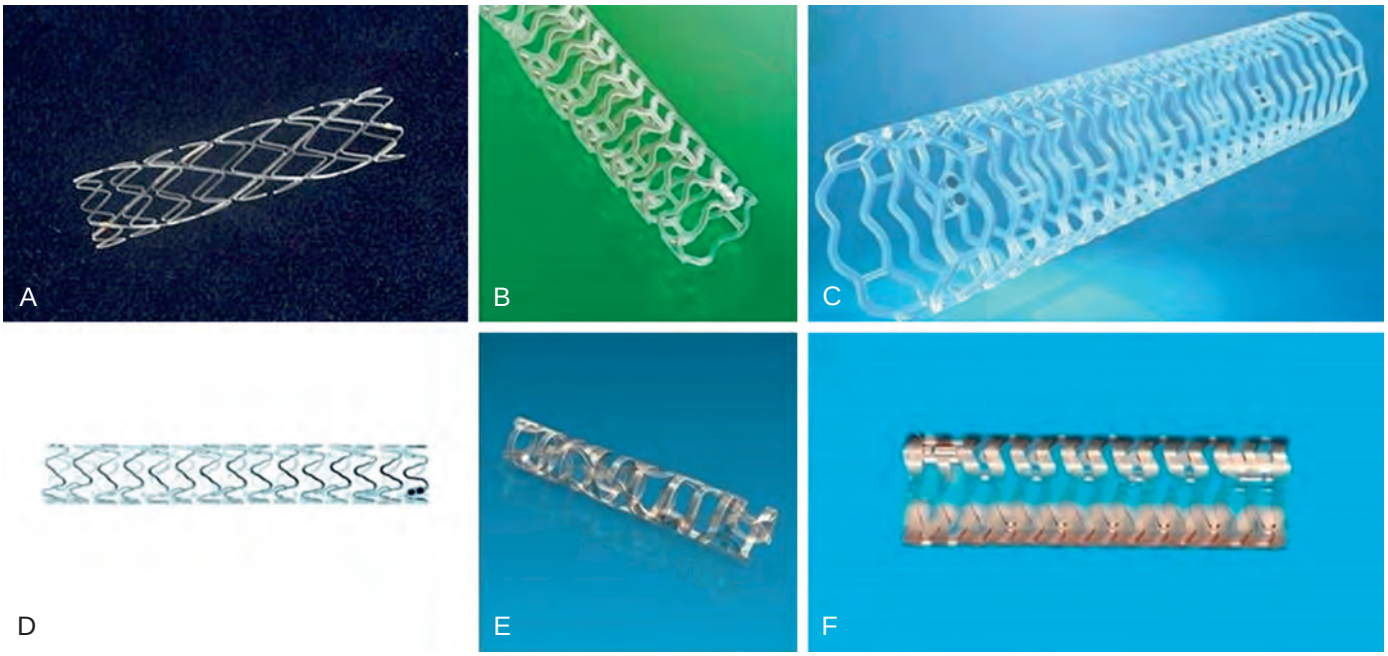


Fig. 3.24 Types of stents. (A) The Igaki-Tamai stent (Kyoto Medical Planning Co., Kyoto, Japan). (B) The ABSORB Bioresorbable Vascular Scaffold (Abbott Vascular, Santa Clara, CA). (C) The DESolve bioresorbable scaffold (Elixir Medical Corporation, Sunnyvale, CA). All three are manufactured from poly-L-lactic acid. (D) The DREAMS magnesium alloy (Biotronik, Berlin, Germany) is a metal bioresorbable vascular scaffold. (E) The ReZolve 2 BRS (Reva Medical, San Diego, CA) is produced on a desaminotyrosine polycarbonate basis. (F) The Ideal BioStent (Xenogenics Corp., Canton, MA) is composed of a salicylate polymer and linker. *(From Wiebe J, Nef HM, Hamm CM. Current status of bioabsorbable scaffolds in the treatment of coronary artery disease.* J Am Coll Cardiol. *2014;64:2541.)*

group, with no significant difference in adverse events. Clinically driven repeat procedures were required in 12.0% and 4.7% of the groups, respectively.[151]

Initial concerns regarding LST were validated with the first-generation DESs, as discussed earlier. This rare but rather drastic complication led to the development of second-generation DESs.[169] Two second-generation DESs have been approved in the United States, the zotarolimus-eluting stent (Endeavor; Medtronic, Minneapolis, MN) in 2011 and the everolimus-eluting stent (Xience; Abbott, Abbott Park, IL, and Promus; Boston Scientific) in 2012. The newer stents use different drugs, polymers, and stent platforms. Comparisons of various DESs have shown differences in some angiographic end points but similar clinical outcomes.

The early enthusiasm for first-generation DESs was tempered after widespread concerns about the increased risks of LST and very late stent thrombosis. In addition to the development of second-generation stents, research was also applied to produce a fully biodegradable scaffold. This new technology offers the possibility of transient scaffolding of the vessel to prevent acute vessel closure and recoil during elution of an antiproliferative drug to counteract constrictive remodeling and excessive neointimal hyperplasia. A recent RCT comparing the everolimus-eluting bioresorbable vascular scaffold (Absorb BVS; Abbott Vascular, Santa Clara, CA) with a traditional DES suggested comparable outcomes at 1 year.[326] However, in the largest published registry using the Absorb BVS, the rate of definite stent thrombosis at 6 months was higher than expected (2.1%).[327] This raised concern about the device's initial strut thickness and whether the late potential benefits might be offset by short-term events. Subsequent single-center randomized trial data contradicted this real-world finding,[328] and more patient data will be required to further evaluate the safety and effectiveness of this unique technology.

Currently, stents are placed at the time of most PCI procedures if the size and anatomy of the vessel permit. Multiple studies have been performed comparing BMSs with DESs in various clinical scenarios.[329,330] There are several reasons not to use a DES in every procedure. First, DESs are not manufactured in sizes greater than 4.0 mm, making them useless in large vessels. Second, a longer course of thienopyridine is required, and this may not be desirable if a surgical procedure is urgently needed because it requires an uncomfortable choice between bleeding and increased risk for cardiac events.[331] Stent thromboses, MIs, and deaths have been reported when antiplatelet therapy is interrupted.[332,333] Third, there are cost considerations: DES is two to three times more expensive than a BMS. Finally, a DES may not be the ideal choice in a patient who requires long-term anticoagulation because bleeding rates are increased when triple therapy is used, as discussed previously (see Chapter 44).

Aspiration Thrombectomy Catheters

Primary PCI in the setting of STEMI has been shown to be the optimal treatment strategy because it offers higher rates of infarct artery patency and lower rates of recurrent ischemia, reinfarction, intracranial hemorrhage, and death compared with thrombolytic therapy. Despite the insertion of an intracoronary stent resulting in a patent epicardial vessel, there are a number of patients in whom normal perfusion is not completely achieved, as evidenced by reduced TIMI flow scores, failure of ST-segment resolution, and poor myocardial blush grade.[334] In several studies, primary PCI with stent placement in STEMI patients resulted in a distal embolization rate of approximately 15%.[335,336] Microembolization may lead to occlusion of arterioles in the microcirculation, thus impairing end-myocardial perfusion. To potentially reduce this distal embolization rate, thrombectomy catheters have been developed and tested in clinical trials.

The AngioJet rheolytic thrombectomy system (Possis Medical, Minneapolis, MN) is one such thrombectomy catheter. It creates a Venturi effect by using six high-velocity saline jets distally at a pressure of 2500 psi and a flow rate of 50 mL/minute to generate a low-pressure zone (<600 mm Hg) and cause a powerful vacuum effect. The catheter is a multilumen 4-Fr system and may be passed through a 6-Fr guiding catheter. One lumen delivers the saline, a second is for

guidewire passage, and a third permits thrombus evacuation with the use of a roller pump.[337] This system creates a recirculation pattern at the catheter tip, emulsifying and removing thrombus without embolization. Rheolytic thrombectomy was first approved for SVGs, and a larger, 6-Fr catheter is used. Although it can remove thrombus from native arteries and SVGs, some trials suggest that it may be less effective than alternative therapies for SVGs.[338,339] Initial studies in small patient populations were encouraging for AMI patients,[340] but a larger trial of 480 patients presenting within 12 hours after the onset of MI demonstrated greater mortality in the rheolytic thrombectomy group.[341] Other devices include the Rescue Catheter (Boston Scientific), the X-Sizer system (ev3, Plymouth, MN), and the TransVascular Aspiration Catheter (Nipro, Osaka, Japan). All of these devices have failed to show a clinical benefit in PCI. Nevertheless, this therapy remains an option for the limited number of patients who have large vessels containing a significant thrombus burden.[342]

Simpler manual aspiration devices also have been developed to facilitate thrombus removal, particularly in the setting of AMI.[343] The prototype was the Export catheter (Medtronic); another device was the Pronto extraction catheter (Vascular Solutions, Minneapolis, MN). Both devices employ a simple design using a tube with two lumens. One lumen tracks over a guidewire that has been advanced through the thrombotic area, and the second lumen is connected to a syringe. Negative pressure is generated with a handheld syringe outside the body. The TAPAS trial randomized 1071 patients undergoing primary PCI for AMI to either PCI alone (control) or thrombus aspiration with the Export catheter followed by PCI. Mortality at 1 year was 3.6% in the group that had thrombus aspiration and 6.7% in the control group ($P = .02$).[344] However, results in other multicenter trials have largely been negative, and metaanalyses have been conflicting with respect to infarct size reduction and improved clinical outcomes. A follow-up study to the TAPAS trial suggested no change in mortality at 1 year between aspiration plus PCI and PCI alone (5.3% vs 5.6%, respectively).[345] Therefore, the use of aspiration thrombectomy at present is somewhat controversial and operator dependent (Fig. 3.25).

Distal Occlusion Devices

PCI in degenerative vein grafts is complicated by a significant incidence of MI that is thought to result from embolization of debris. GPIIb/IIIa inhibition has not decreased MI in this situation.[212] Although other factors, such as spasm in the distal arterial bed, may contribute to the complications during PCI in SVGs, most efforts to address this problem have focused on devices that are designed to capture potential embolic debris released as the probable cause of the no-reflow phenomenon during PCI.[144] These distal protection devices come in two types: vessel occlusive and vessel nonocclusive.

Vessel-occlusive devices use a soft, compliant balloon that is incorporated into a wire. The wire is passed distal to the stenosis and inflated during the PCI. A column of blood is trapped that includes the debris liberated during PCI. The blood and debris are aspirated before deflation of the distal balloon and restoration of flow. The GuardWire (Medtronic) is an FDA-approved device of this type. In the SAFER trial, 801 patients undergoing PCI in SVGs were randomized to distal protection with the GuardWire versus no distal protection. The composite end point of death, MI, and repeat target-vessel revascularization was met by 9.6% in the GuardWire group and 16.5% in the standard care group. MI was reduced by 42% in the distal protection group.[346] However, because of the learning curve required to use this device and the development of more user-friendly nonocclusive devices, the GuardWire is now obsolete.

Fig. 3.25 The Export catheter was used to aspirate thrombotic material in the setting of an acute myocardial infarction.

Nonocclusive devices include various forms of filters as well as the thrombolysis or thrombectomy devices discussed earlier.[347,348] The Filter Wire (Boston Scientific) was the first filter approved. It is a 0.014-inch guidewire that incorporates a nonoccluding, polyurethane membrane filter with 80-µm pores. The system includes a retrieval catheter that fits over the device after PCI is completed (Fig. 3.26). Two clinical trials have been reported, the first comparing the Filter Wire EX with PCI alone and the second randomizing patients to either the Filter Wire EX or the GuardWire.[348,349] The Filter Wire was superior to PCI alone and noninferior to the GuardWire system. Other FDA-approved filter devices are used commonly for endovascular interventions performed on the carotid artery.

Therapy for Chronic Total Occlusions

Chronic total occlusions are defined as vessels that have been occluded for longer than 3 months. There has been steady progress in most areas of interventional cardiology, including the development of multilumen catheters that can allow multiple guidewires to treat a lesion,[350a] the creation of a hybrid strategy that bases treatment on the anatomy of the lesion, the use of anterograde and retrograde approaches, and the use of wires and devices.[350b] However, despite this progress therapy for chronic total occlusions has appeared to lag behind.[350] More recent advances, however, have greatly increased success rates and the ability to improve the symptoms and prognosis of patients with stable CAD, resulting in a rise in percutaneous treatment for these lesions.[351,352] Current data suggest that successful PCI for chronic total occlusions is associated with improvements in patient symptoms, quality of life, LV function, and survival compared with unsuccessful attempts.[353] However, all of the scientific evidence supporting this treatment comes from observational studies; no randomized study comparing percutaneous treatment with medical treatment has been published. This field will likely continue to evolve, but for now it remains a time-consuming procedure with high radiation exposure for both the patient and the operator. More clinical data are required to support its widespread use.

Other Catheter-Based Percutaneous Therapies

Percutaneous Valvular Therapy

Balloon Valvuloplasty

Percutaneous mitral valvuloplasty (PMV) was first performed in 1982 as an alternative to surgery for patients with rheumatic MS. The procedure usually is performed via an antegrade approach and requires expertise in transseptal puncture. During the early years of PMV, simultaneous inflation of two balloons in the mitral apparatus was required to obtain an adequate result. The development of the Inoue balloon (Toray, Houston, TX) in the 1990s simplified this procedure. This single balloon has a central waist for placement at the valve and does not require wire placement across the aortic valve.[354]

The key to PMV is patient selection. Absolute contraindications include a known LA thrombus, an embolic event occurring within the preceding 2 months, and a severe cardiothoracic deformity or bleeding abnormality that prevents transseptal catheterization. Relative contraindications include significant MR, pregnancy, concomitant significant aortic valve disease, and significant CAD.[355] All patients must undergo TEE, to exclude LA thrombus, and transthoracic echocardiography, to classify the patient by anatomic group. The most widely used classification, the Wilkins score, addresses leaflet mobility, valve

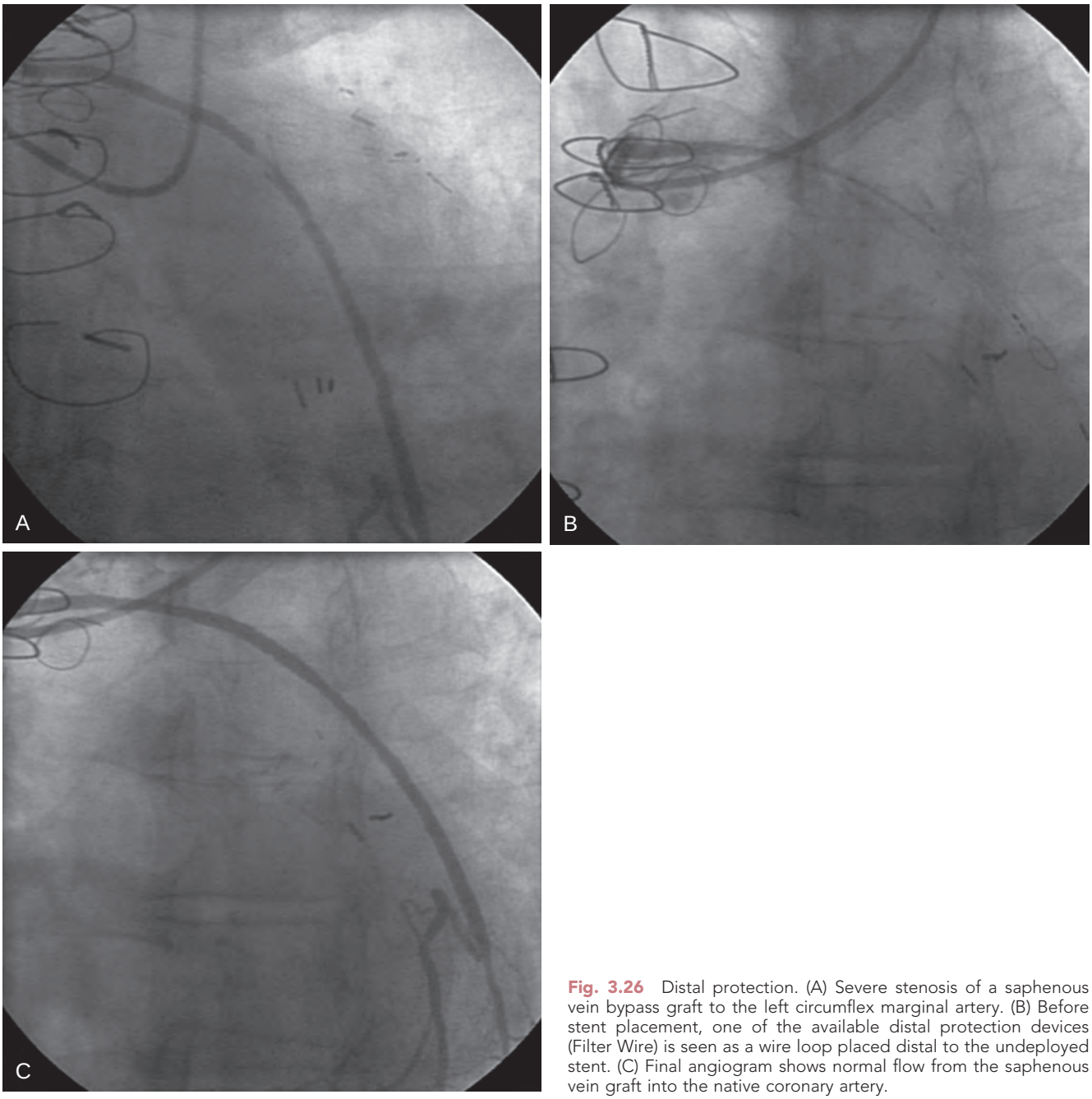


Fig. 3.26 Distal protection. (A) Severe stenosis of a saphenous vein bypass graft to the left circumflex marginal artery. (B) Before stent placement, one of the available distal protection devices (Filter Wire) is seen as a wire loop placed distal to the undeployed stent. (C) Final angiogram shows normal flow from the saphenous vein graft into the native coronary artery.

thickening, subvalvular thickening, and valvular calcification. These scoring systems, along with operator experience, predict outcomes. In experienced hands, the procedure is successful in 85% to 99% of cases.

Risks for PMV include a procedural mortality rate of 0% to 3%, hemopericardium in 0.5% to 12%, and embolism in 0.5% to 5%. Severe MR occurs in 2% to 10% of procedures and often requires emergent surgery.[356] Although peripheral embolization occurs in up to 4% of patients, long-term sequelae are rare. The procedure requires a large puncture in the interatrial septum, which does not close completely in all patients. However, a clinically significant ASD with a $\dot{Q}_p/\dot{Q}_s$ ratio of 1.5 or greater occurs in no more than 10% of cases; surgical repair is seldom necessary. Advances in patient selection, operator experience, and equipment have significantly reduced procedural complications.[356] Restenosis rates are dependent on the degree of commissural calcium.[354] TEE or intracardiac echocardiography is helpful during balloon mitral valvuloplasty.[60] These imaging modalities offer guidance for placement of the transseptal catheter, verification of balloon positioning across the valve, and assessment of procedural success.[356] Long-term results have been good.[357]

Percutaneous balloon aortic valvuloplasty was introduced in the 1980s. This procedure is usually performed via a femoral artery, using large 9- to 11-Fr sheaths and 18- to 25-mm balloons. Initial success rates are acceptable, but restenosis occurs as early as 6 months after the procedure, and almost all patients have restenosis by 2 years. The use of aortic valvuloplasty was largely abandoned after the advent of the transcatheter aortic valve replacement (TAVR) procedure. Currently, percutaneous balloon aortic valvuloplasty is used as a bridge to decision or a bridge to treatment with TAVR in those who are in severe decompensated class IV CHF. Current indications include an inoperable patient willing to accept the restenosis rate for a temporary reduction in symptoms, a patient undergoing noncardiac surgery hoping to decrease the surgical risk, and a patient with poor LV function

attempting to improve ventricular function for further consideration of aortic valve replacement.[358] Symptomatic improvement does occur, with a reduction in gradient of at least 50% in more than 80% of cases. Complications include femoral artery repair in up to 10% of patients, a 1% incidence of stroke, and a less than 1% incidence of cardiac death.[359] Slightly higher complication rates have been described in higher-risk patients.[360] Contraindications to percutaneous balloon aortic valvuloplasty are significant peripheral vascular disease and moderate to severe aortic valve insufficiency. Aortic insufficiency usually increases by at least one grade during valvuloplasty. The development of severe AR acutely leads to pulmonary congestion and possibly death because the hypertrophied ventricle is unable to dilate (see Chapters 21 and 27).

Percutaneous Valve Repair

Catheter-based alternatives to surgical valve replacement have been explored since the 1960s but were not successful until 2000, when percutaneous pulmonic valve replacement was performed.[361] These procedures are performed with the patient under general anesthesia using fluoroscopic and echocardiographic guidance. A bovine jugular valve is sutured onto a platinum-iridium stent and delivered on a balloon. The stent compresses the native valve against the wall of the annulus. Large 22-Fr delivery systems are used. The results in high-risk patients have been promising, and the device is now being tested in a lower-risk group (ie, as a true alternative to surgery). The success of percutaneous pulmonic valve replacement has also prompted interest in percutaneous replacement of the aortic and mitral valves[362,363] (see Chapters 15, 21, and 27).

Percutaneous Mitral Valve Repair

MV repair is preferred over replacement because it is associated with improved survival without the need for anticoagulation. The MV apparatus, including papillary muscle anatomy, is preserved, allowing the ventricle to maintain its shape and function. The two most common mechanisms of valve dysfunction, myxomatous disease and functional regurgitation, are also the most amenable to repair.

Percutaneously, the MV can be repaired with a clip device or with an annuloplasty. The clip devices available are the MitraClip (Evalve, Inc, Menlo Park, CA) and the Mobius II (Edwards Lifesciences, Irvine, CA). There has been more clinical experience with the MitraClip. These devices produce an edge-to-edge repair, opposing the A_2 and P_2 leaflets and simulating the Alfieri repair without requiring a sternotomy or CPB. This decreases the distance between the anterior and posterior leaflets while applying tension to the chordae, the leaflets, and, potentially, the annulus, which stabilizes or even shortens its anteroposterior diameter.[364]

The Alfieri repair[365] was developed by Dr. Alain Alfieri in 1991 for treatment of MR due to anterior leaflet prolapse. He approximated the central segments of the anterior and posterior MV leaflets, creating a double-orifice valve with reduced leaflet excursion and decreased regurgitation. In most patients, the Alfieri stitch was combined with an annuloplasty. Those patients who did not receive an annuloplasty ring still had excellent outcomes, prompting the development of the percutaneous repair.[366]

The clip is delivered though a transseptal puncture followed by deployment of a clip or suture to create a bridge between the anterior and posterior leaflets. The clip can be reopened and repositioned to locate the optimal position, and in some cases two or more clips have to be deployed to ensure an adequate reduction of MR. Within 6 months, the device is incorporated into a tissue bridge, mimicking the result of surgery.

The MitraClip, approved by the FDA in 2012, is a transvenous percutaneous device. It was first used in patients in 2003 and has been implanted in more than 10,000 patients worldwide.[367] This device permanently opposes the A_2 and P_2 segments of the MV leaflets, creating a double orifice (Fig. 3.27). This procedure is performed on a beating heart with the patient under deep sedation or general anesthesia and with fluoroscopic and echocardiographic guidance. Deep sedation is used when intracardiac echocardiography is the imaging modality chosen, and general anesthesia is used when TEE is required.

The MitraClip delivery system includes a steerable guide catheter and the clip delivery system, which comprises a delivery catheter, a steerable sleeve, and the MitraClip device. The MitraClip device is made of a cobalt-chromium metal alloy covered by polypropylene fabric. The clip delivery system, introduced through the femoral vein by the steerable guide catheter, is used to advance and manipulate the MitraClip into proper position and place it on the center segments of the MV leaflets. The MitraClip device, which can be adjusted to fully opened, closed, and inverted positions, grasps and coapts the MV leaflets (Fig. 3.28). The device can also be opened, closed, locked, and unlocked, and the grippers can be raised or lowered. The steerable guide catheter introduces the clip delivery system into the LA via the interatrial septum and then positions it in the approximate location above the MV (Fig. 3.29). Videos 3.3 and 3.4 demonstrate the path of the MitraClip and the MitraClip 1 month after placement.

The steerable catheter is 24 Fr at the femoral vein and 22 Fr after the transseptal puncture. The transseptal puncture is critically important because it determines the path of the clip toward the MV. An inappropriate puncture can decrease device maneuverability. Each arm of the clip is 4 mm long. With the arms extended, and under echocardiographic and fluoroscopic guidance, the clip is aligned perpendicular to the valve with the arms perpendicular to the line of coaptation. The clip is navigated across the mitral orifice and into the left ventricle above the origin of the MR jet.[367] The clip is then slowly retracted, allowing the leaflets to settle between the open arms of the device. The arms are then closed to grasp the leaflet edges, and the valve is interrogated by echocardiography to determine the degree of MR. If the procedure is successful, MR reduction will be immediate. If not, the clip can be readjusted. Once the degree of MR reduction is satisfactory and device stability has been determined, the clip is released. Forty percent of patients require a second clip, and use of as many as three to four clips has been described.[368]

Percutaneous repair of MR is used for patients whose risk is too high for conventional MV surgery; it is not meant to replace surgical techniques in low-risk patients. Specific criteria for MitraClip insertion are a patient with severe symptomatic MR with preserved LV size and function, an asymptomatic patient with LV dysfunction or increased LV size and recent onset of AF or pulmonary hypertension, and a symptomatic patient with severe LV dysfunction characterized by an EF of less than 30% despite maximal medical therapy.[369] Echocardiographic criteria for percutaneous mitral repair are shown in Box 3.15. Initially, clinical and anatomic criteria were based on use of the technique in patients with degenerative MR, but some patients with functional MR can be treated with the MitraClip as long as the jet origin extends beyond the central scallops of the line of coaptation or the jet is panorificial.[367]

Compared with a surgical repair, the quantitative reduction in MR with the MitraClip is reduced but not to the same extent. The advantages of percutaneous MV repair include (1) avoidance of sternotomy and CPB; (2) reduced postoperative mechanical ventilation, length of intensive care unit stay, and transfusion requirements; and (3) improved quality of life and functional capacity. Disadvantages include procedural failure, worsening of MR, and the development of MS. Complications include the creation of a persistent ASD associated with poorer outcomes,[370] torn leaflets and chordae, and rupture of the right or left atrial walls leading to cardiac tamponade. Late surgery in patients with a MitraClip is mainly necessitated by residual MR. Although surgery is more complicated, it is possible for most patients.[371]

Many trials have evaluated the efficacy of the MitraClip. The first set of trials were the EVEREST I, EVEREST II, and EVEREST High-Risk studies. EVEREST I was a phase I study evaluating the safety and efficacy of the clip. The MitraClip was implanted in 24 of 27 patients who had moderate to severe degenerative MV disease without LV dilation and who were candidates for surgical repair. There were four major events (three clip detachments and one limited neurologic event), but

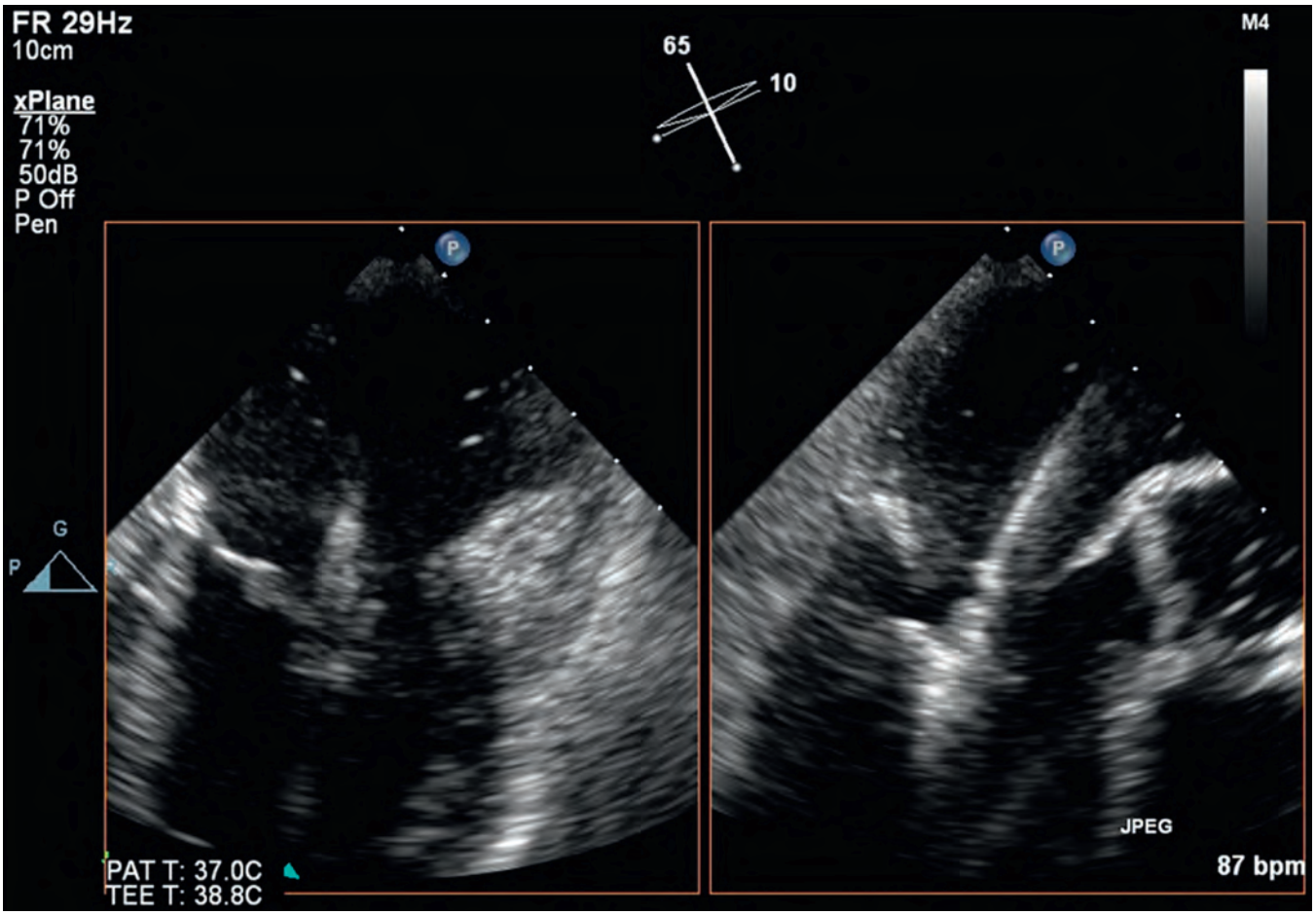


Fig. 3.27 Echocardiographic image of MitraClip placement.

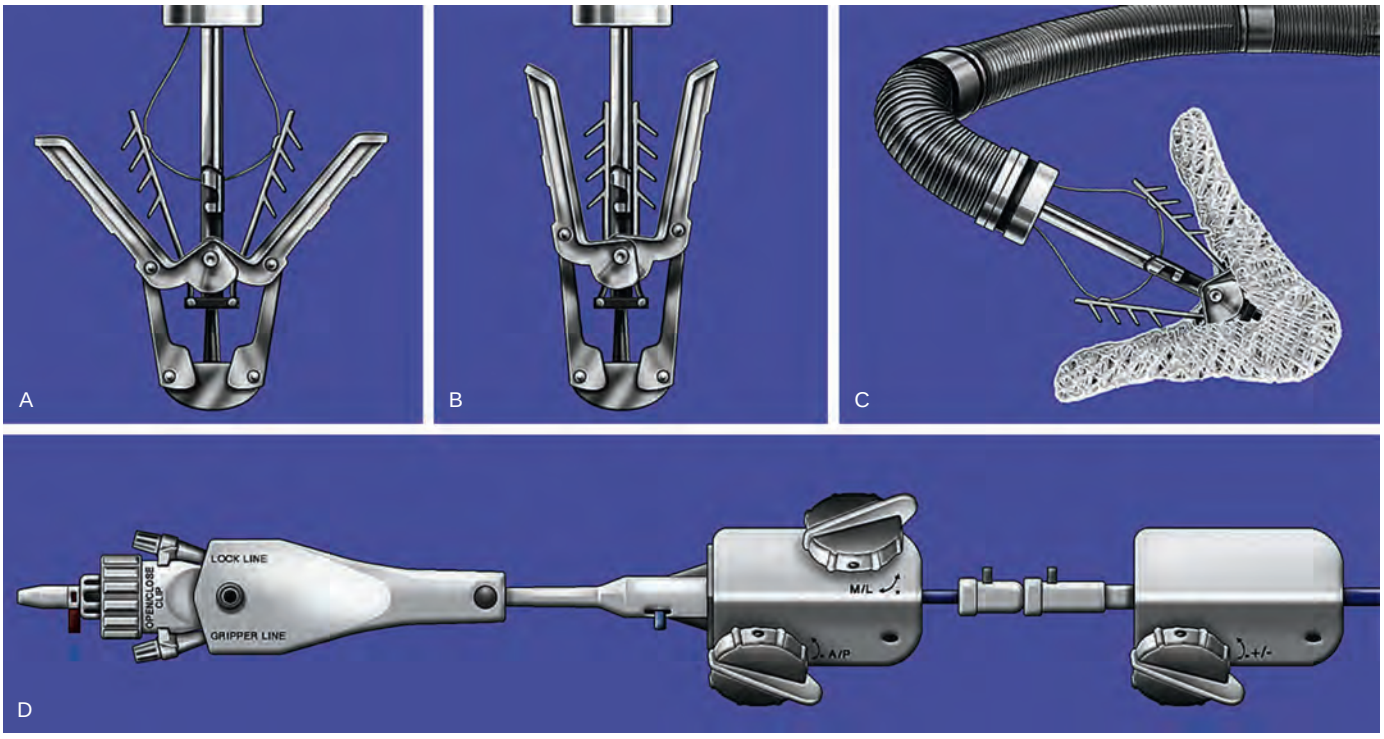


Fig. 3.28 (A) The MitraClip device, without its polypropylene covering, in the open position. (B) The device in closed position. (C) The device with its polypropylene covering. (D) MitraClip delivery system. *(From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63:2057.)*

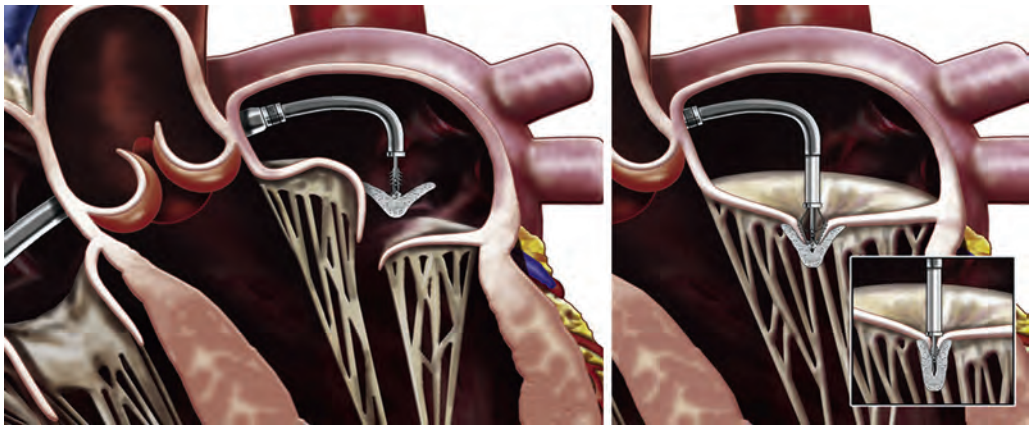


Fig. 3.29 The path of the MitraClip, from the transseptal puncture *(left panel)* to below the center of the mitral valve for deployment of the clip *(right panel). (From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63:2057.)*

BOX 3.15 SELECTION CRITERIA FOR MITRACLIP PLACEMENT

Noncommisural primary regurgitant jet
- Secondary jets, if present, should be clinically insignificant

Mitral valve area ≥4.0 cm
Coaptation length ≥2 mm and depth <11 mm
Mitral regurgitation jet must arise from central two-thirds of coaptation line
Minimal calcification in the leaflet grasping area
No leaflet cleft in the grasping area
Flail width <15 mm and flail gap <10 mm

18 patients remained free from surgery and with MR no worse than mild after 6 months.[372] In phase II of this trial, the efficacy and long-term effects of the MitraClip were compared with those of standard MV surgery. A total of 279 patients were randomized in a 2:1 ratio to undergo either MitraClip placement or surgical MV repair or replacement.[373] Although the mortality rate and proportion of patients with 3+ to 4+ MR were similar at 1 year, patients in the MitraClip group had a higher frequency of 2+ MR and a higher rate of surgery for MV dysfunction (20%, vs 2.2% in the surgical group). However, the percutaneous group demonstrated superior safety because more bleeding requiring transfusion occurred in the surgery group. There were no reports of clip embolization or MS, and the ability for surgical MV reconstruction was retained.[371]

Beneficial effects of the percutaneous clip measured with echocardiography at baseline and 24 hours after the procedure include significant reductions in MR, regurgitant fraction and volume, and LV end-systolic and end-diastolic dimensions and volume.[374] Other signs of reversal in LV remodeling include decreases in LV mass and wall stress, left atrial volume, and vena contracta area.[375–377]

The 4-year EVEREST II follow-up study demonstrated that the long-term results with the MitraClip were similar to those of surgical repair, including freedom from death, low rates of 3+ and 4+ MR echocardiographic indices, and improvement in functional status. Older patients with functional MR had outcomes that were most similar to those of surgery.[378] The EVEREST High-Risk trial studied patients with severe, predominantly functional MR who were deemed to be at high risk for surgical treatment and had an estimated mortality rate greater than 12%. They were treated with the MitraClip, and the results were compared with those in a nonrandomized concurrent control group treated with standard medical therapy.[379] At 1 year, there was a trend toward increased survival in the MitraClip group and a 45% reduction in hospitalization incidence. Other registries involving high-risk patients have shown similar results.[380,381]

Shillinger and associates[382] studied a selected group of 51 older patients who had lower EF values, functional MR, complex valvular abnormalities, and preexisting comorbidities and were treated with the MitraClip. During the procedure, all patients were hemodynamically stable and had no major periprocedural complications. After treatment, most were discharged with an MR grade of 2+, and significant improvement in New York Heart Association (NYHA) functional class occurred in more than 90%. The MitraClip has been effective in critically ill patients as a bailout procedure and in inoperable patients with ruptured papillary muscles, resulting in rapidly improving hemodynamics, ability to reduce or discontinue inotropic therapy, and discharge to home.[381,383,384] The MitraClip has also been shown to be beneficial in nonresponders to cardiac resynchronization therapy. The European PERMIT-CARE trial was performed in patients with symptomatic MR despite optimal medical therapy and cardiac resynchronization therapy. Those who underwent MitraClip repair had a trend toward improvement of their MR and reversal of LV remodeling, and 75% demonstrated improved NYHA functional class at 1 year.[385]

Two trials, the U.S.-based Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT) trial and the European Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF), are examining the safety and effectiveness of the MitraClip in high-risk surgical patients with MR and heart failure randomized to percutaneous mitral repair or standard medical therapy. These studies will help to determine the role of MitraClip therapy in patients with MR who are ineligible for surgical repair or replacement.[373] In 2015, Feldman et al[373a] revealed the 5-year follow-up of the EVEREST II study that compared the 1- and 5-year follow-ups in patients undergoing MitraClip versus surgical repair and found that patients who underwent percutaneous repair required surgery more frequently than those who underwent surgical repair after 1 year. However, at 5 years, both groups had low rates for MV surgery due to MV dysfunction, proving the durability of MitraClip as a treatment for MR.

Anesthetic Management of Percutaneous Mitral Valve Repair

In addition to standard monitors, large-bore IV access (usually peripheral) and invasive arterial monitoring are necessary. Central venous catheterization is required if large-bore peripheral access cannot be obtained or if inotropic or vasopressor support is anticipated. If the procedure is not performed in a hybrid CCL, an OR should be available for unexpected emergencies. If TEE is used, the procedure is done under general anesthesia. Deep sedation can be performed if intracardiac echocardiography is used.

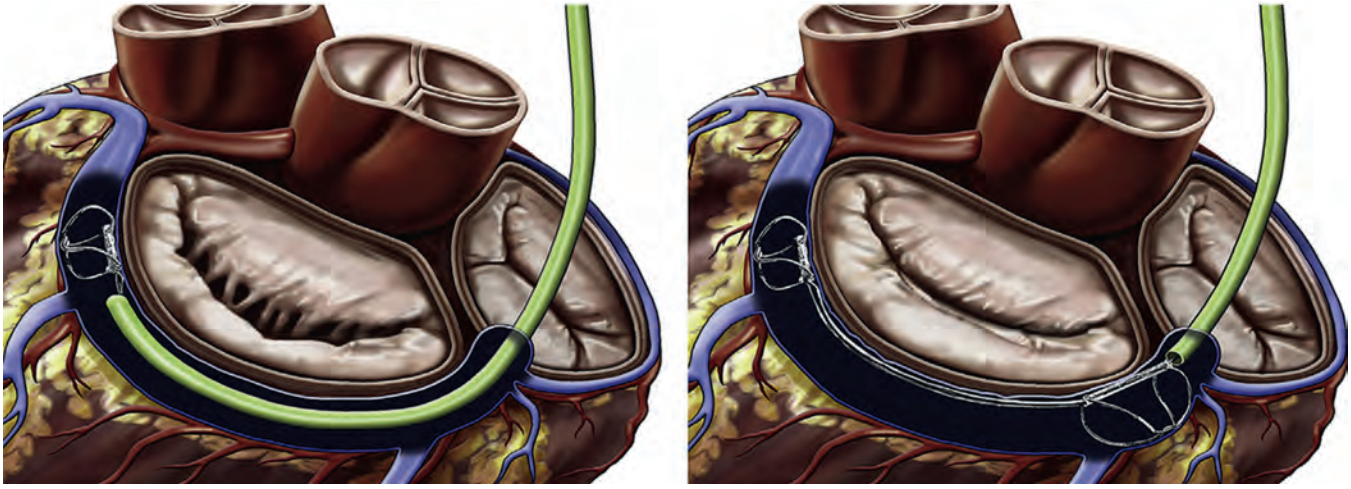


Fig. 3.30 The Cardiac Dimensions Carillon device. The guide catheter is introduced via jugular venous access. The device is inserted into the distal coronary sinus, and the distal anchor is released *(left panel)*; the guide catheter is then pulled back to release the proximal anchor in the coronary sinus ostium. The *right panel* shows the wireform, made of nitinol wire, after release in the coronary sinus. Cinching of the mitral annulus results in compression of the septal lateral dimension and thus the regurgitant orifice. *(From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63:2057.)*

The advantages of general anesthesia are that it allows for TEE monitoring and can facilitate the procedure by keeping the patient still and by allowing prolonged breath-holding during critical portions of clip placement. Depending on patient comorbidities, including the degrees of CAD and LV dysfunction, the anesthetic goals of maintaining a normal to slightly increased HR, a normal to slightly decreased systemic vascular resistance, and a normal to slightly increased preload can be accomplished using any of the available anesthetic agents. In patients with decreased ventricular function, smaller doses of anesthetic agents along with the addition of inotropic agents may be required. These patients also have longer circulatory times for IV anesthetics and shorter onset times for inhaled anesthetics.

Heparin is administered when the intraatrial septum is crossed and additional doses are given as necessary to keep the activated coagulation time longer than 250 seconds. The portions of the procedure in which breath-holding needs to occur are during difficult grasping attempts or during advancement of a second clip from the LA into the left ventricle, to avoid damaging the first clip.[386] Hypotension may occur when the clip crosses the MV orifice and may be caused by the clip's impeding LV filling. Vasoactive agents such as phenylephrine, dopamine, norepinephrine, or even epinephrine may be required to support the circulation. At the end of each grasp and before the release of the device, the blood pressure is raised to simulate preinduction physiology or to produce hypertension. This allows the surgeon to evaluate the extent, location, and severity of any residual MR; whether the clip should be deployed; or whether another clip is necessary. Protamine is administered at the end of the procedure. Most patients can be extubated and, depending on their comorbidities, can be monitored in a step-down unit or intensive care unit postoperatively.[386]

Besides leaflet repair, MV annuloplasty techniques are developing. Annuloplasty is a major component of most MV surgery and may be the only repair to treat functional MR. Annuloplasty reduces the anteroposterior diameter of the valve, promoting better leaflet coaptation and reducing regurgitation. Percutaneous annuloplasty can be achieved indirectly through the coronary sinus or directly from retrograde LV access.

Indirect annuloplasty has been developed because of the close relationship of the coronary sinus to the posterior and lateral MV annulus. A device inserted into the coronary sinus is used to shorten or reshape the annulus, mimicking surgical annuloplasty. A catheter is advanced into the coronary sinus via a transjugular approach. An anchoring device is placed in the distal coronary sinus with a tensioning element that attaches the device to the proximal coronary sinus anchor. This creates tension that is transmitted to the annulus, decreasing its circumference and improving leaflet coaptation. This technique has been considered in high-risk patients with degenerative prolapse and ischemic MR. The limitations include variations in normal coronary sinus anatomy, the varying distance between the coronary sinus and the MV, the possibility of Cx artery compromise, and inability to address anterior annulus problems. Although annuloplasty has been described as restoring MV competency and improving hemodynamic indices such as stroke volume and cardiac index, as well as decreasing left-sided and pulmonary arterial pressures and ameliorating symptoms from MR, a long-term survival benefit has not been demonstrated.[387]

The only system that uses the indirect approach is the Carillon Mitral Contour System (Cardiac Dimension, Kirkland, WA). This device is implanted transjugularly with a 9-Fr delivery catheter[388] (Fig. 3.30). The nitrinol device has proximal and distal anchors connected by a ribbon.[389] The distal anchor is released in the coronary sinus near the anterior commissure, and the proximal anchor sits near the coronary sinus ostium. Tension is placed on the delivery system to plicate the tissue around the MV. Then the valve is interrogated to determine whether the MR has been reduced. If not, the device can be repositioned or removed.[373] In the TITAN trial, a prospective, nonrandomized study of patients with functional MR, 36 of 53 patients underwent successful permanent device implantation with significant reductions in functional MR, including regurgitant volume and effective regurgitant orifice area, and favorable LV remodeling that was sustained for 12 months. These patients also had sustained improvements in functional status, including the 6-minute walk test, functional class, and quality of life, that lasted 24 months.[390] However, in the remaining 17 patients, the device could not be permanently implanted because of difficulty in cannulating the coronary sinus, and this led to an ineffective reduction in MR or a compressed coronary artery. The limitations of the Carillion device include ineffective MR reduction resulting from the separation between the coronary sinus and the MV apparatus that occurs with dilated hearts and compression of the Cx artery.[391]

Direct annuloplasty attempts to reproduce a surgical annuloplasty, and three devices are in development. The Mitralign system (Mitralign, Tewksbury, MA) uses the concept of suture annuloplasty via a retrograde transventricular approach to gain access to the mitral annulus. With the use of radiofrequency energy, guidewires penetrate the mitral annulus into the LA. Pairs of pledgets are implanted in the posterior

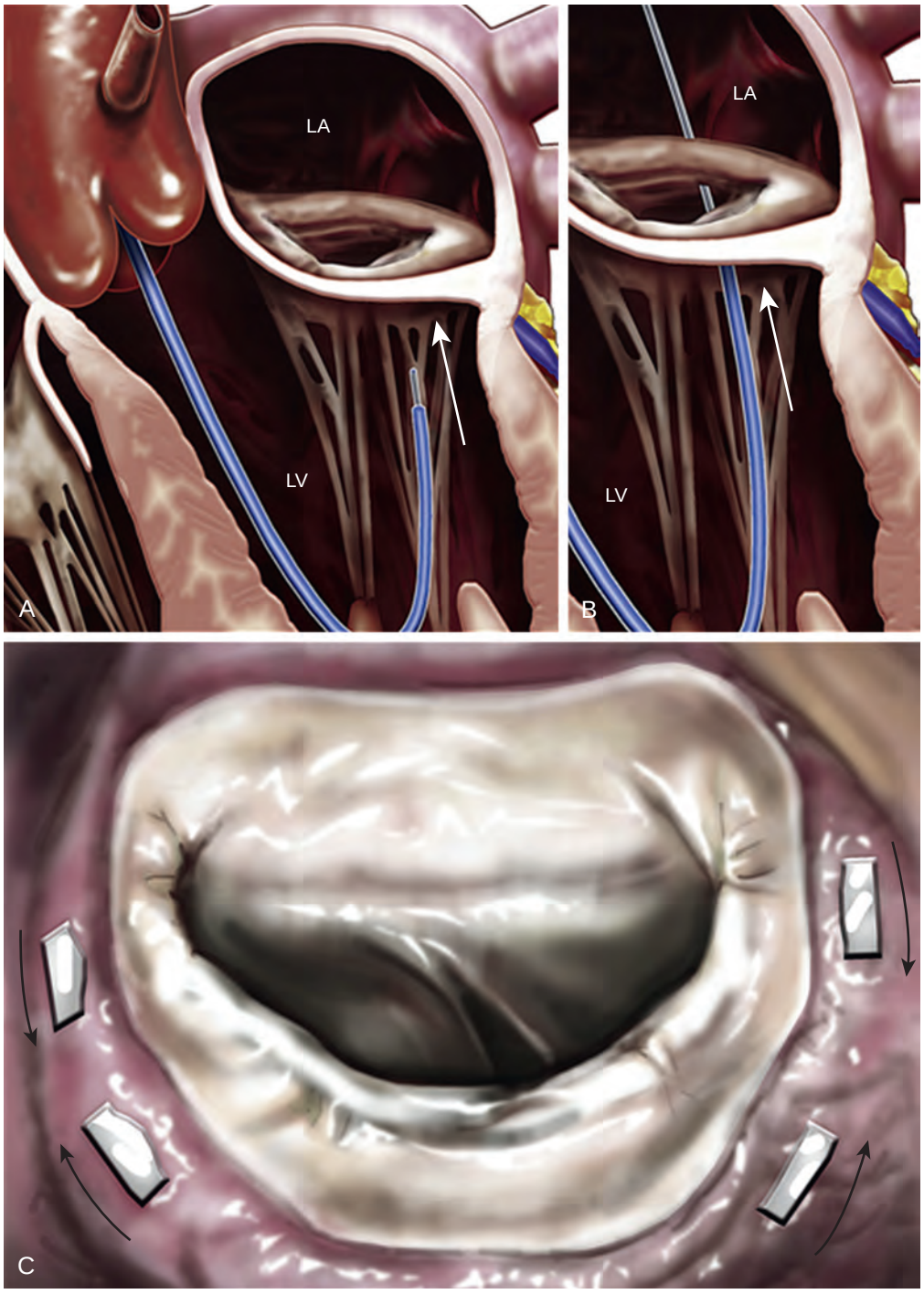


Fig. 3.31 Mitralign annular plication. (A) The retrograde guide catheter has been placed in the left ventricle *(LV)* with the distal catheter tip under the mitral annulus, behind the posterior leaflet. (B) A wire has been passed from the LV through the annulus and into the left atrium *(LA)*. Two pairs of wires are used to place pledgets near both commisures. (C) The pledgets are drawn together to decrease the mitral annular circumference. *(From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63:2057.)*

mitral annulus near A_1-P_1 and A_3-P_3 (Fig. 3.31). These pledgets are cinched together by a suture to reduce the mitral annulus and mitral orifice area.

The Accucinch system (Guided Delivery Systems, Santa Clara, CA) also uses the retrograde transventricular approach (Fig. 3.32). With this system, a series of anchors are implanted beneath the MV in the basilar left ventricle. These anchors are connected by a nitinol wire, and tethering of this wire cinches the basal left ventricle and mitral annulus, decreasing MR and producing remodeling of the basal left ventricle.

The Valtech CardioBand system (Valtech Cardio, Or Yehuda, Israel) is a percutaneous ring that resembles a surgical ring. This ring is delivered transseptally and is implanted on the atrial side of the mitral annulus. Screw anchors are deployed from the posteromedial to the anterolateral commissure in a counterclockwise fashion, with the ring extruded from a delivery catheter in small segments (Fig. 3.33).

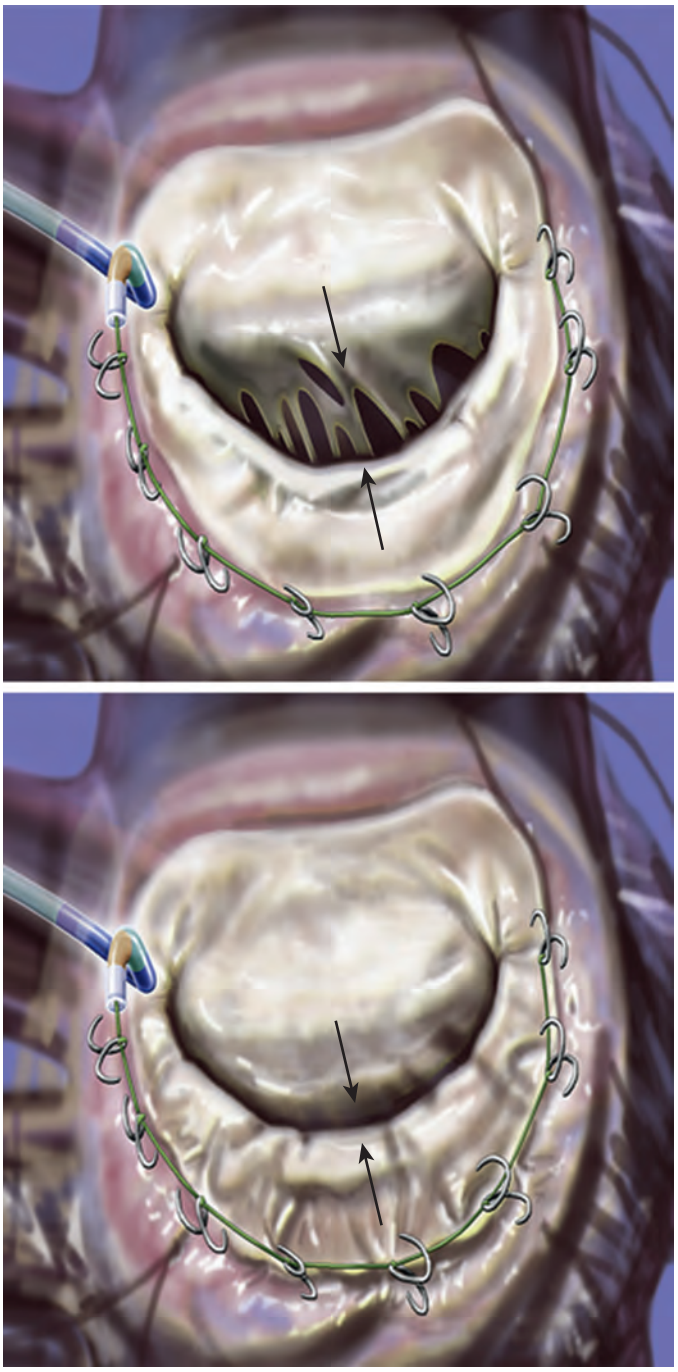


Fig. 3.32 Accucinch device. The Accucinch device is inserted via retrograde catheterization of the ventricle *(top panel)*. The *arrows* highlight the separation of the leaflet edges. Anchors are placed in the posterior mitral valve annulus and connected with a drawstring to cinch the annular circumference. When the cord is tightened, the basilar myocardium and annulus draw the mitral leaflets together *(bottom panel)* to decrease the regurgitant orifice. *(From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63:2057.)*

Annular circumference is reduced by controlling tension on the band, which decreases MR.[392] Several patients have undergone successful percutaneous implantations.

For high-risk patients, percutaneous approaches for leaflet repair, annuloplasty, chordal replacement, and LV remodeling are under development.

Other Catheter-Based Intracardiac Procedures

Alcohol Septal Ablation

HCM is a genetic disorder that can manifest with sudden cardiac death or symptoms of heart failure. A minority of patients have asymmetric septal hypertrophy that leads to dynamic outflow tract obstruction and produces severe symptoms. If this condition is refractory to medical therapy, a surgical procedure for septal tissue removal, and often MV repair or replacement, may be required. Since the mid-1990s, percutaneous methods have been studied to induce a controlled infarction and selectively ablate this overgrown septal tissue[393] (see Chapter 24).

Through a standard guiding catheter, a guidewire is placed in the large proximal septal perforator. A balloon catheter is placed over the wire into the septal perforator and inflated to occlude flow. The wire is removed, and 1 to 3 mL of ethanol is injected through the balloon into the septal perforator and left in place for 5 minutes. Temporary pacing is required in all patients, and a permanent pacemaker is required in some. When the procedure is performed by experienced operators, morbidity and mortality are limited, the gradient is reduced, and symptoms are improved.[394,395] Controversy persists regarding the role of alcohol septal ablation compared with surgical septal myectomy, and procedure selection is best based on the individual patient.[396,397]

Left Atrial Appendage Occlusion

Most strokes in patients with nonvalvular AF arise from thrombus formation in the left atrial appendage (LAA). Occlusion or exclusion of the LAA provides at least a theoretical alternative to oral anticoagulation for stroke prevention in such patients. Warfarin therapy is effective for stroke prevention but is associated with morbidity and mortality, and many patients have contraindications to warfarin. The WATCHMAN LAA system (Atritech, Plymouth, MN) is a covered nitinol device that is implanted percutaneously to seal the appendage. The PROTECT AF trial randomized 707 patients with permanent, persistent, or paroxysmal AF who were at high risk for stroke to appendage occlusion with the WATCHMAN device or warfarin therapy in a 2:1 ratio. The annual stroke rate was 2.3% in the device group and 3.2% in the warfarin group. Pericardial drainage was required in 5% of patients undergoing implantation, although no deaths occurred. Periprocedural stroke and device embolization occurred in 1.1% and 0.6% of patients, respectively.[398] The WATCHMAN device was approved by the FDA in March 2015.

An LAA exclusion device with promising human data is the LARIAT suture delivery system (SentreHEART, Redwood City, CA), which received FDA approval in 2009 for surgical suture placement and knot tying. This hybrid system has been used for LAA ligation and involves the epicardial and transseptal placement of magnet-tipped guidewires, forming a single rail for delivery of an endocardial balloon, and an epicardial snare with a pretied suture loop.[399] There are several advantages to this approach, including complete control of the pericardial space in the event of cardiac perforation, lack of any endovascular hardware left behind, and possible elimination of the need for postprocedure anticoagulation. The major disadvantage of the LARIAT system is the need for simultaneous transseptal and pericardial access. In addition, anatomic variables can limit candidacy for the device, including large LAA diameter, posterior LAA, pericardial adhesions from prior cardiac surgery, and pericarditis.[400] In the treatment of AF, individual patient decisions need to be made by weighing the proven long-term benefits and risks of rate control with warfarin against those of invasive therapies such as catheter ablation and LAA occlusion.

Percutaneous Closure of Patent Foramen Ovale and Septal Defects

The Amplatzer device (AGA Medical Corp., Golden Valley, MN) is FDA approved and is preferred to surgical closure for isolated secundum

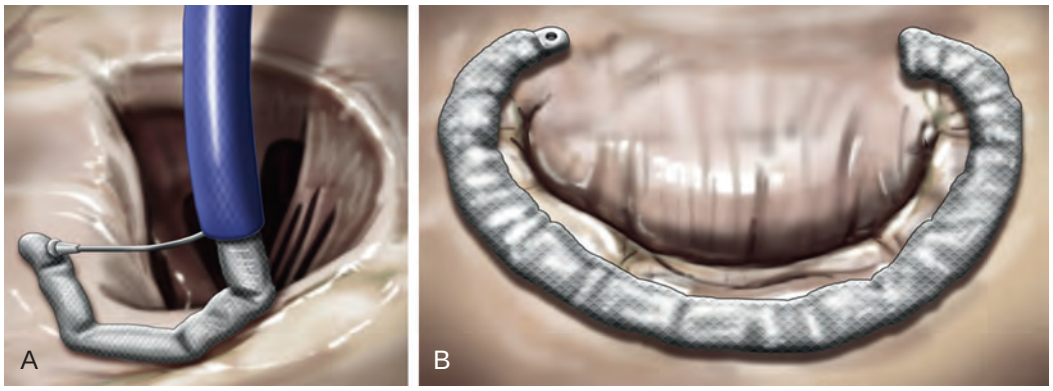


Fig. 3.33 Valtech CardioBand. (A) Transseptal guide catheter delivering angioplasty ring in segments. Each segment is sequentially anchored to the annulus. (B) Final annuloplasty ring encircling the posterior leaflet. *(From Feldman T, Young A. Percutaneous approaches to valve repair for mitral regurgitation.* J Am Coll Cardiol. *2014;63;2057.)*

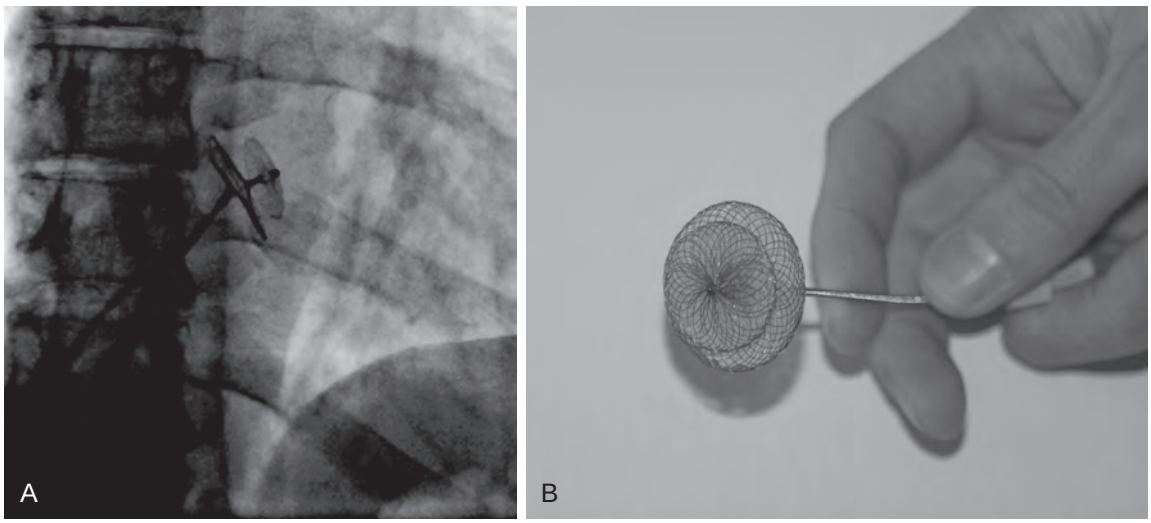


Fig. 3.34 (A) Deployment of a patent foramen ovale (PFO) closure device. (B) PFO closure device.

defects. A newer device, the Helex septal occluder (Gore Medical, Flagstaff, AZ), is an alternative for some smaller defects.[401] Intracardiac or TEE guidance is required.[60] General anesthesia is used frequently, to permit prolonged transesophageal imaging. In appropriately selected patients, success rates are almost 100%, and complications are rare.

Two devices, the Amplatzer PFO Occluder (AGA Medical) and the CardioSEAL (NMT Medical, Boston, MA), were available in the past under the Humanitarian Device Exemption in the United States for use in patients with a PFO who had had a recurrent stroke while receiving warfarin. The devices were withdrawn from the market in 2006 for a variety of reasons, primarily the fact that their use had expanded outside the approved indication without data to support such expanded use. Clinical trials are in progress to determine whether the devices are more effective than anticoagulation in preventing recurrent stroke after the first event (Fig. 3.34). Improvements in migraine headaches after PFO closure have been reported.[402] Surgical closure has been relegated to those few patients whose anatomy precludes percutaneous closure[403] (see Chapters 22 and 24).

These procedures are usually performed with the use of general anesthesia and TEE guidance. The anesthesiologist should know the indication and the hemodynamic effects of the lesion, including the consequences of right-to-left shunting.[404] Use of invasive monitoring depends on the patient's preexisting disease and the presence of right ventricular dysfunction and pulmonary hypertension. Inotropic support, such as the catecholamines, milrinone, or levosimendin, and pulmonary vasodilators, such as nitric oxide or prostacyclin, should be available for patients with severe right ventricular dysfunction and pulmonary hypertension. For patients with severe pulmonary hypertension, ECMO standby should be available. All IV access lines should be de-aired to prevent cerebral emboli. Perioperative complications may include arrhythmias, atrioventricular conduction defects, hypotension, thrombus with pulmonary or systemic embolization, valve dysfunction, Amplatzer device embolization or malposition, worsening of preexisting pulmonary hypertension and right ventricular dysfunction, and cardiac perforation.[404]

Most VSDs have right-to-left flow. The etiology of the lesion can affect management. Postinfarction VSD closure can be more challenging than congenital VSD closure. Patients with postinfarction VSD can be hemodynamically unstable and are more likely to have hypotension and arrhythmias during closure.[405]

The Catheterization Laboratory and the Anesthesiologist

The increasing incidence and complexity of procedures in the CCL or hybrid OR has broadened the scope of anesthesia practice. The CCL is typically in a different location from the main ORs, often in

a remote location or on a different floor. The setup, personnel, and environment are different. The fluoroscope and monitors are large and bulky, and other equipment may also be present in the room, such as leaded screens, defibrillators, code carts, and transesophageal or intracardiac echocardiography machines, limiting the space for the anesthesia machine, monitoring equipment, and cart. Challenges to the anesthesiologist in the CCL include radiation exposure, unfamiliar surroundings, isolation from anesthesia colleagues and resources, limited or ineffectual help from CCL personnel and physicians, and a reduced ability to obtain medications and equipment (eg, a difficult airway cart).[406]

Procedures and interventions in the CCL are more involved and in certain cases are performed on patients who are considered too high-risk for conventional surgery. These procedures take longer to perform and require more attention from the cardiologist. Collaboration and planning between the cardiologist and the anesthesiologist is needed to discuss the patient, the procedure, and the type of anesthetic required for procedural success. A discussion with the CCL nurses and technicians is also beneficial to inform them of the anesthetic plan and how they can assist the anesthesia team, if necessary.

The CCL must be equipped with wall oxygen, air, and suction outlets as well as a scavenging system when use of an inhalation agent is required. Anesthetic and resuscitation medications need to be available at all times, and a mechanism to obtain any additional medications should be discussed. In some CCLs, the automated dispensing cabinets have a draw dedicated for anesthesia-related medications. Although the CCL has monitors to measure HR, noninvasive and invasive blood pressure, central venous pressure, PA pressure, and oxygen saturation, a monitor that measures end-tidal carbon dioxide and inspired and expired concentrations of volatile agents is necessary, especially if a general anesthesia is planned. The anesthesia carts should contain airway equipment, including emergency airway adjuncts such as a laryngeal mask airway and a disposable videolaryngoscope, extra fluids and medications, standard and invasive monitoring supplies, oxygen masks and cannulas that can measure carbon dioxide, and suctioning supplies. Resuscitative medications and devices need to be available at all times. Because the defibrillators in the CCL may be different from those in the OR, the anesthesia staff must comfortable with the equipment. There should also be a means to obtain assistance during an emergency (eg, telephone to call the OR, code button). Patients are frequently far away from the anesthesia team, and with constant movement of the fluoroscopy equipment and table, extensions may be needed to prevent disconnects on the breathing circuit and oxygen tubing, IV and intraarterial lines, and monitors, including end-tidal carbon dioxide tubing.[407] In 2011, the American Society of Anesthesiologists revised its standard for ventilation monitoring in moderate or deep sedation to include end-tidal carbon dioxide monitoring along with qualitative clinical signs.

Depending on the procedure and the patient, a variety of anesthetic techniques are employed in the CCL. Simple catheterization procedures and PCIs are usually performed with minimal sedation and local infiltration under the direction of the cardiologist, according to institutional guidelines.[408] Small doses of midazolam and fentanyl are usually administered for these procedures. Anesthesiologists may be involved if there is a risk of airway, respiratory, or hemodynamic compromise or if the patient is unable to remain still for the procedure.[404]

Regional anesthesia, particularly epidurals, can be beneficial in the management of endovascular abdominal aortic aneurysm repair and in lower extremity stent procedures for vascular patency.[409] General anesthesia is reserved for prolonged interventional procedures and those that require the use of TEE. It is also used for patients who are apneic, pediatric, uncooperative, or critically ill; patients who have difficulty lying still; and patients with pulmonary hypertension, in whom hypoventilation and airway obstruction increases the risk of right ventricular dysfunction.

The preoperative assessment includes the reason for the intervention and the cardiac history, including the type and extent of disease and previous treatments (eg, medications, interventions). Useful information from previous studies includes the type and location of the lesion, left- and right-sided filling pressures, and valvular and ventricular function. Patients may present after a recent MI, in acute heart failure, or with uncontrolled arrhythmias.[404]

In addition to the cardiac history, a complete system-based history should be obtained, focusing on any airway issues, esophageal disease (if the use of TEE is anticipated), renal insufficiency (if dye use is required), use of diuretics (which can cause hypokalemia, increasing the risk of arrhythmias during the procedure), and use of any anticoagulants or antiplatelet agents. Prolonged heparin administration may lead to antithrombin III deficiency, requiring the administration of antithrombin III or fresh-frozen plasma. The patient should also be asked about any dye allergy, and ionic contrast dyes should be avoided in such patients.

Other considerations include urinary catheter placement for prolonged procedures. Blood should be cross-matched and available for procedures associated with bleeding and for those in which the cardiologist administers a variety of medications including anticoagulants (eg, heparin, GPIs) and direct thrombin inhibitors (eg, argatroban, bivalirudin). The cardiologist may also administer bolus medications (eg, nitroglycerin, calcium channel blockers) directly into catheters, and these may produce profound hemodynamic changes. The cardiologist should inform anesthesia personnel in advance of this type of therapy.

TEE is often used as guidance for wire and catheter placement and for determining the location and success of the procedure. If hemodynamic instability occurs during the procedure, TEE can be used to evaluate ventricular and valvular function and fluid status.

The anesthesiologist should be consulted whenever there is a patient issue or the intervention requires regional or general anesthesia. Patient factors include cardiovascular problems (eg, heart failure, hemodynamic instability), need for more extensive monitoring, respiratory conditions (including obstructive sleep apnea), morbid obesity, a known or suspected difficult airway, and severe pulmonary disease. Other considerations are pediatric patients, patients with psychiatric disorders who cannot lie still, patients with claustrophobia, and patients with tolerance to the medications administered by nonanesthesia personnel.[404]

This chapter has provided an overview of the procedures that are performed in the CCL and their anesthetic management. With the increased use of percutaneous therapies, anesthesiologists will play an integral part in the care of these patients.

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4 Cardiac Electrophysiology: Diagnosis and Treatment

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KEY POINTS

1. Cardiac arrhythmias are common and result from an ectopic focus or a reentry circuit.
2. Surgical and catheter-based ablative therapies can abolish the origins of arrhythmias by interposition of scar tissue along the reentrant pathway or by isolating an ectopic area.
3. Supraventricular arrhythmias can be hemodynamically unstable, especially in the setting of structural heart disease. In some cases, persistent tachycardia can lead to tachycardia-induced cardiomyopathy.
4. Accessory pathways are typically interrupted using percutaneous, catheter-based techniques, producing high success rates with minimal complications.
5. Atrioventricular nodal reentrant tachycardia results from altered electrophysiologic properties of the anterior fast pathway and posterior slow pathway fibers that provide input to the atrioventricular node. Interruption of the involved pathway is curative.
6. Atrial flutter typically involves a reentrant circuit that circles the tricuspid valve and crosses the myocardial isthmus between the inferior vena cava and tricuspid valve. Catheter ablation of this region can remedy the arrhythmia.
7. Paroxysmal atrial fibrillation often results from ectopic beats originating in the pulmonary veins. Pulmonary vein isolation with catheter-based ablative energy is indicated for patients who have failed antiarrhythmic therapy and are symptomatic or have evidence of structural heart disease due to atrial fibrillation.
8. Catheter ablation for persistent or long-standing atrial fibrillation is less effective than for paroxysmal atrial fibrillation. Although pulmonary vein isolation is recommended, adjuvant ablation strategies are also employed, including abatement of complex fractionated atrial electrograms and targeting areas of ganglionated plexus.
9. Surgical treatment of atrial fibrillation (ie, maze procedure) has been employed with good success and has been modified to avoid the sinus node in an effort to minimize occurrences of chronotropic incompetence.
10. In adults, most episodes of sudden cardiac death are the result of ventricular tachyarrhythmias due to ischemic and nonischemic cardiomyopathy. Other conditions associated with an increased risk of sudden death include infiltrative cardiac diseases (eg, cardiac sarcoidosis, amyloidosis) and genetically based abnormalities such as hypertrophic cardiomyopathy, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and arrhythmogenic right ventricular dysplasia.
11. Substantial evidence supports use of an implantable cardioverter-defibrillator for primary and secondary prevention of sudden cardiac death.

Cardiac rhythm disturbances are common and an important source of morbidity and mortality.[1,2] The incidence of supraventricular tachycardias (SVTs) ranges from 35 cases per 100,000 person-years for paroxysmal SVTs to 5 to 587 cases per 100,000 person-years for atrial flutter for 50-year-old individuals and those older than 80 years, respectively.[3,4] Atrial fibrillation is the most common sustained cardiac arrhythmia in the general population, affecting more than 2.3 million Americans.[5] Prevalence is strongly associated with age, occurring in less than 1% of individuals younger than 55 years old but in almost 10% of those older than 80 years.[5] Atrial fibrillation increases health resource consumption, heightens the risk of stroke, and increases associated long-term mortality rates.[6]

The treatment of cardiac arrhythmias has shifted over the past 2 decades to catheter-based and surgical ablation from pharmacologic therapy because of the drugs' limited efficacy and increased risk of death due to their negative inotropic and proarrhythmic effects.[7,8] Data from prospective, randomized trials showing improved survival for patients with implantable cardioverter-defibrillators (ICDs) compared with those given antiarrhythmic drugs bolstered the shift to nonpharmacologic treatments.[9]

Current management options for cardiac arrhythmias include surgical and catheter ablative techniques using various energy sources. The principle in all cases is identification of the electrophysiologic mechanism of the arrhythmia followed by ablation of the involved myocardium using surgical incisions, cryothermy, or radiofrequency (RF) current. As the techniques have become more complex and time intensive, the need for anesthesia support has grown. Anesthesiologists caring for patients undergoing these procedures must be familiar with the anatomy of the normal cardiac conduction system, the electrophysiologic basis of common cardiac rhythm disorders, and the various approaches to ablative treatment. In this chapter, we discuss these basic principles and the anesthesia considerations for particular forms of treatment.

Electrophysiologic Principles

Anatomy and Physiology of the Cardiac Pacemaker and Conduction Systems

Sinoatrial Node

The sinoatrial (SA) node (Fig. 4.1) is a spindle-shaped structure composed of highly specialized cells located in the right atrial sulcus terminalis, which is lateral to the junction of the superior vena cava

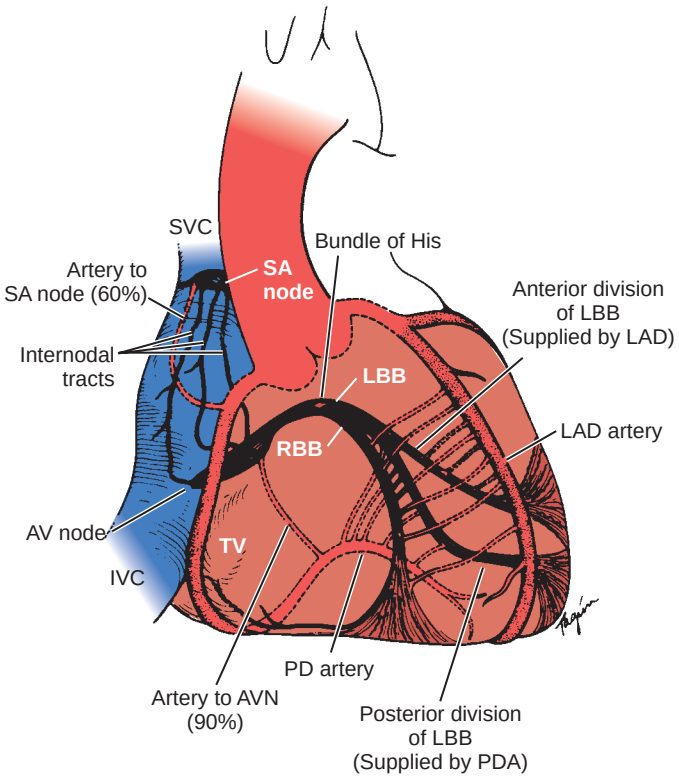


Fig. 4.1 Anatomy of the cardiac conduction system and arterial blood supply. In 60% of patients, the sinoatrial *(SA)* nodal artery is a branch of the right coronary artery, and in the remainder, it arises from the circumflex artery. The atrioventricular *(AV)* node is supplied by a branch from the right coronary artery or posterior descending artery *(PDA)*. *IVC*, Inferior vena cava; *LAD*, left anterior descending coronary artery; *LBB*, left bundle branch; *RBB*, right bundle branch; *SVC*, superior vena cava; *TV*, tricuspid valve. *(From Harthorne JW, Pohost GM. Electrical therapy of cardiac arrhythmias. In Levine HJ, ed.* Clinical Cardiovascular Physiology. *New York: Grune & Stratton; 1976:854.)*

BOX 4.1 ANATOMY OF THE CARDIAC PACEMAKER AND CONDUCTION SYSTEM

Sinus node
Internodal conduction
Atrioventricular junction
Intraventricular conduction system
- Left bundle branch
  - Anterior fascicle
  - Posterior fascicle

Right bundle branch
Purkinje fibers

(SVC) and the right atrium.[10,11] Box 4.1 summarizes the anatomy of the cardiac pacemaker and conduction system.

The SA node contains three cell types (ie, nodal, transitional, and atrial muscle), but no single cell type is solely responsible for initiating the pacemaker impulse. Instead, multiple cells in the SA node discharge synchronously through complex interactions.[12–14] Studies suggest that the SA node consists of three distinct regions and that each is responsive to a separate group of neural and circulatory stimuli.[15] Interactions among these three regions appear to determine the ultimate rate of output of the SA node.

Although the SA node is the primary site of impulse formation, subsidiary atrial pacemakers located throughout the right and left atria can also initiate cardiac impulses.[16–18] A series of studies in dogs and humans confirmed that there is an extensive system of atrial pacemakers widely distributed in the right and left atria and the atrial septum.[15,19–21] Because the atrial pacemaker system occupies a much larger area than the SA node, it can be severed during arrhythmia surgery, impairing rate responsiveness.[10] However, it is extremely difficult to completely abolish SA node activity through catheter-based ablation techniques.

The blood supply to the SA node (ie, SA node artery) is provided from the right coronary artery (RCA) (60% of the population) or the left circumflex coronary artery (see Fig. 4.1). The SA node is richly innervated with postganglionic adrenergic and cholinergic nerve terminals. By releasing acetylcholine, vagal stimulation slows SA nodal automaticity and prolongs intranodal conduction time, whereas adrenergic stimulation increases the discharge rate of the SA node.[10]

Internodal Conduction

Despite previous controversy about the existence of specialized conduction pathways connecting the SA node to the atrioventricular (AV) node, electrophysiologists agree that preferential conduction unequivocally exists and that spread of activation from the SA node to the AV node follows distinct routes by necessity because of the peculiar geometry of the right atrium.[10] The orifices of the superior and inferior cava, fossa ovalis, and ostium of the coronary sinus divide the right atrium into muscle bands, limiting the number of routes available for internodal conduction (see Fig. 4.1). These routes, however, do not represent discrete bundles of histologically specialized internodal tracts comparable to the ventricular bundle branches.[22] A parallel arrangement of myocardial cells in bundles, such as the crista terminalis and the limbus of the fossa ovalis, may account for preferential internodal conduction. Although electrical impulses travel more rapidly through the thick atrial muscle bundles, surgical transection does not block internodal conduction because alternate pathways of conduction through atrial muscle are available.[23]

Atrioventricular Junction and Intraventricular Conduction System

The AV junction (Fig. 4.2) corresponds anatomically to a group of discrete, specialized cells that are morphologically distinct from working myocardium and divided into a transitional cell zone, compact portion, and penetrating AV bundle (ie, His bundle).[24] Based on animal experiments, the transitional zone appears to connect atrial myocardium with the compact AV node.[25] The compact portion of the AV node is located superficially and anterior to the ostium of the coronary sinus and above the insertion of the septal leaflet of the tricuspid valve. The longitudinal segment of the compact AV node penetrates the central fibrous body and becomes the bundle of His. As the node-bundle axis descends into the ventricular musculature, it gradually becomes completely isolated by collagen and is no longer in contact with atrial fibers.

The AV junction is contained within the triangle of Koch, an anatomically discrete region bounded by the tendon of Todaro, tricuspid valve annulus, and ostium of the coronary sinus (Fig. 4.3). The triangle is avoided in all cardiac operative procedures to prevent damage to AV conduction. Individual variation in the anatomy of the AV nodal area depends on the degree of central fibrous body development.[10]

Branching of the node-bundle axis begins at the superior margin of the muscular interventricular septum. At this level, the bundle of His emits a broad band of fascicles, forming the left bundle branch that extends downward as a continuous sheet into the left side of the septum beneath the noncoronary aortic cusp (see Fig. 4.1). The left bundle divides into smaller anterior and broader posterior fascicles, although this is not a consistent anatomic delineation. The right bundle branch usually originates as the final continuation of the bundle of His, traveling subendocardially on the right side of the interventricular septum toward the apex of the right ventricle. The distal branches of the conduction system connect with an interweaving network of Purkinje fibers expanding broadly on the endocardial surface of both ventricles.

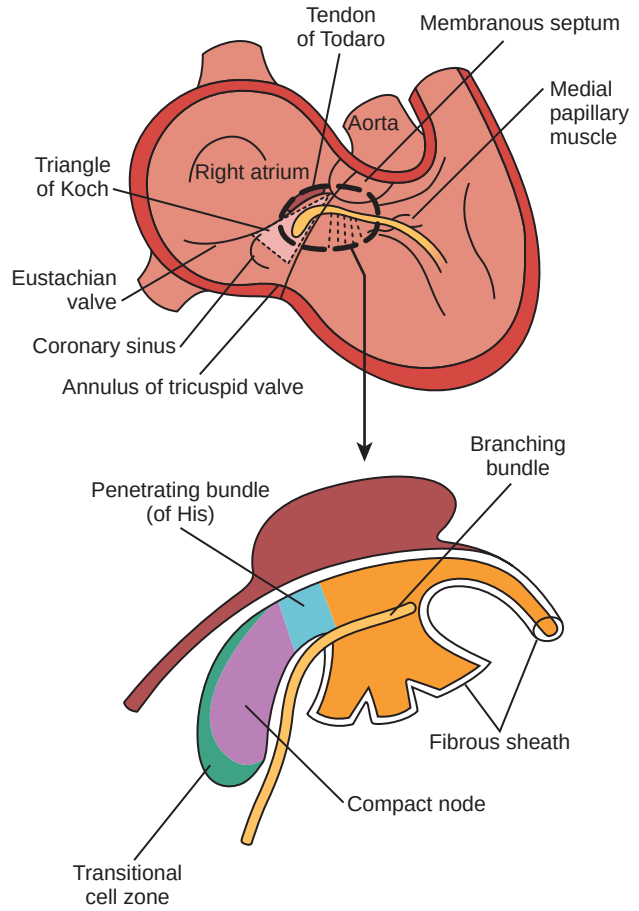


Fig. 4.2 Anatomic relationships of the atrioventricular junction and other cardiac structures. *(From Harrison DC, ed.* Cardiac Arrhythmias: A Decade of Progress. *Boston: GK Hall Medical Publishers; 1981.)*

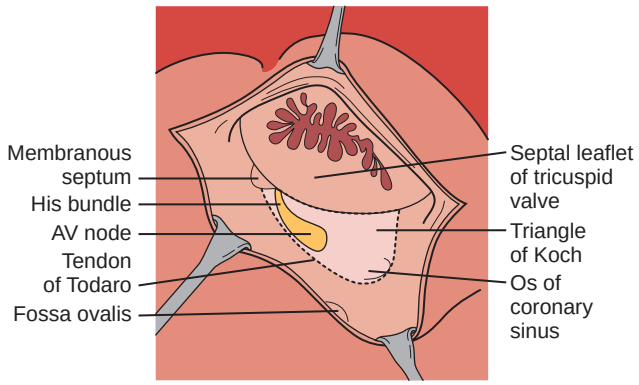


Fig. 4.3 View of right atrial septum through a right atriotomy incision *(superior on the left)*. The triangle of Koch is an important anatomic area that includes the atrioventricular *(AV)* node and proximal portion of the His bundle. This anatomic region is contained in the area between the tendon of Todaro, the tricuspid valve annulus, and a line connecting the two at the level of the os of the coronary sinus. *(From Cox JL, Holman WL, Cain ME. Cryosurgical treatment of atrioventricular node reentry tachycardia.* Circulation. *1987;76:1331.)*

In 85% of the population, most of the blood supply to the AV node is from the RCA, and the left circumflex artery supplies the remainder. The bundle of His is supplied by branches from the anterior and posterior descending coronary arteries.

Innervation of the SA and AV nodes is complex because of substantial overlapping of vagal and sympathetic nerve branches. Stimulation of the right cervical vagus nerve causes sinus bradycardia, whereas stimulation of the left vagus nerve prolongs AV nodal conduction. Stimulation of the right stellate ganglion speeds the SA nodal discharge rate, whereas stimulation of the left ganglion produces a shift in the pacemaker from the SA node to an ectopic site (ie, tissue outside the normal conduction system of the heart that initiates an impulse).[26]

BOX 4.2 ARRHYTHMIA MECHANISMS

Focal mechanisms
- Automatic
- Triggered

Reentrant arrhythmias

Normal automaticity
- Sinoatrial node
- Subsidiary atrial foci
- Atrioventricular node
- His-Purkinje system

Triggered mechanisms occur from repetitive delayed or early afterdepolarizations.

Reentry
- Unidirectional block is necessary.
- Slowed conduction in the alternate pathway exceeds the refractory period of cells at the site of unidirectional block.

Basic Arrhythmia Mechanisms

The mechanisms of cardiac arrhythmias are broadly classified as focal mechanisms that include automatic or triggered arrhythmias or as reentrant arrhythmias (Box 4.2). Cells that display automaticity lack a true resting membrane potential and instead undergo slow depolarization during diastole (Figs. 4.4 and 4.5). Diastolic depolarization results in the transmembrane potential becoming more positive between successive action potentials until the threshold potential is reached, producing cellular excitation. Cells possessing normal automaticity can be found in the SA node, subsidiary atrial foci, AV node, and His-Purkinje system.[10,13,27–29]

The property of slow diastolic depolarization is called *spontaneous diastolic* or *phase 4 depolarization*. Factors that can modify spontaneous diastolic depolarization are shown in Fig. 4.5 and include alterations in the maximal diastolic potential, threshold potential, and rate or slope of diastolic depolarization. The net effect is to influence the rate at which the threshold potential is achieved, resulting in an increase or a decrease in automaticity.

The ionic mechanism of diastolic depolarization involves the funny current (ie, funny channel or pacemaker current), which is expressed in spontaneously active cardiac regions. Diastolic depolarization involves a decrease in net outward potassium ion (K^+) movement or an increase in net inward sodium ion (Na^+) movement, or both.[26,30–33] Pacemaker cells with the fastest rate of phase 4 depolarization become dominant in initiating the cardiac impulse, with other automatic foci subject to overdrive suppression.

Altered automaticity occurs when cells that normally display automaticity (eg, SA node, AV node, Purkinje fibers) change the rate of pacemaker firing. Although the ionic mechanisms resulting in altered automaticity are unchanged, other factors such as those seen in Fig. 4.5 can contribute to an increase in automaticity. Automaticity resulting from abnormal ionic mechanisms, even if occurring in cells that are usually considered automatic (eg, Purkinje fibers), is referred to as *abnormal automaticity*. Abnormal automaticity may also occur in cells in which automaticity is not normally observed (eg, ventricular myocardium).

Arrhythmias caused by a triggered mechanism are initiated from cells that have repetitive afterdepolarizations. Afterdepolarizations are oscillations in the transmembrane potential that occur before (ie, early

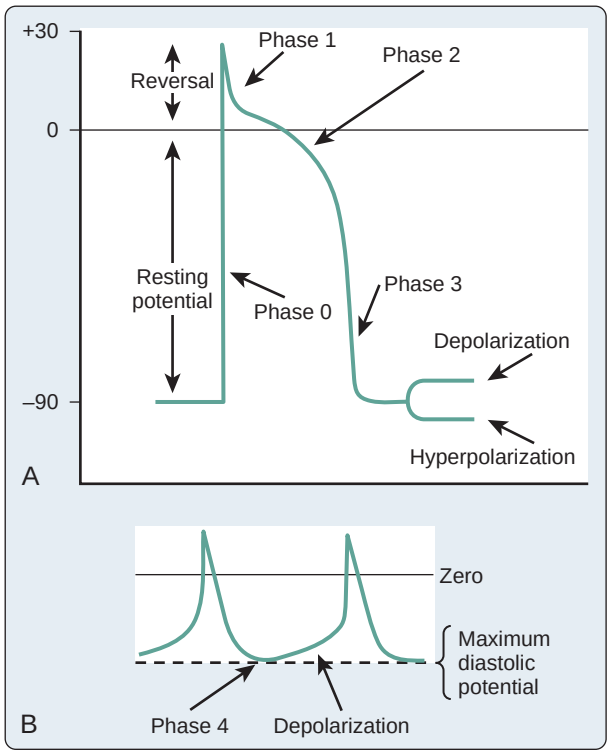


Fig. 4.4 (A) Graph of the cardiac cellular action potential (in millivolts) of the fast-response fiber. (B) Graph of the action potential of slow-response fiber. The slow-response fiber is similar to that found in the sinoatrial node but lacks the rapid upstroke of phase 0. *(From Ferguson TB Jr. Anatomic and electrophysiologic principles in the surgical treatment of cardiac arrhythmias.* Cardiac Surg. *4:19, 1990.)*

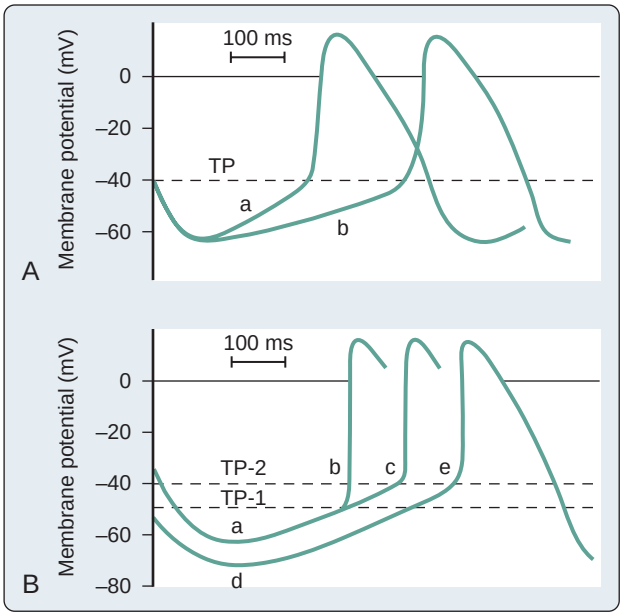


Fig. 4.5 (A) Transmembrane potential of the sinus node. A decrease in the slope of phase 4 or diastolic depolarization *(a to b)* increases the time to reach the threshold potential *(TP)*, slowing the heart rate. *(B)* Heart rate slowing occurs in changing from *TP-1* to *TP-2*, and a longer interval is needed to reach the TP *(b to c)*. Increasing maximal diastolic potential *(a to d)* also slows the heart rate by increasing the time to reach the TP *(b to c)*. *(From Atlee JL III.* Perioperative Cardiac Arrhythmias: Mechanisms, Recognition, Management. *2nd ed. Chicago: Year Book Medical Publishers; 1990:36.)*

afterdepolarizations) or after (ie, delayed afterdepolarizations) membrane repolarization. Different ionic mechanisms are responsible for each form of afterdepolarization, and if the oscillations in membrane potential reach the threshold potential, a triggered cardiac impulse can be generated.[13] Triggered activity is often considered an abnormal form of automaticity. However, because triggered activity requires a prior cardiac impulse (in contrast to automaticity), the abnormal electrophysiologic event cannot be considered a pure form of automaticity.

Reentry is a condition in which a cardiac impulse persists and reexcites myocardium that is no longer refractory.[10] Unidirectional block of impulse conduction is a necessary condition for reentry. The unidirectional block may be in the form of differences in membrane refractoriness (ie, dispersion of refractoriness), and some areas of myocardium are unexcitable, but other areas allow impulse propagation. On repolarization, previously refractory membranes become available for depolarization if the initial impulse has found an alternate route of propagation and returns to the prior site of conduction block. For reentry to occur, slowed conduction in the alternate pathway must exceed the refractory period of cells at the site of unidirectional block.

Partial depolarization of fast-response fibers (ie, depressed fast response) results in reduced Na+ channel availability with a reduced rate of phase 0 of the action potential. The reduced rate of the action potential upstroke of phase 0 can slow conduction and contribute to the previously described conditions conducive to reentry.

Arrhythmias produced by reentrant or triggered mechanisms, but not those due to increased automaticity, can be induced with programmed stimulation in the setting of a diagnostic electrophysiology study (EPS). Pacemaker-induced overdrive suppression is a characteristic of arrhythmias produced by automaticity (see Chapter 5).

Diagnostic Evaluation

The history of symptoms often helps to determine the cause of a patient's palpitations. Abrupt onset and abrupt termination of regular palpitations is consistent with a paroxysmal SVT that most often results from atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT) associated with an accessory AV bypass tract, or atrial tachycardia. Although a history of syncope does not definitively indicate a ventricular or supraventricular cause, it is helpful in determining the how urgently the condition should be evaluated. Whether palpitations are regular or irregular is useful information for differentiating atrial fibrillation as a cause of the symptoms. Precipitating events, number and duration of episodes, and dyspnea, fatigue, or other constitutional symptoms should be sought from the history (Box 4.3).

A 12-lead electrocardiogram (ECG) should be obtained during tachycardia and compared with baseline sinus rhythm ECGs. It is also helpful to run a rhythm strip during periods of intervention such as carotid sinus massage or adenosine administration. Patients with a history of preexcitation manifesting with an arrhythmia should be immediately evaluated because atrial fibrillation in the setting of an accessory pathway can lead to sudden death. For all patients undergoing evaluation of an arrhythmia, an echocardiogram is essential to

BOX 4.3 DIAGNOSTIC EVALUATION OF ARRHYTHMIAS

History of palpitations, syncope, and constitutional symptoms
Physical examination
Twelve-lead electrocardiogram at baseline and during tachycardia if available
Two-dimensional echocardiogram
Twenty-four-hour Holter monitoring of patient-triggered events
Invasive electrophysiologic testing

assess cardiac structural abnormalities and ventricular function. It is particularly warranted for patients with persistent tachycardia, which can lead to tachycardia-associated cardiomyopathy.[34]

Twenty-four-hour Holter monitoring of patient-triggered events may be useful for some patients with frequent but transient symptoms. Other evaluations such as exercise or pharmacologic stress testing have been employed to elicit episodes of tachycardia or determine how robust preexcitation is with increasing heart rates.

Diagnosis of the underlying mechanisms of the arrhythmia may require invasive electrophysiologic testing. Studies involve percutaneous introduction of catheters that provide electrical stimulation and record electrograms from various intracardiac sites. Initial recording sites often include the high right atrium, bundle of His, coronary sinus, and the right ventricle[10,35] (Figs. 4.6 and 4.7). The cardiac activation sequence can be discerned from these recordings along with the surface ECG, as shown in Fig. 4.8 for a patient undergoing evaluation for an accessory AV conduction pathway. The activation sequence is assessed by the depolarization time recorded by the electrodes positioned fluoroscopically at various anatomic sites. A recording obtained during diagnostic evaluation of a patient with a ventricular arrhythmia is shown in Fig. 4.9.

The catheters are most often introduced through the femoral vessels under local anesthesia. Systemic heparinization is required, particularly when catheters are introduced into the left atrium or left ventricle. The most common complications from electrophysiologic testing are those associated with vascular catheterization.[10,36] Other complications include hypotension (1% of patients), hemorrhage, deep venous thrombosis (0.4%), embolic phenomena (0.4%), infection (0.2%), and cardiac perforation (0.1%).[10,37] Proper application of adhesive cardioversion electrodes before the procedure facilitates rapid cardioversion-defibrillation in the event of persistent or hemodynamically unstable tachyarrhythmia resulting from stimulation protocols.

The principles of intraoperative electrophysiologic mapping are similar to those used in the cardiac catheterization suite. Procedures have evolved from early, single-point epicardial mapping systems with a handheld electrode to sophisticated, multichannel, computerized systems. The latter can acquire and store multiple epicardial, intramural, and endocardial electrograms from a single depolarization. Multichannel, computerized mapping allows rapid identification of arrhythmia pathways (eg, accessory pathways) before initiation of cardiopulmonary bypass, reducing the need for excessive cardiac manipulations necessary with a handheld electrode and promoting stable conduction.

Principles of Electrophysiologic Treatment

The paradigm for ablative treatment of cardiac arrhythmias evolved from the surgical treatment of Wolff-Parkinson-White (WPW) syndrome and ventricular tachycardia (VT) developed by Cobb, Sealy, and Boineau and their colleagues.[38–40] The fundamental approach is precise localization of the electrophysiologic substrate for the arrhythmia and ablation of the pathway. In the case of WPW syndrome, the accessory pathway is identified with intraoperative electrophysiologic mapping that initially used handheld electrodes.[10,41] Development of multichannel, computer-based mapping systems allowed identification of the

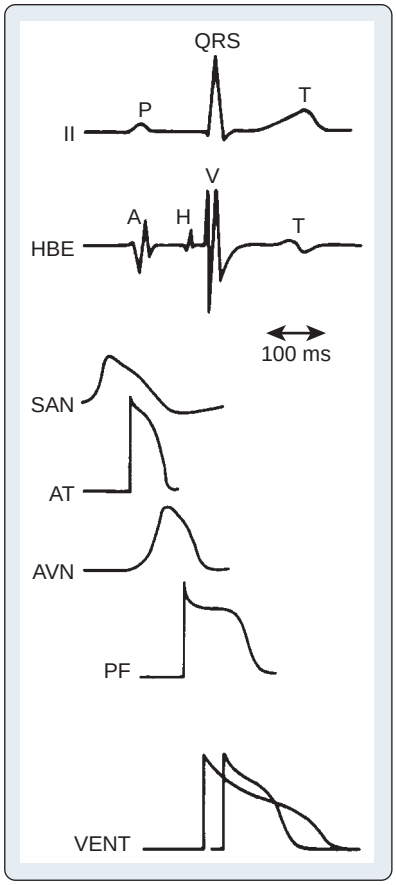


Fig. 4.6 Electrograms from leads placed in various cardiac locations in reference to the surface ECG show the rapid upstroke of the action potential (phase 0) in fast-response fibers compared with the slower upstroke of slow-response fibers. Sequences of action potentials from various cardiac tissues are presented in relation to the surface electrocardiogram and His bundle electrogram. *AT*, Atrium; *AVN*, AV node; *PF*, Purkinje fiber; *SAN*, SA node; *VENT*, ventricle. *(From Atlee JL III.* Perioperative Cardiac Arrhythmias: Mechanisms, Recognition, Management. *2nd ed. Chicago: Year Book Medical Publishers; 1990:27.)*

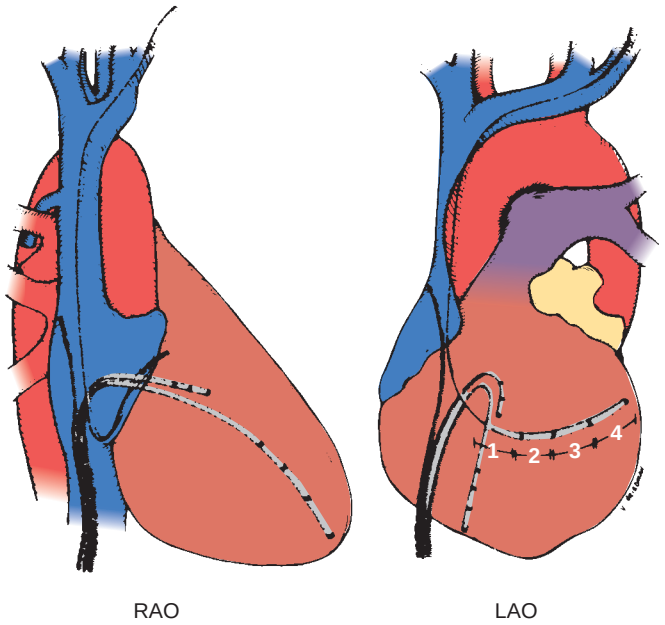


Fig. 4.7 Schematic depiction of an electrophysiologic study of a patient with Wolff-Parkinson-White syndrome. A catheter with multiple recording/pacing electrodes is positioned in the high right atrium, coronary sinus, bundle of His region, and right ventricular apex. Right anterior oblique *(RAO)* projections differentiate anterior from posterior sites. Left anterior oblique *(LAO)* projections differentiate septal from lateral sites. Numbered zones in the LAO projection regionalize electrode positions in the coronary sinus: *1*, posteroseptal; *2*, posterior; *3*, posterior; *4*, posterolateral. *(From Cain ME, Cox JL. Surgical treatment of supraventricular tachyarrhythmias. In: Platia EV, ed.* Management of Cardiac Arrhythmias: The Nonpharmacologic Approach. *Philadelphia: Lippincott; 1987:307.)*

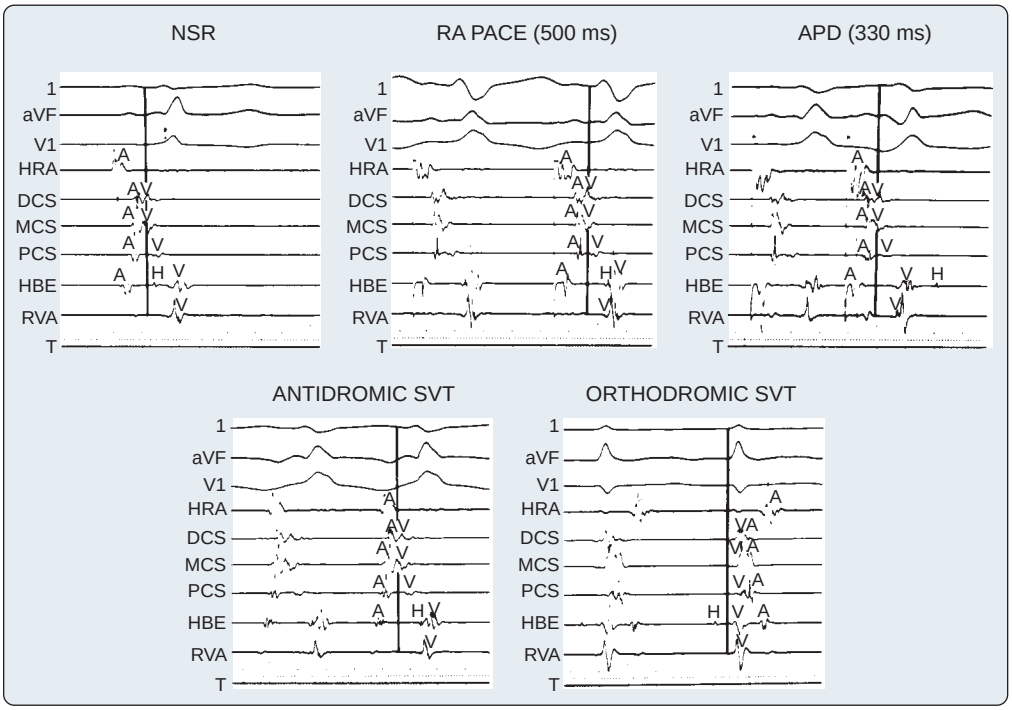


Fig. 4.8 Surface electrocardiogram (ECG) (ie, leads I, aVF, and V_1) and electrograms at various intracardiac sites during normal sinus rhythm *(NSR)*, pacing from the right atrium *(RA PACE)*, after an atrial premature depolarization *(APD)*, and during antidromic and orthodromic supraventricular tachycardia *(SVT)*. The left free wall accessory pathway is identified by the earliest onset of ventricular depolarization at the distal coronary sinus catheter *(DCS)* in relation to the delta wave on the surface ECG *(vertical line)*. This is followed closely by activation in the middle coronary sinus *(MCS)* and proximal coronary sinus *(PCS)* sites. Other catheter locations are the high right atrium *(HRA)*, region on the His bundle electrogram *(HBE)*, and right ventricular apex *(RVA)*. Conduction is followed during SVT by the pattern of cardiac activation from the right atrium *(vertical line)* to the ventricles. *(From Cain ME, Cox JL. Surgical treatment of supraventricular tachyarrhythmias. In: Platia EV, ed.* Management of Cardiac Arrhythmias. *Philadelphia: Lippincott; 1987:308.)*

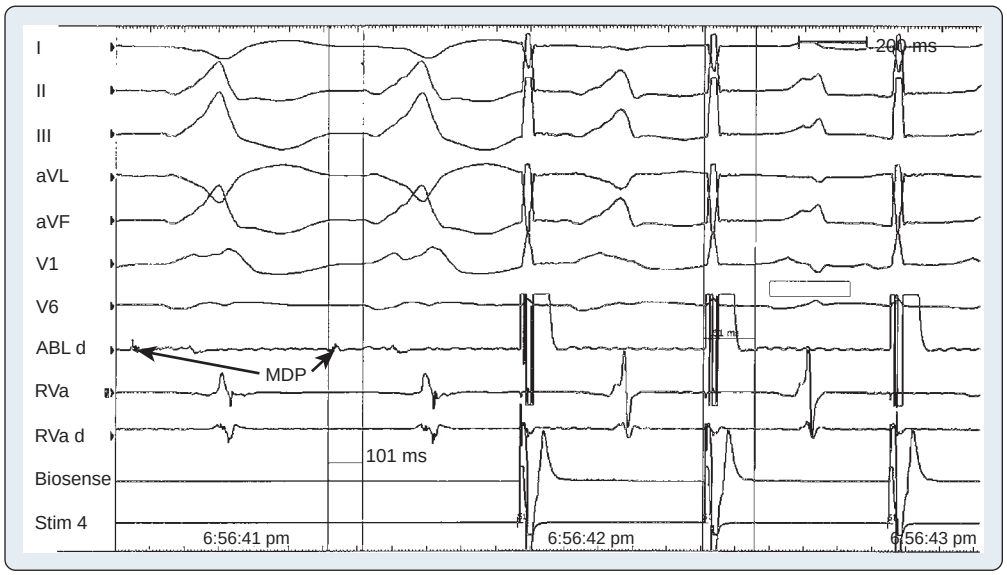


Fig. 4.9 Endocardial mapping of ventricular tachycardia. Surface electrocardiograms and selected endocardial electrograms are shown during sustained ventricular tachycardia in a patient with severe ischemic tachycardia. The mapping catheter distal electrode *(ABL d)* has been positioned at an endocardial site that records a middiastolic potential *(MDP)* that precedes the QRS by 101 ms. Pacing at a cycle length slightly faster than the tachycardia cycle length results in ventricular capture with a QRS morphology that is slightly different from the native tachycardia. The interpretation of this maneuver is that the endocardial pacing site is not at a favorable location for catheter ablation. Pacing at an optimal site for catheter ablation produces a QRS morphology identical to that of the native tachycardia.

BOX 4.4 ELECTROPHYSIOLOGIC ABLATIVE TREATMENT INDICATIONS

Drug-resistant arrhythmias
Drug intolerance
Severe symptoms
Avoiding lifelong treatments

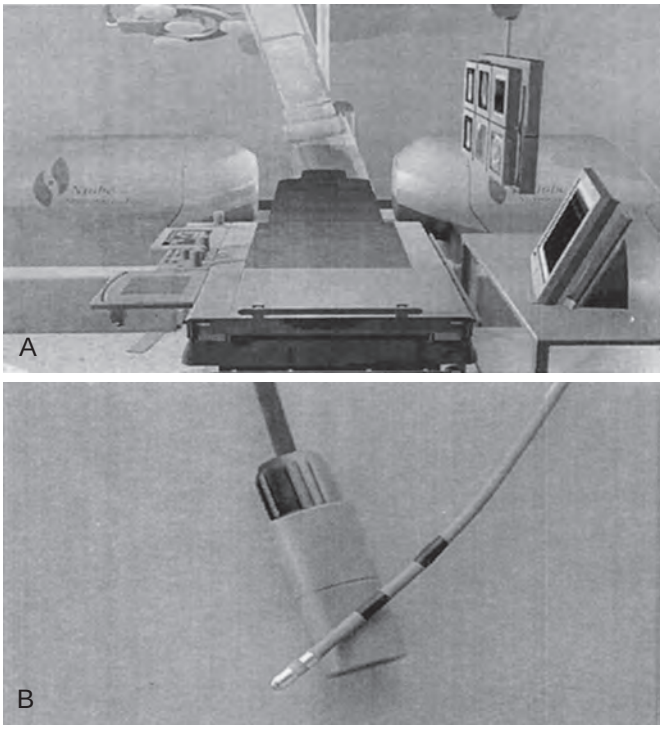


Fig. 4.10 Stereotaxis magnetic catheter navigation system. (A) The Stereotaxis system consists of two permanent magnetic arrays positioned on either side of a standard fluoroscopy table and digital fluoroscopy with a computer control system. The magnetic arrays project a composite magnetic field of 0.08 T in the region of a patient's heart to control the position of a magnetic catheter. (B) The 7-Fr magnetic catheter, which is used with the Stereotaxis system, has two distal electrodes for endocardial pacing, recording, and radiofrequency ablation. An internal permanent magnet allows the catheter to interact with the prevailing magnetic field for motion control.

mechanisms for many arrhythmias (including VT) and their termination by interruption of the underlying substrate.

Experience and insights into arrhythmia mechanisms led to development of the catheter-based methods now routinely used for a variety of supraventricular and ventricular arrhythmias. General indications for ablative treatments include drug-resistant arrhythmias, drug intolerance, severe symptoms, and desire to avoid lifelong drug treatments (Box 4.4).

Manipulation of catheter electrodes in the heart for precise mapping and treatment of arrhythmias can be laborious and time consuming. Robotically and magnetically driven navigational systems and newer catheters have been developed to facilitate the process and improve catheter positioning and stability. With these navigational systems, the catheter tip is localized with three-dimensional fluoroscopy or advanced mapping applications and precisely moved to the myocardial area of interest using a robotic arm or a magnetic field[42] (Fig. 4.10).

Because of the two predominant mechanisms of arrhythmias, surgical and catheter-based treatments often focus on identifying the site

BOX 4.5 ATRIOVENTRICULAR RECIPROCATING TACHYCARDIA ACCESSORY PATHWAY CHARACTERISTICS

- Concealed: accessory pathway displays retrograde conduction.
- Manifest: accessory pathway displays antegrade conduction. Pathways often exhibit retrograde conduction.
- Orthodromic: antegrade conduction from atria to ventricles occurs through the normal atrioventricular (AV) nodal conduction system and retrograde conduction through the accessory pathway.
- Antidromic: antegrade conduction from atria to ventricles occurs through the accessory pathway and retrograde conduction through the AV nodal pathway.
- Abnormal pathways are treated with percutaneous radiofrequency ablation.
- Abnormal pathways are treated surgically from the endocardium to epicardium by transection and/or cryoablation.

of earliest electrical activity (ie, focal automatic or triggered arrhythmias) or identifying the critical isthmus responsible for perpetuating reentrant arrhythmias. Ablation of atrial fibrillation deviates from the traditional paradigm and focuses on isolating the critical anatomic substrate (often the pulmonary veins) responsible for its initiation and perpetuation. The usual aim of electrophysiologic treatments is to interpose scar tissue in the conduction pathway of the arrhythmia. This is accomplished with a properly placed surgical incision or by inducing myocardial injury with the application of energy from a precisely placed catheter.

Various energy sources, including lasers, microwaves, RF current, and extreme cold (ie, cryoablation), have been used for ablation. The most common is RF energy, which destroys myocardium by resistive heating. Success is determined by the volume and depth of tissue injured by RF energy, which is a function of the power delivered, catheter tip size, and amount of convective cooling during energy delivery. Measurement of tissue impedance during application of bipolar RF energy ensures that transmural injury occurs. Depending on the thickness of the tissue, transmural scarring may not occur, and measurement of conduction across the lesion is recommended. Failure to conduct an applied electrical stimulus indicates pathway interruption.

Specific Arrhythmias

Supraventricular Tachyarrhythmias

SVTs are cardiac rhythms with a heart rate greater than 100 beats/minute originating above the division of the common bundle of His. The arrhythmias are often seen as a narrow-complex tachycardia, and in some cases, they can be hemodynamically unstable in the setting of structural heart disease. Tachycardias persisting for weeks to months may lead to tachycardia-associated cardiomyopathy and disabling symptoms.[34]

The differential diagnosis of SVT includes AVRT, AVNRT, atrial tachycardia, inappropriate sinus tachycardia or sinus node reentry, atrial flutter, and atrial fibrillation. Because antiarrhythmic medications have traditionally been used with mixed success, surgical and catheter-based procedures have been developed for their management.

Atrioventricular Reciprocating Tachycardia

Accessory pathways are abnormal strands of myocardium connecting the atria and ventricles across the AV groove, providing alternate routes for conduction that bypass the AV node and bundle of His (Box 4.5). The various classifications used to describe accessory pathways

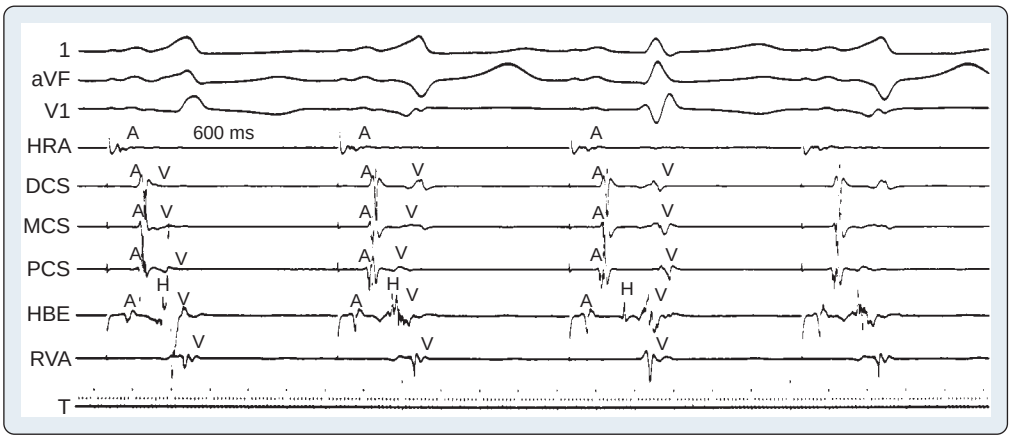


Fig. 4.11 The presence of two accessory pathways is revealed during pacing. The site of earliest ventricular activation is detected with the distal coronary sinus *(DCS)* electrode, indicating a left free wall accessory pathway. The second paced beat shows the site of earliest ventricular activation from the proximal coronary sinus *(PCS)* electrode, indicating a posterior septal accessory pathway. After the third paced beat, neither site is activated due to an anterograde conduction block. In this instance, conduction follows the normal atrioventricular–His bundle and bundle branch pathways. Surface electrocardiographic leads and intracardiac electrograms are organized as in Fig. 4.8. *(From Cain ME, Cox JL. Surgical treatment of supraventricular tachyarrhythmias. In: Platia EV, ed.* Management of Cardiac Arrhythmias. *Philadelphia: Lippincott; 1987:312.)*

are based on their location (eg, tricuspid, mitral), whether they are manifest or concealed on a surface ECG, and the conduction properties exhibited by the pathway (eg, antegrade, retrograde, decremental, nondecremental).[43] *Decremental* conduction along any myocardial tissue describes conduction that is slower as the frequency of impulses reaching it increases. Accessory pathways are more often *nondecremental*; regardless of how quickly impulses reach the pathway, the conduction velocity across the pathway remains the same.

The term *concealed pathway* refers to an accessory pathway that exhibits only retrograde conduction. In this situation, there is no conduction from the atrium to the ventricles through the pathway, which shows no evidence of ventricular preexcitation. In contrast, *manifest pathways* display antegrade conduction from the atrium to the ventricles. Because electrical signals can enter the ventricles from the AV node and the accessory pathway, ventricular preexcitation manifests on the surface ECG as delta waves. Manifest pathways typically conduct in antegrade and retrograde directions. A manifest pathway allows the ventricle to be depolarized (ie, preexcited) before that occurring by the normal route of conduction through the AV node (Figs. 4.11 and 4.12).

During preexcitation, an activation wavefront propagates simultaneously to the ventricles across the bundle of His and the accessory pathway. Because anterograde conduction is delayed at the AV node but not in the accessory pathway, the impulse passing through the accessory pathway initiates ventricular depolarization before the impulse traveling through the normal AV conduction system. The ventricle is preexcited, resulting in a delta wave preceding the QRS complex (see Fig. 4.11).

These electrocardiographic findings (ie, short PR interval and delta wave) were found by Wolff, Parkinson, and White in the 1930s in association with SVT.[44] WPW syndrome is a condition of preexcitation accompanied by tachyarrhythmias due to reentry through the accessory pathway, although only about 30% of individuals with WPW electrocardiographic findings exhibit tachyarrhythmias. Individuals with WPW electrocardiographic findings but without tachyarrhythmias are said to have the WPW signature. AVRT occurs in the absence of the WPW syndrome when the pathway is concealed, and not all tachyarrhythmias in patients with WPW result from the AVRT mechanism.

By identifying the polarity of the delta wave (ie, QRS axis) and precordial R-wave progression, the resting 12-lead ECG can provide clues about the location of the accessory pathway in the left lateral, left posterior, posterior septal, right free wall, or anterior septal regions[45] (Table 4.1). Precise localization depends on the EPS. The investigation can document the AV or other mechanism of the arrhythmia and the conduction properties of the accessory pathways.

TABLE 4.1 Electrocardiographic Patterns for Various Anatomic Locations of Accessory Pathways

Region	*Negative Delta Wave*	*QRS Frontal Axis*	*R>S*[a]
Left lateral free wall	I and/or aVL	Normal	V_1 to V_3
Left posterior free wall	III and aVF	−75 to +75	V_1
Posterior septal	III and aVF	0 to −90	V_2 to V_4
Right free wall	aVR	Normal	V_3 to V_5
Anterior septal	V_1 and V_2	Normal	V_3 to V_5

[a]R>S refers to progression of the R wave in the precordial electrocardiographic leads.
Modified from Lindsay BD, Crossen KL, Cain ME. Concordance of distinguishing electrocardiographic features during sinus rhythm with the location of accessory pathways in the Wolff-Parkinson-White syndrome. *Am J Cardiol.* 1987;59:1093.

The atrial and ventricular insertion sites of the accessory pathway are identified by observing ventricular activation patterns during sinus rhythm and during atrial pacing (see Fig. 4.11). In the setting of an accessory pathway, the interval between the deflection denoting activation of the bundle of His and the earliest ventricular activation (ie, delta wave) is less than the His-ventricular interval. The area with the shortest delta-to-ventricular interval localizes the accessory pathway's ventricular insertion. More than one accessory pathway is suggested by finding different delta-wave morphology with increasing atrial pacing rates or with introduced atrial premature beats (see Fig. 4.12). Atrial activation patterns observed during ventricular pacing, after a ventricular premature beat, or during induced orthodromic SVT can identify the location of the atrial insertion sites.

AVRT can occur as an orthodromic reciprocating tachycardia (ORT) and antidromic reciprocating tachycardia (ART)[46–48] (Fig. 4.13). ORT is by far the most common type and involves antegrade conduction through the normal AV nodal conduction system and retrograde conduction through the accessory pathway. ART involves antegrade conduction down the accessory pathway and retrograde conduction through the AV node. As suggested by their mechanisms, ORT appears as a narrow-complex tachycardia, and ART appears as a wide-complex tachycardia that sometimes can be difficult to distinguish from VT.

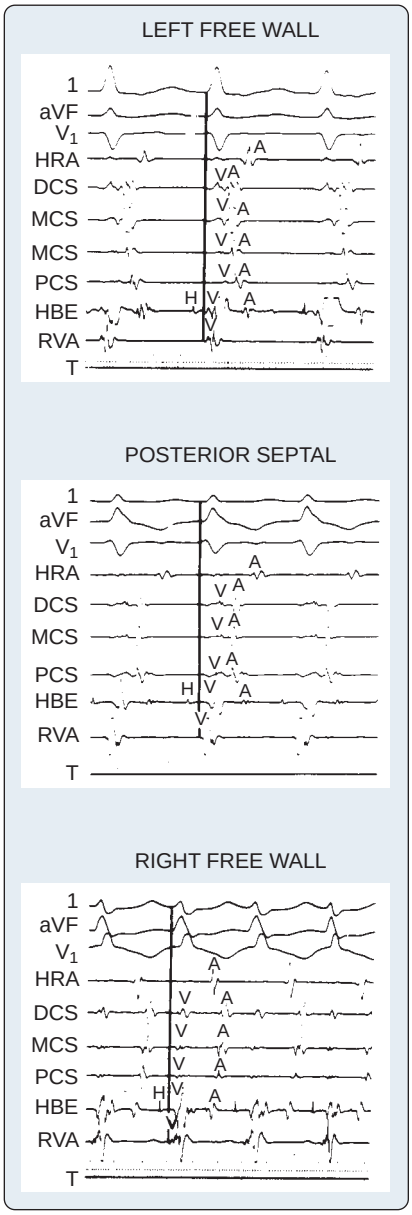


Fig. 4.12 Atrial activation recordings from three patients during orthodromic tachycardia through accessory pathways at distinct locations. Using the *vertical line* as a reference for the QRS complex from the surface electrocardiogram, the first example demonstrates the earliest atrial activation at the distal coronary sinus *(DCS)* site, indicating a left free wall accessory pathway. The posterior septal accessory pathway is indicated by earliest activation of the electrode located in the proximal coronary sinus *(PCS)*. In the last example, atrial activation at the high right atrium *(HRA)* and His bundle *(HBE)* occurs before all the coronary sinus recording sites, indicative of a right free wall accessory pathway. Surface electrocardiographic leads and intracardiac electrograms are organized as in Fig. 4.8. *(From Cain ME, Cox JL. Surgical treatment of supraventricular tachyarrhythmias. In: Platia EV, ed.* Management of Cardiac Arrhythmias. *Philadelphia: Lippincott; 1987:313.)*

Patients with atrial fibrillation and a pathway capable of conducting in an antegrade fashion run the risk of rapid conduction to the ventricles and development of ventricular fibrillation and sudden death. The potential for sudden death due to atrial fibrillation in patients with WPW provides an argument for aggressive ablative treatment when the procedure can be performed in centers with low periprocedural morbidity rates.

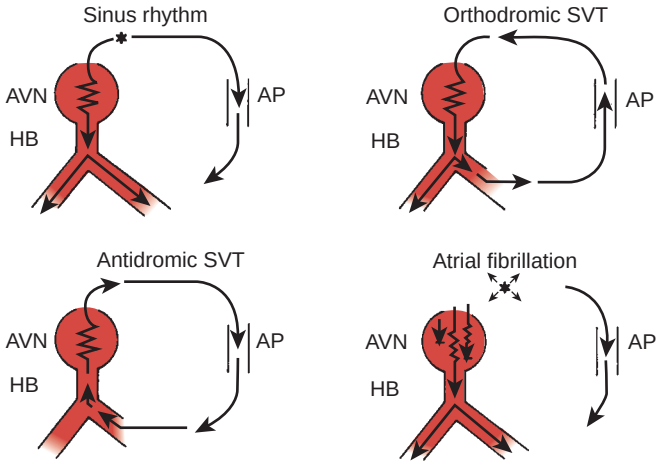


Fig. 4.13 Schematic depiction of conduction through an accessory pathway *(AP)* and the normal conduction system (ie, atrioventricular node *[AVN]* and His bundle *[HB]*) during sinus rhythm, orthodromic supraventricular tachycardia *(SVT)*, antidromic SVT, and atrial fibrillation. *(From Lindsay BD, Branyas NA, Cain ME. The preexcitation syndrome. In: El-Sherif N, Samet P, eds.* Cardiac Pacing and Electrophysiology. *3rd ed. Orlando, FL: Grune & Stratton; 1990.)*

Catheter-Based Therapy for Accessory Pathways

Percutaneous catheter ablation of accessory pathways has largely supplanted surgical treatment. RF ablation is typically performed during EPS after the accessory pathway has been localized. Transseptal or retrograde aortic catheter approaches are used to ablate left-sided accessory pathways, and right-heart catheterization using a venous approach is used to ablate right-sided pathways. Success rates of 95% have been reported using these methods.[43,49–51] Recurrence rates after successful catheter ablation of an accessory pathway usually are less than 5% and are a function of pathway location and stability of the catheter during energy delivery.

Reported complications are low and include those related to vascular access such as hematoma and AV fistula. Other complications are related to catheter manipulations of the left- and right-sided circulation, such as valvular or cardiac damage from the catheter, systemic and cerebral embolization due to catheter manipulation in the aorta, coronary sinus damage, coronary thrombosis and dissection, cardiac perforation, and cardiac tamponade. Complete AV block, cardiac perforation, and coronary spasm due to RF may also occur.

A 1995 survey involving 5427 patients reported serious complications from catheter ablation of accessory pathways in 1.8% of patients and a procedure-related mortality rate of 0.08%.[43,49] Complete AV block is more common with ablation of accessory pathways close to the bundle of His. The procedural success rates for catheter ablation methods are 87% to 99%.[43,50,51] In a randomized study comparing ablation with drug treatment, quality of life, symptom scores, and exercise performance were improved with successful RF ablation.[52]

Atrioventricular Nodal Reentrant Tachycardia

AVNRT results from altered electrophysiologic properties of the anterior fast pathway and posterior slow pathway fibers providing input to the AV node.[10,43,51] In the past, the only treatment for recurrent SVT due to AVNRT was total ablation of the His bundle and permanent pacemaker insertion. Surgical techniques developed in the 1980s provided an alternative that was associated with a high procedural success rate, acceptable morbidity, and preservation of AV conduction.[53–56] Experience with the surgical approach and a better understanding of the physiologic basis for AVNRT led to the development of percutaneous catheter-based treatments.

Interruption of the slow or fast pathway with RF ablation can eliminate AVNRT, with higher success rates reported for ablation of

the slow pathway (68–100%) than for the fast pathway (46–94%).[43,57–60] Complication rates are lower with RF ablation of the slow pathway and include AV block requiring pacemaker insertion (1%)[43] (Box 4.6).

Catheter-Based Therapy for Atrioventricular Nodal Reentrant Tachycardia

Historically, fast-pathway ablation is performed by positioning the catheter adjacent to the AV node–His bundle anterosuperior to the tricuspid valve annulus. The catheter is withdrawn until the atrial electrogram is larger than the ventricular electrogram and the His recording is small or absent. The ECG is closely monitored as RF energy is applied for PR prolongation or heart block. Energy is delivered until there is PR prolongation or the retrograde fast-pathway conduction is eliminated. Noninducibility of AVNRT then is confirmed.

Because of the increased incidence of complete heart block with fast-pathway ablation, most electrophysiologists have adopted ablation of the slow pathway as a safer alternative. Slow-pathway ablation is performed by identifying the pathway along the posteromedial tricuspid annulus near the coronary sinus. Using fluoroscopy, one approach is to divide the level of the coronary sinus os and His bundle recordings into six anatomic regions[61] (Fig. 4.14). Moving anteriorly, lesions are placed beginning with the most posterior region. Rather than using the anatomic approach, the slow pathway can be mapped and then ablated. The end point of slow-pathway ablation is elimination of induced AVNRT.[43,57–60] Development of junctional ectopy during RF ablation of the slow pathway is associated with successful slow-pathway ablation.[10]

BOX 4.6 ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

- Altered electrophysiologic properties of the anterior fast and posterior slow pathways provide input to the atrioventricular node.
- Successful fast pathway ablation occurs when the PR interval is prolonged or fast-pathway conduction is eliminated.
- Successful slow pathway ablation occurs when induced atrioventricular nodal reentrant tachycardia is eliminated.
- Surgical techniques include selective cryoablation.

Focal Atrial Tachycardia

Focal atrial tachycardia accounts for less than 15% of patients undergoing evaluation for SVT.[62] The arrhythmia is caused by atrial activation from a discrete atrial area, resulting in heart rates between 100 and 250 beats/minute.[63] Although a 12-lead ECG may provide clues to the origin of the tachycardia based on the P-wave axis, the site of atrial tachycardia is identified by electrophysiologic investigations, and it tends to reside in certain anatomic zones.[43] Right-sided tachycardias typically originate along the crista terminalis from the SA node to the AV node, and left-sided tachycardias originate from the pulmonary veins, atrial septum, or mitral valve annulus.[63,64]

The mechanisms for atrial tachycardia include abnormal automaticity, triggered activity, and microreentry. Certain characteristics can help to identify the underlying mechanism. Abrupt onset and offset suggest a reentrant mechanism, whereas a pattern of gradual onset (ie, warm up) and offset (ie, cool down) suggests automaticity (Box 4.7).

Catheter-Based Therapy for Focal Atrial Tachycardia

Due to the discrete localized area involved in generating atrial tachycardia, the approach to catheter ablation is the same regardless of the underlying mechanism. The site of tachycardia onset is identified with electrophysiologic mapping and isolated from the remaining atrium by the application of RF current.

The success rate for this approach is 86%, and the recurrence rate is 8%.[43,64–68] Complications occur in 1% to 2% of cases and include

BOX 4.7 FOCAL ATRIAL TACHYCARDIA

- Mechanisms include abnormal automaticity, triggered activity, and microreentry.
- Catheter-based treatment uses radiofrequency ablation.
- Surgical-based treatment uses an incision and cryoablation.

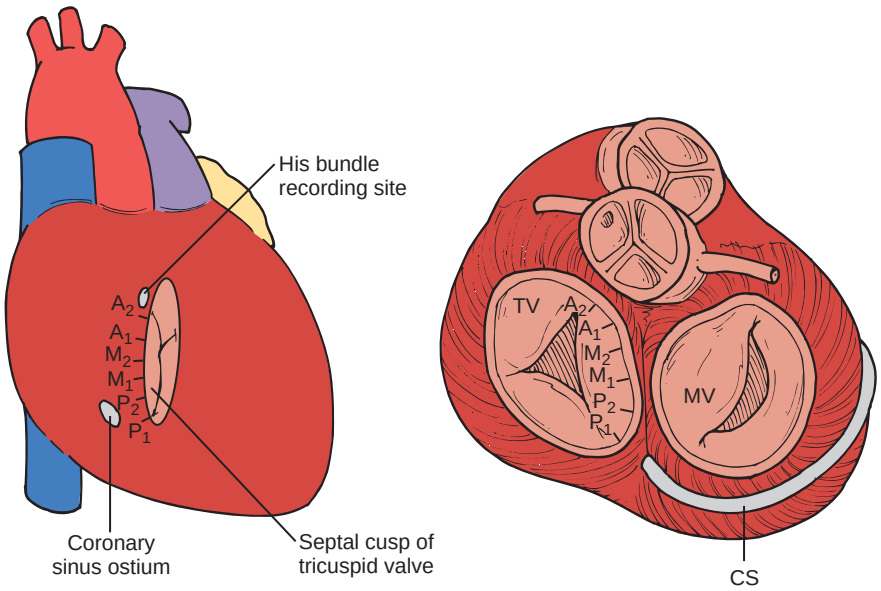


Fig. 4.14 Schematic depiction of sites for atrioventricular nodal modification in relation to other anatomic structures. The posterior location is usually first targeted for ablation of the slow pathway, with subsequent ablative lesions placed more anteriorly depending on the response. *CS*, Coronary sinus; *MV*, mitral valve; *TV*, tricuspid valve. *(From Akhtar M, Jazayeri MR, Sra JS, et al. Atrioventricular nodal reentry: clinical, electrophysiologic, and therapeutic considerations.* Circulation. *1993;88:282.)*

myocardial perforation (rare), phrenic nerve injury, and sinus node dysfunction.[69]

Inappropriate Sinus Tachycardia

Sinus tachycardia is deemed inappropriate when it occurs in the absence of physiologic stressors (eg, increased body temperature, hypovolemia, anemia, hyperthyroidism, anxiety, postural changes, drugs), indicating a failure of normal mechanisms controlling the sinus rate. Proposed mechanisms are enhanced sinus node automaticity or abnormal autonomic regulation, or both. Inappropriate sinus tachycardia is seen most often in women health care providers.

The diagnosis of inappropriate sinus tachycardia is based on nonparoxysmal, persistent resting sinus tachycardia and excessive increases in response to normal physiologic stressors and nocturnal normalization of the rate based on Holter monitoring.[51] The P-wave morphology and endocardial activation are consistent with a sinus origin, and secondary causes have been excluded.

Catheter-based or surgical treatments are considered for a few patients not responding to β-blockers and when symptoms are truly disabling. RF ablative modification of the sinus node promotes dominance of slower depolarizing sinus nodal tissues. The end point of RF application is a change in the P-wave morphology or slowing of the sinus rate.

Reported complications include the need for a permanent pacemaker, SVC syndrome, phrenic nerve injury, and pericarditis.[43,70] Acute and long-term success rates are 76% (ie, catheter) and 66% (ie, surgery).[43,70] Ablation of the sinus node is often reserved for patients who are refractory to medications and highly symptomatic.

Sinus Node Reentrant Tachycardia

Reentrant pathways involving the sinus node may lead to paroxysmal tachycardia rather than nonparoxysmal inappropriate sinus tachycardia.[71] The P-wave morphology is similar to that occurring during sinus rhythm. Like other reentrant tachycardias, the arrhythmia is usually triggered by a premature atrial beat. The endocardial activation sequence during the EPS is in the high right atrium and is similar to sinus rhythm.

The arrhythmia can be initiated with a premature paced beat and is terminated by vagal maneuvers or adenosine administration.[43] The arrhythmia is also responsive to β-blockers, nondihydropyridine calcium channel antagonists, and amiodarone. RF ablation of the identified reentrant pathway can be used for frequently occurring tachycardia episodes not responsive to other treatments.[72]

Atrial Flutter

Atrial flutter usually manifests with acute onset of symptoms (eg, palpitations, shortness of breath, fatigue) accompanied by tachycardia and typical flutter waves on the ECG (Box 4.8). Fixed 2:1 conduction usually occurs with a flutter rate of 300 beats/minute and ventricular rate of 150 beats/minute. When AV conduction is fixed, the heart rate is regular, but varying AV conduction results in an irregular rhythm.

Rapid AV conduction can occur with exercise, in patients with accessory pathways, and paradoxically after administration of class 1C antiarrhythmic drugs.[43] The antiarrhythmic drugs slow the atrial flutter rate, allowing the AV node to support more rapid conduction to the ventricles. This maneuver requires coadministration of drugs with AV conduction-slowing properties (eg, β-blockers).

Atrial flutter is caused by reentry that is referred to as *macroreentry* because the anatomic circuit is large. Typical atrial flutter occupies a circuit that circles the tricuspid valve, crossing the myocardial isthmus between the inferior vena cava (IVC) and the tricuspid valve[43,63] (Fig. 4.15). Counterclockwise rotation through the cava-tricuspid region is usually observed, although other patterns such as clockwise rotation,

BOX 4.8 ATRIAL FLUTTER

Reentry results from a large anatomic circuit.
Macroreentrant pathway is amenable to catheter ablation.

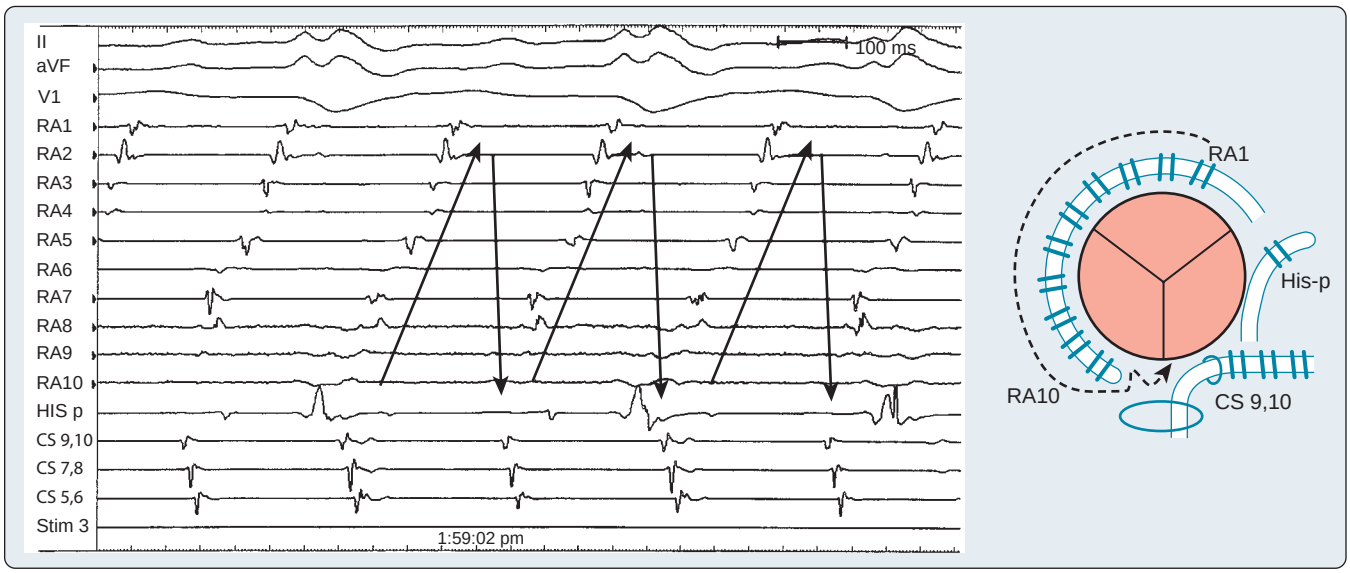


Fig. 4.15 Endocardial mapping of typical atrial flutter. Endocardial signals are recorded from diagnostic catheters. The anatomic basis for this circuit is an electrical wavefront circulating in a counterclockwise direction around the tricuspid valve annulus. A 20-pole catheter has been positioned around the tricuspid valve to record the passage of the activation wavefront by adjacent electrode pairs *RA1* to *RA10*. The wavefront then proceeds across the isthmus connecting the inferior vena cava and the tricuspid valve before passing the ostium of the coronary sinus *(CS)*, recorded by CS electrodes 9 and 10 and the His bundle recording catheter *(HIS p)*. The progress of the activation wavefront is indicated by the *arrows* and by the diagram *(right)*.

double waves, and lower loop reentry (ie, reentry around the IVC) may be seen.[43,73,74] Polarity of the flutter waves on the 12-lead ECG provides insight into the pattern of atrial flutter, especially in patients who have not undergone prior cardiac surgery. Counterclockwise rotation is associated with negative flutter waves in the inferior leads and positive flutter waves in V_1.[43]

The anatomic location of the macroreentrant pathway is amenable to catheter ablation and cure of atrial flutter by creating a linear conduction block across the tricuspid-IVC isthmus. Testing for bidirectional conduction block through the cava-tricuspid region after application of RF energy reduces the likelihood of recurrence.[75,76]

Atrial flutter and atrial fibrillation may coexist, complicating success with catheter ablation methods. Procedural success in treating pure atrial flutter is reported in 80% to 100% of cases, with recurrences reported for less than 5% of patients.[77–81] In a prospective, randomized trial, catheter ablation resulted in sinus rhythm in 80% of patients, compared with 36% of patients treated with antiarrhythmic drugs (mean follow-up of 21 months).[81] Fewer hospitalizations and higher scores on quality-of-life surveys are reported after catheter ablation compared with drug treatment. In the absence of atrial fibrillation, subsequent RF ablation procedures may result in successful elimination of atrial flutter. Even when not present during initial treatment, atrial fibrillation may develop after successful catheter ablation for atrial flutter in 8% to 12% of patients.[43,79]

Atrial scar tissue from prior cardiac surgery (eg, congenital heart surgery, mitral valve surgery, maze procedure) may provide an area for reentry leading to atrial flutter.[64,82–85] Reentrant circuits involving the cava-tricuspid area may coexist, leading to complicated, multiple reentry pathways.[43,85] Characterization of the reentry circuit with electrophysiologic mapping studies may allow successful RF ablation in these circumstances.

Anesthesia Considerations for Supraventricular Arrhythmia Surgery and Ablation Procedures

The approach to the care of patients undergoing percutaneous therapies for supraventricular arrhythmias involves similar principles (Box 4.9). Patients with WPW are usually young and free of other cardiac disease, although the syndrome can be accompanied by the Ebstein anomaly in up to 10% of cases.[41,86] Anesthesiologists must be familiar with preoperative EPS results and the characteristics of associated supraventricular arrhythmias (eg, rate, associated hemodynamic disturbances, syncope), including treatments. Tachyarrhythmias may recur at any time during surgical and percutaneous treatments. Transcutaneous cardioversion-defibrillation adhesive pads are placed before anesthesia induction and connected to a defibrillator-cardioverter. Development of periprocedural tachyarrhythmias is unrelated to any single anesthetic or adjuvant drug.

Treatment of hemodynamically tolerated tachyarrhythmias is aimed at slowing conduction across the accessory pathway rather than the AV node. Therapy directed at slowing conduction across the AV node (eg, β-adrenergic–blocking drugs, verapamil, digoxin) may enhance conduction across accessory pathways and should be used only if proved safe by a prior EPS. Recommended drugs include amiodarone and procainamide. One consideration is that antiarrhythmic drugs may interfere with electrophysiologic mapping. Hemodynamically significant tachyarrhythmias developing before mapping are usually treated with cardioversion.

Accessory pathway ablation is typically performed under conscious sedation, and general anesthesia is reserved for selected patients such as those unable to tolerate the supine position. Considerable experience in anesthetizing patients with WPW for surgical ablation was gained when the treatment approach was prevalent. The effects of anesthetics on accessory pathway conduction have been investigated mostly to evaluate whether the agents interfere with electrophysiologic mapping.

Droperidol depresses accessory pathway conduction, but the clinical significance of small antiemetic doses is likely minimal.[87,88] Opioids and barbiturates have no proven electrophysiologic effect on accessory pathways and are safe in patients with WPW syndrome.[89–92] Normal AV conduction is depressed by halothane, isoflurane, and enflurane, and preliminary evidence suggests that these volatile anesthetics may also depress accessory pathway conduction.[92,93] Although muscle relaxants with anticholinergic effects (eg, pancuronium) have been safely used in patients with WPW, drugs lacking autonomic side effects are most often chosen.[94]

The major goal of managing supraventricular ablative procedures is to avoid sympathetic stimulation and the development of tachyarrhythmias. Clinical studies have evaluated the efficacy of various anesthetic techniques in maintaining intraoperative hemodynamic stability and preventing arrhythmias in patients with WPW syndrome.[10,95,96] An opioid-based anesthetic technique with supplemental volatile anesthetics is typically used.

BOX 4.9 ANESTHESIA CONSIDERATIONS FOR SUPRAVENTRICULAR ARRHYTHMIA SURGERY AND ABLATION PROCEDURES

- Familiarity with electrophysiologic study results and associated treatments
- Transcutaneous cardioversion-defibrillation pads placed before induction
- Hemodynamically tolerated tachyarrhythmias treated by slowing conduction across accessory pathway rather than the atrioventricular node
- Hemodynamically significant tachyarrhythmias treated with cardioversion
- Avoidance of sympathetic stimulation

Atrial Fibrillation

Atrial fibrillation, the most common sustained cardiac arrhythmia in the general population, can lead to palpitations, shortness of breath, chest discomfort, or anxiety due to the irregularly irregular heart rate pattern[5] (Box 4.10). Aims for the treatment of atrial fibrillation include anticoagulation to decrease the risk for stroke and heart rate control to limit symptoms and reduce the risk for tachycardia-associated cardiomyopathy. Restoration of sinus rhythm with cardioversion or antiarrhythmic drugs, or both, is considered in some instances, but data suggest this strategy is no more effective than a strategy of anticoagulation or heart rate control for improving mortality rates for certain populations.[97] Because antiarrhythmic drugs are associated with life-threatening proarrhythmic side effects, the benefits of restoring sinus rhythm may be outweighed by increased mortality due to drug-induced ventricular arrhythmias.[7,8] The rising prevalence of atrial fibrillation and the limitations of pharmacologic treatments have prompted interest in nonpharmacologic treatments.

A growing understanding of the mechanisms of atrial fibrillation led to the introduction of surgical and catheter-based procedures to restore sinus rhythm. Experimental and clinical investigations

BOX 4.10 ATRIAL FIBRILLATION FEATURES

- Associated with multiple reentrant circuits
- May originate from automatic foci in a pulmonary vein or the vena cava
- Treatment with catheter ablation
  - Atrioventricular node ablation with pacemaker placement
  - Curative ablation to restore sinus rhythm
- Surgical therapy with the maze procedure

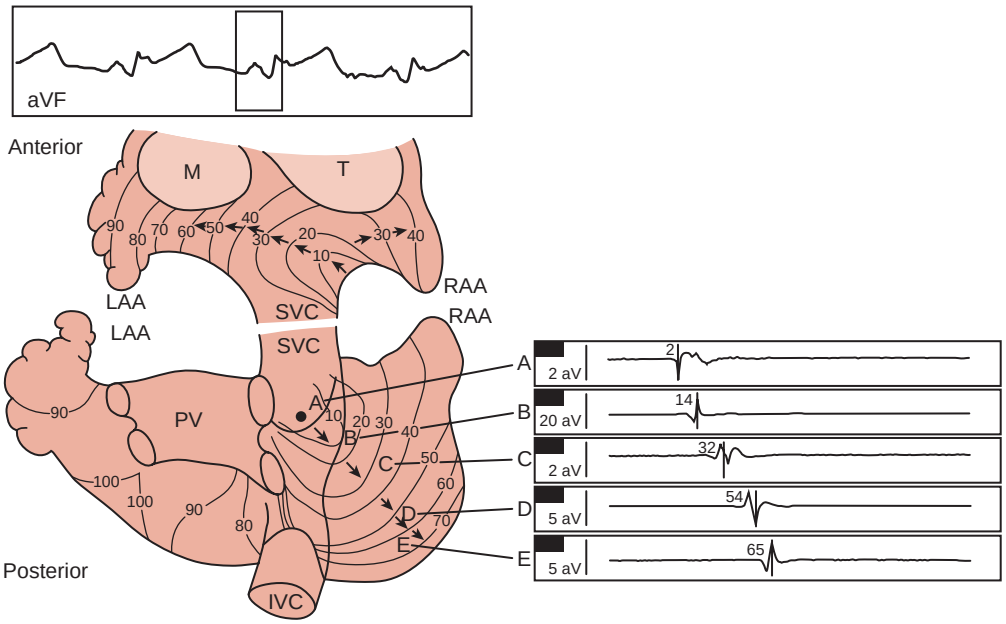


Fig. 4.16 Atrial activation sequence map of a single beat during sinus rhythm in a human. Isochronous lines are in 10-ms increments across the anterior and posterior atrium. The window in the tracing from lead aVF from the surface electrocardiogram *(top)* denotes the P wave chosen to obtain atrial mapping data. The labels on electrograms *A* to *E* correspond to the letters on the map denoting the five electrode positions shown. The time of activation from the electrodes is used to generate the isochronous representation of atrial depolarization. *IVC*, Inferior vena cava; *LAA*, left atrial appendage; *M*, mitral valve; *PV*, pulmonary veins; *RAA*, right atrial appendage; *SVC*, superior vena cava; *T*, tricuspid valve. *(From Cox JL, Canavan TE, Schuessler RB, et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation.* J Thorac Cardiovasc Surg. *1991;101:406.)*

demonstrate that atrial fibrillation is associated with multiple reentrant circuits in the atrium (ie, multiple wavelets) that rapidly and unpredictably change their anatomic location.[98–101] Intraoperative electrophysiologic mapping of a patient in sinus rhythm (Fig. 4.16) and after atrial fibrillation was induced by introducing atrial ectopic beats (Fig. 4.17) demonstrated the random and fleeting nature of the reentrant circuits.[10,101]

The rapidly changing nature of the reentrant circuits precludes a map-directed surgical or ablative strategy for atrial fibrillation. Nonetheless, the realization that certain cardiac structures (eg, pulmonary veins, valve annulus, vena cava) provided the necessary substrate for the fibrillatory reentrant circuits led to the development of an anatomically based operation for atrial fibrillation (ie, Cox maze procedure) with which macroreentrant circuits are interrupted by a series of atrial incisions and cryoablative lesions.[10,101,102]

Investigators have demonstrated that atrial fibrillation in some instances originates from automatic foci in the pulmonary veins or vena cava and that isolating these sites can restore sinus rhythm.[103] Other data have demonstrated focal sources of atrial fibrillation in patients with mitral valve disease.[104,105] These findings are supported by laboratory investigations showing that atrial fibrillation can be maintained by a single atrial source of fibrillatory waves moving away from the originating circuit.[106,107] These and other findings, along with advances in computer-based electrophysiologic mapping systems, opened the possibility of map-guided strategies to eliminate the substrate for atrial fibrillation in some patients.[108–118] The strategy may have the benefit of higher success rates and lower complications than achieved with current procedures.

Catheter-Based Therapy for Atrial Fibrillation

Catheter ablation approaches for atrial fibrillation include AV node ablation with permanent pacemaker placement to control the ventricular rate and catheter ablation procedures that aim to restore sinus rhythm. AV node ablation is used for medically refractory tachycardia due to atrial fibrillation or to eliminate intolerable symptoms due to an irregular heart rate. The procedure requires pacemaker implantation, does not aim to restore sinus rhythm, and does not eliminate the need for anticoagulation.

In an attempt to restore sinus rhythm, ablation strategies involve electrical isolation of the pulmonary veins and not ablating the AV node. It is thought that myocardial sleeves involving the os of the pulmonary veins can initiate atrial fibrillation due to their inherently different electrophysiologic properties. They are electrically isolated to prevent development of atrial fibrillation. Pulmonary vein isolation can be achieved in one of two ways. In the first, complete electrical isolation is achieved by sequential, segmental RF ablation around each pulmonary vein ostium.[103,119] The second strategy is to regionally isolate the posterior left atrium by encircling the pulmonary vein ostia and the surrounding posterior left atrial wall by a circular pattern of adjacent RF ablation lesions (ie, wide area circumferential ablation).[105] A randomized comparison of the two strategies demonstrated a significantly higher success rate with the regional isolation strategy; 88% of patients were free of atrial fibrillation at 6 months compared with 67% free of atrial fibrillation at 6 months using the segmental isolation strategy.[112] The regional isolation procedure also reduces the risk of creating pulmonary venous stenosis that can be associated with the segmental isolation procedure.

Newer technology for catheter-based therapy has improved outcomes for patients. An advancement is the combination of preacquired tomographic reconstructions with electroanatomic mapping (EAM) or three-dimensional image integration (I-EAM). The use of manually controlled, steerable introducers for catheter navigation also has demonstrated a higher clinical success rate compared with nonsteerable sheath technology. Application of ablation catheters that sense the amount of force applied during ablation has also improved therapeutic efficacy.

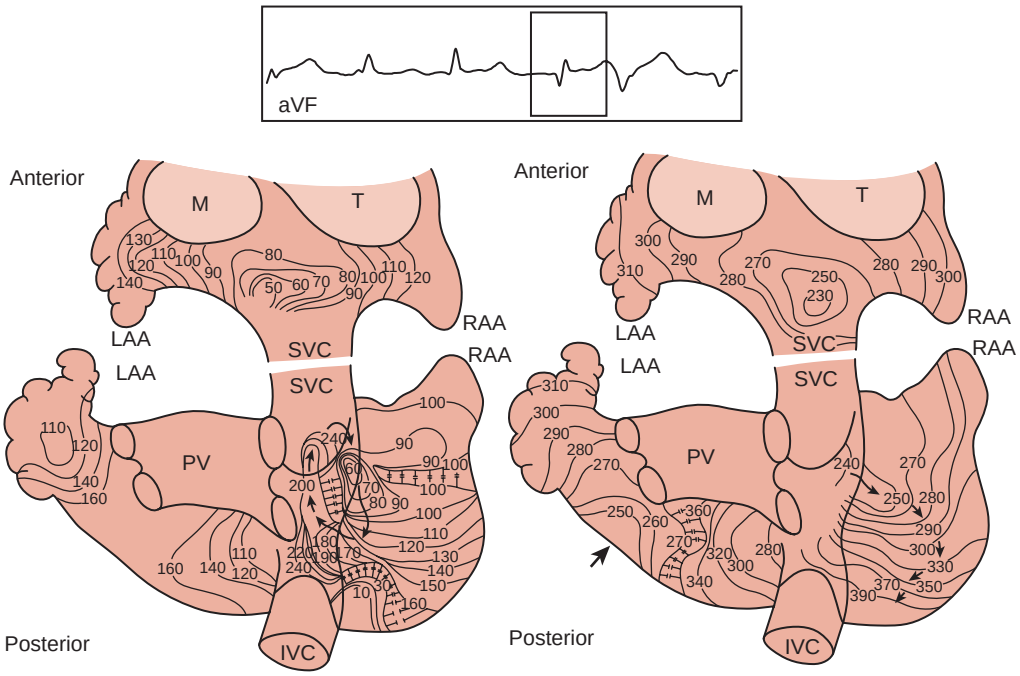


Fig. 4.17 Atrial activation mapping from a human during atrial fibrillation shows a single reentrant circuit. Recordings and isochronous mapping are the same as in Fig. 4.16. The *left* map shows the first 240 ms, with 230 to 400 ms shown in the *right* map. The beat spreads along the anterior and posterior atria *(left)*. Posteriorly, the beat encounters several areas of conduction block, but as it spreads, it encounters myocardium that is repolarized and capable of sustaining conduction. The clockwise, rotating reentrant circuit circulates around natural obstacles such as the orifices of the vena cava. *IVC*, Inferior vena cava; *LAA*, left atrial appendage; *M*, mitral valve; *PV*, pulmonary veins; *RAA*, right atrial appendage; *SVC*, superior vena cava; *T*, tricuspid valve. *(From Cox JL, Canavan TE, Schuessler RB, et al. The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation.* J Thorac Cardiovasc Surg. *1991;101:406.)*

Randomized trials have found that general anesthesia reduces the prevalence of pulmonary vein reconnection in repeat ablations compared with conscious sedation.[120] During these procedures, patient motion and respiration can affect tissue contact with the catheters, which influences lesion quality. Movement and thoracic excursion can similarly lengthen procedural and fluoroscopy time. The improved results with general anesthesia echoed those of other retrospective studies comparing posterior left atrial isolation using high-frequency jet ventilation (HFJV) with intermittent positive-pressure ventilation (IPPV).[121]

Hutchinson and colleagues examined the 1-year freedom from atrial fibrillation rate for three groups of patients receiving circumferential, antral pulmonary vein isolation (PVI)[122] One treatment group had PVI under general anesthesia with IPPV with no I-EAM, steerable introducers, or HFJV. The second treatment group had the procedure under general anesthesia with IPPV and use of I-EAM and steerable introducers. The third treatment group underwent PVI under general anesthesia with I-EAM, steerable introducers, and HFJV.

There was a significant difference in the 1-year freedom from atrial fibrillation rate for the three treatment groups (52% vs 66% vs 74%; $P = .006$). Patients with nonparoxysmal atrial fibrillation also had an incremental increase in the 1-year freedom from atrial fibrillation rate for the three groups (35% vs 54% vs 67%; $P < .001$). The prolonged tissue contact and minimized ablation catheter mobility due to recent advances in mapping, steerable introducers, and HFJV most likely create an improved pulmonary vein lesion.

Methods emulating the surgical maze procedure continue to evolve but remain investigative (discussed later). Linear ablation techniques involve RF energy application along critical sites for the maintenance of atrial fibrillation.[113–116,118,123] Success has been limited with this approach (28–57%), and the procedures require long durations and are associated with radiation exposure. Complication rates remain high (4–50%).

Surgical Therapy for Atrial Fibrillation

Improved understanding of the mechanisms of atrial fibrillation led to development of a surgical procedure by James Cox and others called the *maze procedure*.[101,102,124–128] The moniker stems from the design of the operation, which creates a mazelike pattern of surgical incisions in the functional myocardium, allowing propagation of atrial depolarization throughout the atrium to the AV node while interposed scar tissue interrupts possible routes of reentry. The principal goals of the maze procedure are to interrupt the electrophysiologic substrate for atrial fibrillation (ie, reentrant circuits), restore sinus rhythm, maintain SA nodal–to–AV nodal conduction, preserve AV synchrony, and preserve atrial mechanical function (ie, atrial kick), thereby improving hemodynamic function.

The current maze operation evolved from the original procedure (ie, maze I) introduced in 1987. The maze I procedure consisted of multiple atrial incisions around the SA node, including an incision anterior to the atrial-SVC junction[102–104,127] (Fig. 4.18). That incision through the sinus tachycardia region of the SA node resulted in the unintended consequence of a blunted heart rate in response to exercise and obtunded atrial mechanical function.[128–130]

The procedure was modified (ie, maze II procedure) to include an incision on the anterior right atrium while allowing the sinus impulse to travel anteriorly across the left atrium but preventing it from reentering the right atrial–SVC junction (Fig. 4.19). Although successfully addressing the limitations of the original procedure, the maze II procedure was technically challenging, particularly the approach to the

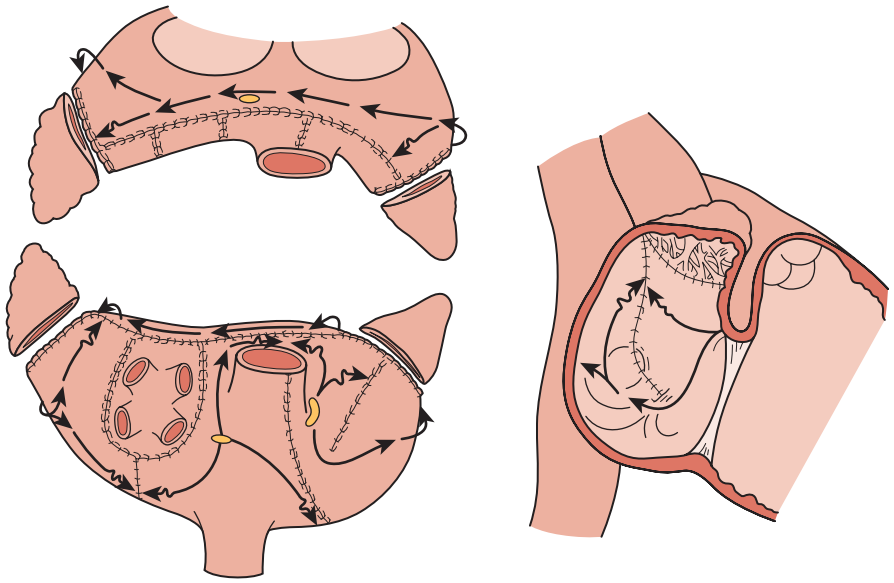


Fig. 4.18 Surgical incisions and resultant conduction pathways of the maze I procedure. The atria *(left)* are splayed open so that the anterior surface is superior and the posterior surface is inferior. The atria are divided in the sagittal plane *(right)*, showing the right atrial septum. Incisions are placed at sites most commonly associated with reentrant circuits *(arrows)* of atrial fibrillation to eliminate the arrhythmia. At the same time, bridges of myocardium are left intact to allow conduction across the atria and to the atrioventricular node, preserving atrial transport function and facilitating sinus rhythm. The pulmonary veins are isolated to eliminate potential conduction of premature beats. *(From Cox JL. Evolving applications of the maze procedure for atrial fibrillation [editorial]. Ann Thorac Surg. 1993'55:578–580.)*

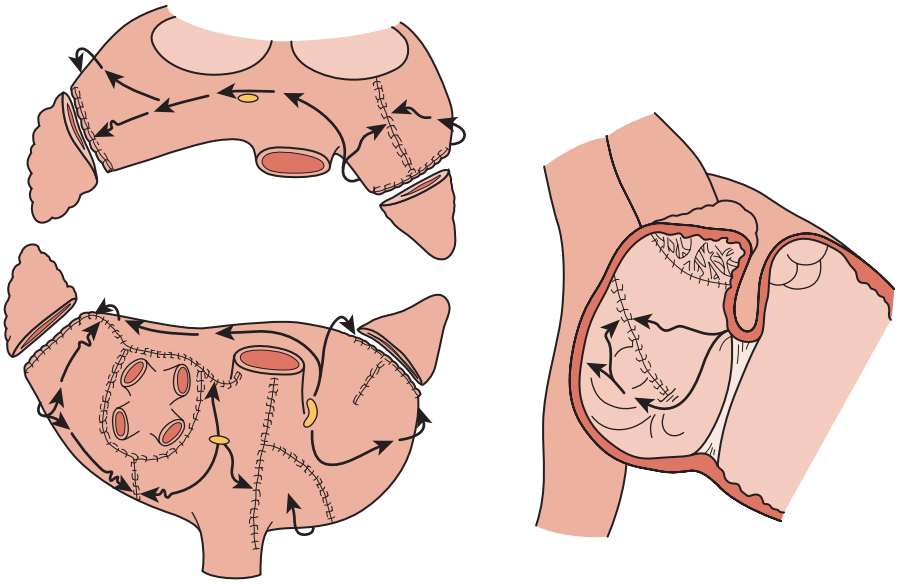


Fig. 4.19 Surgical incisions and conduction pathways of the maze II procedure in views similar to those in Fig. 4.18). The procedure is modified to eliminate incisions through the sinus tachycardia region of the sinus nodal complex performed in the maze I procedure to address chronotropic incompetence. A transverse incision across the dome of the left atrium is moved posteriorly. *(From Cox JL. Evolving applications of the maze procedure for atrial fibrillation [editorial]. Ann Thorac Surg. 1993;55:578–580.)*

left atrium that necessitated division and then reapproximation of the SVC. This problem was addressed by moving the left atrial incision to a more posterior location (Fig. 4.20). These and other modifications led to the introduction of the maze III procedure, which reduced the frequency of chronotropic incompetence, improved atrial transport function, and shortened procedural time.[127]

Surgery for atrial fibrillation continues to advance in two fundamental forms: ablative procedures concomitant with another cardiac operation or as a stand-alone procedure used specifically for terminating atrial fibrillation. Newer energy sources and devices have simplified execution. RF energy consists of alternating electrical current that generates thermal injury and a localized atrial scar. Because unipolar

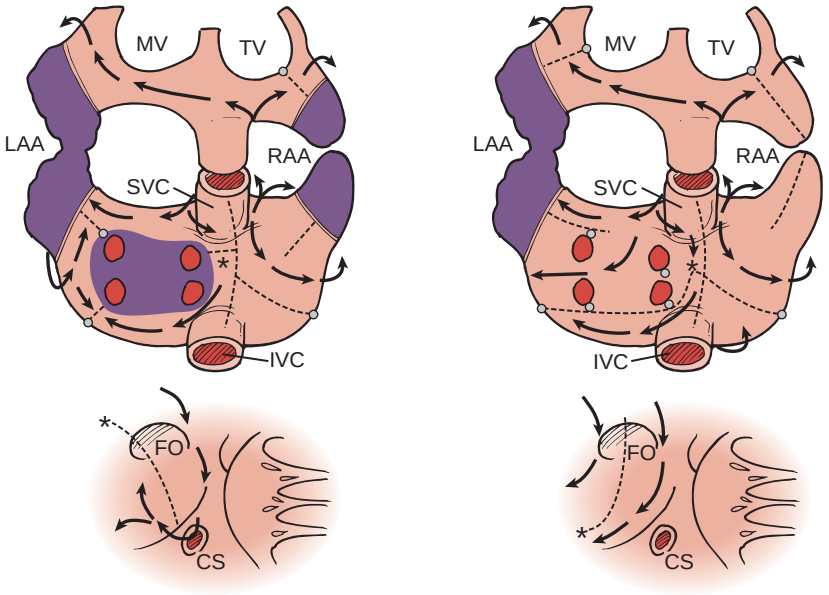


Fig. 4.20 The maze III procedure is shown in views similar to those in Fig. 4.18). The posterior incisions to the vena cava are modified, and the septal incision is placed posterior to the orifice of the superior vena cava. *CS*, Coronary sinus; *FO*, foramen ovale; *IVC*, inferior vena cava; *LAA*, left atrial appendage; *MV*, mitral valve; *RAA*, right atrial appendage; *SAN*, sinoatrial node; *TV*, tricuspid valve *(From Cox JL. Evolving applications of the maze procedure for atrial fibrillation [editorial]. Ann Thorac Surg. 1993;55:578–580.)*

RF energy can cause collateral atrial injury and tissue charring, bipolar probes were developed to minimize the risk. Although bipolar RF energy may be used epicardially for PVI, other ablative lesions require opening the heart, which can be accomplished through a small incision using a purse-string technique.

Because of the generated heat, contiguous structures such as the esophagus have been injured with PVI or posterior atrial lesion generation.[131] When RF energy is employed, the transesophageal echocardiography (TEE) probe should be retracted. However, esophageal injury from RF energy may occur regardless of whether TEE is used during surgery. Monitoring esophageal temperature using a probe fluoroscopically placed behind the left atrium may provide guidance for the operator.

With the availability of these devices, the maze procedure has become a hybrid operation using catheter-delivered RF energy and properly placed surgical incisions. The shortened surgical time allows the maze procedure to be performed with other operations such as mitral valve surgery. Shortened surgical times and lower procedural complexity have also allowed expansion of the eligibility criteria and fostered development of less invasive surgical approaches such as minimally invasive and beating-heart operations. The fundamental requirement for treatment is generation of a transmural lesion that leads to conduction block while minimizing collateral tissue damage. Although the issue of transmurality is somewhat controversial, it remains a basic goal.

The combination of conduction blocks imparted surgically for treating atrial fibrillation is called the *lesion set,* which consists of three components: PVI alone, PVI with lesions connecting to the mitral valve, and lesions involving the right atrium. Cox maze III represents the gold standard of lesion sets in atrial fibrillation surgery. As shown in Fig. 4.20, the pulmonary veins are isolated with lesions connecting to the mitral annulus and left atrial appendage. This constitutes the left-sided lesion set. On the right side, the SVC-IVC line is combined with lesions connecting to the tricuspid annulus and right atrial appendage. Using cryothermy, the coronary sinus is ablated in one spot, and both atrial appendages are removed. The complexity of this procedure and the availability of alternative energy sources motivated surgeons to use other combinations of lesions sets, which are collectively called *modified maze procedures*.

Based on Haissaguerre's seminal paper in 1998,[103] electrical isolation of the pulmonary veins has been used extensively. With modern devices, PVI is very straightforward, and it can be performed epicardially and without cardiopulmonary bypass. Most centers report that up to 80% of patients with paroxysmal atrial fibrillation remain free of the condition 6 months after surgery. For persistent atrial fibrillation, sinus rhythm has been successfully restored in 30% to 40% of patients. The addition of connecting lesions increases the efficacy of the modified maze procedure, especially in patients with persistent or permanent atrial fibrillation.

The right-sided lesion set appears to be important for patients with permanent atrial fibrillation. The lesions also decrease the risk of atrial flutter. Typical atrial flutter arises from the tricuspid isthmus, an area between the coronary sinus, tricuspid annulus, and eustachian valve. Some surgeons omit the right-sided lesion, and if the patient develops atrial flutter postoperatively, ablation is completed using a catheter-based strategy because it is a straightforward procedure in the electrophysiology laboratory.

The left atrial appendage (LAA) is a primary source of intracardiac thrombus in patients with atrial fibrillation, and its exclusion or elimination decreases the thrombotic risk. There are several strategies to manage the LAA. The appendage may be ligated or stapled externally. Because LAA morphology varies, the results can be suboptimal. Left atrial tissue is also very friable, and bleeding from this area can be problematic. The appendage may be completely resected and the base of the appendage oversewn with suture. The LAA may also be excluded from within the atrium. This is easily accomplished with a running suture at the opening of the appendage but requires an atriotomy.

Cryothermy was proposed by Cox and colleagues to simplify the maze III operation.[56] Using a handheld probe, tissue is exposed to a −60 to −90°C temperature, which produces a consistent transmural scar despite being applied only to the heart surface. A variety of flexible and colder probes allow the creation of all lesion sets. The Cox maze IV procedure is the most recent iteration.[132] Bipolar RF and cryoablation are used to create left and right atrial lesion sets. It is still

an extensive intracardiac procedure, but it has outstanding results. The other important practice change is electrical confirmation of PVI.

Conventional, partial sternotomy, and right thoracotomy approaches allow excellent exposure for all lesion sets. The atrium may be opened with a left atriotomy or transseptal approach. As a concomitant procedure, the maze procedure is performed before mitral valve surgery. This allows access to the mitral annulus before placement of a prosthesis. When an atrial fibrillation procedure is combined with coronary artery bypass grafting, the lesions are created before cardioplegic arrest. However, the left-sided pulmonary veins may be difficult to ablate with the beating heart and may be approached after cardioplegic arrest but before bypass graft construction. The left atrium may be reduced in size by resecting atrial tissue between the inferior pulmonary vein and mitral annulus.

Atrial fibrillation procedures may be performed using minimally invasive techniques. A right anterior thoracotomy and femoral cannulation allow access to the left atrium and mitral valve. Alternatively, a bilateral thoracoscopic and off-pump approach has been used.

The choice of atrial fibrillation operation (ie, lesion set and surgical approach) depends on several factors, including the duration and classification of atrial fibrillation, size of the left atrium, and need for concomitant procedures. For example, a patient with paroxysmal atrial fibrillation undergoing coronary artery bypass grafting is well served by a simple epicardial PVI using a bipolar RF ablation device. A patient with heart failure and persistent atrial fibrillation who requires mitral valve intervention is better treated with PVI and connecting lesions. A patient with symptomatic permanent atrial fibrillation and stroke who has failed medical and catheter-based therapy is best treated with a full Cox maze III procedure.

Operative results from many centers show that more than 90% of patients remain free of atrial fibrillation after the classic maze procedure.[130] Episodes of atrial flutter during the immediate perioperative period do not alter the long-term success of sinus rhythm restoration.[130] Procedure-specific complications have included an attenuated heart rate response to exercise resulting in the need for permanent pacemaker implantation.[130] The frequency of these complications is less with newer versions of the procedure. Fluid retention is a common problem after the maze procedure, which is attributed to reduced secretion of atrial natriuretic peptide and elevated levels of antidiuretic hormone and aldosterone.[133,134] The use of furosemide or spironolactone, or both, perioperatively can reduce the likelihood of this complication.[135]

An intended goal of the maze procedure is preservation of atrial transport function. Follow-up of patients early in the experience at Washington University School of Medicine demonstrated that this was achieved for the right atrium in 98% of patients but for the left atrium in only 86% of patients.[136] More detailed analysis revealed that even when left atrial contraction existed, quantitative mechanical function was lower compared with that in control patients.[137,138] In cases of compromised atrial transport function, the incisions used to isolate the pulmonary veins also isolated almost 30% of the left atrial myocardium from excitation.[139]

Preservation of atrial transport function was improved with a maze procedure that used incisions radiating from the SA node (Fig. 4.21) along the path of coronary arteries supplying the atrium rather than across as in the maze III procedure.[140,141] This modification, called the *radial procedure,* was also designed to preserve the right atrial appendage, which is an important source of atrial natriuretic peptide.[142] Compared with the standard maze III procedure, the radial approach results in a more synchronous activation sequence of the left atrium, preserving atrial transport function, and it is equally effective in eliminating the reentrant circuits of atrial fibrillation.

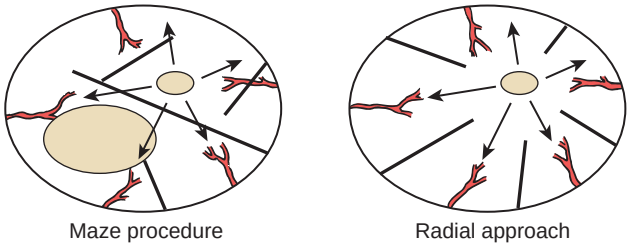


Fig. 4.21 Contrasting concepts of the maze procedure *(left)* and radial approach *(right).* The *small circle* in the middle indicates the sinus node, the *outer circle* indicates the atria, and the *shaded area* indicates atrial myocardium isolated by the incisions. The atrial arterial supply is depicted, and the *arrows* indicate propagation of the depolarizing wavefront. The radial approach preserves atrial arterial blood supply and a more physiologic activation sequence. With the maze procedure, some arteries are divided, and the atrial activation sequence is disrupted. *(From Nitta T, Lee R, Schuessler RB, et al. Radial approach: a new concept in surgical treatment of atrial fibrillation. I. Concept, anatomic and physiologic bases and development of a procedure.* Ann Thorac Surg. *1999;67:27.)*

Anesthesia Considerations

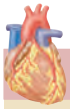
Anesthesiology teams are increasingly asked to care for patients undergoing catheter-based ablative procedures for atrial fibrillation. Monitored anesthesia care may be possible in some situations, but general anesthesia is typically chosen due to the duration of the procedure and the demand for no patient movement during critical lesion placement. Care of the patient undergoing catheter-based therapy or atrial fibrillation surgery is similar. Preparation includes review of preoperative cardiac testing results, assessment of the characteristics of the patient's arrhythmia, and review of the surgical plan and concomitant procedures that may accompany the maze procedure (eg, coronary artery bypass grafting, valve replacement, repair of congenital lesions).

The choice of anesthesia depends on the patient's physical status, including comorbid conditions and ventricular dysfunction. General anesthesia with HFJV can minimize thoracic excursion during respirations, which increases catheter-tissue contact.[121,122] HFJV necessitates the use of intravenous anesthesia, which usually consists of a propofol infusion combined with a short-acting narcotic infusion such as remifentanil. HFJV risks include pneumothorax, barotrauma, inadequate ventilation or oxygenation, respiratory acidosis, pneumomediastinum, gastric distention, and aspiration.[120] These risks are more likely to occur with HFJV than with conventional mechanical ventilation and must be considered as HFJV is increasingly used to improve freedom from atrial fibrillation.

LAA thrombus must be excluded with TEE before proceeding with catheter-based ablation and surgical manipulations. During catheter-based ablation of atrial fibrillation, patients undergo direct arterial pressure and esophageal temperature monitoring. Acute increases in esophageal temperature of only 0.1°C are communicated to the electrophysiologist. Immediately terminating RF energy and cooling the catheter tip with intraprobe saline at room temperature limit the spread of myocardial heating.

Because heparin is administered during the procedure, the activated clotting time is monitored. Constant vigilance is mandated for pericardial tamponade, and immediate transthoracic echocardiography should be performed when abrupt hypotension develops. Percutaneous pericardial drainage is emergently performed, which typically restores blood pressure. Continued collection of pericardial blood after protamine reversal of heparin anticoagulation may necessitate transfer of the patient to the operating room for a sternotomy and repair of the atrial defect.

Patient monitoring modalities for the surgical procedures are similar to those used for other cardiac surgical procedures, including TEE to evaluate ventricular and valvular function, look for new wall motion abnormalities, and assist in evacuation of air from the cardiac chambers at the conclusion of surgery. Ventricular dysfunction (right ventricle more often than the left), at least transiently, and echocardiographic and electrocardiographic ischemic changes (inferiorly more often) are common.[10] Causes include coronary artery air embolization and inadequate myocardial protection. Because the maze procedure



BOX 4.11 VENTRICULAR ARRHYTHMIAS

- Most episodes of ventricular tachycardia or fibrillation result from coronary artery disease and dilated or hypertrophic cardiomyopathy.
- Implantable cardioverter-defibrillator placement is the standard of care with or without medical treatment for life-threatening ventricular arrhythmias and structural heart disease.
- Catheter ablation is adjuvant therapy for medically refractory monomorphic ventricular tachycardia.
- Surgical therapy includes endocardial resection with cryoablation.
- Anesthesia considerations focus on preoperative catheterization, echocardiography, and electrophysiologic testing.
- Monitoring of surgical patients is dictated by the underlying cardiac disease.

entails placement of multiple atrial incisions, initial atrial compliance and performance of the atria appear altered. TEE evaluation of atrial activity is performed after separation from the extracorporeal circulation and decannulation.[10]

Ventricular Arrhythmias

As with supraventricular arrhythmias, the treatment of ventricular fibrillation and VT is aimed at addressing underlying mechanisms (eg, myocardial ischemia; drug-induced, electrolyte, or metabolic abnormalities). In most patients with life-threatening ventricular arrhythmias and structural heart disease, ICD placement is the standard of care with or without concomitant antiarrhythmic drug therapy.[143] In patients with significant structural heart disease, catheter ablation is considered as an adjuvant therapy for medically refractory monomorphic VT.

Rarely, VT occurs in the setting of a structurally normal heart. This syndrome of a primary electrical disorder usually is caused by a focal, triggered mechanism that occurs mostly in younger patients and originates from the right ventricular outflow tract or apical septum [144–146] (Box 4.11). ICDs are not typically indicated in these cases.

Catheter Ablation Therapy for Ventricular Tachycardia

The mechanism for VT can be identified in the electrophysiology laboratory using programmed stimulation.[147,148] Single or multiple extrastimuli are introduced during an excitable gap of cardiac depolarization until a sustained VT develops that is similar in morphology to that of the spontaneous arrhythmia. The diagnostic hallmark of VT due to a reentrant circuit is the ability to entrain the tachycardia by pacing slightly faster than the tachycardia cycle length and demonstrate fusion.[149]

Traditional catheter mapping techniques for guiding catheter ablation of VT position the ablation catheter within a protected isthmus of the reentrant circuit. The pathologic characteristics of this site are thought to be viable myocardium surrounded by scar tissue that is electrically isolated from the bulk of the ventricular myocardium except at the entrance and exit sites. These techniques have important shortcomings because most VTs are not hemodynamically stable enough for mapping and multiple morphologies of inducible VT are commonly identified in a single patient.

Newer strategies that rely on three-dimensional computerized mapping techniques attempt to identify important areas of myocardial scar, such as the perimeter that may participate in reentrant circuits. By strategic placement of areas of conduction block guided by these maps, significant cure rates have been obtained without the necessity of mapping individual reentrant circuits.[150] In rare instances, VT circuits may involve the conduction system, such as in bundle branch reentry or fascicular VT that is easily ablated with RF energy.[151]

There are no data from prospective, randomized trials of VT ablation, but case series report success rates ranging from 37% to 86%.[133,152–158] The latter results mostly represented patients with drug-resistant VT or multiple VT morphologies, and treatment was performed as a last-ditch effort to control the arrhythmia. Reported success rates are higher after RF ablation for primary VT.

Major complications from catheter ablation procedures for VT in the setting of structural heart disease include stroke, myocardial infarction, heart failure exacerbation, vascular injury, and death. The incidence of these complications appears to be low despite the lengthy procedure times that are commonly required.[150]

Anesthesia Considerations

Anesthesia management of patients undergoing catheter-based procedures to ameliorate ventricular arrhythmias is primarily based on the patient's underlying cardiac disease and other comorbidities. Candidates often have coronary artery disease, severely impaired left ventricular function, and dysfunction of other organs (eg, liver, kidney). Because they are receiving multiple medications that may interact with anesthetics (eg, vasodilation from angiotensin-converting enzyme inhibitors), a thorough review of the patient's underlying conditions and treatments is mandated. Special attention is given to cardiac catheterization results and preoperative echocardiogram findings. Information regarding characteristics of the patient's arrhythmia such as ventricular rate, hemodynamic tolerance, and method of arrhythmia termination should be sought.

Prior or current treatment with amiodarone is a particular concern. The long elimination half-life (about 60 days) of amiodarone requires that potential side effects such as hypothyroidism be considered perioperatively.[159] The α-adrenergic and β-adrenergic properties of amiodarone may lead to hypotension during anesthesia, but most anesthesiologists are familiar with the management of this complication. Much attention has been given to bradycardia associated with amiodarone during anesthesia that may be resistant to atropine.[160–164] Methods for temporary cardiac pacing should be readily available to care for patients receiving amiodarone on a long-term basis. Retrospective reports suggest a greater need for inotropic support for patients receiving preoperative amiodarone therapy because low systemic vascular resistance has been observed.[161,162]

Pulmonary complications thought to be related to pulmonary toxicity from amiodarone have been reported.[106,164] In a series of 67 patients receiving preoperative amiodarone, 50% developed acute respiratory distress syndrome that could not be attributed to other factors, including the intraoperative fraction of inspired oxygen (see Chapter 11).[164]

Monitoring includes direct arterial pressure monitoring and central venous access is necessary for administration of vasoactive drugs if needed. Means for rapid cardioversion-defibrillation should be readily available when inserting any central venous catheter. Self-adhesive electrode pads are used most often and connected to a cardioverter-defibrillator before anesthesia induction. Premature ventricular beats induced during these procedures can easily precipitate the patient's underlying ventricular arrhythmia, which may be difficult to convert to sinus rhythm.[162,165] Selection of anesthetics for arrhythmia ablation is dictated mostly by the patient's physical status. General anesthesia with endotracheal intubation is typically chosen due to the duration of the procedures, but deep sedation is also employed.

Because anesthetics can influence cardiac conduction and arrhythmogenesis, there is concern about their ability to alter electrophysiologic mapping results.[166,167] Effects of volatile anesthetics on ventricular arrhythmias vary in different experimental models and according to the mechanism of the arrhythmia. Data showing proarrhythmic, antiarrhythmic, and no effects of volatile anesthetics on experimental

BOX 4.12 IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

- ICDs can pace and provide tiered therapy for tachyarrhythmias (eg, shocks, antitachycardia pacing).
- Insertion of modern devices typically is done with percutaneous techniques.
- ICDs are indicated for the primary or secondary prevention of sudden cardiac death.
- ICDs reduce overall mortality rates compared with standard treatment alone.
- ICDs are indicated for patients surviving sudden death without a reversible cause, those with ischemic cardiomyopathy with an ejection fraction ≤30%, and those with ischemic or nonischemic cardiomyopathy with an ejection fraction of ≤35% and NYHA class II or III heart failure symptoms.

ICD, Implantable cardioverter-defibrillator; *NYHA*, New York Heart Association.

arrhythmias have been reported.[13,166–173] Nonetheless, the small doses administered during ablative procedures may have minimal effects on electrophysiologic mapping. Opioids have had no effects on the inducibility of VT.[170,173,174]

Implantable Cardioverter-Defibrillators

Decreased device size, longer battery life, and improved treatment algorithms have enhanced the reliability of ICDs (Box 4.12). Current ICDs can provide tiered therapy consisting of antitachycardia pacing and shocks to terminate potentially life-threatening ventricular arrhythmias. All ICDs can pace the heart to treat bradycardia as a single-chamber, dual-chamber, or biventricular system.

Advances in lead technology and implementation of a biphasic waveform have considerably reduced defibrillation energy requirements.[175,176] These improvements have simplified lead implantation with the use of transvenous insertion methods instead of the epicardial patch electrodes used in prior generations. Insertion of modern devices uses percutaneous techniques rather than a more invasive median sternotomy, except when body habitus precludes the approach (eg, pediatric population).

The ICD consists of a pulse generator and transvenous leads that continuously monitor the heart rate. When the heart rate exceeds the programmed limit, therapy is initiated that may include a brief burst of rapid pacing (ie, antitachycardia pacing) followed by a biphasic shock if the arrhythmia persists. Electrogram storage capabilities allow review of the appropriateness of delivered treatments and changes in ventricular arrhythmia characteristics. The style of ICD (ie, one, two, or three leads) is chosen based on a patient's requirement for antibradycardia pacing (ie, single- or dual-lead devices) or cardiac resynchronization therapy (ie, biventricular pacing) for medically refractory heart failure and interventricular conduction delay.

Technologic aspects of ICDs have been reviewed (see Chapter 5).[175] Defibrillation voltage is much higher than can be delivered with existing batteries, necessitating the use of storage capacitors and transformers. After the ICD has detected an arrhythmic event, the device begins to charge its capacitor. During charging and immediately after the capacitor has been fully charged, continuation of the arrhythmia is confirmed, and the device delivers therapy. If during the charge or immediately after charging is complete the arrhythmia spontaneously terminates, the energy is dumped to avoid unnecessary energy delivery. If energy is delivered, the device uses a redetection algorithm to assess whether the arrhythmia was successfully terminated. If the arrhythmia persists, the device recharges its capacitor and repeats the process. If the arrhythmia has terminated, the episode is declared complete.

Although much of the ICD's ability to determine whether an arrhythmia needs therapy is based on the rate, all ICDs can apply various algorithms to differentiate ventricular from supraventricular arrhythmias. They include criteria for abruptness of onset, intracardiac signal morphology, and rate stability (ie, stable with VT but irregular with atrial fibrillation).[175] An atrial lead can sometimes enhance the discrimination of atrial fibrillation with a rapid ventricular response from VT.[175]

Guidelines for implantation of ICDs have been issued by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society[177] (Box 4.13). ICDs are indicated for the primary or secondary prevention of sudden cardiac death. Recommendations are based on data from large, multicenter investigations that have compared ICD therapy with standard care, including antiarrhythmic drugs. For patients with prior cardiac arrest due to VT or ventricular fibrillation (ie, secondary prevention), the data show that ICDs lower the mortality risk by 20% to 30% compared mostly with amiodarone or β-adrenergic receptor blockers.[177–180] Similarly, the relative mortality rate is reduced by 49% to 54% with ICD treatment for patients with nonsustained VT or inducible ventricular arrhythmias with programmed stimulation compared with standard care or serial drug testing in patients with ischemic left ventricular dysfunction.[181,182]

The most persuasive data on primary prevention of sudden death with ICD treatment for patients with ischemic and nonischemic cardiomyopathy come from the MADIT II[181] and SCD-HeFT[183] trials. In contrast to other studies, these two randomized trials did not require a history of inducible or spontaneous ventricular arrhythmias. Enrollment criteria were instead based on the ejection fraction alone (≤30%) in the setting of ischemic cardiomyopathy (ie, MADIT II) or the ejection fraction (≤35%) with New York Heart Association (NYHA) class II or III heart failure symptoms with any type of end-stage cardiomyopathy (ie, SCD-HeFT).[183] Patients were continued on conventional treatments, including β-blockers, angiotensin-converting enzyme inhibitors, and HMG-CoA reductase inhibitors (ie, statins).

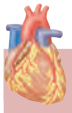
After more than 4 years of follow-up, ICD treatment was associated with a significant reduction in all-cause mortality compared with conventional treatment. Other conditions such as inherited long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia, and infiltrative disorders (including cardiac sarcoidosis) may warrant ICD insertion for prevention of sudden cardiac death, although data from large, randomized studies are lacking due to the relative infrequency of the conditions. In the future, genetic screening may provide valuable information about the risk of sudden death for patients with these less common entities.[151,184]

Anesthesia Considerations

Insertion of ICDs is usually performed in the catheterization suite. The procedure typically includes defibrillation testing to ensure an acceptable margin of safety for the device. VT or ventricular fibrillation is induced by the introduction of premature beats timed to the vulnerable repolarization period. External adhesive pads are placed before the procedure and connected to an external cardioverter-defibrillator to provide backup shocks if the device is ineffective.

Monitored anesthesia care is typically chosen, but a short-acting general anesthetic may be given for defibrillation testing. General anesthesia may be chosen for patients with severe concomitant diseases (eg, chronic lung disease, sleep apnea) when control of the airway is desired. Simultaneous insertion of biventricular pacing systems with an ICD is performed for an increasing population of patients with impaired left ventricular dysfunction with or without ventricular conduction delay.

In addition to standard patient monitoring, continuous arterial blood pressure monitoring may be considered during monitored anesthesia care to rapidly assess return of blood pressure after defibrillation testing. Defibrillation testing has been associated with ischemic electroencephalographic (EEG) changes of 7.5 ± 1.8 seconds (mean



BOX 4.13 AMERICAN COLLEGE OF CARDIOLOGY, AMERICAN HEART ASSOCIATION, AND HEART RHYTHM SOCIETY GUIDELINES FOR INSERTION OF IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

Class I Heart Failure

- Survivors of cardiac arrest due to VF or sustained VT after excluding reversible causes
- Patients with structural heart disease and spontaneous, sustained VT, whether hemodynamically stable or unstable
- Patients with syncope of undetermined origin with clinically relevant sustained VT or VF induced at electrophysiology study
- Patients with an LVEF ≤35% due to prior MI occurring at least 40 days earlier and who have NYHA functional class II or III disease
- Patients with nonischemic dilated cardiomyopathy who have an LVEF ≤35% and NYHA functional class II or III disease
- Patients with LV dysfunction due to prior MI occurring at least 40 days earlier with an LVEF ≥30% and who have NYHA class I disease
- Patients with nonsustained VT due to prior MI with an LVEF ≤40% with inducible VF or sustained VT at electrophysiology study

Class IIa Heart Failure

- Patients with unexplained syncope, LV dysfunction, and nonischemic cardiomyopathy
- Patients with sustained VT and normal LV function
- Patients with hypertrophic cardiomyopathy and at least one risk factor for sudden cardiac death
- Patients with arrhythmogenic RV dysplasia with at least one risk factor for sudden cardiac death
- Patients with long QT syndrome with syncope and/or sustained VT while on β-blockers
- Nonhospitalized patients awaiting heart transplantation
- Patients with Brugada syndrome who have syncope or those with documented VT not resulting in cardiac arrest
- Patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving β-blockers
- Patients with cardiac sarcoidosis, giant cell myocarditis or Chagas disease

Class IIb Heart Failure

- Patients with nonischemic heart disease who have an LVEF ≤35% and who have NYHA class I disease
- Patients with long QT syndrome and risk factors for sudden cardiac death
- Patients with syncope and structural heart disease when evaluation has failed to define a cause
- Patients with familial cardiomyopathy associated with sudden cardiac death
- Patients with LV noncompaction

Class III Heart Failure

- ICD implantation not indicated for patients whose reasonable life expectancy at an acceptable functional status is <1 year even if they meet other criteria

Therapeutic Indications by Functional Class

- Class I: There is evidence or general agreement that the treatment is useful and effective.
- Class IIa: Weight of the data or evidence favors benefit of the therapy.
- Class IIb: The conditions for which usefulness or efficacy of the treatment are less well established.
- Class III: Intervention is not indicated.

ICD, Implantable cardioverter-defibrillator; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *RV*, right ventricular; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

± SD) after arrest.[185] The changes were transient and not associated with persistent ischemic EEG changes or exacerbation of an existing neurologic deficit, and significant deterioration in neuropsychometric performance was not detected. Repeated defibrillation testing is usually well tolerated without deterioration of cardiac function even in patients with left ventricular ejection fractions less than 35%. Nonetheless, the means of pacing must be available in case bradycardia develops after cardioversion-defibrillation. Restoration of circulatory function after defibrillation testing often is accompanied by tachycardia and hypertension, necessitating treatment with a short-acting β-blocker or vasoactive drugs, or both.

ICD-associated complications may be related to insertion or the device itself. Percutaneous insertion is typically done through the subclavian vein, predisposing the patient to pneumothorax. Cardiac injury (including perforation) is a remote possibility. Cerebrovascular accident and myocardial infarction have been reported, but mostly with the use of older device insertion methods.[10] Device-related complications include multiple shocks that may lead to myocardial injury or refractory hypotension.[186,187] Device infections are particularly difficult to manage, often requiring device and lead explantation.

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5 Cardiac Implantable Electrical Devices

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KEY POINTS

Preoperative Key Points

1. Identify the type of cardiac implantable electronic device (CIED) (eg, transvenous implantable pacemaker, intracardiac pacemaker, transvenous implantable cardioverter-defibrillator, subcutaneous implantable cardioverter-defibrillator) and the manufacturer of the generator.
2. Establish contact with the patient's CIED physician or clinic to obtain records and perioperative prescription (Heart Rhythm Society [HRS]). Have the CIED interrogated by a competent authority shortly before the procedure (American Society of Anesthesiologists [ASA]).
3. Obtain appropriate records from the CIED clinic (HRS) or preoperative interrogation (ASA). Ensure that the device will appropriately pace the heart.
4. Consider replacing any CIED near its elective replacement period in a patient scheduled to undergo either a major operation or surgery within 25 cm of the generator.
5. Determine the patient's underlying rate, rhythm, and pacing dependency to determine the need for asynchronous or external backup pacing support.
6. If magnet use is planned, then ensure that magnet behavior (pacing mode, rate, atrioventricular delay, shock therapy suspension) is appropriate for the patient.
7. Consider programming minute ventilation and other rate responsiveness features off, if present.
8. Consider programming rate enhancements off, if present.
9. Consider increasing the pacing rate to optimize oxygen delivery to tissues for major operations.
10. If electromagnetic interference is likely or if a central venous catheter guidewire will be placed into the chest, then consider asynchronous pacing for the pacing-dependent patient and suspension of antitachycardia therapy for any implantable cardioverter-defibrillator (ICD) patient. Magnet application might be effective, although magnet use has been associated with inappropriate ICD discharge. Magnet application will never create asynchronous pacing in any type of ICD.

Intraoperative Key Points

1. Monitor cardiac rhythm/peripheral pulse with pulse oximeter (plethysmography) or arterial waveform.
2. Consider disabling the "artifact filter" on the electrocardiographic monitor. If a minute ventilation sensor is active, then ensure that respiratory rate monitoring is disabled.
3. Ask the surgeon to avoid the use of the monopolar electrosurgical unit (ESU) or limit ESU bursts to <4 seconds separated by at least 2 seconds. Use the bipolar ESU if possible; if not possible, then pure cut (monopolar ESU) is better than "blend" or "coag."
4. Place the ESU dispersive electrode in such a way as to prevent electricity from crossing the generator-heart circuit, even if the electrode must be placed on the distal forearm and the wire covered with sterile drape.
5. If the ESU causes ventricular oversensing, resulting in pacing quiescence or atrial oversensing with inappropriate high rate ventricular pacing, then limit the period(s) of asystole, relocate the dispersive electrode, or place a magnet over the pacemaker (not indicated for any ICD).
6. Temporary pacing might be needed, and consideration should be given to the possibility of CIED failure.
7. Consider avoiding sevoflurane, isoflurane, or desflurane in the patient with long QT syndrome.

Postoperative Key Points

1. Have the CIED interrogated by a competent authority postoperatively. Some rate enhancements can be reinitiated, and optimum heart rate and pacing parameters should be determined. The ICD patient must be monitored until the antitachycardia therapy is restored.

Battery operated, implantable pacing devices (collectively, cardiac implantable electronic devices [CIEDs]) were first introduced in 1958, 4 years after the invention of the transistor. Although several generations of physicians have been trained since, these devices remain one of the most poorly understood aspects of medical care throughout the world. Often, these devices are ignored in the overall care of a patient with the erroneous (and possibly life-threatening) belief that mere application of a magnet will prevent any perioperative problem, as well as treat any situation that arises.[1,2] Frequently, implantable cardioverter-defibrillators (ICDs) are labeled as a simple pacemaker, a situation during which the antitachycardia therapy or the inability to deliver magnet-driven asynchronous pacing in a pacing-dependent patient might be overlooked.[3] Nevertheless, the presence of a CIED with therapeutic capability can significantly complicate a patient's life—whether for access to an airport owing to metal and bomb detection equipment, a surgical procedure, a diagnostic procedure such as a computerized axial tomography (CAT) or magnetic resonance imaging (MRI), end-of-life care planning, and funeral or cremation activities. In addition to pacemakers and defibrillators, CIEDs include devices such as implanted loop recorders, with no therapeutic capability, but

whose capability to detect both tachyarrhythmias and bradyarrhythmias remains underutilized in the preoperative evaluation of a patient.

CIED complexity, calculation, data storage abilities, and size minimization allowing direct implantation into the chamber(s) of the heart have grown in a manner similar to that seen within the computer or cell phone industry. The natural progression of pacemaker developments led to the invention of the transvenous implantable cardioverter-defibrillator (TV-ICD) around 1980. As this technology has advanced, the lines between simple pacing generators and defibrillators have become less clear. For example, every TV-ICD currently implanted has robust antibradycardia pacing capability; and patients, the news media, and even physicians often misidentify an implanted defibrillator as a pacemaker. The consequence of mistaking any TV-ICD for a conventional pacemaker can lead to patient harm, mostly attributable to electromagnetic interference (EMI) resulting in inappropriate ICD therapy. In TV-ICDs manufactured before 2009 by Guidant or Cardiac Pacemakers, Inc. (CPI) (now owned by Boston Scientific, Natick, MA), high-energy therapies could have been permanently disabled by magnet placement.[4] However, in October, 2009, Boston Scientific changed their program software to eliminate this feature in nearly every Guidant or CPI TV-ICD that remains implanted. Fig. 5.1 shows a three-lead defibrillation system and identifies the right ventricular (RV) shock coil, which differentiates a TV-ICD system from a conventional pacemaker system.

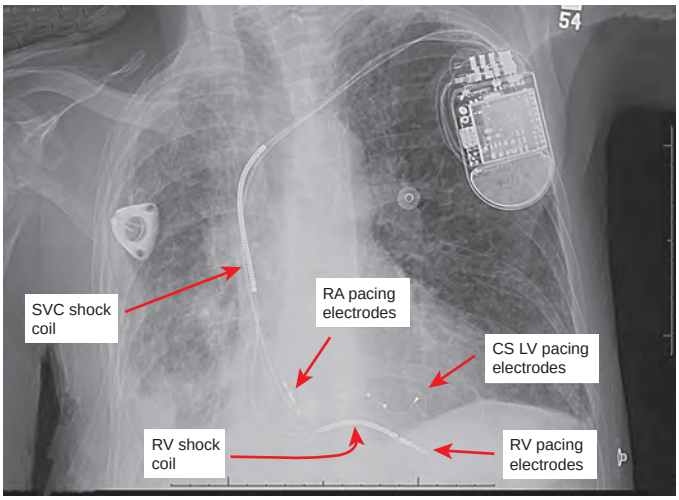


Fig. 5.1 Defibrillator system with biventricular (BiV) antibradycardia pacemaker capability. Note that three leads are placed: a conventional, bipolar lead to the right atrium; a true bipolar right ventricular (*RV*) lead with shock coils in the right ventricle and the superior vena cava (*SVC*), and a quadripolar lead to the coronary sinus (*CS*). This system is designed to provide "resynchronization (antibradycardia) therapy" in the setting of a dilated cardiomyopathy with a prolonged QRS complex (and frequently with a prolonged P-R interval as well). The bipolar lead in the right atrium will perform both sensing and pacing function. The true bipolar (discrete tip and ring) electrodes in the right ventricle provide pacing and sensing function. The presence of a "shock" conductor (termed *shock coil*) on the RV lead in the right ventricle distinguishes a defibrillation system from a conventional pacemaking system. The lead in the CS depolarizes the left ventricle, and this particular catheter has four electrodes in the CS to allow optimization of left ventricular (*LV*) pacing (a close-up of the St. Jude generator is demonstrated in Fig. 5.4I). Because of the typically wide native QRS complex in a left bundle branch pattern, failure to capture the left ventricle can lead to ventricular double-counting (and inappropriate antitachycardia therapy) in a BiV transvenous implantable cardioverter-defibrillator (ICD) system. Many defibrillation systems also have a shock coil in the SVC, which is most often electrically identical to the defibrillator case (called the *can*). When the defibrillation circuit includes the ICD case, it is called *active can configuration*. Incidental findings on this chest radiograph include the presence of a right-sided implanted central venous catheter, right pleural effusion, and scoliosis.

The development of the subcutaneous ICD[5] (S-ICD) (Fig. 5.2), as well as the leadless transcatheter-deployed intracardiac pacemaker[6] (IC-PM) (Fig. 5.3), further complicates this issue. S-ICDs are larger than their transvenous counterparts, cannot provide antitachycardia or sustained antibradycardia pacing, and generally have higher

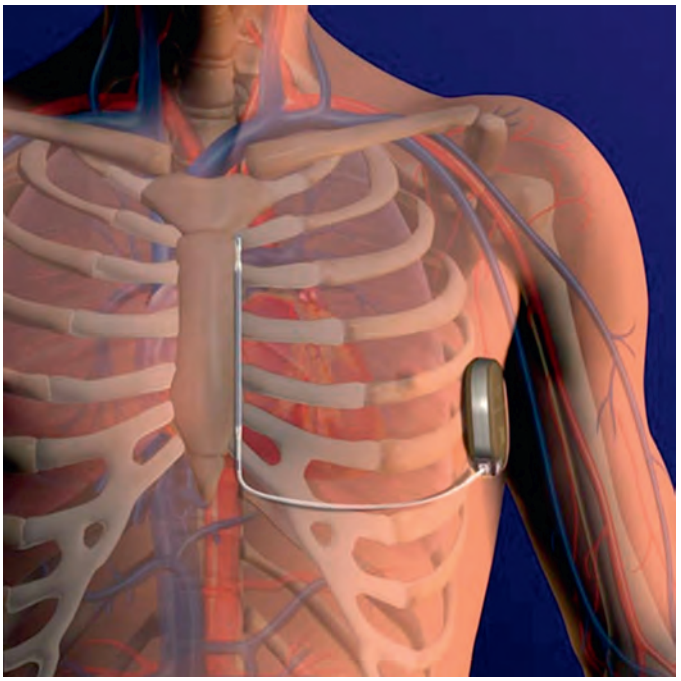


Fig. 5.2 The Boston Scientific subcutaneous implantable cardioverter-defibrillator (S-ICD). Illustration demonstrates an S-ICD (CE mark 2009; US Food and Drug Administration approval 2012), which consists of a generator implanted along the lateral chest wall with a subcutaneous lead tunneled into position over the heart. *(Used with permission. Hauser RG. The subcutaneous implantable cardioverter-defibrillator: should patients want one?* J Am Coll Cardiol. *2013;61:20–22.)*

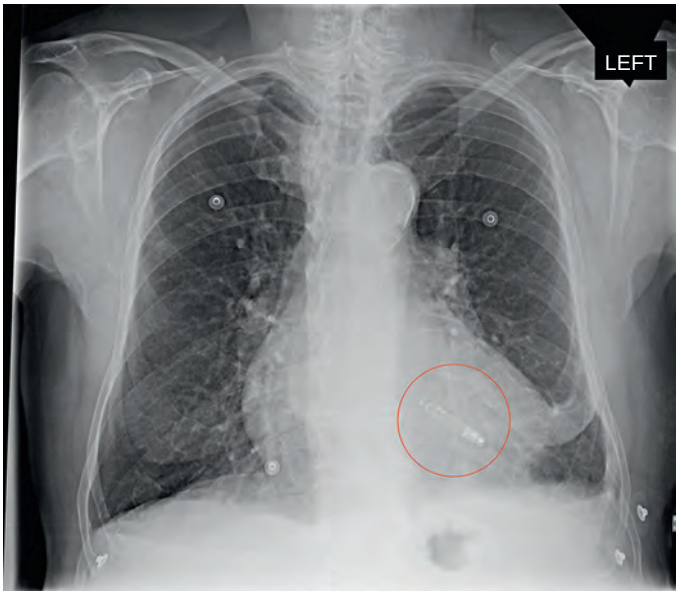


Fig. 5.3 The St. Jude Nanostim leadless intracardiac pacemaker. A leadless pacemaker is shown in the right ventricle *(circle)* on this posteroanterior chest film. Leadless pacemakers are currently approved for implant in several countries outside of the United States. *(X-ray image courtesy of Vivek Reddy, MD, Icahn School of Medicine at Mount Sinai, New York, NY.)*

defibrillation thresholds (DFTs) than TV-ICDs. The IC-PMs likely behave differently from their transvenous-deployed cohorts, especially with respect to overall features and magnet placement. They might be identified only as a generic implant on an x-ray image rather than the actual type of device, owing to information lag on the part of radiologists.

The diversity and complexity of cardiac pulse generators, as well as the multitude of programmable parameters, limits the number of sweeping generalizations that can be made about the perioperative care of the patient with an implanted pulse generator. Population aging, continued enhancements in implantable technology, and new indications for implantation will lead to growing numbers of patients with these devices in the new millennium. Currently, four advisories or guidelines have been published in three countries endorsed by several societies regarding the care of the perioperative patient with a device.[7–10] Table 5.1 compares and contrasts these statements. Work by the Association for the Advancement of Medical Instrumentation to standardize magnet responses has been ongoing since 2000 but without much success (see https://standards.aami.org/kws/public/projects/project/details?project_id=53).

Although incredibly reliable, both transvenous pacemakers (TV-PMs) and TV-ICDs have nonzero failure rates. US Food and Drug Administration (FDA) data for the 13-year period from 1990 to 2002 show 0.5% of TV-PMs and 2.1% of TV-ICDs were explanted annually for reasons other than battery replacement.[11] In a subsequent study, for the period from 2003 to 2007, Laskey and colleagues[12] reported a 0.4% annual failure rate for conventional TV-ICDs and a 2.3% failure rate for TV-ICDs delivering cardiac resynchronozation therapy.[12]

Radiology Imaging Issues

Many patients with a CIED require a computed tomography (CT) scan or an MRI during their lifetime. Both modalities have the ability to interfere with normal CIED function. CT scans directly over the generator can cause oversensing (see Glossary) (which can lead to inappropriate pacing cessation),[13] although Hussein and associates[14] report that this scenario remains clinically rare. However, pacing-dependent patients undergoing high-power axial (vs helical) CAT scans in which the x-ray beam crosses the generator might need special monitoring or reprogramming.

MRI represents another imaging modality requiring special monitoring and CIED reprogramming.[15] This report of 54 patients with modern TV-PMs undergoing 62 scans basically provided a road map for conduction of MRIs in which the benefit of the MRI outweighed the theoretic risk to the patient. Currently, over 3000 patients with both TV-PMs and TV-ICDs appear to have undergone these procedures

TABLE 5.1 Comparison of Perioperative Cardiac Implantable Electronic Device Advisories

	Preoperative Recommendation	*Intraoperative Magnet Use*	*ESU Dispersive Electrode Placement*	*Postoperative Recommendation*	**Emergency Procedures**	
					PM	*ICD*
ASA Periop	"Timely interrogation" before elective surgery	Shuns magnet use in favor of reprogramming.	Prevents presumed current path from crossing the chest and CIED system.	Interrogation is recommended. Footnotes added to 2011 revision suggest that CIED reinterrogation is not needed if no monopolar ESU is used.	(silent)	
HRS/ASA	PM interrogation within 12 months ICD interrogation within 6 months CRT interrogation within 3–6 months CIED physician must provide prescription for perioperative care	Magnet use is suggested for asynchronous pacing (when needed in PM patients) and disabling ICD high-energy therapy, provided that patient position does not interfere with magnet access or observation.	Prevents presumed current path from crossing the chest and CIED system.	For most cases involving EMI (especially those inferior to umbilicus and when no preoperative reprogramming was performed), interrogation can take place within 1 month as an ambulatory procedure. For reprogrammed CIEDs, hemodynamically challenging cases, cardiothoracic surgery, RFA, and external cardioversion, interrogation can take place before transfer from cardiac telemetry.	Use 12-lead ECG to identify pacing need, presume dependence if 100% pacing. Use magnet to mitigate pacing inhibition.	Use magnet to suspend ICD tachyarrhythmia therapy. Maintain cardiac monitoring until postoperative interrogation.
CAS-CCS	De-novo interrogation is not likely needed, but the CIED physician must provide a prescription for perioperative care.	Where reasonable, magnet use is suggested for asynchronous pacing (when needed in PM patients) and disabling ICD high-energy therapy.	No mention	Clear plan for postoperative care is established before elective case.	Use 12-lead ECG to identify pacing need, presume dependence if 100% pacing; maintain careful monitoring to determine magnet action, >5 second pauses if ESU interferes with CIED.	
MHRA[a]	Preoperative contact with the pacemaker ICD follow-up clinic for evaluation and perioperative recommendations	Caution is advised since programming can affect magnet behavior.	"…ensure that the return electrode is anatomically positioned so that the current pathway between the diathermy electrode and return electrode is as far away from the pacemaker/defibrillator (and leads) as possible."	Follow-up clinic prescribes postoperative follow-up.	Attempt to follow routine steps; postoperative interrogation is needed as soon as possible. Magnet might create asynchronous pacing.	Magnet might prevent inappropriate discharge.

No recommendations have been published for the leadless intracardiac pacemaker or the subcutaneous ICD.

[a]Recommendations appear relevant only if EMI will be present.

ASA, American Society of Anesthesiologists; *CAS,* Canadian Anesthesiologists Society; *CCS,* Canadian Cardiovascular Society; *CIED,* cardiac implantable electronic device; *CRT,* cardiac resynchronization therapy (any CIED that has both right ventricular– and left ventricular–pacing capability); *ECG,* electrocardiography; *EMI,* electromagnetic interference; *ESU,* electrosurgical unit (*Bovie*); *HRS,* Heart Rhythm Society; *ICD,* implantable cardioverter-defibrillator; *MHRA,* Medicines and Healthcare Products Regulatory Agency; *PM,* pacemaker; *RFA,* radio frequency ablation.

without significant incident, other than an occasional device electrical reset.[16,17] In the United States, TV-PMs manufactured by Biotronik and Medtronic carry "MR Conditional" labeling. Conditions include magnet strength not exceeding 1.5 tesla (T), patient selection criteria, special monitoring requirements, and magnetic resonance (MR) scan limitations. Several companies outside the United States also have conditional MR labeling for both TV-PMs and TV-ICDs. The FDA believes that unconditional or *MR safe* labeling of CIEDs for MR scanning is unlikely.[18] Devices from Medtronic with "MR Conditional" labeling have a unique x-ray identifier (Fig. 5.4H). Pacing-dependent patients remain at increased risk,[19] and most centers will not perform any MRI on a pacing-dependent patient with an ICD.

Pacemakers

Since 1958, more than 3000 pacemaker models have been marketed in the United States alone. Determining the actual number of implants and prevalence of devices is difficult. A variety of economic and market reports suggest that more than 300,000 adults and children in the United States underwent pacemaker placement (new or revision) in 2014. It is likely that well over 3 million patients in the United States have pacemakers today. Many factors lead to confusion regarding the behavior of a device and the perioperative care of a patient with a device, especially since case reports, textbooks, and literature reviews have not kept pace with technologic developments, and many of these reviews contain incorrect statements.[20,21] In addition, sometimes the preoperative consultation process leads to improper advice as well.[22] Furthermore, a patient might have a very old but possibly still functioning pacing system.

Whether a patient with a pacemaker has significant comorbid disease remains to be investigated. However, the care of these patients requires attention to both their medical and psychologic problems. Additionally, an understanding of pulse generators and their likely idiosyncrasies in the surgical unit or procedure room is needed. Whether the patient with a pacemaker is at increased perioperative risk remains unknown, but two reports suggest that these patients deserve extra perioperative attention. In 1995, Badrinath and colleagues[23] retrospectively reviewed ophthalmic surgery cases in one hospital in Madras, India, from 1979 through 1988 (14,787 cases) and wrote that the presence of a pacemaker significantly increased the probability of a mortal event within 6 weeks postoperatively, regardless of the anesthetic technique. In 2008, Pili-Floury and colleagues[24] reported a prospective study of 65 consecutive patients undergoing any anesthetic for any invasive noncardiac procedure unrelated to their device. They found seven (11%) postoperative myocardial infarctions, two (3%) patients developed left ventricular failure, and two (3%) patients died of cardiac causes during their index hospitalization.

No discussion of pacemakers can take place without an understanding of the generic pacemaker code (North American Society of Pacing and Electrophysiology [NASPE]/British Pacing and Electrophysiology Group [BPEG] generic [NBG] code), last updated in 2002.[25] Shown in Table 5.2, the code describes the basic behavior of the pacing device. Pacemakers also come with a variety of terms generally unfamiliar to the anesthesiologist, many of which are shown in the glossary at the end of this chapter.

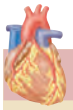
Pacemaker Indications

Common indications for permanent pacing are shown in Box 5.1 and are reviewed in detail elsewhere.[26] Conventional pacing devices have been approved by the FDA for three-chamber pacing (right atrium, both ventricles) to treat dilated cardiomyopathy (DCM),[27,28] (also called biventricular [BiV] pacing or cardiac resynchronization therapy [CRT]). Additionally, specially programmed devices are used to treat hypertrophic obstructive cardiomyopathy (HOCM) in both adults and children.[29,30] BiV pacing and HOCM indications require careful attention to pacemaker programming, since effective pacing in these patients often requires a pacing rate greater than native sinus or junctional escape rate (often accomplished with drugs) and an atrioventricular (AV) delay shorter than the native P-R interval so that the ventricle is paced 100% of the time.[31] Inhibition or loss of pacing (ie, from native conduction, atrial irregularity, ventricular irregularity, development of junctional rhythm, or EMI) can lead to deteriorating hemodynamics in these patients. BiV pacing can lengthen the Q-T interval in some patients, producing torsade de pointes.[32] The newest CRT devices now include a programmable feature that initiates an immediate pace of the other ventricle upon a sensed ventricular event. One significant consequence of this feature is the possibility of inappropriate ventricular pacing in response to EMI.[33] Left atrial or biatrial pacing remains under clinical investigation to prevent atrial fibrillation.[34]

Pacemaker Magnets

Despite often-repeated folklore, most pacemaker manufacturers warn that magnets were never intended to treat pacemaker emergencies or to prevent EMI effects. Rather, magnet-activated switches, both electronic (Hall effect sensor, giant magnetoresistor) and mechanical (reed switch), were incorporated to produce pacing behavior that demonstrates remaining battery life and, sometimes, pacing threshold safety factors. Only rarely will magnet application increase pacing output; consequently, any patient who has an inadequate safety margin for myocardial depolarization might actually be harmed by magnet placement.[1]

Placement of a magnet over a generator might produce no change in pacing since *not all pacemakers switch to a continuous asynchronous mode when a magnet is placed*. The Medtronic "Micra" leadless IC-PM has no magnet sensor. Pacemakers might also be nonresponsive to magnet placement owing to programming (including the default



BOX 5.1 PACEMAKER INDICATIONS

Symptomatic bradycardia from sinus node disease
Symptomatic bradycardia from atrioventricular (AV) node disease
Long QT syndrome
Hypertrophic obstructive cardiomyopathy (HOCM)[a]
Dilated cardiomyopathy (DCM)[a]

[a]See text and Pacemaker Programming for special precautions.

TABLE 5.2 NASPE/BPEG Generic (NBG) Defibrillator Code

Position I	*Position II*	*Position III*	*Position IV*	*Position V*
Pacing Chamber(s)	Sensing Chamber(s)	Response(s) to Sensing	Programmability	Multisite Pacing
O = None	**O** = None	**O** = None	**O** = None	**O** = None
A = Atrium	**A** = Atrium	**I** = Inhibited	**R** = Rate Modulation	**A** = Atrium
V = Ventricle	**V** = Ventricle	**T** = Triggered		**V** = Ventricle
D = Dual (A+V)	**D** = Dual (A+V)	**D** = Dual (T+I)		**D** = Dual (A+V)

BPEG, British Pacing and Electrophysiology Group; *NASPE,* North American Society of Pacing and Electrophysiology,

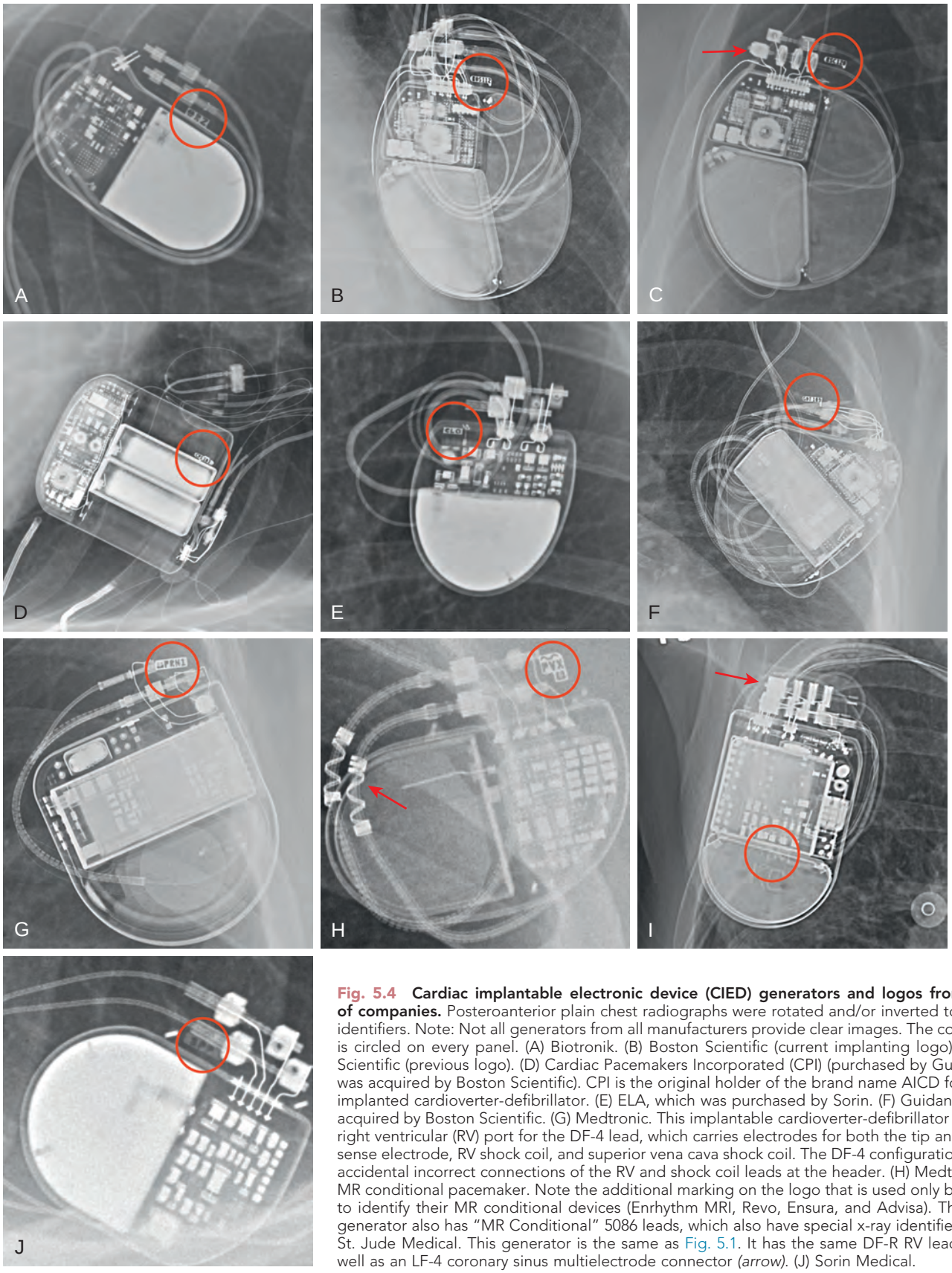
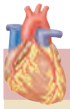


Fig. 5.4 Cardiac implantable electronic device (CIED) generators and logos from a variety of companies. Posteroanterior plain chest radiographs were rotated and/or inverted to show x-ray identifiers. Note: Not all generators from all manufacturers provide clear images. The company logo is circled on every panel. (A) Biotronik. (B) Boston Scientific (current implanting logo). (C) Boston Scientific (previous logo). (D) Cardiac Pacemakers Incorporated (CPI) (purchased by Guidant, which was acquired by Boston Scientific). CPI is the original holder of the brand name AICD for automatic implanted cardioverter-defibrillator. (E) ELA, which was purchased by Sorin. (F) Guidant, which was acquired by Boston Scientific. (G) Medtronic. This implantable cardioverter-defibrillator (ICD) has an right ventricular (RV) port for the DF-4 lead, which carries electrodes for both the tip and ring pace/sense electrode, RV shock coil, and superior vena cava shock coil. The DF-4 configuration eliminates accidental incorrect connections of the RV and shock coil leads at the header. (H) Medtronic Advisa MR conditional pacemaker. Note the additional marking on the logo that is used only by Medtronic to identify their MR conditional devices (Enrhythm MRI, Revo, Ensura, and Advisa). This particular generator also has "MR Conditional" 5086 leads, which also have special x-ray identifiers *(arrow)*. (I) St. Jude Medical. This generator is the same as Fig. 5.1. It has the same DF-R RV lead header, as well as an LF-4 coronary sinus multielectrode connector *(arrow)*. (J) Sorin Medical.



BOX 5.2 PACEMAKER MAGNET BEHAVIOR[a]

- Asynchronous pacing without rate responsiveness using parameters possibly not in the patient's best interest at 85–100 bpm (Asynchronous pacing is the most common behavior except for Biotronik pacemakers. All pacemakers manufactured by Biotronik, Boston Scientific, and St. Jude Medical have programmable magnet behavior.
- Unexpected behavior (eg, VOO pacing in Medtronic or VDD pacing in Biotronik dual-chamber pacemaker), suggesting elective replacement has been reached and the pacemaker should be interrogated promptly
- No apparent rhythm or rate change
- Magnet mode permanently disabled by programming (possible with Biotronik, Boston Scientific, St. Jude Medical) or temporarily suspended (see Medtronic)
- Program rate pacing in the patient who is already paced (many older pacemakers)
- Improper monitor settings with pacing near the current heart rate (pace filter on)
- No magnet sensor (Medtronic Micra leadless pacemaker, some pre-1985 Cordis, Telectronics models)
- Brief (10–100 bpm) asynchronous pacing, then return to program values (most Biotronik and Intermedics pacemakers)
- Continuous or transient loss of pacing
- Inadequate pacing output safety margin with failure to depolarize the myocardium
- Pacemaker enters diagnostic "Threshold Test Mode" (some Intermedics, Medtronic, St. Jude Medical devices, depending on model and programming)
- Discharged battery (some pre-1990 devices)

[a]Also see Appendix 5.1.

mode) or safety mode after an electrical reset from EMI or component failure. Although >90% of pacemakers have high-rate (85 to 100 bpm) asynchronous pacing with magnet application, some respond with only a brief (10 to 100 bpm) asynchronous pacing event, reverting to the original pacing mode and rate thereafter. Box 5.2 provides common magnet behavior for conventional pacemakers, and Appendix 5.1 shows complete magnet results for each manufacturer.

For all generators, calling the manufacturer remains the most reliable method for determining magnet response and using this response to predict remaining battery life. Only rarely can the manufacturer supply the actual custom programming of a device, and manufactures might be unwilling to commit to perioperative care without direct contact with a CIED physician. A list of telephone numbers is provided in Appendix 5.3 at the end of this chapter.

For generators with programmable magnet behavior (Biotronik [Berlin, Germany, US Headquarters Lake Oswego, OR], Boston Scientific, and St. Jude Medical [Syl Mar, CA]), only an interrogation with a programmer can reveal current magnet settings. As Appendix 5.1 shows, pacemaker magnet behavior remains unstandardized and complicated. Nevertheless, one group has published a method to identify the generator manufacturer from the magnet response, assuming completely normal behavior; that is, the device has not undergone elective replacement or a safety reset.[35]

Preanesthetic Evaluation and Pacemaker Reprogramming

Preoperative management of the patient with a pacemaker includes evaluation and optimization of coexisting disease(s). No special laboratory tests or radiographs (chest films are remarkably insensitive for determining most lead problems) are needed for the patient with a pacemaker. Such testing should be dictated by the patient's underlying disease(s), medication(s), and planned intervention. For programmable devices, interrogation with a programmer remains the only reliable method for evaluating lead performance and obtaining current program information. A chest film might be useful to identify the CIED manufacturer (see Fig. 5.4) or to document the position of the coronary sinus (CS) lead in a patient with a BiV pacemaker or defibrillator, especially if central venous catheter placement is planned, since spontaneous CS lead dislodgement was found in more than 11% of patients in early studies[36,37] without much improvement to date.[38] A chest radiograph is certainly indicated for the patient with a device problem discovered during their pacemaker evaluation. Costelloe and associates[39] have published several examples of common defects that can be identified with chest radiography, and Rozner[40] has shown several common presentations of x-ray–identifiable problems.

The prudent anesthesiologist will review the patient's pacemaker history and follow-up schedule. Before its name change to Heart Rhythm Society (HRS), the North American Society of Pacing and Electrophysiology (NASPE) published a consensus statement suggesting that pacemakers should be routinely evaluated with telephone checks for battery condition at least every 3 months. This recommendation also included a comprehensive evaluation (interrogation) at least once a year with additional checks for devices implanted less than 6 or greater than 48 (dual chamber) or 72 (single chamber) months.[41] Updated recommendations continue to include some sort of pacemaker evaluation, whether in person or remote, every 3 to 12 months, depending on the clinical status and needs of the patient.[26,42]Multiple societies recommend against using industry-employed allied professionals without physician review.[43]

The literature contains sparse data about follow-up interval and perioperative patient outcomes. Failure to provide early follow-up after implantation increases the likelihood of death among all CIED patients[44] and TV-ICD patients,[45] whether or not perioperative outcomes are affected by recent versus late or no interrogation can be determined. Nevertheless, two reports suggest that perioperative patients have unmet CIED needs. In a series of 65 patients scheduled for anesthesia, Pili-Floury and colleagues[24] reported the need to reprogram in 12% of patients. In abstract form, Rozner and associates[46] reported a 2-year retrospective review of follow-up intervals in patients with pacemakers who presented for an anesthetic, finding that more than 32% of 172 patients presenting for an anesthetic at their hospital did not meet the HRS/NASPE guideline for comprehensive evaluation. They also reported that 5% of the patients presented for their anesthetic with a pacemaker in need of replacement for battery depletion, and nearly 10% of patients had less-than-optimal pacing settings.

The timing of any preoperative interrogation depends on the local practice and selection of a pacemaker advisory. The American Society of Anesthesiologists (ASA) recommends interrogation within 3 months of the procedure. HRS/ASA, Canadian Anesthesiologists Society (CAS)/Canadian Cardiovascular Society (CCS), and Medicines and Healthcare Products Regulatory Agency (MHRA) recommend review of CIED records and communication with the patient's CIED physician and clinic. For conventional pacemakers, HRS/ASA also recommends interrogation within 12 months of the procedure, shortening that period to 3 to 6 months for CRT devices.[47] Nevertheless, the evaluation of a CIED remains labor intensive, taking approximately 27 minutes in the absence of a problem.[48]

Important features of the preanesthetic device evaluation are shown in Box 5.3. Determining pacing dependency might require temporary reprogramming to a VVI mode with a low rate. In patients from countries where pacemakers might be reused,[49–51] battery performance might not be related to the length of implantation in the current patient. It should also be noted that in a registry of 345 pacemaker generator failures, 7% of failures were not related to battery depletion,[52] and Maisel and colleagues[11] reported a 12-year experience during which pacing systems failed (unrelated to battery depletion) at 0.5% per year.

Appropriate reprogramming (Box 5.4) might be the safest way to avoid intraoperative problems, especially if monopolar Bovie electrosurgery will be used. For lithotripsy, consideration should be given to programming the pacing function out of an atrial-paced mode, as some lithotriptors are designed to fire on the R wave, and the atrial

BOX 5.3 PREANESTHETIC PULSE GENERATOR (PACEMAKER, IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR) EVALUATION

Determining the indication for and the date of initial device placement
Identifying the number and types of leads
Determining the last generator test date and battery status
Obtaining a history of generator events (if any)
Obtaining the current program information (device interrogation)
Ensuring that generator discharges become mechanical systoles with adequate safety margins
Ensuring that magnet detection is enabled
Determining whether the pacing mode should be reprogrammed

BOX 5.4 PACEMAKER REPROGRAMMING PROBABLY NEEDED

Any rate responsive device (Problems are well known,[177,178] problems have been misinterpreted with potential for patient injury,[65,67,179,180] and the FDA has issued an alert regarding devices with minute ventilation [MV] sensors [see Box 5.5 for pacemakers with MV sensors].[73])
Special pacing indication (hypertrophic obstructive cardiomyopathy [HOCM], dilated cardiomyopathy [DCM], pediatric patient)
Pacing-dependent patient
Major procedure in the chest or abdomen
Special Procedures (see Box 5.6)

pacing stimulus could be misinterpreted as the contraction of the ventricle.[53]

Whether CIED manufacturers stand ready to assist with this task or whether this task should be performed by industry-employed affiliated personnel remains controversial (see Appendix 5.3 for company telephone numbers). Reprogramming a pacemaker to asynchronous pacing at a rate greater than the patient's underlying rate usually ensures that EMI will not affect pacing. Reprogramming to asynchronous pacing *will not* protect it from internal damage or reset caused by EMI.

Experts do not agree on the use of asynchronous pacing. Setting a device to asynchronous mode to prevent inappropriate oversensing and ventricular output suppression can cause the CIED to ignore premature atrial or ventricular systoles, which could have the potential to create a malignant rhythm in the patient with significant structural compromise of the myocardium.[54] Reviews by Stone and McPherson,[55] as well as Rozner,[56] and several case reports[57–60] demonstrate inappropriate R-on-T pacing with the development of a malignant ventricular rhythm. Hayes and Strathmore[61] suggest the VVT mode for the pacing-dependent patient, since EMI will generally increase the pacing rate rather than inhibit the pacing output. However, they do not consider the upper pacing rate for this mode. Although some pacemakers (Boston Scientific) limit VVT pacing rates to the maximum tracking rate, others (Medtronic Corporation, Minneapolis, MN) will pace to the lower of the runaway pacing rate (typically around 200 bpm) or the minimum V-V interval defined by the ventricular refractory period, which is typically 200 msec (representing 300 bpm). There are two other caveats for this mode. For the patient with a dual-chamber device and in need of AV synchrony to sustain cardiac output, hemodynamics might be compromised during VVT operation, since ventricular pacing will take place without regard to atrial activity. Additionally, considerable increases and decreases in paced rate could result during EMI if the pacing device does not include rate smoothing. If VVT

BOX 5.5 PACEMAKERS WITH MINUTE VENTILATION (BIOIMPEDANCE) SENSORS

Boston Scientific/Guidant/Cardiac Pacemakers, Inc. (CPI)—All "BSC" labeled (x-ray) pacemakers except CRT-P; Altrua 40 or 60 (S401, S402, S403, S404, S601, S602, S603, S606); Insignia Plus or Ultra (1190, 1194, 1290, 1291, 1297, 1298); Pulsar, Pulsar Max I and II (1170, 1171, 1172, 1180, 1181, 1270, 1272, 1280). Note: Outside the United States "BSC" labeled (x-ray) CRT-P, TV-ICD, and CRT-D have programmable bioimpedance sensor technology.
Sorin (was ELA) Medical—Brio (112, 212, 222); Chorus RM (7034, 7134); Opus RM (4534); Reply DR and SR (no number); Rhapsody (D2410 [outside United States only], DR2530); Symphony (DR2550. SR2250); Talent (113, 133, 213, 223, 233). Outside US pacemakers with minute ventilation sensor technology also includes Kora MR Conditional (100DR, 100 SR) and Reply 200 (DR, SR).
Medtronic—Kappa 400 series (KDR401, KDR403, KSR401, KSR403)
Telectronics/St. Jude—Meta (1202, 1204, 1206, 1230, 1250, 1254, 1256); Tempo (1102, 1902, 2102, 2902)

CRT-D, Cardiac resynchronization therapy with defibrillation capability; *CRT-P*, cardiac resynchronization therapy pacing; *TV-ICD*, transvenous implantable cardioverter-defibrillator.

reprogramming is to be considered, then the manufacturer should be contacted regarding programming for the upper rate.

In general, rate responsiveness and other enhancements (eg, hysteresis, sleep rate, AV search) should be disabled by programming, since many of these can mimic pacing system malfunction (Fig. 5.5).[62–65] Mechanisms to reduce or prevent RV pacing, present in both pacemakers and TV-ICDs, include algorithms that allow dropped QRS events or demonstrate profound second-degree Mobitz I block (RhythmiQ, Boston Scientific; Managed Ventricular Pacing, Medtronic; Ventricular Intrinsic Preference, St. Jude Medical; AAISafeR, Sorin).

Note that for many CPI-logo Boston Scientific devices, the physician's manual recommends increasing the pacing voltage to "5 volts or higher" in cases in which the monopolar ESU unit will be used. In 1986, Levine and associates[66] noted an increase in the amount of energy required to pace the ventricle (ie, a pacing threshold increase) in the setting of intrathoracic surgery and monopolar ESU use. Both Pili-Floury and colleagues[24] and Rozner and associates[46] have reported increases in atrial (Rozner only) and ventricular (both reports) pacing thresholds after surgeries involving pacemaker (but not TV-ICD) cases in which monopolar ESU was used, large volume and blood shifts were observed, or both. Although many of the surgeries were thoracic explorations, no pacing threshold changes were noted for these cases. No cardiopulmonary pump cases were reviewed in these cohorts.

Special attention must be given to any device with a minute ventilation (bioimpedance) sensor (Box 5.5), since inappropriate tachycardia, sometimes with treatment leading to patient injury, has been observed secondary to mechanical ventilation,[67,68] monopolar Bovie ESU,[67,69,70] and connection to an electrocardiographic (ECG) monitor with respiratory rate monitoring.[71–73]

Intraoperative (or Procedure) Management

No special monitoring or anesthetic technique is required for the patient with a pacemaker. However, monitoring of the patient must include the ability to detect mechanical systoles, since EMI, as well as devices such as a nerve stimulator, can interfere with QRS complex and pacemaker spikes on the ECG.[74] To demonstrate pacing pulses, most ECG monitor filtering must be changed to eliminate or reduce high-frequency filtering. However, the Medicines and Healthcare Products Regulatory Agency (MHRA) cautions that ECG monitors can misinterpret these pacing artifacts as QRS complexes and therefore display a

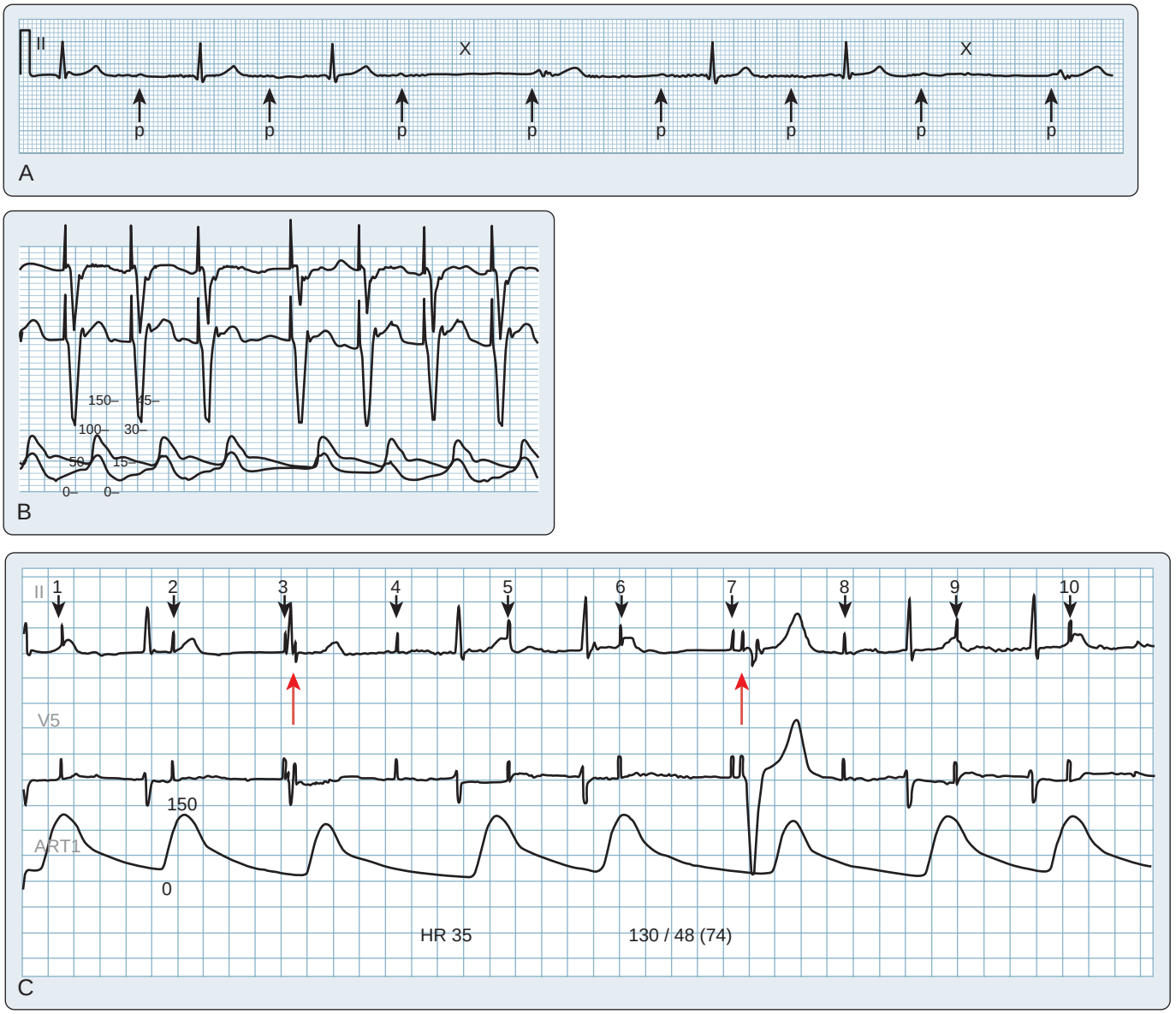


Fig. 5.5 (A) The feature "managed ventricular pacing" mimics pacing system malfunction. This patient has a sinus rate of 50 bpm and a native PR interval of nearly 500 msec. Her Medtronic pacing device was set to AAIR-DDDR (called *managed ventricular pacing* [MVP]), which does not pace the ventricle in response to an atrial event until a native QRS is not conducted (dropped). The next atrial event will be followed by an immediate (60 msec) paced QRS. This figure shows two such events *(X)* after the third and seventh P waves. The subsequent paced QRS morphologic axis is nearly orthogonal to the sensing axis, which is labeled (but might not actually be) lead 2, depending on the placement of the actual leads. MVP does not permit two consecutive dropped QRS events, and if two of any four QRS events are dropped, then the pacing device paces in DDD mode for at least 1 minute before resuming MVP. However, since oversensing from monopolar electrosurgery can convince a pacing device that ventricular systoles are present, a patient with atrioventricular (AV) nodal disease undergoing surgery with monopolar electrosurgery could demonstrate many dropped QRS events. (B) The feature "search hysteresis" mimics pacemaker malfunction. This patient has a single chamber VVI pacemaker set to a lower rate of 70 bpm. It was placed for complete AV block. This programmable feature causes the pacemaker to delay pacing every 256th event for 1400 msec (equal to a rate of 50 bpm). This delay in pacing is shown between the third and fourth QRS complexes. From top to bottom, the tracings are Lead II, Lead V_5, the invasive arterial pressure, and the central venous pressure. Hysteresis (where the pacemaker delays pacing after an intrinsic event) and Search Hysteresis often confuse caregivers regarding pacemaker malfunction (called *pseudomalfunction*). This electrocardiographic tracing could also result from ventricular oversensing, usually related to the T wave. (C) This strip from an implantable cardioverter-defibrillator (ICU) bedside monitor (GE Medical, Hartford, CT) demonstrates typical monitor misreporting of heart rate in the setting of pacing. In this case, the perfused heart rate is approximately 55 bpm, but the monitor has recorded a bradycardia alarm at 35 bpm. This patient also has a profound first-degree AV block, second-degree heart block Mobitz type I (Wenckebach), and pacing system pseudomalfunction owing to managed ventricular pacing (as in A). The third P pace *(numbered down arrows)* occurred without an intervening QRS from the prior P pace, which caused the MVP mechanism to emit a ventricular pace *(up arrows)*. However, the postatrial ventricular blanking caused the pacemaker to functionally undersense the native QRS. To prevent R-on-T pacing, Medtronic MVP issues the backup ventricular pulse 60 msec after the atrial event. No QRS occurred after P pace #6; consequently, another MVP 60 msec sequence was emitted at P pace 7. In this event, the right ventricular pace depolarized the right ventricle. The atrial pace on the QRS at P wave pace #3 is called *pseudo-pseudo fusion pacing*.

nonzero heart rate for an asystolic patient.[7] Mechanical systoles are best evaluated by pulse oximetry, plethysmography, or arterial waveform display; at least one of these monitoring modalities is recommended for these cases by both ASA and HRS/ASA advisories.[10,47] Fig. 5.5C shows underreporting of the ECG heart rate in a paced patient.

Some patients might need an increased pacing rate during the perioperative period to meet an increased oxygen demand. Although many modalities currently exist to evaluate myocardial oxygen delivery, none have been systematically tested in pacing patients.

With respect to anesthetic technique, no studies have championed one technique over another. Nevertheless, a number of reports of prolongation of the QT interval with the use of isoflurane or sevoflurane have been published. Halothane appears to reduce this interval.[75–79] No interactions have been reported for enflurane or desflurane. Drugs such as high-dose opiates and dexmedetomidine suppress underlying rhythms, possibly rendering a patient pacing dependent and reducing any margin of safety for pacing system failure.

Monopolar Bovie ESU use remains the principal intraoperative issue for the patient with a pacemaker. For the 12 years ending in 1997, the FDA was notified of 456 adverse events with pulse generators, 255 from ESU, and a "significant number" of device failures. Although this FDA User Facility Reporting Bulletin is no longer available, EMI from monopolar ESU likely remains the most common form of medically induced EMI in the hospital environment. Monopolar ESU is more likely to cause problems than bipolar ESU, and patients with unipolar electrode configuration are more sensitive to EMI than those with bipolar configurations. Coagulation ESU will likely cause more problems than nonblended "cutting" ESU.[80,81] Additionally, the dispersive electrode should be placed such that the presumed current path from the hand tool to the electrode does not cross the chest.[80] No data have been published regarding the safety of a whole-body dispersive electrode.

Spurious reprogramming of any CIED manufactured after 1995 from EMI should be nearly impossible, but strong EMI can produce an electrical reset or inappropriate detection of battery depletion, which might change the programming mode and/or rate. If monopolar ESU is to be used, then the dispersive electrode should be placed to ensure that the presumed current path does not cross the pacemaker system. For cases such as head and neck surgery, the electrode might be best placed on the shoulder contralateral to the implanted device. For breast and axillary cases, the electrode might need to be placed on the ipsilateral arm with the wire prepped into the field by a sterile plastic cover. Procedures with special pacing ramifications are shown in Box 5.6.

The use of an ultrasonic cutting device, commonly called a *harmonic scalpel*, has been championed to prevent EMI while providing the surgeon with the ability to cut and to coagulate tissue. A number of case reports have demonstrated successful surgery without EMI issues in these patients.[82–85]

MRI deserves special mention. In general, MR examinations have been contraindicated in patients with a pacemaker or TV-ICD.[86,87] However, a landmark paper showing that MRI could be safely conducted in some patients has led to the performance of MRI evaluations in these patients,[88] and several centers throughout the world perform MR scanning as an off-label procedure.[16] Nevertheless, not all MR sequences and energy levels have been studied; therefore judicious monitoring and caution are advised, and the FDA is unlikely to permit unlimited and unmonitored MR examinations.[18,89] Both Medtronic (Enrhythm MRI, Revo, Ensura, Advisa) and Biotronik (Entovis, Eluna) currently manufacture pacemaker systems with MR conditional labeling in the United States. Several manufacturers have "MR Conditional" devices in clinical trial and devices labeled for MR examinations in countries outside the United States.

Pacemaker Failure

Pacemaker failure has three causes: (1) failure of capture, (2) lead failure, or (3) generator failure. Failure of capture attributable to a defect at the level of the myocardium (ie, the generator continues to fire but no myocardial depolarization takes place) remains the most difficult problem to treat. Myocardial changes that result in noncapture include myocardial ischemia or infarction, acid-base disturbances, electrolyte abnormalities, or abnormal levels of antiarrhythmic drug(s). Temporary pacing—transvenous, transcutaneous, transthoracic, or transesophageal—might inhibit pacemaker output at voltages that will not produce myocardial capture.[90] Sympathomimetic drugs generally lower pacing threshold. Outright generator and lead failures are rare.

BOX 5.6 SPECIAL PROCEDURES IN PATIENTS WITH IMPLANTABLE GENERATORS

Lithotripsy. Is acceptable with precautions to protect the generator and, possibly, with programming out of an atrial pacing mode.[53]

Transurethral resection and uterine hysteroscopy. Procedures using monopolar electrosurgery can be easily accomplished after device reprogramming.

Magnetic resonance imaging (MRI). Several companies have MRI conditional labeling for transvenous pacemakers (TV-PMs) (inside and outside of the United States), as well as transvenous implantable cardioverter-defibrillators (TV-ICDs) (outside of the United States only). MRI examinations in any patient with a cardiac implantable electronic device (CIED) requires special personnel capable of rhythm interpretation and immediate CIED reprogramming, as well as monitoring equipment capable of providing electrocardiographic (ECG) and pulse oximeter plethysmographic monitoring from inside the magnetic resonance suite. Patient selection is limited, and most centers currently refuse pacing-dependent patients with implantable cardioverter-defibrillators (ICDs).

Electroconvulsive therapy. This therapy possibly requires asynchronous (nonsensing) pacing mode.[181]

Nerve stimulator testing and therapy. Inappropriate detection of transcutaneous electrical nerve stimulation (TENS), as well as neuromuscular and chiropractic electrical muscle stimulation, as ventricular tachycardia or ventricular fibrillation has been reported.[182,183]

Temporary Pacemakers

Several techniques are available to the anesthesiologist to establish reliable temporary pacing during the perioperative period or in the intensive care unit.[91] Cardiovascular anesthesiologists are more likely than generalists to routinely used temporary transvenous or epicardial pacing in their practices. Temporary cardiac pacing can serve as definitive therapy for transient bradyarrhythmias or as a bridge to permanent generator placement.

The various forms of temporary pacing include many transvenous catheter systems, transcutaneous pads, transthoracic wires, and esophageal pacing techniques. This section reviews the indications for temporary cardiac pacing and discusses the techniques available to the anesthesiologist. Many of the references in this section are old, since temporary pacing is an old technique and not many advances have taken place in the past 10 to 15 years. Table 5.3 summarizes these techniques.

Regardless of temporary modality, most implantable pacemakers or ICDs need to be reprogrammed when placing a transvenous pacing device. Electrical energy entering the body from a temporary pacing device can be sensed by the permanent device on the atrial lead, the ventricular lead, or both. Energy sensed on a ventricular lead can result in an inappropriate shock from any ICD or pacing inhibition from a pacemaker or TV-ICD. Pacing inhibition in a pacing-dependent patient will produce asystole. If energy enters the CIED on the atrial lead in a dual-chamber device, then rapid ventricular pacing might result (intrinsic atrial rate plus temporary atrial rate). The CIED might

TABLE 5.3 Comparison of Temporary Pacing Techniques

Temporary Pacing Method	*Time to Initiate*	*Chambers Paced*	*Advantages*	*Disadvantages*	*Uses*
Transcutaneous	1–2 minutes	Right ventricle	Simple, rapid, safe	Variable capture, chest wall movement, patient discomfort	Arrest, intraoperative, prophylactic
Transesophageal	Minutes	Left atrium	Reliable atrial capture, safe, simple	Requires special generator	Prophylactic atrial pacing, overdrive pacing for supraventricular tachyarrhythmias, monitoring atrial electrogram
Transvenous semirigid	3–20 minutes	Atrium and/or ventricle	Most reliable, well-tolerated	Invasive, time consuming, potential complications	Arrest, prophylactic, maintenance
Transvenous flow-directed	3–20 minutes	Right ventricle	Simple, does not require fluoroscopy	Invasive, stability questions, less readily available	Arrest, intraoperative, prophylactic, maintenance
Pacing pulmonary artery catheter (PAC)	Minutes (if PAC is in place)	Atrium and/or ventricle	Reliable ventricular capture, well-tolerated	Requires specific PAC, which must be placed first	Arrest, intraoperative, prophylactic, maintenance
Epicardial pacing Wires	<1 minute	Atrium and/or ventricle	Reliable short-term	Postoperative only, early lead failure	Arrest, prophylactic, maintenance
Transthoracic	10-60 seconds	Ventricle	Rapid and simple	Many potential complications	Arrest only

detect an atrial arrhythmia condition, resulting in ventricular pacing only, which might produce untoward hemodynamic effects.

Temporary Pacing Generator

Several companies market a variety of single- and dual-chamber temporary external pacing generators. Many dual-chamber generators permit AV programming that might not be in the best interest of the patient, and these inappropriate parameters might be accepted without warning by the generator.[58] For example, a commonly practiced, but clearly off-label use, involves the programming of a dual chamber (ie, DDD) pacing mode in a system with no functional atrial lead. Because the generator cannot detect the lack of an atrial lead, it will issue an atrial pacing stimulus when deemed appropriate. During the period of postatrial ventricular blanking, the generator cannot sense on the ventricular lead while pacing on the atrial lead; consequently, any spontaneous ventricular event taking place within 20 to 60 msec of the atrial pace will not be sensed. As a result, a ventricular stimulus will be delivered approximately 200 msec later, creating an R-on-T pace that can initiate ventricular tachycardia (VT).[57]

Indications for Temporary Pacing

Temporary pacemakers are commonly used after cardiac surgery[92] in the treatment of drug toxicity resulting in arrhythmias, with certain arrhythmias complicating myocardial infarction, and for intraoperative bradycardia attributable to beta blockade. On occasion, the placement of a temporary pacing system can assist in hemodynamic management in the perioperative period. Abnormal electrolytes, preoperative beta-blocker use, and many of the intraoperative drugs have the potential to aggravate bradycardia and bradycardia-dependent arrhythmias.[93] Because drugs used to treat bradyarrhythmias have a number of important disadvantages compared with temporary pacing, hemodynamically unstable perioperative bradyarrhythmias should be considered an indication for temporary pacing (Table 5.4). If the patient already has epicardial wires or a pacing catheter or wires, or transesophageal pacing is feasible, then pacing is preferred to pharmacologic therapy. However, transcutaneous and ventricular-only transvenous pacing, even if feasible, may exacerbate hemodynamic problems in patients with heart disease, because these pacing modalities do not preserve AV synchrony (ie, produces ventricular or global activation).

Nearly every indication for a permanent pacemaker is an indication for temporary pacing in patients without a pacemaker who, because of circumstances (eg, emergency surgery, critical illness) cannot have elective permanent pacemaker implantation. Temporary pacing may also be needed before the implantation of a permanent pacemaker to stabilize patients with hemodynamically significant ventricular bradycardia.

TABLE 5.4 Temporary Pacing Indications

Patient Condition	*Event Requiring Temporary Pacing*
Acute myocardial infarction (AMI)	Symptomatic bradycardia, medically refractory New bundle branch block with transient complete heart block Complete heart block Postoperative complete heart block Symptomatic congenital heart block Mobitz II with AMI New bifascicular block Bilateral bundle branch block and first-degree AV block Symptomatic alternating Wenckebach block Symptomatic alternating bundle branch block
Tachycardia treatment or prevention	Bradycardia-dependent VT Torsade de pointes Long QT syndrome Treatment of recurrent supraventricular tachycardia or VT
Prophylactic	Pulmonary artery catheter placement with left bundle branch block (controversial) New AV block or bundle branch block in acute endocarditis Cardioversion with sick sinus syndrome Postdefibrillation bradycardia Counteract perioperative pharmacologic treatment causing hemodynamically significant bradycardia AF prophylaxis postcardiac surgery Postorthotopic heart transplantation

AF, Atrial fibrillation; AV, atrioventricular; *VT,* ventricular tachycardia.

Temporary pacing is also indicated if a patient with a myocardial infarction complicated by second- or third-degree heart block is scheduled for emergency surgery. Bifascicular block in an asymptomatic patient is not reason enough for temporary pacing preoperatively.[94] Bellocci and colleagues[95] reported no occurrence of complete heart block in 98 patients with preoperative bifascicular block undergoing general anesthesia, despite 14% having prolonged conduction through their His-Purkinje system. The development of new bifascicular block preoperatively, though, suggests perioperative myocardial ischemia or infarction, and temporary pacing might be required. Surgical resection of neck and carotid sinus tumors may give rise to bradyarrhythmias, which require temporary cardiac pacing during surgical manipulation. Neurosurgical procedures involving the brainstem may also be associated with significant bradycardia.

Temporary antitachycardia pacing (ATP) is most commonly used after cardiac surgery.[96] With increased availability of effective noninvasive pacing technology, ATP might be offered to other perioperative patients as well. Even when used properly, these techniques can induce more dangerous arrhythmias, and proper resuscitation equipment should be available.

Atrioventricular junctional tachycardia (AVJT) can occur after cardiopulmonary bypass, during which it could be a manifestation of reperfusion injury or possibly inadequate myocardial protection during the pump run. AVJT does not respond well to most drug therapy, although its rate (≤120 bpm in adults) may be slowed by β-adrenergic blockers or edrophonium. AVJT is best managed by atrial or AV-sequential overdrive pacing, because both of these modalities will preserve AV synchrony. Frequently, sinus rhythm resumes upon withdrawal of temporary pacing.

Most sudden-onset paroxysmal supraventricular tachycardia (PSVT) is initiated by a premature beat, which could be of atrial, AV junctional, or ventricular in origin. PSVT may be terminated by competitive, atrial "underdrive" pacing (paced rate < PSVT rate) if, by chance, an atrial capture beat interferes with the circulating wavefront perpetuating the tachycardia. By contrast, with overdrive pacing, PSVT is paced at a rate 10% to 15% in excess of the tachycardia rate until there is evidence of 1:1 capture with paced beats. Pacing is continued at this rate for 20 to 30 seconds, then gradually slowed to some predetermined rate, and finally terminated. As with all pacing modalities, a gradual reduction in pacing rate is recommended to reduce the risk of prolonged asystole when pacing is terminated in patients known to have sinus node dysfunction. If pacing fails to terminate PSVT, or PSVT produces circulatory collapse, then immediate direct current cardioversion is recommended.

Type I atrial flutter (flutter rate less than 320 to 340 bpm) is pace terminable, but type II flutter (more than 340 bpm) is not. Type I flutter is treated by atrial overdrive pacing at a rate 15 to 20 beats more than the flutter rate, which is increased by 10 to 20 bpm amounts if the first attempt is not successful. Once atrial capture is evident, pacing is continued for 20 to 30 seconds, and then slowed as for PSVT. Usually, overdrive pacing, with prompt restoration of normal sinus rhythm, can terminate type I atrial flutter.

Relative contraindications to transvenous ventricular pacing include digitalis toxicity with VT, tricuspid valve prostheses, or the presence of a coagulopathy. Pacing in the setting of severe hypothermia might induce ventricular fibrillation (VF) or alter the normal compensatory physiologic mechanisms to the hypothermia, although one prospective study in dogs using transcutaneous pacing suggests that pacing decreases rewarming time.[97] Atrial fibrillation, multifocal atrial tachycardia, and significant AV conduction system disease are relative contraindications to transvenous *atrial* pacing.

Transvenous Temporary Pacing

Transvenous cardiac pacing provides the most reliable means of temporary pacing. Temporary transvenous pacing is dependable and well-tolerated by patients. With a device that can provide both atrial and ventricular pacing, transvenous pacing can maintain AV synchrony and improve cardiac output. Disadvantages include the need for practitioner experience, time to place the wire(s) appropriately to provide capture, the potential complications of catheter placement and manipulation, and the need for fluoroscopy in many cases. Three different types of typical transvenous leads are shown in Fig. 5.6.

Rapid catheter position is most easily obtained by using the right internal jugular vein, even without fluoroscopy,[98] although a prudent practitioner might want to document the final position(s) of the catheters clearly. The left subclavian vein is also easily used in emergent situations. Other sites are often impassable without fluoroscopy. In addition, brachial and femoral routes can increase the frequency of lead dislodgments during motion of the extremities, especially during patient transport.

Once central access is obtained, the lead is guided into position using hemodynamic data (not possible with the simple bipolar lead catheter) or by fluoroscopic guidance. ECG guidance is less desirable. The right atrial appendage and RV apex provide the most stable catheter positions. Techniques for placement into these positions are part of cardiology training and are likely foreign to most anesthesiologists. When fluoroscopy is unavailable or in emergency situations, a flow-directed catheter can be attempted using ECG guidance. Once the right ventricle is entered, the balloon is deflated, if used, and the catheter is gently advanced until electrical capture is noted. Flow-directed catheters and a right internal jugular approach afford the shortest insertion times.[99] The reported incidence of successful capture in urgent situations without fluoroscopy ranges from 30% to 90%.[98,100,101]

Once catheters are positioned, pacing is initiated using the distal electrode as the cathode (negative terminal) and the proximal electrode as the anode (negative terminal). Ideally, the capture thresholds should be less than 1 mA and generator output should be maintained at three times threshold as a safety margin. In dual-chamber pacing, AV delays between 100 and 200 msec are used. Many patients are sensitive to this parameter. Cardiac output optimization with echocardiography and/or mixed venous oxygen saturation can be used to maximize hemodynamics when adjusting AV delay.[102] AV sequential pacing is clearly beneficial in many patients,[102–106] but starting emergency pacing with *ventricular* capture alone should be remembered. Interference of external pacemaker generators by walkie-talkies and cellular digital phones is a potential risk.[107,108] Radiofrequency scanning systems used to identify retained surgical material can interfere with pacing,[109,110] and some manufacturers recommend reprogramming to an asynchronous pacing mode. Clinicians should also be aware of all complications related to transvenous lead placement.[111]

Pacing Pulmonary Artery Catheters

The pulmonary artery AV-pacing thermodilution catheter (see Fig. 5.6C) was described by Zaidan[112] in 1983. It allows for AV-sequential pacing via electrodes attached to the outside of the catheter, as well as routine pulmonary artery catheter (PAC) functions. The combination of the two functions into one catheter eliminates the need for separate insertion of temporary transvenous pacing electrodes. However, several potential disadvantages exist with this catheter including: (1) varying success in initiating and maintaining capture,[112] (2) external electrode displacement from the catheter,[113] and (3) relatively high cost as compared with standard PACs. The Paceport PAC (see Fig. 5.6B) provides ventricular pacing with a separate bipolar pacing lead (Chandler probe), which allows for more stable ventricular pacing and hemodynamic measurements.[114] This catheter has been used for successful resuscitation after cardiac arrest during closed chest cardiac massage when attempts to capture with transcutaneous or transvenous flow-directed bipolar pacing catheters have failed. However, this unit does not provide the potential advantages associated with atrial pacing capability. The pulmonary artery AV Paceport adds a sixth lumen to allow the placement of an atrial J-wire, flexible tip bipolar pacing lead. Both of these Paceport catheters are placed by transducing the RV port to ensure correct positioning of the port 1 to 2 cm distal to the tricuspid valve. This position usually guides the ventricular wire (Chandler probe) to the apex where adequate capture should occur with minimal current requirements. Although ventricular capture is easily obtained, atrial capture can be more difficult and less reliable.[102] This catheter has been successfully used after cardiac surgery.[102,115] The atrial wire can be used to diagnose supraventricular tachyarrhythmias (SVTs) by atrial electrograms and to overdrive atrial flutter and reentrant SVTs.[116]

Transcutaneous Pacing

Transcutaneous pacing, first described by Zoll,[117] is readily available and can be rapidly implemented in emergency situations. Capture rate is variable, and the technique may cause pain in awake patients, but it is usually tolerated until temporary transvenous pacing can be instituted. It may be effective even when endocardial pacing fails.[118] Transcutaneous pacing continues to be the method of choice for prophylactic and emergent applications.[119]

Typically, the large patches are placed anteriorly (negative electrode or cathode) over the palpable cardiac apex (or V_3 lead location) and posteriorly (positive electrode or anode) at the inferior aspect of the scapula. The anode has also been placed on the anterior right chest with success in healthy volunteers.[120] The skin should be cleaned with

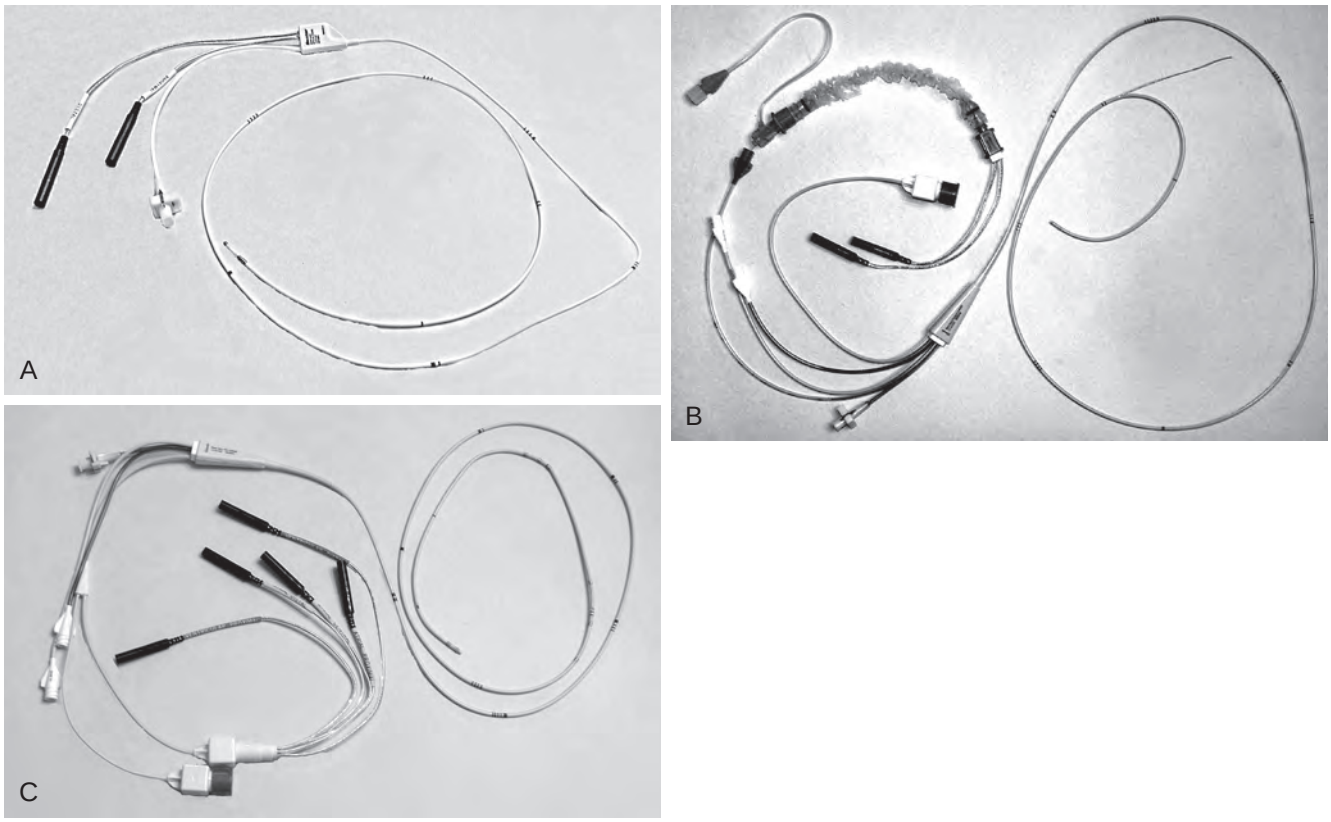


Fig. 5.6 A variety of transvenous pacing leads. (A) A simple, flow-directed, bipolar pacing wire is placed through a 6F introducer sheath and is advanced (usually under fluoroscopy) into the atrium or ventricle until mechanical systoles result from the electrical pacing event (called *pacing capture*). The principle disadvantage of this lead is the lack of hemodynamic measurements to guide placement. (B) A specially adapted pulmonary artery catheter (PAC) is shown with a channel for a bipolar, ventricular pacing wire. The bipolar pacing wire, side-port adapter, and condom are packaged separately from the PAC. Note that the electrode is protruding from its orifice just distal to the 20-cm mark on the PAC. (C) An atrioventricular (AV)–capable, pacing PAC is shown. Five electrodes are present: two for ventricular pacing and three for atrial pacing. This catheter is positioned to provide adequate ventricular capture, after which atrial pacing is attempted using two of the three atrial electrodes. Sometimes, the entire PAC must be repositioned to obtain atrial capture. In the setting of a functioning AV node, the presence of a narrow complex QRS after the atrial pace can determine atrial capture. In the setting of a significant AV block, atrial capture can be difficult to assess.

alcohol (but not abraded) to reduce capture threshold and improve patient comfort. Abraded skin can cause more discomfort. Typical thresholds are 20 to 120 mA, but pacing may require up to 200 mA at long pulse durations of 20 to 40 msec.[121] Transcutaneous pacing appears to capture the right ventricle, followed by near simultaneous activation of the entire left ventricle. The hemodynamic response is similar to that of RV endocardial pacing. Both methods can cause a reduction in left ventricular systolic pressure, a decrease in stroke volume, and an increase in right-sided pressures attributable to AV dyssynchrony. Palpation or display of a peripheral pulse should confirm capture. Maintenance current should be set at least 5 to 10 mA above threshold as tolerated by the patient. Success rates appear to be highest when the system is used prophylactically or early after arrest—upward of 90%.[122,123] When used in emergent situations, successful capture rates are usually lower but range from 10% to 93%.[124–126] This technique has also been used to terminate VT, AV nodal reentrant tachycardia, and AV-reciprocating tachycardia.[126,127]

Coughing and discomfort from cutaneous stimulation are the most frequent problems. The technique poses no electrical threat to medical personnel, and complications are rare. There have been no reports of significant damage to myocardium, skeletal muscle, skin, or lungs in humans, despite continuous pacing up to 108 hours and intermittent pacing up to 17 days.[117,122,128] Several commercially available defibrillators include transcutaneous pacing generators as standard equipment.

Esophageal Pacing

Another technique available to anesthesiologists is esophageal atrial pacing (EAP), and it has been shown to be quite reliable,[128–131] even in children.[132] However, EAP requires a functional, intact atrium and AV node; thus this modality should not be used in the patient with paroxysmal or persistent atrial fibrillation. EAP is relatively noninvasive and well-tolerated, even in the majority of awake patients, and it appears to be devoid of serious complications. This modality is useful for heart rate support of cardiac output, overdrive suppression of reentrant SVT, and for diagnostic atrial electrograms. Ventricular capture must be excluded before attempts at rapid atrial pacing for overdrive suppression to prevent potential VT or VF. Some surgical positions (eg, three-quarter prone) can increase the chance of unintentional ventricular capture.[133]

Problems with esophageal pacing include: (1) the necessity for special generators that must provide 20 to 30 mA of current with wide pulse widths of 10 to 20 msec, and (2) the ability to pace only the left atrium reliably and not the left ventricle, which can be a significant problem in emergency situations.[129] By comparison, typical temporary

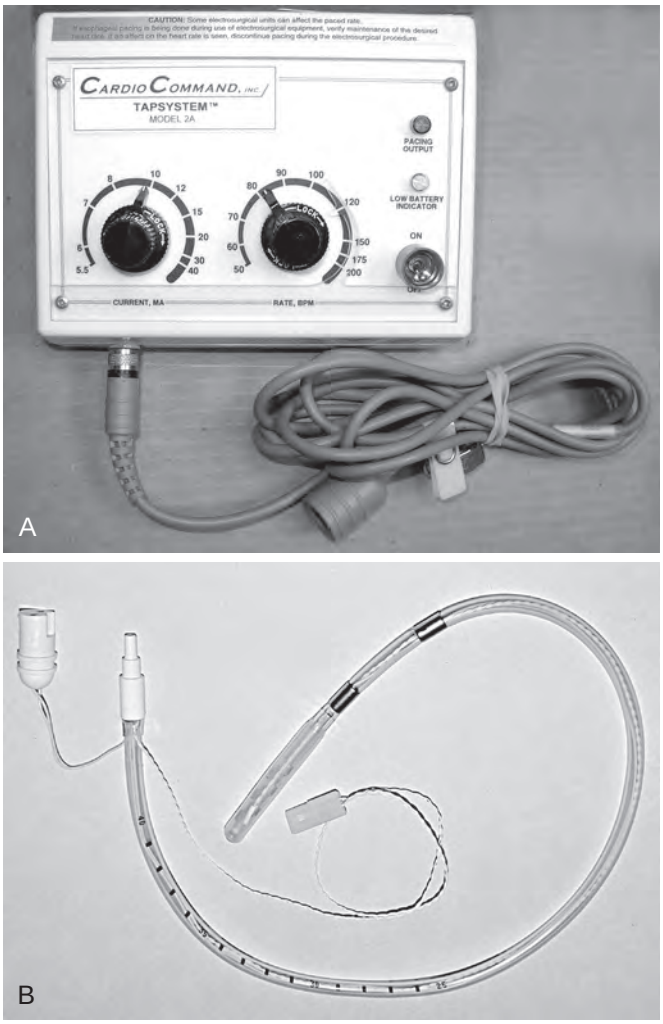


Fig. 5.7 A typical transesophageal pacing generator (A) and esophageal stethoscope with bipolar electrodes (B) are shown. The esophageal stethoscope is placed between 30 and 40 cm from the teeth, and pacing is initiated at a rate greater than the patient's native heart rate using an output setting of at least 20 mA. An increase in peripheral pulse rate determines atrial capture. Detection of capture using only electrocardiographic monitoring can be difficult to discern, as the pacing impulse from these generators produces a large artifact and often distorts the surface electrocardiogram.

generators designed for endocardial pacing have a maximum output of 20 mA with pulse width durations of only 1 to 2 msec.

A typical transesophageal pacing generator and lead are shown in Fig. 5.7. As noted in the figure, the pacing stimulus is delivered in asynchronous atrial-only mode through a modified esophageal stethoscope. AOO pacing is initiated by connecting the system and placing the esophageal stethoscope to a depth of 30 to 40 cm from the teeth. Capture should be confirmed using the peripheral pulse (ie, from the pulse oximeter, plethysmogram, or an invasive hemodynamic monitor) since the pacing stimulus is often large, relative to the QRS, and frequently fools the ECG counting algorithm on the monitor (Fig. 5.8). Atrial capture is obtained in virtually all patients using outputs of 8 to 20 mA, and the output should be set to two to three times the threshold for capture. Thresholds are not influenced by weight, age, atrial size, or previous cardiac surgery.[131]

Transesophageal *ventricular* pacing is generally unreliable, yet the optimal site appears to be 2 to 4 cm distal to the atrial site.[134] The esophageal pacing instrument can also be used (with a special adapter) to record the intraatrial electrogram.

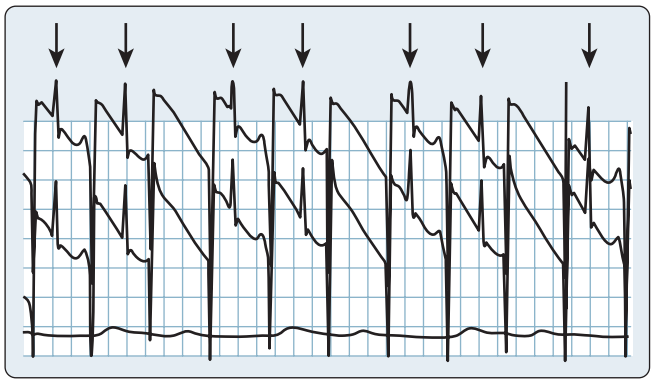


Fig. 5.8 An electrocardiographic strip from a patient with a transesophageal pacemaker demonstrates atrial capture and Wenckebach second-degree atrioventricular nodal block. An 84-year-old man with coronary artery disease and taking atenolol developed a sinus bradycardia (rate 37 bpm) with hypotension during a general anesthetic for transurethral bladder resection. An esophageal pacemaker was placed, and the rate was set to 85 bpm (AOO pacing mode). The top two tracings are electrocardiographic leads II and V5. The downward depolarization artifacts are the pacing stimuli from the esophageal pacemaker (15-mA output). The upward depolarization events are the QRS inscriptions *(downward arrows)*. Atrial P waves can be found shortly after the esophageal pulse. Note the lengthening PR interval with the dropped ventricular depolarizations. Also note how distorted the electrocardiographic signal becomes in the setting of an esophageal pacemaker. The third tracing is the pulse oximeter plethysmographic waveform. The small graticules (representing the 40-msec time points) and the monitor text were digitally removed from this strip to increase the contrast.

No long-term complications with this modality have been described. Induction of ventricular tachyarrhythmias during rapid atrial pacing has been noted. No significant esophageal trauma has been reported, despite long-term therapy of up to 60 hours.[135] Phrenic nerve stimulation has been described.[130]

Transthoracic Pacing

Transthoracic pacing has been used for over 35 years and involves the direct introduction of a pacing wire or needle through the thorax into the ventricular cavity. Several commercial kits are available, and even the use of a spinal needle has been described. The technique is rapid, simple, and does not require venous access or fluoroscopy. In contrast to other temporary pacing modalities, a large potential for misadventure exists and no study demonstrates any benefit in survival. Transcutaneous techniques have supplanted this procedure in essentially all situations.

Postanesthesia Pacemaker Evaluation

Any pacemaker that has been reprogrammed for the perioperative period should be reevaluated and programmed appropriately. For nonreprogrammed devices, most manufacturers recommend interrogation to ensure proper functioning and remaining battery life if any monopolar ESU was used. The ASA advisory recommends interrogation before discharging the patient from monitored care,[10] whereas the HRS/ASA statement suggests that immediate postoperative interrogation is needed only for hemodynamically challenging cases or when significant EMI occurs superior to the umbilicus while operating.[47]

Whether a patient with a pacemaker needs a postoperative evaluation continues to generate controversy. In their retrospective review, Trankina and colleagues[136] reported 6% of 169 patients showed a problem during postoperative checks of pacemakers. Senthuran and associates[137] suggested that failure to perform a postoperative pacemaker check led to an unexpected postoperative death in Great Britain, and both Pili-Floury and colleagues[24] and Rozner and associates[46]

TABLE 5.5 NASPE/BPEG Generic (NBG) Defibrillator Code

Position I: Shock Chamber(s)	*Position II: Antitachycardia Pacing Chamber(s)*	*Position III: Tachycardia Detection*	*Position IV: Antibradycardia Pacing Chamber(s)*
O = None	**O** = None	**E** = Electrogram	**O** = None
A = Atrium	**A** = Atrium	**H** = Hemodynamic	**A** = Atrium
V = Ventricle	**V** = Ventricle		**V** = Ventricle
D = Dual (A+V)	**D** = Dual (A+V)		**D** = Dual (A+V)

BPEG, British Pacing and Electrophysiology Group; *NASPE,* North American Society of Pacing and Electrophysiology.

reported perioperative pacing issues that could be found and mitigated at the postoperative check.

Implantable Cardioverter-Defibrillators

The development of an implantable, battery-powered device able to deliver sufficient energy to terminate VT or VF has represented a major medical breakthrough for patients with a history of ventricular tachyarrhythmias. These devices prevent death in the setting of malignant ventricular tachyarrhythmias,[138–140] and they clearly remain superior to antiarrhythmic drug therapy.[141,142] Initially approved by the FDA in 1985, the implantation rate currently exceeds 12,000 TV-ICDs per month in the United States,[143] averaging over 2500 for the 4 years of primary prevention from 2006 through 2010.[144] Industry sources report that more than 300,000 patients have these devices today.

A significant number of technologic advances have been applied since the first TV-ICD was placed, including considerable miniaturization (pectoral pocket placement with transvenous leads) and battery improvements that now permit permanent pacing with these devices. Thus confusing a pectoral ICD with a pacemaker is easy.

Similar to pacemakers, ICDs have a generic code to indicate lead placement and function, which is shown in Table 5.5[145] The most robust form of identification, called the *label form*, expands the fourth character into its component generic pacemaker code (NBG code, see Table 5.2).

All ICDs have many programmable features, but essentially they measure each cardiac R-R interval and categorize the rate as normal, too fast (short R-R interval), or too slow (long R-R interval). When the device detects a sufficient number of short R-R intervals within a period (all programmable), it will begin an antitachycardia event. For appropriately programmed TV-ICDs, the internal computer will decide and choose ATP (less energy use, better tolerated by the patient) or shock, depending on the presentation and device programming. S-ICDs do not perform ATP at this time. If shock is chosen, then an internal capacitor is charged.

Most ICDs are programmed to reconfirm VT or VF after charging to prevent inappropriate shock therapy. Some TV-ICDs will deliver immediate ATP while charging the capacitor in preparation for a shock. Typically, ICDs have six to eight therapies available for each type of event (VT, fast VT, VF), and some of these therapies can be repeated before moving to the next higher energy sequence. Thus ICDs can deliver many shocks per event. In any ICD with ATP, once a shock is delivered, no further ATP will take place.

Inappropriate shock therapy (IST) occurs in 20% to 40% of ICD patients, with shocks for rhythm other than VT or VF,[146–148] Atrial fibrillation with rapid ventricular response and supraventricular tachycardia remain the most common causes of inappropriate shock therapy,[149] although unmitigated hospital-induced EMI appears to play a role in more than 4% of all ISTs.[150] Whether inappropriate shocks injure patients remains a subject of considerable debate, but a significant number of patients who receive IST will demonstrate elevated troponin levels in the absence of an ischemic event,[151] and a death has been reported.[152] Additionally, any TV-ICD therapy (appropriate or inappropriate) has been associated with increased mortality, whether merely ATP[153] or shock.[154–156] Statin therapy might reduce the incidence of IST through a reduction in atrial fibrillation,[157] and dual-chamber ICD technology might reduce IST from atrial fibrillation as well. Programmable features in current ICDs to differentiate VT from a tachycardia of supraventricular origin include[158]:

1. Onset criteria. In general, the onset of VT is abrupt, whereas the onset of SVT has sequentially shortening R-R intervals.
2. Stability criteria. In general, the R-R interval of VT is relatively constant, whereas the R-R interval of atrial fibrillation with rapid ventricular response is quite variable.
3. QRS width criteria. Some ICDs measure the QRS width using the RV lead tip to ICD case-sensing pathway. In general, the QRS width in SVT is narrow (<110 msec), whereas the QRS width in VT is wide (>120 msec).
4. "Intelligence." Dual-chamber devices attempt to associate atrial activity with ventricular activity.
5. Morphology waveform analysis. Analysis of waveform structure is compared with stored historical templates.

Note that once the R-R interval becomes sufficiently short for VF detection, the ICD will begin a shock sequence. As previously noted, once the device delivers any shock therapy, no further ATP will take place.

An ICD with antibradycardia pacing capability will begin pacing when the R-R interval is too long. In July of 1997, the FDA approved devices with sophisticated dual-chamber pacing modes and rate responsive behavior for ICD patients who need permanent pacing (approximately 20% of ICD patients). Currently, S-ICDs provide antibradycardia pacing only after shock therapy.

Implantable Cardioverter-Defibrillator Indications

Initially, ICDs were placed for hemodynamically significant VT or VF. Newer indications associated with sudden death include: long QT syndrome, Brugada syndrome (right bundle branch block, S-T segment elevation in leads V_1–V_3), and arrhythmogenic RV dysplasia.[159] Recent studies suggest that ICDs can be used for primary prevention of sudden death (ie, before the first episode of VT or VF) in young patients with hypertrophic cardiomyopathy,[160] and data from the second Multicenter Automatic Defibrillator Intervention Trial (MADIT II) suggest that any post-MI patient with ejection fraction (EF) less than 30% should undergo prophylactic implantation of an ICD.[161] At the present time, however, the Centers for Medicare and Medicaid requires a prolonged QRS interval (greater than 120 msec) to qualify for ICD placement in this group. A review of 318,000 implants in patients over 65 years of age for the period 2006 to 2010 demonstrated improvements in 6-month all-cause mortality, 6-month rehospitalization rate, and device complications when compared with matched control subjects.[144]

Several trials have included patients with nonischemic cardiomyopathy, as well. Data from the "Sudden Cardiac Death in Heart Failure Trial" (SCD-HeFT)[142] and the "Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation" (DEFINITE)[162] study now suggest that ICD placement will lower mortality in any patient with EF less than 35%, regardless of the cause of the cardiomyopathy. The DEFINITE results are important, as these patients were randomized only after the initiation of beta-blockade and angiotensin-converting enzyme (ACE)–inhibitor therapy, which form the backbone of medical therapy for cardiomyopathy.

Three-chamber (leads placed in the right atrium, right ventricle, and CS) ICDs (see Fig. 5.1) for CRT (also called BiV pacing) have been FDA approved for patients with DCM and prolonged QRS intervals.

BOX 5.7 IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR INDICATIONS

Prophylactic use for patients with:
- Ischemic cardiomyopathy surviving 40 days and longer with EF of 30% or less and NYHA Class I or EF of 35% or less and NYHA Class II/III
- Nonischemic cardiomyopathy with an EF of 35% or less and NYHA Class II/III

Ventricular fibrillation or ventricular tachycardia from nonreversible cause
Ischemic cardiomyopathy, EF 40% or less, NSVT, inducible at electrophysiologic study
Brugada syndrome (right bundle branch block, S-T elevation V_1–V_3)[a]
Arrhythmogenic right ventricular dysplasia[a]
Long QT syndrome
Hypertrophic cardiomyopathy[a]
Infiltrative cardiomyopathy

EF, Ejection fraction; *NSVT*, nonsustained ventricular tachycardia; *NYHA*, New York Heart Association.
[a]Requires one or more risk factors for sudden cardiac arrest.

Two-chamber (leads placed in the right atrium and right ventricle) ICDs are in clinical trial for patients with HOCM who have experienced VT or VF. Box 5.7 reviews ICD indications.

Dilated Cardiomyopathy

With the advent of cardiac resynchronization therapy pacing (CRT-P) for the patient with DCM and prolonged QRS interval,[163] and the approval of ICDs with CRT capability (cardiac resynchronization therapy with defibrillation capability [CRT-D]), the presence of a defibrillator with BiV pacing will become more common. Currently, approximately 550,000 new diagnoses of congestive heart failure (CHF) are made annually in the United States,[164] and the prevalence of this disease includes 5.7 million patients[165] without much change over the past decade.[166] Significant risk factors for the development of CHF include both ischemic heart disease and hypertension.[167] These data, combined with the recent results from SCD-HeFT[142] and MADIT II[161] trials (ICD is indicated in any patient with cardiomyopathy and EF less than 30% to 35%), suggest that the number of patients eligible to receive a defibrillator to include CRT-P will increase dramatically. Whether any country's economy can absorb this economic burden remains to be seen. At present, CRT-P improves functional status and quality of life[168] and reduces heart failure events[169] primarily by decreasing the dyssynchrony between the two ventricles in the dilated heart whether the CRT device includes ICD capability (called CRT-D) or not (called CRT-P). Additionally, CRT-D and has been shown to reduce mortality in some but not all studies.[28] However, approximately 30% of patients who undergo CRT implantation achieve no additional benefit from the multichamber pacing.[170]

Implantable Cardioverter-Defibrillator Magnets

Similar to pacemakers, magnet behavior in some ICDs can be altered by programming. Most devices will suspend tachyarrhythmia detection (and therefore therapy) when a magnet is appropriately placed to activate the magnet sensor. Some devices from Boston Scientific, Pacesetter, and St. Jude Medical can be programmed to ignore magnet placement. If the magnet mode is off, then intraoperative EMI is likely to produce repeated shocks.[1] *Antitachycardia therapy in some Guidant and CPI devices can be permanently disabled by magnet placement for 30 seconds*,[4] although upgrades to the Boston Scientific programmer and ICD attrition through battery depletion or patient death has virtually eliminated this setting. In general, magnet application will not affect antibradycardia pacing rate (except Sorin [Milano, Italy, US Headquarters Arvado, CO]) or pacing mode. Interrogating the device and calling the manufacturer remain the most reliable method for determining magnet response. Magnet effects on ICDs are shown in Appendix 5.2.

Note that reliable confirmation of appropriate magnet placement, and therefore suspension of antitachyarrhythmic therapy, is present only in Boston Scientific ICDs (tone) and Sorin ICDs (pacing rate change to 90 bpm if the battery is good; 80 if the battery is at elective replacement). Medtronic marketed a Smart-Magnet device that houses a magnet and electronics to show appropriate disablement of the ICD functions in their device, but this device is not generally available. When using a Smart-Magnet, the "FOUND" light is often extinguished during EMI from the ESU, even though the magnet remains in place. Despite these features in Medtronic and Boston Scientific ICDs, numerous anecdotal reports exist of inappropriate shock therapy during electrosurgery, most often a result of movement of the magnet during patient repositioning.

Preanesthetic Evaluation and Implantable Cardioverter-Defibrillator Reprogramming

In general, ALL patients with an ICD should be evaluated for the need to disable high-voltage therapy before the commencement of any procedure, although such action might be unnecessary in a setting without EMI or placement of a metal guidewire into the chest.[171] The comments in the pacing section (and in Boxes 5.3 through 5.6) apply here for any ICD with antibradycardia pacing. Guidelines from HRS/NASPE suggest that every patient with an ICD have an in-office comprehensive evaluation every 3 to 6 months.[42] Devices with CRT-P must have a sufficiently short AV delay for sensed events to ensure that all ventricular activity is paced. Failure of ventricular pacing (either right or left) attributable to native AV conduction or threshold issues has been associated with inappropriate antitachycardia therapy (ie, shock).[172]

Intraoperative (or Procedure) Management

At this time, no special monitoring (attributable to the ICD) is required for the patient with any ICD. ECG monitoring and the ability to deliver external cardioversion or defibrillation must be present during the time of ICD disablement. Although many recommendations exist for defibrillator pad placement to protect the ICD, it should be remembered that the patient, not the ICD, is being treated.

No special anesthetic techniques have been championed for the patient with an ICD. Most of these patients will have severely depressed systolic function, dilated ventricular cavities, and significant valvular regurgitation, and the choice of anesthetic technique should be dictated by the underlying physiologic derangements that are present. Conflicting data have been published regarding the choice of anesthetic agent(s) and changes to DFT. In 1993, Gill and colleagues[173] examined DFT in dogs and concluded that neither halothane nor isoflurane changed DFT in open-chest defibrillation, compared with a pentobarbital infusion. However, Weinbroum and associates[174] evaluated DFTs in humans during ICD implantation and found that halothane, isoflurane, and fentanyl increased DFT. Even with these increases, the increased DFTs found were still substantially lower than the maximum energy generally available in ICDs, and these increases would not have been noted under usual ICD testing conditions. As previously noted, both isoflurane and sevoflurane have been reported to lengthen the QT interval, which could increase the risk of torsades de pointes in certain patients.

Caution should be observed when placing a central venous catheter in any patient with an ICD. In the patient with an integrated bipolar ventricular sensing configuration, an inappropriate 30 joule shock was delivered as a result of noise artifact created by the guidewire on the ventricular shock coil (which was serving as the ICD heart rate sensor). The output of the ICD was short-circuited and attributable to the presence of a shock coil in the superior vena cava, and the ICD was unknowingly rendered ineffective. Only after failure to

deliver subsequent therapy was this problem noted, and the patient subsequently expired.[175] It is important to note that some ICDs are configured to the "integrated bipolar sensing configuration" even in the presence of a true bipolar RV lead.

Postanesthesia Implantable Cardioverter-Defibrillator Evaluation

Any ICD that underwent suspension of high-voltage therapy must be reinterrogated and reenabled. All stored events should be reviewed and counters should be cleared, since the next device evaluator might not receive information about the EMI experience of the patient and make erroneous conclusions regarding the patient's arrhythmia events. One patient death that has been reported to the FDA was attributed to the failure to reactivate antitachycardia therapy in a patient with an ICD after a cardiac ablation procedure.[176]

Summary

CIEDs remain a poorly understood therapeutic modality, despite their presence in the medical environment for over 50 years. CIEDs represent the cutting edge of implanted, sophisticated electronics in patients who have need for artificial pacing and/or automated cardioversion-defibrillation of their heart. Both the aging of the population and the ability to care for patients with increasingly complex disease suggest that many more patients with these devices will require subsequent surgery. Safe and efficient clinical management of these patients depends on an understanding of implantable systems, indications for their use, and the perioperative needs that they create.

Glossary

Atrioventricular (AV) Delay Time that a dual chamber system waits after detecting (or initiating) an atrial event before pacing the ventricle. Some generators shorten this time as the heart rate increases (termed *"rate adaptive AV delay"* or *"dynamic AV delay"*). Some generators can be programmed to extend the AV delay to search for intrinsic conduction ("search AV delay"). Some generators will prolong an AV delay after any atrial event during which the last ventricular event was intrinsic ("AV delay hysteresis"). In a patient with a conducting AV node, the sensed AV delay will be slightly longer than the "P-R" interval on the surface electrocardiogram (see "Fusion Beat" and "Pseudofusion Beat"), since the ventricular sensing element is attached to the apex of the right ventricle and detects the depolarization only after RV activation.

Bipolar Lead An electrode with two conductors. Bipolar sensing is more resistant to oversensing from muscle artifact or stray electromagnetic fields. Some pacing generators can be programmed to unipolar mode even in the presence of bipolar electrodes.

Dynamic Atrioventricular Delay See Atrioventricular (AV) Delay.

Electrogram Mode Passive acquisition and internal storage of electrocardiographic data for diagnostic purposes while pacing (or monitoring) with programmed parameters.

Fusion Beat Pacemaker spike delivered shortly before a native depolarization of the ventricle, which alters the morphologic pattern of the QRS, often misdiagnosed as undersensing. Fusion beat is caused by the position of the sensing electrode, relative to the depolarizing wavefront. Confirmation of appropriate sensing behavior can be made by lengthening the sensing interval (ie, lengthening the AV delay). Fusion beats suggest ventricular capture.

Generator Device with a power source and circuitry to produce an electrical impulse designed to be conducted to the heart. Typically, pacing generators are placed in a pectoral pocket, and leads are inserted into the right atrium, right ventricle, or both. Since 1995, though, implantable cardioverter-defibrillators have also been approved for pectoral pocket placement.

Hysteresis If present, the amount the patient's intrinsic rate must fall below the programmed rate before the generator begins pacing. Some pacers periodically decrease the pacing rate to search for resumption of intrinsic activity (called *search hysteresis*). These functions, when present, can mimic pacemaker malfunction.

Implantable Cardioverter-Defibrillator (ICD) Mode Designation of chamber(s) shocked, chamber(s) paced for antitachycardia pacing, method of tachycardia detection, and chambers paced for antitachycardia therapy. Table 5.5 shows the NASPE/BPEG generic ICD code.

Managed Ventricular Pacing Some evidence suggests that right ventricular (RV) pacing increases mortality in patients with intact AV nodal conduction. As a result, several companies have algorithms to reduce the incidence of RV pacing. Pacing modes called *managed ventricular pacing* (Medtronic) or AAI Safe-R (ELA Medical) can permit an occasional dropped QRS (more likely with managed ventricular pacing than with AAI Safe-R). However, no pacing device should allow two consecutive dropped QRS events. After several beats with a dropped QRS, however, these devices begin pacing in a true DDD mode for several cardiac cycles. These dropped QRS events can mimic pacing system malfunction (pseudomalfunction).

Oversensing Detection of undesired signals that are interpreted as cardiac activity. Oversensing can lead to pacemaker-driven tachycardia (pacing device, DDD mode with atrial oversensing and ventricular tracking); ventricular pause (pacing device with electrosurgical-induced ventricular oversensing, leading the pacer to detect ventricular activity), or inappropriate shock (defibrillator, event oversensing).

Pacing Mode Designation of chamber(s) paced, chamber(s) sensed, sensing response, rate responsiveness, and antitachydysrhythmia function for a pacemaker system. Table 5.2 shows the NASPE/BPEG generic pacemaker code.

Postventricular Atrial Blanking Period (PVAB) Present only in a dual-chamber pacemaker, the PVAB is the period immediately after any ventricular event during which atrial events will not be detected by the atrial sensing circuitry. In general, PVAB is used to determine where, in the postventricular period, atrial event counting should resume for mode switch determination. PVAB is the early part of postventricular atrial refractory period (PVARP).

Postventricular Atrial Refractory Period (PVARP) Present only in a dual-chamber pacemaker, the PVARP is the period immediately after any ventricular event during which atrial events are ignored (for the purpose of pacing the ventricle). In some devices, atrial events during PVARP (but after the expiration of the PVAB timer) will be counted for atrial rate determinations, leading to possible mode switch. The duration of PVARP added to the AV delay (called total atrial refractory period [TARP]) determines the 2:1 block rate of pacing. Some devices allow the PVARP to vary, based on the heart rate.

Programmed Rate (also Automatic Rate) Lowest sustained regular rate during which the generator will pace. Typically, the device begins pacing when the patient's intrinsic rate falls below this value.

Pseudofusion Beat (PFB) Pacemaker spike delivered shortly after a native depolarization without alteration of the QRS morphologic pattern. PFBs are often misdiagnosed as undersensing, and they result from the position of the sensing electrode relative to the depolarizing wavefront (see "Fusion Beat"). Confirmation of appropriate sensing behavior can be made by lengthening the sensing interval (ie, decreasing the program rate [atrial fibrillation] or lengthening the AV delay [ventricular PFB]). PFB cannot be used to confirm electronic capture.

Rate Enhancements Features such as rate adaptive AV delay (shortens the AV delay with increasing heart rate); AV search hysteresis (lengthens or shortens the AV delay to produce intrinsic AV conduction); atrial fibrillation suppression, also called *dynamic atrial overdrive*, increases the lower rate upon appearance

of native atrial depolarization so as to create nearly constant atrial pacing but at a rate only slightly higher than the patient's intrinsic rate); rate smoothing (limits changes in ventricular paced rates attributable to changes in atrial rates, rising and falling rate limits can be programmed); sleep rate (see glossary term Sleep Rate); ventricular rate regulation (similar to rate smoothing but is used to prevent atrial fibrillation); and hysteresis (see glossary term Hysteresis). Each of these enhancements can produce pacing or nonpacing that can mimic pacemaker dysfunction, and these enhancements should be programmed *OFF* before any anesthetic is administered.

Rate Modulation Ability of the generator to sense the need to increase the heart rate. Mechanisms include: (1) mechanical sensor in the generator to detect motion or vibration; (2) electronic detection of Q-T interval (shortens during exercise) or transthoracic impedance to measure changes in respiration; or (3) sensor(s) for central venous blood temperature or oxygen saturation. Some generators now incorporate multiple sensors.

Runaway Pacing Rate Highest pacing rate (typically around 200 bpm) that could occur in the setting of multiple internal component failures in a cardiac generator.

Sleep Rate (also Circadian Rate) The rate (lower than the programmed rate) at which the pacing generator will pace during programmed "nighttime" hours.

Total Atrial Refractory Period (TARP) Present only in dual-chamber pacing devices, the TARP refers to the sum of the PVARP and the AV delay, and it determines the point at which the pacing device will pace the ventricle every other atrial event. This 2:1 block rate can be calculated by dividing 60,000 (msec per min) by the TARP (measured in msec). This 2:1 block results from the ignoring of the atrial event during the PVARP, so these 2:1 blocks appear only when ventricular pacing is needed in a patient and the 2:1 block rate is lower than the maximum tracking rate. In some pacing devices, the dynamic AV delay will make the calculation of TARP dependent on the atrial rate, and many of the programmers will report the final 2:1 block rate for any given combination of programmed parameters.

Undersensing Failure to detect a desired event.

Unipolar Lead Electrode with only one conductor. Some devices with bipolar leads are programmed to the unipolar lead mode. Systems with unipolar leads produce larger spikes on the electrocardiogram than bipolar leads. Systems with unipolar leads use the generator case as the second conductor.

Upper Sensor Rate (USR; also Upper Activity Rate [UAR]) Maximum rate to which a rate modulated pacemaker can drive the heart. USR is not affected by UTR, since the pacemaker is pacing the atrium when the USR becomes active.

Upper Tracking Rate (UTR; also called Upper Rate Limit [URL]) Pacemakers programmed to VDDxx or DDDxx mode cause the ventricles to track atrial activity. Should a patient develop an atrial tachyarrhythmia, such as a supraventricular tachycardia, atrial fibrillation or atrial flutter, the generator acts to limit ventricular pacing. When the atrial rate exceeds the UTR, the generator can change mode (ie, switch to DDI) or introduce second-degree AV block. Second-degree blocks can be Mobitz type I (Wenckebach) or Mobitz type II, depending on a variety of programmed settings within the pacemaker.

Ventricular Intrinsic Preference Programmed extension of the AV delay intended to reduce RV pacing by provoking native AV conduction, specific to St. Jude devices. The AV delay can be extended to as much as 450 msec. Periodically at programmed intervals, AV delay is extended across several cardiac cycles by the ventricular intrinsic preference (VIP) setting to test for intrinsic conduction.

Ventricular Refractory Period (VRP) Period immediately after any ventricular event during which the pacing device will not respond to a sensed event on the ventricular channel. Depending on the manufacturer and programming, though, events sensed during VRP might be counted for determining a high-rate ventricular condition.

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APPENDIX 5.1 Pacemaker Response to Magnet Placement

Pacemaker Company		*Magnet Mode Designation*	*Explanation*
Biotronik	INOS	ASYNCH (default)	Asynchronous VOO (even if dual-chamber device) pacing at 70 or 90 bpm, depending on programming, if normal conditions. 80 bpm at ERI. There is no way to determine the magnet rate without the programmer or magnet application.
		SYNCH	VVI (even if dual-chamber device) pacing at 70 or 90 bpm, depending on programming, if normal conditions. 80 bpm at ERI. There is no way to determine the magnet rate without the programmer or magnet application. Also, if the patient's intrinsic ventricular rate is greater than 80 bpm, then there will be no way to identify ERI.
	DROMOS	ASYNCH	See AUTO.
		SYNCH	See SYNCH.

APPENDIX 5.1 Pacemaker Response to Magnet Placement—cont'd

Pacemaker Company		*Magnet Mode Designation*	*Explanation*
	All Others	AUTO (default)	If normal conditions, 10 asynchronous events at 90 bpm, then returns to original programmed mode without rate responsiveness. Pacing is at lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, 10 asynchronous events at 80 bpm in VOO mode, then either VDD (dual chamber) or VVI (single chamber) pacing at 11% lower than the lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
		ASYNCH	Asynchronous pacing at 90 bpm if normal conditions. At ERI, 80 bpm (single step change) in VOO mode, regardless of original programming. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
		SYNCH	If normal conditions, pacing in original programmed mode without rate responsiveness. Pacing is at lowest available rate (LRL, sleep rate, or hysteresis rate). If battery at ERI, then either VDD (dual chamber) or VVI (single chamber) pacing at 11% lower than lowest available rate. For any dual-chamber mode (DDD, DDI, or VDD), the AV delay shortens to 100 msec while the magnet is in place.
Boston Scientific includes Guidant Medical CPI	"BSC" x-ray label	ASYNCH (default)	Asynchronous pacing with 100 msec AV delay at 100 bpm if normal conditions, 90 bpm in IFI, and 85 bpm at ERT (single-step changes). All models shorten the pulse width to 50% on the third paced ventricular event (TMT).
		OFF	No change, magnet is ignored. Magnet mode is OFF after a "power on reset" or activation of "Safety Core," which can occur secondarily to EMI.
		PTM mode	No change in pacing. Magnet application initiates data collection.
	All others ("BSC," "GDT," "CPI" x-ray labels)	ASYNCH (default)	If normal conditions, asynchronous pacing with 100 msec AV delay at 100 bpm. If ERI, 85 bpm (single-step change). The Insignia and Altura models have an intermediate step (90 bpm) at ERN. Most models shorten the pulse width to 50% on the third paced ventricular event (TMT). For Triumph and Prelude models, see Medtronic pacemakers.
		OFF	No change, magnet is ignored. OFF is the magnet mode after a "power on reset," which can occur secondarily to EMI.
		Electrogram mode	No change in pacing. Magnet application initiates data collection.
Intermedics (purchased by Guidant, 1998, now Boston Scientific, but special programmer needed)			Five asynchronous events at 90 bpm (regardless of battery voltage), then 60 additional asynchronous events at LRL if normal conditions, 90 bpm if ERI, and 80 bpm if EOL. The fifth paced event is emitted at 50% of the originally programmed pulse width (TMT). After the 65th asynchronous event, the magnet is ignored.
Medtronic (See Cautions in the text following this table.)	Standard transvenous pacemaker		Asynchronous pacing at 85 bpm (programmed mode) if normal conditions, 65 bpm SOO regardless of original programming if ERI (single-step change). Medtronic pacemakers (except Enrhythm P1501 and all "Surescan" models) pace the first three events at 600 msec intervals (rate = 100 bpm) with a short AVd. During the first three to seven asynchronous events, most Medtronic pacemakers emit one or more ventricular pulses at a reduced pulse width or voltage (TMT). Also, Medtronic pacemakers default to single-chamber pacing at 65 bpm, without rate responsiveness, upon reset or detection of ERI when no magnet is present. Important caveat: a Medtronic dual-chamber pacemaker in AAI mode will revert to VVI on ERI or reset, which might result in asystole and death with a dysfunctional ventricular lead but atrial pacing dependence.
	Micra leadless intracardiac pacemaker		No magnet response.
Sorin (was ELA Medical)			Asynchronous pacing at 96 bpm gradually declining to 80 bpm at ERI. ELA pacemakers take eight additional asynchronous pacing cycles (the final two cycles are at LRL with long atrioventricular delay) upon magnet removal.
St. Jude Medical	SJM x-ray logo; standard transvenous pacemaker	Battery Test (default)	Asynchronous pacing at 100 bpm (older models 98.6 bpm) gradually decreasing to 86.3 bpm at ERI.
		OFF	No magnet response.
		Event snapshots	No change in pacing. Magnet application causes pacemaker to collect data. Identity and Entity models lack this feature.
		Event snapshots + Battery Test	For a magnet placed 2 seconds, pacing mode and rate are unchanged and the device stores an electrogram. If the magnet is placed ≥5 seconds, the Battery Test mode (see above) is activated. Identity and Entity models lack this feature.
	Pacesetter x-ray logo(ψ); standard transvenous pacemaker	Battery Test (default)	Asynchronous pacing, and the rate depends on specific model. In general, a pacing rate of less than 90 bpm should prompt further evaluation.
		OFF	No magnet response.
		VARIO mode (present in some models)	VARIO results in a series of 32 asynchronous pacing events. The rate of the first 16 paces reflects battery voltage, gradually declining from 100 bpm to 85 bpm at ERI. The next 15 paces are used to document ventricular pacing capture safety margin. The rate will be 119 bpm with gradually declining pacing voltage. The 16th pace of this group is at no output. The next pace restarts the 32 event sequence. The 32-event sequence repeats while the magnet remains in place.
	Nanostim leadless intracardiac pacemaker	ON (default)	Asynchronous pacing at 100 bpm for eight cycles, then 90 bpm if normal conditions; 65 bpm if ERI.
		OFF	No magnet response.
Telectronics	Meta 1202		Asynchronous pacing at 99 bpm, gradually declining to <93 at ERI.
	Meta 1204 1206 1256		Asynchronous pacing at 100 bpm, gradually declining to < 82.5 bpm at ERI.
	Meta 1230 1250 1254		Asynchronous VOO pacing (regardless of original programming) at >85 bpm, gradually declining to <78 bpm at ERI.

Continued

APPENDIX 5.1 Pacemaker Response to Magnet Placement—cont'd

Pacemaker Company	*Magnet Mode Designation*	*Explanation*
Tempo		Asynchronous pacing at 100 bpm, gradually declining to 80 bpm at ERI.
All Others		Contact St. Jude Medical.

The effect(s) of appropriately placing a magnet over a pacemaker is(are) shown. Column 1 shows the pacemaker manufacturer. If the manufacturer has multiple responses, then Column 1 is subdivided. If the magnet response is programmable, then Column 2 shows the various magnet modes available. The first mode shown is the default. A device reset from EMI might produce some other mode (ie, magnet mode disabled). Column 3 shows the effect on pacing therapy for the magnet mode shown in Column 2. Unless otherwise specified, asynchronous pacing takes place, without rate responsiveness, in the chambers originally programmed. Thus a dual-chamber program would result in DOO pacing, and a single-chamber program would result in VOO (unless an atrial device, which would be AOO) pacing, and a biventricular, dual-chamber device would be DOOOV.

AVd, Atrioventricular delay (For dual-chamber pacing, AVd is a programmed value [see Glossary]. However, the AVd can be shortened during the first 3 to 15 events upon magnet placement. Note that a short AVd can reduce stroke volume and produce untoward hemodynamics in some patients.); *EOL,* end of life; (Device should be replaced immediately.); *ERI,* elective replacement indicator (Device should be promptly replaced. The US Food and Drug Administration requires pacemakers to perform safely for at least 3 months from the onset of the ERI.); *ERN,* elective replacement near (Device should be undergoing monthly checks [IFI].); *ERT,* elective replacement time (Is the same as ERI. For Boston Scientific Pacemakers [Guidant, CPI labels also] at ERT, rate responsive programming is cancelled. At 3 months after ERT, only single-chamber operation continues.); *IC-PM,* intracardiac pacemaker; *IFI,* intensified follow-up interval (Device needs monthly battery checks.); *LRL,* lower rate limit (Programmed lower rate, or set point, of the pacemaker.); *SOO,* single-chamber asynchronous pacing; *SSI,* single-chamber, inhibited mode (If implanted for ventricular pacing, then SSI is in VVI mode. For an atrial pacemaker, SSI is in AAI mode.); *TMT,* threshold margin test (Emission of a single pacing pulse [except VARIO; see St. Jude Medical—Pacesetter logo] at a lower amplitude or pulse width to demonstrate adequacy of pacing output relative to pacing threshold. Typically, this is the third or fifth pacing pulse. Failure to capture (pace) on this event suggests an inadequate safety margin for capture. Properly programmed atrial-only pacemakers are unlikely to demonstrate this feature.); *TV-PM,* transvenous pacemaker.

Cautions

Any dual-chamber pacemakers undergoing a "power on reset" or "Safety Cored Event" (BSC Boston labeled devices) from an electrical fault or exposure to strong EMI could cause a "power on reset," or "Safety Core Event," which causes the pacemaker to switch to VVI pacing only, regardless of prior pacing programming. For a dual-chamber pacemaker with a bad RV lead and programmed to atrial pacing only (AAI, AOO) in a pacing-dependent patient, this event could cause patient injury or death.

All Medtronic transvenous pacemakers except Enrhythm P1501, EMDR series, Revo, Advisa, and Ensura suspend magnet detection for up to 60 minutes following the removal of the programming head after an interrogation session, unless specific programming action (which requires multiple button depressions) is taken before removing the programming head.

APPENDIX 5.2 Implantable Cardioverter-Defibrillator Response to Magnet Placement

ICD Manufacturer		*Magnet Mode Designation*	*Effect on Tachy Therapy*	*Effect on Brady Therapy (regular pacing)*	*Magnet Mode Confirmation*
Biotronik			Disables	No effect	None
Boston Scientific (Guidant Medical, CPI)	Transvenous BSC; all BOS (except 119, 203) x-ray labels	ON (default)	Disables	No effect	Short beep every second or constant tone[a]
		OFF	No effect	No effect	None
	Transvenous GDT, CPI BOS 119, BOS 203 x-ray labels	ON (default)	Disables	No effect	Short beep with each R wave, or constant tone[a]
		OFF	No effect	No effect	None
	Subcutaneous		Disables	No effect. S-ICD has no regular pacing. However, postshock pacing (VVI, 50 bpm, 30 seconds, nonprogrammable) is terminated.	Short beep with each R wave, whether ICD therapy is on or off, for the first 60 seconds of magnet application. Thereafter, no confirmation.
Medtronic	AT-500[b]		Disables	No effect	None
	All others[c]		Disables	No effect	
Pacesetter and St. Jude Medical		Normal (default)	Disables	No effect	
		Ignore	No effect	No effect	None
Sorin (was ELA Medical)			Disables	The pacing rate, but not mode, changes to 96 bpm (new device) declining to 80 bpm, indicating elective replacement time.	Pacing rate changes as noted.

EMI, Electromagnetic interference; *ICD,* implantable cardioverter-defibrillator; *S-ICD,* subcutaneous implantable cardioverter-defibrillator.

The effect(s) of appropriately placing a magnet over an ICD are shown. Column 1 shows the manufacturer. Some manufacturers have multiple responses that can be determined by the x-ray identifier. If the magnet response is programmable, then Column 2 shows the various magnet modes available. The first mode shown is the default mode. A device reset from EMI might produce some other mode (ie, magnet mode disabled). Column 3 shows the effect on antitachycardia therapy (defibrillation, cardioversion, and antitachycardia pacing) for the magnet mode shown in Column 2. Only ICDs from Sorin Medical alter their antibradycardia pacing rate upon magnet placement (Column 4), and this pacing rate can be used to predict remaining battery life provided that the patient's native heart rate is less than the magnet rate. Only ICDs from Boston Scientific/Guidant/CPI produce reliable audio feedback for confirmation of magnet placement (Column 5). For devices from Pacesetter/St. Jude Medical, a device interrogation is required to determine the magnet mode.

[a]Any Boston Scientific/Guidant/CPI ICD that does not emit sound when a magnet is applied should undergo an immediate device interrogation. A stethoscope might be needed; for electronic stethoscopes, only the "Diaphragm" mode should be used since filtering in the "Bell" mode might not permit the sound to be transmitted to the earpiece.

For Boston Scientific/Guidant/CPI ICDs, if magnet mode is programmed to ON, appropriate magnet placement disables tachy detection and therapy, and tachy therapies remain disabled for as long as the magnet remains appropriately applied. When magnet mode is enabled in these devices, the ICD will emit either a constant tone or a beep to identify appropriate magnet placement. If the device emits a constant tone, then tachy therapy is disabled whether or not a magnet is present, and tachy therapy will not be present even after the magnet is removed. If any of these ICDs emit a beep (ICDs with GDT or CPI x-ray codes emit each beep with any paced or sensed R wave; ICDs with BOS or BSC x-ray code emits a beep every second), then a properly working ICD will be enabled for tachy therapy upon magnet removal.

Note that the "Change Tachy Mode with Magnet" feature is present only in very few remaining GDT and CPI x-ray labeled devices. When programmed ON, after 30 seconds of continuous magnet application the tachy mode will toggle (ie, it will switch from enabled when the magnet is removed [beeping with magnet correctly applied] to permanently disabled [constant tone when magnet is correctly applied] or vice versa.) This mode has been phased out for most BOS/GDT/CPI ICD families, and software in programmers since October of 2009 is designed to disable and eliminate this feature.

[b]The Medtronic AT-500 series atrial defibrillators provide antitachycardia pacing in the atrium ONLY, and usually after a delay often exceeding 1 minute from onset of atrial tachyarrhythmia. They do not have any shock coils on any lead and are very difficult to distinguish from a conventional two-chamber pacemaker. They have NO apparent magnet response. The x-ray identifier on these devices includes the Medtronic "M" but the first character is "I." All other Medtronic cardiac generators have the Medtronic "M" with the first letter identifier "P."

[c]Some Medtronic ICDs will emit a tone for 15 to 30 seconds when a magnet is placed on the device. However, this tone is not continuous with magnet placement, and it will not be interrupted with immediate magnet removal. As a result, the tone cannot be used for confirmation of appropriate magnet placement.

APPENDIX 5.3 Cardiac Implantable Electronic Device Manufacturer Phone Numbers

Biotronik	800-547-0394
Boston Scientific	800-227-3422
Cardiac Pacemakers, Inc.—(CPI (Boston Scientific)	800-227-3422
ELA Medical (Sorin)	800-352-6466
Guidant Medical (Boston Scientific)	800-227-3422
Medtronic	800-505-4636
Sorin	800-352-6466
St. Jude Medical	800-722-3774
Vitatron (Medtronic)	800-328-2518

Companies listed in **BOLD** market defibrillators.

6 Cardiac Physiology

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KEY POINTS

1. The cartilaginous skeleton, myocardial fiber orientation, valves, blood supply, and conduction system of the heart determine its mechanical capabilities and limitations.
2. The cardiac myocyte is engineered for contraction and relaxation, not protein synthesis.
3. Laplace's law describes the transformation of alterations in muscle tension and length observed during contraction and relaxation in vitro into phasic changes in pressure and volume that occur in the intact heart.
4. The cardiac cycle is a highly coordinated, temporally related series of electrical, mechanical, and valvular events.
5. A time-dependent, two-dimensional projection of continuous pressure and volume during the cardiac cycle creates a phase space diagram that is useful for the analysis of systolic and diastolic function of each cardiac chamber in vivo.
6. Each cardiac chamber is constrained to operate within its end-systolic and end-diastolic pressure-volume relationships when contractile state and compliance are constant.
7. Heart rate, preload, afterload, and myocardial contractility are the main determinants of pump performance.
8. Preload is the quantity of blood that a cardiac chamber contains immediately before contraction begins, and afterload is the external resistance to emptying with which the chamber is confronted after the onset of contraction.
9. Myocardial contractility is quantified using indices derived from pressure-volume relationships, isovolumic contraction, the ejection phase, or power analysis, but these indices have significant limitations because the contractile state and loading conditions are interrelated.
10. Pressure-volume diagrams are useful for describing the mechanical efficiency of energy transfer between elastic chambers, such as the left ventricle and the proximal arterial vasculature.
11. Diastolic function is the ability of a cardiac chamber to effectively collect blood at a normal filling pressure.
12. Left ventricular diastole is a complicated sequence of temporally related, heterogeneous events; no single index of diastolic function completely describes this period of the cardiac cycle.
13. Left ventricular diastolic dysfunction is a primary cause of heart failure in as many as 50% of patients.
14. The left ventricular pressure-volume framework allows the invasive analysis of diastolic function during isovolumic relaxation, early filling, and atrial systole.
15. Transmitral and pulmonary venous blood flow velocities, tissue Doppler imaging, and color M-mode propagation velocity are used to noninvasively quantify the severity of diastolic function.
16. The pericardium exerts important restraining forces on chamber filling and is a major determinant of ventricular interdependence.
17. The atria serve three major mechanical roles, as conduits, reservoirs, and contractile chambers.

The heart is an electrically self-actuated, phasic, variable-speed hydraulic pump composed of two dual-component, elastic, muscular chambers, each consisting of an atrium and a ventricle connected in series that simultaneously provide an equal quantity of blood to the pulmonary and systemic circulations. All four chambers of the heart are responsive to the stimulation rate, muscle stretch immediately before contraction (ie, preload), and the forces resisting further muscle shortening after contraction has begun (ie, afterload). The heart efficiently provides its own energy supply through an extensive coronary circulation.

The heart rapidly adapts to changing physiologic conditions by altering its inherent mechanical properties (ie, Frank-Starling mechanism) and by responding to neurohormonal and reflex-mediated signaling. Overall performance is determined by the contractile characteristics of the atria and ventricles (ie, systolic function) and by the ability of its chambers to effectively collect blood at normal filling pressures before the subsequent ejection (ie, diastolic function). This innate duality implies that heart failure may occur as a consequence of abnormalities in systolic or diastolic function.

A comprehensive understanding of cardiac physiology is essential for the practice of cardiac anesthesia. At an average heart rate of 75 beats/minute, the heart contracts and relaxes more than 3 billion times during the length of a typical human life, supplying oxygen and nutrients required to meet the body's metabolic requirements. The fundamentals of cardiac physiology are discussed in this chapter, with an emphasis on the mechanics that allow the heart to achieve this truly remarkable performance.

Functional Implications of Gross Anatomy

Structure

The heart's anatomy determines many of its major mechanical capabilities and limitations. The annuli of the valves, the aortic and pulmonary

arterial roots, the central fibrous body, and the left and right fibrous trigones form the heart's skeletal foundation. This flexible, strong, cartilaginous structure is located at the superior aspect (ie, base) of the heart. It provides support for the translucent, macroscopically avascular valves, resists the forces of developed pressure and blood flow within the chambers, and provides a site of insertion for superficial subepicardial muscle.[1] Most atrial and ventricular muscle is not directly connected to the central fibrous skeleton. It instead arises from and inserts within adjacent surrounding myocardium. This observation is consistent with the well-known embryologic derivation of the heart from an expanded arterial blood vessel.[2]

An interstitial collagen fiber network composed of thick type I collagen cross-linked with thin type III collagen also provides important structural support to the myocardium. The protein elastin is interwoven in this collagen matrix, providing additional flexibility and elasticity to the heart without compromising its strength. In contrast to William Harvey's original assertion,[3] atrial and ventricular myocardium cannot be separated into distinct bands or layers by the use of an unwinding dissection technique.[4,5] Instead, myocardium is a continuum of interconnecting cardiac muscle fibers. Accordingly, the term "layer" is used metaphorically in this section.

The left atrium (LA) and right atrium (RA) are composed of two relatively thin, orthogonally oriented layers of myocardium. The walls of the right ventricle (RV) and left ventricle (LV) are thicker (approximately 5 and 10 mm, respectively) than those of the atria and consist of three muscle layers: interdigitating deep sinospiral, superficial sinospiral, and superficial bulbospiral. Well-ordered, differential alterations in fiber angle extending from the endocardium to the epicardium are especially apparent in ventricular myocardium and are spatially conserved (Fig. 6.1).[6]

Subendocardial and subepicardial muscle fibers of the LV follow perpendicular, oblique, and helical routes from the base to the apex, but the orientation of these interdigitating sheets of cardiac muscle reverses direction at approximately the LV midpoint. LV fiber architecture resembles a flattened figure eight (Fig. 6.2). Contraction of obliquely arranged subepicardial and subendocardial fibers causes LV chamber shortening along its longitudinal axis, concomitant with a characteristic twisting action that increases the magnitude of force generated by the LV during systole above that produced by basal-apical muscle fiber shortening alone. Transition of this primarily helical geometry into a more spherical configuration may contribute to reduced systolic function during evolving heart failure.[7] Elastic recoil of the systolic wringing motion during LV relaxation is also a crucial determinant of diastolic suction, which facilitates adequate LV filling during hypovolemia and strenuous exercise.[8,9]

In contrast to the subepicardial and subendocardial layers, midmyocardial fibers are circumferentially oriented around the LV cavity's diameter. As expected, their contraction reduces chamber diameter.

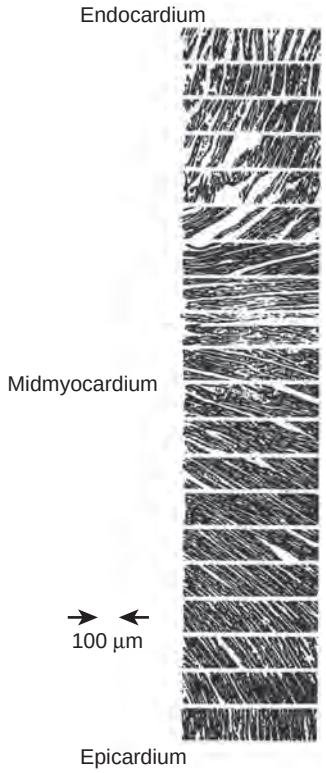

Fig. 6.1 Sequence of photomicrographs depicts myocardial fiber angles at successive sections from the endocardial surface *(top)* to the epicardial surface *(bottom)* through the thickness of the left ventricular anterior wall. Notice the transition in myocardial fiber orientation relative to wall thickness from the subendocardium (ie, perpendicular) to the midmyocardium (ie, parallel). A mirror image transition in fiber orientation is observed from the midmyocardium to the subepicardium. *(From Katz AM.* Physiology of the Heart. *3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.)*

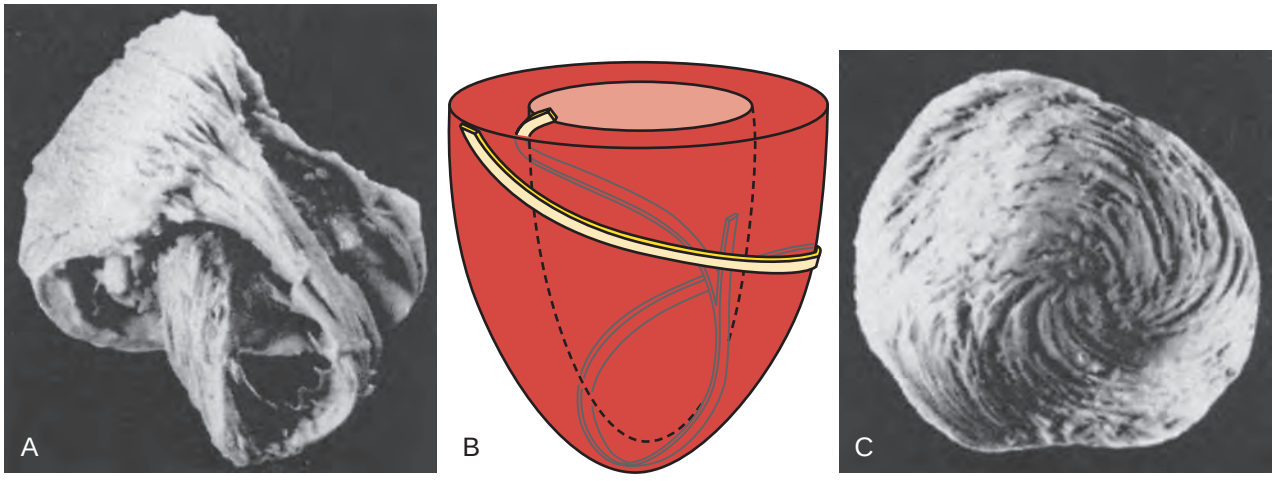

Fig. 6.2 The spiral orientation of fiber continuity in the left ventricle. (A) Photograph demonstrates a dissection of the human left ventricular (LV) anterior and lateral walls and shows spiral cardiac muscle bundles sweeping from the base to the apex. (B) Schematic diagram of the helical orientation. (C) Photograph shows a dissection of endocardial fiber orientation at the LV apex and the spiral fiber structure. *(From Katz AM.* Physiology of the Heart. *3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)*

The LV free walls are thickest near the base and gradually thin toward the apex because of a progressive decline in the relative number of midmyocardial fibers. Subendocardial layers of the LV and RV combine with LV midmyocardium extending from the LV free wall to create the interventricular septum.[1] Structural elements derived primarily from the LV, but not the RV, form the septum. As a result, the septum normally thickens toward the LV chamber during contraction. However, the interventricular septum may move toward the RV chamber during systole under pathologic conditions such as RV distention (eg, from an acute increase in pulmonary arterial pressure) or pressure-overload RV hypertrophy (eg, from a chronic left-to-right shunt).

As in the LV free wall, a gradual decrease in the number of midmyocardial fibers produces a characteristic basal-to-apical reduction in interventricular septum thickness. The LV apical free wall is composed of subendocardial and subepicardial fibers, but the apical interventricular septum contains only LV and RV subendocardium. These regional differences in LV wall thickness and laminar myocardial fiber orientation contribute to load-dependent alterations in LV mechanics.[10] Irregular ridges of subendocardium, called *trabeculae carnae* (Latin for "meaty ridges"), are commonly observed along the apical LV chamber border and within the RV; the precise physiologic implications of these structural features are unknown. Endocardial endothelium lines the subendocardium on the LV chamber surface and may play a minor role in the regulation of myocardial function.[11]

The LV apex and interventricular septum remain relatively fixed in space within the mediastinum, but the lateral and posterior walls move toward the anterior and right during contraction. These actions displace the LV longitudinal axis from a plane oriented toward the mitral valve (ie, favoring LV filling) to a position that is more parallel to the LV outflow tract (ie, facilitating ejection). The anterior-right movement of lateral and posterior LV walls also produces the point of maximal impulse, which is typically palpable on the anterior chest wall in the left fifth or sixth intercostal space in the midclavicular line. Subendocardial and subepicardial fiber shortening, papillary muscle contraction, and mechanical recoil resulting from ejection of blood into the aortic root also cause the LV base to descend toward the apex during systole. Synchronous contraction of LV myocardium shortens the LV long axis, decreases the LV chamber diameter, and rotates the apex in an anterior-right direction toward the chest wall. LV ejection is also associated with an apex-to-base gradient in wall tension, creating the intraventricular pressure gradient required to efficiently transfer stroke volume (SV) from the LV into the aorta.

The RV is located in a more right-sided, anterior position than the LV within the mediastinum. Unlike the thicker-walled, ellipsoidal LV that propels oxygenated blood from the pulmonary venous circulation into the high-pressure systemic arterial vasculature, the thinner-walled, crescentic RV pumps deoxygenated venous blood into a substantially lower pressure, more compliant pulmonary arterial tree.

The activation sequence of the LV is temporally uniform, but the RV contracts in a peristaltic manner, in part because it is composed of embryologically distinct inflow and outflow tracts. The RV moves toward the interventricular septum with a bellows-like action. The interventricular septum and LV provide a splint against which the RV free wall shortens during contraction. LV contraction also makes an important contribution to RV systolic function (ie, systolic ventricular interdependence).[12] These factors give the less muscular RV a mechanical advantage that allows it to eject an SV equivalent to that of the LV. However, the thinner RV is more vulnerable to acute decompensation with modest increases in afterload because the thicker LV can generate pressure-volume work that is fivefold to sevenfold greater than the RV can produce. Conversely, the RV is more compliant and accommodates excess volume more easily than the LV.

The atrioventricular (AV) groove separating the RA and the RV and the adjacent tricuspid valve annular plane (ie, components of the RV base) shorten toward the RV apex during contraction. This motion may be used as an index of RV contractile function by echocardiographic quantification of RV free wall tricuspid annular-plane systolic excursion (TAPSE).[13]

Valves

Two pairs of valves ensure unidirectional blood flow through the right and left sides of the heart. The pulmonic and aortic valves are trileaflet structures located at the RV and LV outlets, respectively, and they operate passively with changes in hydraulic pressure. The pulmonic valve leaflets are identified by their anatomic positions (ie, right, left, and anterior), whereas the name of each aortic valve leaflet is derived from the presence or absence of an adjacent coronary ostium.

The pulmonic and aortic valves open as a consequence of RV and LV ejection, respectively. The effective orifice area of each valve during maximal systolic blood flow is only modestly less than the total cross-sectional area of the valve annulus. The proximal aortic root contains dilated segments (ie, sinuses of Valsalva) located immediately behind each leaflet. The sinuses of Valsalva prevent the aortic valve leaflets from closely approaching or adhering to the aortic wall by facilitating the formation of eddy currents during ejection, preventing the right and left coronary leaflets from occluding their respective coronary ostia. The eddy currents within the sinuses of Valsalva also assist with aortic valve closure when ejection ceases by ensuring that the leaflets remain fully mobile during early diastole.[14] The normal velocity of blood flow through the aortic valve (approximately 1.0 m/s) creates vortices of flow between the aortic valve leaflets and the sinuses of Valsalva that serve to further prevent leaflet-aortic wall contact.[15] In contrast to the aortic root, the proximal pulmonary artery does not contain sinuses.

The thin, flexible, and very strong mitral valve separates the LA from the LV. The mitral valve is an oval, hyperbolic paraboloid[16,17] (ie, saddle-shaped structure) containing two leaflets, identified as anterior and posterior on the basis of their anatomic locations. The valve leaflets coapt in a central curve, with the anterior mitral leaflet forming the convex border. The anterior mitral leaflet is oval and occupies a greater central diameter across the annulus, whereas the posterior mitral leaflet is crescent-shaped and extends further around the annular circumference. As a result, the cross-sectional area of each leaflet is similar. The leaflets are physically joined at anterior-lateral and posteromedial commissures, which are located superior to corresponding papillary muscles. The leaflets thicken slightly along the line of coaptation. The positive pressure gradient between the LA and LV chambers near the end of LV relaxation combined with LV mechanical recoil cause the mitral valve to open, whereas retrograde blood flow toward the valve during LV contraction forces the previously open valve leaflets in a superior direction and ensures their coaptation.

Thin fibrous threads, called *chordae tendineae*, attach to the papillary muscles and prevent inversion of the valve leaflets during contraction. Primary and secondary chordae tendineae insert into the valve edges and the clear and rough zones of the valve bodies (located approximately one-third of the distance between the valve edge and the annulus), respectively, of the leaflets. Tertiary chordae tendineae extend from the posteromedial papillary muscle and insert into the posterior mitral leaflet or the adjacent myocardium near the annulus. Each papillary muscle is an outpouching of subendocardial myocardium that provides chordae tendineae to both mitral valve leaflets and contracts synchronously with the LV itself. Papillary muscle contraction tightens the chordae tendineae, inhibiting excessive leaflet motion beyond the normal coaptation zone and preventing regurgitation of blood.[18] The mitral annular circumference also decreases modestly during LV contraction through a sphincter-like action of the surrounding subepicardial myocardium, reducing the total annular area and assisting in valve closure.[19]

The functional integrity of the mitral valve apparatus is crucial to overall cardiac performance. The apparatus ensures unidirectional blood flow from the LA to the LV by preventing regurgitant flow into the LA and proximal pulmonary venous circulation. It also contributes

to LV systolic function through papillary muscle contributions to LV apical posteromedial and anterior-lateral contraction. It is not surprising that severing chordae tendineae—papillary muscle attachments during mitral valve replacement reduces global LV contractile function. Papillary muscle ischemia or infarction may also contribute to the development of LV systolic dysfunction through a similar mechanism in addition to producing acute mitral regurgitation.

The anterior (ie, anterosuperior), posterior (ie, inferior or mural), and septal (ie, medial) leaflets and their corresponding chordae tendineae and papillary muscles comprise the tricuspid valve that regulates blood flow from the RA to the RV. The anterior and septal leaflets are usually larger than the posterior leaflet. The presence of a septal papillary muscle distinguishes the morphologic RV from the LV in patients with certain forms of congenital heart disease (eg, transposition of the great vessels). A lateral band of myocardium (ie, moderator band) connects the apical anterior and septal papillary muscles and demarcates the RV inflow and outflow tracts.

The RV contains a large quantity of coarse trabeculae carnae throughout the chamber, whereas relatively fine trabeculations characterize the LV subendocardial surface. The reason for the difference in trabeculation is unknown. The tricuspid valve does not have a clearly defined collagenous annulus, unlike the mitral valve. Instead, the RA myocardium is separated from the RV by the AV groove that lies immediately above, may fold into the origin of the tricuspid leaflets, and contains the proximal portion of the right coronary artery.

Blood Supply

Blood flow to the heart is supplied by the left anterior descending coronary artery (LAD), the left circumflex coronary artery (LCCA), and right coronary artery (RCA). Most blood flow to the LV occurs during diastole, when aortic blood pressure exceeds the LV pressure, establishing a positive pressure gradient in the coronary arteries, all three of which contribute to the LV's blood supply. Acute myocardial ischemia resulting from a critical coronary artery stenosis or abrupt occlusion causes a predictable pattern of LV injury based on the known distribution of blood supply. The LAD and its branches (including septal perforators and diagonals) supply the medial one-half of the LV anterior wall, the apex, and the anterior two-thirds of the interventricular septum. The LCCA and its obtuse marginal branches supply the anterior and posterior aspects of the lateral wall, whereas the RCA and its distal branches supply the medial portions of the posterior wall and the posterior one-third of the interventricular septum.

The coronary artery that supplies blood to the posterior descending artery (PDA) defines the right or left dominance of the coronary circulation. Right dominance (ie, PDA supplied by the RCA) is observed in approximately 80% of patients, whereas left dominance (ie, PDA supplied by the LCCA) occurs in the remainder. Direct connections between the distal coronary arteries or collateral blood vessels between the major coronary arteries may also provide alternative routes of blood flow to the myocardium distal to a severe coronary artery stenosis or complete occlusion. However, these connections vary and are often unpredictable in the human coronary circulation.

The RCA (in approximately two-thirds of patients) or the LCCA frequently provides the sole blood supply to the posteromedial papillary muscle, which renders this structure particularly vulnerable to acute ischemia or infarction. Nevertheless, one-third of patients have a dual blood supply (ie, RCA and LCCA) to the posterior papillary muscle[20] and therefore are less susceptible to posteromedial papillary muscle ischemic injury. Because the LAD and LCCA usually provide coronary blood flow to the anterior-lateral papillary muscle, ischemic dysfunction of the muscle is relatively uncommon.

In contrast to the LV, coronary blood flow to the RA, LA, and RV occurs throughout the cardiac cycle because systolic and diastolic aortic blood pressures exceed the pressures within these chambers. The RCA and its branches supply most of the RV, but the RV anterior wall also may receive blood from branches of the LAD. RV dysfunction may occur because of RCA or LAD ischemia.

Coronary blood flow to the LA is derived from branches of the LCCA.[21,22] Augmented LA contractile function resulting from a Frank-Starling mechanism usually occurs in the presence of acute myocardial ischemia or infarction resulting from LAD occlusion,[23] but the compensatory response may not be observed during compromise of LCCA blood flow because of LA ischemia.[24]

Branches of the RCA and LCCA provide coronary blood flow to the RA.[21] For example, a nodal artery from the RCA (55% of patients) or the LCCA (45%) supplies blood to the sinoatrial (SA) node. Similarly, RCA or, less commonly, LCCA branches supply blood flow to the AV node depending on the right or left dominance. A critical stenosis or acute occlusion in either of these two perfusion territories may delay the transmission of electrical signals through the proximal conduction system and cause bradyarrhythmias.

Conduction

The mechanism by which the heart is electrically activated plays a crucial role in its mechanical performance.[25] The SA node is the primary cardiac pacemaker if marked decreases in firing rate, conduction delays or blockade, or accelerated firing of secondary pacemakers (eg, AV node, bundle of His) do not occur. The anterior, middle (Wenckebach), and posterior (Thorel) internodal pathways transmit the initial SA node depolarization rapidly through the RA myocardium to the AV node (Table 6.1). A branch (ie, Bachmann bundle) of the anterior internodal pathway also transmits the SA node depolarization from the RA to the LA across the atrial septum.

Internodal pathways may be clearly demonstrated in the electrophysiology laboratory, but histologic examination most often does not identify anatomically unique bundles of morphologically distinct cardiac cells that are capable of more rapid impulse conduction than the atrial myocardium itself. The cartilaginous skeleton of the heart isolates the atria from the ventricles by acting as an electrical insulator. Atrial depolarization is not indiscriminately transmitted throughout the heart but is instead directed to the ventricles through the AV node and its distal conduction pathway (ie, bundle of His). Electrical isolation of the atrial chambers from the ventricular chambers and the normal transmission delay through the slowly conducting AV node establishes the sequential pattern of atrial followed by ventricular contraction.

Pathologic accessory pathways (eg, bundle of Kent) between the atria and ventricles may bypass the AV node and contribute to the development of reentrant supraventricular tachyarrhythmias (eg, Wolff-Parkinson-White syndrome). The bundle of His pierces the connective tissue insulator of the cartilaginous cardiac skeleton and transmits the AV depolarization signal through the right and left bundle branches to the RV and LV myocardium, respectively, by an extensive Purkinje

TABLE 6.1 Cardiac Electrical Activation Sequence

Structure	*Conduction Velocity (m/s)*	*Pacemaker Rate (beats/min)*
SA node	<0.01	60–100
Atrial myocardium	1.0–1.2	None
AV node	0.02–0.05	40–55
Bundle of His	1.2–2.0	25–40
Bundle branches	2.0–4.0	25–40
Purkinje network	2.0–4.0	25–40
Ventricular myocardium	0.3–1.0	None

AV, Atrioventricular; *SA*, sinoatrial.

From Katz AM. *Physiology of the Heart.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

network located within the inner one-third of the ventricular walls. The bundle of His, the bundle branches, and the Purkinje network are composed of His-Purkinje fibers that ensure rapid, coordinated distribution of depolarization. This electrical configuration facilitates synchronous ventricular contraction and coordinated ejection.

Artificial cardiac pacing (eg, epicardial RV pacing) bypasses the normal conduction system and produces dyssynchronous LV activation. This dyssynchrony causes uncoordinated contraction that may reduce global LV systolic function, and it is a frequent cause of a new regional wall motion abnormality after cardiopulmonary bypass in cardiac surgical patients. This type of contractile dyssynchrony is also associated with chronic RV apical pacing (eg, for treatment of sick-sinus syndrome or an AV conduction disorder) and is known to cause detrimental effects on LV chamber geometry and function.[26] Recognition of the key relationship between a normal electrical activation sequence and LV contractile synchrony forms the basis for the successful use of cardiac resynchronization therapy in some patients with heart failure.[27]

Cardiac Myocyte Anatomy and Function

Ultrastructure

The ultrastructure of the cardiac myocyte is an elegant example of form following function. The sarcolemma is the external membrane of the cardiac muscle cell. This bilayer lipid membrane contains ion channels (eg, Na^+, K^+, Ca^{2+}, Cl^-), active and passive ion transporters (eg, Na^+/K^+-ATPase, Ca^{2+}-ATPase, Na^+/Ca^{2+} or Na^+/H^+ exchangers), receptors (eg, β_1-adrenergic, muscarinic cholinergic, adenosine, opioid), and transport enzymes (eg, glucose transporter) that modulate intracellular ion concentrations, regulate homeostasis of electrophysiology, mediate signal transduction, and provide substrates for metabolism. Sarcolemmal invaginations (ie, transverse [T] tubules) penetrate deeply within the myoplasm to facilitate rapid, synchronous transmission of cellular depolarization.

The myocyte contains large numbers of mitochondria that are responsible for the generation of high-energy phosphates (eg, adenosine triphosphate [ATP], creatine phosphate) required for contraction and relaxation (Fig. 6.3). The sarcomere is the contractile unit of the cardiac myocyte. Its myofilaments are arranged in parallel, cross-striated bundles of thin fibers that contain actin, tropomyosin, and the troponin complex and thick fibers that are primarily composed of myosin and its supporting proteins. Sarcomeres are connected in series, and the long and short axes of each myocyte simultaneously shorten and thicken, respectively, during contraction.

Light and electron microscopic observations have elucidated sarcomere structure. Thick and thin fibers functionally interact in an area called the *A band*, which becomes wider as the sarcomere shortens, indicating more pronounced overlap. The sarcomere region containing only thin filaments is called the *I band*. The width of this band is reduced during myocyte contraction. One *Z line* (from the German *zuckung*, meaning "to twitch") bisects each I band. The Z line is the border at which two adjacent sarcomeres are joined. An A band and two split I bands (between the Z lines) constitute the length of each sarcomere. The A band also contains a central *M band* composed of thick filaments oriented in a cross-sectional hexagonal arrangement by myosin binding protein C.

Each cardiac myocyte contains a dense sarcoplasmic reticulum (SR) network that surrounds the contractile proteins. The SR is the primary calcium ion (Ca^{2+}) reservoir of the cardiac myocyte, and its extensive distribution ensures an almost homogenous dispersal and reaccumulation of activator Ca^{2+} throughout the myofilaments during contraction and relaxation, respectively. The SR contains specialized structures known as subsarcolemmal cisternae that are located adjacent to the sarcolemma and the T tubules. These cisternae contain ryanodine receptors that are the SR's primary Ca^{2+} release channel and stimulate Ca^{2+}-induced Ca^{2+} release from the SR immediately upon sarcolemmal depolarization.

The contractile apparatus and the mitochondria that supply its energy comprise more than 80% of the myocyte's total volume, whereas the cytosol and nucleus occupy less than 15%. Contraction (not protein synthesis) is the predominant function of the cardiac myocyte. Intercalated disks mechanically join adjacent myocytes by the fascia adherens (which links actin molecules at each Z line) and desmosomes, and they create electrical transparency between myocytes through gap junctions that allow diffusion of ions and small molecules.

Proteins of the Contractile Apparatus

The contractile apparatus has six major components: myosin, actin, tropomyosin, and the three-protein troponin complex. Myosin (500 kDa, 0.17 µm long) contains a pair of intertwined α-helical proteins (ie, tails), each with a globular head that binds the actin molecule, and two adjoining pairs of light chains. Enzymatic digestion of myosin reveals light meromyosin that is composed of the tail sections and heavy meromyosin that contains the globular heads and

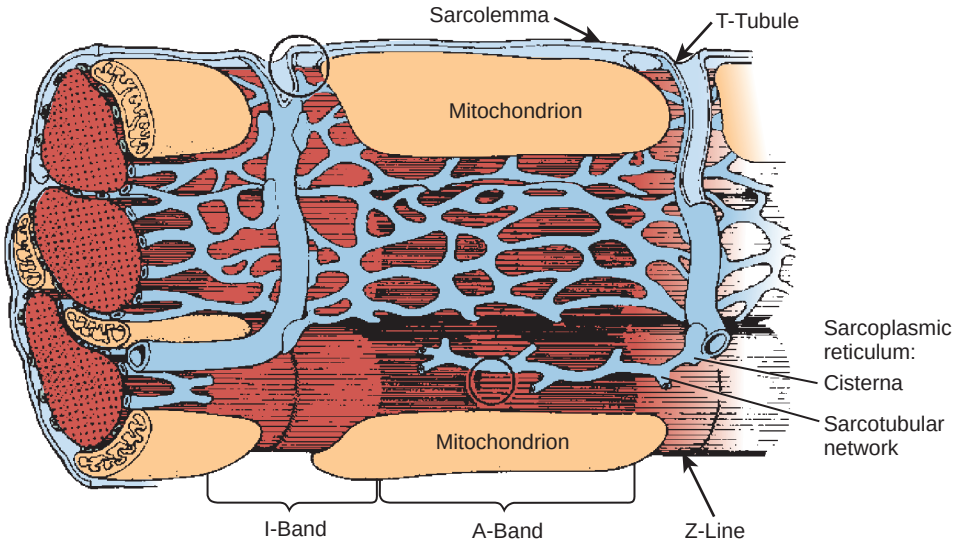

Fig. 6.3 Arnold Katz's schematic depiction of the ultrastructure of the cardiac myocyte. *(From Katz AM. Physiology of the Heart. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)*

the light chains. The primary structural support of the myosin molecule is the light meromyosin. The globular heads of the myosin dimer contain two hinges that are located at the distal light chain tail—double helix junction. The hinges are responsible for myofilament shortening during contraction.

Binding of the myosin head to the actin molecule stimulates a cascade of events initiated by activation of a myosin ATPase that mediates hinge rotation and actin release during contraction and relaxation, respectively. Myosin ATPase activity is a major determinant of the maximal velocity of sarcomere shortening. Several myosin ATPase isoforms have been identified in adult and neonatal atrial and ventricular myocardium that are distinguished by their relative ATPase activity. Myosin molecules are oriented in series along the length of the thick filament, and are joined tail to tail in the filament's center at the M line. This orientation produces equivalent shortening of each one-half of the sarcomere as the actin molecules are pulled toward the center.

The four light chains in the myosin complex are considered regulatory or essential. Regulatory myosin light chains influence myosin-actin interaction by modulating Ca^{2+}-dependent protein kinase phosphorylation. Essential light chains serve important but not precisely defined roles in myosin activity because their removal denatures the myosin molecule. From a pathologic perspective, myosin light chain isoform alterations from ventricular to atrial forms occur in LV hypertrophy that may contribute to contractile dysfunction.[28] Genetic modulation of light chain isoform expression may form the basis of reduced contractile function in some disease states.

Thick filaments are composed of myosin and its binding protein and contain titin, a long, elastic molecule that attaches myosin to the Z lines. Titin is a major contributor to myocardial elasticity, and similar to a bidirectional spring, it acts as a length sensor by establishing greater passive restoring forces as sarcomere length approaches its maximum or minimum.[29] Titin compression and stretching are observed during decreases and increases in load that limit additional shortening and lengthening of the sarcomere, respectively. Titin is another elastic element (in addition to actin and myosin) that mediates the stress-strain behavior of cardiac muscle.[30]

Actin, the major component of the thin filament, is a 42-kDa, oval, globular protein (ie, G-actin) with a diameter of 5.5 nm in greatest dimension. Actin also exists in a polymerized, filamentous configuration (ie, F-actin) wound in double-stranded helical chains of G-actin monomers that resemble two intertwined strands of pearls. Each complete helical revolution of F-actin contains 14 G-actin monomers and is 77 nm long. F-actin does not directly hydrolyze high-energy nucleotides, but the molecule does bind adenosine diphosphate (ADP) and divalent cations such as Ca^{2+} and Mg^{2+}. Actin functions as the activator (hence its name) of myosin ATPase through its reversible binding with myosin. The actin-myosin complex hydrolyzes ATP, supplying the energy required to cause the conformational changes in the myosin heads that mediate the cycle of contraction and relaxation within the sarcomere.

Tropomyosin is a major inhibitor of the interaction between actin and myosin in the myocyte sarcomere. The 40-nm-long molecule consists of a rigid, double-stranded, α-helical, coiled protein linked by a single disulfide bond. Human tropomyosin contains 34-kDa α and 36-kDa β isoforms and may exist as a homodimer (68 or 72 kDa) or heterodimer (70 kDa).[31] A Ca^{2+}-dependent interaction of tropomyosin with the troponin complex initiates excitation-contraction coupling. The association between sarcolemmal membrane depolarization and the resultant binding of actin and myosin is responsible for myocyte contraction. Tropomyosin also stiffens the thin filament because of its position within the longitudinal cleft between the interwoven F-actin helices. Several cytoskeletal proteins, including α-actinin, β-actinin, and nebulette, anchor the thin filaments to the Z lines of the sarcomere.[32]

The troponin complex consists of three proteins that regulate the contractile apparatus. Each serves a distinct role.[33] Troponin complexes are interspersed at 40-nm intervals along the thin filament. A highly conserved, single isoform of troponin C (named for the molecule's Ca^{2+}-binding ability) exists in cardiac muscle. Troponin C consists of a central nine-turn α-helix separating two globular regions that contain four discrete, divalent, cation-binding amino acid sequences, two of which (ie, sites I and II) are Ca^{2+} specific. As a result, the troponin C molecule responds directly to the changes in intracellular Ca^{2+} concentration during depolarization and repolarization of the cardiac myocyte.

The 23-kDa troponin I (ie, inhibitor troponin) exists as a single isoform. Troponin I alone weakly interferes with the actin-myosin interaction, but it becomes the major inhibitor of actin-myosin binding when combined with tropomyosin. This inhibition is responsive to receptor-operated signal transduction because the troponin I molecule contains a serine residue that is susceptible to protein kinase A (PKA)–mediated phosphorylation through the intracellular second messenger cyclic adenosine monophosphate (cAMP). Phosphorylation of this serine residue reduces the ability of troponin C to bind Ca^{2+}, an action that facilitates relaxation during administration of positive inotropic drugs, including β-adrenoceptor agonists (eg, dobutamine) and phosphodiesterase fraction III inhibitors (eg, milrinone).

Troponin T (ie, form that can bind other troponin molecules and tropomyosin) is the largest of the troponin proteins and has four major human isoforms. Troponin T serves as an anchor for the other troponin molecules and may influence the relative Ca^{2+} sensitivity of troponin C.[34]

Calcium-Myofilament Interaction

Binding of Ca^{2+} and troponin C produces a sequence of conformational changes in the troponin-tropomyosin complex that expose the specific myosin-binding site on actin (Fig. 6.4). Small amounts of Ca^{2+} are bound to troponin C when the intracellular Ca^{2+} concentration is low during diastole (10^{-7} M). Under these conditions, the troponin complex confines each tropomyosin molecule to the outer region of the groove between F-actin filaments and prevents the myosin-actin interaction by inhibiting the formation of cross-bridges between these proteins.

The resting inhibitory state is rapidly transformed by the 100-fold increase in intracellular Ca^{2+} concentration (to 10^{-5} M) occurring as a consequence of sarcolemmal depolarization that opens L- and T-type Ca^{2+} channels, allows Ca^{2+} influx from the extracellular space, and stimulates ryanodine receptor–mediated Ca^{2+}-induced Ca^{2+} release from the SR. Ca^{2+} binding to troponin C occurs under these conditions, an action that elongates the troponin C protein and enhances its interactions with troponin T and I. These Ca^{2+}-mediated allosteric alterations in the structure of the troponin complex weaken the interaction between troponin I and actin, promote repositioning of the

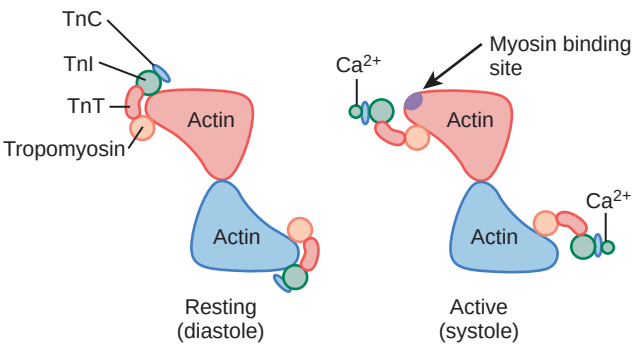

Fig. 6.4 Cross-sectional schematic illustration demonstrates the structural relationship between the troponin-tropomyosin complex and the actin filament under resting conditions (ie, diastole) and after Ca^{2+} binding (ie, systole). Ca^{2+} binding produces a conformational shift in the troponin-tropomyosin complex toward the groove between the actin molecules, exposing the myosin binding site on actin. *TnC,* Troponin C; *TnI,* troponin I; *TnT,* troponin T. *(From Katz AM.* Physiology of the Heart. *3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)*

tropomyosin molecule relative to the F-actin filaments, and minimize the inhibition of actin-myosin binding by tropomyosin that occurs during low intracellular Ca^{2+} concentrations.[35]

Binding of Ca^{2+} to troponin C stimulates several changes in the chemical conformation of the regulatory proteins that result in the exposure of the myosin-binding site on the actin molecule. Opening of the myosin-binding site allows cross-bridge formation and contraction to occur. Subsequent dissociation of Ca^{2+} from troponin C fully reverses the antagonism of inhibition, preventing further myosin-actin interaction and facilitating relaxation by rapidly restoring the original conformation of the troponin-tropomyosin complex on F-actin.

An energy-dependent ion pump located in the SR membrane, the sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA), removes most Ca^{2+} ions from the myofilaments and the myoplasm after the sarcolemmal membrane becomes repolarized. Activator Ca^{2+} is stored in the SR at a concentration of approximately 10^{-3} M and is transiently bound to calsequestrin and calreticulin until the next sarcolemmal depolarization occurs and the ryanodine receptor–activated SR channels open again.

Another Ca^{2+}-ATPase and a Na^{+}/Ca^{2+} exchanger (passively driven by ion concentration gradients) are located in the sarcolemmal membrane and play roles in the removal of Ca^{2+} from the myoplasm after repolarization. Phospholamban is a 6-kDa protein located in the SR membrane that modulates the activity of SERCA by partially inhibiting the dominant form (ie, type 2a) of this Ca^{2+} pump under baseline conditions. However, PKA-induced phosphorylation of phospholamban antagonizes this baseline inhibition and enhances SERCA-mediated Ca^{2+} uptake into the SR.[36] Medications such as dobutamine and milrinone that act by modifying PKA-mediated signal transduction enhance the rate and extent of relaxation by facilitating Ca^{2+} reuptake (ie, positive lusitropic effect) while simultaneously increasing the amount of Ca^{2+} available for the next contractile activation (ie, positive inotropic effect).

Biochemistry of Myosin-Actin Interaction

The biochemistry of cardiac muscle contraction is most often described using a four-component kinetic model (Fig. 6.5).[37] High-affinity binding of ATP to the catalytic domain of myosin initiates a coordinated sequence of events that results in sarcomere shortening. The myosin ATPase enzyme hydrolyzes the ATP molecule into ADP and inorganic phosphate. These products remain bound to myosin, forming an active complex that retains the reaction's chemical energy as potential energy. In the absence of actin, ADP and phosphate eventually dissociate from myosin, and the muscle remains relaxed.

When the myosin-ADP-phosphate complex is bound to actin, myosin ATPase activity is markedly enhanced, and the energy released by ATP hydrolysis is translated into mechanical work. First, myosin binding to actin releases the phosphate anion from the myosin head, producing a tension-inducing molecular conformation within the cross-bridge.[38] Second, release of ADP and potential energy from this activated orientation combine to rotate the cross-bridge (ie, power stroke) at the hinge point separating the helical tail from the globular head of the myosin molecule. Each cross-bridge rotation generates approximately 3.5×10^{-12} newtons of force, and myosin moves 11 nm along the actin molecule.[39] Third, the active-state myosin-actin complex does not immediately dissociate from actin after rotation; it remains in a low-energy bound state (ie, rigor). Fourth, dissociation of the myosin and actin molecules occurs only when a new ATP molecule binds to myosin. This four-step process is then repeated, assuming an adequate supply of ATP and lack of inhibition of the myosin-binding site on actin by the troponin-tropomyosin complex.

Several factors affect cross-bridge biochemistry and the sarcomere shortening that it produces. The maximal velocity of unloaded muscle shortening (V_{max}) is directly related to myosin ATPase activity. The 100-fold increase in intracellular Ca^{2+} concentration associated with sarcolemmal depolarization enhances myosin ATPase activity by a factor of five before it interacts with actin, increasing V_{max}. The extent of sarcomere shortening during contraction also depends on sarcomere length before sarcolemmal depolarization. This length-dependent activation (ie, preload) is known as the Frank-Starling effect in the intact heart, and it may be related to an increase in myofilament Ca^{2+} sensitivity, more optimal spacing between actin and myosin, or titin-induced elastic recoil. Abrupt increases in load during shortening (ie, Anrep effect) or after an extended pause between a series of contractions (ie, Woodworth phenomenon) cause transient increases in

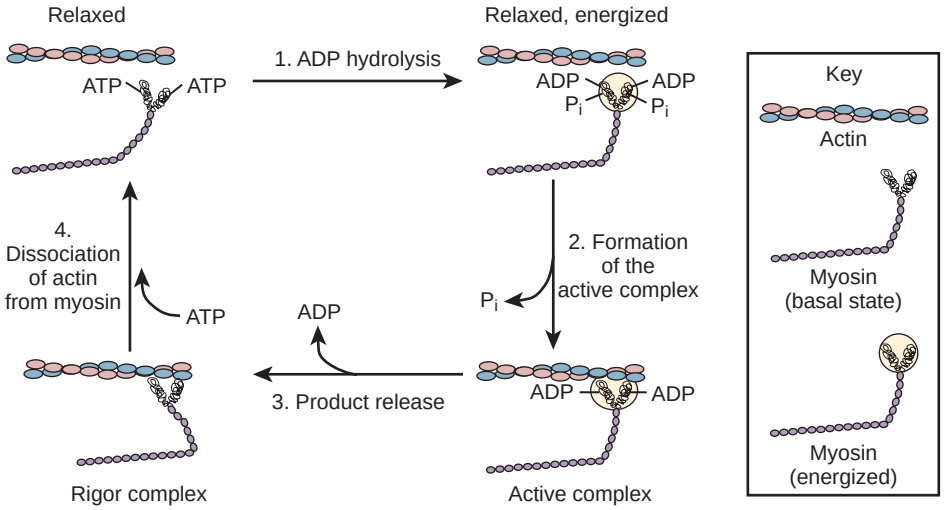

Fig. 6.5 The four-step reaction mechanism for actin-myosin ATPase begins with ATP bound to the myosin heads. Hydrolysis of myosin-bound ATP *(step 1)* energizes the myosin heads, which retain the products of the reaction, ADP and P_i, as potential energy. At the end of this reaction, the muscle remains relaxed because myosin is not attached to actin. Dissociation of phosphate occurs when the activated myosin heads bind to the actin filament *(step 2)*. The dissociation of ADP from the myosin heads releases the chemical energy of the ATP hydrolysis and shifts the position of the myosin cross-bridge, performing mechanical work *(step 3)*. Binding of new ATP molecules to the myosin head dissociates this rigor complex and completes the cycle *(step 4)*. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; P_i, phosphate. *(From Katz AM. Physiology of the Heart. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)*

contractile force through such a length-dependent activation mechanism. An increase in stimulation frequency also augments shortening through enhanced myofilament Ca^{2+} sensitivity and more pronounced release of Ca^{2+} from the SR.

Laplace's Law

The sarcomere generates tension and shortens during contraction. The developed tension is released and the sarcomere lengthens during relaxation. However, the intact heart produces pressure on and forces ejection of a volume of blood. The alterations in muscle tension and length observed in the sarcomere require transformation into the phasic changes in pressure and volume that occur in the intact heart.[40]

Laplace's law facilitates conversion of the contractile behavior of individual sarcomeres or isolated, linear cardiac muscle preparations in vitro into three-dimensional chamber function in vivo, permitting systematic examination of the intact heart's ability to function as a hydraulic pump. The relationship between myocyte length and chamber volume (V) may be modeled as a pressurized, spherical shell (Fig. 6.6),[41] for which volume is proportional to the cube of the radius (r): $V = 4\pi r^3/3$. This model may be pedagogically useful for the following discussion, but the LV and the atria are more precisely described using prolate ellipsoidal geometry, which defines three axes corresponding to the anteroposterior, septal-lateral, and long-axis diameters (D_{AP}, D_{SL}, and D_{LA}, respectively) such that $V = \pi D_{AP} D_{SL} D_{LA}/6$. This technique of measuring LV or atrial volume more closely approximates anatomic reality and has been validated extensively in experimental animals[42,43] and humans.[44,45] However, the method does not apply when attempting to describe RV volume because of the unique bellows-shaped structure of this chamber.[46]

The relationship between wall stress (ie, tension exerted over a cross-sectional area) and pressure within a cardiac chamber is complex. Laplace's law relates wall stress to pressure and chamber geometry, which may be determined based on three assumptions.[40] First, the chamber is spherical with a uniform wall thickness (h) and an internal radius (r). Second, the stress (σ) throughout the thickness of the chamber wall is constant. Third, the chamber remains in static equilibrium (ie, is not actively contracting). Tension development within each sarcomere causes a corresponding increase in wall stress that is translated into the generation of hydraulic pressure within the chamber. In this context, internal pressure (P) is defined as an orthogonal distending force exerted against the chamber walls, and wall stress is a shear force exerted around the circumference of the chamber that resists the distention.[40]

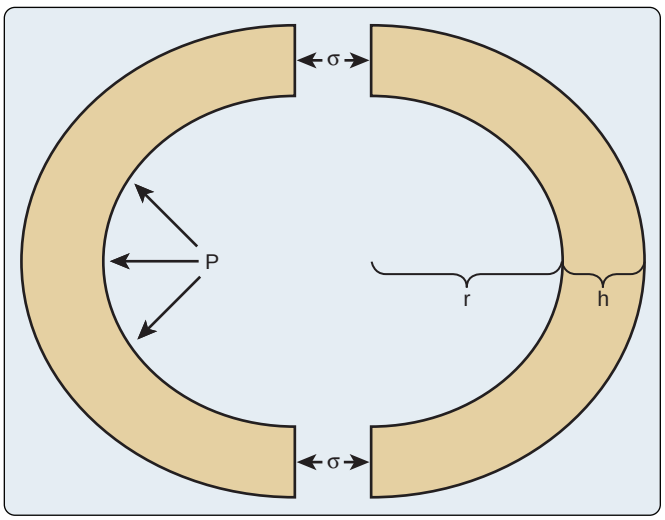

Fig. 6.6 Opposing forces within a theoretical LV sphere that determine Laplace's law. The LV pressure *(P)* tends to push the sphere apart, whereas wall stress *(σ)* holds the sphere together. *h*, Thickness; *LV*, left ventricular; *r*, radius.

Bisecting the chamber into two equal halves exposes the internal forces within it (see Fig. 6.6). The product of internal pressure and wall cross-sectional area (πr^2) represents the total force pushing chamber hemispheres apart. In contrast, the total force within the chamber walls resists this distracting force and is equal to σ times the cross-sectional wall area. The two forces must balance for the chamber to remain in equilibrium such that $P\pi r^2 = \sigma[\pi (r + h)^2 - \pi r^2]$. Removal of redundant terms simplifies this equation to $Pr = \sigma h(2 + h/r)$. The chamber wall is normally thin relative to its internal radius. As a result, the h/r term may be neglected, and the remaining expression may be rearranged to become the familiar $\sigma = Pr/2h$.

Laplace's law for a thin-walled, static sphere indicates that wall stress varies directly with internal pressure and radius and inversely with wall thickness. Despite the observation that the ratio of wall thickness to radius is not entirely negligible (h/r = 0.4) at LV end-diastole in the intact heart,[47] Laplace's law provides a very useful description of the factors that contribute to changes in LV or atrial wall stress. For example, LV dilation (ie, increased r) associated with chronic aortic insufficiency increases global LV wall stress that reflects greater tension on each sarcomere within the chamber wall.[48] Similarly, the persistent elevation of LV pressure (P) observed in the setting of severe aortic stenosis also produces greater stress on the LV wall. The increases in wall stress resulting from chronic volume or pressure overload are directly translated into greater myocardial oxygen consumption because the myofilaments require more energy to develop enhanced tension. In contrast, an increase in wall thickness (h) causes a reduction in global wall stress and tension developed by individual sarcomeres. Laplace's law predicts that hypertrophy is an important compensatory adaptation to chronically altered chamber load that reduces the tension generated by each muscle fiber.

Prolate ellipsoidal models of chamber geometry and those incorporating orthogonal radial, circumferential, and meridional components of wall stress require more complex derivations of Laplace's law[49] that may be corrected with dimensional measurements obtained using echocardiography.[50] Formal derivations of these models are beyond the scope of this chapter, but they are available elsewhere.[51,52] Despite their relative mathematical complexity, the principles linking changes in length and tension in the sarcomere to pressure, volume, and wall thickness in the intact heart are consistently demonstrated in these models.

In contrast to the assumption used in the derivation of Laplace's law described earlier, wall stress is not uniformly distributed across LV thickness in the intact heart.[51] Instead, wall stress is greatest in the subendocardium and progressively declines to a minimum at the epicardial surface. These regional differences in wall stress become especially important in LV pressure-overload hypertrophy, which results from aortic valve stenosis or poorly controlled essential hypertension.[54] Under these conditions, the subendocardium is exposed to more pronounced increases in interventricular pressure concomitant with greater myocardial oxygen consumption that make it more susceptible to acute myocardial ischemia. The combination of elevated subendocardial wall stress and increased myocardial oxygen consumption is particularly deleterious in the setting of a flow-limiting coronary artery stenosis and often contributes to the relatively common occurrence of subendocardial myocardial infarction in the absence of complete coronary occlusion in patients with severe LV hypertrophy.

The Cardiac Cycle

A schematic illustration of the cardiac cycle is useful for demonstrating the highly coordinated, temporally related series of electrical, mechanical, and valvular events that occur with contraction and relaxation of the cardiac chambers (Fig. 6.7).[55] A single cardiac cycle occurs in 0.8 s at a heart rate of 75 beats/minute. Synchronous depolarization of RV and LV myocardium (as indicated by the electrocardiogram QRS complex) initiates contraction of and produces a rapid increase in

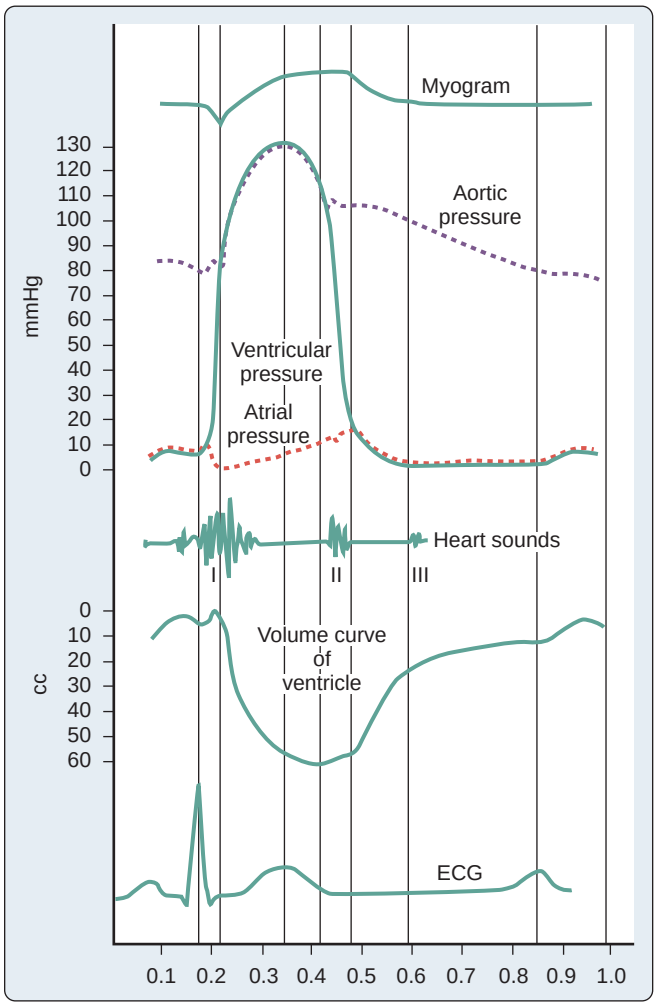

Fig. 6.7 Carl Wiggers' original illustration depicting the electrical, mechanical, and audible events of the cardiac cycle, including the electrocardiogram; aortic, left ventricular, and left atrial pressure waveforms; left ventricular volume waveform; and heart tones associated with mitral and aortic valve closure. *(From Wiggers CJ: The Henry Jackson Memorial Lecture. Dynamics of ventricular contraction under abnormal conditions.* Circulation. *1952;5:321–348.)*

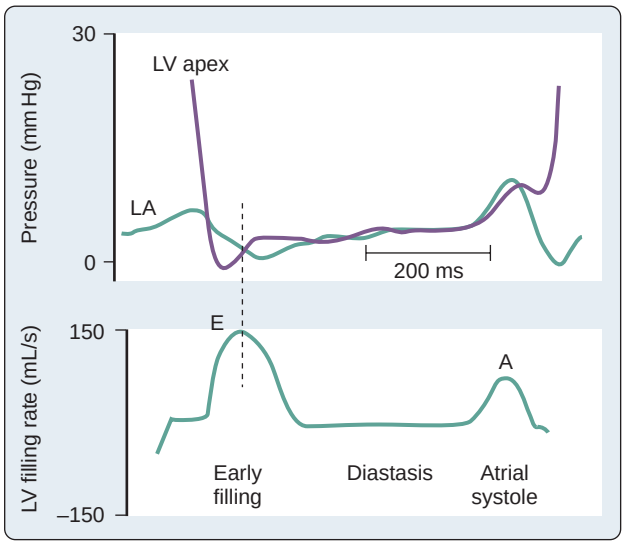

Fig. 6.8 Diagram depicting the relationship between left ventricular *(LV)* and left atrial *(LA)* pressure *(top)* and the corresponding LV filling rate *(bottom)* during early filling *(E)*, diastasis, and atrial systole *(A)*. The LV pressure initially falls below the LA pressure, creating a pressure gradient between the chambers that causes early LV filling. *(From Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care.* Circulation. *2009;120:802–809.)*

pressure within these chambers (ie, systole). Closure of the tricuspid and mitral valves occurs when RV and LV pressures exceed the corresponding atrial pressures and causes the first heart sound (S_1).

LV systole is divided into isovolumic contraction, rapid ejection, and slower ejection phases. LV isovolumic contraction describes the time interval between mitral valve closure and aortic valve opening during which LV volume remains constant. This event is somewhat analogous to isometric (ie, constant length) contraction of isolated cardiac muscle in papillary muscle preparations in vitro. Nevertheless, global LV geometry is transformed from an ellipsoidal shape at end-diastole to a more spherical configuration during isovolumic contraction because the length of the longitudinal axis (ie, base to apex) shortens, and LV wall thickness increases.[56] The maximal rate of increase of LV pressure (dP/dt_{max}) occurs during LV isovolumic contraction and may be used to estimate myocardial contractility in vivo. True isovolumic contraction does not occur in the RV because of the sequential nature of contraction of the inflow and outflow tracts.[57] The pressures in the aortic and pulmonic roots fall to their minimal value immediately before the corresponding valves open. Rapid ejection occurs when LV and RV pressures exceed aortic and pulmonary arterial pressures, respectively.

Approximately two-thirds of the end-diastolic volume of each ventricle is ejected during the rapid-ejection phase. Dilation of the elastic aorta and proximal great vessels and the pulmonary artery and its proximal branches occurs concomitant with the rapid increase in volume as the kinetic energy of LV and RV contraction is transferred to the aorta and pulmonary artery, respectively, as potential energy. The pressure gradients cause the aortic and pulmonic valves to close, an action that produces the second heart sound (S_2). This event signifies the end of systole and the beginning of diastole. The aortic valve closes slightly before the pulmonic valve during inspiration because RV ejection is modestly prolonged by augmented venous return. The temporal discrepancy between aortic and pulmonic valve closure causes physiologic splitting of S_2. The normal end-diastolic (V_{ed}) and end-systolic (V_{es}) volumes are approximately 120 and 40 mL, respectively. The difference between V_{ed} and V_{es} (ie, the SV) is 80 mL, and the ratio of SV to V_{ed} (ie, the ejection fraction or EF) is 67%.[58]

Compliance of the proximal systemic and pulmonary arterial vessels determines the amount of potential energy that is stored and subsequently released to their respective distal vascular beds during diastole. Further ejection of additional blood from the LV and RV drops precipitously as the pressures within the aorta and pulmonary artery reach their maximal values. Ejection stops entirely when the LV and RV begin to repolarize and the arterial forces resisting further ejection are greater than the ventricular forces continuing to propel blood forward. As the period of slower ejection comes to an end, aortic and pulmonary artery pressures exceed LV and RV pressures.

LV diastole is divided into isovolumic relaxation, early ventricular filling, diastasis, and atrial systole. LV isovolumic relaxation defines the period between aortic valve closure and mitral valve opening during which LV volume remains constant. LV pressure falls very rapidly as the myofilaments relax. When LV pressure falls below LA pressure, the mitral valve opens, and blood volume stored in the LA enters the LV driven by the initial pressure gradient between the chambers. LV pressure continues to fall after mitral valve opening as sarcomere relaxation is completed and myocardial elastic components recoil (Fig. 6.8).[59–61] These factors contribute to the creation of a pressure gradient between the LA and LV that extends from the base to the apex.[60] The rate and extent of LV pressure decline and the LA pressure when the mitral

valve opens determine the initial magnitude of the pressure gradient between these chambers.[62]

Early LV filling occurs very rapidly, as indicated by the observation that the peak blood flow velocity across the mitral valve during this phase of diastole may exceed the flow rate across the aortic valve during LV ejection.[63] Vortex formation from the primary mitral blood flow jet also facilitates selective filling of the LV outflow tract.[64,65] Delays in LV relaxation may occur as a consequence of age or disease processes (eg, ischemia, hypertrophy) and are a common cause of attenuated early LV filling because the initial LA-LV pressure gradient is reduced.[66] After the mitral valve opens, the pressure gradient between the LA and LV depends on the relative pressure within each chamber. Most of the increase in LV volume observed during early ventricular filling occurs while LV pressure continues to decrease. The LV pressure falls to a subatmospheric level if blood flow across the mitral valve is completely obstructed.[8,67]

The data imply that the LV can continue to fill through the diastolic suction mechanism even if LA pressure is zero.[68,69] The diastolic suction effect is crucial for the preservation of early LV filling during profound hypovolemia and strenuous exercise. The early filling phase of diastole normally provides 70% to 75% of the total SV ejected during the subsequent LV contraction and ends when LA and LV pressures equilibrate or the gradient between these chambers transiently reverses. The mitral valve remains open, and pulmonary venous blood flow directly traverses the LA into the LV after the LA and LV pressures have equalized. The LA acts as a simple conduit during this diastasis phase of diastole, and LV filling markedly slows as a result. The small amount of blood flow from pulmonary veins occurring during diastasis usually adds less that 5% to the total LV SV.[70] Progressive increases in heart rate shorten and may completely eliminate diastasis, but tachycardia has little meaningful effect on overall LV filling because the contribution during diastasis is minor.

Atrial systole is the final phase of diastole. LA contraction increases the pressure in this chamber, creating a second positive pressure gradient for blood flow from the LA and LV during end-diastole. The peristaltic pattern of LA contraction and the unique anatomy of the pulmonary venous–LA junction largely prevent retrograde blood flow into the pulmonary veins during atrial systole at normal LA pressures.[71] Atrial systole usually accounts for 15% to 25% of total LV SV, but this LA component becomes especially important to the maintenance of LV filling in pathologic states characterized by delayed LV relaxation or reduced LV compliance.[72] Similarly, improperly timed LA contraction or the onset of atrial tachyarrhythmias (eg, atrial fibrillation) may cause profound hemodynamic compromise in patients with myocardial ischemia or pressure-overload hypertrophy who depend on atrial systole for LV filling. Descriptions of RV diastole are very similar to those used to characterize LV diastole, with the exception that true isovolumic relaxation most likely does not occur in the RV.

The LA pressure waveform is composed of three major deflections during normal sinus rhythm. The LA contracts immediately after the P wave of atrial depolarization, producing the *a* wave of atrial systole. This *a* wave may be enhanced by an increase in LA preload or contractile state. The rate of decline of the *a* wave is an index of LA relaxation,[73] similar to the rate of LV pressure fall during isovolumic relaxation. LV contraction with the onset of systole causes a pressure wave to be transmitted to the LA in retrograde fashion by closure of the mitral valve, resulting in a small increase in LA pressure. The *c* wave may be more pronounced in the setting of mitral valve prolapse.

During late LV isovolumic contraction, LV ejection, and most of LV isovolumic relaxation, pulmonary venous blood progressively fills the LA and gradually increases LA pressure, resulting in the LA *v* wave. The *v* wave may be enhanced in the setting of mitral regurgitation or reductions in LA compliance.[74]

RA pressure waveform deflections are very similar to those observed in the LA. The RA *a-c-v* waveform morphology is transmitted to the jugular veins and may be clinically observed in the neck during routine physical examination in the supine position. In contrast to the biphasic nature of LA and RA pressure waveforms, the volume waveforms of these chambers are essentially monophasic. For example, minimum LA volume occurs immediately after the completion of LA contraction and corresponds closely to the mitral valve closure, whereas maximal LA volume is observed immediately before the mitral valve opens.

Pressure-Volume Diagrams

A time-dependent, two-dimensional plot of continuous LV pressure and volume throughout a single cardiac cycle creates a phase space diagram, which is useful for analysis of LV systolic and diastolic function in the ejecting heart (Fig. 6.9). Otto Frank initially described the theoretic foundations of this technique at the end of the 19th century.[75,76] In the 1970s, Hiroyuki Suga and Kiichi Sagawa were the first to widely apply pressure-volume analysis after technologic advances enabled the continuous measurement of high-fidelity LV pressure with a miniature micromanometer implanted in the chamber and LV volume with sonomicrometry and a conductance catheter.[77–79] In 1988, the authors provided a detailed description of pressure-volume analysis of cardiac function in *Cardiac Contraction and the Pressure-Volume Relationship* (Oxford University Press, New York).

Alterations in LV pressure with respect to volume occur in a counterclockwise fashion over time. The cardiac cycle begins at end-diastole (see Fig. 6.9, point A). An abrupt increase in LV pressure at constant LV volume occurs during isovolumic contraction. Opening of the aortic valve occurs when LV pressure exceeds aorta pressure (see Fig. 6.9, point B) and ejection begins. LV volume decreases rapidly as blood is ejected from the LV into the aorta and proximal great vessels. When

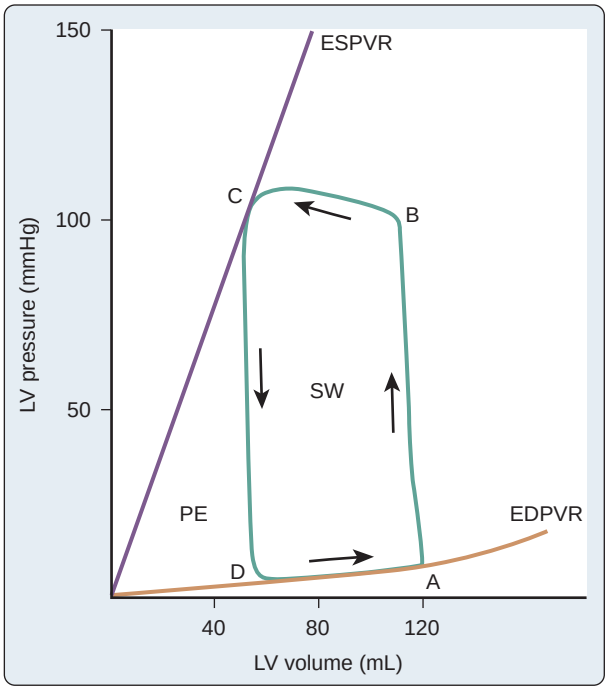

Fig. 6.9 As shown in the steady-state left ventricular *(LV)* pressure-volume diagram, the cardiac cycle proceeds in a time-dependent, counterclockwise direction *(arrows)*. Points A, B, C, and D correspond to LV end-diastole (ie, closure of the mitral valve), opening of the aortic valve, LV end-systole (ie, closure of the aortic valve), and opening of the mitral valve, respectively. Segments AB, BC, CD, and DA represent isovolumic contraction, ejection, isovolumic relaxation, and filling, respectively. The left ventricle is constrained to operate within the boundaries of the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR, respectively). The area inscribed by the LV pressure-volume diagram represents the stroke work *(SW)* (ie, kinetic energy) performed during the cardiac cycle. The area to the left of the LV pressure-volume diagram between ESPVR and EDPVR is the remaining potential energy *(PE)* of the system. The sum of SW and PE is the pressure-volume area.

LV pressure declines below aortic pressure at the end of ejection, the aortic valve closes (see Fig. 6.9, point C). This event is immediately followed by a rapid decline in LV pressure in the absence of changes in LV volume (ie, isovolumic relaxation). The mitral valve opens when LV pressure falls below LA pressure (see Fig. 6.9, point D), initiating LV filling. The LV pressure-volume diagram is completed as the LV refills its volume for the next contraction concomitant with relatively small increases in pressure during early filling, diastasis, and LA systole.

The steady-state LV pressure-volume diagram provides advantages over temporal plots of individual LV pressure and volume waveforms when identifying major cardiac events without electrocardiographic correlation (eg, aortic or mitral valve opening or closing) or evaluating acute alterations in LV loading conditions. For example, end-diastolic and end-systolic volumes may immediately be recognized as the lower right (point A) and upper left (point C) corners of the diagram, respectively, allowing rapid calculation of SV and EF. Movement of the right side of the pressure-volume diagram to the right is characteristic of an increase in preload concomitant with a larger SV, whereas an increase in afterload causes the pressure-volume diagram to become taller (ie, greater LV pressure) and narrower (ie, decreased SV) (Fig. 6.10). The area of the diagram precisely defines the LV pressure-volume (stroke) work (ie, kinetic energy) for a single cardiac cycle.

As illustrative as a single LV pressure-volume diagram may be for obtaining basic physiologic information, the dynamic changes of a series of these LV pressure-volume diagrams occurring during an acute alteration in LV load over several consecutive cardiac cycles provide unique insights into LV systolic and diastolic function. A series of differentially loaded LV pressure-volume diagrams may be produced using transient changes in preload or afterload with mechanical (ie, vena caval or aortic constriction, respectively) or pharmacologic (ie, sodium nitroprusside or phenylephrine infusions, respectively) interventions.

The nested set of diagrams allows calculation of relatively heart rate– and load-insensitive estimates of myocardial contractility in vivo such as the end-systolic pressure-volume relationship (ESPVR, the slope of which is called *end-systolic elastance* [E_{es}])[79] and the stroke work (SW)–end-diastolic volume relationship, a linear Frank-Starling analog also known as preload recruitable SW.[80] The family of pressure-volume diagrams also describes the end-diastolic pressure-volume relationship (EDPVR) that characterizes LV compliance and is an important determinant of LV filling.[40]

The ESPVR and EDPVR define the operating constraints of the LV (see Figs. 6.9 and 6.10). The ESPVR and EDPVR are determined by the intrinsic properties of the LV during systole and diastole, respectively, but the relative positions of the end-diastolic and end-systolic points that lie along these lines for any given cardiac cycle are established primarily by venous return (ie, preload) and arterial vascular tone (ie, afterload).[81] This model emphasizes that analysis of overall cardiovascular performance in vivo must not consider the LV and the circulation with which it interacts as independent entities.[82] The area to the left of the steady-state LV pressure-volume diagram that lies between the ESPVR and the EDPVR is the remaining potential energy of the system (see Fig. 6.9) and is an important factor in determining the LV energetics and mechanical efficiency.[83] RV systolic and diastolic function also may be quantified using the principles of this pressure-volume theory.[84]

Pressure-volume analysis provides a useful illustration of the pathophysiology of LV systolic or diastolic dysfunction as underlying causes for heart failure.[85] For example, a decrease in the ESPVR slope indicates that a reduction in myocardial contractility has occurred. This observation is consistent with pure LV systolic dysfunction. The event is often accompanied by a compensatory LV dilation (ie, movement of the pressure-volume diagram to the right) along a normal EDPVR (Fig. 6.11). The increase in preload may preserve SV and cardiac output (CO), but occurs at the cost of higher LV filling and pulmonary venous pressures.[81] In contrast, an increase in the EDPVR denotes a reduction in LV compliance such that LV diastolic pressure is higher at each LV volume. Under these circumstances, myocardial contractility may remain relatively normal (ie, ESPVR does not change), but LV filling pressures are elevated, producing pulmonary venous

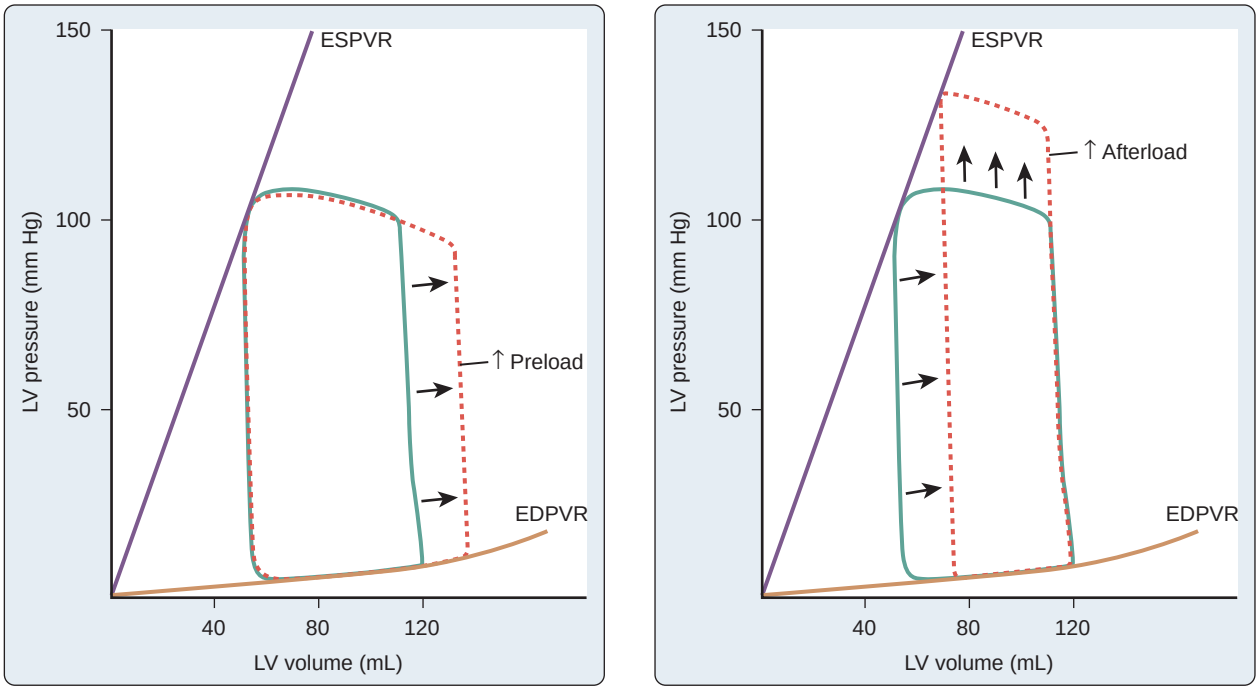

Fig. 6.10 Schematic illustrations of the alterations in the steady-state LV pressure-volume diagram produced by a pure theoretical increase in LV preload *(left)* or afterload *(right)*. Additional preload directly increases stroke volume *(SV)* and LV end-diastolic pressure, whereas an acute increase in afterload produces greater LV pressure but reduces SV. *EDPVR*, End-diastolic pressure-volume relationship; *ESPVR*. end-systolic pressure-volume relationship; *LV*, left ventricular.

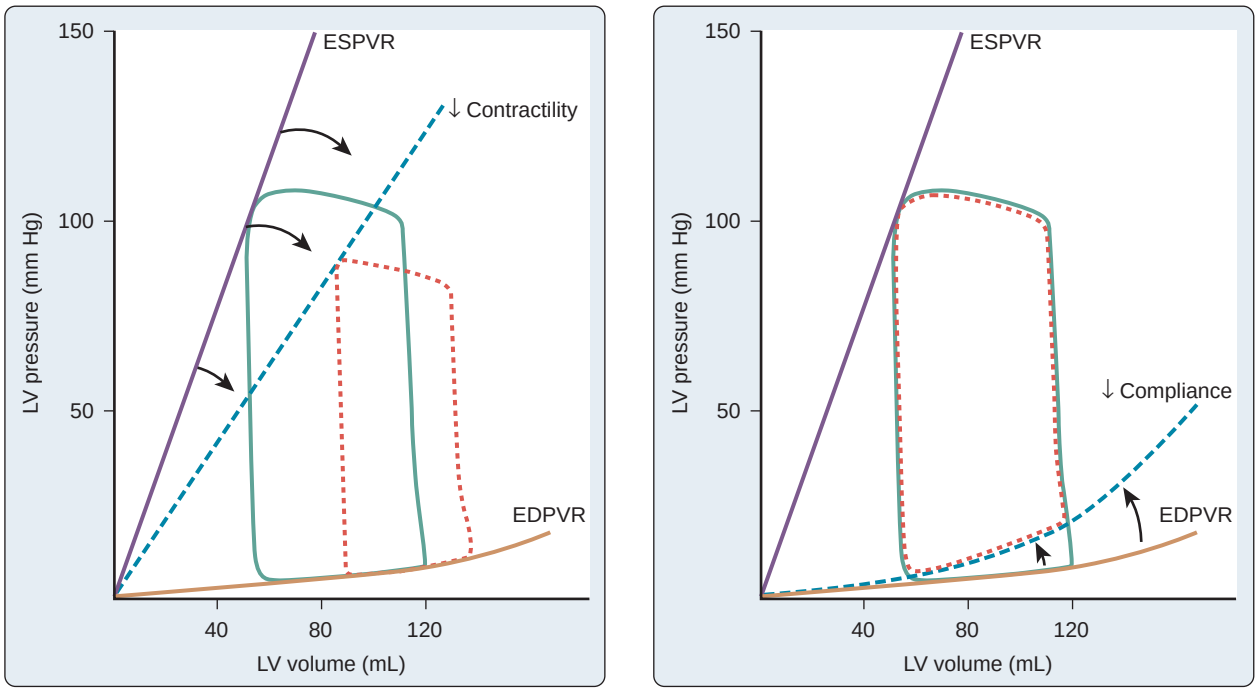

Fig. 6.11 Schematic illustrations of the alterations in the steady-state LV pressure-volume diagram produced by a reduction in myocardial contractility, as indicated by a decrease in the slope of the ESPVR (*left*), and a decrease in LV compliance as indicated by an increase in the position of the EDPVR (*right*). The diagrams emphasize that heart failure may result from LV systolic or diastolic dysfunction independently. *EDPVR*, End-diastolic pressure-volume relationship; *ESPVR*. end-systolic pressure-volume relationship; *LV*, left ventricular.

congestion and clinical symptoms (Fig. 6.11). Simultaneous depression of the ESPVR and elevation of the EDPVR indicate LV systolic and diastolic dysfunction. SV and CO may be severely reduced because available compensatory changes in preload or afterload, depicted by movement of the steady-state LV pressure-volume diagram within the ESPVR and the EDPVR boundaries, are quite limited.

The pressure-volume plane may be extrapolated to a single region or dimension of the LV, and analogous LV pressure-dimension relationships may then be analyzed.[86–88] For example, ultrasonic transducers placed within the LV wall may be used in the laboratory setting to measure changes in segment length[89] or LV diameter[90] during the cardiac cycle. Transducers also may be placed on the LV epicardial and endocardial surfaces to measure continuous changes in wall thickness.[88] The time for ultrasound to be transmitted between a pair of transducers is directly proportional to the length between them (ie, Doppler principle).

Segment length or chamber diameter normally increases during diastole and shortens during systole analogous to changes in continuous LV volume, whereas myocardial wall thickness decreases in diastole and increases during systole.[91] The changes in regional segment length and wall thickness during the cardiac cycle form the basis for speckle-tracking echocardiography.

Acute changes in LV loading conditions may be used to develop a series of diagrams for measurement of LV end-systolic and end-diastolic pressure–segment length, pressure–wall thickness, or pressure-dimension relationships. The use of regional compared with global LV pressure-volume analysis is particularly advantageous when studying the mechanical consequences of myocardial ischemia.[92] For example, acute occlusion of a major coronary artery produces a time-dependent collapse of the steady-state LV pressure-length diagram in the central ischemic zone consistent with a rapidly progressing decline and eventual complete absence of regional SW (Fig. 6.12). In contrast, the LV pressure–segment length diagram tilts to the right in a moderately ischemic area such as a border zone surrounding a central ischemic region. The diagram may be divided into three regions that correspond to systolic lengthening (ie, due to paroxysmal systolic aneurysmal bulging of the ischemic zone), postsystolic shortening (ie, shortening in the ischemic zone that occurs after ejection as a result of tethering to adjacent normal myocardium), and a variable area between the two that makes a contribution to regional LV SW (Fig. 6.13). These parameters may be used to quantify the relative severity of regional myocardial ischemia.[93]

Pressure-volume analysis may be applied to the study of atrial function. In contrast to the almost rectangular shape of the LV pressure-volume diagram, the steady-state LA or RA pressure-volume diagram is composed of two intersecting loops arranged in a horizontal figure-eight pattern that incorporates active (ie, A loop) and passive (ie, V loop) components (Fig. 6.14).[94] The unusual shape of the LA pressure-volume diagram results from the biphasic morphology of the LA pressure waveform (discussed earlier).

Beginning at LA end-diastole (ie, corresponding to the end of LV diastasis), the active component of the diagram traces a counterclockwise outline as the LA ejects its contents into the LV through the open mitral valve. LA end-systole (ie, corresponding to LV end-diastole) marks the end of atrial contraction and is defined at minimal LA volume. Identification of LA end-diastole and end-systole on the diagram facilitates calculation of LA SV and emptying fraction (ie, analogous to LV EF).

After the mitral valve closes, LA filling occurs during LV systole and isovolumic relaxation. LA pressure and volume gradually increase as the chamber is filled with pulmonary venous blood during this reservoir phase, forming the bottom part of the A loop and the upper part of the V loop. The area of the A loop represents active LA SW[95] (ie, analogous to LV SW, the area inscribed by the LV pressure-volume diagram). The passive component (ie, V loop) of the LA pressure-volume diagram proceeds in a clockwise direction (see Fig. 6.14).

Total LA reservoir volume is easily determined from the steady-state LA pressure-volume diagram as the difference between maximal and minimal LA volumes.[73] The V loop area represents the total passive elastic energy stored by the LA during the reservoir phase, and it is an

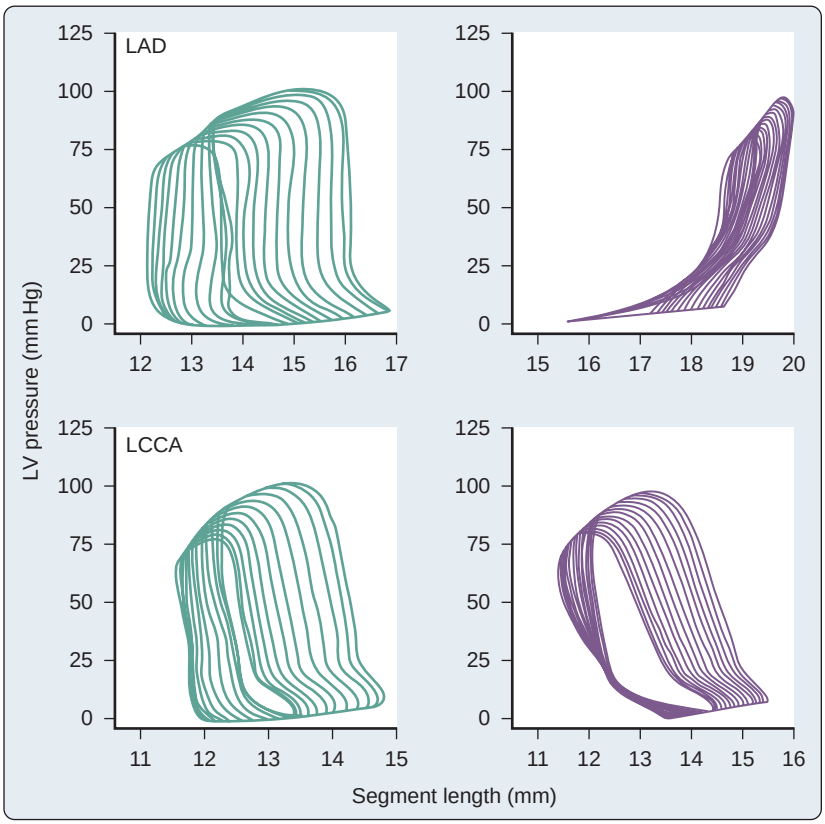

Fig. 6.12 Differentially loaded left ventricular (LV) pressure–segment length diagrams depict an abrupt occlusion of the inferior vena cava in the left anterior descending *(LAD)* and left circumflex coronary artery *(LCCA)* perfusion territories before *(left)* and during *(right)* a 2-minute occlusion of the LAD in a conscious, chronically instrumented dog. Aneurysmal systolic lengthening, postsystolic shortening, loss of effective stroke work, and diastolic creep (ie, segment expansion) occur in the LAD LV pressure–segment length diagram in response to ischemia in this region. Corresponding isovolumic shortening and early diastolic lengthening in the LCCA LV pressure–segment length diagram also occur as the contraction and relaxation of non–ischemic-zone myocardium and partially compensate for the adjacent dyskinetic region. *(Modified from Pagel PS, Hettrick DA, Lowe D, et al. Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs.* Anesthesiology. *1995;83:1021–1035.)*

index of reservoir function.[96] The slope of the line between minimal LA pressure of the A loop and maximum LA pressure in the V loop has been used as an index of static LA compliance. Regional myocardial ischemia[24] or severe LV dysfunction[97] increases the slope of this line, indicating a decrease in compliance. LA emptying after mitral valve opening causes a rapid decline in LA volume that forms the bottom portion of the V loop. Additional pulmonary venous return also enters the LA during LV diastasis, but this blood flow does not alter LA volume because the mitral valve is open.

The LA conduit phase occurs between mitral valve opening and LA end-diastole, and LA conduit volume is calculated as the difference between maximum and end-diastolic volumes (see Fig. 6.14). The relationships among LA loading conditions, LA and LV contractile states, the rate and extent of LA relaxation, LA elastic properties, and pulmonary venous blood flow determine the relative areas of the A and V loops and the point of intersection between them.[94] Analogous to observations of the LV acute alterations in LA loading conditions may be used to assess LA myocardial contractility and dynamic compliance using LA end-systolic and end-reservoir pressure-volume relationships.[43,98,99]

Determinants of Pump Performance

The ability of each cardiac chamber to function as a hydraulic pump depends on how effectively it can collect (ie, diastolic function) and eject (ie, systolic function) blood. For the sake of this discussion, we focus on the LV, but the principles that determine LV pump performance are equally applicable to the other chambers.

From a clinical perspective, LV systolic function is most often quantified using CO (ie, product of heart rate and SV) and EF. These variables depend on the intrinsic contractile properties of the LV myocardium, the quantity of blood the chamber contains immediately before contraction commences (ie, preload), and the external resistance to emptying with which it is confronted (ie, afterload). The interactions among preload, afterload, and myocardial contractility establish the SV generated during each cardiac cycle (Fig. 6.15).

When combined with heart rate and rhythm, preload, afterload, and myocardial contractility determine the volume of blood that the LV can pump per minute (ie, CO), assuming adequate venous return. Mitral or aortic valve malfunction (eg, regurgitation) or an anatomically abnormal route of intracardiac blood flow (eg, ventricular septal defect with left-to-right shunt) reduces effective forward flow, limiting the use of SV, CO, and EF as indices of LV systolic performance.

The LV's structural integrity is an important determinant of its systolic function. Pulmonary venous blood flow, LA function, mitral valve dynamics, pericardial restraint, and the active (ie, relaxation) and passive elastic (ie, compliance) properties of the LV during diastole determine its ability to properly fill. LV diastolic function is considered normal when these factors combine to provide an LV preload that provides sufficient CO to satisfy cellular metabolism without elevations

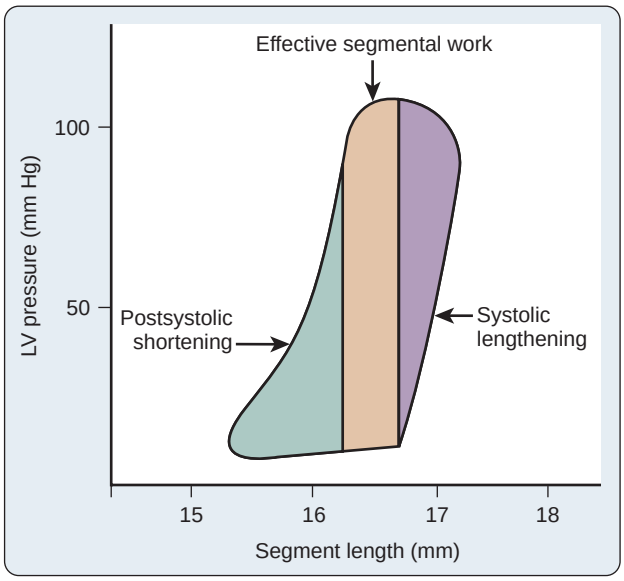

Fig. 6.13 The steady-state left ventricular (LV) pressure–segment length is measured within the border zone of the central ischemic region during acute occlusion of the left anterior descending coronary artery in a dog. Areas of systolic lengthening *(right)* and postsystolic shortening *(left)* produced by partial ischemia and tethering to the central ischemic zone do not contribute to segmental work, but a small area of the diagram *(center)* demonstrates effective segment shortening that contributes to global LV stroke work.

in pulmonary venous and mean LA pressures (ie, normal values of approximately 10 mm Hg for each).[100] In contrast, LA or mitral valve dysfunction, delayed LV relaxation, reduced LV compliance, or increased pericardial pressure may substantially restrict the ability of the LV to properly fill unless pulmonary venous and LA pressures increase. LV diastolic dysfunction is invariably associated with greater pulmonary venous and LA pressures. LV diastolic dysfunction may produce signs and symptoms of congestive heart failure independent of changes in LV systolic function.

Heart Rate

An alteration in the stimulation frequency of isolated cardiac muscle produces a parallel change in LV contractile state. The Bowditch, staircase, or *treppe* (German for "stair") phenomenon is a force-frequency relationship in which a gradual increase in muscular contraction follows rapidly repeated stimulation. The effect has been demonstrated in isolated LV muscle[101] and intact LV.[102] Enhanced Ca^{2+} cycling efficiency and increased myofilament Ca^{2+} sensitivity are responsible for the stimulation-rate dependence of the contractile state.

Maximal contractile force occurs at 150 to 180 stimulations per minute during isometric contraction of isolated cardiac muscle. From a clinical perspective, the treppe-induced increase in LV contractility is especially important during exercise by matching CO to venous return, which occurs at heart rates approaching 175 beats/minute in highly trained athletes. However, contractility deteriorates above this heart rate because the intracellular mechanisms responsible for Ca^{2+} removal from the contractile apparatus are overwhelmed, and LV diastolic filling time is markedly attenuated.[103] These factors directly contribute to the development of hypotension during tachyarrhythmias or very rapid pacing. An increase in heart rate within the normal physiologic range has little effect on overall pump performance despite the modestly associated increase in LV contractile state,[104] but tachycardia and the resultant treppe-induced enhanced contractility are essential compensatory mechanisms that maintain CO during disease states characterized by severely restricted LV filling (eg, pericardial tamponade, constrictive pericarditis).[105]

Myocardial hypertrophy decreases the stimulation rate at which the peak treppe effect occurs, and the phenomenon may be completely abolished in failing myocardium. The force-frequency relationship is also illustrated when a prolonged delay is observed between beats (eg, associated with an AV conduction abnormality) or after an LV extrasystole because the force of the subsequent LV contraction is enhanced. This phenomenon is called the *interval-strength effect*. A time-dependent increase in the amount of Ca^{2+} available for contractile activation and an increase in preload resulting from greater diastolic filling are most likely responsible for this effect.[106,107]

Preload

The definition of preload as sarcomere length immediately before the onset of myocyte contraction is very useful, as is the degree of muscle stretch applied to isolated cardiac muscle before it is stimulated to contract in the laboratory (Fig. 6.16). However, these concepts may have less practical utility in an ejecting heart because of the dynamic, three-dimensional changes in geometry that occur in each chamber throughout the cardiac cycle. As a result, preload is most often defined as the volume of blood contained within each chamber at its end-diastole (although here we refer primarily to the LV). This blood volume effectively establishes the length of each myocyte immediately before isovolumic contraction and is related to LV end-diastolic wall stress.[108] However, precise real-time measurement of continuous LV volume throughout the cardiac cycle (including LV volume at end-diastole) remains a technically challenging problem.[109]

Continuous LV volume may be approximated using ultrasonic sonomicrometers implanted in a three-dimensional orthogonal array in the LV subendocardium,[110] and mathematical models may then be applied to generate remarkably accurate estimates of LV volume in the laboratory. The conductance catheter is another extensively validated method of measuring continuous LV volume in experimental animals[111] and patients in the cardiac catheterization laboratory.[112,113] The technique involves placement of a multiple-electrode catheter within the LV cavity to establish a series of cylindrical electric current fields and measure time-varying voltage potentials from which intraventricular conductance is determined and LV volume is estimated.[114]

Continuous LV volume waveforms derived using sonomicrometry or conductance catheter techniques are beneficial for formal pressure-volume analysis of LV systolic and diastolic function in vivo (discussed later), but the use of invasive methods to determine LV end-diastolic volume is impractical in patients undergoing cardiac surgery. Similarly, LV volume may be accurately measured using noninvasive methods such as radionuclide angiography or dynamic magnetic resonance imaging (MRI), but these techniques cannot be used in the operating room. Instead, cardiac anesthesiologists most often rely on approximations of LV end-diastolic volume using two-dimensional transesophageal echocardiography (TEE), although advances in three-dimensional TEE imaging may facilitate real-time estimates of LV end-diastolic volume during surgery.[115–117] The transgastric LV midpapillary short-axis imaging plane is particularly useful for estimating LV end-diastolic area or diameter. For example, an acute decrease in LV preload may be easily recognized by a corresponding reduction in the end-diastolic area and diameter of the chamber concomitant with physical contact (ie, kiss) between the anterior-lateral and posteromedial papillary muscles.

LV preload may be estimated using a variety of other methods, each of which has inherent limitations (Fig. 6.17). LV end-diastolic pressure may be measured invasively in the cardiac catheterization laboratory or during surgery by advancing a fluid-filled or pressure transducer–tipped catheter from the aorta across the aortic valve or through the LA and across the mitral valve into the LV chamber. LV end-diastolic pressure is related to end-diastolic volume based on the nonlinear EDPVR and may not accurately quantify end-diastolic volume.[118]

Cardiac anesthesiologists commonly use several other estimates of LV end-diastolic volume that depend on measurements obtained upstream from the LV, including mean LA, pulmonary capillary

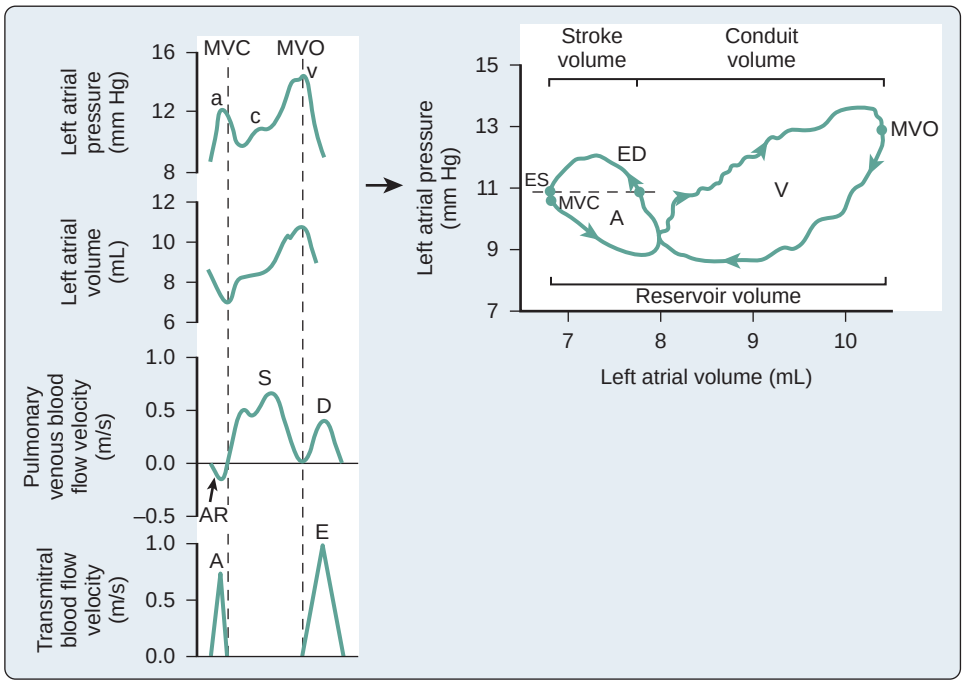

Fig. 6.14 Left atrial (LA) pressure and volume waveforms *(left)* and the corresponding steady-state LA pressure-volume diagram *(right)* inscribed in phase space by these waveforms during a single cardiac cycle. The corresponding schematic pulmonary venous and transmitral blood flow velocity waveforms are also depicted *(left)*. The *a* wave of LA pressure corresponds to atrial systole, the *c* wave represents the small increase in LA pressure that occurs during early left ventricular (LV) isovolumic contraction, and the *v* wave identifies the increase in LA pressure associated with LA filling. In contrast to this biphasic LA pressure waveform, the morphology of the LA volume waveform is monophasic. The resulting LA pressure-volume diagram is shaped in a horizontal figure-eight pattern. *Arrows* indicate the time-dependent direction of movement around the diagram. The A portion of the diagram (ie, left loop) incorporates active LA contraction and temporally proceeds in a counterclockwise fashion. The V portion of the diagram (ie, right loop) represents passive LA reservoir function and proceeds in a clockwise manner over time. The points of mitral valve closure *(MVC)* and opening *(MVO)* are depicted on the individual waveforms and on the LA pressure-volume diagram. LA end-diastole *(ED)* is the point immediately before LA contraction at which LA pressure corresponds to LA end-systolic *(ES)* pressure *(horizontal dashed line)*. LV isovolumic contraction, ejection, and most isovolumic relaxation occur between MVC and MVO, as shown on the LA pressure-volume diagram. The pulmonary venous blood flow velocity waveform consists of an atrial reversal *(AR)* wave, a biphasic *S* wave that occurs during LV systole, and a *D* wave that is observed with opening of the mitral valve. The corresponding atrial systole *(A)* and early LV filling *(E)* waves of transmitral blood flow velocity are shown. The AR and D waves of pulmonary venous blood flow velocity occur in conjunction with the A and E waves of transmitral blood flow velocity, respectively. *(From Pagel PS, Kehl F, Gare M, et al. Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography,* Anesthesiology. *2003;98:975–994.)*

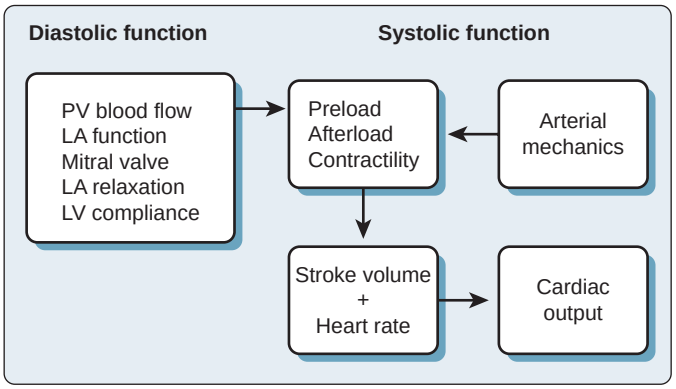

Fig. 6.15 Major factors that determine left ventricular *(LV)* diastolic *(left)* and systolic *(right)* function. Pulmonary venous *(PV)* blood flow, left atrial *(LA)* function, mitral valve integrity, LA relaxation, and LV compliance combine to determine LV preload.

occlusion (wedge), pulmonary arterial diastolic, RV end-diastolic, and RA (central venous) pressures. These estimates of LV end-diastolic volume are affected by functional integrity of the structures that separate each measurement location from the LV. For example, a correlation between RA and LV end-diastolic pressures assumes that the fluid column between the RA and LV has not been adversely influenced by pulmonary disease, airway pressure during respiration, RV or pulmonary vascular pathology, LA dysfunction, mitral valve abnormalities, or LV compliance. The complex relationships among these structures may be fully intact in healthy individuals, but this is often not the case in patients with significant pulmonary or cardiac disease.

Correlation among LV end-diastolic volume, pulmonary artery occlusion pressure, and RA pressure is notoriously poor in patients with compromised LV systolic function,[119] and measurement of pressures upstream from the LV may be of limited clinical utility in the assessment of LV preload under these circumstances. The terms *preload* and *end-diastolic volume* are used as synonyms in the remainder of this chapter.

Afterload

Afterload is the additional load to which cardiac muscle is subjected immediately after the onset of a contraction. This definition of afterload is intuitively clear and easily quantified in an isolated cardiac muscle preparation (see Fig. 6.16), but it is more difficult to envision and measure in the intact cardiovascular system, even under tightly controlled experimental conditions (Box 6.1). Impedance to LV or RV ejection by the mechanical properties of the systemic or pulmonary arterial vasculature provides the basis for the definition of afterload in vivo.

Several methods have been used to quantify afterload. Aortic input impedance, or $Z_{in}(\omega)$, is the ratio of aortic pressure (ie, forces acting on the blood) to blood flow (ie, resultant motion). It is derived from power spectral or Fourier series analysis of high-fidelity measurements of aortic pressure and blood flow. $Z_{in}(\omega)$ incorporates arterial viscoelasticity, frequency dependence, and wave reflection,[120,121] and it is characterized by modulus and phase angle spectra expressed in the frequency domain (Fig. 6.18).[122]

$Z_{in}(\omega)$ is most often interpreted using an electrical three-element Windkessel model[123] of the arterial circulation because the frequency dependence of $Z_{in}(\omega)$ makes this parameter difficult to interpret. The Windkessel model identifies three primary features of $Z_{in}(\omega)$: characteristic aortic impedance (Z_c), total arterial compliance (C), and total arterial resistance (R) (Fig. 6.19).[124] Z_c represents resistance to LV ejection produced by the aorta and great vessels; C is determined primarily by the compliance of the proximal large arterial vasculature (ie, energy storage component); and R equals the combined resistances of the remaining arterial circulation. The three-element Windkessel model closely approximates $Z_{in}(\omega)$ under a variety of physiologic conditions.[123–125] RV afterload has been described using pulmonary input impedance spectra interpreted with a similar Windkessel model.

The mechanical forces to which the LV is subjected during ejection also may be used to define LV afterload. Increases in LV pressure and wall thickness occur during isovolumic contraction and are accompanied by a large reduction in LV volume (ie, radius) after the aortic valve opens. These combined factors cause a dramatic increase in LV systolic wall stress as predicted by Laplace's law. LV systolic wall stress reaches a maximum during early LV ejection and declines thereafter.[49]

The changes in continuous LV systolic wall stress have a number of important consequences. For example, peak LV systolic wall stress is a major stimulus of LV concentric hypertrophy in disease states characterized by chronic pressure-overload (eg, poorly controlled essential hypertension, aortic valve stenosis).[49,126] The integral of LV systolic wall stress with respect to time is an indicator of myocardial oxygen demand.[127] The relationship between LV wall stress at end-systole and the heart rate–corrected maximal velocity of circumferential fiber

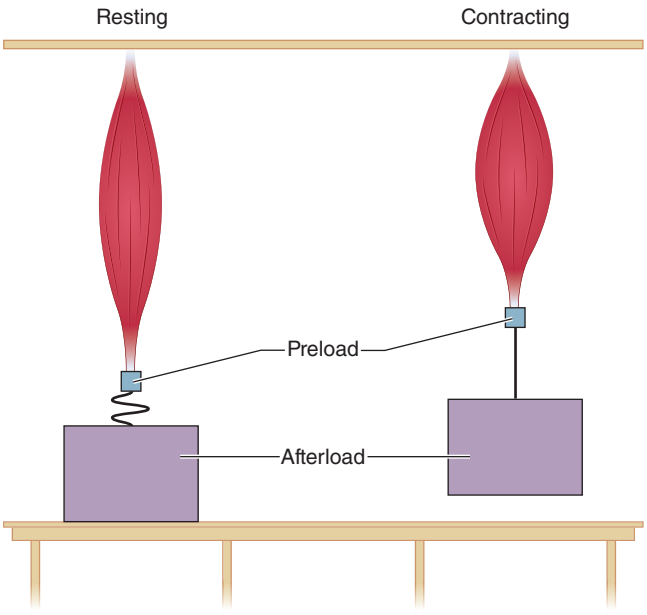

Fig. 6.16 Loading conditions placed on an isolated papillary muscle before and during contraction. The muscle is initially stretched with a small load (ie, preload) *(left)*, but when it contracts, it is almost immediately subjected to an additional, much larger load (ie, afterload) *(right)*. The relative size of preload and afterload in the diagram illustrate the loading conditions to which the intact left ventricle is exposed before and after the aortic valve opens. *(From Katz A. Physiology of the Heart. Philadelphia: Lippincott Williams & Wilkins; 2001.)*

BOX 6.1 INDICES OF LEFT VENTRICULAR AFTERLOAD

Aortic input impedance (magnitude and phase spectra)
Windkessel parameters
- Characteristic aortic impedance (Z_c)
- Total arterial compliance (C)
- Total arterial resistance (R)

End-systolic pressure
End-systolic wall stress
Effective arterial elastance (E_a)
Systemic vascular resistance

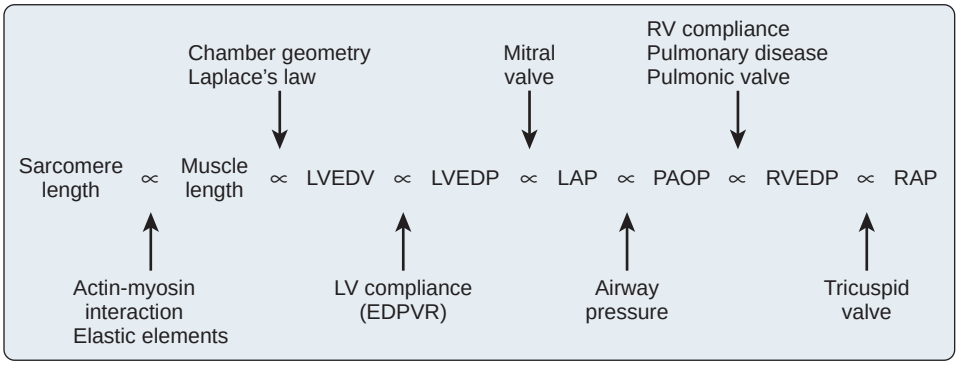

Fig. 6.17 Several factors influence experimental and clinical estimates of sarcomere length as a pure index of the preload of the contracting left ventricular *(LV)* myocyte. *EDPVR*, End-diastolic pressure-volume relationship; *LAP*, left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *LVEDV*, left ventricular end-diastolic volume; *PAOP*, pulmonary artery occlusion pressure; *RAP*, right atrial pressure; *RV*, right ventricular; *RVEDP*, right ventricular end-diastolic pressure.

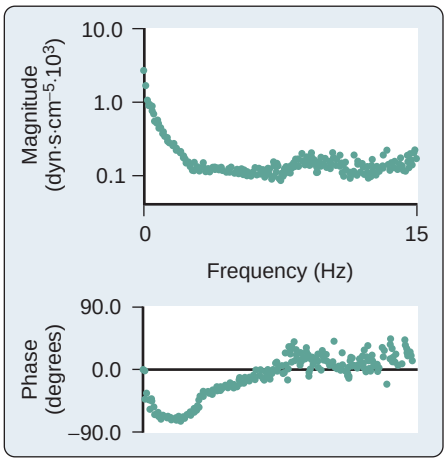

Fig. 6.18 A typical aortic input impedance, $Z_{in}(\omega)$, spectrum obtained from a conscious, chronically instrumented dog. $Z_{in}(\omega)$ has frequency-dependent magnitude *(top)* and phase *(bottom)* components. The $Z_{in}(\omega)$ magnitude at 0 Hz is equal to total arterial resistance. The average of the $Z_{in}(\omega)$ magnitude spectra between 2 and 15 Hz determines characteristic aortic impedance (Z_c). *(Modified from Hettrick DA, Pagel PS, Warltier DC. Differential effects of isoflurane andhalothane on aortic input impedance quantified using a three-element Windkesselmodel.* Anesthesiology. *1995;83(2):361–373.)*

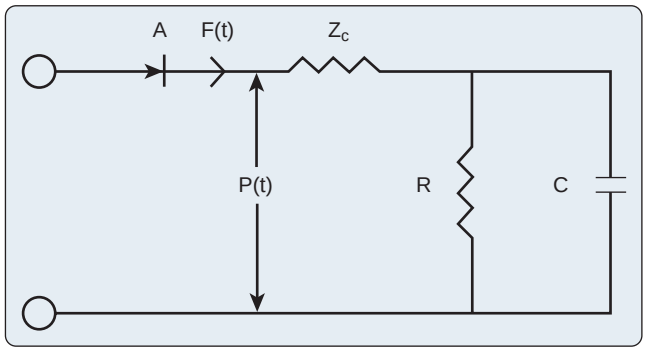

Fig. 6.19 Electrical analog of the three-element Windkessel model of aortic input impedance, $Z_{in}(\omega)$. Diode *A* represents the aortic valve. The time-dependent blood flow, *F(t)*, entering the arterial system from the left ventricle first encounters the resistance of the proximal aorta and great vessels (ie, characteristic aortic impedance [Z_c]). Total arterial resistance *(R)* and total arterial compliance *(C*, the energy storage component of the arterial vasculature) determine further arterial blood flow, which is associated with a time-dependent change in arterial pressure, *P(t)*, from the aortic root to the capillary bed. *(Modified from Hettrick DA, Pagel PS, Warltier DC. Differential effects of isoflurane andhalothane on aortic input impedance quantified using a three-element Windkesselmodel.* Anesthesiology. *1995;83(2):361–373.)*

shortening (V_{cfs}) during contraction has been used as a relatively heart rate– and load-independent index of contractile state in humans (each parameter may be derived noninvasively using echocardiography).[128] LV end-systolic wall stress identifies the magnitude of force that prevents further fiber shortening at the end of ejection, determining the degree of LV emptying that may occur at a fixed inotropic state. LV end-systolic wall stress defines the instantaneous myocardial force at end-ejection for each chamber size, thickness, and pressure and incorporates internal cardiac forces and those external to the heart (ie, arterial system) that oppose it.[129–131]

As discussed with Laplace's law, LV geometric assumptions, the nonlinear force distribution between the subendocardium and subepicardium, and the nonuniformity of wall thickness throughout the LV may complicate the use of LV end-systolic wall stress as a quantitative index of LV afterload.[53] These potentially confounding factors are

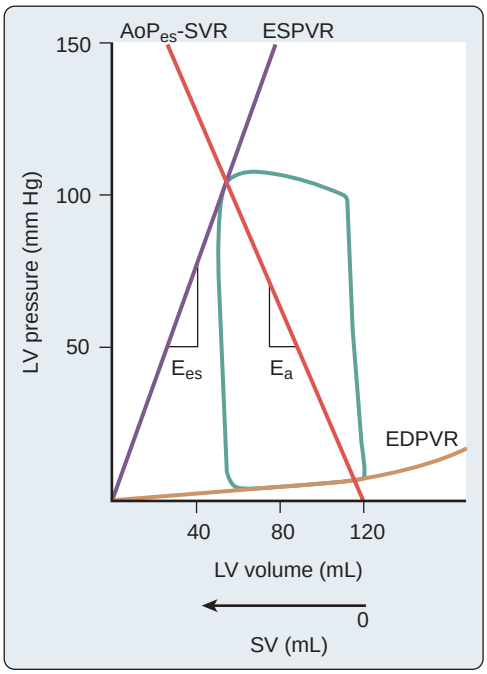

Fig. 6.20 The left ventricular *(LV)* end-systolic pressure-volume relationship *(ESPVR)* and aortic end-systolic pressure–stroke volume *(SV)* relationship *(AoP_{es}-SVR)* are used to determine LV-arterial coupling as the ratio of end-systolic elastance *(E_{es})* (ie, slope of ESPVR) and effective arterial elastance *(E_a)* (ie, slope of AoP_{es}-SVR). *EDPVR*, End-diastolic pressure-volume relationship.

particularly relevant in the setting of acute or chronic regional wall motion abnormalities (eg, critical coronary artery stenosis or occlusion, LV remodeling after infarction).

Optimal transfer of energy from the LV to the arterial circulation during ejection requires that the two elastic chambers are mechanically coupled.[132,133] LV-arterial coupling is another useful model for quantifying LV afterload. LV-arterial coupling is most often described using a series elastic chamber model in which LV E_{es} and effective arterial elastance (E_a) are determined in the pressure-volume plane using the slopes of the LV end-systolic pressure-volume and aortic end-systolic pressure-SV relationships, respectively (Fig. 6.20).[134] The ratio of E_{es} to E_a defines coupling between the LV and arterial circulations,[135,136] identifies the SV that may be transferred between these elastic components, and provides a useful foundation with which to study energetics and myocardial efficiency.[83]

E_a is strictly a composite coupling variable that is affected by total arterial resistance and total arterial compliance, but the parameter also has been suggested as a measure of LV afterload that is somewhat analogous to LV end-systolic wall stress.[132] The product of E_a and heart rate also approximates systemic vascular resistance (SVR). Nevertheless, E_a alone most likely should not be used to quantify LV afterload because the variable does not strictly incorporate alterations in characteristic aortic impedance, an important high-frequency component of arterial mechanics, nor does it consider arterial wave reflection properties.

The magnitude of $Z_{in}(\omega)$primarily depends on total arterial resistance[137] and may be reasonably approximated by SVR, the most commonly used estimate of LV afterload in clinical anesthesiology. SVR is the ratio of pressure to flow (ie, analogous to Ohm's law), which is calculated using the familiar formula (MAP-RAP)80/CO, in which MAP is the mean arterial pressure, RAP is the RA pressure, CO is cardiac output, and 80 is a constant that converts the units of mm Hg/min per liter to dynes·s·cm^{-5}. However, SVR is inherently inadequate as a quantitative description of LV afterload because the parameter ignores the mechanical characteristics of the blood (eg, viscosity, density) and arterial walls (eg, compliance); does not consider the

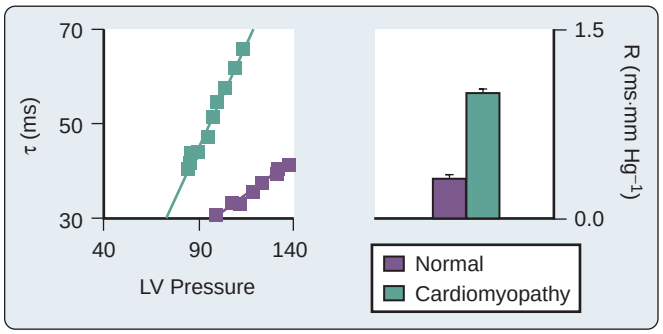

Fig. 6.21 Linear relationship between the time constant of isovolumic relaxation *(τ)* and left ventricular *(LV)* end-systolic pressure during inferior vena caval occlusion *(left)* in a conscious dog before *(purple squares)* and after *(green squares)* the development of rapid LV pacing-induced cardiomyopathy. The histogram illustrates the slope *(R)* of the τ-LV end-systolic pressure relationship before *(purple)* and after *(green)* chronic rapid pacing and indicates that the LV isovolumic relaxation is more sensitive to alterations in LV pressure in this model of heart failure. *(Modified from Pagel PS, Hettrick DA, Kersten JR, et al. Isoflurane and halothane do not alter the enhanced afterload sensitivity of left ventricular relaxation in dogs with pacing-induced cardiomyopathy.* Anesthesiology. *1997;87:952–962.)*

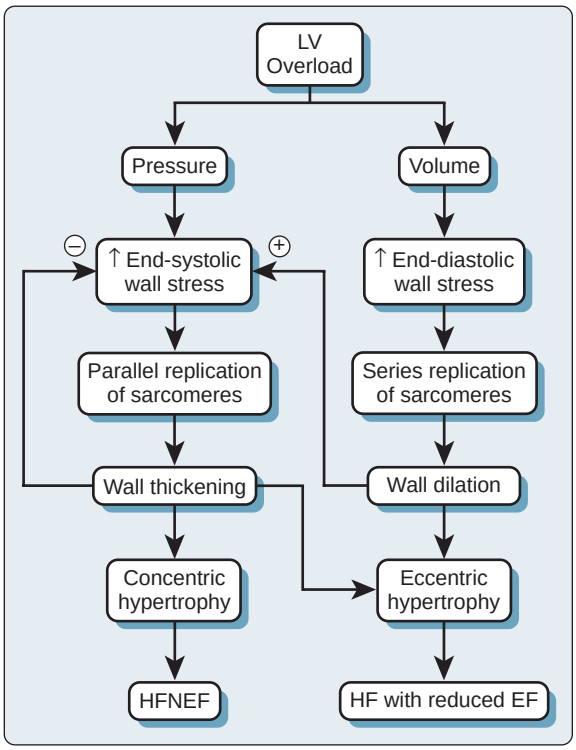

Fig. 6.22 Left ventricular *(LV)* pressure and volume overload produce compensatory responses based on the nature of the inciting stress. Wall thickening reduces (–) and chamber dilation increases (+) end-systolic wall stress, as predicted by Laplace's law. LV pressure-overload hypertrophy has been linked to heart failure with a normal ejection fraction *(HFNEF)*, but LV volume overload most often causes heart failure *(HF)* with a reduced ejection fraction *(EF)*.

frequency-dependent, phasic nature of arterial blood pressure and blood flow (ie, SVR assumes constant blood flow); and fails to incorporate arterial wave reflection. The phasic contributions to arterial load are especially important in the setting of advanced age, peripheral vascular disease, and tachycardia.[138,139] As a result, SVR cannot be reliably used to quantify changes in LV afterload produced by vasoactive drugs or cardiovascular disease and instead should be used as a nonparametric estimate of LV afterload.[140]

Four major components mediate LV afterload in the intact cardiovascular system:

1. Physical properties of arterial blood vessels (eg, diameter, length, elasticity, number of branches)
2. LV wall stress, which is determined by LV pressure development and the geometric changes in the LV chamber required to produce it
3. Total arterial resistance, which is determined primarily by arteriolar smooth muscle tone
4. Volume and physical properties of blood (eg, rheology, viscosity, density)

An acute increase in LV afterload is most often well tolerated in the setting of normal LV systolic function, but the failing LV may be exquisitely sensitive to an acute increase in afterload (Fig. 6.21),[141,142] and the event is likely to precipitate further LV dysfunction. Reflex activation of the sympathetic nervous system occurs in response to LV systolic dysfunction, but this compensatory mechanism also inadvertently increases LV afterload and may further decrease CO, especially when combined with pathologic abnormalities that reduce arterial compliance (eg, atherosclerosis).

LV hypertrophy is an important adaptive response to chronic elevations in LV afterload that reduces LV wall stress by increasing wall thickness. The adaptation may preserve LV systolic function, but the greater mass of LV myocardium associated with hypertrophy also substantially increases the risk of myocardial ischemia and contributes to the development of LV diastolic dysfunction (Figs. 6.22 and 6.23). The primary therapeutic objective in the management of elevated LV afterload is reduction of the inciting stress.

Descriptions of RV afterload are similar to those described for the LV but with two major differences. The pulmonary arterial vasculature is more compliant than its systemic arterial counterpart, and the RV is more sensitive to acute changes in afterload than the LV. The ability of the AV valves to open freely and the compliance of the LV and RV are the primary determinants of LA and RA afterload, respectively. A model of LA afterload analogous to LV-arterial coupling used combined LA and LV pressure-volume analysis to characterize LA compensatory responses to changes in LA afterload.[97,99]

Myocardial Contractility

Rigid control of loading conditions and measurement of the magnitude, velocity, and force of muscle shortening facilitate precise determination of the inotropic state in isolated cardiac muscle preparations, but quantifying myocardial contractility in the intact heart is a challenging problem. Quantification of LV contractility would allow cardiac anesthesiologists to reliably evaluate the effects of pharmacologic interventions or pathologic processes on LV systolic function.

A standard for myocardial contractility in vivo has not been developed, and all contractile indices proposed, including those derived from pressure-volume analysis, have significant limitations because the contractile state and loading conditions are fundamentally related at the level of the sarcomere.[143,144] Interpretation of a change in LV systolic function in vivo must always be considered within the constraints of the loading conditions under which it was measured, regardless of the technique used to estimate contractility. Many indices of myocardial contractility are classified in four broad categories (Box 6.2): pressure-volume relationships, isovolumic contraction, ejection phase, and power analysis.

End-Systolic Pressure-Volume Relationships

Because the LV is an elastic chamber, the relationship between its pressure and volume may be described in terms of time-varying elastance (ie, ratio of pressure to volume) during the cardiac cycle.[77,78] LV elastance increases during systole as LV pressure rises and LV volume declines. Maximal LV elastance (E_{max}) occurs at or very near end-systole, most often corresponding to the left upper corner of the

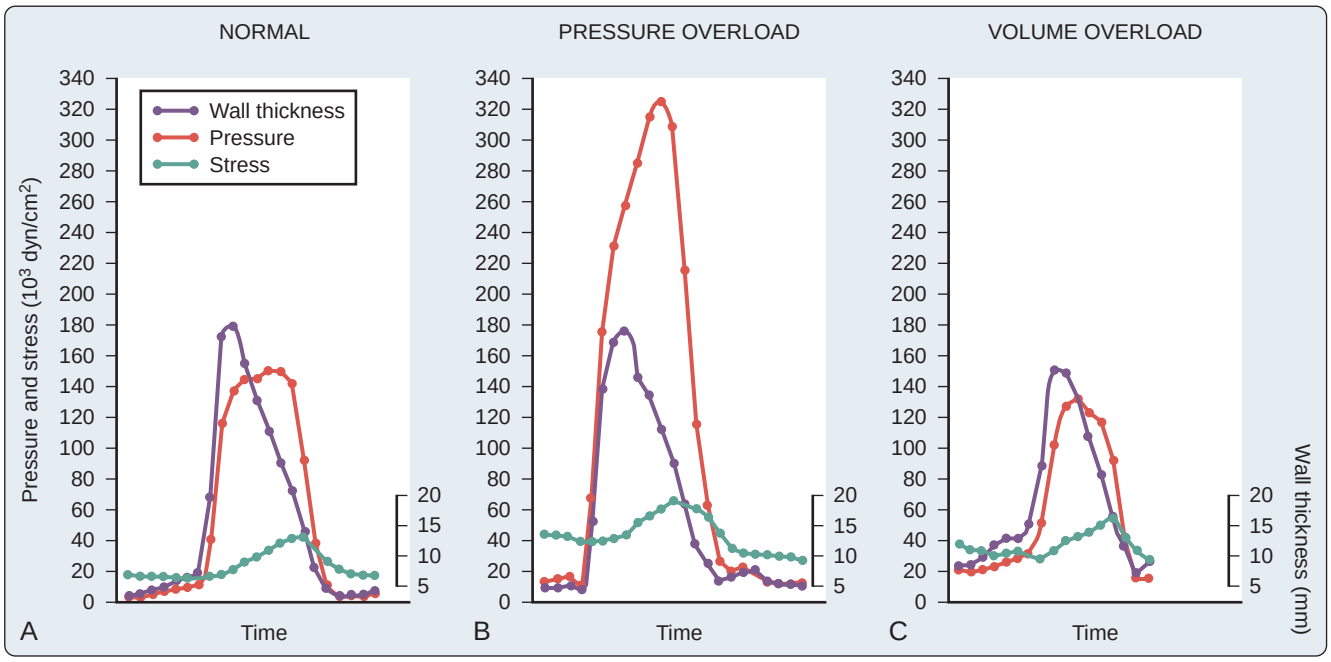

Fig. 6.23 Left ventricular (LV) pressure *(red circles)*, wall thickness *(purple circles)*, and wall stress *(green circles)* during the cardiac cycle. Compared with (A) the normal left ventricle, (B) LV pressure-overload hypertrophy occurs concomitant with dramatic increases in LV pressure, but compensatory increases in wall thickness maintain wall stress in the normal range and configuration. End-diastolic stress is markedly elevated in (C) LV volume-overload hypertrophy. *(From Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle, J Clin Invest. 1975;56:56–64.)*

BOX 6.2 INDICES OF LEFT VENTRICULAR CONTRACTILITY

Pressure-Volume Analysis
End-systolic pressure-volume relation (E_{es})
Stroke work–end-diastolic volume relation (M_{sw})

Isovolumic Contraction
dP/dt_{max}
dP/dt_{max} /50
$dP/dt_{max}/P$
dP/dt_{max}-end-diastolic volume relation (dE/dt_{max})

Ejection Phase
Stroke volume
Cardiac output
Ejection fraction
Fractional area change
Fractional shortening
Wall thickening
Velocity of shortening

Ventricular Power
PWR_{max}
PWR_{max}/EDV^2

dE/dt_{max}, Slope of the dP/dt_{max}–end-diastolic volume relationship; *dP/dt_{max}*, maximum rate of increase of left ventricular pressure; *EDV*, end-diastolic volume; *E_{es}*, end-systolic elastance; *M_{sw}*, slope of the stroke work–end-diastolic volume relationship; *P*, peak left ventricular pressure; *PWR_{max}*, maximum left ventricular power (product of aortic pressure and blood flow).

steady-state LV pressure-volume diagram. Analogously, minimal LV elastance is observed at end-diastole.

The equation $E(t) = P(t)/[V(t) - V_0]$ describes time-varying elastance, E(t). P(t) and V(t) are the time-dependent changes in LV pressure and volume, respectively, during the cardiac cycle, and V_0 is the LV volume at 0 mm Hg of LV pressure (ie, unstressed volume). The relationship between each E_{max} of a differentially loaded series of LV pressure-volume diagrams establishes the ESPVR and is linear within the normal physiologic range at a constant inotropic state.

The slope (ie, E_{es}) of the ESPVR is a quantitative index of LV contractile state that incorporates afterload because the analysis is conducted at end-systole (Fig. 6.24). As a result, the time-varying elastance equation may be rewritten at end-systole as $P_{es} = E_{es}(V_{es} - V_0)$, in which P_{es} and V_{es} are LV end-systolic pressure and volume, respectively. An increase or decrease in the magnitude of E_{es} produced by a positive or negative inotropic drug (eg, dobutamine or esmolol), respectively, quantifies the corresponding change in LV contractility that has occurred.

Regional LV contractility may also be determined using pressure-dimension relationships based on determinations of continuous segment length, LV midpapillary short-axis diameter, or wall thickness,[77,78,145] and it usually reflects global LV systolic function in the absence of regional wall motion abnormalities.[110] LV end-systolic pressure-volume or dimension relationships have been derived noninvasively using radionuclide angiography[146] or echocardiography[147] with automated border detection[148] to measure continuous LV volume or area. Single-beat estimates of E_{es} (ie, determined as the simple ratio of P_{es} to V_{es} or derived using a modified time-varying elastance method) have been proposed that may provide quantitative information about contractile state assuming that the value V_0 remains small.[149,150] The principle of time-varying elastance also has been successfully applied to the study of RV[84] and atrial contractility[43] (Fig. 6.25) in the intact heart.

The time-varying elastance model of LV contractility is elegant from an engineering perspective, but several potential pitfalls have been identified that may limit its clinical utility as an index of the inotropic state. The position of unstressed volume (V_0) does not consistently remain constant during alterations in contractility.[79,151] For example, administration of dobutamine increases E_{es} and shifts the ESPVR to the left (ie, decrease in V_0), presumably resulting from

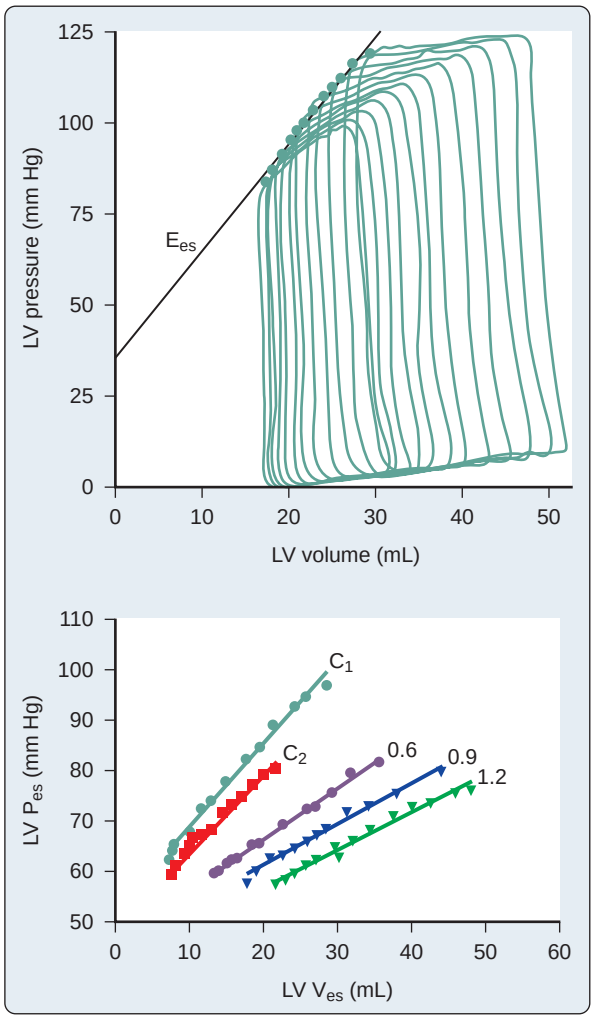

Fig. 6.24 Method used to derive the left ventricular *(LV)* end-systolic pressure-volume relationship (ESPVR) from a series of differentially loaded LV pressure-volume diagrams generated by abrupt occlusion of the inferior vena cava in a canine heart in vivo. *Top panel*: The pressure-volume ratio or maximal elastance (E_{max}) for each pressure-volume diagram is identified *(left upper corner)*, and a linear regression analysis is used to define the slope or end-systolic elastance (E_{es}) and volume intercept of the ESPVR. *Bottom panel:* The effects of isoflurane (0.6, 0.9, and 1.2 minimum alveolar concentrations) on the ESPVR are shown. C_1, Control 1 (before isoflurane); C_2, control 2 (after isoflurane); P_{es}, LV end-systolic pressure; V_{es}, LV end-systolic volume. *(Modified from Hettrick DA, Pagel PS, Warltier DC. Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency,* Anesthesiology. *1996;85:403–413.)*

β_2-adrenoceptor–mediated vasodilation,[151] whereas acute coronary artery occlusion–induced regional LV dysfunction has the opposite effect.[152] Because E_{es} and V_0 may reflect alterations in LV contractility, an index of the inotropic state based on the combined effects of the variables was postulated.[153]

Several consecutive LV pressure diagrams must be obtained over a range of LV loading conditions to accurately define E_{es} and V_0, but this necessary intervention may inadvertently produce baroreceptor reflex–mediated increases in heart rate and contractility during generation of the ESPVR by activating the sympathetic nervous system.[154] E_{max} may not occur precisely at end-systole in the setting of markedly elevated or reduced LV afterload and may be delayed or occur earlier, respectively.[155] As a result, E_{max} may deviate from its normal position in the left upper corner of the LV pressure-volume diagram, introducing potential errors in the derivation of ESPVR.

E_{es} inherently depends on chamber size (despite efforts to standardize its measurement) because the units of E_{es} are mm Hg/mL.[156,157] The volume dependence of E_{es} may complicate direct comparison of the contractile state between patients with different LV sizes. Other limitations of the use of E_{es} as an index of contractile state include lack of measurement precision,[158] nonlinearity,[159] load sensitivity,[160] dependence on underlying autonomic nervous system balance[161] or ejection-mediated alterations on LV pressure generation,[162] and interaction with LV diastolic function.[163] Despite these concerns, the ESPVR is a superb conceptual tool with which to define the contractile state and its interactions with loading conditions in vivo.

Stroke Work–End-Diastolic Volume Relationships

Early studies by Frank[75] and Patterson and colleagues[164] defined a fundamental relationship between LV pump performance (eg, CO) and preload determined using indirect indices of LV filling (eg, central venous pressure). Sarnoff and Berglund[165] extended these seminal investigations in his landmark description of ventricular function curves that related estimates of SW to filling pressures. In this familiar framework, movement of an LV function curve upward or to the left indicated that an increase in the contractile state had occurred because the LV was able to generate more SW at an equivalent preload. Unfortunately, Sarnoff's LV function curves were inherently nonlinear and difficult to quantify because the technology available at the time did not allow him to precisely measure LV SW and end-diastolic volume.

Glower and colleagues used a high-fidelity LV micromanometer and three-dimensional orthogonal endocardial sonomicrometers to measure continuous LV pressure and volume, respectively, in a pressure-volume reexamination of Sarnoff's original hypothesis.[80] The investigators demonstrated that the relationship between each LV SW–V_{ed} pair obtained from a series of differentially loaded LV pressure-volume diagrams was linear, and $SW = M_{sw}(V_{ed} - V_{sw})$, in which M_{sw} and V_{sw} were the slope and volume intercept of the relationship (Fig. 6.26). M_{sw} as shown to quantify alterations in the LV inotropic state in a relatively load-independent manner because preload was already incorporated.

Similar linear relationships between regional work and dimensional measurements (eg, segment length, wall thickness) may be used to quantify changes in the regional contractile state. LV SW-V_{ed} relationships may be calculated with the same series of pressure-volume diagrams used to determine the ESPVR. As a result, two independent contractile indices may be derived and compared from the identical experimental data.

The SW-V_{ed} relationship offers several advantages over the ESPVR for the determination of LV or RV contractility. The SW-V_{ed} relationship is highly linear and reproducible over a wide variety of loading conditions, arterial blood pressures, and contractile states because LV pressure and volume data from the entire cardiac cycle are incorporated into its calculation.[80,158] Conversely, the ESPVR displays more pronounced curvilinear behavior and may be more susceptible to instrument noise because it is determined at a single instantaneous time point (ie, end-systole).[160] The ESPVR may also demonstrate some degree of afterload sensitivity,[166] but the SW-V_{ed} relationship is essentially afterload independent over a wide physiologic range.[80] Unlike E_{es}, the unit of M_{sw} is mm Hg. M_{sw} allows direct comparisons of contractility to be made between patients with various LV sizes because M_{sw} is independent of chamber dimensions.

The SW-V_{ed} relationship has two distinct disadvantages compared with the ESPVR. First, integration of data from the entire cardiac cycle implies that the SW-V_{ed} relationship does not strictly separate LV systolic events from those that occur during diastole. For example, a decrease in LV compliance without a simultaneous change in the ESPVR (eg, LV pressure-overload hypertrophy) may introduce errors into the determination of the LV contractile state using the SW-V_{ed} relationship.[144] Second, partial collapse of the LV pressure-volume diagram during regional myocardial ischemia[93] makes calculation of LV contractility more difficult using the SW-V_{ed} relationship compared

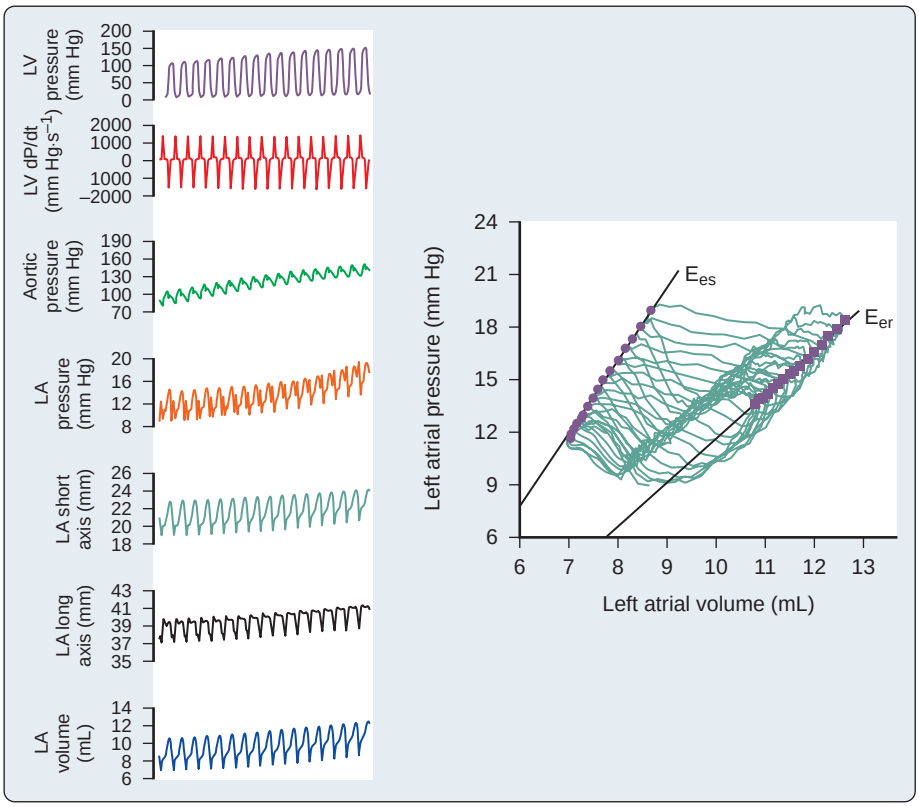

Fig. 6.25 Continuous tracings of left ventricular *(LV)* pressure, rate of increase in LV pressure (dP/dt), aortic pressure, left atrial *(LA)* pressure, LA short- and long-axis dimensions, and LA volume waveforms *(left)* and the corresponding LA pressure-volume diagrams *(right)* resulting from intravenous administration of phenylephrine (200 µg) in a canine heart in vivo. The LA maximal elastance *(circles)* and end-reservoir pressure and volume *(squares)* for each pressure-volume diagram were used to obtain the slopes (E_{es} and E_{er}) and extrapolated volume intercepts of the LA end-systolic and end-reservoir pressure-volume relationships to quantify the LA contractile state and chamber stiffness, respectively. *(From Pagel PS, Kehl F, Gare M, et al: Mechanical function of the left atrium: new insights based on analysis of pressure-volume relations and Doppler echocardiography,* Anesthesiology. *2003;98:975–994.)*

with the ESPVR.[167] Despite these potential shortcomings, the SW-V_{ed} relationship provides a useful index of LV or RV contractile function in the intact heart that has been successfully applied in a variety of experimental settings and in patients with heart disease.

Isovolumic Indices of Contractility

The maximum rate of increase of LV pressure (dP/dt_{max}) is the most commonly derived index of the global LV contractile state during isovolumic contraction. Precise determination of LV dP/dt_{max} requires high-fidelity, invasive measurement of continuous LV pressure and usually is performed in the cardiac catheterization laboratory. LV dP/dt_{max} also may be noninvasively estimated using TEE in patients undergoing cardiac surgery by analysis of the continuous-wave Doppler mitral regurgitation waveform.[168]

LV dP/dt_{max} is sensitive to acute alterations in contractile state,[169] but it is probably most useful when quantifying directional changes in contractility rather than establishing an absolute baseline value.[170] LV dP/dt_{max} is essentially afterload independent because the peak rate of increase of LV pressure occurs before the aortic valve opens unless severe myocardial depression or pronounced arterial vasodilation exists.[171] However, LV preload profoundly affects dP/dt_{max}, and increases in LV dP/dt_{max} produced by greater preload or an enhanced contractile state are virtually indistinguishable. LV mass, chamber size, and mitral or aortic valve disease also affect LV dP/dt_{max}.

The LV dP/dt_{max} may not detect changes in the contractile state produced by regional myocardial ischemia because LV dP/dt_{max} is an index of global LV systolic function. The failure of LV dP/dt_{max} to detect an alteration in regional dysfunction resulting from compromised coronary perfusion may occur because of a compensatory increase in contractility in the remaining normal myocardium through activation of the Frank-Starling mechanism or an increase in sympathetic nervous system activity.

The rate of increase of LV pressure at a fixed developed pressure (eg, dP/dt measured at 50 mm Hg [dP/dt_{50}]) and the ratio of dP/dt to peak developed LV pressure (dP/dt/P) have also been proposed as isovolumic indices of contractility. These measures of the LV contractile state may be somewhat less preload dependent than LV dP/dt_{max}, but neither provides unique additional information compared with LV dP/dt_{max}.

The preload dependence of LV dP/dt_{max} may be used to derive another index of myocardial contractility based on the pressure-volume framework. The relationship between each pair of LV dP/dt_{max} and V_{ed} values obtained from a differentially loaded series of LV pressure-volume diagrams is linear, and $dP/dt_{max} = dE/dt_{max}(V_{ed} - V_0)$, where dE/dt_{max} is the slope and V_0 is the volume intercept of the relationship.[172] Like E_{es} and M_{sw}, the alterations in dE/dt_{max} produced by inotropic drugs or cardiac disease may be used to quantify changes in the LV contractile state. For example, the LV dP/dt_{max}-V_{ed} relationship can precisely determine alterations in contractility in the normal and regionally ischemic LV.[172, 173]

LV dE/dt_{max} and E_{es} are mathematically related,[173] and interventions that shift the ESPVR without altering E_{es} also shift the volume intercept of the LV dP/dt_{max}-V_{ed} relationship without changing dE/dt_{max}.[144]

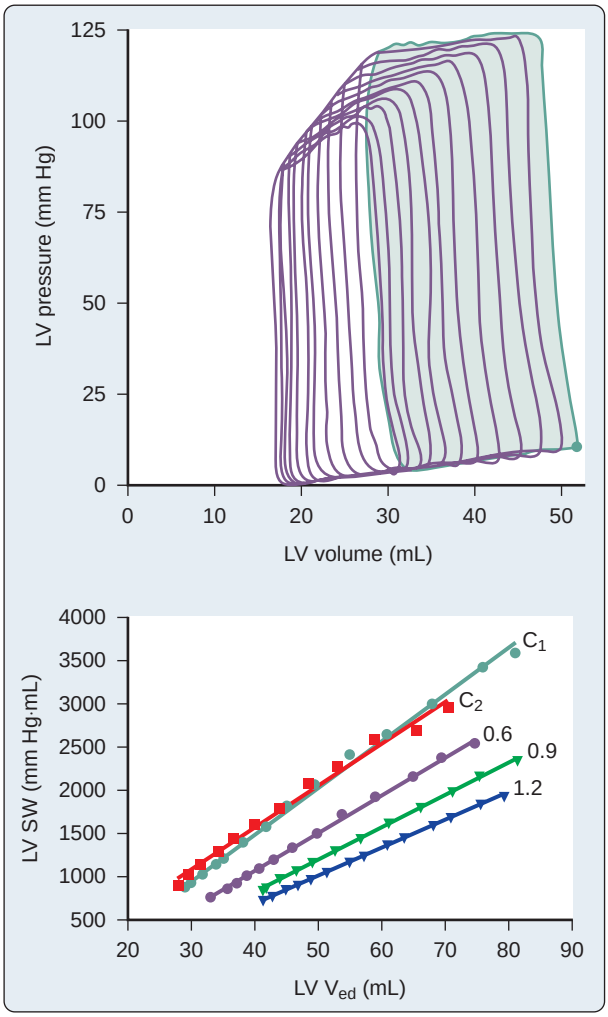

Fig. 6.26 Method used to derive the relationship between left ventricular *(LV)* stroke work *(SW)* and end-diastolic volume *(V_{ed})* from a series of differentially loaded LV pressure-volume diagrams generated by abrupt occlusion of the inferior vena cava in a canine heart in vivo. The area of each LV pressure-volume diagram (ie, *shaded area*), corresponding to SW, is plotted against the corresponding V_{ed} *(top panel)*, and a linear regression analysis is used to define the SW-V_{ed} relationship. The effects of isoflurane (0.6, 0.9, and 1.2 minimum alveolar concentrations) on the SW-V_{ed} relationship are shown in the *bottom panel*. C_1, Control 1 (before isoflurane); C_2, control 2 (after isoflurane). *(Modified from Hettrick DA, Pagel PS, Warltier DC. Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency,* Anesthesiology. *1996;85:403–413.)*

Similar to the ESPVR, the LV dP/dt_{max}-V_{ed} relationship becomes more curvilinear at greater LV volumes or contractile states, a finding that is predicted based on isolated cardiac muscle mechanics.[174] Direct comparison among the ESPVR, SW-V_{ed} relationship, and LV-dP/dt_{max} relationship also indicated that dE/dt_{max} might be more variable than E_{es} or M_{sw} during acute changes in contractile state.[158] RV dP/dt_{max}-V_{ed} relationships also have been described.[46]

Ejection-Phase Indices of Contractility

Examination of the degree (eg, EF, SV) or the rate (eg, velocity of shortening) of LV ejection forms the basis of all currently used ejection-phase indices of the LV contractile state, including newer echocardiographic parameters derived from tissue Doppler imaging, myocardial stress-strain relationships, speckle tracking technology, and endocardial color kinesis. From a clinical perspective, the most common ejection-phase index of LV contractility is EF, for which $EF = V_{ed} - V_{es}/V_{ed}$.

LV EF may be calculated using a variety of noninvasive techniques (eg, radionuclide angiography, functional MRI, echocardiography). Cardiac anesthesiologists most often measure LV EF using two-dimensional TEE. Midesophageal four- or two-chamber images are obtained at LV end-systole and end-diastole. They are subsequently analyzed by applying Simpson's rule of disks, which defines the volume as the sum of a finite series of cylinders of various diameters and thicknesses (Fig. 6.27). This method of measuring LV EF is simple, but it is rather time-consuming despite integrated TEE software and may be impractical during rapidly changing hemodynamic conditions.

Two closely related parameters, fractional shortening (FS) and fractional area of change, are often calculated as surrogate measures of LV EF in the midpapillary short-axis plane using images obtained at end-systole and end-diastole. FS is calculated from endocardial measurements of anteroposterior (or septolateral) wall diameter as $FS = D_{ed} - D_{es}/D_{ed}$, in which D_{ed} and D_{es} are the endocardial end-diastolic and end-systolic diameters, respectively (Fig. 6.28).

Fractional area change (FAC) may be determined using the same midpapillary short-axis images by manually tracing the endocardial borders (with the papillary muscles most often excluded) at end-systole and end-diastole. Computer software automatically integrates the end-systolic and end-diastolic areas (ie, A_{es} and A_{ed}, respectively) within each endocardial tracing, and FAC is calculated as $A_{ed} - A_{es}/A_{ed}$. These and all other ejection-phase indices inherently depend on the LV contractile state and loading conditions.[82]

Because preload is incorporated into the denominators of EF, FAC, and FS (ie, V_{ed}, A_{ed}, and D_{ed}, respectively), the indices are relatively unaffected by moderate preload alterations in the setting of normal mitral and aortic valve function.[174] Myocardial stress-strain relationships or speckle tracking techniques also may include modifications (eg, Lagrangian or natural strain) designed to minimize intrinsic preload-dependency. However, EF, FAC, FS, and variables derived from the newer technologies decrease linearly with increases in afterload and vary inversely with heart rate. They are relatively insensitive indices of LV contractile state.

Similar to the observations for LV dP/dt_{max}, EF and FAC are global measures of pump performance that may not reflect the regional contractile dysfunction produced by myocardial ischemia or infarction. Ejection-phase indices also may provide inaccurate information about contractility in the setting of mitral or aortic valvular disease, LV chamber enlargement, or LV hypertrophy.[126,175,176] Similar difficulties with load and heart rate dependency are encountered when ejection-phase indices are used in an attempt to quantify the RV or atrial contractile state.

The velocity of myocardial fiber shortening provides information about the LV contractile state during ejection. Maximal or mean velocity of circumferential fiber shortening may be determined using a variety of invasive and noninvasive techniques. The midpapillary short-axis view on TEE is especially useful for cardiac anesthesiologists measuring these variables in the operating room. Maximal velocity of circumferential fiber shortening (V_{cfs}) is calculated as the ratio of FS to ejection time and may be more sensitive to changes in the contractile state than EF because the velocity (not magnitude) of shortening is evaluated. Nevertheless, V_{cfs} also varies directly with heart rate and inversely with changes in afterload, similar to other ejection-phase indices.[171]

Methods for correcting the inherent heart rate and afterload dependency of V_{cfs} have been suggested based on the force-velocity behavior of isolated cardiac muscle. For example, a linear relationship was shown between LV end-systolic wall stress and heart rate–corrected V_{cfs}. The slope of this relationship provided a relatively heart rate– and afterload-independent index of the LV contractile state in healthy patients[129] and those with hypertension or valvular disease.[126,128] A similar relationship between EF and effective arterial elastance was described.[177] Unfortunately, these and other analogous techniques[178] have not achieved widespread clinical application because extensive, time-consuming analysis is required after data acquisition, making them impractical in an operating room setting.

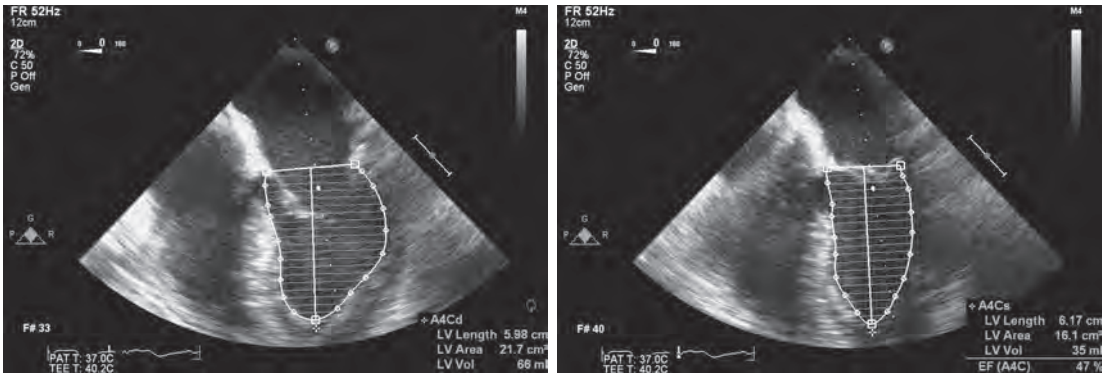

Fig. 6.27 Calculation of ejection fraction from midesophageal four-chamber images obtained at left ventricular (LV) end-diastole *(left)* and end-systole *(right)* using Simpson's rule. After the LV endocardial border is identified in each image, the software generates a series of thin cylindrical disks *(parallel white lines)* and determines the volume based on their sum. LV ejection fraction is then calculated using the standard formula. In this example, the LV ejection fraction is 47%.

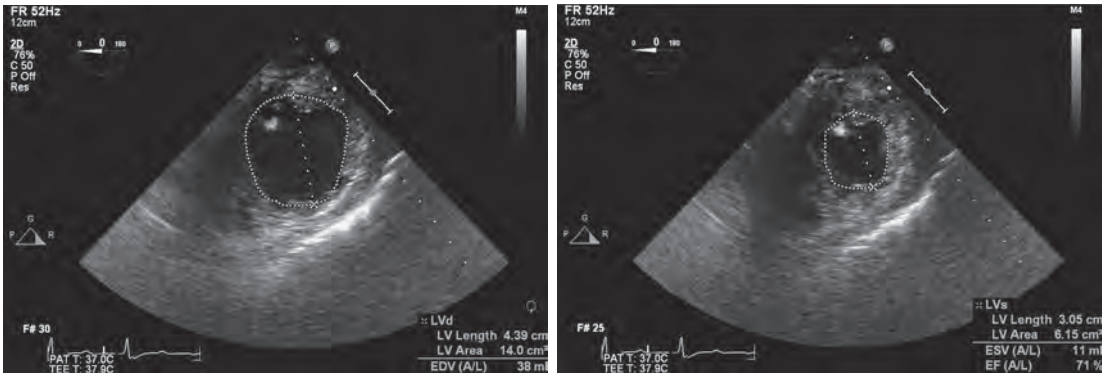

Fig. 6.28 Calculation of fractional area change (FAC) and fractional shortening (FS) from the left ventricular (LV) midpapillary short-axis images obtained at end-diastole *(left)* and end-systole *(right)*. The LV endocardial border is manually traced (excluding the papillary muscles). The software integrates the area inscribed and determines the diameter of the LV chamber. In this example, FAC is 69%, and FS is 59%.

Contractile Indices Based on Ventricular Power

The product of LV pressure and aortic or blood flow defines LV power, which is another index of the inotropic state. Maximal LV power (PWR_{max}) and the rate of increase of LV power during ejection are sensitive to changes in contractile state,[179,180] but these indices are also profoundly affected by LV preload. In contrast, the ratio of LV PWR_{max} to the square of end-diastolic volume is substantially less preload dependent and allows assessment of the LV contractile state from data obtained during a single cardiac cycle.[181]

Alterations in the LV contractile state determined using the preload-adjusted PWR_{max} technique correlate with those calculated with the ESPVR (E_{es}) and the LV dP/dt_{max}-V_{ed} relationship (dE/dt_{max}), and may be measured using noninvasive arterial blood pressure (eg, oscillometry) along with two-dimensional and Doppler echocardiography to define pressure, flow, and dimension variables.[182,183] A regional power quotient using end-diastolic segment length (SL_{ed}) also correlated with the regional SW-SL_{ed} (M_{sw}) and accurately quantified depression of LV contractility produced by volatile anesthetics.[184]

Coupling, Energetics, and Efficiency

The pressure-volume framework is useful to describe the transfer of kinetic energy between two elastic chambers. This mechanical coupling defines the blood volume that may be ejected from one chamber into another. Coupling between the LV and arterial circulation is most often described, but similar relationships between the LA and the LV[99] or analogous structures on the right side of the heart[185] also have been reported.

LV-arterial coupling is defined by the ratio of the slopes of the ESPVR (E_{es}) and the aortic end-systolic pressure-SV relationship (E_a) (see Fig. 6.20) that denote their respective elastances.[133] Ideal coupling between the LV and the arterial circulation indicates optimal transfer of SW between the chambers and occurs when the ratio of their elastances is unity at rest[135] or during exercise.[186,187] LV contractile dysfunction (ie, decrease in E_{es}) or greater resistance to LV ejection (ie, increase in E_a) reduces the E_{es}/E_a ratio to less than 1, indicating that kinetic energy transfer is no longer ideal.[188]

An E_{es}/E_a ratio less than 1 may occur when the global LV contractile state is depressed and compensatory activation of the sympathetic nervous system causes arterial vasoconstriction.[189] The severity of abnormal LV-arterial coupling correlates with serum B-type natriuretic peptide concentration (ie, biochemical marker of LV systolic dysfunction), and an E_{es}/E_a ratio less than 0.68 predicts long-term mortality for patients after myocardial infarction.[190] Tachycardia also increases E_a and worsens LV-arterial coupling in heart failure.[191]

Positive inotropic drugs or vasodilators may improve LV-arterial coupling in heart failure by increasing E_{es} or reducing E_a, respectively.[192] LV-arterial coupling is relatively preserved in the setting of a low end-tidal concentration (0.6 MAC) of desflurane, sevoflurane, or isoflurane (Fig. 6.29), but coupling degenerates when higher concentrations of volatile anesthetics are administered because the magnitude of vasodilation (ie, decrease in E_a) is unable to compensate for greater LV contractile depression (ie, decrease in E_{es}).[134]

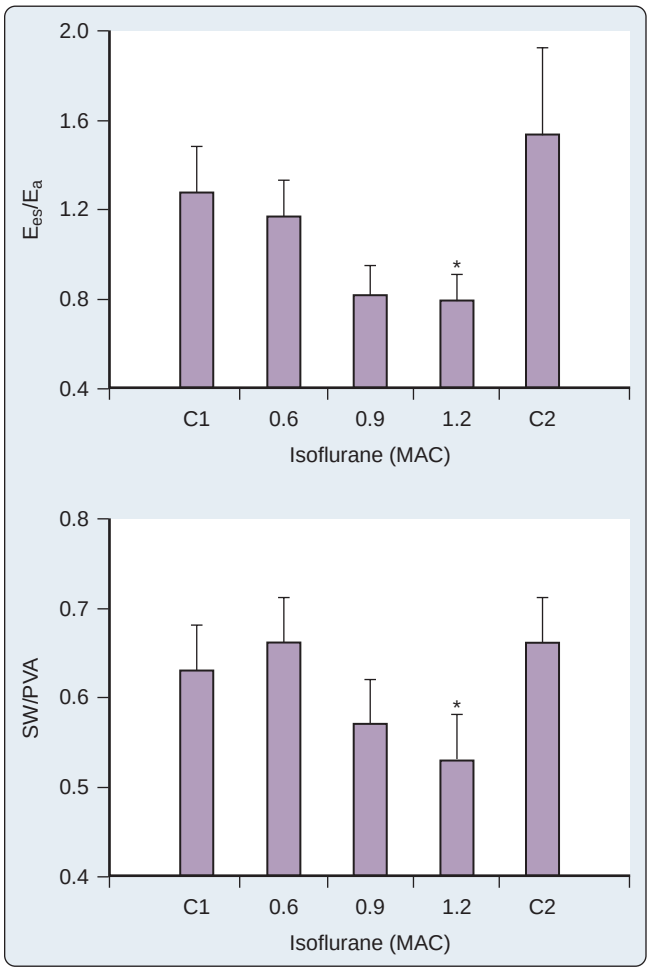

Fig. 6.29 Histograms illustrate the effects of isoflurane (0.6, 0.9, and 1.2 minimum alveolar concentrations [MACs]) on left ventricular (LV)–arterial coupling (ie, LV end-systolic elastance/effective arterial elastance [E_{es}/E_a]) *(top panel)* and energy transfer efficiency (ie, stroke work/pressure-volume area [*SW/PVA*]) *(bottom panel)*. Isoflurane reduces LV-arterial coupling and energy transfer efficiency in a dose-related manner. C_1, control 1 (before isoflurane); C_2, control 2 (after isoflurane). *(From Hettrick DA, Pagel PS, Warltier DC: Desflurane, sevoflurane, and isoflurane impair canine left ventricular-arterial coupling and mechanical efficiency,* Anesthesiology. *1996;85:403–413.)*

EF can be related to the ratio of E_{es} to E_a such that $EF/(1 - EF) = E_{es}/E_a$. It follows from this equation that an EF of 50% produces ideal LV-arterial coupling because $E_{es}/E_a = 1$ under these conditions.[193] The relationship between the EF and coupling ratio also predicts that EF is reduced when E_{es}/E_a is less than 1 because SV is less efficiently transferred from the LV to the arterial vasculature.

LV energetics may be quantified in pressure-volume phase space. Total energy is defined as the sum of the SW generated during a single cardiac cycle (ie, kinetic energy or area within the pressure-volume diagram) and the potential energy that remains in the chamber wall at end-systole as a result of compression of myocardial elastic elements.[83] The triangular area bounded above by the ESPVR, below by the EDPVR, and to the left by the isovolumic relaxation portion of the steady-state pressure-volume diagram defines the remaining potential energy (see Fig. 6.9). This potential energy has the same units as SW (mm Hg • mL = 1.33×10^{-4} joules) and is converted into heat during diastole.[194]

The sum of kinetic and potential energy is called the *pressure-volume area* (PVA)[195] and is linearly related to myocardial oxygen consumption ($M\dot{V}O_2$) such that $M\dot{V}O_2 = \alpha(PVA) + \delta$, in which α is the slope of the relationship and δ denotes basal metabolism in the absence of contraction, or $M\dot{V}O_2$ when PVA is 0.[196–198] The area beneath the $M\dot{V}O_2$-PVA line includes the sum of kinetic and potential energies associated with contraction and relaxation combined with the energy required for the maintenance of cellular function.

Administration of a positive or negative inotropic medication causes the $M\dot{V}O_2$-PVA relationship to shift up or down, respectively, in a parallel manner without a change in the slope of the relationship.[197–199] As a result of the observation, the relationship between $M\dot{V}O_2$ and PVA may be reformulated as $M\dot{V}O_2 = \alpha(PVA) + \beta(E_{es}) + \delta$, in which β is the offset (ie, sensitivity) of the $M\dot{V}O_2$-PVA relationship to E_{es}. This modification indicates that the total energy consumed for excitation-contraction coupling increases or decreases during an enhanced or reduced LV contractile state, respectively, but the energy required for basal metabolism is unaffected.[197]

Another ramification of the pressure-volume energetics framework is that the relative contribution of kinetic and potential energy (ie, PVA) to $M\dot{V}O_2$ is unchanged during alterations in myocardial contractility because the slope (α) of the relationship remains constant. This observation suggests that the biochemical conversion of high-energy phosphates into mechanical activity at the level of the myofilaments is not fundamentally altered by the inotropic state.[197] Alterations in LV compliance (as indicated by the position of the EDPVR) do not substantially influence $M\dot{V}O_2$ despite small changes in PVA because the kinetic and potential energies generated during systole are the predominant determinants of $M\dot{V}O_2$.[194]

LV efficiency also may be described using pressure-volume analysis.[135,200] The SW/PVA ratio indicates the mechanical energy that is converted into external work and is an index of energy transfer efficiency.[136,201] The SW/PVA ratio responds predictably to alterations in the LV contractile state and afterload. For example, an increase in E_{es} produced by a positive inotropic medication enhances the amount of mechanical energy that is converted into work. As a result, the SW/PVA ratio increases.[187] In contrast, greater LV afterload decreases SW and energy transfer efficiency.[201] These observations underscore that LV-arterial coupling is the primary determinant of the SW/PVA ratio.[202]

SW/PVA is mathematically related to E_{es}/E_a, and $SW/PVA = 1/[1 + 0.5(E_a/E_{es})]$.[203] For example, administration of a volatile anesthetic (eg, a vasodilating negative inotropic medication) causes a dose-related decrease in SW/PVA because LV E_{es} is depressed to a greater extent than E_a (see Fig. 6.29).[134] Because E_{es}/E_a is related to EF,[193] the ratio of SW to PVA may be rewritten as $2/[(1/EF) - 1]$. This equation demonstrates that a decrease in EF is associated with less efficient conversion of total mechanical energy into external work.

The ratio of PVA to measured $M\dot{V}O_2$ provides a useful index of the conversion of metabolic to mechanical energy,[204] whereas the product of SW/PVA and $PVA/M\dot{V}O_2$ ($SW/M\dot{V}O_2$) indicates the efficiency with which the LV transfers its metabolic energy into physical work. The ratio of SW to $M\dot{V}O_2$ increases with positive inotropic medications[205] and during exercise,[187] but it is substantially reduced[206] and predicts mortality[207] for patients with heart failure.

Evaluation of Diastolic Function

The ability of each chamber to efficiently fill under normal pressure conditions is essential for the best possible overall cardiac performance. LV diastolic function has been studied most extensively, but the relaxation, filling, and distensibility characteristics of the more compliant RV and the atrial chambers also have been described. This section focuses on LV diastolic function, but many of the techniques used to quantify LV diastolic function also may be applied to the study of RV diastology.

LV diastole encompasses a complicated sequence of temporally related, heterogeneous events (Box 6.3; see Fig. 6.15), and no single index of LV diastolic function can comprehensively describe this period of the cardiac cycle or selectively identify patients at highest risk for developing clinical signs and symptoms of heart failure resulting

BOX 6.3 DETERMINANTS OF LEFT VENTRICULAR DIASTOLIC FUNCTION

Heart rate and rhythm
LV systolic function
Wall thickness
Chamber geometry
Duration, rate, and extent of myocyte relaxation
LV untwisting and elastic recoil
Magnitude of diastolic suction
LA-LV pressure gradient
Passive elastic properties of LV myocardium
Viscoelastic effects (rapid LV filling and atrial systole)
LA structure and function
Mitral valve structure and function
Pulmonary venous blood flow
Pericardial restraint
RV loading conditions and function
Ventricular interdependence
Coronary blood flow and vascular engorgement
Compression by mediastinal masses

LA, Left atrial; *LV*, left ventricular; *RV*, right ventricular.

BOX 6.4 COMMON CAUSES OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

Age >60 y
Acute myocardial ischemia (supply or demand)
Myocardial stunning, hibernation, or infarction
Ventricular remodeling after infarction
Pressure-overload hypertrophy (eg, aortic stenosis, hypertension)
Volume-overload hypertrophy (eg, aortic or mitral regurgitation)
Hypertrophic obstructive cardiomyopathy
Dilated cardiomyopathy
Restrictive cardiomyopathy (eg, amyloidosis, hemochromatosis)
Pericardial diseases (eg, tamponade, constrictive pericarditis)

from filling abnormalities.[208] Most indices of LV diastolic function depend on heart rate, loading conditions, and myocardial contractility, and alterations in these variables require careful interpretation within these limitations.

Despite inherent difficulties, the crucial nature of LV diastolic function is emphasized by the striking observation that as many as 50% of patients with heart failure do not have a substantial reduction in LV EF.[209,210] This *heart failure with normal ejection fraction* (HFNEF), previously called *diastolic heart failure*, occurs most frequently in elderly women with poorly controlled essential hypertension, obesity, renal insufficiency, anemia, general deconditioning, or atrial fibrillation.[211] Many of these risk factors contribute to the progressive development of LV hypertrophy and fibrosis that adversely affect LV filling characteristics and increases the risk of heart failure.[211]

The pathophysiology of HFNEF appears to be multifactorial (Table 6.2). It involves delayed LV relaxation, reduced compliance,[212,213] and abnormal ventricular-arterial stiffening.[214,215] Regardless of the underlying cause (Box 6.4), diastolic dysfunction is a ubiquitous feature of HFNEF. Diastolic dysfunction is uniformly identified in all patients with heart failure resulting from LV systolic dysfunction.[216] The severity of LV diastolic dysfunction and its response to medical therapy are important determinants of exercise tolerance[217] and mortality[218] in patients with heart failure independent of concomitant LV systolic dysfunction.

From the perspective of the cardiac anesthesiologist, LV diastolic dysfunction has significant implications in determining the LV response to acute alterations in loading conditions that occur during and after surgery. For example, cardiopulmonary bypass temporally exacerbates preexisting LV diastolic dysfunction in cardiac surgical patients.[219] Volatile and intravenous anesthetics alter LV relaxation and filling properties in the normal and failing heart.[220] Assessing the existence and severity of LV diastolic dysfunction remains an important objective in the management of patients undergoing cardiac surgery.

Invasive Evaluation of Diastolic Function

Isovolumic Relaxation

Based on the previous discussions of intracellular Ca^{2+} homeostasis and myosin-actin interaction, relaxation of the cardiac myocyte is an energy-dependent process requiring active removal of Ca^{2+} from the myoplasm. This event results in rapid dissociation of the contractile proteins and recoil of elastic elements compressed during contraction.

TABLE 6.2 Left Ventricular Structure and Function in Chronic Heart Failure

Parameter	*LV Systolic Heart Failure*	*LV Diastolic Heart Failure*
Remodeling		
End-diastolic volume	Increased	Normal
End-systolic volume	Increased	Normal
LV mass	Increased	Increased
Geometry	Eccentric	Concentric
Cardiac myocyte	Increased length	Increased diameter
Extracellular matrix	Decreased collagen	Increased collagen
LV Systolic Properties		
Stroke volume	Decreased (or normal)	Normal (or decreased)
Stroke work	Decreased	Normal
M_{sw}	Decreased	Normal
E_{es}	Decreased	Normal (or increased)
Ejection fraction	Decreased	Normal
dP/dt_{max}	Decreased	Normal
Preload reserve	Exhausted	Limited
LV Diastolic Properties		
End-diastolic pressure	Increased	Increased
τ	Increased	Increased
β	Normal (or increased)	Increased

β, Myocardial stiffness constant; dP/dt_{max}, maximum rate of increase of LV pressure; E_{es}, slope of the LV end-systolic pressure-volume relationship; *LV*, left ventricular; M_{sw}, slope of the LV stroke work–end-diastolic volume relationship; τ, time constant of LV isovolumic relaxation.

Modified from Aurigemma GP, Zile MR, Gaasch WH. Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function. *Circulation.* 2006;113:296–304.

Delays in relaxation may be viewed as a form of active elasticity because failure of actin-myosin cross-bridges to dissociate occurs when energy supply is inadequate or intracellular Ca^{2+} homeostasis is dysfunctional.[221,222] The delay in relaxation is important because early LV filling may be substantially attenuated, and overall LV filling may become increasingly dependent on LA systole. The subsequent loss of LA contraction occurring, for example, with the onset of atrial fibrillation often precipitates acute signs and symptoms of heart failure in patients with diseases in which delayed LV relaxation is an especially prominent feature (eg, severe pressure-overload hypertrophy, hypertrophic obstructive cardiomyopathy [HCM]). Delayed global LV relaxation produced as a consequence of hypoxemia[223] or regional myocardial ischemia in a relatively large perfusion territory also may translate into reduced LV compliance (ie, upward shift of the EDPVR).[224,225]

LV relaxation delays compromise early diastolic subendocardial coronary blood flow because failure to complete actin-myosin dissociation and facilitate elastic recoil prolong the compression of intramyocardial coronary arterioles.[226] Evaluation of LV isovolumic relaxation

provides essential information about early diastolic mechanical behavior that directly influences subsequent events during chamber filling.

An invasively implanted, high-fidelity pressure transducer is required to precisely determine the rate and extent of LV pressure decline during isovolumic relaxation. Analogous to the use of LV dP/dt_{max} as an index of the inotropic state during isovolumic contraction, the peak rate of LV pressure decrease (dP/dt_{min}) has been used to quantify isovolumic relaxation during the early phase of diastole. LV dP/dt_{min} is regarded as an unreliable index of relaxation because the parameter is highly dependent on the magnitude of LV end-systolic pressure[227] and examines only a single time point near the onset of relaxation. Instead, LV relaxation is most often described based on the observation that LV pressure decline follows an exponential time course between aortic valve closure and mitral valve opening.

LV relaxation may be quantified using a time constant (τ) derived from the equation $P(t) = P_0e^{-t/\tau}$, in which P(t) is time-dependent LV pressure, P_0 is LV pressure at end-systole, e is the natural exponent, and t is time (ms) after LV end-systole. Although conceptually useful, this exponential equation is flawed because it mathematically constrains LV pressure to fall to 0 mm Hg. However, it is known that LV pressure may fall to subatmospheric pressures during marked hypovolemia or intense exercise[67] or remain greater than 0 mmHg when forces outside the LV are acting on it (eg, pericardial tamponade, constrictive pericarditis).[228] As a result, a more physiologically relevant model of isovolumic relaxation allows calculation of the time constant assuming a nonzero asymptote of LV pressure decay such that $P(t) = P_0e^{-t/\tau} + P_a$, in which P_a is the true end point of pressure decline.[229]

Regardless of the method used to derive the time constant, increases in τ quantify delays in LV relaxation that occur during disease processes such as myocardial ischemia,[230] pressure-overload hypertrophy,[231] or HCM[232] or as a consequence of negative inotropic drugs, including volatile anesthetics.[233] Conversely, reductions in τ indicate more rapid LV relaxation that may be observed during tachycardia, sympathetic nervous system activation, or administration of positive inotropic medications.

Interpretation of changes in τ produced by drugs or disease requires qualification because LV loading conditions affect the time constant.[40] For example, LV preload and τ are directly related[229,234] unless arterial pressure remains relatively constant.[235] Similarly, τ is linearly related to afterload because afterload affects the duration, rate, and extent of LV ejection.[40] The afterload dependence of LV relaxation is enhanced in the failing heart (see Fig. 6.21).[142,236] This observation has important clinical ramifications because afterload reduction enhances LV systolic function, facilitates LV relaxation, and indirectly improves early LV filling dynamics in patients with heart failure.[141] Interpretation of changes in the time constant of LV isovolumic relaxation requires consideration of the loading conditions under which τ is measured.[237] Invasive quantification of LA relaxation also has been reported using methods similar to those described in the LV.[73]

Filling

Invasive measurement of continuous LV volume allows indices of LV filling to be easily calculated, but LV volume waveforms also may be obtained noninvasively using echocardiography, angiography, and dynamic MRI. Regardless of the method used to obtain a continuous LV volume signal, its first derivative with respect to time (dV/dt) produces a biphasic waveform characterized by peaks corresponding to early LV filling and LA systole (ie, E and A waves, respectively). The dV/dt waveform is closely related to the transmitral blood flow and annular velocity signals obtained using conventional pulsed-wave echocardiography and tissue Doppler imaging, respectively.

Using the continuity equation, the products of the time-velocity integrals of transmitral blood flow velocity E and A signals (ie, TVI_E and TVI_A) and the mitral valve area can be shown to be identical to the areas inscribed by the E and A waves obtained from differentiation of the LV volume waveform, respectively. A wide variety of filling parameters may be determined using the dV/dt waveform, including the E and A wave peak filling rates, the deceleration rate and half-time

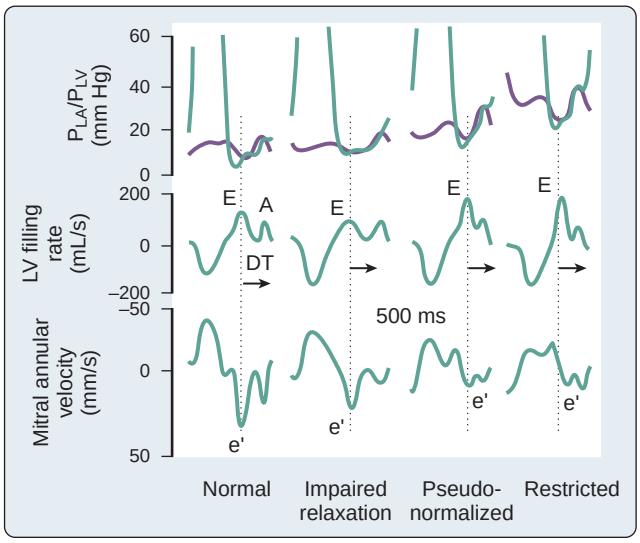

Fig. 6.30 Simultaneous tracings show the relationships between left atrial pressure *(P_{LA})* and left ventricular pressure *(P_{LV})*, the left ventricular *(LV)* filling rate during early filling *(E)* and atrial systole *(A)*, and the early mitral annular velocity *(e')* under normal conditions and during evolving diastolic dysfunction (ie, impaired relaxation, pseudonormal, and restrictive). Notice the initial lengthening of E-wave deceleration time *(DT)* during impaired relaxation and the subsequent shortening of DT as diastolic function worsens. *(From Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care.* Circulation. *2009;120:802–809.)*

of the E wave, the E/A ratio, the areas (obtained by integration) of the E and A waves (corresponding to early LV filling and LA systole blood volumes, respectively), the ratio of early LV filling to total LV end-diastolic volumes (ie, percentage of early LV filling), and measurements of time intervals of these events. Progressive development of heart failure produces similar changes in the dV/dt morphology compared with the transmitral blood flow velocity waveform, as indicated by the transition of delayed relaxation through pseudonormal and restrictive filling patterns (Fig. 6.30).[238]

An analogous set of parameters may be derived from continuous measurement of the LV dimension (eg, segment length, wall thickness).[239] However, the relative accuracy with which the variables may be extrapolated to describe global LV filling depend on implicit geometric assumptions, the LV region examined, and the absence of regional wall motion abnormalities.[208]

Passive Mechanical Behavior

Derived from a series of differentially loaded LV pressure-volume diagrams, the EDPVR describes LV passive elastic compliance. The relationship between end-diastolic pressure (P_{ed}) and volume (V_{ed}) is exponential such that $EDP = Ae^{KVed} + B$, in which K is the modulus of chamber stiffness (ie, end-diastolic elastance) and A and B are curve-fitting constants (Fig. 6.31). An increase in K produced by a disease process such as pressure-overload hypertrophy indicates that the LV chamber has become less compliant. This implies that a higher LV pressure will result for a given filling volume.

The modulus of chamber stiffness also may be derived from a single LV pressure-volume diagram by using pairs of diastolic pressure and volume data points obtained after relaxation is complete (ie, during diastasis and LA systole) to avoid viscoelastic effects[240] or estimated noninvasively using the deceleration time of the transmitral blood flow velocity E wave.[241]

The EDPVR provides a simple model of LV compliance that is conceptually useful, but its interpretation is subject to important limitations. LV geometry, mass, and wall thickness influence the modulus of chamber stiffness. Comparison of changes in K between patients

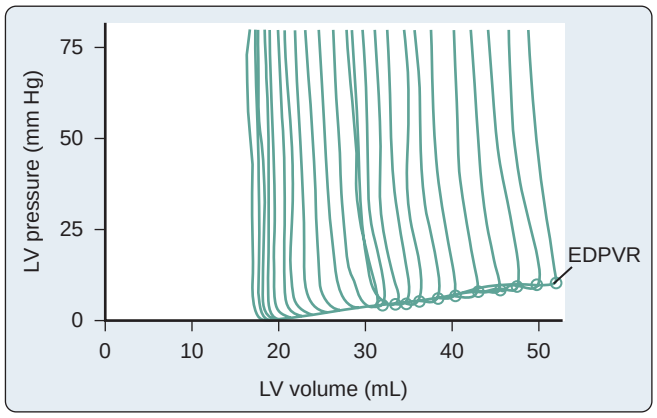

Fig. 6.31 Method used to derive the left ventricular *(LV)* end-diastolic pressure-volume relationship *(EDPVR)* from a series of differentially loaded LV pressure-volume diagrams generated by abrupt occlusion of the inferior vena cava in a canine heart in vivo. The end-diastolic pressure and volume data from each diagram *(right lower corner)* are related by a monoexponential relationship such that $P_{ed} = Ae^{KVed} + B$, where P_{ed} and V_{ed} are the end-diastolic pressure and volume, respectively; e is the natural exponent; K is the modulus of stiffness; and A and B are curve-fitting constants.

requires normalization of these variables.[237] Because the relationship between end-diastolic pressure and end-diastolic volume is exponential, comparisons of the modulus of chamber stiffness between patients or interventions should be made using a similar range of pressure and volume. Measurements of the modulus of chamber stiffness do not consider parallel shifts in the EDPVR.[40] For example, an acute increase in pericardial pressure causes a parallel upward shift of the EDPVR, indicating that LV pressure is greater at each LV volume.[85]

The relative position of the EDPVR, not the magnitude of the modulus of chamber stiffness alone, is equally important in defining overall LV passive mechanical characteristics because a shift in the relationship up or to the left indicates that a higher LV pressure is required to distend the LV to a given volume.[242] Similar descriptions of LA compliance have been reported using differentially loaded end-reservoir pressure-volume diagrams.[99]

The material properties of the myocardium itself (independent of LV size, geometry, and external forces) may be derived from stress-strain relationships. Because myocardium is an elastic material, Hooke's law governs its behavior, indicating that myocardium develops a resisting force (ie, stress [σ]) as its length (ie, strain [ε]) increases. The forces resisting further increases in myocardial length increase as the muscle is stretched, a process that occurs in vivo during LV filling. Strain is the percent change in muscle length (L) from unstressed muscle length (L_0), which is typically estimated at an LV pressure of 0 mm Hg in the intact heart. Lagrangian [$\varepsilon = (L - L_0)/L_0$] or natural ($\varepsilon = L/L_0$) strain is most often used to normalize muscle length. The stress-strain relationship is exponential such that $\sigma = \alpha(e^{\beta\varepsilon} - 1)$, where α is the coefficient of gain and β is the modulus of myocardial stiffness.[240] A shift of the nonlinear stress-strain relationship up and to the left is consistent with an increase in β that occurs in diseases such as HCM, amyloidosis, and hemochromatosis.

Myocardium is an elastic material, but it also demonstrates viscous properties. Viscoelasticity is observed when the forces resisting further alterations in length depend on the magnitude of the change in length and rate with which this change occurs. Viscoelastic effects are most evident in the intact heart during early LV filling, when the rate of change of LV volume is greatest, but they also may be observed during LA systole. Stress-strain relationships incorporating viscoelastic properties may be described using the equation $\sigma = \alpha(e^{\beta\varepsilon} - 1) + \eta(d\varepsilon/dt)$, in which η is the viscoelastic constant and $d\varepsilon/dt$ is the rate of change of strain.[243] An increase in viscous effects may modestly attenuate but is not a major determinant of early LV filling in the normal heart.[244]

Noninvasive Evaluation of Diastolic Function

Isovolumic Relaxation

Isovolumic relaxation time (IVRT) is the period between aortic valve closure and mitral valve opening. IVRT is the most commonly used noninvasive surrogate of invasively derived indices of LV relaxation (eg, dP/dt_{min}, τ). IVRT may be measured with M-mode echocardiography or continuous-wave Doppler echocardiography as the interval between the cessation of aortic blood flow and the onset of transmitral blood flow in the modified midesophageal five-chamber or deep transgastric TEE imaging planes.

The rate of LV relaxation and the difference between LV end-systolic pressure and LA pressure at the mitral valve opening are the major determinants of IVRT in the absence of mitral or aortic valve disease.[245] As a result, IVRT depends on LV relaxation and loading conditions. For example, an increase in LV afterload prolongs IVRT by increasing LV pressure at aortic valve closure, whereas an increase in LA pressure shortens IVRT.

In an attempt to partially circumvent the load-dependence of IVRT, Doppler echocardiographic analysis of mitral or aortic regurgitant jet velocity has been used in combination with the modified Bernoulli equation ($\Delta P = 4v^2$, in which ΔP is the pressure gradient and v is regurgitant blood flow velocity in m/s) to noninvasively estimate the time constant of LV relaxation.[246] However, this technique has not been widely applied in clinical echocardiography because τ is also load dependent.

Transmitral Blood Flow Velocity

Pulsed-wave Doppler echocardiographic evaluation of the pattern of transmitral blood flow velocity forms the basis of noninvasive analysis of LV diastolic function.[247] RV filling properties also may be assessed using pulsed-wave Doppler analysis of transtricuspid blood flow velocity. Cardiac anesthesiologists most often use the midesophageal four-chamber view to record the transmitral blood flow velocity profile by placing a pulsed-wave sample volume between the tips of the mitral leaflets during diastole to obtain a high-quality spectral envelope.

Similar to the invasively derived dV/dt waveform described earlier, the normal pattern of transmitral blood flow velocity contains two peaks associated with early LV filling and LA systole (E and A waves, respectively) (Fig. 6.32).[248] The ratio of peak E-wave to peak A-wave velocities (E/A ratio) is used to characterize the relative contributions of early and late filling to the final LV end-diastolic volume. Time-velocity integrals of the E and A waves (TVI_E and TVI_A, respectively) may be combined with measurements of mitral valve area to quantify the magnitude of blood flow (ie, volume) by application of the continuity equation. The time required for deceleration of the E wave (ie, deceleration time) also is commonly measured as an indicator of the influence of LV relaxation on the pressure gradient between the LA and LV that determines the magnitude and extent of early LV filling.

Normal values of these variables are age dependent and demonstrate a gradual slowing of LV relaxation as age increases (Table 6.3). E-wave velocity and E/A ratio decrease with advancing age, whereas IVRT, deceleration time, and A-wave velocity increase,[249] changes that predispose elderly patients to the development of exercise intolerance and heart failure. Progressive stiffening of the myocardial cartilaginous structure, loss of myocyte elasticity, increased LV muscle mass, and elevated arterial pressure are the major causes of age-related LV filling abnormalities.[250,251]

The alterations in transmitral blood flow velocity related to age are indicative of delayed relaxation, the least severe of three major abnormal LV filling patterns that characterize the continuum of LV diastolic dysfunction (see Fig. 6.30). Clinical symptoms, exercise tolerance, New York Heart Association (NYHA) functional class, and mortality rates are closely correlated with the relative severity of LV diastolic dysfunction.[252] A reduction in early LV filling and a greater contribution of LA systole to overall LV filling are pathognomonic findings in this delayed relaxation pattern. An E/A ratio less than 1

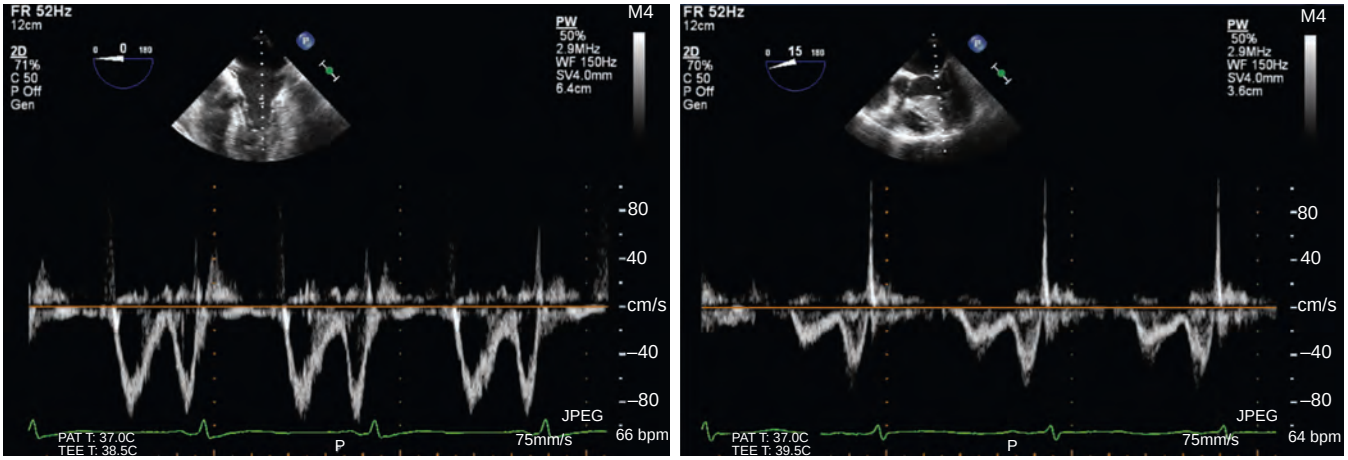

Fig. 6.32 Transmitral blood flow velocity waveforms obtained using pulsed-wave Doppler echocardiography under normal conditions *(left)* and during delayed relaxation *(right)*.

TABLE 6.3 Stages of Left Ventricular Diastolic Dysfunction

Parameter	*Normal Age 21-49 y*	*Normal Age >50 y*	*Delayed Relaxation*	*Pseudonormal Filling*	*Restrictive Filling*
E/A	>1	≥1	<1	1–2	>2
DT (ms)	<220	<220	>220	150–200	<150
IVRT (ms)	<100	<100	>100	60–100	<60
S/D	<1	≥1	≥1	<1	<1
Ar (cm/s)	<35	<35	<35	≥35[a]	≥25[a]
V_p (cm/s)	>55	>45	<45	<45	<45
e′ (cm/s)	>10	>8	<8	<8	<8

[a]Except in cases of left atrial failure.

Ar, Pulmonary venous atrial reversal blood flow velocity; *DT*, early left ventricular filling deceleration time; *e′*, peak early diastolic annular myocardial velocity; *E/A*, transmitral early left ventricular filling-to-atrial systole blood flow velocity ratio; *IVRT*, isovolumic relaxation time; *S/D*, pulmonary venous systolic-to-diastolic blood flow velocity ratio; V_p, color M-mode transmitral blood flow propagation velocity.

From Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol.* 1998;32:865–875.

and a deceleration time that is prolonged because of a delay in LV relaxation reduce the initial LV-LA pressure gradient and extend the duration of early LV filling, respectively.[238] The enhanced contribution of LA systole occurs primarily through a Frank-Starling mechanism, increases A-wave size, and compensates for the reduction in early LV filling, preserving relatively normal LV end-diastolic volume. In addition to advanced age, the delayed relaxation pattern is often observed in patients with essential hypertension, pressure-overload LV hypertrophy, and ischemic heart disease.

A pseudonormal pattern of transmitral blood flow velocity appears after the delayed relaxation profile as the underlying disease worsens. The E/A ratio increases to a value greater than 1, and this pseudonormal pattern may be indistinguishable from a normal LV filling pattern when other indices of diastolic dysfunction (eg, pulmonary venous blood flow velocity pattern, tissue Doppler imaging, color M-mode echocardiography) are not examined or when maneuvers to acutely alter loading conditions (eg, Valsalva, nitroglycerin infusion) are not performed.[253] Elevated LA pressure restores the normal LA-LV pressure gradient on mitral valve opening and increases E wave velocity to a normal value despite the continued presence of an LV relaxation abnormality.

The pseudonormal pattern of LV filling may be recognized by a shorter E-wave deceleration time (<200 ms, which is consistent with a reduction in early diastolic LV compliance[221]) or by the reappearance of the delayed relaxation pattern during a decrease in preload.[254] In contrast, the delayed relaxation profile does not appear when preload is reduced in patients with normal LV diastolic function.

The restrictive pattern denotes severe, end-stage LV diastolic dysfunction. LA pressure is profoundly elevated, and the LA-LV pressure gradient is augmented far beyond what is necessary to compensate for the LV relaxation delay. The peak E-wave velocity (>1 m/s) becomes markedly greater than its A-wave counterpart, and the E/A exceeds a value of 2. E-wave deceleration time also becomes very rapid (<150 ms) as LV compliance is further reduced (see Table 6.3).

The restrictive filling pattern frequently is observed in patients with NYHA class IV heart failure resulting from a variety of causes,[255,256] and it is a characteristic finding in those with severe constrictive pericarditis,[257] restrictive cardiomyopathy,[258] or rejection of a transplanted heart[259] independent of changes in LV systolic function. Failure of the restrictive filling pattern to revert to a less severe pseudonormal or delayed relaxation profile in response to a diuretic or a vasodilator is associated with a grim prognosis.[247] Two opposing parabolic curves describing changes in the E/A ratio and deceleration time may be used to illustrate changes in LV diastolic function related to age or progressive deterioration from delayed relaxation to restrictive physiology (Fig. 6.33).

In addition to load dependence, several other factors, including heart rate, abnormal AV conduction, atrial arrhythmias, and mitral valve disease, may adversely influence evaluation of transmitral blood flow velocity patterns. For example, sinus tachycardia and first-degree AV block produce partial or complete fusion of the E and A waves. Fusion complicates assessment of individual peak velocities, time-velocity integrals, and deceleration time. Atrial flutter produces variably loaded LA contractions, depending on the extent of the accompanying AV block, whereas atrial fibrillation completely eliminates the active LA contribution to LV filling.

Severe mitral stenosis limits LV filling, and the transmitral blood flow velocity measurements obtained in cases of stenosis are unreliable for LV diastolic function analysis. Mitral regurgitation increases LA pressure independent of changes in LV diastolic function; this

effect makes isolated recognition of LV diastolic dysfunction difficult or impossible using transmitral blood flow velocity profiles. Normal sinus rhythm and the absence of hemodynamically significant mitral valve disease are required when the morphology of transmitral blood flow velocity is used for the analysis of LV diastolic function (see Chapters 14 and 15).

Pulmonary Venous Blood Flow Velocity

The pulmonary venous blood flow velocity pattern is analyzed to noninvasively determine LV diastolic dysfunction,[260] quantify the degree of mitral regurgitation,[261] or estimate pulmonary capillary occlusion and mean LA pressures.[262] The pattern of hepatic venous blood flow velocity provides important information about the relative severity of RV diastolic dysfunction or tricuspid regurgitation.

Cardiac anesthesiologists most often interrogate pulmonary venous blood flow velocity by placing a pulsed-wave sample volume between 0.5 and 1.0 cm within the right or left superior pulmonary vein in a modified midesophageal bicaval or four-chamber TEE imaging plane, respectively, to obtain a crisp velocity profile.[263] Color-flow Doppler mapping is often used to identify the best location within a pulmonary vein to place the sample volume.

TEE is the preferred method for pulmonary venous blood flow velocity analysis because the anatomic proximity of the right and left upper pulmonary veins to the esophagus provides optimal imaging windows with minimal ultrasound scatter by intervening tissue.[264] The pulmonary venous blood flow velocity profile depends on LV relaxation, filling, and compliance; heart rate; LA and LV loading conditions; and LA contractile function.[265] Conclusions about LV diastolic function derived using this technique require interpretation with these potential limitations in mind. The pulmonary venous blood flow velocity profile is most often combined with the transmitral LV filling pattern and not used as an independent prognostic indicator of disease progression.[266]

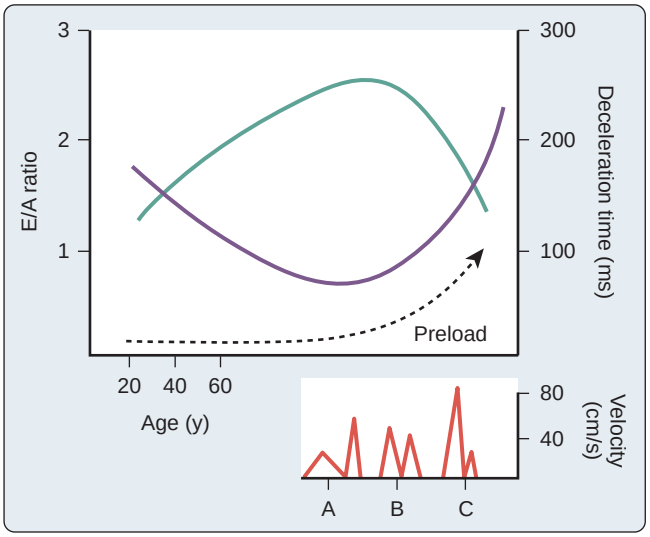

Fig. 6.33 Changes in the ratio of transmitral blood flow velocity during early left ventricular filling and atrial systole *(E/A ratio, purple curve)* and in deceleration time *(green curve)* associated with age and the development of left ventricular diastolic dysfunction. The *dashed line* represents left ventricular preload, which increases as diastolic dysfunction worsens. The lower right diagram demonstrates impaired relaxation *(A)*, pseudonormal *(B)*, and restrictive *(C)* left ventricular filling patterns of diastolic dysfunction measured using pulsed-wave Doppler echocardiography.

The normal pulmonary venous blood flow velocity pattern is composed of a single, small, negative deflection that indicates retrograde flow from the LA chamber into the pulmonary veins (ie, atrial reversal [Ar] wave), and two large, positive deflections that indicate forward flow from the pulmonary veins into the LA.[267] LA preload, LA contractile state, and LV pressure during late diastole affect the magnitude and duration of the Ar wave.[268]

The first positive deflection is known as the S (systolic) wave and occurs during LV systole and isovolumic relaxation when the mitral valve is closed. The S wave displays a biphasic morphology (S_1 and S_2, which are not equivalent to the first and second heart sounds) originating from a series of LA, LV, and RV events.[269] LA relaxation after contraction and the consequent reduction in LA pressure facilitates forward blood flow from the pulmonary veins into the LA during early LV isovolumic contraction.[268] Mitral annular descent toward the apex during LV systole (ie, approximately 1.3 cm in healthy individuals) also causes a piston-like effect that draws blood from the pulmonary veins into the LA.[270] These actions combine to produce S_1. Mitral annular descent may be markedly attenuated in patients with reduced LV systolic function, emphasizing that LV contractility plays an important role in the extent of LA filling.[271]

Transmission of the RV systolic pressure pulse through the pulmonary circulation contributes to additional LA filling later during LV contraction to produce S_2. S_1 and S_2 are most often combined into a single S wave when using pulmonary venous blood flow velocity patterns to assess LV diastolic function.

The second positive deflection (ie, D wave) of the pulmonary venous blood flow velocity pattern occurs immediately after the opening of the mitral valve. The rapid drop in LA pressure that accompanies early LV filling allows subsequent blood flow from the pulmonary veins into the LA (Fig. 6.34). The peak velocity and time-velocity integral of the D wave depend on LV compliance and the magnitude of early LV filling.[272] Factors that attenuate early LV filling (eg, delayed LV relaxation, reduced LV compliance, mitral stenosis) cause decreases in D-wave velocity.[273]

Similar to the pattern of transmitral blood flow velocity, the pulmonary venous blood flow velocity profile is age dependent. The S/D ratio, the peak Ar velocity, and the Ar duration increase with age,[248] consistent with the enhanced importance of LA systole to LV filling during the gradual development of delayed LV relaxation. However, the compensatory increase in LA pressure that restores the E-wave velocity and E/A ratio in pseudonormal physiology attenuates systolic pulmonary venous blood flow and begins to produce pulmonary venous congestion. The S wave becomes progressively blunted, and the S/D ratio falls below 1 while the magnitude and duration of the Ar wave continue to increase, allowing an easily recognizable distinction between otherwise morphologically similar normal and pseudonormal transmitral blood flow velocity patterns.[260]

As restrictive LV diastolic dysfunction develops, the changes are more pronounced concomitant with further elevations in LV diastolic and LA pressures. The S/D ratio declines as systolic LA filling is further

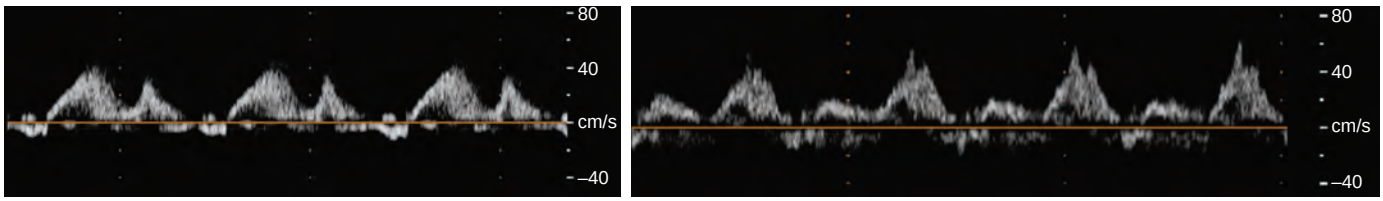

Fig. 6.34 Pulmonary venous blood flow velocity waveforms obtained using pulsed-wave Doppler echocardiography under normal conditions *(left)* and during increased left atrial pressure *(right)*.

attenuated, and the D wave deceleration time becomes more rapid as the LV becomes less compliant (see Fig. 6.34). The Ar blood flow velocity exceeds 35 cm/s, and the duration of the Ar wave becomes greater than that of the corresponding transmitral A wave unless overt LA failure occurs.[274] An Ar-A duration greater than 30 ms is strongly predictive of elevated LV end-diastolic pressure.[275] As observed with transmitral blood flow velocity profiles, atrial arrhythmias, AV conduction abnormalities, and mitral valve disease limit the use of pulmonary venous blood flow patterns for the evaluation of LV diastolic function.

Tissue Doppler Imaging

Interrogation of septal or lateral mitral annular motion using low-velocity (10 to 15 cm/s) pulsed-wave Doppler provides additional information about the relative severity of LV diastolic dysfunction (see Fig. 6.30).[276] Mitral annular motion is an index of the relative LV long-axis lengthening rate during filling. Averaging of septal and lateral tissue Doppler imaging is recommended to account for the effects of regional differences in function.[277]

Cardiac anesthesiologists most often use the midesophageal four-chamber TEE view to acquire tissue Doppler waveforms during LV filling. Similar to the transmitral blood flow velocity profile, the tissue Doppler waveform demonstrates peak velocities associated with early LV filling and LA systole (e′ and a′, respectively), and the e′/a′ ratio demonstrates the relative contributions of these events to the final LV end-diastolic volume. The ratio of transmitral E to tissue Doppler e′ waves (E/e′) is a reliable estimate of elevated LV filling pressure.[278] For example, a septal E/e′ ratio less than 8 strongly suggests that LV filling pressure is normal, but an E/e′ ratio greater than 15 usually indicates that LV end-diastolic pressure is increased.[279] The E/e′ ratio is especially useful for establishing the diagnosis of HFNEF.[280,281]

The determinants of tissue Doppler e′ and a′ velocities are similar to those described for transmitral E and A velocities, respectively. The rate and extent of LV isovolumic relaxation, LV systolic function, and LV preload are the major hemodynamic factors that determine tissue Doppler e′ velocity. Tissue Doppler e′ velocity appears to be less affected by preload than transmitral E velocity, especially when LV relaxation is delayed.[282] As a result, the e′/a′ ratio is less likely to display overt delayed relaxation and subsequent pseudonormal profiles than its transmitral E/A counterpart as LV diastolic dysfunction progresses and LA pressure rises. The relative preload independence of e′ during abnormal LV relaxation also increases the time interval between the onset of the transmitral E and tissue Doppler e′ velocities ($T_{E\text{-}e'}$), which has been shown to be a noninvasive estimate of the time constant (τ) of LV isovolumic relaxation.[283] Unlike transmitral E wave velocity, tissue Doppler e′ velocity is particularly useful in distinguishing between constrictive pericarditis (ie, e′ is normal) and restrictive cardiomyopathy (ie, e′ is reduced).[284]

LA contractile function and LV diastolic pressure are the primary factors that influence the magnitude of tissue Doppler a′ velocity. As observed with transmitral and pulmonary venous blood flow velocities, tissue Doppler velocities are age dependent such that e′ velocity and e′/a′ ratio decrease, whereas a′ velocity and E/e′ increase with age. In addition to age, the use of tissue Doppler imaging to quantify LV diastolic dysfunction may be limited by mitral annular calcification, a prosthetic mitral valve or ring, or mitral valve disease and by technical difficulties in obtaining a reproducible, clean envelope of low-velocity annular motion during diastole.[248]

Color M-Mode Propagation Velocity

The flow propagation velocity (V_p) of the blood column extending from the mitral valve to the apex during early LV filling may be reliably obtained using color M-mode echocardiography, and it is another index of LV diastolic function.[285] V_p is relatively preload insensitive,[286] is particularly useful for evaluating LV relaxation abnormalities,[287] and correlates with invasively derived indices of LV relaxation (eg, τ).[285]

The midesophageal four-chamber imaging plane allows the cardiac anesthesiologist to acquire a color Doppler M-mode envelope by placing the M-mode scan line into the center of LV inflow aligned from base to apex. After adjusting the Nyquist limit to ensure that the highest velocity is blue, V_p is determined as the slope of the first aliasing velocity (Fig. 6.35).[248] A V_p value greater than 50 cm/s is normal and quantifies the rapid movement of blood from the mitral valve to the

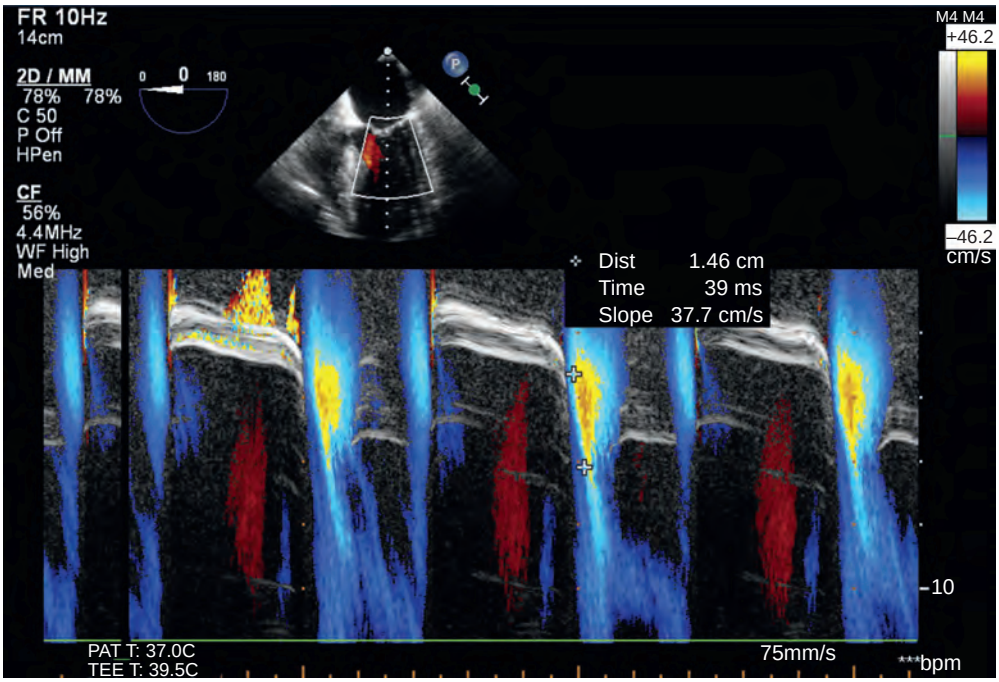

Fig. 6.35 Determination of color M-mode mitral valve blood flow propagation velocity (V_p). A color Doppler M-mode envelope is obtained by placing the M-mode scan line into the center of left ventricular (LV) inflow aligned from base to apex. V_p is determined as the slope of the first aliasing velocity. A value of V_p less than 45 cm/s suggests that early LV filling is attenuated, consistent with LV diastolic dysfunction.

apex, mediated by the pressure gradient between these intraventricular regions (ie, apical suction) during early LV filling.[285,288]

The extent of relaxation and the elastic recoil of the LV are the primary determinants of V_p. Clinical conditions (eg, myocardial ischemia, HCM) in which these factors are attenuated reduce V_p by decreasing the apical suction during early LV filling.[289,290] Nevertheless, the use of V_p as a quantitative index of LV diastolic dysfunction may be limited by other factors, including alterations in chamber geometry, contractile dyssynchrony, and blood flow vortex formation, that become increasingly important in determining the magnitude of apical suction as heart failure evolves.[291] The ratio of transmitral E-wave velocity to V_p (E/V_p) is related to LV filling pressure and has been used as a noninvasive estimate of pulmonary capillary occlusion pressure.[288] For example, an E/V_p ratio greater than 2.5 indicates that wedge pressure is greater than 15 mm Hg, a finding that is common in restrictive physiology.[283]

Pericardial Forces

The pericardium is a sac that encloses the heart, proximal great vessels, distal vena cavae, and pulmonary veins. The smooth surface of the visceral pericardium combined with the lubrication provided by 15 to 35 mL of pericardial fluid (ie, plasma ultrafiltrate, myocardial interstitial fluid, and a small quantity of lymph) and surfactant phospholipids reduce friction and facilitate normal cardiac movement during systole and diastole.

The pericardium also acts as a mechanical barrier that separates the heart from other mediastinal structures and limits abnormal displacement of the heart through its inferior (ie, diaphragmatic) and superior (ie, great vessels) attachments. The fibrous layer of the parietal pericardium determines the J-shaped pericardial pressure-volume relationship (Fig. 6.36), which indicates that the pericardium is substantially less compliant than LV myocardium. As a result of this lack of elasticity, the pericardium has very limited volume reserve and is capable of accommodating only a small increase in volume before a large increase in pressure occurs.[292]

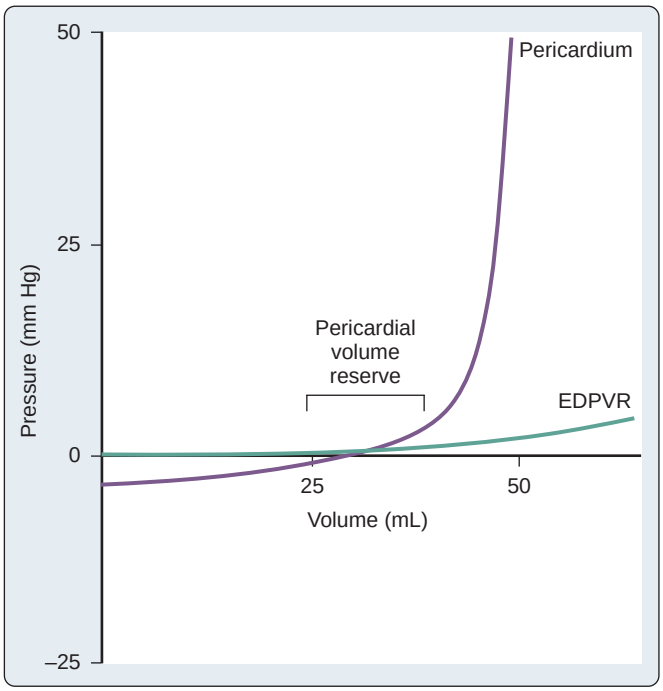

Fig. 6.36 Pressure-volume relationship of the pericardium compared with the left ventricular end-diastolic pressure-volume relationship *(EDPVR)*. Large increases in pericardial pressure occur after the reserve volume is exceeded.

Pericardial pressure is usually subatmospheric (range, –5 to 0 mm Hg), varies with changes in intrathoracic pressure, and produces little or no mechanical effect in a normal heart under euvolemic conditions.[293] Instead, the pericardium exerts a critical restraining force on the filling of all four cardiac chambers,[294] and the effect is exaggerated during pericardial compression (eg, tamponade, constrictive pericarditis) or acute increases in chamber dimension (eg, volume loading).

Pericardial restraint is most apparent in the thinner-walled atria and RV, and it is the primary determinant of the diastolic pressure and volume of these chambers. The pericardium resists further increases in atrial and RV chamber size during volume loading, and pressure within these chambers rises more rapidly than predicted on the basis of myocardial elasticity alone.

The pericardium also plays an important role in LV filling,[295] as an acute increase in pericardial pressure causes a parallel upward shift of the LV EDPVR.[296] Elevation of the EDPVR combined with more pronounced diastolic ventricular interdependence (ie, interaction) is responsible for the severely restricted LV filling observed during pericardial tamponade. Conversely, atrial volume, RV and LV end-diastolic volumes, SV, and CO increase after pericardiectomy because pericardial restraining forces are no longer present and the myocardium is the only remaining determinant of the compliance of each chamber.

In contrast to the effects of an acute increase in pericardial or cardiac chamber volume, chronic pericardial effusion or chamber enlargement progressively stretches the pericardium, increasing its compliance and attenuating or abolishing its restraining effects. This compensatory response to a gradual, chronic increase in pericardial load explains why hemodynamic instability often does not occur in the setting of a very large (>1000 mL) pericardial effusion or profound biventricular dilation that would otherwise precipitate severe hemodynamic instability.

The pericardium plays an essential role in ventricular interdependence (ie, influence of the pressure and volume of one ventricle on the mechanical behavior of the other). The pericardium restrains the LV and RV equally despite the inherent differences in compliance between the chambers. An increase in RV size (eg, ischemia, volume overload) causes pericardial pressure to increase, reducing LV compliance and restricting LV filling.[297] Similarly, acute LV distention (eg, application of an aortic cross-clamp) encroaches on the RV, shifts its EDPVR up and to the left, and limits RV filling.[298] These observations emphasize that the relative position and direction of movement of the interventricular septum are not the only factors that determine ventricular interdependence.

Evidence for diastolic ventricular interaction is readily apparent using pulsed-wave echocardiography to determine changes in RV and LV filling during spontaneous ventilation.[299] Inspiration decreases intrathoracic pressure, enhances venous return, and causes modest RV distention. These effects mildly reduce LV filling by decreasing compliance of the chamber, resulting in small declines in mean arterial pressure and CO. During expiration, RV filling is attenuated, and LV filling is augmented. Compression of the ventricular chambers during pericardial tamponade[300] or constrictive pericarditis[301] markedly exaggerates these respiratory changes in RV and LV filling. Maintenance of spontaneous ventilation is crucial under these circumstances because negative intrathoracic pressure preserves venous return to some degree, whereas institution of positive-pressure ventilation may rapidly cause cardiovascular collapse by profoundly limiting venous return.

Determinants of Atrial Function

The maximum velocity of shortening of LA myocardium is equivalent to or greater than that of LV myocardium under similar loading conditions.[302,303] LA emptying fraction primarily depends on the LA preload and contractile state in vivo unless the LA dilates and its myofilaments are extended beyond optimal operating length.[304] Under these circumstances, the emptying fraction falls precipitously, and LA contraction no longer makes a meaningful contribution to final LV end-diastolic volume.

Alterations in the activity of the autonomic nervous system produce similar changes in the LA compared with the LV contractile state.[305] For example, increases in the LA emptying fraction and the LA contribution to LV filling occur as a result of sympathetic nervous system activation,[306] whereas parasympathetic stimulation causes a direct negative inotropic effect. Volatile anesthetics cause a similar degree of myocardial depression in the LA compared with LV myocardium in vivo.[99,307]

LV compliance and pressure during late diastole determine the afterload to which the LA is subjected during its contraction. LV diastolic dysfunction increases LA afterload and the amount of energy the LA must expend to perform similar pressure-volume work. Analogous to the changes in myofilament composition occurring in response to chronic increases in LV afterload, upregulation of the β-myosin isoform in atrial myocardium is an important compensatory response to elevated LA afterload that preserves the LA emptying fraction.[308] However, the LA, like the RV, has less muscle mass and operates at lower pressures than the LV.

The LA is substantially more susceptible to afterload mismatch than the LV, and increases in LA afterload and energy use produced by impaired LV filling often lead to LA contractile failure.[273] For example, an initial increase in the LA emptying fraction may be observed early in the course of developing LV failure, but LA contractile dysfunction eventually occurs as LV compliance declines and end-diastolic pressure increases.[309] Conversely, drug therapy for chronic hypertension reduces LA and LV afterload and improves the active contribution of the LA to LV filling.[310] Remodeling and reduced compliance of the LA also occur in response to LV diastolic dysfunction. These effects further restrict pulmonary venous blood flow into the LA during the reservoir and conduit phases and may lead to the development of pulmonary edema.

Several factors determine LA reservoir and conduit function. LA relaxation after contraction normally facilitates forward flow from the pulmonary veins during early LV isovolumic contraction,[268] whereas relaxation abnormalities produced by LA ischemia, hypertrophy, or dilation attenuate the ability of the chamber to function effectively as a reservoir. Descent of the LV base toward the apex during LV systole is also an important determinant of LA reservoir function.[270] This action is markedly attenuated in the setting of severe LV contractile dysfunction. As a result, LA reservoir function decreases because pulmonary venous return during the S_1 phase is markedly reduced or entirely absent.[271] Transmission of RV SV through the pulmonary circulation to the LA occurs during the late reservoir phase (S_2).[311] RV systolic dysfunction also adversely affects LA reservoir function.

In addition to the previous factors, LA compliance plays a vital role in the ability of the chamber to act as a reservoir and a conduit. LA diseases in which compliance is reduced are associated with impaired LA filling.[74,312] Pressure-volume analysis has demonstrated that the LA appendage is more compliant than the main body of the chamber[313,314] and plays an essential role in LA filling. Temporary LA appendage exclusion[315] or permanent removal[313] reduces compliance of the remaining LA, attenuating reservoir function and blunting subsequent early LV filling. These effects are particularly important in the setting of LA dilation or hypertension. The pericardium limits LA passive filling, and pericardiectomy was shown to increase LA compliance, enhance early LV filling rate, and augment conduit function and, to a lesser extent, reservoir function.[98]

Exercise and age produce characteristic changes in LA function. LA contractility and reservoir function are enhanced during exercise.[316] The increase in reservoir capacity contributes to the formation of a larger LA-LV pressure gradient during early LV filling and increases LV SV and CO. An increase in conduit function has been observed in endurance athletes compared with normal persons.[317] In contrast to these findings, LA dilation and declines in passive emptying occur in healthy elderly individuals[318] concomitant with a compensatory increase in LA ejection force[319] and augmentation of LA contribution to LV end-diastolic volume.[320] LA dilation also increases storage fraction (ie, ratio of LA reservoir to LV SV),[321] but dilation may contribute to further increases in LA wall stress and eventual LA contractile dysfunction in the elderly.[322]

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7 Coronary Physiology and Atherosclerosis

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KEY POINTS

1. To care for patients with coronary artery disease in the perioperative period safely, the clinician must understand how the coronary circulation functions in health and disease.
2. Coronary endothelium modulates myocardial blood flow by producing factors that relax or contract the underlying vascular smooth muscle.
3. Vascular endothelial cells help maintain the fluidity of blood by elaborating anticoagulant, fibrinolytic, and antiplatelet substances.
4. One of the earliest changes in coronary artery disease, preceding the appearance of stenoses, is the loss of the vasoregulatory and antithrombotic functions of the endothelium.
5. The mean systemic arterial pressure and not the diastolic pressure may be the most useful and reliable measure of coronary perfusion pressure in the clinical setting.
6. Although sympathetic activation increases myocardial oxygen demand, activation of α-adrenergic receptors causes coronary vasoconstriction.
7. It is unlikely that one substance alone (eg, adenosine) provides the link between myocardial metabolism and myocardial blood flow under a variety of conditions.
8. As coronary perfusion pressure decreases, the inner layers of myocardium nearest the left ventricular cavity are the first to become ischemic and display impaired relaxation and contraction.
9. The progression of an atherosclerotic lesion is similar to the process of wound healing.
10. Lipid-lowering therapy can help restore endothelial function and prevent coronary events.

When caring for patients with coronary artery disease (CAD), the anesthesiologist must prevent or minimize myocardial ischemia by maintaining optimal conditions for perfusion of the heart. This goal can be achieved only with an understanding of the many factors that determine myocardial blood flow in both health and disease. This chapter begins with an overview of the structure and function of coronary arteries. Rapid progress has been made in the past several decades in the understanding of the physiology of blood vessels, particularly the role of the endothelium in maintaining flow. After this overview is an analysis of the major determinants of coronary blood flow. Physiologic or pharmacologic interventions alter myocardial flow by their effects on these factors. The section on coronary pressure-flow relationships explains the important concepts of autoregulation and coronary reserve. Studies of the coronary circulation are sometimes misinterpreted because of inadequate understanding of the complex interrelationships among the heart, the coronary circulation, and the peripheral circulation. The discussion of pathophysiology begins with a description of the process of atherosclerosis and the current understanding of how this disease evolves and causes clinical events. Next, the anatomy and hemodynamic effects of a coronary stenosis are explained. Coronary collateral function and development are reviewed here. These concepts are the basis of predicting how significantly the stenoses seen on angiography will impair myocardial perfusion. The topic of the final section is the pathophysiology of myocardial ischemia. Here, the concepts learned in the preceding sections are applied in an analysis of clinical ischemic syndromes. The final section highlights future directions in the treatment of CAD.

Anatomy and Physiology of Blood Vessels

The coronary vasculature has been traditionally divided into three functional groups: (1) large conductance vessels visible on coronary angiography, which offer little resistance to blood flow; (2) small resistance vessels ranging in size from approximately 250 nm to 10 μm in diameter; and (3) veins. Although it has been taught that arterioles (precapillary vessels <50 μm in size) account for most coronary resistance, studies indicate that under resting conditions, 45% to 50% of total coronary vascular resistance resides in vessels larger than 100 μm in diameter (Fig. 7.1).[1–3] The reason may be, in part, the relatively great length of the small arteries. During intense pharmacologic dilation, the proportion of total coronary vascular resistance contributed by larger arteries and veins is even greater.[1] The regulation of tone in coronary arteries larger than 100 μm in diameter plays an important role in delivering adequate myocardial perfusion.[4] One of the early changes in CAD is a diminished ability of the endothelium of epicardial coronary arteries to dilate in response to increased flow (see "Endothelium-Derived Relaxing Factors," later in the chapter). Advances in technology have enabled measurement, in the beating heart, of diameters of coronary vessels as small as 15 μm. It is becoming evident that, in response to a given intervention, different size classes of coronary vessels can change diameter with different intensity or even in opposite directions.[5,6] This heterogeneity of response according to vessel size would be an important consideration in predicting the effects of vasoactive agents on myocardial perfusion. For example, a drug that dilated large vessels and collaterals but not arterioles would be beneficial to patients with CAD (see the later section "Coronary Steal").

Normal Artery Wall

The arterial lumen is lined by a monolayer of endothelial cells that overlies smooth muscle cells (Fig. 7.2). The inner layer of smooth muscle cells, known as the intima, is circumscribed by the internal elastic lamina. Between the internal elastic lamina and external elastic

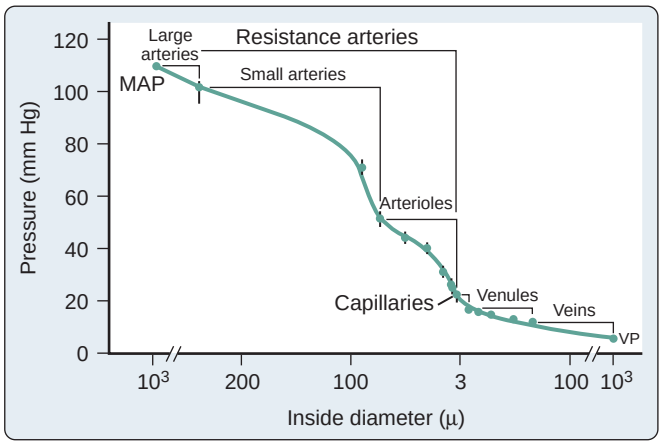


Fig. 7.1 Pressure decline through the hamster cheek pouch circulation illustrates the resistance and nomenclature of various portions of the vascular bed. The important contribution of small arteries to vascular resistance is clearly shown here. Similar observations have been made in the coronary circulation. *MAP,* Mean arterial pressure; *VP,* venous pressure. Error bars indicate SE. *(From Davis MJ, Ferrer PN, Gore RW. Vascular anatomy and hydrostatic pressure profile in the hamster cheek pouch.* Am J Physiol. *1986;250:H291.)*

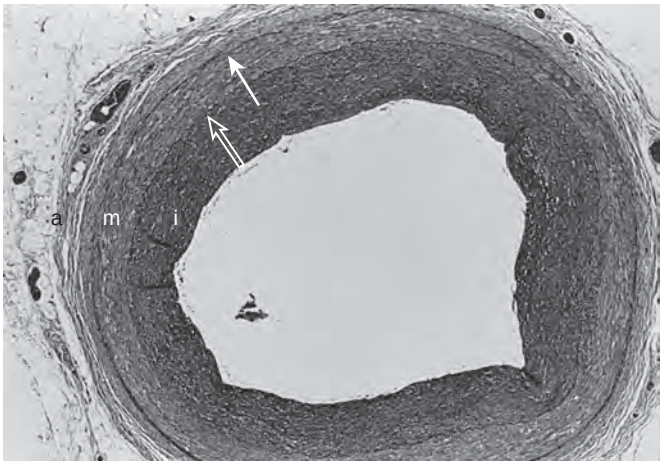


Fig. 7.2 Normal human coronary artery of a 32-year-old woman. The intima *(i)* and media *(m)* are composed of smooth muscle cells. The adventitia *(a)* consists of a loose collection of adipocytes, fibroblasts, vasa vasorum, and nerves. The media is separated from the intima by the internal elastic lamina *(open arrow)* and the adventitia by the external elastic lamina *(closed arrow)* (Movat's pentachrome–stained slide; original magnification ×6.6).

lamina is another layer of smooth muscle cells, the media. Outside the external elastic lamina is an adventitia that is sparsely populated by cells but consists of complex extracellular matrix (primarily collagen and elastin fibers) and the microvessels that comprise the vasa vasorum.

Intima

Traditionally, the intima has been considered the most important layer of the artery wall.[7] The intima can vary from an endothelial monolayer to a more complex structure with an endothelium overlying a patchwork of extracellular matrix and vascular smooth muscle cells. As part of the normal development of many large arteries, smooth muscle cells populate this space and form a neointima. This diffuse form of intimal thickening consists of several layers of smooth muscle cells and connective tissue. For convenience, the intima-to-media ratio is often measured, and the normal range is 0.1 to 1.0. The intima represents a physiologic adaptation to changes in arterial flow and wall tension, and the mechanisms that underlie its development remain poorly understood. The intima is made up of two distinct layers.[8] As seen on electron microscopy, the inner layer subjacent to the luminal endothelium contains an abundance of proteoglycan ground substance.[9] Smooth muscle cells found in this layer are usually distributed as isolated cells in a sea of matrix, rather than as contiguous layers. A few macrophages may also be found in this layer, under the endothelial monolayer. The outer, musculoelastic layer of the intima is adjacent to the internal elastic lamina and contains smooth muscle cells and elastic fibers.

Media

In normal adult arteries, several smooth muscle cell subpopulations with distinct lineages exist within the media.[9] These diverse cell populations likely fulfill different functions to maintain homeostasis in the artery wall. For example, in response to pressure elevations, increases in smooth muscle cell mass and extracellular matrix may be required. Alternatively, for arteries to be able to stretch both longitudinally and circumferentially, smooth muscle cells with variable orientations of cytoskeletal fibers must be present. These distinct cell types may be important in both health and disease. The biologic determinants of medial smooth muscle cell diversity are unknown.[10]

Adventitia

The adventitia, the outermost layer of the artery wall, normally consists of a sparse collection of fibroblasts, microvessels (vasa vasorum), nerves, and few inflammatory cells. Most of the vasa vasorum that nourish the inner layers of the artery wall originate in the adventitia. Traditionally, the adventitia was ignored and was not thought to play a role in vascular lesion formation. However, more recent studies elucidated the role of the adventitia as not only a source of inflammatory cells in the development of atherosclerosis, but also a hub for paracrine signaling in maintaining vascular homeostasis in a variety of vascular diseases.[11]

Transmembrane and Transcellular Communication

Blood vessels respond to a multitude of neural, humoral, and mechanical stimuli in fulfilling their role in homeostasis. When norepinephrine, released from adrenergic nerve terminals in the adventitia, binds to receptors on the vascular smooth muscle cell membrane, a series of events takes place, culminating in a change in vessel diameter. Much progress has been made in understanding this transmembrane signaling since the discovery of cyclic adenosine monophosphate (cAMP) in the late 1950s. Hormones circulating in the blood must interact with receptors on endothelial cells before the message reaches the vascular smooth muscle cells. The mechanism of communication between cells has been one of the central themes of biologic research in the last decades. Future understanding of cardiovascular disease will likely be based on identification of abnormalities of the molecules involved in transmembrane and transcellular communication. A brief introduction to these topics is provided here.

Fig. 7.3 illustrates examples of pathways of transmembrane signaling. Up to five components can be involved: (1) receptor, (2) G protein, (3) effector producing a second messenger, (4) phosphorylation of regulator protein, and (5) the consequent change in cell behavior. G proteins (guanine nucleotide binding regulatory proteins) are made up of three subunits (α, β, γ) and float in the cell membrane. On contact with a ligand-receptor complex, guanosine diphosphate on the α subunit is replaced by guanosine triphosphate. The activated α subunit then dissociates from the β-γ complex and can interact with several membrane targets (see Fig. 7.3B). For example, β-receptor activation results in the activation of G_s (s = stimulate), which stimulates the synthesis of cAMP by adenylyl cyclase. Muscarinic receptor activation activates a G_i (i = inhibit) protein that inhibits adenylyl cyclase. A single G protein can

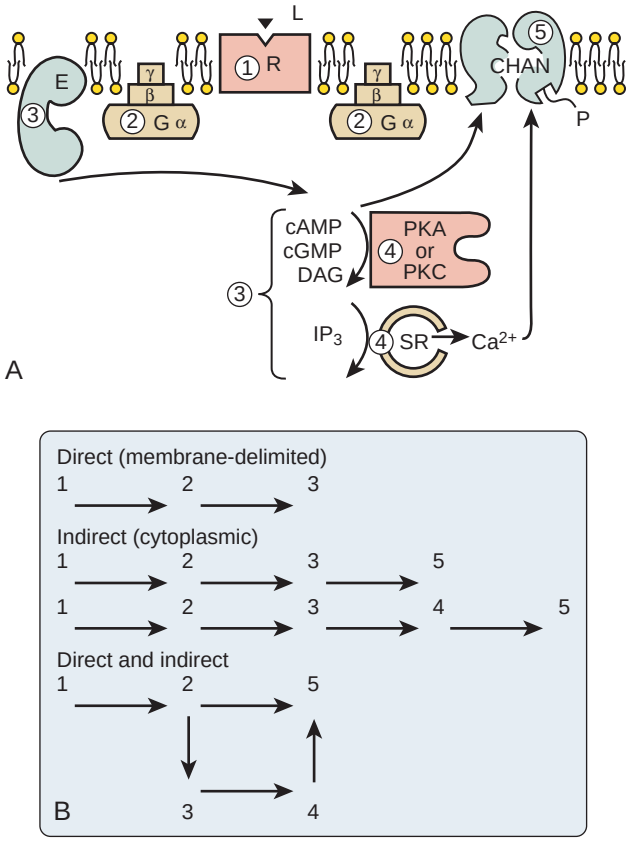


Fig. 7.3 Steps in the process whereby hormone-receptor binding results in a change in cell behavior. In this example, the final result is the opening of an ion channel. (A) A hormone or ligand *(L)* binds to a receptor *(R)* embedded in the cell membrane. The receptor-ligand complex interacts with G protein *(G)* floating in the membrane, with resulting activation of the α subunit *(Gα)*. The activated α subunit can then follow different pathways (B). Effector enzymes in the membrane *(E)*, such as adenylyl cyclase, cyclic guanosine monophosphate *(cGMP)*, phospholipase C, or phospholipase A_2, change the cytoplasmic concentration of their "messengers": cyclic adenosine monophosphate *(cAMP)*, cGMP, diacylglycerol *(DAG)*, and inositol-1,4,5-triphosphate *(IP_3)*. These soluble molecules activate protein kinase A or C *(PKA, PKC)*, or release calcium *(Ca^{2+})* from sarcoplasmic reticulum *(SR)*. Subsequently, cell behavior is changed by phosphorylation of an ionic channel on the cell membrane *(CHAN)* or by release of Ca^{2+} from SR. (B) Several pathways coupling receptor activation to final effect are illustrated. It is likely that multiple pathways are activated concomitantly, both facilitatory and inhibitory. In this way, the final response can be determined by the sum of the effects of several stimuli. *(From Brown AM, Birnbaumer L. Ionic channels and their regulation by G-protein subunits.* Annu Rev Physiol. *1990;52:197.)*

interact with more than one effector. In this way the G protein can be a branch point for the regulation of multiple effectors in response to a single signal. These proteins have already been implicated in human disease; cholera toxin covalently modifies G_s so that it becomes persistently active in stimulating adenylyl cyclase in intestinal epithelial cells, thus likely causing the severe diarrhea of cholera.

Several second-messenger systems have been characterized. G_s can directly enhance conductance through calcium channels, with the increased intracellular calcium acting as a second messenger. The cyclic nucleotides, cAMP and cyclic guanosine monophosphate (cGMP), act as second messengers. Their intracellular action is terminated when they are cleaved by phosphodiesterase enzymes, which, in turn, are also regulated by stimuli and second messengers. The breakdown products of membrane phosphoinositide constitute another, more recently recognized, set of second messengers.[12] In response to agonists such as vasopressin, G protein is activated, leading to activation

TABLE 7.1 Substances Produced by Vascular Endothelium

Antithrombotic Substances	*Procoagulants*
Prostacyclin	von Willebrand factor
Antithrombin III	Collagen
Plasminogen activator	Fibronectin
Protein C	Thromboplastin
α_2-Macroglobulin	Thrombospondin
Glycosaminoglycans (heparin)	Plasminogen inhibitors Platelet-activating factor Thromboxane A_2

From Bassenge E, Busse R. Endothelial modulation of coronary tone. *Prog Cardiovasc Dis.* 1988;30:349.

TABLE 7.2 Vasoactive Substances Processed by Vascular Endothelium

Uptake and Metabolism	*Enzymatic Conversion or Degradation*
Norepinephrine	Angiotensin I to angiotensin II (ACE)
Serotonin	Angiotensin II to angiotensin III (angiotensinase)
Prostaglandins (E_1, E_2, $E_{2\alpha}$)	Bradykinin degradation (ACE)
Leukotrienes	Substance P degradation
Adenosine	

ACE, Angiotensin-converting enzyme.
From Bassenge E, Busse R. Endothelial modulation of coronary tone. *Prog Cardiovasc Dis.* 1988;30:349.

of the membrane-associated enzyme phospholipase C. This enzyme cleaves phosphatidylinositol-4,5-biphosphate on the inner leaflet of the plasma membrane, to produce inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG). Both are second messengers. IP_3 diffuses through the cytoplasm and mobilizes calcium from intracellular stores. DAG remains within the plasma membrane and activates protein kinase C, which modulates cellular activity by phosphorylating intracellular proteins. In many cell types, activation of the same receptors that control phosphoinositide breakdown also results in the liberation of arachidonate or eicosanoids (prostaglandins, leukotrienes, and thromboxanes). The resultant change in cell behavior can be opening of an ion channel, contraction or relaxation of smooth muscle, secretory activity, or initiation of cell division (see Chapter 8).

Endothelium

Although the vascular endothelium was once thought of as an inert lining for blood vessels, it is more accurately characterized as a very active, distributed organ with many biologic functions. It has synthetic (Table 7.1) and metabolic (Table 7.2) capabilities and contains receptors for a variety of vasoactive substances (Box 7.1). Functions of the endothelium that may play an important role in the pathophysiology of ischemic heart disease are discussed here.

Endothelium-Derived Relaxing Factors

The first vasoactive endothelial substance to be discovered was prostacyclin (PGI_2), a product of the cyclooxygenase pathway of arachidonic acid metabolism (Fig. 7.4 and Box 7.2).[13] The production of PGI_2 is activated by shear stress, pulsatility of flow, hypoxia, and a variety of vasoactive mediators. On production it leaves the endothelial cell and acts in the local environment to cause relaxation of the underlying smooth muscle or to inhibit platelet aggregation. Both actions are mediated by the stimulation of adenylyl cyclase in the target cell to produce cAMP.

In 1980, Furchgott and Zawadzki[14] observed that the presence of an intact endothelium was necessary for acetylcholine-induced vasodilation. Investigators have since shown that many physiologic stimuli cause vasodilation by stimulating the release of a labile, diffusible, nonprostanoid molecule termed *endothelium-derived relaxing factor* (EDRF) (see Fig. 7.4), now known to be nitric oxide (NO). NO is the basis of a widespread paracrine signal transduction mechanism

BOX 7.1 STIMULATORS OF ENDOTHELIUM-MEDIATED VASODILATION

Transmitters
Acetylcholine
Norepinephrine

Peptides
Angiotensin
Bradykinin
Calcitonin gene–related peptide
Oxytocin
Substance P
Vasoactive intestinal peptide
Vasopressin

Platelet or Blood Components
Adenosine
Adenosine diphosphate
Adenosine triphosphate
Serotonin
Thrombin
Trypsin

Local Hormones
Histamine
Platelet-activating factor

Physicochemical Stimuli
Hypoxia
Mechanical stress (pulsatility)
Shear stress (flow)

Modified from Bassenge E, Busse R. Endothelial modulation of coronary tone. *Prog Cardiovasc Dis.* 1988;30:349.

BOX 7.2 ENDOTHELIUM-DERIVED RELAXING AND CONTRACTING FACTORS

Healthy endothelial cells have an important role in modulating coronary tone by producing:
- vascular muscle relaxing factors
  - prostacyclin
  - nitric oxide
  - hyperpolarizing factor
- vascular muscle contracting factors
  - prostaglandin H_2
  - thromboxane A_2
  - endothelin

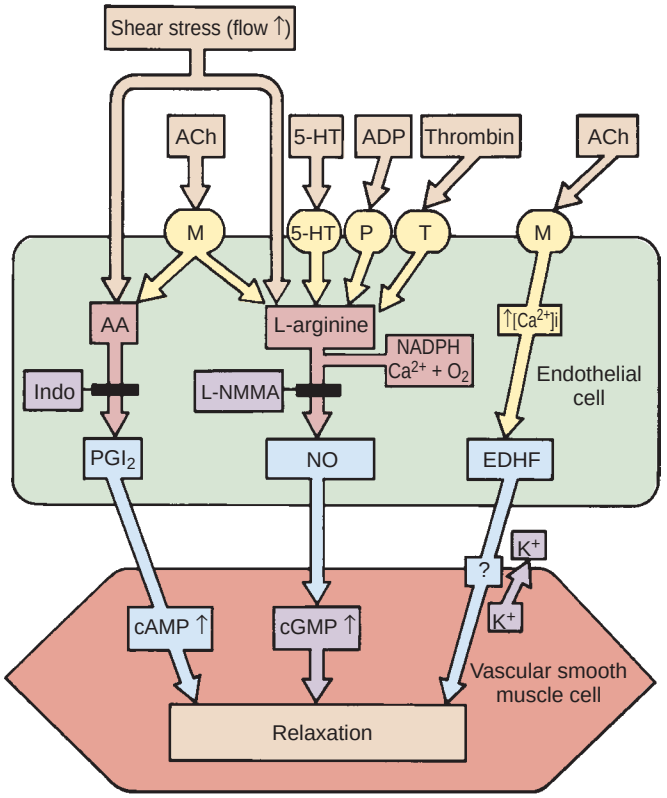


Fig. 7.4 The production of endothelium-derived vasodilator substances. Prostacyclin *(PGI_2)* is produced by the cyclooxygenase pathway of arachidonic acid *(AA)* metabolism, which can be blocked by indomethacin *(Indo)* and aspirin. PGI_2 stimulates smooth muscle adenylyl cyclase and increases cyclic adenosine monophosphate *(cAMP)* production, actions that cause relaxation. Endothelium-derived relaxing factor *(EDRF)*, now known to be nitric oxide *(NO)*, is produced by the action of NO synthase on L-arginine in the presence of reduced nicotinamide adenine dinucleotide phosphate *(NADPH)*, oxygen *(O_2)*, and calcium *(Ca^{2+})* and calmodulin. This process can be blocked by arginine analogues such as N^G-monomethyl-L-arginine *(LNMMA)*. NO combines with guanylate cyclase in the smooth muscle cell to stimulate production of cyclic guanosine monophosphate *(cGMP)*, which results in relaxation. Less well characterized is an endothelium-derived hyperpolarizing factor *(EDHF)*, which hyperpolarizes the smooth muscle membrane and probably acts by activation of potassium *(K^+)* channels. *ACh*, Acetylcholine; *ADP*, adenosine diphosphate; *$[Ca^{2+}]_i$*, intracellular calcium; *5-HT*, serotonin; *M*, muscarinic receptor; *P*, purinergic receptor; *T*, thrombin receptor. *(From Rubanyi GM. Endothelium, platelets, and coronary vasospasm.* Coron Artery Dis. *1990;1:645.)*

whereby one cell type can modulate the behavior of adjacent cells of a different type.[15,16] NO is a very small lipophilic molecule that can readily diffuse across biologic membranes and into the cytosol of nearby cells. The half-life of the molecule is less than 5 seconds so that only the local environment can be affected. NO is synthesized from the amino acid L-arginine by NO synthase (NOS). In vascular endothelium, the enzyme (eNOS or NOS_3) is always present (constitutive) and resides in the cytoplasm. Its function depends on the presence of calcium (Ca^{2+}) and calmodulin as well as tetrahydrobiopterin. The enzyme is activated in response to receptor occupancy or physical stimulation (see Box 7.1). When NO diffuses into the cytosol of the target cell, it binds with the heme group of soluble guanylate cyclase; the result is a 50- to 200-fold increase in production of cGMP, its secondary messenger. If the target cells are vascular smooth muscle cells, vasodilation occurs; if the target cells are platelets, adhesion and aggregation are inhibited. In vascular smooth muscle, cGMP leads to activation of protein kinase G, which phosphorylates various intracellular target proteins, including the myosin light-chain regulatory subunit and proteins that control intracellular calcium.[17]

NO is probably the final common effector molecule of nitrovasodilators (including sodium nitroprusside and organic nitrates such as nitroglycerin). The cardiovascular system is in a constant state of active vasodilation that depends on the generation of NO. The molecule is more important in controlling vascular tone in veins and arteries compared with arterioles. When the microcirculation dilates in response to metabolic myocardial demand (eg, exercise), increased flow through epicardial coronary arteries augments shear stress at the endothelium. This change leads to release of NO, which causes vascular smooth muscle relaxation and dilation of the conductance vessels, thereby facilitating the increase in flow. The importance of the loss of this mechanism in atherosclerosis is underlined by the finding that in this situation more than 50% of the resistance to flow in the coronary circulation resides in vessels larger than 100 μm in diameter (see Fig. 7.1). Abnormalities in the ability of the endothelium to produce NO

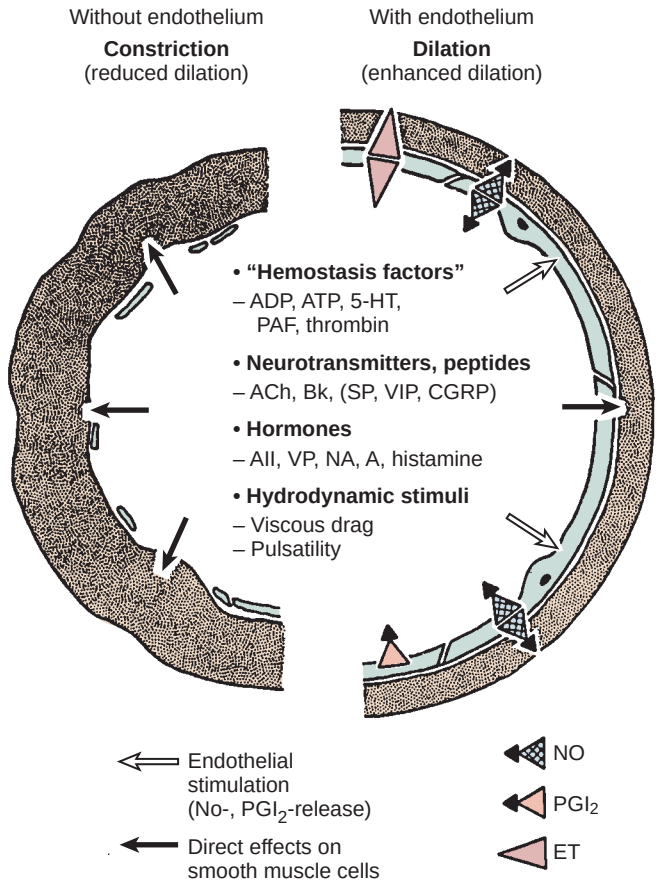


Fig. 7.5 The role of endothelium in the control of coronary tone. Intact endothelium has an important modulatory role in the effect of numerous factors on vascular smooth muscle. In the absence of a functional endothelium (mechanical trauma, atherosclerosis), many factors act directly on smooth muscle to cause constriction *(left side).* Under normal conditions *(right side),* the release of nitric oxide (*NO;* endothelium-derived relaxing factor *[EDRF]*) and prostacyclin *(PGI_2)* stimulated by these same factors can attenuate constriction or cause dilation. PGI_2 release is predominantly into the lumen, whereas EDRF release is similar on both the luminal and abluminal sides. Substances in parentheses elicit only vasodilation. *A,* Adenosine; *ACh,* acetylcholine; *ADP,* adenosine monophosphate; *AII,* angiotensin II; *ATP,* adenosine triphosphate; *Bk,* bradykinin; *CGRP,* calcitonin gene–related peptide; *ET,* endothelin; *5-HT,* serotonin; *NA,* norepinephrine; *PAF,* platelet-activating factor; *SP,* substance P; *VIP,* vasoactive intestinal polypeptide; *VP,* vasopressin. *(From Bassenge E, Heusch G: Endothelial and neurohumoral control of coronary blood flow in health and disease.* Rev Physiol Biochem Pharmacol. *1990;116:77.)*

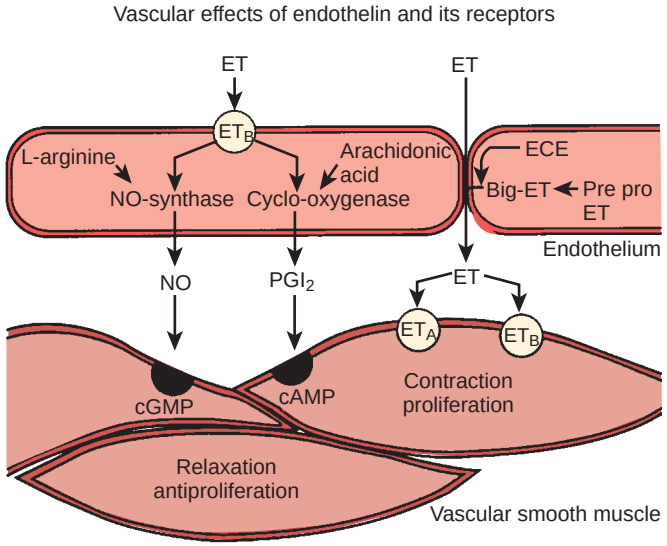


Fig. 7.6 Endothelin *(ET)* released abluminally interacts with ET_A and ET_B receptors on vascular smooth muscle to cause contraction. Activators of ET_B receptors on endothelial cells cause vasodilation. *cAMP,* Cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *ECE,* endothelin-converting enzyme; *NO,* nitric oxide; *PGI_2,* prostacyclin. *(From Luscher TF. Do we need endothelin antagonists?* Cardiovasc Res. *1997;29:2089. Reproduced with permission of Elsevier Science-NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, the Netherlands.)*

likely plays a role in diseases such as diabetes, atherosclerosis, and hypertension.[18,19] The venous circulation of humans seems to have a lower basal release of NO and an increased sensitivity to nitrovasodilators compared with the arterial side of the circulation.[20]

Many agents, such as acetylcholine and norepinephrine, can cause contraction when they are applied directly to the vascular smooth muscle membrane; conversely, relaxation occurs when they are applied to the intact endothelium (Fig. 7.5). The net effect of neural or humoral stimuli depends on a combination of direct effects mediated by binding to vascular smooth muscle receptors and indirect effects related to the ligand binding to endothelial receptors causing NO release from the endothelium. In the presence of healthy endothelium, vasodilation usually predominates. When the endothelium is absent (eg, injured vessel) or diseased (eg, atherosclerosis), vasoconstriction may be the net effect. NO has important roles in neurohumoral regulation of vascular tone, in prevention of intravascular platelet aggregation, and in the structural adaptation of blood vessels to the demands of blood flow and pressure.

Endothelium-Derived Contracting Factors

Contracting factors produced by the endothelium include prostaglandin H_2, thromboxane A_2 (generated by cyclooxygenase), and the peptide endothelin. Endothelin is a potent vasoconstrictor peptide (100-fold more potent than norepinephrine) with remarkable similarities to the toxin of the burrowing asp.[21] Both have potent coronary constrictor activity to which the strong cardiac toxicity and lethality of the toxin are attributed.[22] Three closely related 21–amino acid peptides have been identified: endothelin-1 (ET-1), ET-2, and ET-3. The primary product of vascular endothelium is ET-1, which is synthesized from prepro-ET-1 within vascular endothelial cells by the action of endothelin-converting enzymes. ET-1 is not stored but is rather rapidly synthesized in response to stimuli such as ischemia, hypoxia, and shear stress and is released predominantly abluminally (toward the underlying smooth muscle).[23] In vascular smooth muscle cells, ET-1 binds to specific membrane receptors (ET_A) and, through phospholipase C, induces an increase in intracellular calcium resulting in long-lasting contractions.[24] It is also linked by a G_i protein to voltage-operated calcium channels. This peptide has greater vasoconstricting potency than any other cardiovascular hormone, and in pharmacologic doses it can abolish coronary flow, thereby leading to ventricular fibrillation and death.[25] Another receptor subtype, ET_B, is expressed by both smooth muscle and endothelium and binds ET-1 and ET-3 equally well (Fig. 7.6). When isolated vessels are perfused with ET-1, initial NO-mediated vasodilation results from binding with ET_B receptors on the endothelial cells, followed by contraction secondary to binding of ET-1 to ET_A receptors on the vascular smooth muscle membrane. Studies with bosentan, a combined oral ET_A and ET_B receptor antagonist, demonstrated that endothelin exerts a basal coronary vasoconstrictor tone in humans.[26] Evidence indicates that endothelin may play a role in the pathophysiology of pulmonary and arterial hypertension, atherosclerosis, myocardial ischemic syndromes, and heart failure.[23] Clinical trials of bosentan in patients with congestive heart failure[27] and hypertension have shown promise, but hepatic side effects have

BOX 7.3 ENDOTHELIAL INHIBITION OF PLATELETS

Healthy endothelial cells have a role in maintaining the fluidity of blood by producing:
- anticoagulant factors: protein c and thrombomodulin
- fibrinolytic factor: tissue-type plasminogen activator
- platelet inhibitory substances: prostacyclin and nitric oxide

BOX 7.4 DETERMINANTS OF CORONARY BLOOD FLOW

The primary determinants of coronary blood flow are:
- perfusion pressure
- myocardial extravascular compression
- myocardial metabolism
- neurohumoral control

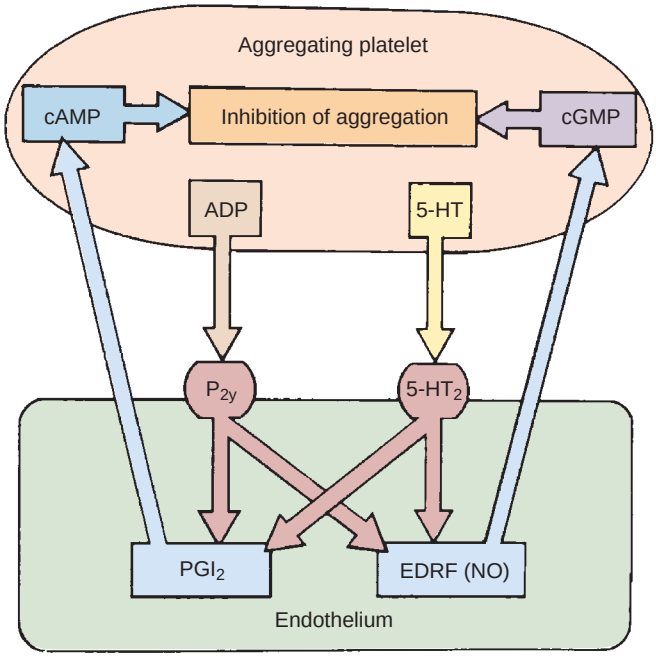


Fig. 7.7 Inhibition of platelet adhesion and aggregation by intact endothelium. Aggregating platelets release adenosine diphosphate *(ADP)* and serotonin *(5-HT)*, which stimulate the synthesis and release of prostacyclin (PGI_2) and endothelium-derived relaxing factor (*EDRF;* nitric oxide *[NO]*), which diffuse back to the platelets and inhibit further adhesion and aggregation and can cause disaggregation. PGI_2 and EDRF act synergistically by increasing platelet cyclic adenosine monophosphate *(cAMP)* and cyclic guanosine monophosphate *(cGMP)*, respectively. By inhibiting platelets and also increasing blood flow by causing vasodilation, PGI_2 and EDRF can flush away microthrombi and prevent thrombosis of intact vessels. P_{2y}, purinergic receptor. *(From Rubanyi GM. Endothelium, platelets, and coronary vasospasm.* Coron Artery Dis. *1990;1:645.)*

limited the dose to less than 500 mg daily; the primary indication for bosentan therapy is severe pulmonary hypertension.[28]

Endothelial Inhibition of Platelets

A primary function of endothelium is to maintain the fluidity of blood. This is achieved by the synthesis and release of anticoagulant (eg, thrombomodulin, protein C), fibrinolytic (eg, tissue-type plasminogen activator), and platelet inhibitory (eg, PGI_2, NO) substances (Box 7.3).[29] Mediators released from aggregating platelets stimulate the release from intact endothelium of NO and PGI_2, which act together to increase blood flow and decrease platelet adhesion and aggregation (Fig. 7.7).

With vital roles in modulating the tone of vascular smooth muscle, inhibiting platelets, and processing circulating chemicals, it seems clear that endothelial cell dysfunction would cause or contribute to ischemic syndromes. Evidence indicates endothelial dysfunction in atherosclerosis, hyperlipidemia, diabetes, and hypertension.[30] Procedures such as coronary artery surgical procedures and angioplasty disrupt the endothelium and may in part contribute to vascular dysfunction and accelerate atherosclerotic disease. The role of endothelium in the pathophysiology of myocardial ischemia is discussed later (see "Dynamic Stenosis").

Determinants of Coronary Blood Flow

Under normal conditions, coronary blood flow has four major determinants: (1) perfusion pressure, (2) myocardial extravascular compression, (3) myocardial metabolism, and (4) neurohumoral control. Changes in myocardial perfusion caused by different interventions can be explained by analyzing the effects of those interventions on these four factors.

Perfusion Pressure and Myocardial Compression

Coronary blood flow is proportional to the pressure gradient across the coronary circulation (Box 7.4). This gradient is calculated by subtracting downstream coronary pressure from the pressure in the root of the aorta. The determination of downstream pressure is complicated because the intramural coronary vessels are compressed with each heartbeat.

During systole, the heart throttles its own blood supply. The force of systolic myocardial compression is greatest in the subendocardial layers, where it approximates intraventricular pressure. Resistance resulting from extravascular compression increases with blood pressure, heart rate, contractility, and preload. Because it is difficult to measure intramyocardial pressure, the relative importance of these factors is controversial.[31,32] Flow is impeded both by direct compression and by shear caused by twisting of vessels as the heart contracts. Myocardial extravascular compression is less in the right ventricle, where pressures are lower and coronary perfusion persists during systole (Fig. 7.8). In pathologic conditions associated with pulmonary hypertension, right coronary blood flow assumes a phasic pattern similar to left coronary flow. Under normal conditions, extravascular compression contributes only a small component (10% to 25%) to total coronary vascular resistance. When the coronary vessels are dilated by pharmacologic agents such as dipyridamole or during ischemia, the effects of extravascular compression on myocardial perfusion become more important (see "Transmural Blood Flow," later).

With each contraction the intramural vessels are squeezed, and blood is expelled forward into the coronary sinus and in retrograde fashion into the epicardial arteries. The large coronary arteries on the epicardial surface act as capacitors, charging with blood during systole and expelling blood into the coronary circulation during diastole.[33] Coronary capacitance likely explains the findings of Bellamy,[34] who reported that flow in the proximal left anterior descending coronary artery of dogs ceased when arterial pressure decreased to less than 45 mm Hg. It was suggested that flow throughout the coronary circulation stopped at pressures far in excess of the pressure at the coronary sinus. This pressure at which flow stopped was termed *critical closing pressure* or *zero-flow pressure* (P_{zf}). This suggestion had important implications in the calculation of coronary resistance because the

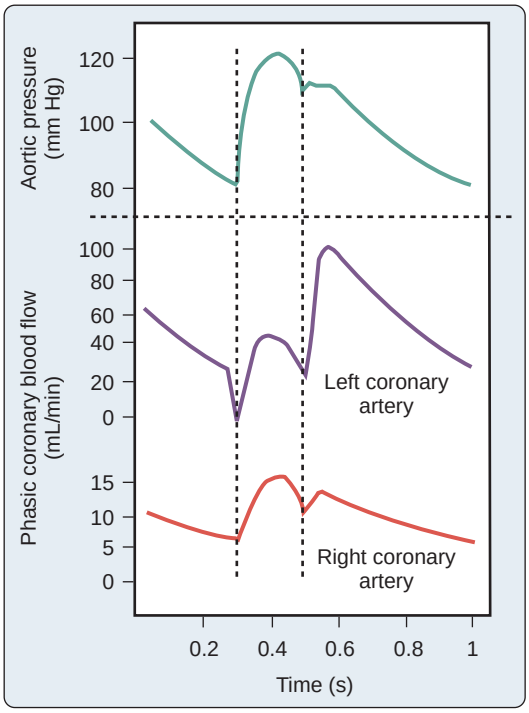
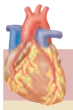


Fig. 7.8 Blood flow in the left and right coronary arteries. The right ventricle is perfused throughout the cardiac cycle. Flow to the left ventricle is largely confined to diastole. *(From Berne RM, Levy MN. Special circulations. In: Berne RM, Levy MN, eds.* Physiology. *St. Louis: Mosby; 1988:540–560.)*

effective downstream pressure would be P_{zf} and not the much lower coronary venous pressure. This is analogous to a stream with a waterfall, in which flow rate over the waterfall depends on the drop from the source to the waterfall edge and is unaffected by the distance to the bottom of the falls. Investigators later suggested that flow through the intramural coronary vessels continues after coronary inflow near the ostia (measured by Bellamy[34]) has ceased.[35,36] Evidence indicates that antegrade movement of red blood cells in 20-µm arterioles continues until coronary pressure is a few millimeters of mercury higher than coronary sinus pressure.[37] Thus the concept of a critical closing pressure greatly in excess of coronary sinus pressure is probably not valid in the coronary circulation.

Although the true downstream pressure of the coronary circulation is likely close to the coronary sinus pressure, other choices may be more appropriate in clinical circumstances. In patients with CAD, the subendocardial layers of the left ventricle are at greatest risk of ischemia and necrosis (see "Transmural Blood Flow," later). Because these layers are perfused mostly when the aortic valve is closed, the most appropriate measure of the driving pressure for flow here is the average pressure in the aortic root during diastole. This value can be approximated by aortic diastolic or mean pressure. Pressures monitored in peripheral arteries by routine methods in clinical settings can differ from central aortic readings. The reasons for this difference are distortion of the pressure waveform as it is propagated through the arterial tree and inaccuracies associated with the hydraulic and electronic components of the monitoring system. Under these conditions, the mean arterial pressure may be the most reliable measure of coronary driving pressure. The true downstream pressure of the left ventricular subendocardium is the left ventricular end-diastolic pressure, which can be estimated by pulmonary artery occlusion pressure. When the right ventricle is at risk of ischemia (eg, severe pulmonary hypertension), right ventricular diastolic pressure or central venous pressure may be a more appropriate choice for measuring downstream pressure.



BOX 7.5 MYOCARDIAL METABOLISM

Several molecules have been proposed as the link between myocardial metabolism and myocardial blood flow, including:

- oxygen
- reactive oxygen species
- carbon dioxide
- adenosine

Current evidence suggests that a combination of local factors, each with differing importance during rest, exercise, and ischemia, acts together to match myocardial oxygen delivery to demand.

Myocardial Metabolism

Myocardial blood flow, like flow in the brain and skeletal muscle, is primarily under metabolic control. Even when the heart is cut off from external control mechanisms (neural and humoral factors), its ability to match blood flow to its metabolic requirements is almost unaffected.[30] Because coronary venous oxygen tension is normally 15 to 20 mm Hg, only a small amount of oxygen is available through increased extraction. A major increase in myocardial oxygen consumption ($M\dot{V}O_2$), beyond the normal resting value of 80 to 100 mL O_2/100 g of myocardium, can occur only if oxygen delivery is increased by augmentation of coronary blood flow. Normally, flow and metabolism are closely matched, so that over a wide range of oxygen consumption coronary sinus oxygen saturation changes little.[38] Flow and metabolism could be coupled either through feedback or feedforward control or a combination of both. Feedback control requires myocardial oxygen tension to fall and provide a signal that can then increase flow. That would require vascular tone to be linked either to a substrate that is depleted, such as oxygen or adenosine triphosphate (ATP), or to the accumulation of a metabolite such as carbon dioxide or hydrogen ion. The lack of a decrease in myocardial oxygenation with large increases in $M\dot{V}O_2$ under physiologic conditions suggests the presence of feedforward as well as feedback control. Feedforward control would couple blood flow to oxidative metabolism and could therefore match oxygen delivery and consumption without accumulating a signal. Reactive oxygen species have been proposed as mediators of feedforward control.[39]

Despite intensive research over the past several decades, the mediator or mediators linking myocardial metabolism so effectively to myocardial blood flow are still unknown (Box 7.5). Feigl[38] proposed six criteria for a chemical transmitter between the cardiac myocyte and the coronary vascular smooth muscle cell:

1. The transmitter is released under appropriate conditions and can be recovered from the tissue under those conditions.
2. Transmitter substance infused into the target tissue should faithfully mimic physiologic activation.
3. The biochemical apparatus for production of the proposed transmitter is present in the tissue in an appropriate location.
4. A mechanism for inactivation or uptake, or both, of the transmitter is present at an appropriate location in the tissue.
5. The action of various inhibitors and blocking agents on synthesis, release, target-organ receptor function, or transmitter inactivation should have effects consistent with the hypothesis. Blocking agents should give the same effect whether the transmitter is released physiologically or is artificially applied.
6. Quantitative studies should indicate that the amount and time course of transmitter release under physiologic conditions are appropriate to give the indicated effect.

Many potential mediators of metabolic regulation have been proposed.[40] Although NO has a role in many coronary vasoregulatory pathways, it does not fulfill the role of metabolic regulator because blockade of NOS does not alter the increase in myocardial blood flow associated with an increase in myocardial oxygen demand.[41] The arguments for oxygen, carbon dioxide, and adenosine are briefly examined.

Oxygen

For oxygen to regulate coronary flow through a direct vascular action, the coronary smooth muscle would have to be more sensitive to lack of oxygen than the working cardiocytes. Coronary microvessels in vitro do not relax until the partial pressure of oxygen (P_{O_2}) is less than 5 mm Hg, a level much lower than the average P_{O_2} of 20 mm Hg in cardiac muscle cytosol.[42,43] With $M\dot{V}O_2$ held constant, increases in arterial oxygen content cause coronary flow to decrease, whereas decreases in arterial oxygen content cause flow to increase. These changes could explain only 40% of the increase in flow observed with tachycardia.[44] It is undecided whether the constancy of myocardial oxygen tension is the cause or the consequence of the excellent match between myocardial metabolism and myocardial blood flow.[45]

Reactive Oxygen Species

Increased production of hydrogen peroxide (H_2O_2) has been proposed as a feedforward response to increased $M\dot{V}O_2$.[39] As myocardial oxidative metabolism increases, leak of electrons from mitochondria is heightened and results in the production of superoxide, which is rapidly converted by superoxide dismutase into H_2O_2, known to be a coronary vasodilator.[46,47] In vitro and in vivo data have supported the role of H_2O_2 in coupling flow and metabolism.

Carbon Dioxide

The end product of substrate oxidation is carbon dioxide, the formation of which is directly related to the level of cardiac work. Carbon dioxide is highly diffusible and can easily reach coronary smooth muscle cells. Unfortunately, it is very difficult to separate the effects on coronary tone of increasing carbon dioxide from concomitant increases in other metabolites. Broten and colleagues[44] pump perfused the left main coronary artery of dogs and used an oxygenator in the perfusion circuit to alter coronary arterial partial pressure of carbon dioxide (PCO2) and P_{O_2} at a constant level of myocardial metabolism. Increases in arterial and coronary sinus P_{CO_2} augmented coronary blood flow in the absence of changes in $M\dot{V}O_2$. A synergistic action of P_{CO_2} and P_{O_2} was observed; the increase in flow with elevation of P_{CO_2} was much greater at low P_{O_2} and vice versa. The effect of increasing carbon dioxide, however, could not completely account for flow changes associated with an increase in $M\dot{V}O_2$.

Adenosine

Adenosine is a powerful coronary vasodilator through its activation of receptors on vascular endothelium and smooth muscle. In 1963, both Berne[48] and Gerlach and associates[49] independently demonstrated the production of adenosine in ischemic heart muscle. These investigators hypothesized that the release of adenosine may serve as a feedback signal inducing coronary vasodilation and augmenting coronary blood flow in proportion to myocardial metabolic needs. Initially, it was suggested that adenosine formation was coupled to myocardial oxygen tension.[48] To explain metabolic regulation by adenosine under both normoxic and ischemic conditions, a substrate theory was proposed whereby adenosine production is linked to the cardiac energy state by the regulation of cytosolic AMP concentration.[50] According to this theory, increases in cardiac work lead to a fall in ATP potential that results in a quantitatively appropriate change in cytosolic AMP concentration, thereby leading to increased adenosine release. In this way the rate of adenosine production is determined by the myocardial oxygen supply-to-demand ratio. It is likely that adenosine causes coronary arteriolar dilation through stimulation of A_1-receptors directly coupled to ATP-sensitive K^+ (K^+_{ATP}) channels and A_2-receptor–mediated elevation of cAMP/protein kinase A that leads to vasodilation in part by opening of K^+_{ATP} channels.[51,52]

Evidence against the adenosine hypothesis is accumulating. Adenosine deaminase is an enzyme that, when introduced in sufficient quantity into the myocardium, can significantly reduce the interstitial concentration of adenosine. Aminophylline and theophylline interfere with the coronary dilating effects of adenosine by acting on the receptor on vascular smooth muscle. Experiments using these agents to inhibit adenosine effect showed that resting coronary blood flow, exercise-induced coronary dilation, autoregulation, and reactive hyperemia are largely unrelated to adenosine.[53–56] Measuring coronary microvessel diameters in beating hearts in situ, Kanatsuka and colleagues[6] found that when $M\dot{V}O_2$ was doubled by pacing, vessels between 40 and 380 μm dilated, whereas when a similar increase in flow was induced by the infusion of adenosine or dipyridamole at constant $M\dot{V}O_2$, only vessels smaller than 150 μm dilated. Although adenosine does not seem to have an important role in metabolic regulation in the normal heart, adenosine blockade has been shown to cause a lowering in blood flow to hypoperfused myocardium sufficient to decrease systolic segment shortening.[57]Adenosine may have other important roles in ischemia, in which evidence indicates a cardioprotective action.[58,59]

Current evidence suggests that a combination of local factors acts together, perhaps with differing importance in different situations, to match myocardial oxygen delivery to demand. The extreme difficulty of designing an experiment that can distinguish the effects of individual factors on coronary blood flow suggests that the exact mechanism of metabolic coronary regulation will not soon be elucidated.

Neural and Humoral Control

Neural Control

The role of neural control in the regulation of myocardial blood flow is difficult to study because sympathetic or parasympathetic activation can cause profound changes in heart rate, blood pressure, and contractility. The resulting changes in coronary tone, mediated by metabolic regulation, can mask the concomitant direct effects of autonomic nerves on coronary smooth muscle. Studies of isolated vessels have given results that contradict in vivo studies in part because of damage to the endothelium during preparation. Despite these difficulties, exploring the role of autonomic control has elicited much interest because it is implicated in the pathogenesis of myocardial ischemia.

Coronary Innervation

The heart is supplied with branches of the sympathetic and parasympathetic divisions of the autonomic nervous system. Thicker vagal fibers end in the adventitia of coronary vessels, whereas fine nonmedullated sympathetic fibers end on vascular smooth muscle cells.[60] Large and small coronary arteries and veins are richly innervated. The sympathetic nerves to the heart and coronary vessels arise from the superior, middle, and inferior cervical sympathetic ganglia and the first four thoracic ganglia. The stellate ganglion (formed when the inferior cervical and first thoracic ganglia merge) is a major source of cardiac sympathetic innervation. The vagus nerve supplies the heart with efferent cholinergic nerves.

Parasympathetic Control

Vagal stimulation causes bradycardia, decreased contractility, and lower blood pressure. The resultant fall in $M\dot{V}O_2$ causes metabolically mediated coronary vasoconstriction. When myocardial metabolism is held constant, however, cholinergic coronary dilation is consistently observed in response to exogenous acetylcholine, electrical vagal stimulation, and reflex activation through baroreceptors, chemoreceptors, and ventricular receptors.[30,38,61] These effects can be abolished by atropine.

In patients with angiographically normal coronary arteries the response to intracoronary acetylcholine injection is predominantly dilation, whereas in atherosclerotic segments of epicardial arteries constriction is observed.[62–64] Acetylcholine injected intraluminally binds to muscarinic receptors on the endothelium and stimulates the release of NO, which causes smooth muscle dilation. Acetylcholine is not normally found circulating in the blood but is released from

BOX 7.6 α-ADRENERGIC CORONARY CONSTRICTION

Sympathetic activation causes increased heart rate, contractility, and blood pressure that lead to a marked metabolically mediated increase in coronary blood flow. Surprisingly, the direct effect of sympathetic stimulation on the coronary vessels is vasoconstriction, sufficient to restrict the increase in blood flow and increase oxygen extraction.

vagal fibers and reaches the coronary smooth muscle from the adventitial side. Surprisingly, activation of muscarinic receptors on vascular smooth muscle cells causes constriction. Parasympathetic stimulation normally causes coronary vasodilation. This response depends on the ability of the coronary endothelium to elaborate NO and perhaps also endothelium-derived hyperpolarizing factor (see earlier).[65,66] Parasympathetic control has not been shown to be important in the initiation of myocardial ischemia.

β-Adrenergic Coronary Dilation

β-Receptor activation causes dilation of both large and small coronary vessels even in the absence of changes in blood flow.[30,38] Studies in animals indicate that both β_1- and β_2-receptors are present throughout the coronary circulation but that α_1-receptors predominate in the conductance vessels, whereas β_2-receptors predominate in the resistance vessels. Mature canine coronary collaterals respond similarly to the conductance vessels.[67,68] β-Adrenergic coronary artery dilation may improve the speed and accuracy of coronary blood flow regulation during exercise.[69]

α-Adrenergic Coronary Constriction

Activation of the sympathetic nerves to the heart results in increases in heart rate, contractility, and blood pressure that lead to a marked, metabolically mediated increase in coronary blood flow (Box 7.6). This finding suggested to early investigators that the effect of sympathetic coronary innervation is vasodilation. More recent investigation revealed that the direct effect of sympathetic stimulation is coronary vasoconstriction, which is in competition with the metabolically mediated dilation of exercise or excitement. Whether adrenergic coronary constriction is powerful enough to diminish blood flow in ischemic myocardium further or whether it can have some beneficial effect in the distribution of myocardial blood flow is controversial.

Classification

α-Adrenergic receptors can be classified anatomically as presynaptic or postsynaptic and according to their pharmacologic properties as α_1 and α_2 (Table 7.3). The receptors can be further divided into subtypes according to their signal transduction mechanism (G-protein subtype) and second messenger (eg, adenylyl cyclase, phospholipase C).[70]

Presynaptic α-Receptors

α-Receptors on cardiac sympathetic nerve terminals mediate feedback inhibition of neuronal norepinephrine release. Both α_1- and α_2-receptors seem to be involved because exercise-induced increases in heart rate and contractility can be potentiated by either idazoxan (α_2-blockade) or prazocin (α_1-blockade).[71]

Cardiac Muscle Cells

Activation of myocardial α_1-receptors results in a positive inotropic effect that, in contrast to β-receptor activation, is associated with prolongation of contraction. Although normally of minor functional importance, this effect may serve as an inotropic reserve mechanism when β-receptor–mediated inotropy is impaired (eg, hypothyroidism, cardiac failure, long-term propranolol treatment).[72] The importance of this mechanism in humans is uncertain. An increase in inotropy secondary to stimulation of myocardial α-receptors would result in increased $M\dot{V}O_2$ and metabolically mediated coronary dilation.

TABLE 7.3 Classification of α-Adrenergic Receptor Subtypes in the Heart

Selective Agonists	*Selective Antagonists*	*Effects of Activation*
α_1-Receptor		
Phenylephrine	Prazosin	*Presynaptic:* feedback inhibition of norepinephrine release
Methoxamine		*Postsynaptic:* coronary vasoconstriction, increase in myocardial inotropism, arrhythmias
α_2-Receptor		
Clonidine	Yohimbine	*Presynaptic:* feedback inhibition of norepinephrine release
Azepexole	Rauwolscine	*Postsynaptic:* coronary vasoconstriction, arrhythmias (?)
BHT 920	Idazoxan	
UK 14, 304		

[a]Norepinephrine is a nonselective agonist. Phentolamine and phenoxybenzamine are nonselective antagonists. Phenylephrine also causes β-receptor activation.
Modified from Heusch G. Alpha-adrenergic mechanisms in myocardial ischemia. *Circulation.* 1990;81:1, by permission of the American Heart Association.

Coronary Endothelium

Binding of norepinephrine to α_2-receptors on vascular endothelium stimulates the release of NO, which acts to relax vascular smooth muscle. The endothelium can also limit the effect of norepinephrine by metabolizing it. In these ways the endothelium modulates the direct constrictive effects of α-adrenergic activation. Abnormal endothelial function in atherosclerosis may predispose to excessive α-adrenergic constriction and is implicated in the pathogenesis of myocardial ischemia (see "Dynamic Stenosis," later).

Coronary Resistance

The magnitude of α-adrenergic vasoconstriction that occurs in the coronary bed is small compared with that in the skin and skeletal muscle. In the presence of β-blockade, intense sympathetic stimulation results in only a 20% to 30% increase in coronary resistance.[73] Mohrman and Feigl[74] examined the effect of sympathetic activation on coronary flow in the absence of β-blockade. The net effect of α-receptor vasoconstriction was to restrict the metabolically related flow increase by 30%, thereby increasing oxygen extraction and decreasing coronary sinus oxygen content.

Epicardial coronary diameter changes little during sympathetic stimulation.[75] α_1-Adrenergic and α_2-adrenergic receptors are found throughout the coronary circulation; however, α_1-receptors seem to be more important in the large epicardial vessels, whereas α_2 predominates in small coronary vessels less than 100 μm in diameter.[76] Studies of mature coronary collateral vessels in dogs generally failed to provide evidence of α-receptor–mediated vasoconstriction.[77] After heart transplantation, patients demonstrated a lesser increase in myocardial blood flow after a cold pressor test in denervated regions of the heart.[78] The authors argue that this was not the result of increased myocardial metabolism secondary to myocardial β-receptor activation. They suggest that sympathetic innervation has an important role in coronary vessel dilation during stress.

Exercise

α-Adrenergic coronary constrictor tone during exercise is exerted predominantly by circulating catecholamines.[79] Numerous studies indicate that myocardial blood flow during exercise is limited by α vasoconstriction.[30] In a study of exercising dogs, Huang and Feigl[80] found that despite an increase in total coronary flow in an α-blocked region of myocardium, flow to the inner, subendocardial layer was diminished. These results suggest a beneficial effect of α-adrenergic

coronary constriction on the distribution of blood flow within the myocardium.

Myocardial Ischemia

Buffington and Feigl[81] demonstrated the persistence of α-adrenergic coronary vasoconstriction distal to a moderate coronary stenosis during norepinephrine infusion. Investigations in dogs demonstrated that as coronary reserve is depleted by increasing stenosis severity, the response to sympathetic stimulation shifts from metabolically induced coronary dilation to coronary constriction.[82,83] These observations suggest that sympathetic coronary vasoconstriction limits coronary blood flow even during myocardial ischemia, when autoregulatory reserve is exhausted (see "Coronary Reserve," later). No consensus has been reached on the importance of α_1- versus α_2-receptors in ischemic myocardium.[30] Using constant flow coronary perfusion in anesthetized dogs, Nathan and Feigl[84] compared the transmural distribution of myocardial blood flow in α-blocked and intact regions of myocardium during hypoperfusion. Surprisingly, α-blockade diverted blood flow from the subendocardium to the subepicardium. This finding suggests that α vasoconstriction had limited flow more in the subepicardium, thereby producing an anti-steal effect and improved perfusion of the more vulnerable inner layers of the left ventricle. Chilian and Ackell[85] found similar results in exercising dogs with artificial coronary stenosis. Conversely, work by Baumgart and Heusch[86] and by Seitelberger and colleagues[87] demonstrated improved subendocardial perfusion distal to a severe coronary stenosis with α_2-receptor blockade. This controversy is unresolved.[88,89] α-Receptor blockers have not been shown to have a role in the treatment of myocardial ischemia in patients with CAD.

Studies in Humans

Studies indicate that little α-adrenoceptor–mediated tone is present in resting humans.[90] Clinical studies have failed to provide convincing evidence that α-adrenergic coronary constriction plays an important role in Prinzmetal variant angina (angina with ST-segment elevation at rest).[91] During sympathetic activation, however, evidence indicates that α vasoconstriction can precipitate myocardial ischemia by further narrowing diseased coronary arteries. This effect has been shown during isometric exercise, during dynamic exercise, and with the cold pressor test (see "Dynamic Stenosis," later).[92–97]

Humoral Control

A complete understanding of the effects of circulating substances on the coronary vessels would require determining their effects on large versus small coronary vessels while separating direct effects on coronary vessels from changes in tone mediated by changes in myocardial metabolism. This issue is further complicated by the critical role of an intact vascular endothelium in modulating these responses (see "Endothelium," earlier). Some of the better-studied agents are discussed briefly.

The peptide hormones include vasopressin (also known as arginine vasopressin), atrial natriuretic peptide, vasoactive intestinal peptide, neuropeptide Y, and calcitonin gene–related peptide.[40] Of these hormones, vasopressin and atrial natriuretic peptide have been the most closely studied. Investigators have demonstrated in dogs that vasopressin, in concentrations 3 to 30 times those found in stressed patients, can cause vasoconstriction sufficient to produce myocardial ischemia.[98] In large coronary arteries, the dilator response (through NO) likely exceeded the constrictor response.[30] In physiologic concentrations, vasopressin acts primarily as an antidiuretic hormone with little effect on the coronary circulation. Atrial natriuretic peptide can cause endothelium-dependent coronary dilation but is not known to have significant vascular effects in physiologic concentrations.[99]

Angiotensin-converting enzyme (ACE) is present on vascular endothelium and converts angiotensin I to angiotensin II, which causes coronary vasoconstriction. Angiotensin II also facilitates the release of norepinephrine from presynaptic adrenergic nerve terminals. ACE inactivates bradykinin, which can attenuate vasoconstriction by NO stimulation. Thus angiotensin-converting enzyme inhibition can reduce coronary tone by suppressing angiotensin II formation and degrading bradykinin and perhaps also by decreasing norepinephrine release. Despite these theoretical considerations, ACE inhibition has not been shown to be of benefit in human myocardial ischemia other than through control of afterload.[100]

PGI_2 and thromboxane A_2 are synthesized from arachidonic acid in a reaction catalyzed by cyclooxygenase. PGI_2 is synthesized in the vascular endothelium and, in addition to inhibiting platelet aggregation, induces vasodilation (see "Endothelium-Derived Relaxing Factors," earlier). Thromboxane A_2 is mainly synthesized in platelets and causes platelet aggregation and vasoconstriction in the presence of damaged vascular endothelium. In response to thromboxane A_2 the intact endothelium releases NO, thereby causing both vasodilation and platelet disaggregation, mechanisms to maintain patency of normal vessels (see "Endothelial Inhibition of Platelets"). Unlike platelets, the vascular endothelium can synthesize proteins de novo, and thus cyclooxygenase acetylation through aspirin administration has a lesser effect in reducing vascular PGI_2 than platelet thromboxane A_2. Other than in platelet-vessel interactions and inflammation, prostaglandins are not known to have an important role in the regulation of coronary blood flow.[30] Serotonin (5-HT) is another platelet product that can cause endothelium-dependent dilation of coronary arterial vessels smaller than 100 μm but causes constriction of larger epicardial coronary arteries.[101]

Histamine receptors are present in the coronary vessels. Histamine-1 (H_1) receptors are located on vascular smooth muscle cells of large and small coronary arteries and mediate vasoconstriction. H_2 receptors are located on smooth muscle cells of arterioles and mediate vasodilation. H_1 receptors are also located on vascular endothelium and can mediate vasodilation by stimulation of NO release. In patients with vasospastic angina and endothelial dysfunction, administration of exogenous histamine can cause vasospasm.[51,102]

Coronary Pressure-Flow Relations

Autoregulation

Autoregulation is the tendency for organ blood flow to remain constant despite changes in arterial perfusion pressure.[103] Autoregulation can maintain flow to myocardium served by stenotic coronary arteries despite low perfusion pressure distal to the obstruction. This is a local mechanism of control and can be observed in isolated, denervated hearts. If $M\dot{V}O_2$ is fixed, coronary blood flow remains relatively constant between mean arterial pressures of 60 and 140 mm Hg. At a given cardiac workload, the level of flow (determined by metabolic regulation) is maintained constant over a broad range of pressure by autoregulation (Fig. 7.9).

To study autoregulation, coronary perfusion pressure must be varied while holding $M\dot{V}O_2$ constant. This is difficult in the heart because changing aortic pressure alters both the perfusion pressure for the coronary arteries and the afterload of the left ventricle. Thus changes in aortic pressure inevitably change $M\dot{V}O_2$. This problem is overcome by cannulating the coronary arteries and perfusing them with a pump. However, even when heart rate and aortic pressure are held constant, $M\dot{V}O_2$ alters with changing coronary pressure. This is because myocardial contractility and metabolism increase when coronary pressure is raised to a level greater than the normal autoperfused level. This phenomenon is known as the Gregg effect and may be explained by the "garden hose" hypothesis of Lochner whereby engorgement of the coronary vasculature elongates the myocardial sarcomere length during diastole and contractile strength is increased as a result of the Frank-Starling mechanism (for a detailed review see Feigl[38] and Gregg[104]).

In addition to the Gregg effect, two other issues complicate studies of autoregulation: collateral flow and myocardial oxygen extraction. If pressure is lowered in the left coronary artery and not in the right, a

pressure gradient for flow will exist from the right to the left coronary artery through collateral vessels. Flow measured proximally in the left coronary artery then underestimates flow reaching the myocardium. Normal coronary sinus oxygen tension (CSO_2) is less than 20 mm Hg. Dole and Nuno[105] observed that autoregulation was effective when CSO_2 was less than 25 mm Hg but was completely lost when CSO_2 exceeded 32 mm Hg. Autoregulation can be intensified by vasoconstriction (increased oxygen extraction) and attenuated by vasodilation (decreased oxygen extraction).[105,106] The degradation of autoregulation with α-receptor blockade suggests a benefit of adrenergic coronary vasoconstriction.[107]

Early reports indicated that autoregulation is less effective in the right ventricle than in the left. Investigators currently suggest that increases in right coronary artery pressures may produce large changes in $M\dot{V}O_2$, perhaps in response to an exaggerated Gregg effect. When changes in myocardial metabolism are taken into account, autoregulation in the right and left ventricles is similar.[108,109]

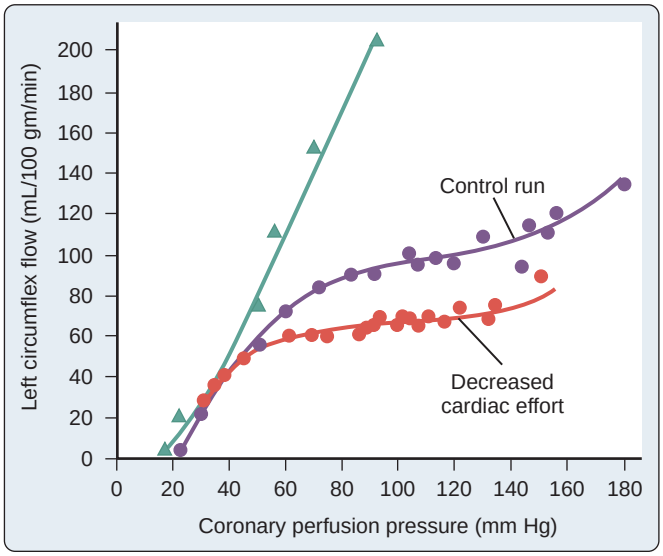


Fig. 7.9 Autoregulation at two levels of myocardial oxygen consumption. Pressure in the cannulated left circumflex artery was varied independently of aortic pressure. When pressures were suddenly raised or lowered from 40 mm Hg, flow instantaneously increased with pressure *(steep line, triangles)*. With time, flow decreased to the steady-state level determined by oxygen consumption *(circles)*. The vertical distance from the steady-state (autoregulating) line to the instantaneous pressure-flow line is the autoregulatory flow reserve (see text). *(From Mosher P, Ross J Jr, McFate PA, Shaw RF. Control of coronary blood flow by an autoregulatory mechanism.* Circ Res. *1964;14:250.)*

Quantitation of the degree of autoregulation must involve a comparison of the observed change in vascular resistance with the change in resistance that would have occurred in the absence of flow autoregulation. Some degree of autoregulation exists when the relative change in flow (ΔF/F) is less than the relative change in pressure (ΔP/P). From these definitions, Dole[106] derived an autoregulation index that can be used to quantify the effects of different agents on coronary autoregulation.[110]

Three theories have been proposed to explain coronary autoregulation: (1) the tissue pressure theory, (2) the myogenic theory, and (3) the metabolic theory.[111] The tissue pressure hypothesis proposes that changes in perfusion pressure result in directionally similar changes in capillary filtration and therefore tissue pressure. In this way extravascular resistance would oppose changes in flow with changes in perfusion pressure. Experimental evidence has shown, however, that no relationship exists between the degree of autoregulation and the magnitude of change in tissue pressure. Arterial smooth muscle contracts in response to augmented intraluminal pressure; this is known as the myogenic response. This response has been demonstrated in coronary arterioles in the presence and absence of functioning endothelium.[112]

The argument for myogenic regulation of coronary flow is that myocardial metabolic changes are not rapid enough to explain large decreases in resistance after coronary occlusions for one or two heartbeats. However, myocardial metabolic events have been shown to occur during the course of a single cardiac contraction.[113]

The metabolic theory of autoregulation proposes that coronary arteriolar tone is determined by the balance of myocardial oxygen supply and demand. An increase in flow greater than the requirements of metabolism would wash out metabolites or cause accumulation of substrates, and this would be the signal for an appropriate change in coronary tone. Although metabolic regulation and autoregulation are separate phenomena, they may have a common underlying mechanism. Metabolic regulation is discussed earlier (see "Myocardial Metabolism"). For an instructive, three-dimensional, graphic analysis of the interrelations among coronary artery pressure, myocardial metabolism, and coronary blood flow, see Feigl and colleagues.[114]

Coronary Reserve

Myocardial ischemia causes intense coronary vasodilation. After a 10- to 30-second coronary occlusion, restoration of perfusion pressure is accompanied by a marked increase in coronary flow. This large increase in flow, which can be five or six times resting flow in dogs, is termed *reactive hyperemia*. The repayment volume is greater than the debt volume (Fig. 7.10). However, no overpayment of the oxygen debt occurs because oxygen extraction falls during the hyperemia.[115] The presence of high coronary flows when coronary venous oxygen content is high suggests that mediators other than oxygen are responsible for this metabolically induced vasodilation.[38] The difference between resting coronary blood flow and peak flow during reactive

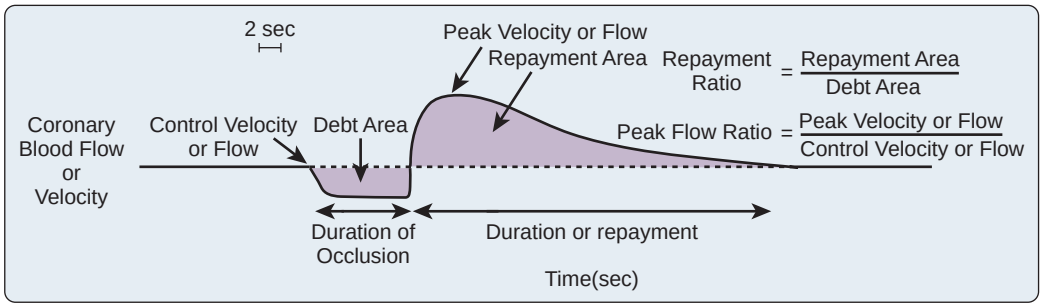
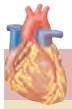


Fig. 7.10 Schematic diagram of the reactive hyperemic response to a 10-second coronary occlusion. *(Redrawn from Marcus M, Wright C, Doty D, et al: Measurements of coronary velocity and reactive hyperemia in the coronary circulation of humans.* Circ Res. *1981;49:877–891.)*



BOX 7.7 TRANSMURAL BLOOD FLOW

- When coronary perfusion pressure is inadequate, the inner one-third of the left ventricular wall is the first region to become ischemic or necrotic.
- During systole, intramyocardial pressure is highest in the inner layers of the ventricle, and this restricts perfusion to that region.
- In eccentric hypertrophy, this effect is exaggerated, and the subendocardium is at increased risk of ischemia.

hyperemia represents the autoregulatory coronary flow reserve: the further capacity of the arteriolar bed to dilate in response to ischemia. Fig. 7.9 shows that the flow reserve is the vertical distance from the autoregulating pressure-flow curve (circles) to the nonautoregulating curve (triangles). The reserve is greater at higher perfusing pressure and lower $M\dot{V}O_2$. Unlike cannula-perfused preparations in which these data are obtained, in the clinical setting increases in pressure elevate both perfusing pressure and $M\dot{V}O_2$. Reactive hyperemia responses have been used in animals and humans to estimate coronary reserve in conditions such as obstructive coronary disease, aortic stenosis, and left ventricular hypertrophy (see "Hemodynamics," later).[116–118] The myocardial fractional flow reserve (FFR) is calculated by dividing the pressure in a coronary vessel distal to a stenosis during maximal pharmacologic dilation by the aortic root pressure. This ratio can be easily measured in the angiography suite and has been recommended as a useful index of the functional severity of coronary stenoses of intermediate morphologic severity on angiography, as well as a measure of residual obstruction after interventions[119,120] (see "Intracoronary Evaluation of Atherosclerosis," later).

That the coronary resistance vessels are maximally dilated when coronary perfusion pressure is reduced sufficiently to cause myocardial ischemia is generally accepted. In fact, agents such as adenosine, carbochromen, and dipyridamole can cause further increases in coronary flow in the presence of intense ischemia, when autoregulatory reserve is believed to be exhausted. This pharmacologic vasodilator reserve is greater than the autoregulatory vasodilator reserve. If flow to ischemic myocardium can be increased by pharmacologic dilation of resistance vessels, the use of these agents should reverse ischemic dysfunction and metabolism. Arteriolar dilators have, in general, not been found to be beneficial during myocardial ischemia. Coronary blood flow in the different layers of the ventricle must be reviewed to understand the reason (Box 7.7).

Transmural Blood Flow

It is well known that when coronary perfusion pressure is inadequate, the inner one-third to one-fourth of the left ventricular wall is the first region to become ischemic or necrotic.[121] This increased vulnerability of the subendocardium may reflect an increased demand for perfusion or a decreased supply, compared with the outer layers. Transmural distribution of oxygen consumption, use of oxidizable substrates, activity of glycolytic and mitochondrial enzymes, tissue contents of endogenous substrates, high-energy phosphates, lactate, isoforms of contractile proteins, and fiber stress and fiber shortening have been studied extensively. In general, these studies indicate that if such differences exist between the layers of the left ventricle, they are unlikely to exceed 10% to 20%.[38,122] Preferential underperfusion of the subendocardium probably is the primary determinant of its increased vulnerability.

Regional blood flow in the myocardium is usually determined using radioactive microspheres. These plastic beads, labeled with a radioisotope, are injected into the bloodstream. The assumption is that they mix uniformly with blood and are distributed in proportion to blood flow, as if they were red blood cells.[123] Because they are rigid and larger than red blood cells (9- or 15-μm diameters are usually chosen), these beads are trapped in the microcirculation. At the end of an experiment, the heart can be divided into small blocks and the amount of radioactivity in each piece measured in a gamma counter. The blood flow to each block of tissue is proportional to the number of microspheres in each piece, which can be determined from its radioactivity. By using different radioisotopes as labels, several sets of microspheres can be injected during an experiment, thus giving "snapshots" of flow at the time of each injection. It is difficult to reduce the variability of the technique to less than 10%.[38,124] By using this technique, subendocardial blood flow is found to be approximately 10% greater than subepicardial blood flow under normal circumstances. This gives a normal subendocardial-to-subepicardial or inner-to-outer (I/O) blood flow ratio of 1:10. This ratio is maintained at normal perfusing pressures even at heart rates higher than 200 beats/minute.

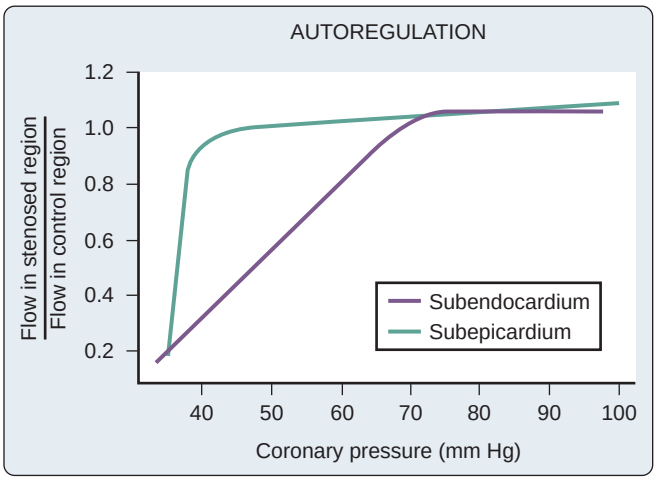


Fig. 7.11 Pressure-flow relationships of the subepicardial and subendocardial thirds of the left ventricle in anesthetized dogs. In the subendocardium, autoregulation is exhausted and flow becomes pressure dependent when pressure distal to a stenosis falls to less than 70 mm Hg. In the subepicardium, autoregulation persists until perfusion pressure falls to less than 40 mm Hg. Autoregulatory coronary reserve is less in the subendocardium. *(Redrawn from Guyton RA, McClenathan JH, Newman GE, Michaelis LL. Significance of subendocardial ST segment elevation caused by coronary stenosis in the dog.* Am J Cardiol. *1977;40:373.)*

If coronary artery pressure is gradually reduced, autoregulation is exhausted, and flow decreases in the inner layers of the left ventricle before it begins to decrease in the outer layers (Fig. 7.11). This finding indicates less flow reserve in the subendocardium than in the subepicardium. The limits of autoregulation depend on the level of cardiac work (see "Autoregulation," earlier) and on the experimental conditions. In conscious dogs, the mean coronary artery pressure at which evidence of subendocardial ischemia appeared was 38 mm Hg at a heart rate of 100 beats/minute, and it increased to 61 mm Hg at 200 beats/minute. Subepicardial flow during tachycardia did not fall even at pressures as low as 33 mm Hg.[125] Because subepicardial flow is rarely inadequate, a subendocardial-to-subepicardial blood flow ratio close to 1.0 indicates adequate subendocardial flow and an appropriate matching of myocardial oxygen supply to oxygen demand. For this reason, the I/O blood flow ratio is often used as a measure of the adequacy of myocardial blood flow.

Three mechanisms have been proposed to explain the decreased coronary reserve in the subendocardium: (1) differential systolic intramyocardial pressure, (2) differential diastolic intramyocardial pressure, and (3) interactions between systole and diastole. Because the force of systolic myocardial compression is greatest in the inner layers of the ventricle and is low at the subepicardium, investigators believed that the outer layers of the heart were perfused throughout the cardiac

cycle, whereas the subendocardium was perfused only during diastole. The subendocardium would have to obtain its entire flow during only a portion of the cycle and therefore would have to have a lower resistance. Studies suggesting very little systolic flow, even to the outer layers, argued against this explanation.[121] The second mechanism is based on the high coronary artery pressures observed when coronary flow has ceased during a long diastole, P_{zf} (see "Perfusion Pressure and Myocardial Compression," earlier).[34] The shape of the pressure-flow relation during a long diastole suggests that P_{zf} is higher in the subendocardium. This means that perfusion pressure for the subendocardium is lower in diastole compared with the outer layers of myocardium. Available evidence suggests that P_{zf} is not high in any layer and is unlikely to be more than 2 to 3 mm Hg higher in the subendocardium than in the subepicardium.[121] Hoffman[121] and Hoffman and Spaan[108] proposed an interaction between systole and diastole as the explanation for the increased vulnerability of the subendocardium to ischemia. During systole, intramyocardial pressure is high enough throughout most of the ventricular wall to squeeze blood out of the intramural vessels and into the extramural coronary veins and arteries. Because the compressive force is greatest in the subendocardium, vessels here are the narrowest at the end of systole. At the beginning of diastole, blood is directed first to vessels with the lowest resistance, then to the larger vessels in the subepicardium, and last to the most severely narrowed vessels in the subendocardium. In this way, should the duration of diastole or the diastolic perfusion pressure be reduced, the subendocardial muscle would receive the least flow. Spaan[31] presented an interesting analysis of the interaction between arterial pressure and force of contraction as an intramyocardial pump. Although this theory is compatible with existing evidence, support for it remains indirect until it becomes possible to measure phasic pressures and flows in separate layers of myocardium.

When the left ventricle hypertrophies in response to a pressure load (aortic stenosis, hypertension), myofibrillar growth outstrips the capillary network, with resulting decreased capillary density and increased diffusion distances. The net effect is to reduce coronary autoregulatory reserve.[126] The transmural gradient of reserve is also exaggerated, so that the subendocardium is at increased risk of ischemia in the hypertrophied heart compared with normal.[127]

In addition to the transmural gradient of coronary reserve from outer to inner layer of the left ventricle, marked variation of reserve occurs between small regions of myocardium within a layer.[128] This heterogeneity of flow reserve may explain why pharmacologic reserve exceeds autoregulatory reserve (see "Coronary Reserve," earlier). During hypoperfusion regional myocardial blood flow is decreased, but in all layers some small pieces of muscle have no flow reserve left, whereas adjacent pieces can have substantial reserve. Fewer pieces retain reserve in the subendocardium than in the subepicardium. The increase in flow in response to an infusion of adenosine results from increased flow in the small regions with reserve, with no change in the adjacent fully dilated regions.[129–131] These findings suggest that ischemia causes maximal coronary vasodilation and that increases in flow with adenosine or dipyridamole are caused by dilation of vessels in nonischemic regions. Contrasting evidence was provided by Duncker and Bache,[51] who used a balloon occluder to simulate coronary stenosis in exercising dogs. The occluder was adjusted to maintain distal coronary pressure constant at 43 mm Hg. During exercise, an intracoronary infusion of adenosine increased blood flow to all myocardial layers and improved regional systolic segment shortening. Although this is evidence of vasodilator reserve in ischemic myocardium, the constant distal pressure preparation does not faithfully mimic coronary stenosis because it makes transmural steal impossible (see "Coronary Steal," later). In general, pharmacologic dilation of resistance vessels has the potential to worsen ischemia by producing coronary steal. Dilation of larger penetrating vessels (50 to 500 µm in diameter) with nitrovasodilators could preferentially decrease resistance to blood flow to the subendocardium, and this may, in addition to favorable effects on the systemic circulation, explain the usefulness of nitrates in the treatment of angina.[51]

Atherosclerosis

The atherosclerotic lesion consists of an excessive accumulation of smooth muscle cells in the intima, with quantitative and qualitative changes in the noncellular connective tissue components of the artery wall and intracellular and extracellular deposition of lipoproteins and mineral components (eg, calcium) (Box 7.8). By definition, *atherosclerosis* is a combination of "atherosis" and "sclerosis." The term *sclerosis* refers to the hard collagenous material that accumulates in lesions and is usually more voluminous than the pultaceous "gruel" of the atheroma (Fig. 7.12).

Stary[132] noted that the earliest detectable change in the evolution of coronary atherosclerosis in young people was the accumulation of intracellular lipid in the subendothelial region that gave rise to lipid-filled macrophages or "foam cells." Grossly, a collection of foam cells may give the artery wall the appearance of a "fatty streak." In general, fatty streaks are covered by a layer of intact endothelium and are not characterized by excessive smooth muscle cell accumulation. At later stages of atherogenesis, extracellular lipoproteins accumulate in the musculoelastic layer of the intima and eventually form an avascular core of lipid-rich debris that is separated from the central arterial lumen by a fibrous cap of collagenous material. Foam cells are not usually seen deep within the atheromatous core but are frequently found at the periphery of the lipid core.

BOX 7.8 ATHEROSCLEROSIS

- The atherosclerotic process begins in childhood and adolescence.
- The progression of an atherosclerotic lesion resembles the process of wound healing.
- Inflammation, lipid infiltration, and smooth muscle proliferation have important roles in atherogenesis.
- Impairment of endothelial function is an early consequence of atherosclerosis.
- Statin therapy has been shown to improve endothelial function, impede development of atherosclerosis, and in some cases reverse established disease.

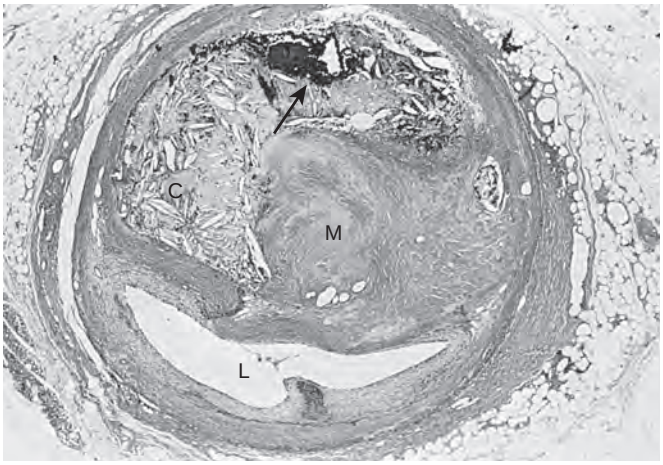


Fig. 7.12 Atherosclerotic human coronary artery of an 80-year-old man. He has severe narrowing of the central arterial lumen *(L)*. The intima consists of a complex collection of cells, extracellular matrix *(M)*, and a necrotic core with cholesterol *(C)* deposits. Rupture of plaque microvessels has resulted in intraplaque hemorrhage *(arrow)* at the base of the necrotic core (Movat's pentachrome–stained slide; original magnification ×40).

Atherogenesis

Certain human arteries are more prone to develop atherosclerosis than others. For example, the coronary, renal, and internal carotid arteries, as well as some areas of the aorta, are known to be common sites of lesion formation.[132] In the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, the aorta and right coronary arteries of 1378 young people 15 to 34 years old who died as a result of trauma were studied.[133] Two-dimensional maps of lipid-laden fatty streaks and fibrous plaques were made for each vessel. Although atherosclerosis is usually clinically silent until middle age or later, these investigators found that the disease process begins in adolescence or childhood. Moreover, fatty streaks and fibrous plaques do not occur randomly in the circulation, but rather they follow a well-defined distribution pattern. For example, in the right coronary artery fatty streaks were found with the highest probability in the proximal 2 cm of this vessel, a location that closely parallels the distribution of raised fibrous lesions. In the abdominal aorta, however, where aortic lesions are commonly found, the high prevalence of fatty streaks did not always correlate with the prevalence of raised fibrous lesions. Therefore, at least in the aorta, the role of childhood fatty streaks in the development of adult fibrous lesions is uncertain.

The atherogenic stimuli that promote the progression of early lesions to clinically relevant stenoses are not known. The development of CAD is associated with various risk factors. Dyslipidemias, hypertension, diabetes mellitus, cigarette smoking, and a family history of premature CAD are known to correlate with premature vascular disease. The association between lipid disorders and atherogenesis is best understood and is discussed later. More recently, genetic factors that predispose to development of atherosclerosis have been identified, and early work suggests that changes in response to inflammation may in part explain the hereditary nature of the disease.[134,135] Unfortunately, with the exception of dyslipidemia and hypertension, targeted pharmacotherapy for the remaining risk factors is lacking.

Historically, two classic theories of atherogenesis were proposed. According to von Rokitansky's thrombogenic (or encrustation) theory,[136] fibrin is the initiating factor in lesion development. Later, Duguid[137] expanded on this theory by suggesting that atherosclerosis is the result of altered fibrinolysis, whereas more recent studies documented the overexpression of prothrombotic factors, such as plasminogen activator inhibitor-1, in atherosclerotic plaques.[138] Alternatively, Virchow's inhibition (or insudation) theory[139] proposed in 1856 that atherosclerotic lesions were the result of altered vessel wall permeability.

Variations of this theory have been suggested by others, and all support the concept that the accumulation of various plasma components, including lipoproteins, may be important during lesion formation. For example, Ross and Glomset[140] blended the concepts of these original hypotheses into the "response-to-injury" hypothesis in which both lipid infiltration and thrombus formation play important roles in atherogenesis. Similarly, Schwartz and colleagues[141] compared arterial narrowing in atherosclerotic arteries with the process of wound healing. This perspective has advantages because it allows a multifactorial process such as atherosclerosis to be broken down into components of a more completely understood process such as the biology of a skin wound. For example, wound healing of any form begins with the formation of a clot (fibrin- and fibronectin-containing gel) that fills the wound and provides a provisional matrix for inflammatory cells, fibroblasts, and newly formed microvessels.[142,143] This phase is followed by the proliferation and migration of fibroblasts into the wound.[144] By day 7 after injury, microvessels grow into the base of the wound and form granulation tissue. As the wound matures and undergoes contracture, these blood vessels regress and fibroblasts disappear. After resorption of microvessels, tissue hypoxia develops and likely plays a role in the completion of the final scarring process.[145]

As discussed later, ample evidence suggests that many similar events take place during arterial wound healing; however, because atherosclerosis is a chronic process, vascular lesion formation probably involves indolent levels of inflammation with ongoing cycles of injury and repair over many years.[142,146,147]

Arterial Wall Inflammation

Studies have demonstrated the presence of monocytes or macrophages and T lymphocytes in arteries not only with advanced lesions but also in arteries with early atherosclerotic lesions in young adults.[148,149] Moreover, in experimental atherosclerosis, leukocyte infiltration into the vascular wall is known to precede smooth muscle cell hyperplasia.[150] Once inside the artery wall, mononuclear cells may play several important roles in lesion development. For example, monocytes may transform into macrophages and become involved in the local oxidation of low-density lipoproteins (LDLs) and accumulation of oxidized LDLs. Alternatively, macrophages in the artery wall may act as a rich source of factors that, for example, promote cell proliferation, migration, or the breakdown of local tissue barriers. The process of local tissue degradation may be important for the initiation of acute coronary artery syndromes because loss of arterial wall integrity may lead to plaque fissuring or rupture.[151]

Normally, the endothelium exhibits a low affinity for circulating leukocytes. The transmigration of leukocytes into the artery wall must occur as a facilitated process. The release of proinflammatory cytokines such as interleukin-1 may promote the expression of leukocyte adhesive molecules.[152] For simplicity, the interaction between leukocytes and the endothelium can be considered to involve three steps.[153] First, leukocytes in the bloodstream must loosely associate and roll along the endothelium, a process mediated by selectins expressed on endothelial cells.[152] Second, firm adhesion of these leukocytes to endothelial cells occurs by the interaction between integrins, such as $\alpha_4\beta_1$ (also known as very late antigen-4), expressed on leukocytes, and counterreceptors, such as vascular cell adhesion molecule-1, on endothelial cells.[154] Finally, the transmigration of leukocytes into the subendothelial space is mediated by various migration-inducing factors, such as monocyte chemoattractant protein-1.[155]

Dysfunction, discontinuity, or injury of the endothelial cell monolayer has been postulated to play a significant role in facilitating the transmigration of leukocytes into the intima and the development of intimal hyperplasia. However, the premise that regrowth of healthy endothelium limits neointimal accumulation is inconsistent with the results of several independent lines of investigation. For example, in experimental models, smooth muscle cell proliferation is not increased in arterial regions devoid of an endothelium.[156] Moreover, restoration of the endothelium, as could be achieved by seeding endothelial cells back into a denuded artery, does not decrease neointimal accumulation after vascular interventions.[157] The presence of endothelium in the central lumen of an artery and resistance to intimal growth do not appear to be inextricably linked. Finally, the endothelium is not restricted to the central lumen because the artery wall also has a rich supply of microvessels (ie, vasa vasorum).[158–161] The vasa vasorum likely comprise another portal of entry for inflammatory cells into the artery wall, particularly because the expression of certain adhesion molecules is more abundant in the endothelium lining these microvessels than in the central arterial lumen.[162]

Role of Lipoproteins in Lesion Formation

The clinical and experimental evidence linking dyslipidemias with atherogenesis is well established and need not be reviewed here. However, the exact mechanisms by which lipid moieties contribute to the pathogenesis of atherosclerosis remain elusive. Although the simple concept of cholesterol accumulating in artery walls until flow is obstructed may be correct in certain animal models, this theory is not correct for human arteries.

Much of the pioneering work in understanding cholesterol metabolism is based on seminal observations by Brown and Goldstein.[163] The work of these two investigators focused on LDL, the so-called bad form of cholesterol, and the absence (or deficient forms) of the

LDL receptor that are seen in familial hypercholesterolemia. Patients with familial hypercholesterolemia have high levels of LDL cholesterol and have accelerated forms of atherosclerosis as cholesterol moieties enter the cell by an alternate route. In the absence of a functional LDL receptor, LDL cholesterol is oxidized and taken up by scavenger receptors of monocytes and macrophages resident within the artery wall. Steinberg[164] integrated these data into a theory of atherogenesis that highlights the central role of LDL oxidation and the formation of lipid-laden monocytes in fatty streaks.

One of the major consequences of cholesterol accumulation in the artery wall is thought to be impairment of endothelial function. The endothelium is more than a physical barrier between the bloodstream and the artery wall. Under normal conditions, the endothelium is capable of modulating vascular tone (eg, through NO), thrombogenicity, fibrinolysis, platelet function, and inflammation. In the presence of traditional risk factors, particularly dyslipidemias, these protective endothelial functions are reduced or lost. The loss of these endothelium-derived functions may occur in the presence or absence of an underlying atherosclerotic plaque and may simply imply that atherogenesis has begun. Aggressive attempts to normalize atherosclerotic risk factors (eg, diet and lipid-lowering therapies) may markedly attenuate endothelial dysfunction, even in the presence of extensive atherosclerosis. Some clinical studies demonstrated dramatic improvements in endothelial function, as well as in cardiovascular morbidity and mortality, with the use of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, or "statins."[165–167] Future studies may help clarify the exact mechanisms by which dyslipidemias (and other risk factors) alter endothelial function.

Smooth Muscle Cell Proliferation, Migration, and Arterial Remodeling

The dominant cell type in atherosclerotic lesions is the smooth muscle cell, and as lesions progress the number of smooth muscle cells in the artery wall tends to increase. Therefore smooth muscle replication must occur at some time during atherogenesis. Perhaps the first line of evidence that cell replication occurs in human arteries is from the observation that atherosclerotic plaques contain monoclonal cell populations. Elegant studies by Benditt and Benditt[168] demonstrated that groups (or clones) of cells that arose from a single progenitor cell were present in tissue from atherosclerotic coronary arteries of women who were deficient in glucose-6-phosphate dehydrogenase (G6PD). Because G6PD is an X-chromosome–linked enzyme that has two isoforms, cells would express only one isoform, with the other isoform suppressed on the inactivated X chromosome. Groups of cells in an atherosclerotic plaque that contain only one isoform of G6PD are likely the result of proliferation of a single progenitor cell. Murry and colleagues[169] studied the monoclonality of atherosclerotic plaques by using X chromosome inactivation patterns. Using the polymerase chain reaction, these investigators examined the monoclonality of plaques according to the methylation pattern of the human androgen receptor gene, a highly polymorphic locus on the X chromosome for which 90% of women are heterozygous. These investigators noted that diseased and normal arteries contain monoclonal populations (or patches) of cells. They speculated that the monoclonality of plaques could result from expansion of a preexisting monoclonal patch of cells, rather than mutation or selection of individual cells in the artery wall.

Little is known about when and why cells proliferate in the artery wall. However, it is known that rapid expansion in neointimal smooth muscle cell mass occurs early in life. Sims and associates[170,171] described the accumulation of intimal smooth muscle cells in the left anterior descending coronary artery of neonates. Using electron microscopy, these investigators demonstrated interruptions in the internal elastic lamina in coronary arteries where a neointima had formed. These interruptions in the internal elastic lamina are not present in all human arteries. Indeed, the internal mammary artery, which typically is devoid of atherosclerosis, has an intact internal elastic lamina. Investigators have suggested that medial smooth muscle cells migrate inward through breaks in the internal elastic lamina to expand and form a neointima. The frequency and degree of smooth muscle cell replication in adult coronary arteries were examined by various investigators. Most of these studies demonstrated very low replication rates in tissue from both normal and diseased arteries.[172–175] Whether these low cell replication rates are sufficient to result in gradually advanced lesions or whether sporadic bursts of replication occur in response to injury is unknown. Finally, it is recognized that programmed cell death, or apoptosis, occurs in the artery wall.[176] The accumulation of cells in the artery wall is a function of not only cell proliferation but also apoptosis.

The role of smooth muscle cell migration in adult CAD is poorly understood. Investigators have suggested, however, that like fibroblasts that migrate into the base of a wound, arterial wall smooth muscle cells migrate inward to expand plaque mass. Smooth muscle cell migration into the intima was studied in various animal models of neointimal formation (eg, rat carotid artery model).[10] Most of these models demonstrated the inward migration of medial smooth muscle cells after normal arteries were subjected to balloon injury. Certain growth factors (eg, platelet-derived growth factor) were shown to play an important role in facilitating smooth muscle cell migration in these models.[177–179] Unfortunately, the clinical relevance of these experimental observations remains to be clarified because the milieu for cell migration in complex human lesions appears to be very different from that of normal animal arteries that are subjected to injury. More information is required on the factors that regulate smooth muscle cell migration, as well as why smooth muscle cells differ in their propensity to migrate after injury.

Finally, the buildup of atherosclerotic plaque does not always translate into the formation of arterial obstructions.[142] For example, Glagov and colleagues[180] noted that human vessels can accumulate massive amounts of atherosclerotic plaque without encroaching on the central arterial lumen. Instead, abluminal expansion of the artery wall may occur until 40% of the area encompassed by the internal elastic lamina is occupied by plaque; no further enlargement may occur thereafter, and luminal narrowing may ensue. Although this form of compensatory enlargement is referred to as "remodeling," the term is confusing because it has different meanings in different contexts (Figs. 7.13 and 7.14).[181–182] For example, remodeling has also been used to describe the arterial response to changes in blood flow (eg, during pregnancy or in the neonatal period) or pressure (eg, hypertension).[183] In addition, remodeling has been invoked as a key component of the response to arterial injury, although with quite a different meaning.[184] In animal models of arterial injury as well as in studies of human coronary arteries that have undergone angioplasty (or percutaneous transluminal coronary angioplasty), "shrinkage" or constrictive remodeling of the artery wall is a major determinant of luminal narrowing, whereas neointimal formation plays a minor role in this process.[185–192]

How arterial wall constriction is accomplished or why some but not all arteries undergo compensatory dilatation to preserve lumen area is incompletely understood.[141,193,194] Blood flow and shear stress are known to play critical roles in remodeling. The response of arteries to chronic alterations in blood flow is endothelium dependent.[182,195] For example, Langille and O'Donnell[195] demonstrated in rabbit carotid arteries that decreased blood flow resulted in narrowing of the vessel diameter that was unchanged with papaverine and was likely caused by structural changes in the artery wall. However, when the endothelium was removed from these vessels, the response to reduced blood flow was abolished. In atherosclerotic arteries that contain a rich network of endothelial cell-lined microvessels or vasa vasorum, the role of the endothelium in regulating remodeling may be important.[180,196,197]

Pathophysiology of Coronary Blood Flow

Coronary Artery Stenoses and Plaque Rupture

Coronary atherosclerosis is a chronic disease that develops over decades and remains clinically silent for prolonged periods (Box 7.9).

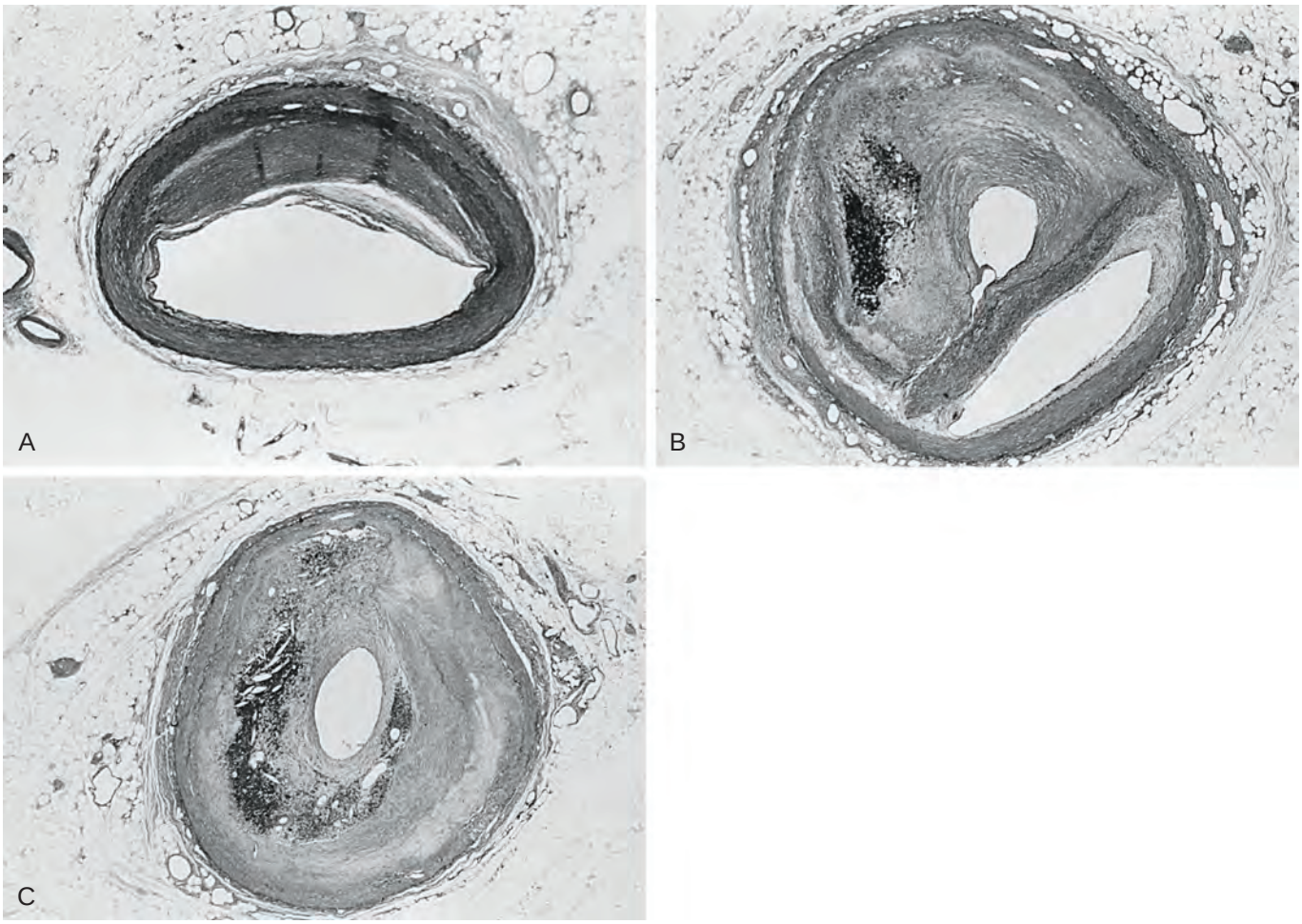


Fig. 7.13 Arterial remodeling. Serial sections of an atherosclerotic human left circumflex coronary artery (Movat's pentachrome–stained slide; original magnification ×40). (A) Proximal. (B) Middle. (C) Distal. Narrowing of the central arterial lumen is visible in the middle and distal sections; however, the total arterial area of these sections is also larger than that of the proximal section. The ability of arteries to undergo compensatory enlargement is referred to as *arterial remodeling*.

BOX 7.9 PATHOPHYSIOLOGY OF CORONARY BLOOD FLOW

- In most patients experiencing a myocardial infarction, the coronary occlusion occurs at the site of less than 50% stenosis.
- Plaque rupture leads to incremental growth of coronary stenoses and can cause coronary events.
- Plaque rupture occurs at the shoulder of the plaque where inflammatory cells are found.

Clinical manifestations of CAD occur when the atherosclerotic plaque mass encroaches on the vessel lumen and obstructs coronary blood flow to cause angina. Alternatively, cracks or fissures may develop in the atherosclerotic lesions and result in acute thromboses that cause unstable angina or myocardial infarction.

Patients with stable angina typically have lesions with smooth borders on angiography. Only a few coronary lesions are concentric; most have complex geometry varying in shape over their length. Eccentric stenoses, with a remaining pliable, musculoelastic arc of normal wall, can vary in diameter and resistance in response to changes in vasomotor tone or intraluminal pressure. Most human coronary artery stenoses are compliant.[198] The intima of the normal portion of the vessel wall is often thickened, thus making endothelial dysfunction probable (see "Dynamic Stenosis," later). In contrast, patients with unstable angina usually have lesions characterized by overhanging edges, scalloped or irregular borders, or multiple irregularities. These complicated stenoses likely represent ruptured plaque or partially occlusive thrombus, or both.[199] On angiography these lesions may appear segmental, confined to a short segment of an otherwise normal proximal coronary artery. At autopsy, however, the most common pathologic finding is *diffuse* vessel involvement with superimposed segmental obstruction of greater severity.[200] In a diffusely narrowed vessel, even modest progression of luminal narrowing can be significant. In such an artery, rating the significance of the obstruction by the percentage of diameter reduction relative to adjacent vessel segments underestimates its physiologic importance.[201,202] Therefore understanding the characteristics of atherosclerotic plaques is of central importance to the management of acute coronary artery syndromes.

The intuitive notion that the severity of coronary artery stenoses should correlate with the risk of complications from CAD was disproved by several key investigations. Ambrose and associates[203] reviewed the coronary angiograms of 38 patients who had had Q-wave myocardial infarction in the interval between serial studies. On the preinfarct angiograms, the mean percentage of stenosis at the coronary segment that was later responsible for infarction was only 34%.

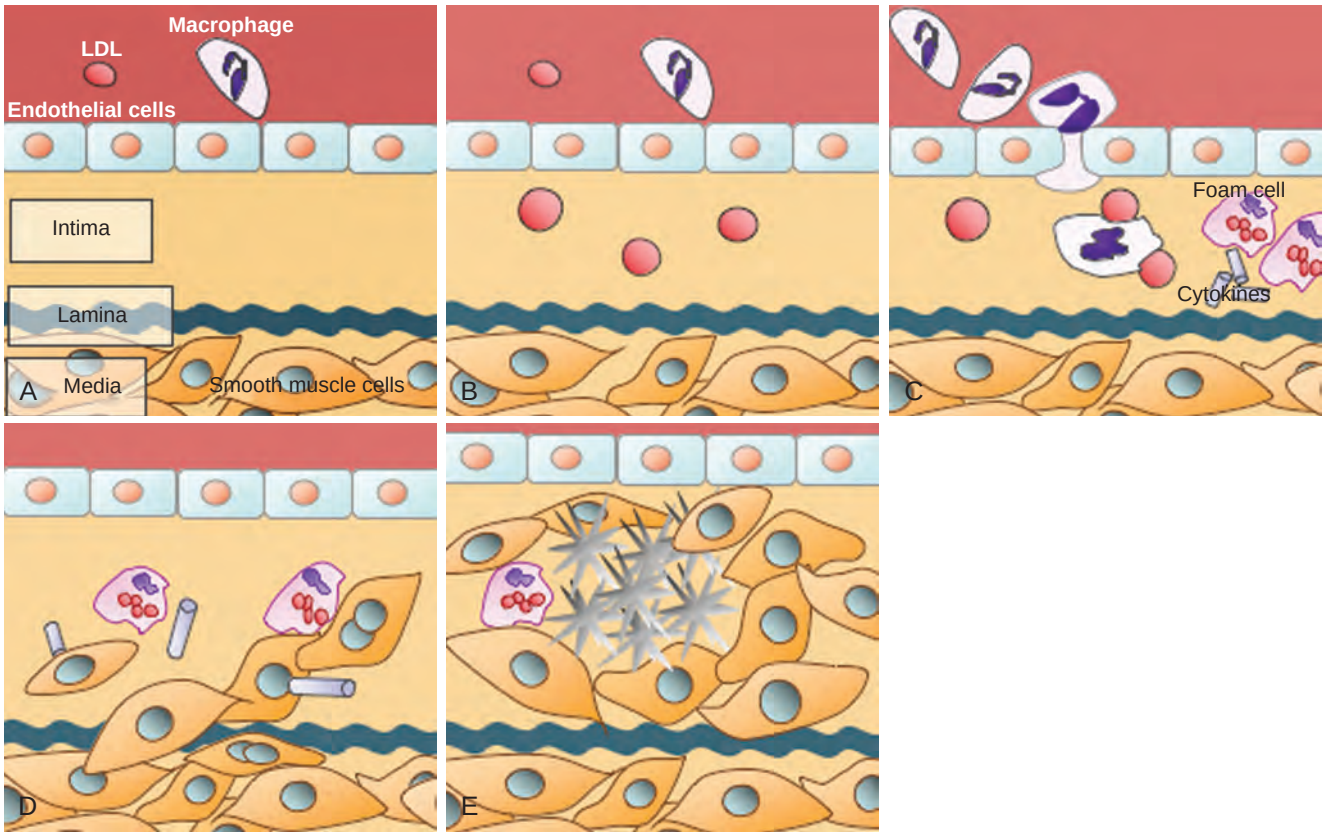


Fig. 7.14 A model of atherogenesis in human coronary arteries. (A) Infiltration of the intima by low-density lipoproteins *(LDL)* stimulates expression of adhesion molecules on the luminal surface of the endothelium and facilitates macrophage translocation into the intima. (B) Uptake of LDL by scavenger receptors on macrophages gives rise to foam cells. Infiltration of mononuclear cells and uptake of LDL stimulate secretion of proinflammatory cytokines, such as interleukin-1, that further promote accumulation of macrophages in the intima and stimulate division and migration of medial smooth muscle cells. (C) Ongoing inflammation stimulates accumulation of smooth muscle cells, foam cells, and extracellular matrix in the intima. (D) Ongoing inflammation can lead to regional apoptosis and development of a necrotic core with accumulation of cholesterol deposits. (E) Arterial remodeling is demonstrated by marked intimal thickening with minimal encroachment on the arterial lumen.

Similarly, Little and colleagues[204] reviewed the coronary angiograms of 42 patients who also had this procedure performed at an interval before and after myocardial infarction. Total occlusion of a previously patent artery was observed in 29 patients; yet for 19 of these occluded arteries, the degree of stenosis was less than 50% on the initial angiogram. Therefore, although the revascularization of arteries with critical stenoses in target lesions is appropriately indicated to reduce symptoms and myocardial ischemia, a risk of further cardiac events remains because atherosclerosis is a diffuse process, and mild or modest angiographic stenoses are more likely to result in subsequent myocardial infarction than are severe stenoses.

With this background comes the problem of predicting which arterial segments with minimal angiographic disease will later develop new critical stenoses. Clues to the solution emerged from careful pathologic studies of lesions by Davies and Thomas.[205] Superficial intimal injury (plaque erosions) and intimal tears of variable depth (plaque fissures) with overlying microscopic mural thrombosis are commonly found in atherosclerotic plaques. In the absence of obstructive luminal thrombosis, these intimal injuries do not cause clinical events. However, disruption of the fibrous cap, or plaque rupture, is a more serious event that typically results in the formation of clinically significant arterial thromboses. From autopsy studies it is known that rupture-prone plaques tend to have a thin, friable fibrous cap.[206] The site of plaque rupture is thought to be the shoulder of the plaque, in which substantial numbers of mononuclear inflammatory cells are commonly found.[207] The mechanisms responsible for the local accumulation of these cells at this location in the plaque are unknown; presumably, monocyte chemotactic factors, the expression of leukocyte cell adhesion molecules, and specific cytokines are involved.[162,208] Moreover, macrophages in plaques have been shown to express factors such as stromelysin, which promote the breakdown of the extracellular matrix and thereby weaken the structural integrity of the plaque.[151] Currently, no effective strategies have been designed to limit the possibility of plaque rupture; however, as discussed later, aggressive lipid-lowering therapy may be a helpful preventive measure.

Hemodynamics

If accurate angiographic assessment of the geometry of a coronary stenosis is made, hydrodynamic principles can be used to estimate the physiologic significance of the obstruction.[209] Energy is lost when blood flows through a stenosis because of entrance effects, frictional losses in the stenotic segment, and separation losses secondary to turbulence as blood exits the stenosis (Fig. 7.15). The Eq. relating stenosis geometry to hemodynamic severity is:

$$\Delta P = fQ + sQ^2$$

where ΔP is the pressure drop across the stenosis, Q is the volume flow of blood, f is a factor accounting for frictional effects, and s accounts for separation effects.

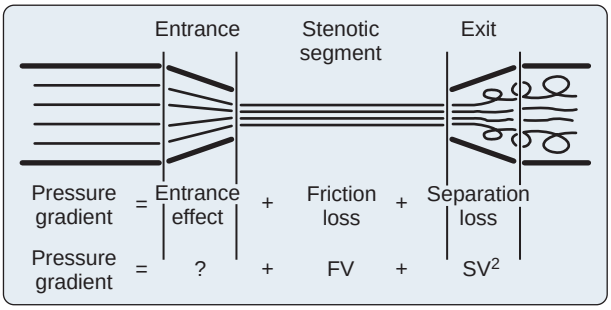


Fig. 7.15 Sources of energy loss across a stenosis. Equations that (accurately) predict the pressure gradient across a stenosis usually ignore entrance effects. Frictional losses are proportional to blood velocity but are usually not important except in very long stenoses. Separation losses, resulting from turbulence as blood exits the stenosis, increase with the square of blood velocity (V^2) and account for more than 75% of energy loss. *F,* Friction coefficient (Poiseuille); *S,* separation coefficient (see text). *(From Marcus ML: The physiologic effects of a coronary stenosis. In: Marcus ML, ed.* The Coronary Circulation in Health and Disease. *New York: McGraw-Hill; 1983:242–269. Reproduced with permission of The McGraw-Hill Companies.)*

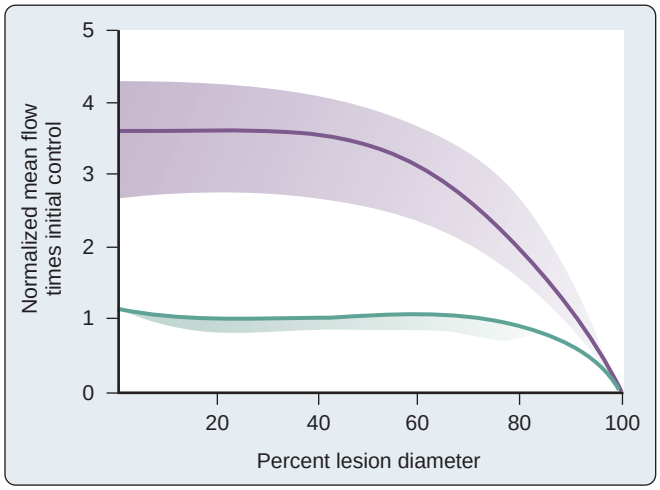


Fig. 7.16 Effect of increasing stenosis severity at resting *(bottom line)* and maximal *(top line)* coronary flows. At rest, lumen diameter must be reduced by more than 80% before flow decreases. Because pressure drop across a stenosis increases exponentially with blood velocity, maximal coronary flow is restricted by a 50% diameter reduction. *(From Gould KL, Lipscomb K. Effect of coronary stenoses on coronary flow reserve and resistance.* Am J Cardiol. *1974;34:48.)*

Based on the Poiseuille law for laminar flow:

$$f = \frac{8\pi\eta L A_n}{A_s^2}$$

where η is the blood viscosity, L is stenosis length, An is the cross-sectional area of the normal vessel, and As is the cross-sectional area of the stenosis. The separation or turbulence factor is:

$$s = \frac{\rho k}{2}\left(\frac{A_n}{A_s} - 1\right)^2$$

where ρ is blood density, and k is an experimentally determined coefficient.

Thus frictional losses are directly proportional to the first power of stenosis length but are inversely proportional to the square of the area (or fourth power of diameter). Separation losses are particularly prominent because they increase with the square of flow. Even at resting flows, more than 75% of energy loss results from this turbulence when blood exits the stenosis. Except for very long stenoses, the frictional term can be neglected.[198] The amount of energy loss or pressure drop across the obstruction therefore increases exponentially as flow rate increases. For this reason, exercise, anemia, and arteriolar vasodilator drugs (eg, dipyridamole) are poorly tolerated in the presence of severe stenosis. Fig. 7.16 illustrates that although resting flow is unaffected until coronary diameter is reduced by more than 80%, maximal flow begins to fall when diameter is reduced by 50%.

Resting flow in Fig. 7.16 remains constant as lumen diameter decreases because the coronary arterioles progressively dilate, thereby reducing the resistance of the distal coronary bed sufficiently to compensate for the resistance of the stenosis. As the severity of the stenosis increases further, the arteriolar bed can no longer compensate, and flow begins to fall. As stenosis severity increases, distal perfusion pressure falls, arterioles dilate to maintain flow until autoregulation is exhausted (in the subendocardium first), and flow becomes pressure dependent. As illustrated in Fig. 7.9, the distal pressure (or stenosis diameter) at which flow becomes pressure dependent is lower at low levels of myocardial metabolism ($M\dot{V}O$). The interpretation of normal resting flow can be difficult in the presence of CAD. A coronary artery supplying blood through collaterals to a large mass of myocardium requires high resting flow rates, and even mild stenosis may be flow limiting.

The frequently used term *critical stenosis* is usually defined as coronary constriction sufficient to prevent an increase in flow over resting values in response to increased myocardial oxygen demands.[210] This is a greater degree of obstruction than angiographically significant stenosis, which is usually defined as a reduction in cross-sectional area of 75%, equivalent to a 50% decrease in the diameter of a concentric stenosis.[202] A critical stenosis is demonstrated experimentally by blunting or abolishing reactive hyperemia (see "Autoregulation," earlier). This is evidence that autoregulation has been exhausted in at least the inner layer of myocardium (see "Transmural Blood Flow," earlier). The critical nature of the stenosis is relative to the resting $M\dot{V}O_2$. If oxygen demand decreases, some coronary autoregulatory reserve is recovered and the stenosis is no longer critical. The failure to recognize this situation has led to misinterpretation of studies designed to demonstrate coronary steal (see later).

Coronary Collaterals

Coronary collaterals are anastomotic connections, without an intervening capillary bed, between different coronary arteries or between branches of the same artery. In the normal human heart, these vessels are small and have little or no functional role. In patients with CAD, well-developed coronary collateral vessels may play a critical role in preventing death and myocardial infarction. Individual differences in the capability of developing a sufficient collateral circulation are determinants of the vulnerability of the myocardium to coronary occlusive disease.[211] Great interspecies variation is observed in the ability of the collateral circulation to support myocardial perfusion after acute coronary occlusion; pigs and rats have very little collateral circulation and have infarcts in almost all the area at risk, whereas dogs and cats with better collateralization have infarcts in less than 75% of the area at risk.[212] In the guinea pig, collaterals are so well developed that coronary occlusion does not even decrease myocardial blood flow. Differences also occur in the location of collateral vessels. In dogs collaterals develop in a narrow subepicardial zone, at the border of the potentially ischemic region, whereas in pigs a dense subendocardial plexus develops in response to coronary occlusion. In the presence of coronary disease, humans exhibit a small number of large epicardial collateral vessels and numerous small subendocardial vessels.

In response to coronary occlusion, native coronary collateral vessels (present from birth) do not passively stretch but undergo an active growth process that within 8 weeks in dogs can restore perfusion sufficient to support normal myocardial function even during exercise.

Human collaterals have a tortuous corkscrew-like pattern visible on angiography. The reason may be an embryonal pattern of vascular development in which longitudinal growth of smooth muscle cells occurs at the same time as radial growth. In the nongrowing adult heart, this increase in length results in tortuosity.[213] Much interest has been shown in discovering the factors that control collateral vessel growth in the hope of providing therapy for patients who cannot undergo revascularization otherwise.

Arteriogenesis refers to the transformation of preexisting collateral arterioles into functional arteries with a thick muscular coat and the acquisition of viscoelastic and vasomotor properties.[214] Fujita and Tambara[215] provided an overview of the process: a high-grade coronary stenosis decreases distal intraarterial pressure and results in an increased pressure gradient across the preexisting collateral network. Increased collateral blood flow results in increased shear stress at the endothelium, which upregulates cell adhesion molecules. Upregulation leads to adherence of monocytes, which transform into macrophages, and the production and release of growth factors such as granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1, and basic fibroblast growth factor. Angiogenesis is not directly related to collateral vessel development but rather refers to the proliferation, migration, and tube formation of capillaries in the central area of ischemic regions.[216] The development of a treatment to promote collateral growth in patients with intractable CAD is currently a subject of intense investigation. Experimental approaches include mechanical strategies to increase shear stress as well as cell therapies.[217] Ischemic preconditioning, sometimes used in off-pump coronary artery surgical procedures, may in part be mediated by collateral recruitment.[218]

Evidence in dogs suggests that mature coronary collaterals respond differently to neurohumoral stimulation than do normal coronary arteries. Collaterals do not constrict in response to α-receptor activation but do dilate in response to β_1- or β_2-agonists. They constrict in response to prostaglandin $F_{2\alpha}$ and angiotensin II, but less so than do normal vessels. Remarkably, collateral vessels constrict in response to vasopressin to a much greater extent than normal vessels. In vivo studies in dogs indicated that levels of vasopressin present during stress (hemorrhage, cardiopulmonary bypass) diminished flow to collateral-dependent myocardium. This finding likely reflects both constriction of collateral vessels and enhanced vasoconstriction of the resistance vessels in the collateral-dependent myocardium.[77] It is possible that the endothelial cells of both types of vessels are dysfunctional.[219] Relaxation in response to nitroglycerin is enhanced. This is a further mechanism for the beneficial effects of nitroglycerin in CAD. The deleterious effects of coronary arteriolar dilators such as adenosine and dipyridamole are discussed later (see "Coronary Steal").

Investigators have estimated that, in humans, perfusion through collaterals can equal perfusion through a vessel with a 90% diameter obstruction.[220] Although coronary collateral flow can be sufficient to preserve structure and resting myocardial function, muscle dependent on collateral flow usually becomes ischemic when oxygen demand rises to more than resting levels.[221] A metaanalysis carried out in 2012[222] estimated that, among patients with stable CAD, the presence of "high collateralization" is associated with a reduction in mortality rates of greater than 30% compared with patients with low collateralization. It is possible that evidence from patients with angina underestimates collateral function of the population of all patients with CAD. Perhaps persons with coronary obstructions but excellent collateralization remain asymptomatic and are not studied.

Pathogenesis of Myocardial Ischemia

Ischemia is the condition of oxygen deprivation accompanied by inadequate removal of metabolites consequent to reduced perfusion.[223] Clinically, myocardial ischemia is a decrease in the blood flow supply-to-demand ratio that results in impaired function. No universally accepted gold standard exists for the presence of myocardial ischemia. In practice, symptoms, anatomic findings, and evidence of myocardial dysfunction must be combined before concluding that myocardial ischemia is present.[224] Conclusive evidence of anaerobic metabolism in the setting of reduced coronary blood flow (relative to demand) would be convincing. Such evidence is extremely difficult to obtain, even in experimental preparations.

Determinants of Ratio of Myocardial Oxygen Supply to Demand

An increase in myocardial oxygen requirement beyond the capacity of the coronary circulation to deliver oxygen results in myocardial ischemia (Box 7.10). This is the most common mechanism leading to ischemic episodes in chronic stable angina and during exercise testing. Intraoperatively, the anesthesiologist must measure and control the determinants of $M\dot{V}O_2$ and protect the patient from "demand" ischemia. The major determinants of $M\dot{V}O_2$ are heart rate, myocardial contractility, and wall stress (chamber pressure × radius/wall thickness). Shortening, activation, and basal metabolic requirements are minor determinants of $M\dot{V}O_2$ (Fig. 7.17).

An increase in heart rate can reduce subendocardial perfusion by shortening diastole. Coronary perfusion pressure may fall in response to reduced systemic pressure or increased left ventricular end-diastolic

BOX 7.10 DETERMINANTS OF MYOCARDIAL OXYGEN SUPPLY-TO-DEMAND RATIO

The major determinants of myocardial oxygen consumption are:

- heart rate
- myocardial contractility
- wall stress (chamber pressure × radius / wall thickness)

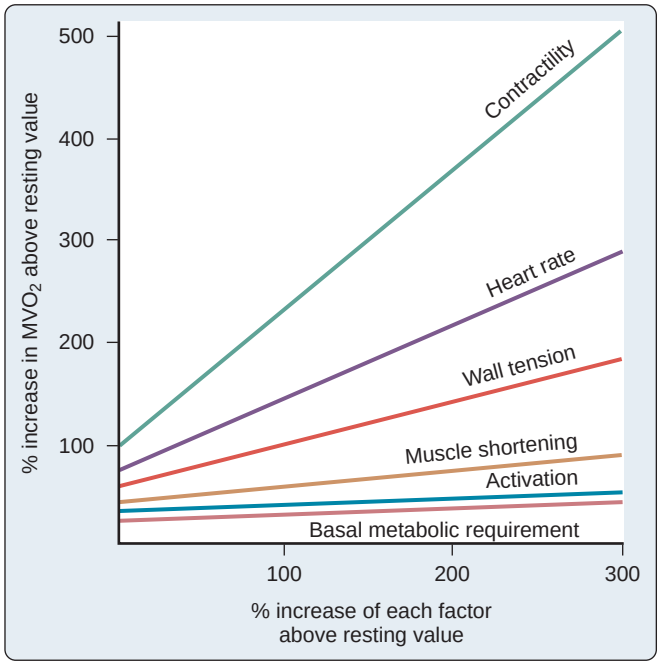


Fig. 7.17 Relative importance of variables that determine myocardial oxygen consumption ($M\dot{V}O_2$). Each line roughly approximates the effect of manipulating one variable without changing the others. Most interventions cause changes in several of the variables at the same time. The importance of contractility, which is difficult to monitor in practice, is apparent. *(From Marcus ML. Metabolic regulation of coronary blood flow. In: Marcus ML, ed.* The Coronary Circulation in Health and Disease. *New York: McGraw-Hill; 1983:65–92. Reproduced with permission of The McGraw-Hill Companies.)*

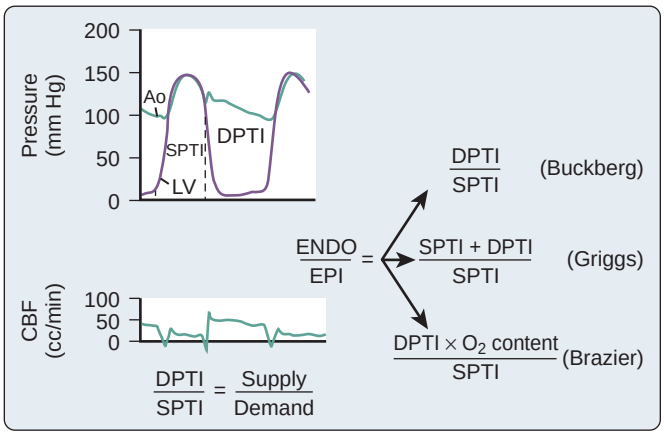


Fig. 7.18 Three indices, proposed to predict the adequacy of subendocardial perfusion in normal dogs, illustrate the variables determining myocardial oxygen supply and demand. The systolic pressure-time index *(SPTI)* relates to oxygen demand. The diastolic pressure-time index *(DPTI)* relates to the supply of coronary blood flow *(CBF)* to the inner layers of the left ventricle. Arterial oxygen content *(O_2 content)* is important when there are large changes in hematocrit. *Ao,* Aortic pressure; *ENDO,* subendocardial layer of left ventricle; *EPI,* subepicardial layer of the left ventricle; *LV,* left ventricular pressure. *(From Hoffman JIE, Buckberg GD. Transmural variations in myocardial perfusion. In: Yu PN, Goodwin JF, eds.* Progress in Cardiology. *Philadelphia: Lea & Febiger; 1976:37.)*

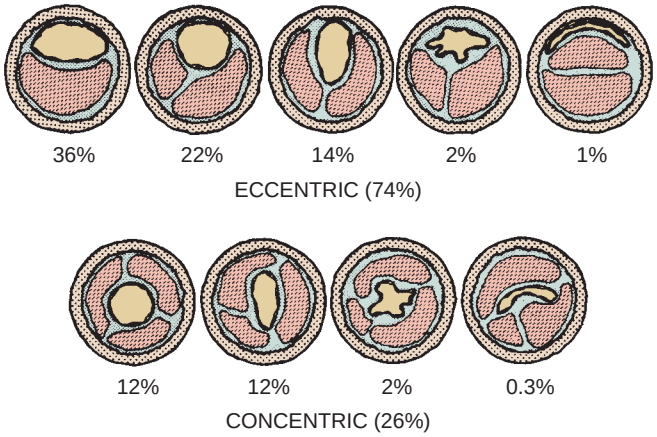


Fig. 7.19 Drawings and incidence of the various types of structure of stenoses observed in human coronary artery specimens. In almost three-fourths of vessels with greater than 50% narrowing, the residual arterial lumen was eccentric and partially circumscribed by an arc of normal arterial wall. In such lesions, a fall in intraluminal pressure or an increase in vasomotor tone can cause lumen diameter to decrease sufficiently to precipitate myocardial ischemia. *(From Brown BG, Bolson EL, Dodge HT. Dynamic mechanisms in human coronary stenosis. Circulation. 1984;70:917; redrawn from Freudenberg H, Lichtlen PR. The normal wall segment in coronary stenoses—a postmortem study.* Z Kardiol. *1981;70:863.)*

pressure. With the onset of ischemia, perfusion may be further compromised by delayed ventricular relaxation (decreased subendocardial perfusion time) and decreased diastolic compliance (increased left ventricular end-diastolic pressure). Anemia and hypoxia can also compromise delivery of oxygen to the myocardium. Several indices of myocardial oxygen supply-to-demand ratio have been proposed to guide therapy. The rate-pressure product (heart rate × systolic blood pressure) gives a good estimate of $M\dot{V}O_2$ but does not correlate well with ischemia. A patient with a systolic pressure of 160 mm Hg and a heart rate of 70 beats/minute has a much lower likelihood of ischemia than does a patient with a systolic pressure of 70 mm Hg and a heart rate of 160 beats/minute, although both patients have a rate-pressure product of 11,200. The ratio of the diastolic pressure-time index (DPTI) to the systolic pressure-time index (SPTI) was devised to estimate subendocardial perfusion and takes into account determinants of oxygen delivery (Fig. 7.18).[225–227] When blood oxygen content was included, the index became a good predictor of endocardial flow in animals with normal coronary arteries. The ratio of mean arterial pressure to heart rate has been proposed as a correlate of myocardial ischemia.[228] In dogs with moderate to severe coronary stenoses, systolic shortening was best with high pressures and low heart rate and worst with low pressure and high heart rate. None of these indices has proved reliable in the clinical setting. The major value of these indices is to bring attention to the important variables determining the supply-to-demand ratio, These variables should be measured (or estimated) and controlled individually.

Dynamic Stenosis

Patients with CAD can have variable exercise tolerance during the day and between days. Ambulatory monitoring of the electrocardiogram has demonstrated that ST-segment changes indicative of myocardial ischemia, in the absence of changes in oxygen demand, are common.[229] These findings are explained by variations over time in the severity of the obstruction to blood flow imposed by coronary stenoses.

Although the term *hardening of the arteries* suggests rigid, narrowed vessels, in fact most stenoses are eccentric and have a remaining arc of compliant tissue (Fig. 7.19). A modest amount (10%) of shortening of the muscle in the compliant region of the vessel can cause dramatic changes in lumen caliber.[198] This was part of Prinzmetal's original proposal to explain coronary spasm. Maseri and associates[230] suggest that the term *spasm* be reserved for "situations where coronary constriction is both focal, sufficiently profound to cause transient coronary occlusion, and is responsible for reversible attacks of angina at rest" (ie, variant angina). Although this syndrome is rare, lesser degrees of obstruction in response to vasoconstrictor stimuli are common among patients with CAD.

Sympathetic tone can be increased by the cold pressor test (immersing the arm in ice water) or by isometric handgrip testing. In response to this maneuver, coronary resistance decreased in normal subjects but increased in patients with coronary disease, some of whom experienced angina.[231] This increase in resistance appears to be mediated by α-receptors because it can be prevented by phentolamine. Studies using quantitative coronary angiography have documented reductions in caliber in diseased vessels in contrast to dilation of vessels in normal subjects.[97,232] Zeiher and colleagues[232] showed that the same vessel segments that constricted with the cold pressor test also constricted in response to an infusion of acetylcholine. Because the normal, dilatory response to acetylcholine depends on intact endothelium, these findings suggest that the abnormal response of stenotic coronary arteries is the result of endothelial dysfunction.

Animal models of coronary vasospasm demonstrated that enhanced vascular smooth muscle reactivity may also underlie vasospasm.[233] Rho, a guanosine triphosphate–binding protein, sensitizes vascular smooth muscle cells to calcium by inhibiting myosin phosphatase activity through an effector protein called Rho-kinase. Upregulation of this pathway may be a mechanism of coronary vasospasm. Rho-kinase inhibitors have been shown to block agonist-induced vasoconstriction of internal thoracic artery segments from patients undergoing coronary artery surgical procedures.[234]

In addition, in patients with coronary disease, some of the angiographically normal appearing segments also respond abnormally.[64,235] It seems likely that endothelial dysfunction precedes the appearance of visible stenoses during the development of coronary atherosclerosis. In patients with angiographically smooth coronary arteries, Vita and associates[236] found that an abnormal response to acetylcholine was correlated with serum cholesterol, male sex, age, and family history of coronary disease. The normal dilation of epicardial coronary arteries

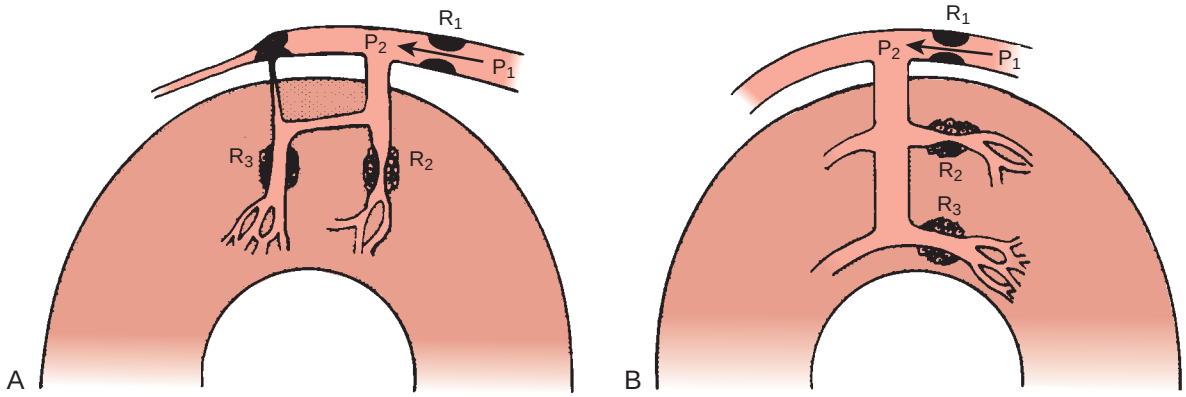


Fig. 7.20 Conditions for coronary steal in different areas of the heart and between the subendocardial and subepicardial layers of the left ventricle. (A) Collateral steal. (B) Transmural steal. See text for details. P_1, Aortic pressure; P_2, pressure distal to the stenosis; R_1, stenosis resistance; R_2 and R_3, resistance of autoregulating and pressure-dependent vascular beds, respectively. *(From Epstein SE, Cannon RO, Talbot TL. Hemodynamic principles in the control of coronary blood flow.* Am J Cardiol. *1985;56:4E.)*

in response to increased blood flow (shear stress) was shown to be absent in atherosclerotic vessels.[237] In addition, investigators demonstrated that patients with coronary disease respond to serotonin with coronary vasoconstriction instead of the normal vasodilatory response.[238,239] The concentrations of serotonin used were within the range found in coronary sinus blood of patients with coronary disease. Extremely high concentrations of serotonin may be found on the endothelium at the site of aggregating platelets.[238] All these findings point to the central role of endothelial dysfunction in the abnormal coronary vasomotion of patients with atherosclerosis (see "Endothelium," earlier).[240]

Coronary Steal

Steal occurs when the perfusion pressure for a vasodilated vascular bed (in which flow is pressure dependent) is lowered by vasodilation in a parallel vascular bed, with both beds usually distal to a stenosis. Two kinds of coronary steal are illustrated: collateral and transmural (Fig. 7.20).

Fig. 7.20A shows collateral steal in which one vascular bed (R_3), distal to an occluded vessel, is dependent on collateral flow from a vascular bed (R_2) supplied by a stenotic artery. Because collateral resistance is high, the R_3 arterioles are dilated to maintain flow in the resting condition (autoregulation). Dilation of the R_2 arterioles increases flow across the stenosis R_1 and decreases pressure P_2. If R_3 resistance cannot further decrease sufficiently, flow there decreases, thus producing or worsening ischemia in the collateral-dependent bed. The values of all the resistances, including collaterals, and the baseline myocardial metabolic state determine how powerful the vasodilator stimulus must be to produce ischemia in the collateral bed. Failure to recognize this has confounded studies of vasodilator drugs. If collateral vessels are extremely well developed or if $M\dot{V}O_2$ is low, sufficient autoregulatory reserve may remain in the collateral-dependent bed to maintain adequate myocardial blood flow even with the administration of a moderately powerful vasodilator.

Transmural steal is illustrated in Fig. 7.20B. Normally, vasodilator reserve is less in the subendocardium (see "Transmural Blood Flow," earlier). In the presence of stenosis, flow may become pressure dependent in the subendocardium, whereas autoregulation is maintained in the subepicardium. This situation is illustrated in Fig. 7.11, in which at a perfusion pressure of 50 mm Hg, flow has fallen in the subendocardium while at the same time the subepicardium retains autoregulatory reserve. Dilation of the subepicardial arterioles, R_2, then increases flow across the stenosis (R_1), thereby causing P_2 to fall and resulting in decreased flow to the subendocardium as subepicardial flow increases.

The term *steal* is most appropriate when the vasodilation is caused by a pharmacologic agent (adenosine, dipyridamole) producing "luxury" flow (beyond metabolic requirements) in the vascular bed with coronary reserve (R_2). The same redistribution of blood flow also occurs during exercise in response to metabolically mediated vasodilation. The study of coronary steal clearly demonstrates the complex interrelationships among the determinants of myocardial blood flow.

Intracoronary Evaluation of Atherosclerosis

A detailed description of diagnostic and therapeutic procedures performed in the cardiac catheterization laboratory is provided in Chapter 3. However, given that an integral understanding of the anatomy and physiologic impact of the coronary artery and the atherosclerotic lesion is necessary for the appropriate interpretation and use of these technologies, a brief review of new developments in invasive assessment is provided here.

Standard coronary arteriography gives operators a two-dimensional representation of the lumen. By examining arteries in multiple views, the operator estimates coronary stenoses by comparison of the lumen diameter at the point of maximal narrowing with adjacent disease-free segments. However, as discussed earlier, development of the atherosclerotic plaque results not only in luminal encroachment but also in arterial remodeling,[180] meaning that significant disease may be overlooked on traditional angiography. Thus newer technologies such as intravascular ultrasonography (IVUS) and optical coherence tomography (OCT) rapidly became the gold standard for defining the coronary anatomy and determining the severity of a stenosis.

Intravascular Ultrasound

IVUS of coronary arteries was first popularized in the 1990s,[241] and subsequent refinement of catheter delivery systems and commercialization made it a common component of the modern catheterization laboratory. Compatible with most guiding catheters, IVUS probes are delivered to the coronary arteries by standard angiographic techniques, and both manual and mechanical pullback of the IVUS probe allows operators to assess real-time cross-sectional images through use of a miniaturized ultrasound probe. Complementary software can then allow users to generate either longitudinal or three-dimensional reconstructions of the interrogated vessel.

IVUS images demonstrate remarkable fidelity to cross-sectional histologic specimens and permit accurate visualization and measurement of the intima, the media, and in some instances the adventitia (Fig. 7.21). Arterial remodeling with significant intimal hyperplasia but relatively intact lumen diameter can thus identify occult disease not

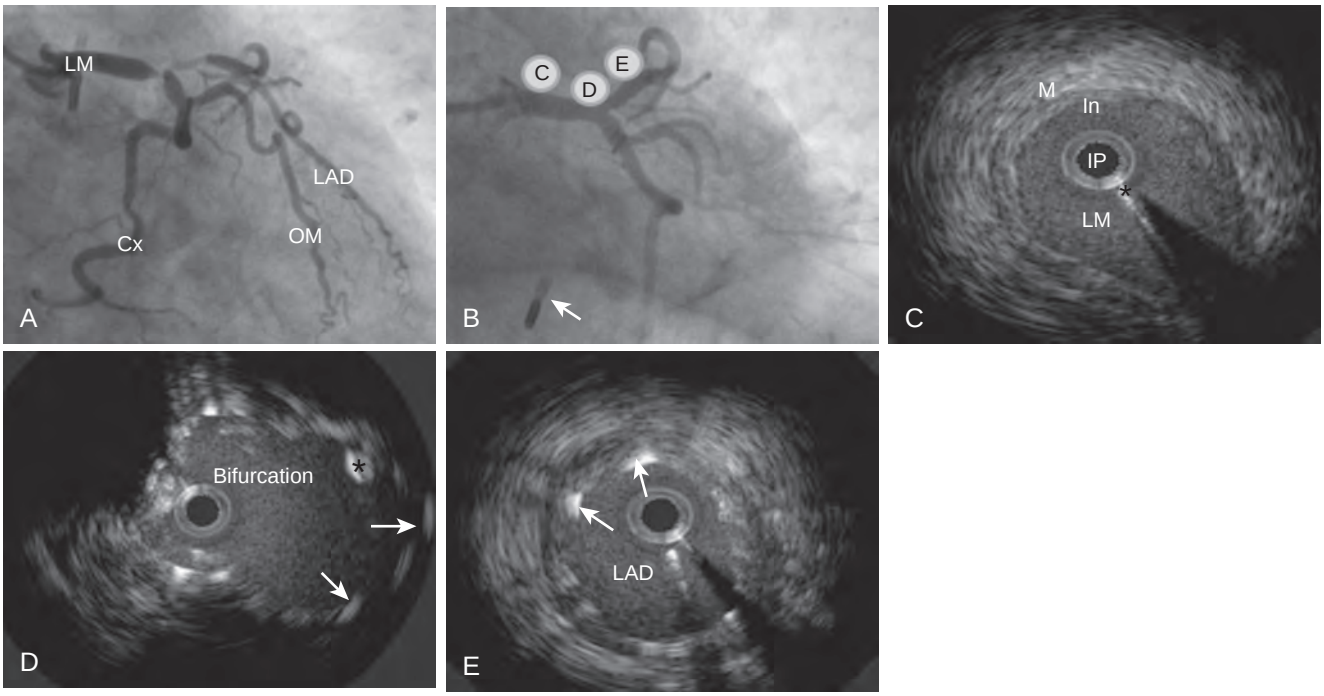


Fig. 7.21 Intravascular ultrasonography *(IVUS)* for assessment of human coronary arteries. (A) Right anterior oblique projection of the left coronary circulation. The left main coronary artery *(LM),* left anterior descending coronary artery *(LAD),* circumflex artery *(Cx),* and obtuse marginal artery *(OM)* are seen. Severe distal LM stenosis is seen bifurcating into the LAD and Cx. (B) Postpercutaneous intervention angiogram demonstrates no residual stenosis. Drug-eluting stents were placed in the LM, LAD, and Cx. The tip of an aortic balloon pump can be seen *(arrow).* Letters indicate the location of IVUS images for correlating panels. (C–E) IVUS images of the LM, LM bifurcation, and LAD, respectively. *Arrows,* Stent struts; *asterisk,* guidewire; *In,* intima; *IP,* IVUS probe; *M,* media.

otherwise appreciated on standard angiography. One landmark article noted that even if only minor luminal irregularities exist, atherosclerotic disease can be demonstrated throughout most other vessels in the coronary circulation, a finding suggesting that luminograms may be simply the tip of the atherosclerotic iceberg.[242] Indeed, IVUS is now commonly used to quantify intermediate-severity lesions more accurately,[243] appropriately assess the size of vessels, or delineate regions that are otherwise difficult to assess on standard angiography such as left main CAD. Especially given that undersized or malapposed stents are known to cause subsequent stent thrombosis, this ability is of significant importance from a clinical perspective. Moreover, IVUS allows operators to assess arteries after percutaneous intervention for adequate stent deployment and for complications, such as arterial dissection, that can be missed on standard angiography.[244] However, IVUS is not limited simply to documenting and quantifying atherosclerotic burden. Plaque composition can also be assessed qualitatively and classified based on acoustic impedance by allowing differentiation among fibromuscular "soft" lesions, dense "fibrous" lesions, and "calcified" hyperechoic lesions.[245] Although accurate prognostication remains limited, ongoing studies are aimed at identifying which plaques are "vulnerable" or susceptible to rupture, thus causing acute vessel closure and myocardial infarction.[246,247] The widespread adoption of IVUS has been limited largely by cost and increased procedural time; however, metaanalysis of both randomized and observational studies suggested an impact on clinical outcomes after percutaneous coronary intervention (PCI).

Optical Coherence Tomography

OCT provides a complimentary tool to IVUS for assessing coronary anatomy. OCT is a real-time catheter-based technology that uses near-infrared light in place of ultrasound to generate cross-sectional images. In this way OCT is able to generate a 10-fold increase in axial resolution compared with IVUS and can image structures as small as 10 to 15 μm.[247] Consequently, OCT has permitted even greater insight into coronary stenting and the intricacies of vascular biology.[248,249] Specifically, OCT enables classification and quantification of plaque morphology including identification of thin fibrous caps, lipid, and calcium without equivocation (Fig. 7.22). Most importantly, however, OCT affords unparalleled assessment of coronary stents after implantation including re-endothelization profiles, dissection flaps, stent apposition, and thrombus, thereby providing a wealth of information both for planning PCI and for stent optimization after deployment.[247,250] This technology has been particularly helpful with the development of bioresorbable vascular scaffolds, which resorb over a period of 2 years.[251,252] The greater resolution of this technology not only better visualizes stent struts but also greatly improves the detection of stent malapposition and prolapsed tissue.[253] However, convincing studies that OCT-guided PCI reduces events are lacking, and studies are needed to determine the impact of this imaging technology on patients' outcomes.

Fractional Flow Reserve

Although IVUS and OCT provide anatomic information on coronary artery structure, atherosclerotic plaque morphology, and luminal dimensions, neither technology is able to assess the physiologic significance of a coronary stenosis or detect myocardial ischemia. Indeed, the goal of revascularization is the relief of ischemia to improve symptoms and to reduce the risk of adverse outcomes. Numerous studies have highlighted the limitations of angiography alone in identifying responsible atherosclerotic plaques.

FFR is the ratio of the pressure distal (P_{distal}) to the pressure proximal ($P_{proximal}$) to a coronary stenosis when in a state of maximal coronary flow (assuming resistance is constant under hyperemia and the mean venous pressure is negligible). Practically, this ratio is assessed in the cardiac catheterization laboratory using wires equipped with pressure sensors that are placed distal to a coronary

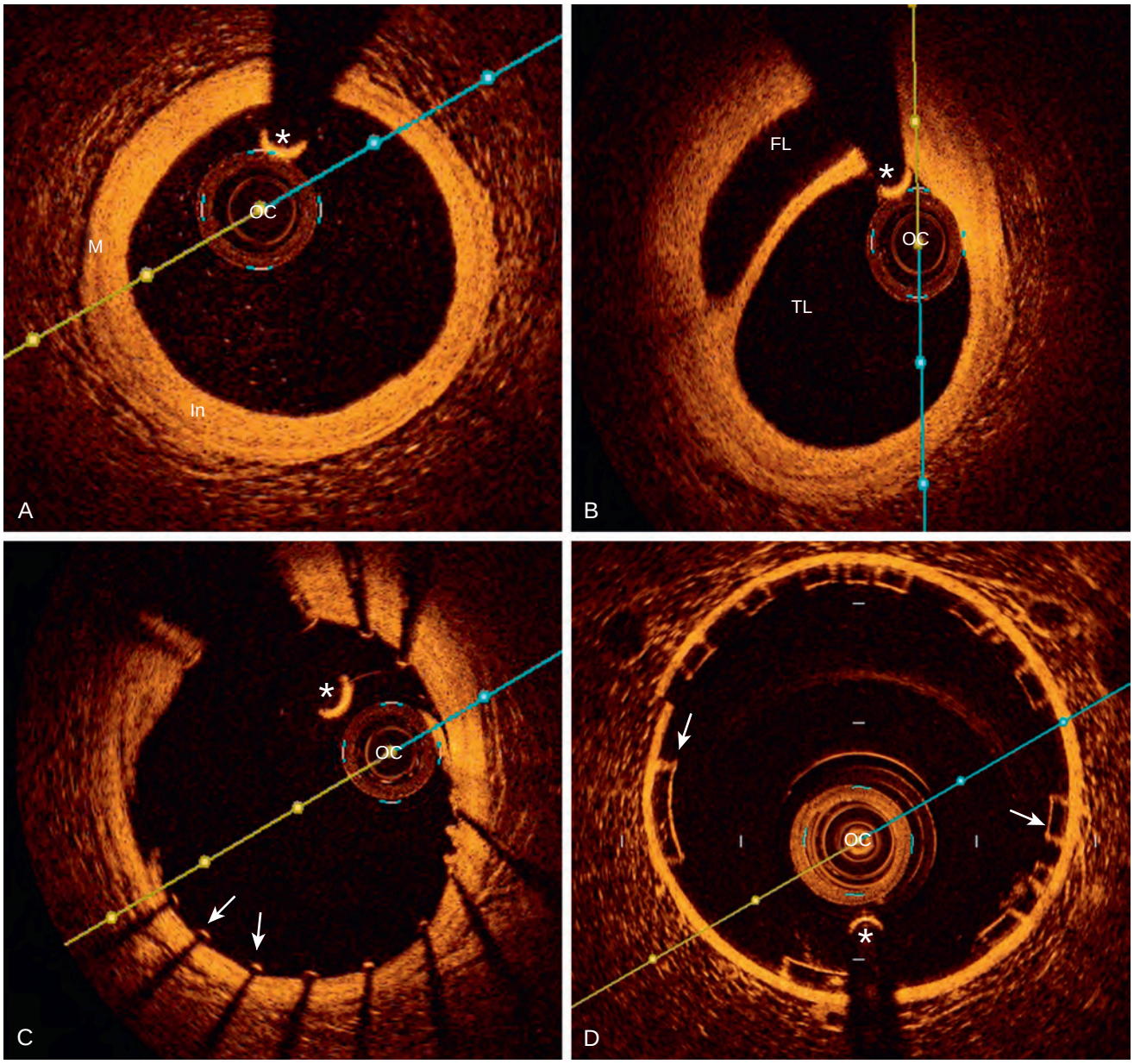


Fig. 7.22 Optical coherence tomography images. (A) Right coronary artery demonstrating mild intimal *(In)* thickening. The media *(M)* is represented by the thin dark band. (B) Resolution of a dissection flap with the wire in the true lumen *(TL)* and a clear false lumen *(FL)* present. (C) Stenotic atherosclerotic plaque after percutaneous coronary intervention with a drug-eluting metallic stent. *Arrows* represent stent struts. (D) Deployed bioresorbable vascular scaffold *(BVS)*. *Arrows* indicate scaffold struts. *Asterisk,* Guidewire; *OC,*optical coherence tomography catheter.

stenosis. Hyperemia is subsequently induced using adenosine (or less frequently nitroprusside), and the FFR ratio is calculated using the following formula:

$$FFR = P_{distal} / P_{proximal}$$

Typically, one would expect the flow to be equal throughout an artery (ie, a pre-to-post ratio of 1) without any stenosis. Studies have demonstrated that a reduced FFR value (ie, an FFR <0.75–0.8) is predictive of myocardial ischemia on noninvasive testing.[254] Although a correlation exists between angiographic and physiologic severity, this assumption does not always hold true because the drop in flow is a function not only of the degree of stenosis but also of the size of the vascular bed the coronary serves. Thus when assessing multiple intermediate lesions on angiography, FFR enables interventional cardiologists to identify functionally significant lesions and to target revascularization to those lesions for which revascularization will confer benefit.[255] Indeed, the FAME-I (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial randomized patients with multivessel CAD to undergo angiography-guided or FFR-guided PCI and demonstrated reduced rates of stent implantation, death, myocardial infarction, and repeat revascularization at 1 year.[120] This trial was followed by the FAME-II trial, which studied patients with multivessel CAD and similarly showed improved outcomes in patients who underwent physiologically guided PCI.[256]

Overall, coronary angiography remains the cornerstone of the assessment and management of obstructive CAD. However, novel intravascular assessment tools shed new light on the assessment of CAD at both an anatomic (IVUS, OCT) and a physiologic (FFR) level,

thus further refining both our approach to coronary intervention and our appreciation of underlying vascular biology.

Future Directions

A major need exists not only to identify but also to treat the vulnerable nonstenotic plaque that is prone to rupture. Although angiography is ideal for imaging the lumen of arteries, it provides little information about the atherosclerotic process within the vessel wall. Unfortunately, newer imaging techniques such as IVUS and OCT have yet to evolve as practical modalities that can be used to predict which patients are at risk for acute coronary syndromes secondary to plaque rupture. It is unlikely that either of these imaging modalities alone will be successful in identifying the at-risk patient or lesion; rather, biomarkers of risk will probably help identify patients in need of invasive assessment or medical intensification.[257,258]

Most recently, a focus on the adventitia of the coronary artery and its' role in initiation of inflammation in the vessel wall and subsequent development of atherosclerosis has been renewed.[11,259] Although much effort has been devoted to studying the intima and media in development of vascular lesions, the adventitia is just now garnering the focus it may deserve. The adventitia is unique in that it houses the vasa vasorum that provide nutrients and vasoactive factors and act as portals of entry for inflammatory cells into the media and intima of epicardial coronary arteries. Moreover, the adventitia alone supplies all neural input to the vessel wall, input that has been implicated in plaque progression and destabilization.[260] Supporting this notion of an "outside-in" hypothesis to the development of atherosclerosis is that changes in the adventitial vasa vasorum often precede intimal changes.[261] In addition to atherosclerosis, the adventitia has also been implicated as a source of cells in neointimal development after vascular injury such as balloon angioplasty.[262,263] Given the dynamic nature of the adventitia in disease and the unique role it serves in vessel homeostasis, an understanding of adventitial biology is lacking.

Finally, the need remains to identify genuine targets for lessening atherosclerotic burden outside of LDL reduction. To date, the most compelling clinical data support the ubiquitous use of statins in patients to prevent future clinical events. However, statin-associated muscle symptoms such as muscle pain, stiffness, or tenderness affect as many as one-third of treated patients and influence their quality of life and the ability to titrate therapy to target doses.[264] Data from the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial suggested added benefit with the addition of ezetimibe in patients who have had acute coronary syndromes; this benefit was still derived by lowering LDL cholesterol levels. A novel class of agents, called PCSK9 inhibitors, is also under early clinical investigation and may offer a third class of agents, although these studies remain preliminary. Nonetheless, despite the ever increasing understanding of the molecular processes that underlie lesion development, investigators have failed to develop truly novel therapies that affect disease progress. The goal remains expanding an understanding of how anatomy, physiology, and biology influence disease development and progression to prevent rather than treat myocardial infarctions.

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8

Molecular and Genetic Cardiovascular Medicine

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KEY POINTS

1. The rapid development of molecular biologic and genetic techniques has greatly expanded the understanding of cardiac functioning, and these techniques are beginning to be applied clinically.
2. Cardiac ion channels form the machinery behind the cardiac rhythm; cardiac membrane receptors regulate cardiac function.
3. Sodium, potassium, and calcium channels are the main ion channel types involved in the cardiac action potential. Many subtypes exist, and their molecular structure is known in some detail, thus allowing a molecular explanation for phenomena such as voltage sensing, ion selectivity, and inactivation.
4. Muscarinic and adrenergic receptors, both of the G-protein–coupled receptor class, are the main regulators of cardiac function.
5. Adenosine plays important roles in myocardial preconditioning through an action on adenosine triphosphate–regulated potassium channels and is an effective antiarrhythmic drug by its action on G-protein–coupled adenosine receptors.
6. Volatile anesthetic agents significantly affect calcium channels and muscarinic receptors.
7. Powerful genetic analysis techniques are being used to better understand adverse cardiovascular events through molecular approaches. Research using these techniques has begun to explore links between genomics and perioperative adverse cardiovascular events.
8. Treatment through gene therapy is evolving in cardiovascular medicine, although it currently does not have a prominent role in the perioperative setting.

The past decades have witnessed what may be termed a revolution in the biomedical sciences, as molecular and genetic methodologies suddenly jumped onto the clinical scene. The birth of molecular biology is commonly identified with the description of the structure of deoxyribonucleic acid (DNA) by Watson and Crick in the 1950s.[1] For many years afterward, molecular biology was explored in research laboratories but was not translated into the clinical realm. During this time much molecular biology research focused on the laborious process of sequencing the human genome and identifying genes that encode specific proteins. Although at the time most workers in the field realized that these advances would one day be of immense importance to clinical medicine, the exact place that these advances would take was unclear.

Now, long since the discovery of the structure of DNA, the human genome has been sequenced completely. The development of the polymerase chain reaction, a technique of remarkable simplicity and flexibility, has dramatically increased the speed with which many molecular biology procedures can be performed, and it has allowed the invention of many new techniques. More recent years have seen the development of approaches allowing screening of large amounts of genetic material for changes associated with disease states. As a result of these and other developments, molecular biology has become a practical tool for studying the expression and functioning of proteins in health and disease.

Cardiovascular medicine has benefited from these advances. Not only have the electrophysiologic and pumping functions of the heart been placed on a firm molecular footing, but also the underlying molecular mechanisms have been determined for numerous pathologic cardiac states, thereby allowing progress in therapeutic development. Nothing indicates that the pace of progress in molecular biology is slowing down. If anything, the opposite is the case, and more dramatic advances may be expected in the years to come. Thus techniques such as gene therapy may become effective therapeutic options in cardiac disease.

This chapter reviews key aspects of molecular and genetic cardiovascular medicine, with specific emphasis on medical issues relevant to the anesthesiologist. The myocyte membrane signaling proteins are of prime importance in this respect, and the two major classes—membrane channels and membrane receptors—are discussed. Simply stated, membrane channels form the machinery behind cardiac rhythms, and the receptors are involved in regulation of cardiac function. This statement is, of course, an overgeneralization because close interactions among the various systems exist. In fact, the interactions between cardiac channels and receptors have stimulated some of the more exciting areas of investigation in molecular cardiovascular medicine. In describing each of these proteins, a brief overview of the general properties of the class is provided, and then several examples specific to the cardiovascular system are discussed. Each section ends with a discussion of some clinical correlates flowing from the material discussed.

The actions of anesthetic agents on the molecular mechanisms of cardiac function and dysfunction comprise an area of active investigation. Much detail remains to be filled in, but it is clear that anesthetic agents, at clinically relevant concentrations, interact with numerous cardiac signaling systems. Although it is too early to explain completely the cardiac effects of the various anesthetic agents through these mechanisms, no doubt exists that such interactions can be of significant clinical relevance. Considering the rapid pace of research in this area, rather than attempting to be all inclusive, this chapter discusses two investigational areas for which clinical relevance seems high: (1) function of cardiac calcium (Ca^{2+}) channels, and (2) the actions of the muscarinic acetylcholine (ACh) receptors.

The final section of this chapter looks at the role of genetics in cardiovascular medicine, again with emphasis on developments of relevance to adverse cardiovascular events after cardiac operations and procedures. Techniques for genetic diagnostic screening and their applications in the clinical setting are discussed. In addition, the potential of genetic therapy is described briefly, although at this time these advances do not yet influence the care of the cardiac surgical patient.

In addition to providing an overview of the current state of knowledge, this chapter demonstrates a few of the many methodologies that have been used to obtain these results, to enable the reader to access the current literature with more ease. In quoting the literature, the authors have therefore chosen to provide references to many of the original articles describing techniques and findings, complemented by references to more recent review articles to provide a current viewpoint.

Machinery Behind the Cardiac Rhythm: Ion Channels

The cardiac action potential results from the flow of ions through *ion channels,* which are the membrane-bound proteins that form the structural machinery behind cardiac electrical excitability. In response to changes in electrical potential across the cell membrane, ion channels open and allow the passive flux of ions into or out of the cell along their electrochemical gradients. This flow of charged ions results in a current, which alters the cell membrane potential toward the *equilibrium potential* (E) for the ion, which is the potential at which the electrochemical gradient for the ion is zero. Depolarization of the cell could, in principle, result from an inward cation current or an outward anion current; for repolarization, the reverse is true. In excitable cells, action potentials are mainly caused by the flow of cation currents. Membrane depolarization results principally from the flow of sodium (Na^+) down its electrochemical gradient (E_{Na} is approximately +50 mV), whereas repolarization results from the outward flux of potassium (K^+) down its electrochemical gradient (E_K is approximately −90 mV). Opening and closing of ion channels selective for a single ion result in an individual ionic current. The integrated activity of many different ionic currents, each activated over precisely regulated potential ranges and at different times in the cardiac cycle, results in the cardiac action potential. Ion channels are usually highly (but not uniquely) *selective* for a single ion, hence the terms *K^+ channels, Na^+ channels,* and so forth. Channels may *rectify,* that is, pass current in one direction across the membrane more easily than the other. Electrical and chemical stimuli, which lead to opening and closing of the channel, cause a conformational change in the channel molecule *(gating).* The rate of change of channel conformation *(gating kinetics)* may be rapid, in which case the channel opens *(activates)* almost immediately (eg, Na^+ channels), or relatively slowly, resulting in a delay in channel activation (eg, delayed rectifier K^+ channels). After activation, ion channels may stay open until closed by another stimulus (eg, repolarization of the membrane), or they may close *(inactivate)* in the presence of a continued stimulus. Inactivated channels do not usually reopen on repeat stimulation until they have recovered from inactivation (Box 8.1).

Patch Clamping

Much of the understanding of the molecular mechanisms behind the action potential derives from the development and implementation of three techniques: (1) *patch clamping,* which allows recording of ion flow through individual channel molecules; (2) *voltage clamping* of isolated cardiac cells; and (3) *cloning and heterologous expression* of ion channel genes. Comparison of ionic currents recorded in isolated myocytes with currents recorded from cells expressing ion channel genes resulted in the identification of many of the ion channel molecules that underlie the cardiac action potential.

The development of the voltage clamp technique in the early 1950s and its application to multicellular preparations of cardiac muscle allowed identification of the major ionic currents that underlie the cardiac action potential. The whole-cell currents recorded by the technique were smooth waveforms derived from summation of the activity of thousands of ion channels, and many different patterns of events at the single-channel level, arising from more than one molecular species, can summate to produce identical whole-cell current waveforms. Patch clamping allows resolution of events at the single-channel level. In this technique, small patches of cell membrane (<1 μm^2) are isolated electrically and physically in the tip of a glass micropipette.[2] Single-channel events can then be resolved because only a few ion channel molecules are present in the patch. Current flowing across the patch typically jumps between well-defined values corresponding to sudden opening and closing of the ion-conducting pore (Fig. 8.1A). The whole-cell current is the sum of the currents through all the individual channels in the cell membrane; summation of the current flowing through a single channel during repeated stimuli reproduces the macroscopic whole-cell current (see Fig. 8.1). As channel opening and closing in response to a stimulus are stochastic phenomena, the regulation of ion flow, whether resulting from a change in membrane potential or from

BOX 8.1 PROPERTIES OF ION CHANNELS

Ion selectivity
Rectification (passing current more easily in one direction than the other)
Gating (mechanism for opening and closing the channel):
- activation (opening)
- inactivation (closing)

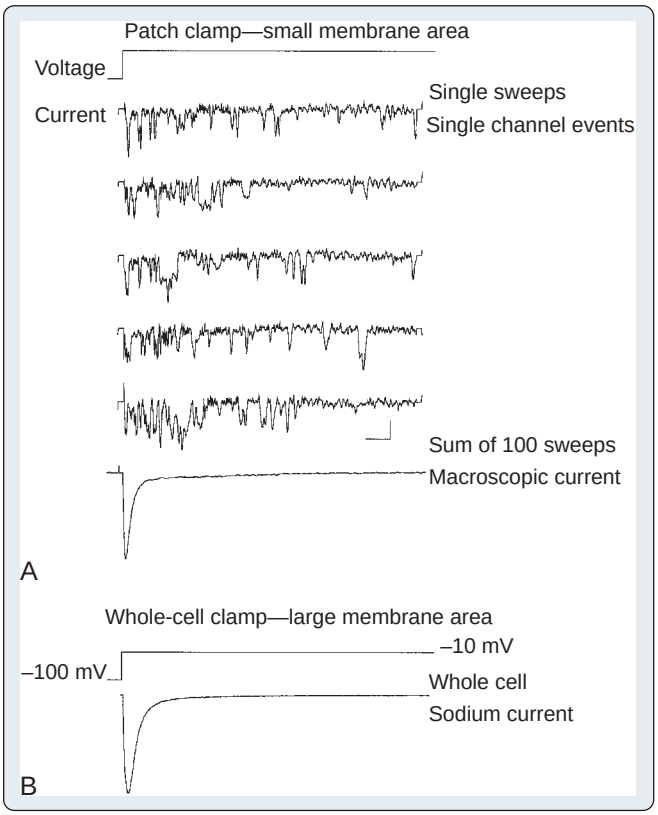


Fig. 8.1 Voltage clamp recordings from muscle sodium channels. (A) Patch-clamp recordings. Individual sodium channel openings are recorded as short-lived downward deflections. Openings are concentrated in the first part of the trace. The *top five traces* represent a single depolarizing clamp pulse. (B) The sum of 100 such pulses *(bottom trace)* recreates the whole-cell current.

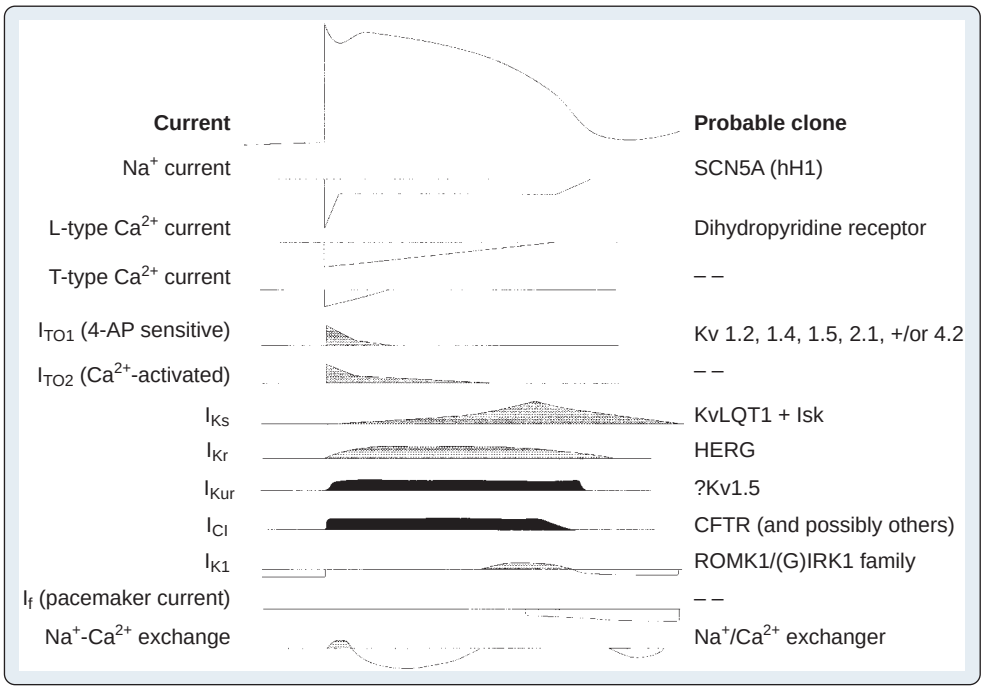


Fig. 8.2 Ionic currents underlying the cardiac action potential. Currents are listed on the *left*, and the ion channel genes encoding the currents are listed on the *right*. *4-AP*, 4-Aminopyridine; *Ca^{2+}*, calcium; *CFTR*, cystic fibrosis transmembrane regulator; I_{Cl}, chloride current; I_{K1}, I_{Kr}, I_{Ks}, I_{KUR}, potassium currents; I_{TO}, transient outward current; *Na^+*, sodium. *(From Roden DM, Lazzarra R, Rosen R, et al. Multiple mechanisms in the long QT syndrome: current knowledge, gaps and future directions.* Circulation. *1996;94:1996.)*

interaction with regulator molecules, is usually achieved by altering the *probability* that the channel will be open. Thus in Fig. 8.1, which shows records from human cardiac muscle Na^+ channels, the channels open *(activate)* a few milliseconds after depolarization because the probability that the channel will be open increases. Similarly, as the channels spontaneously close *(inactivate)*, the open probability decreases.

An ion current with distinct electrical and pharmacologic properties indicates the presence of a population of identical ion channel molecules. Application of molecular techniques has allowed the identification of many ion channel molecules and hence a better understanding of the currents that underlie the cardiac action potential. Tailoring of pharmacologic agents that interact with specific channel types to shape the action potential is an unrealized dream.

BOX 8.2 CARDIAC ACTION POTENTIAL

Phase 0 (rapid upstroke): primarily Na^+ channel opening
Phase 1 (early rapid repolarization): inactivation of Na^+ current, opening of K^+ channels
Phase 2 (plateau phase): balance between K^+ and Ca^{2+} currents
Phase 3 (final rapid repolarizations): activation of Ca^{2+} channels
Phase 4 (diastolic depolarization): balance between Na^+ and K^+ currents

Ca^{2+}, Calcium; *K^+*, potassium; *Na^+*, sodium.

Electrical Events Underlying the Cardiac Action Potential

Fig. 8.2 shows a diagram of a cardiac action potential with a summary of the ionic currents flowing during each phase. The probable molecular identity of the ion channels that underlie these currents is also given. This section examines the biophysical properties of these currents; subsequent sections focus on possible molecular mechanisms underlying the biophysical phenomena.

Resting Membrane Potential and the Role of the Inwardly Rectifying Potassium Current

The resting cardiac membrane potential is maintained close to the equilibrium potential for K^+ (E_K) by a background, inwardly rectifying, highly selective K^+ current (I_{K1}). Under physiologic conditions, the E_K is approximately −90 mV, and displacement of the membrane potential from this value should result in an inward or outward current through I_{K1}, thus returning the membrane potential toward E_K. However, although I_{K1} passes significant *inward* current at potentials negative to E_K, at positive potentials, the channels display inward rectification (ie, they pass inward current more easily than outward current), which limits outward current flow and reduces the tendency for I_{K1} to hyperpolarize the membrane. This process has obvious significance for an excitable cell; inward rectification[3] allows the initiation of action potentials and limits cellular K^+ loss during the action potential. I_{K1} is large in ventricular cells, smaller in atrial cells, and almost absent in nodal tissue.[4] For this reason, ventricular cells rest near E_K and have a high threshold for excitation, atrial cells have a more positive resting potential, and nodal cells have no defined resting potential.

Phase 0: Rapid Upstroke of the Cardiac Action Potential

The rapid upstroke of the cardiac action potential (phase 0) is caused by the flow of a large inward Na^+ current (I_{Na}) (Box 8.2).[5] I_{Na} is activated by depolarization of the sarcolemma to a threshold potential of −65 to −70 mV. I_{Na} activation, and hence the action potential, is an all-or-nothing response. Subthreshold depolarizations have only local effects on the membrane. After the threshold for activation of fast Na^+ channels is exceeded, Na^+ channels open (ie, I_{Na} activates), and Na^+ ions enter the cell down their electrochemical gradient. This action results in displacement of the membrane potential toward the equilibrium

potential for Na^+ ions, approximately +50 mV. I_{Na} activation is transient, lasting at most 1 to 2 ms because, simultaneous with activation, a second, slightly slower conformational change in the channel molecule occurs: inactivation, which closes the ion pore in the face of continued membrane depolarization (see Figs. 8.1A and B). The channel cannot open again until it has recovered from inactivation (ie, regained its resting conformation), a process that requires repolarization to the resting potential for a defined period. Thus the channels cycle through three states: (1) *resting* (and available for activation), (2) *open,* and (3) *inactivated*. While the channel is inactivated, it is absolutely refractory to repeated stimulation. Stimuli that occur during recovery from inactivation result in opening of fewer Na^+ channels (because not all have recovered), and the subsequent action potential has a reduced maximal rate of depolarization and slower conduction velocity. Na^+ channels do not need to open to become inactivated. If the resting membrane potential depolarizes for some time, inactivation will occur in some channels, and subsequent stimulation will result in an action potential of reduced amplitude and conduction velocity.

Phase 1: Early Rapid Repolarization

The early rapid repolarization phase of the action potential, which follows immediately after phase 0, results both from rapid inactivation of the majority of the Na^+ current and from activation of a transient outward current (I_{TO}), carried mainly by K^+ ions. On depolarization of the membrane, I_{TO} activates rapidly, over approximately 20 ms, before spontaneously inactivating. I_{TO} comprises two separate currents: the rapidly inactivating I_{TO1}, which is activated by depolarization and blocked by 4-aminopyridine; and the slowly inactivating I_{TO2}, which is activated by elevated intracellular Ca^{2+} (possibly explaining the observation that action potential duration tends to decrease with rapid heart rates and hypercalcemia)[6,7] (Fig. 8.3).

In addition to its effect on phase 1, I_{TO}, in combination with the delayed rectifier K^+ currents (I_{Kr} and I_{Ks}) and I_{K1}, also contributes to membrane repolarization. Arrhythmogenic prolongation of the action potential in myocardial cells recovered from patients with myocardial hypertrophy[8] and congestive cardiomyopathy,[6] as well as from the border zone of myocardial infarction (MI) in animals,[9] appears to result from depression of I_{TO}.

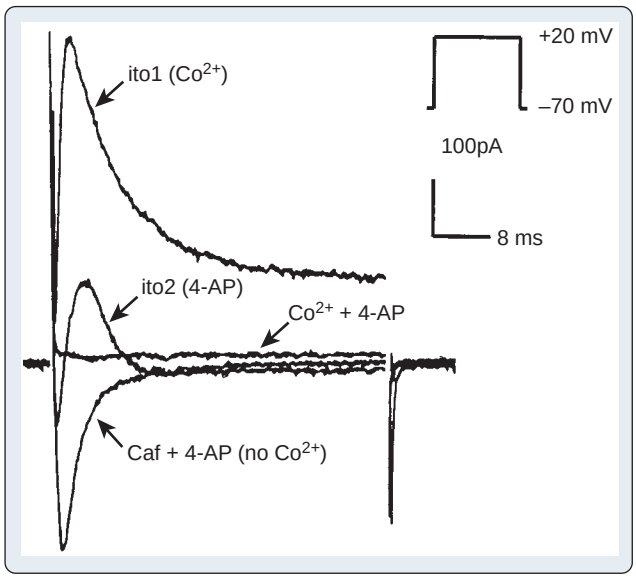


Fig. 8.3 Voltage clamp recordings from an atrial myocyte showing pharmacologic separation of transient outward current 1 ($I_{TO1;}$ *ito1*) and I_{TO2} *(ito2).* In the presence of cobalt ions *(Co^{2+}),* only I_{TO1} is seen. When Co^{2+} is omitted and 4-aminopyridine *(4-AP)* is added, I_{TO2} is revealed. Caffeine *(Caf)* eliminates I_{TO2}, thus leaving the underlying inward calcium current. In the presence of both 4-AP and Co^{2+}, all outward currents are inhibited. *(From Wang Z, Fermini B, Nattel S. Delayed rectifier outward current and repolarization in human atrial myocytes.* Circ Res. *1993;73:276.)*

Phases 2 and 3: Plateau Phase and Final Rapid Repolarization

The action potential plateau and final rapid repolarization are mediated by a balance between the slow inward current and outward, predominantly K^+ current. During the plateau phase, membrane conductance to all ions falls, and very little current flows. K^+ conductance is low because of inward rectification of I_{K1} (ie, inward current passes more easily than outward current), so little outward current flows despite the large outward electrochemical gradient for K^+ ions and the delayed onset of the outwardly rectifying K^+ currents (I_{Ks}, I_{Kr}, and I_{Kur}). The resulting small outward current is balanced by inward current, predominantly through L-type Ca^{2+} channels ($I_{Ca\text{-}L}$), but also through a slowly inactivating population of Na^+ channels and a small inward flux of chloride (Cl^-) ions, possibly carried by the cardiac variant of the adenosine triphosphate (ATP)–dependent channel (abnormalities of which underlie cystic fibrosis).[10,11] Phase 3, regenerative rapid repolarization, results from time-dependent inactivation of L-type Ca^{2+} current and increasing outward current through delayed rectifier K^+ channels. The net membrane current becomes outward, and the cell repolarizes.

Slow Inward Calcium Current

The slow inward current ($I_{Ca\text{-}L}$) is activated by depolarization of the cell to potentials less negative than −40 to −50 mV. In ventricular and atrial myocytes and in Purkinje fibers, $I_{Ca\text{-}L}$ is activated by the regenerative depolarization caused by I_{Na} during phase 0 of the action potential. $I_{Ca\text{-}L}$ does not contribute significantly to phase 0 because, in comparison with I_{Na}, it activates much more slowly (over approximately 10 ms) and is smaller in amplitude. $I_{Ca\text{-}L}$ also inactivates slowly and therefore contributes the major inward current during the plateau of the action potential. $I_{Ca\text{-}L}$ flows through L-type (long-lasting) Ca^{2+} channels, which are sensitive to block by dihydropyridines (eg, nifedipine), and activation of contraction is related to the magnitude of the resulting Ca^{2+} influx.[12] Gating of $I_{Ca\text{-}L}$ is generally similar to I_{Na} in that channel opening and closing depend on membrane potential and time. Ca^{2+} channels are also dynamically regulated by the autonomic nervous system.[13] β-Agonists activate $I_{Ca\text{-}L}$ (and hence increase myocardial contractility) indirectly by activating adenylyl cyclase through a guanosine triphosphate (GTP)–binding protein, G_s (Fig. 8.4). The resulting increase in intracellular cyclic adenosine monophosphate (cAMP) activates protein kinase A (PKA), which phosphorylates the Ca^{2+} channel. Phosphorylated channels open in response to membrane depolarization; nonphosphorylated channels do not, so the effect of β-adrenergic stimulation is to increase the number of functional channels. The electrophysiologic result is illustrated in Fig. 8.5, which shows enhancement of the slow inward current by increase of AMP level in single-channel Ca^{2+} channels and intact cells. β-Adrenergic effects on $I_{Ca\text{-}L}$ are antagonized by ACh, which, in myocardial cells, activates M_2 muscarinic receptors and inhibits adenylyl cyclase through activation of the GTP-binding protein G_i.

In the relatively depolarized pacemaker cells, which lack I_{K1}, I_{Na} is inactivated, and the slow inward current is solely responsible for the upstroke of the action potential. $I_{Ca\text{-}L}$ also can generate slowly propagated action potentials in diseased or damaged myocardial cells in which I_{Na} has been inactivated by depolarization. These *slow responses,* which may occur in the border zone of MIs, are important because they may cause the slow conduction that can lead to reentrant arrhythmias.

Delayed Rectifier Potassium Currents

Delayed rectifier K^+ channels are present in all cardiac myocytes. They open slowly (over 200 to 300 ms) after depolarization of the membrane to the plateau level (−10 mV and greater), and produce a K^+-selective outward current, I_K. I_K does not inactivate on prolonged depolarization (unlike I_{Na} and $I_{Ca\text{-}L}$), and the channels close on repolarization of the membrane. Unlike I_{K1}, I_K displays outward rectification (ie, it passes

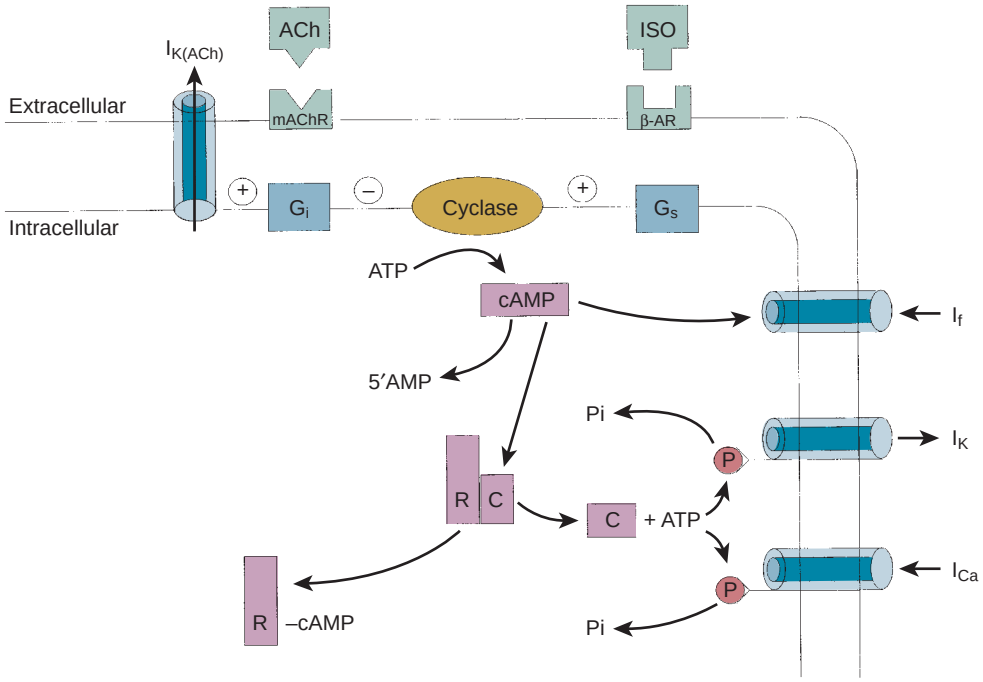


Fig. 8.4 Autonomic regulation of ion currents. *ACh,* Acetylcholine; *5′AMP,* adenosine 5′- monophosphate; *β-AR,* β-adrenergic receptor; *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophosphate; *Cyclase,* adenylyl cyclase; G_i and G_s, guanosine triphosphate–binding proteins; I_{Ca}, calcium current; I_f, pacemaker current; I_K and $I_{K(ACh)}$, potassium currents; *ISO,* isoproterenol; *mAChR,* M_2 muscarinic receptor; *P,* phosphate; *Pi,* pyrophosphate; *R* and *C,* regulatory and catalytic subunits, respectively, of protein kinase A.

outward current more easily than inward current). This is expected behavior for a K^+-selective channel because both the concentration and electrical gradients for K^+ are outward. Thus for any depolarizing displacement of membrane potential from E_K, the driving force is larger in an outward direction. Similar to $I_{Ca\text{-}L}$, I_K is under autonomic control (see Fig. 8.4). β-Adrenergic stimulation enhances I_K by a mechanism similar to that of the enhancement of $I_{Ca\text{-}L}$, thus ensuring repolarization of the cell in the presence of increased inward Ca^{2+} current.[14]

Three components of I_K, carried by different channel molecules, can be distinguished. A rapidly activating component, I_{Kr}, is blocked by the compound E4031 (a class III antiarrhythmic agent), which leaves a slower activating component, I_{Ks}, unaffected.[15] This process is illustrated in Fig. 8.6, which also emphasizes the importance of I_K in the regulation of repolarization and hence of action potential duration. A third component, the ultrarapidly activated delayed rectifier, I_{Kur}, can be distinguished in atrial (but not ventricular) myocytes.[16] This additional repolarizing current partly explains the enhancement of repolarization in atrial myocardium when compared with ventricle and Purkinje fibers.

Repolarization in Different Cardiac Tissue Types

Phase 3 repolarization in atrium and pacemaker tissues, but not in ventricular myocardium, is also enhanced by the presence of a large outward repolarizing K^+ current ($I_{K[ACh]}$).[17,18] This potential independent current is activated indirectly by stimulation of muscarinic (M_2-type) receptors by ACh or purinergic (A-type) receptors by adenosine.[19] This channel is potential independent and is activated by binding of an activated, membrane-bound GTP-binding protein (G_i), as discussed later.[20]

Action potential duration varies among cells in normal ventricle.[21] A gradient in action potential duration exists across the myocardium (from epicardium to endocardium), and specialized midmyocardial cells (M cells) have been identified that exhibit prolongation of action potential duration at slow stimulation rates, possibly as a result of a decrease in I_{Ks}.

Phase 4: Diastolic Depolarization and Pacemaker Current

Phase 4 diastolic depolarization, or normal automaticity, is a normal feature of cardiac cells in the sinus and atrioventricular nodes, but subsidiary pacemaker activity is also observed in the His-Purkinje system and in some specialized atrial and ventricular myocardial cells (see Chapter 4). Pacemaker discharge from the sinus node normally predominates because the rate of diastolic depolarization in the sinoatrial node is faster than in other pacemaker tissues. Pacemaker activity results from a slow net gain of positive charge, which depolarizes the cell from its maximal diastolic potential to threshold.

Pacemaker cells in the sinus node are relatively depolarized, with a maximal diastolic potential of −60 to −70 mV and a threshold potential of −40 mV. Rapid regenerative depolarization (phase 0) depends on opening of T-type and then L-type Ca^{2+} channels. Repolarization is dependent on activation of delayed rectifier K^+ channels, and the maximum diastolic potential is approximately −80 mV. Pacemaker channels are activated by hyperpolarization to this potential and produce a slow inward Na^+ current, I_f. This current flows against slowly inactivating delayed rectifier K^+ currents and results in diastolic depolarization.[22] Because the current is nonselective among cations, its reversal potential lies between E_K and E_{Na}, at approximately −10 mV, and activation of I_f tends to depolarize the cell toward this value. Similar to $I_{Ca\text{-}L}$, I_f is under autonomic control (see Fig. 8.4) through GTP-dependent binding proteins G_s and G_i, which regulate cAMP production by adenylyl cyclase.[23,24] β-Adrenergic stimulation shifts the voltage dependence of activation of I_f to more depolarized potentials, so for any hyperpolarizing stimulus, more I_f is activated and diastolic depolarization is enhanced. ACh has the opposite effect (Fig. 8.7).

Molecular Biology of Ion Channels

The preceding sections focus on the electrical events that underlie cardiac electrical excitability and on the identification of cardiac ionic currents on the basis of their biophysical properties. This section

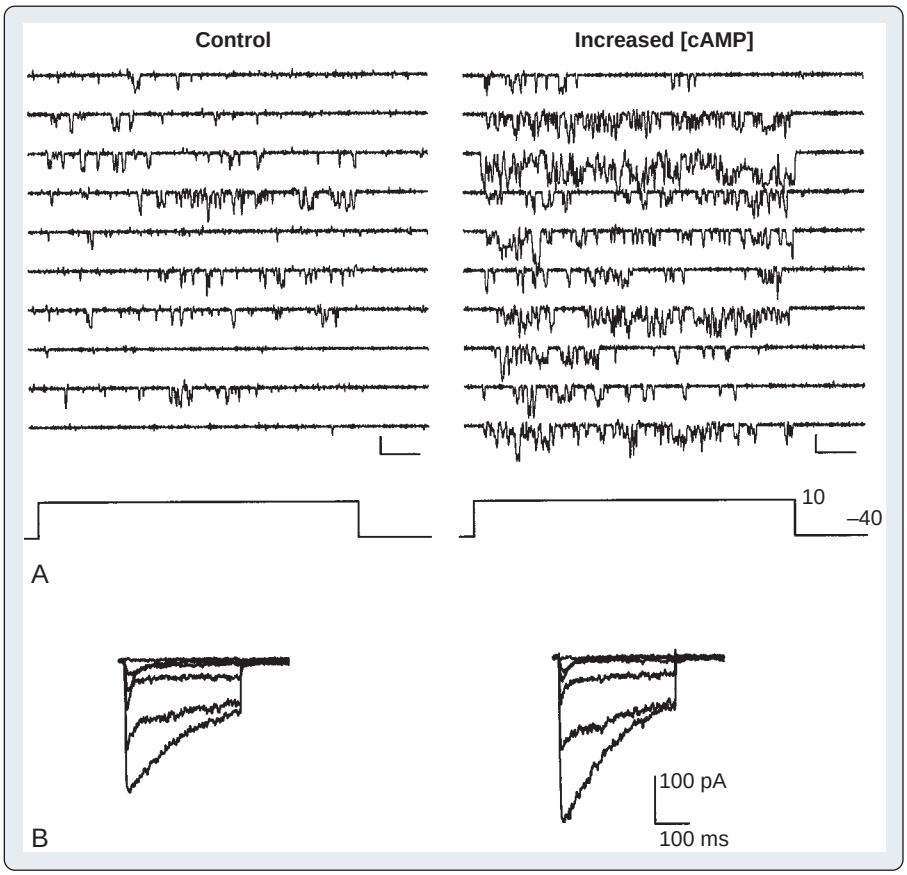


Fig. 8.5 Effects of elevated cyclic adenosine monophosphate *(cAMP)* on cardiac calcium channels. (A) Single-channel recordings. (B) Whole-cell currents. *Left panels* are control recordings; *right panels* show the effect of elevation of intracellular cAMP (in this case, induced by exposure to parathyroid hormone). Note the increased probability of channel opening and resulting increase in whole-cell current in the presence of increased cAMP. *(Modified from Rampe D, Lacerda AE, Dage RC, Brown AM. Parathyroid hormone: an endogenous modulator of cardiac calcium channels.* Am J Physiol. *1991;261:H1945.)*

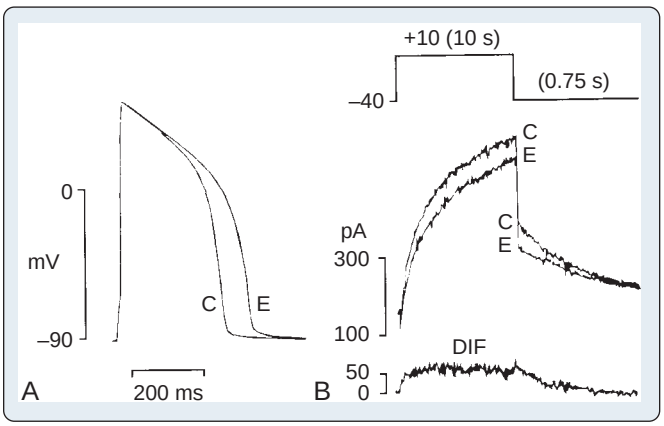


Fig. 8.6 (A) Effect on action potential duration of blockade of inward rapidly activating potassium current *(I_{Kr})* by E4031 in isolated guinea pig ventricular myocytes. After application of E4031, outward repolarizing currents are inhibited and action potential duration is increased. (B) Voltage clamp records showing separation of I_{Kr} and inward slowly activating potassium current *(I_{Ks})* by E4031. The control delayed rectifier K^+ current *(C)* is partially inhibited by E4031 *(E)*, and the difference between the two currents *(DIF)* represents I_{Ks}. *(From Sanguinetti MC, Jurkiewicz NK. Two components of cardiac delayed rectifier K^+ current: differential sensitivity to block by class III antiarrhythmic agents.* J Gen Physiol. *1990;96:195. Reproduced from* The Journal of General Physiology *by copyright permission of The Rockefeller University Press.)*

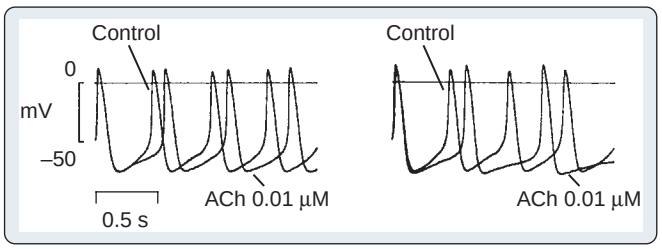


Fig. 8.7 Effect of acetylcholine *(ACh)* on spontaneous pacemaker activity in isolated sinoatrial node cells. Pacemaker activity in control solution is compared with activity in increasing doses of ACh. Note the slowing of diastolic depolarization and resultant slowing of heart rate. *(From DiFrancesco D. Current I and the neuronal modulation of heart rate. In: Zipes DP, Jaliffe J, eds.* Cardiac Electrophysiology From Cell to Bedside. *Philadelphia: Saunders; 1990:28.)*

reviews the molecular structures behind these electrical phenomena. The first step in understanding the molecular physiology of cardiac electrical excitability is to identify the ion channel proteins responsible for the ionic currents. Fig. 8.2 gives the current classification of the ion channel responsible for each of the cardiac ionic currents. Voltage-gated Na^+ and L-type Ca^{2+} channels have firm molecular candidates. Similarly, channel molecules with properties similar to delayed rectifier K^+ channels, the 4-aminopyridine–sensitive component of I_{TO}, the inward rectifier I_{K1}, the ligand-gated K^+ channel $I_{K(ACh)}$, and the pacemaker current I_f have been cloned. Fig. 8.8 shows diagrams of

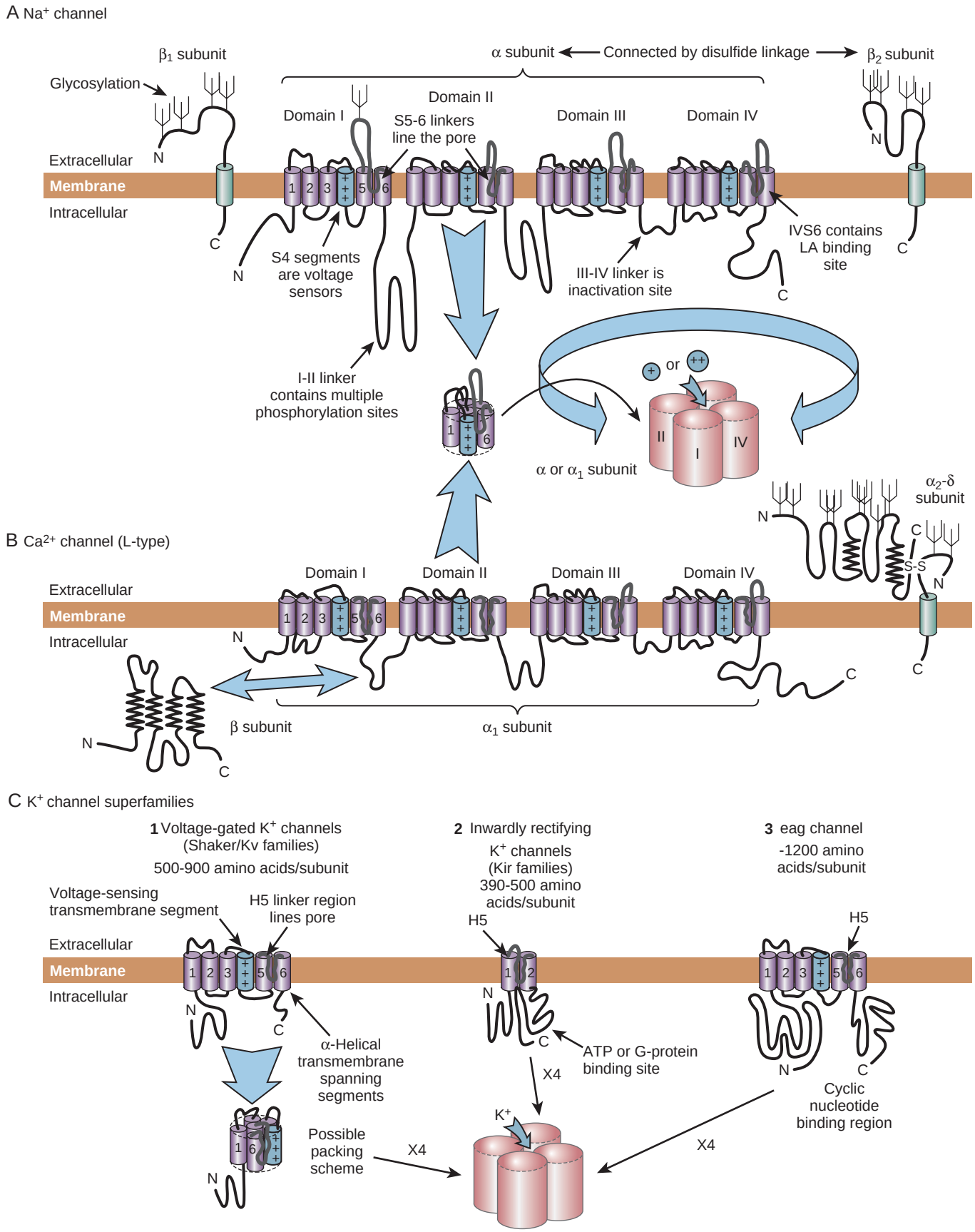


Fig. 8.8 Diagrams of ion channel molecular structure. (A) Sodium *(Na^+)* channel. (B) Calcium *(Ca^{2+})* channel. (C) Potassium *(K^+)* channels. *ATP,* Adenosine triphosphate; *LA,* local anesthetic.

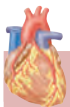
the predicted membrane topology of some of these channels. Voltage-gated Na^+, Ca^{2+}, and K^+ channels exist as conglomerates of molecules, consisting of a large α subunit and several accessory subunits (labeled β, γ, and δ in Fig. 8.8). The α subunit alone is usually sufficient to induce channel activity in biologic membranes, but its activity is modulated by the presence of the accessory subunits. The diagrams in Fig. 8.8 were deduced from hydrophobicity analysis of the primary structure of the major channel polypeptides. Regions of the polypeptides predicted to span the membrane are those that contain a high concentration of hydrophobic amino acids, whereas peptides linking these transmembrane sections are hydrophilic. Similarities among the various channels strongly suggest a common evolutionary ancestry. Na^+ and Ca^{2+} channel α subunits (see Figs. 8.8A and B) are strikingly similar, each consisting of four homologous transmembrane domains (labeled I to IV), linked by cytoplasmic peptides. Each homologous domain contains six linked membrane-spanning segments (labeled S1 to S6). These large polypeptides, containing more than 2000 amino acids, form a tetrameric structure and generate Na^+ or Ca^{2+} channel activity in biologic membranes. Voltage-gated K^+ channel α subunits, in contrast, are much smaller (see Fig. 8.8C) and consist of a single transmembrane domain with six membrane-spanning segments, an arrangement similar to one of the individual domains of Na^+ and Ca^{2+} channels. Four molecules are noncovalently linked in the membrane to produce a tetrameric structure, similar to an Na^+ or Ca^{2+} channel, to produce K^+ channel activity. The structure of the inwardly rectifying K^+ channel molecules, I_{K1} and $I_{K(ACh)}$, is dissimilar to that of other K^+ channels (see Fig. 8.8C). The molecules are much less complex, having only two membrane-spanning segments, although these segments share considerable homology with the S5 and S6 segments of the classic voltage-gated K^+ channel.

Voltage-gated ion channel activity requires that the channel molecule should sense and respond to changes in membrane potential, form an ion-selective membrane pore, and (in some cases) inactivate despite continuing depolarization. The molecular mechanisms for these phenomena are examined in separate sections later.

Molecular Mechanisms

Voltage Sensor

Channel proteins respond to changes in electrical potential across the cell membrane by conformational changes *(gating)* that result from electrostatic interactions between charged portions of the molecule and the membrane electric field (Box 8.3). Gating of the channel is associated with a measurable flow of electrical charge through the membrane lipid bilayer (called *gating current*), as a zone of the molecule rich in electrical charge moves within the membrane.[25] This charge movement is linked to opening of the channel pore. The voltage sensor of voltage-dependent ion channels resides in the mobile S4 membrane-spanning segments, α-helical structures unusually rich in positively charged amino acids.[26] At rest, each of the positive charges in the S4 segment is balanced by fixed negative charges in other segments of the molecule. The resting membrane potential (negative inside) forces the (mobile) positive charges inward and the fixed negative charges outward. This dynamic equilibrium holds the channel pore closed. On depolarization, the force pulling the positive charge inward is relieved; positive charges (the S4 segments) are repelled outward and assume new partners with the fixed negative membrane charges. This charge movement comprises the *gating current*. If the depolarizing stimulus is short, repolarization of the membrane is followed by a gating current of equal and opposite magnitude as the S4 segment relaxes to its original position. If the depolarizing stimulus is prolonged, however, the movement of the S4 segments induces a conformational change in the channel molecule, which prohibits easy return to baseline. This conformational change in the channel molecule is manifested as activation (or channel opening), which is closely coupled to channel closing (or inactivation in channels that inactivate; see later). Thus small changes in the membrane electric field cause conformational changes in the channel molecule that result in opening (and closing) of the channel pore. An S4 segment rich in positive charge is a remarkably consistent feature of voltage-gated ion channels from numerous different species and with various ion selectivities. The dependence of channel activation on membrane potential is proportional to the density of positive charge in the S4 segment.



BOX 8.3 MOLECULAR MECHANISMS OF ION CHANNELS

Voltage sensor
Gating mechanism (activation and inactivation)
Ion pore
Selectivity filter

Ion Channel Pore and Selectivity Filter

The presence of four homologous domains in voltage-gated Na^+ and Ca^{2+} channels suggests that basic ion channel architecture consists of a transmembrane pore surrounded by the four homologous domains arranged symmetrically (see Fig. 8.8). The membrane-spanning segments each form an α helix, so the walls of the pore are derived from α-helical segments from each of the four domains. A pore formed from four such α helices would have limiting dimensions of 3 by 5 Angstrom units, similar to the size inferred for the Na^+ channel pore by measurement of the permeability of cations of different sizes.[27,28]

The selectivity filter is formed by the S5 and S6 membrane-spanning segments of each domain together with their peptide linker.[29] As emphasized in Fig. 8.8, unlike the hydrophilic extracellular linkers between other membrane-spanning segments, the S5/S6 linker is sufficiently hydrophobic to place it (at least partially) within the membrane lipid bilayer. The channel pore is lined both by the S5/S6 linker and the S5 and S6 membrane-spanning segments. Point mutations in the S5/S6 linker have dramatic effects on channel ion selectivity and reduce channel conductance to its primary ion. Extensive site-directed mutagenesis experiments of the S5/S6 linkers from various channels suggest that these linkers form a funnel that allows the passage of a specific ion into the pore. In Na^+ channels, selectivity is imposed by two rings of negatively charged amino acids at the outer mouth of the funnel, which collect Na^+ ions for transmission into the cell.[27]

Channel Inactivation

Inactivation gating is the process by which ion channels close in the presence of continuing depolarization. Inactivation is characteristic of voltage-gated Na^+ and Ca^{2+} channels, as well as the K^+ channels underlying I_{TO}. Inactivation begins after activation gating as a second, slower conformational change in the molecule that halts the ion flux through the channel. Inactivation gating is thus closely coupled to activation gating, and ionic current flows only while both the activation and inactivation gates are open simultaneously. In Na^+ channels, the inactivation gate is formed by the intracellular peptide linker between homologous domains III and IV (Fig. 8.9A).[30] This peptide is postulated to act as a hinged lid, which moves upward to plug the ion pore (and thus halt current flow) shortly after membrane depolarization.[26] For the channel to recover from inactivation (ie, to be ready to open in response to a new depolarizing stimulus), the III/IV linker peptide must resume its resting position, a process that requires hyperpolarization of the membrane to the resting potential for a finite period. Site-directed mutagenesis of the III/IV linker peptide has revealed a trio of hydrophobic amino acid residues (isoleucine [I], phenylalanine [F], and methionine [M]), near the domain III end of the peptide, that are crucial for normal channel inactivation. Replacement of just one of these residues (the phenylalanine) almost completely removes inactivation. These residues are postulated to latch onto a receptor in the channel pore to close the channel.

The molecular basis of inactivation in K^+ channels is different from that in Na^+ channels. Because the four domains of K^+ channels are

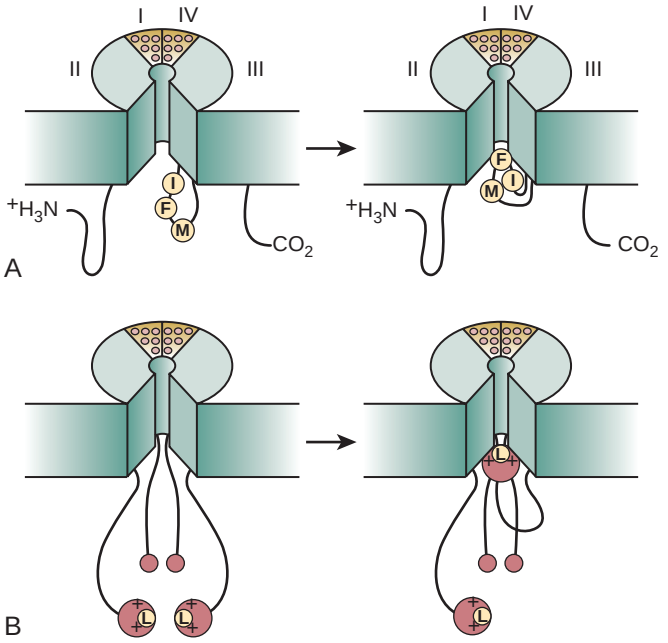


Fig. 8.9 Mechanism of inactivation of sodium *(Na^+)* and potassium *(K^+)* channels. (A) Hinged-lid mechanism of Na^+ channel inactivation. (B) Ball-and-chain mechanism of K^+ channel inactivation. *CO_2*, Carboxy terminus; *F*, phenylalanine; *H_3N*, amino terminus; *I*, isoleucine; *L*, leucine; *M*, methionine. *(From Catterall WA. Structure and function of voltage-gated ion channels.* Annu Rev Biochem *1995;64:493, by permission of the* Annual Review of Biochemistry, *Volume 64, ©1995, by Annual Reviews, Inc.)*

formed by noncovalently linked molecules, no interdomain linkers exist to plug the channel pore. In K^+ channels, a picture of an N-terminal ball-and-chain mechanism has emerged (see Fig. 8.9B).[31] The terminal 20 or so amino acids are very hydrophobic and are postulated to swing up and attach to the open pore. The next few amino acids contain several positively charged residues that draw the whole N-terminal end up to the membrane. These two domains act as a ball. The remaining amino acids, up to the beginning of the transmembrane S1 segment, act as a chain. If the chain is made longer, inactivation is slower, and vice versa.

Clinical Correlates

Ion Channels and Antiarrhythmic Drugs

Drug therapy of cardiac arrhythmias would ideally be targeted at an individual ionic current, thereby tailoring the cardiac action potential in such a way that abnormal excitability is reduced but normal rhythmicity is unaffected. This goal remains unrealized. The prototype antiarrhythmic agents (eg, disopyramide and quinidine) have diverse effects on cardiac excitability and, similar to agents introduced more recently, frequently exhibit significant proarrhythmic activity with potentially fatal consequences. In the Cardiac Arrhythmia Suppression Trial (CAST), the mortality rate among asymptomatic patients after MI was approximately doubled by treatment with the potent Na^+ channel-blocking agents encainide and flecainide, an effect likely attributable to slowing of conduction velocity with a consequent increase in fatal reentrant arrhythmias.[32] The results of CAST prompted efforts to approach antiarrhythmic drug therapy by prolonging action potential duration (eg, dofetilide), a strategy with some support from animal studies, but one that also may cause proarrhythmia through induction of polymorphic ventricular tachycardia (the acquired long QT syndrome [LQTS]).[33] Drugs that prolong action potential duration all block I_{Kr}, and it is not clear that this therapeutic goal will result in arrhythmia control without induction of clinically significant proarrhythmia. The only drugs currently available that definitely prolong life by reducing fatal arrhythmias are β-blockers (eg, the First International Study of Infarct Survival [ISIS-1], 1997), and these agents have no channel-blocking effects.

TABLE 8.1 Major Long QT Syndromes and Genes

Type	*Gene*	*Current*	*Chromosome*	*Comment*
LQT1	*KCNQ1 (KvLQT1)*	I_{Ks}	11	Induced by stress and exercise
LQT2	*KCNH2 (hERG)*	I_{Kr}	7	Induced by noise, emotional stress
LQT3	*SCN5A*	I_{Na}	3	Sleep, β-blockers less effective

I_{Kr}, Inward rapidly activating potassium current; *I_{Ks}*, inward slowly activating potassium current; *I_{Na}*, inward sodium current; LQT1 to 3, long QT syndrome 1 to 3.

Ion Channels in Disease

Elucidation of the molecular mechanisms of the cardiac action potential is beginning to have a direct impact on patient management. This is most obvious in patients with inherited genetic abnormalities of ion channels that lead to cardiac sudden death. Two groups of diseases illustrate this point: LQTS and Brugada syndrome. An understanding of the molecular mechanism of cardiac electrical excitability is also starting to lead to the emergence of gene therapies and stem cell therapies that may in the future allow manipulation of cardiac rhythm and function.

Long QT Syndromes

LQTSs are estimated to occur in as many as 1 in 2000 people.[34] These syndromes are caused by inherited abnormalities that prolong the cardiac action potential and can result in early afterdepolarizations (ie, oscillations in the action potential during the plateau phase) that can trigger extrasystoles and death from polymorphic ventricular tachycardia (torsades de pointes).[35] To date, 15 LQTS subtypes have been identified and classified on the basis of the affected gene.[34,35] Three genes account for approximately 75% of diagnosed cases of LQTS (Table 8.1).[34,35] LQTS results from abnormally prolonged cardiac repolarization caused by either enhancement of inward depolarizing current or reduction of outward current. LQT3 is mediated by a gain-of-function mutation of the cardiac Na^+ channel that results in slow or incomplete channel inactivation, most commonly from a deletion of three amino acids from the inactivation gate.[35] LQT1 and LQT2 result from loss-of-function mutations of the slowly activating and rapidly activating delayed rectifier K channels, I_{Ks} and I_{Kr}, respectively. LQT5 and LQT6 result in reductions of I_{Kr} and I_{Ks} function through mutations in channel accessory subunits. Loss of repolarizing current prolongs the QT interval, and this leads to the syndrome. LQT4 is unique in that it results from a mutation in ankyrin B, an adapter protein that binds to the Na^+ pump and Na^+/Ca^{2+} exchanger. The resulting effects on cellular Ca^{2+} homeostasis cause ventricular arrhythmias.[36] Identification of the molecular substrate for LQTS allows detection of the disease in asymptomatic carriers and helps determine treatment. β-Blockers (preferably those with longer half-life such as propranolol or nadolol) are considered first-line therapeutic agents for LQT1 and LQT2, whereas Na^+ channel blockers are considered for LQT3.[35] Stem cell and gene therapy research is being performed, and investigators are reporting inroads into potential translation to clinical treatment of patients with inherited LQTS.[37–40]

Brugada Syndrome

The Brugada syndrome comprises a group of ion channel abnormalities that affect cardiac repolarization and can result in cardiac sudden death from polymorphic ventricular tachycardia and ventricular fibrillation. Brugada syndrome is characterized by incomplete right bundle branch block and persistent ST-segment elevation in the anterior precordial leads of the electrocardiogram (ECG).[41] Although two-thirds of patients with Brugada syndrome have no known genetic cause of

the disorder, variants within 19 different genetic loci have been associated with the findings in Brugada syndrome on the ECG. These genes involve cardiac Na^+, Ca^{2+} and K^+ channels.[35,42] The genetic variant most frequently identified in patients with Brugada syndrome is within the *SCN5A* gene on chromosome 3. This channel mutation reduces depolarizing Na^+ current. This results in loss of the action potential dome, an effect that is most marked in the right ventricular epicardium where the transient outward current I_{TO1} is strongly expressed (hence the ST-segment elevation in the anterior chest leads on the ECG). Early repolarization of the epicardial action potential results in a transmural repolarization gradient, and this can lead to reentry and sudden cardiac death.[43] Work remains to be done to elucidate the full spectrum of molecular mechanisms contributing to this condition.

Controlling Cardiac Functioning: Receptors

Receptors are membrane proteins that transduce signals from the outside to the inside of the cell. When a *ligand*—a hormone carried in blood, a neurotransmitter released from a nerve ending, or a local messenger released from neighboring cells—binds to the receptor, it induces a conformational change in the receptor molecule. This process changes the configuration of the intracellular segment of the receptor and results in activation of intracellular systems, with various potential effects ranging from enhanced phosphorylation and changes in intracellular (second) messenger concentrations to activation of ion channels.

Receptor Classes

Receptors are grouped in several broad classes, and the most important are the *protein tyrosine kinase receptors* and the *G-protein–coupled receptors* (GPCRs). The protein tyrosine kinase receptors are large molecular complexes that incorporate phosphorylating enzyme activity in the intracellular segment. Ligand binding induces activation of this enzyme activity. Because phosphorylation is one of the major mechanisms of cellular regulation (see, for example, the phosphorylation of the Ca^{2+} channel described earlier), such receptors can have numerous cellular effects (Box 8.4). GPCRs are much smaller than protein tyrosine kinase receptors. Ligand binding results in activation of an associated protein *(G protein)* that subsequently influences cellular processes. The receptors discussed in this section all belong to the GPCR superfamily, and the properties of this class are discussed in some detail.

The number of GPCRs is large. For more than 100 receptors, function has been defined. In addition, the olfactory epithelium expresses hundreds of GPCRs, which are thought to mediate the sense of smell, and another large group, with unknown function, is expressed on sperm cells. Taken together, the superfamily has more than 1000 members.

All these receptors have similar molecular characteristics. They are generally several hundred to 1000 amino acids in length and contain 7 stretches of 20 to 25 hydrophobic amino acids. These hydrophobic domains are thought to form α helices and traverse the membrane, thus anchoring the receptor to the cell (Fig. 8.10). For this reason, the family is often referred to as the seven transmembrane family. Although crystallographic data are not yet available for the clinically relevant GPCRs, the seven-transmembrane domains are believed to be arranged in a funnel-like structure, the inside of which forms the ligand-binding domain. The intracellular domains, particularly the third intracellular loop and the C terminus, bind to the G protein.

The heart and blood vessels express various GPCRs. The β-adrenergic and muscarinic ACh receptors are those most important for regulation of cardiac functioning, but several others play relevant modulatory roles. These include the α-adrenergic, adenosine A_1, ATP, histamine H_2, vasoactive intestinal peptide (VIP), and angiotensin II receptors.

G Proteins

G proteins (GTP-binding proteins) have two families: the small (cytoplasmic) G proteins and the heterotrimeric (membrane) G proteins. Common to both groups is their mechanism of function. In their resting state, they bind a molecule of guanosine diphosphate (GDP). When activated by a GPCR (in the case of heterotrimeric G proteins) or by an intracellular messenger (in the case of cytoplasmic G proteins), this GDP is exchanged for a GTP molecule. The activated G protein can now perform functions within the cell, as discussed later, until it is inactivated when an intrinsic enzyme activity hydrolyzes the GTP to a GDP. The critical point about this hydrolytic activity is that it is (molecularly speaking) very slow, on the order of seconds. As a result, brief activation of a receptor (on the order of milliseconds) can lead to more prolonged activation of the intracellular signaling machinery.

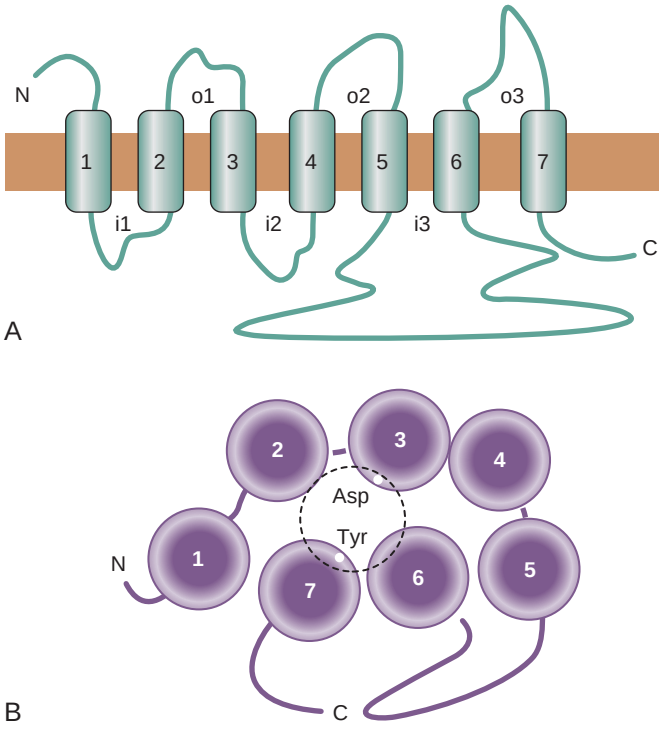
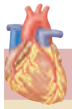


Fig. 8.10 Model of G-protein–coupled receptor. (A) Linear model. Seven hydrophobic stretches of approximately 20 amino acids are present, presumably forming α-helices that pass through the cell membrane, thus forming seven transmembrane domains (*t1* to *t7*). Extracellularly, the amino terminus *(N)* and three outside loops (*o1* through *o3*) are found; intracellularly there are similarly three loops (*i1* through *i3*) and the carboxy terminus *(C)*. (B) *Top-down view.* Although in (A), the molecule is pictured as a linear complex, the transmembrane domains are thought to be in close proximity, forming an ellipse with a central ligand-binding cavity *(dashed circle)*. Asp and Tyr refer to two amino acids important for ligand interaction. G-protein binding takes place at the i3 loop and the carboxy terminus.

BOX 8.4 G-PROTEIN–COUPLED RECEPTORS

β-Adrenergic receptors
α-Adrenergic receptors
Muscarinic acetylcholine receptors
Adenosine A_1 receptors
Adenosine triphosphate receptors
Histamine H_2 receptors
Vasoactive intestinal peptide receptors
Angiotensin II receptors



BOX 8.5 G-PROTEIN CLASSES

G_s: activates adenylate cyclase
G_i: inhibits adenylate cyclase
G_q: activates phospholipase C
G_o: subtype of G_i, found mostly in brain; activates phospholipase C
G_k: subtype of G_i, linked to K^+ channels

GPCRs bind to *heterotrimeric* G proteins, so called because they consist of three subunits: α, β, and γ. Of these, the β and γ subunits are so tightly associated that, for practical purposes, they can be viewed as a single unit, often termed the βγ unit. The α subunit contains both the GDP-GTP binding domain and the hydrolytic activity, and it was classically thought to be the "business end" of the molecule, with the βγ unit roaming freely and inactively, serving as an anchor and a sink of free α units. This turns out not to be the case; the βγ subunit has activating functions as well, as discussed later in relation to the muscarinic K^+ channel.

Several classes of heterotrimeric G proteins exist, indicated by subscripts (Box 8.5). The classic types are G_s and G_i, which stimulate and inhibit, respectively, the enzyme adenylate cyclase, thereby leading to changes in cytoplasmic cAMP concentrations. G_q proteins (and G_o in brain) activate phospholipase C (PLC) and thereby induce the generation of inositol-1,4,5-triphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol bisphosphate (PIP_2). IP_3 acts on its own receptor-channel complex on intracellular Ca^{2+} storage sites and induces release of Ca^{2+} from these sites, thus increasing intracellular Ca^{2+} concentrations. DAG activates protein kinase C (PKC), an action leading to phosphorylation of various targets (including the receptors that initiated the cascade). Cloning efforts have shown each of these classes of G proteins to consist of several members, but their functional differences are incompletely defined.

Adrenergic Receptors and Signaling Pathways

Adrenergic Receptors

Main control over cardiac contractility is provided by the β-adrenergic signaling pathways, which can be activated by circulating catecholamines (derived from the adrenal glands) or those released locally from adrenergic nerve endings on the myocardium.

The two main subtypes of β-adrenergic receptors are the β_1 and β_2 subclasses. A β_3 subtype also exists, but its role in the cardiovascular system is unclear[44]; its most important role is in fat cells. Both β_1- and β_2-receptors are present in the heart, and both contribute to the increased contractility induced by catecholamine stimulation (this is different from the situation in vascular muscle, where β_2-adrenergic stimulation induces relaxation). Under normal conditions, the relative ratio of β_1- to β_2-receptors in heart is approximately 70:30, but as discussed later, this ratio can be changed dramatically by cardiac disease.

The β-adrenergic receptors are closely related structurally as well as functionally. Both the β_1- and β_2-adrenergic receptors couple to G_s proteins and, as described earlier, thereby activate adenylate cyclase, thus leading to increased intracellular levels of cAMP. Some differences in their intracellular signaling are likely, however. For example, investigators have suggested that β_2-receptors couple more effectively than β_1-receptors and induce greater changes in cAMP levels.[45] In addition to their effect on cAMP signaling, β-receptors may couple to myocardial Ca^{2+} channels.[46] However, these additional actions are species specific, and care should be taken in extrapolating animal data to humans.

The inotropic and electrophysiologic effects of β-adrenergic signaling are indirect results of increases in intracellular cAMP levels. cAMP activates a specific protein kinase (PKA) that, in turn, is able to phosphorylate several important cardiac ion channels (including L-type Ca^{2+} channels, Na^+ channels, voltage-dependent K^+ channels, and Cl^- channels). Phosphorylation alters channel functioning, and the resulting changes in membrane electrophysiology modify myocardial behavior.

The α-adrenergic receptors, like their β-receptor counterparts, can be divided into two groups: α_1- and α_2-receptors. Both groups consist of several closely related subtypes, with different tissue distributions and functions that are as yet not fully differentiated. In general, α_1-receptors couple to G_q proteins and thereby activate PLC, a process that results in increases in intracellular Ca^{2+} concentrations. α_2-Receptors couple to G_i proteins, which inhibit adenylate cyclase and consequently reduce intracellular cAMP concentrations.

The primary role of α-receptors is in the vasculature, where α_1-receptors on vascular smooth muscle are the main mediators of neuronally mediated vasoconstriction. α_2-Receptors on the neurons themselves function in a negative feedback loop to control α-adrenergic vasoconstriction.

In the heart, the primary subtype present is α_1. Activation of these receptors leads to a modest increase in cardiac contractility.[47]

Regulation of β-Receptor Functioning

β-Receptor stimulation allows the dramatic increases in cardiac output of which the human heart is capable, but this β-receptor effect is clearly intended to be a temporary measure. Prolonged adrenergic stimulation has significant detrimental effects on the myocardium, with pronounced increases in cAMP levels resulting in increased intracellular Ca^{2+} concentrations, reduced RNA and protein synthesis, and finally cell death. Thus β-receptor modulation is best viewed as part of the "fight-or-flight" response: beneficial in the short term, but detrimental if depended on for too long. Cardiac failure, in particular, has been shown to be associated with prolonged increases in adrenergic stimulation, even to the extent that norepinephrine "spillover" from cardiac nerve endings can be detected in the blood of patients in heart failure.[48]

For this reason, the regulation of β-receptor functioning has received significant attention, and investigators now know that several mechanisms are capable of modifying adrenergic responsiveness of the myocyte. Unfortunately, it appears that the reduction of adrenergic responsiveness necessary to prevent cell death in the presence of adrenergic overstimulation may be in large part responsible for the decreased myocardial performance that is the hallmark of cardiac failure.

One mechanism for decreasing β-receptor functioning is the *downregulation* (ie, decrease in density) of receptors. In cardiac failure, receptor levels are reduced up to 50%. β_1-Receptors downregulate more than β_2-receptors do, thus resulting in a change in the β_1/β_2 ratio; in the failing heart, this ratio is approximately 3:2.[49] Various molecular mechanisms exist for this downregulation. In the long term, β_1-receptors are degraded and permanently removed from the myocyte cell surface. In the short term, receptors can be temporarily removed from the cell membrane and "stored" in intracellular vesicles, where they are not accessible by an agonist. These receptors are, however, fully functional and can be recycled to the membrane when adrenergic overstimulation has ceased.[50]

An additional method by which β-adrenergic receptor functioning can be modified is through phosphorylation of the agonist-occupied receptor by a specific β-adrenergic receptor kinase (β-ARK, which can itself be activated by βγ subunits).[51] Phosphorylation by this kinase allows a protein, β-arrestin, to bind to the receptor where it inhibits receptor functioning.[52] In addition, the β-receptor can be phosphorylated by PKA, which itself can be activated by several other receptors. The detrimental actions of adrenergic overstimulation can also be modified by activation of muscarinic receptors, as discussed in the next section.

Despite the existence of these various regulatory mechanisms and the known detrimental effects of adrenergic overstimulation, paradoxic increases in β-receptor functioning occur in clinical disease states. For example, under ischemic conditions, β-receptors are upregulated, so after periods of ischemia as brief as 15 minutes, significant increases in expressed and functional receptor levels are found. Reperfusion rapidly decreases the number of receptors back to their normal levels.

Muscarinic Receptors and Signaling Pathways

Muscarinic Acetylcholine Receptors

The second major receptor type in cardiac regulation is the muscarinic receptor. Although five subtypes of muscarinic receptors exist, only one of these (M_2) is present in cardiac tissue. Most of these muscarinic receptors are present on the atria. Indeed, it was formerly thought that the ventricles had no vagal innervation, but this view turns out to be incorrect. The ventricles are innervated by the vagus nerve, and muscarinic receptors are in fact present in the ventricles, albeit at lower concentrations than in the atria. The amount of muscarinic receptor protein in atrium is approximately twofold greater than in ventricle (200 to 250 vs 70 to 100 fmol/mg protein).[53] Thus, although the primary function of cardiac muscarinic signaling is heart rate control through actions at the atrial level, vagal stimulation can directly influence ventricular functioning.

M_2-muscarinic receptors couple to G_i proteins, thereby inhibiting adenylate cyclase and decreasing intracellular levels of cAMP. The M_2 receptors have been used as an elegant model to determine the site of G-protein binding to the receptor. Exchanging approximately 20 amino acids of the third intracellular loop (i3) (see Fig. 8.10) between M_2 and M_3 receptors resulted in altered coupling; M_2 receptors mutated in this manner were now able to release Ca^{2+} from intracellular IP_3-sensitive stores by coupling to G_q.[54]

In the impulse-generating system of the heart, a more important signaling mechanism than changes in cAMP is opening of an inwardly rectifying K^+ channel (K_{ACh}) in the plasma membrane. The coupling between M_2 receptor and K_{ACh} is performed by G_K, a member of the G_i class of G proteins. It is not the α subunit of G_K that activates K_{ACh}, but rather the $\beta\gamma$ subunit.[55] As discussed later, cardiac adenosine receptors also couple to this channel.

Whereas the adenylate cyclase system is ubiquitous, differential expression of K_{ACh} determines the actions of muscarinic signaling on the heart. K_{ACh} is largely absent from ventricular tissue. Therefore in the ventricle, muscarinic signaling primarily involves decreases in cAMP levels, and because these levels are low under resting conditions, little effect is seen unless the heart has been stimulated previously by adrenergic agents. In other words, in the absence of adrenergic stimulation, ACh has little effect on the ventricle; in conditions of high adrenergic tone, however, muscarinic stimulation can modify the adrenergic effects, as discussed in the next section.

Regulation of Muscarinic Acetylcholine Receptors

Whereas the role of atrial muscarinic receptors in impulse generation and the conduction system is straightforward, the role of ventricular muscarinic receptors is not as clear. It appears that under nonstressed conditions, muscarinic signaling has little influence on cardiac contractility. In contrast, the system may act as a brake on overstimulation by adrenergic receptors (see earlier discussion). The effects of muscarinic signaling, which almost universally oppose those induced by adrenergic signaling (because muscarinic receptors couple to G_i and adrenergic receptors couple to G_s), may counteract adrenergic effects and thereby preserve cardiac functioning during prolonged stress responses.

Unfortunately, these compensatory mechanisms may not be available in the aging heart. Increased age is accompanied by changes in cardiac muscarinic receptor expression that may make it more difficult for the heart to respond to adrenergic stress. In senescent rats, muscarinic receptor density was decreased by approximately 50%.[56] Adrenergic receptor levels also were decreased, but to a lesser extent. As a result, the adrenergic-to-muscarinic receptor ratio is increased, from 0.29 in young adults to 0.42 in senescent animals. Although the physiologic implications of these changes are not well known, the data at least suggest that the muscarinic systems in the aged heart may not be as well prepared to react to prolonged adrenergic stimulation, such as observed in hypertension and cardiac failure.

With the exception of age, muscarinic receptors are minimally affected in settings that profoundly modify β-receptor expression. For example, no consistent data support changes in muscarinic receptor expression in hypertension, cardiac failure, or ischemic heart disease.[57,58] Therefore imbalances between adrenergic and muscarinic stimulation may occur in each of these situations.

Regulation of G-Protein Functioning

In view of the profound changes in GPCR expression that occur in various disease states, the expression and function of G proteins in cardiovascular disease have been studied with interest. G_s proteins appear unchanged in cardiac failure, both in expression level and in function. With G_i proteins, the situation is more interesting because $G_{i\alpha}$ is considered to have a secondary role in addition to its inhibition of adenylate cyclase. Under normal conditions, G_i is present in greater amounts than G_s. Activation of receptors coupled to G_i would therefore lead to the release of a large number of free $\beta\gamma$ subunits. These subunits could combine with any free $G_{s\alpha}$, thereby making it unavailable for activation of adenylate cyclase.[59] In addition, these $\beta\gamma$ units can enhance the phosphorylation of β-receptors by β-ARK.[60] In failing human cardiac tissue, the amount of G_i (as assessed by ADP ribosylation by pertussis toxin) is increased.[61] Although this would be expected to make muscarinic signaling more efficacious (thereby helping counteract the adrenergic overstimulation), it has been difficult to correlate these changes with alterations in adenylate cyclase functioning. It is similarly unclear whether the reported increases in G_i levels are a result of increased messenger RNA (mRNA) expression or increased stability of the G protein itself.

The catalytic subunit of adenylate cyclase appears little influenced by cardiac disease. Pressure overload is the only situation in which a consistent decrease in its activity has been observed.[62]

Other Receptors

As stated earlier, the heart and vasculature express many GPCRs apart from the adrenergic and muscarinic receptors. A few examples are mentioned here. Angiotensin receptors mediate hormonal vasoconstriction in the vascular tree and are also present in the heart, although their function there is not fully defined. Receptors for several purinergic compounds are also expressed in the heart and are the subject of intense investigation, as discussed in the next section. In addition, histamine H_2 and VIP receptors are present, and H_2 receptors mediate the inotropic action of histamine.

Although less is understood about the role and regulation of these receptors than about their adrenergic and cholinergic counterparts, it is clear that some receptors are affected by cardiovascular disease. For example, VIP receptors are downregulated by 70% in idiopathic dilated cardiomyopathy (DCM), whereas histamine receptors are unaffected.[63] In general, receptors coupled to G_i show little alteration in expression and function during disease states, whereas G_s-coupled receptors are affected more profoundly.

Clinical Correlates

Understanding of the role of adenosine in cardiac regulation has expanded significantly over the past decades. Its established use as an antiarrhythmic compound and its probable role in cardiac preconditioning are two examples of clinical advances resulting from this increase in understanding. Adenosine acts through a GPCR, by activating several intracellular signaling systems. This section discusses the molecular aspects of adenosine signaling, as well as their clinical implications. More detailed reviews on the topic are available.[64,65]

Adenosine Signaling

Although adenosine can be generated by several pathways, in the heart, it is usually found as a dephosphorylation product of AMP.[66] Because AMP accumulation is a sign of a low cellular energy charge, an increased adenosine concentration is a marker of unbalanced energy demand and supply; thus ischemia, hypoxemia, and increased

catecholamine concentrations are all associated with increased adenosine release.[67] Adenosine is rapidly degraded by various pathways, both intracellularly and extracellularly. As a result, its half-life is extremely short, on the order of 1 second.[68] Therefore, not only is it a marker of a cardiac "energy crisis," but also its concentrations fluctuate virtually instantly with the energy balance of the heart; it provides a real-time indication of the cellular energy situation.

Adenosine signals through GPCR of the purinergic receptor family. Two subclasses of purinoceptors exist: P_1 (high affinity for adenosine and AMP) and P_2 (high affinity for ATP and ADP). The P_1 receptor class can be divided into two main receptor subtypes: A_1 and A_2. A_1 receptors are present mostly in the heart and when activated inhibit adenylate cyclase; A_2 receptors are present in the vasculature and when activated stimulate adenylate cyclase. The A_2 receptors mediate the vasodilatory actions of adenosine. The A_1 receptors mediate its complex cardiac effects, and they are the topic of the remainder of this section.

The A_1 adenosine receptor couples to (at least) two intracellular signaling systems. Both actions are mediated by G proteins of the G_i class. The first intracellular system is one already encountered: the K_{ACh} channel. Presumably, through the same G_K protein, adenosine activates this channel in the same way as does M_2 muscarinic stimulation, and the cardiac electrophysiologic effects of ACh and adenosine are therefore similar. The specific effect of adenosine depends on the cardiac tissue studied because K_{ACh} expression varies with location. As discussed earlier, whereas the channel is present in large amounts in the atrial conduction system and atrial myocardium, it is virtually absent in the ventricle. Therefore in the unstimulated heart, adenosine shortens the atrial action potential, decreases atrial refractoriness, and decreases atrial contractile force, but it is almost without effect on the ventricle.[69]

The second intracellular signaling system activated is a G_i protein that inhibits adenylate cyclase. Given that cAMP levels are quite low under resting conditions, this mechanism plays a minor role until cAMP concentrations are increased by adrenergic stimulation of the heart. Therefore cAMP-mediated cardiac actions of adenosine are observed only under conditions of adrenergic drive. Because the adenylate cyclase system is present throughout the heart, its effects are widespread; L-type Ca^{2+} channel functioning is diminished (by inhibiting cAMP-induced phosphorylation of the channel) in atrium as well as ventricle, thus resulting in decreased inotropy and shortening of the action potential.[70]

Antiarrhythmic Actions of Adenosine

From these molecular actions of adenosine, its clinical effects can be deduced easily. The antiarrhythmic actions are largely a result of its activation of K_{ACh}. Recalling the tissue distribution of K_{ACh}, it could be anticipated that adenosine would be much more effective in the treatment of supraventricular arrhythmias than ventricular arrhythmias, and such is indeed the case. Because of its negative chronotropic effects on the atrial conduction system, the compound is most effective in treating supraventricular tachycardias that contain a reentrant pathway involving the atrioventricular node. The efficacy of adenosine in terminating such tachycardias has been reported as greater than 90%.[71] In contrast, it is consistently ineffective in tachycardias not involving the atrioventricular node.[72]

Most ventricular tachycardias are insensitive to adenosine. The only exception is again easily deduced from the compound's molecular mechanism of action; a rare form of exercise- or catecholamine-induced ventricular tachycardia responds promptly to adenosine.[73] Presumably, in this setting, adenosine-mediated inhibition of adenylate cyclase counteracts the stimulatory effects of catecholamines.

Occasionally, adenosine may be useful because of its ability to differentiate between true ventricular tachycardia and supraventricular tachycardia with aberrant conduction. In view of concerns that the often already precarious cardiovascular status of patients in ventricular tachycardia could be temporarily worsened by vasodilatation, many clinicians have been hesitant to use adenosine for this purpose. In contrast, adenosine has been found very useful as a diagnostic agent for supraventricular tachycardias. Care should be taken, however, in the patient with Wolff-Parkinson-White syndrome, who may respond with increases in ventricular rate and hemodynamic deterioration.

The side effects of adenosine would be significant if the half-life of the compound were not as short as it is. Many of the adverse effects result from activation of A_2 receptors in the vascular system: flushing, headache, and lightheadedness. Chest pain, anxiety, nausea, vomiting, and occasional bronchospasm are also seen. However, these effects are usually short-lived, and if the patient has been adequately warned about their occurrence, they are rarely of significance. Profound but brief electrophysiologic responses are observed on the ECG, ranging from premature atrial and ventricular beats to short periods of asystole. Again, these findings are rarely significant.

Adenosine and Myocardial Preconditioning

Myocardial preconditioning is the phenomenon in which brief exposure of the myocardium to ischemic conditions allows it to withstand subsequent, more prolonged exposure. The phenomenon has received much attention because its application in the clinical setting may allow the heart to better withstand, for instance, the insults of cardiac surgical procedures. Thus the mechanisms of this effect were investigated in the hope that they could be activated directly, without the need for ischemia. Various mechanisms may account for preconditioning and have been reviewed in the literature.[65,74,75]

Mitochondria play an important role in modulating cell function and survival during myocardial ischemia and reperfusion through multiple channels including mitochondrial Ca^{+2} and K_{ATP} channels and the mitochondrial permeability transition pore.[76] The mitochondrial K_{ATP} channel (mitoK_{ATP}) is a G-protein–linked K^+ channel located on the mitochondrial membrane that is a key mediator in myocardial preconditioning. Opening of this channel by using compounds that selectively open mitoK_{ATP} without affecting other cellular K_{ATP} channels[77] was shown to have a protective effect, whereas inhibition of the channel (with the channel blocker glibenclamide) increases ischemic damage to the myocardium. For example, abolition by glibenclamide of preconditioning was shown in a study measuring ST-segment changes and cardiac pain in patients undergoing balloon angioplasty.[78] Similar findings were observed in various animal studies. K_{ATP}, like K_{ACh}, belongs to the class of G-protein–coupled inward rectifier-type channels; its structure is indicated in Fig. 8.10. In contrast to K_{ACh}, however, it appears to be modulated primarily by changes in intracellular ATP derivatives. For example, intracellular increases in ATP levels have a direct inhibitory effect on the channel. In addition, K_{ATP} can be modulated by PKC, which phosphorylates the channel. PKC can be activated directly by ischemic conditions or by activation of α-adrenergic and adenosine receptors. In addition, adenosine also may be able to influence behavior of K_{ATP} in the same manner that it regulates K_{ACh}: through a G_i protein.[79]

The mechanisms by which mitoK_{ATP} opening is protective are still a focus of investigation. Potential beneficial effects involve inhibition of mitochondrial Ca^{2+} uptake, regulation of mitochondrial volume, and modulation of the generation of reactive oxygen species. Of interest from the anesthesiologist's point of view are observations that volatile anesthetic agents induce preconditioning by similar mechanisms. For example, sevoflurane preconditions human myocardium against hypoxia through activation of K_{ATP} channels and activation of A_1-adenosine receptors.[80] Similarly, lidocaine was shown to induce protection against inflammatory stimulation of endothelial and vascular smooth muscle cells by affecting mitoK_{ATP}.[81]

Anesthetic Actions

Although the functioning and physiologic roles of the receptors and channels described are of obvious importance to the anesthesiologist, from a practical perspective, the interactions between anesthetic drugs and these signaling molecules are at least as relevant. As mentioned previously, the effects of anesthetic agents on such proteins may be

beneficial to the cardiovascular system. However, detrimental interactions may also exist.

Volatile anesthetic agents are administered in extremely high concentrations as compared with most other pharmacologic agents. For example, most cardiovascular drugs are administered in doses that result in micromolar blood concentrations. Such doses are effective because a half-maximal effect on the site of action can be attained with these concentrations. Anesthetic agents, in contrast, require low millimolar concentrations in blood to be effective, almost a thousand times as much. Although they commonly are referred to as "potent agents," they are certainly not very potent as compared with many other pharmacologic compounds. As a result, it is not surprising that these compounds have a wide range of actions in addition to their primary effect site (which, of course, is still not defined completely). In addition, volatile anesthetic agents are lipophilic compounds, and if under laboratory conditions concentrations are increased even further, they can be found to interact with almost any preparation exhibiting a certain degree of lipophilicity. As a result, data demonstrate interactions between volatile anesthetic agents and virtually every component of the cardiovascular system. The problem then is not in ascertaining which channels and receptors interact with the anesthetic agents, but rather in identifying which of all these interactions are clinically important, and this has been difficult to determine. A first test that should be applied, of course, is that of reasonable concentrations; if effects are not observed at 1 to 2 minimal alveolar concentration (MAC) equivalents, it is unlikely that an interaction has clinical relevance. Because many experiments are performed at temperatures lower than 37°C, temperature correction of anesthetic solubility is an important issue. It is also important that actions are shown in several models. Effects observed in an isolated system may not necessarily be reproduced in an organ or whole-animal model; in that case, the relevance of the finding is in doubt. This issue has been reviewed in some detail.[82]

Injected anesthetic agents are less troublesome in this regard. Most of these drugs act at defined sites (the γ-aminobutyric acid [$GABA_A$] receptor-channel complex for most of them; the primary action of ketamine on the *N*-methyl-D-aspartate [NMDA] receptor-channel complex is an exception), they are more potent, and they are therefore active at significantly lower concentrations. However, this does not necessarily mean that they are without other interactions, as their various side effect profiles show.

This section focuses on some of the interactions between anesthetic agents and the molecular systems described earlier: those interactions with the most support in the literature and that also help explain some of the specific side effects of anesthetic drugs. Thus rather than providing a detailed overview of all interactions reported, several well-described examples with probable clinical relevance are presented. Unfortunately, many of these interactions have not yet been described in the molecular and submolecular detail desired. Although it may be known that an anesthetic agent inhibits functioning of a receptor or channel type, the location in the molecule where this interaction takes place is not usually identified. Usually, it cannot even be ascertained that the interaction occurs with the protein itself, rather than with the lipid membrane environment surrounding the protein. More detailed site-directed mutagenesis and the study of chimeric molecules are likely to shed light on these issues.

Interactions With Channels: Calcium Channels

Of the various ion channels present in the heart, those most likely to be significantly affected by anesthetic agents in the clinical setting are the voltage-gated Ca^{2+} channels. However, interactions with other cardiac channel types may also be relevant (particularly with K^+ channels, such as the K_{ATP} channel, described earlier).

Anesthetic actions on cardiac Ca^{2+} channels have been studied in a variety of models. The original observations that halothane blocked Ca^{2+} flux into heart cells date back to 1975,[83] and much specific information has been gained since. In particular, voltage-clamp and patch-clamp studies have contributed significantly to an understanding of the interactions between anesthetic agents and Ca^{2+} channels and have elegantly described the effects of anesthetic agents on electrophysiologic behavior. However, it is not straightforward to assign the observed electrophysiologic effects to a molecular substrate. This issue is only beginning to be addressed with the use of recombinant technology.

Almost all volatile anesthetic agents inhibit L-type Ca^{2+} channels.[84,85] Inhibition is modest, approximately 25% to 30% at 1 MAC anesthetic, but certainly sufficient to account for the physiologic changes induced by the anesthetic agents. Volatile anesthetic agents decrease peak current and also tend to increase the rate of inactivation.[86] Maximal Ca^{2+} current is therefore depressed, and duration of Ca^{2+} current is shortened. Together, these actions significantly limit the Ca^{2+} influx into the cardiac myocyte. However, some specific actions may depend on the particular anesthetic agent studied. In the presence of β-adrenergic stimulation, halothane, but not sevoflurane, is associated with long-lasting enhancement of Ca^{2+} channel function that may contribute to its proarrhythmic effects.[87] Xenon is without effect on cardiac Ca^{2+} channels, a finding that partly explains its lack of effect on myocardial contractility. Other types of Ca^{2+} channels have different sensitivities. Neuronal (N-type) channels have been shown to be resistant to volatile anesthetic agents. T-type channels in general tend to be much more sensitive than L-type channels; at clinical concentrations of most volatile anesthetic agents, T currents are inhibited 50% or more.

The effects of volatile anesthetic agents on cardiac Ca^{2+} channels can be modulated greatly by concurrent interactions of the compounds with other cardiac signaling systems. As discussed later, volatile anesthetic agents inhibit function of several types of muscarinic ACh receptor systems. Because Ca^{2+} channel function can be inhibited by muscarinic signaling, as discussed earlier, clinicians would anticipate additional interactions when this system is exposed to volatile anesthetic agents, and such is the case. Halothane and isoflurane further inhibited currents through Ca^{2+} channels when either volatile anesthetic was applied after inhibition produced by previous muscarinic stimulation. However, when muscarinic receptors were stimulated after administration of volatile anesthetic, its effect was reduced. Thus, whereas volatile anesthetic agents directly inhibit L-type channels, they also interfere with channel modulation by GPCR.[88]

Both volatile and injected anesthetic agents have been reported to inhibit cardiac L-type Ca^{2+} channels in some models. However, the concentrations used generally exceed those used in clinical practice. Thiopental and methohexital block L-type Ca^{2+} currents.[85,89] Similarly, propofol has been reported to inhibit these channels, but at concentrations well beyond the clinical range.

Interactions With Receptors: Muscarinic Receptors

As with cardiac channels, anesthetic interactions with a variety of GPCRs may be of potential relevance to cardiovascular side effects of anesthetic compounds. However, most of these potential interactions have not been described in significant detail. The two main control systems of myocardial functioning, the muscarinic and adrenergic systems, have been studied to some extent, and a generalizing conclusion can be that muscarinic receptors are and adrenergic receptors are not sensitive to many anesthetic agents. Thus the focus is on muscarinic receptors in this section.

Determination of anesthetic effects on GPCR is in some ways more complex than determination of the effects on channels. Although the receptors are smaller and consist of a single subunit, they are only one component of very complex signaling pathways. Therefore it is not sufficient to determine the effects on the receptor itself; actions on intracellular signaling should also be investigated.

No doubt exists that at least some volatile anesthetic agents interfere with muscarinic signaling. Unfortunately, most of these investigations have not studied the heart or even looked specifically at the M_2 receptor, the only subtype expressed in cardiac tissue.

Aronstam and colleagues published a series of articles reporting the effect of various anesthetic agents on muscarinic receptor binding; a summary of their findings has also appeared in print.[90] Several studies investigated the effect of halothane on agonist and antagonist binding.[91,92] The conclusions drawn from this work were as follows: (1) the anesthetic agent enhanced antagonist binding by slowing the rate of ligand dissociation, and (2) the anesthetic agent inhibited agonist binding (by 48%, using 10% halothane).

The site of action of these effects was studied in more detail by investigating the interactions of anesthetic agents with G-protein functioning.[93] As discussed earlier, G proteins are activated by GDP-GTP exchange. Intrinsic but remarkably slow enzyme activity hydrolyzes GTP back to GDP, thereby inactivating the G protein after several seconds. While active, the G protein is no longer able to couple to the receptor, and uncoupled receptors exhibit a decreased affinity for their agonist. This decrease in activity can be induced in the experimental setting by including a nonhydrolyzable analogue of GTP, such as Gpp(NH)p, in the reaction mixture, thereby resulting in irreversibly activated G proteins. This effect is known as the GTP shift in receptor affinity. Halothane shifts the Gpp(NH)p concentration-response relationship to the right. In other words, a greater concentration of the GTP analogue was necessary to induce a similar decrease in agonist binding. In the absence and presence of 5% halothane, the half-maximal inhibitory concentration (IC_{50}) values for the inhibitory effect on agonist binding of Gpp(NH)p were 0.7 and 83 μM, respectively—a 100-fold difference. These findings were interpreted as an ability of halothane to stabilize high-affinity G-protein–receptor complexes.

Therefore halothane appears to affect receptor binding, as well as receptor–G-protein interaction. In a subsequent study, the effect of the anesthetic agent on G-protein functioning—its ability to hydrolyze bound GTP—was investigated. Halothane was found not to inhibit binding of radiolabeled GTP analogue to G proteins.[91] However, the anesthetic agent completely blocked the stimulation of G-protein GTPase activity induced by ACh, with a half-maximal effect at the clinically relevant halothane concentration of 0.3 mM. The site of this effect was not determined. Similar findings were obtained with other anesthetic agents. Halothane also has been shown to interfere with G-protein–mediated Ca^{2+} sensitization in airway smooth muscle by inhibiting G proteins.[94] More recently, however, the interaction between halothane and purified recombinant G_i was investigated. In contrast to the findings described earlier, no effect of the anesthetic on G_i protein function was found.[95] The earlier results may therefore have been contaminated by interactions with other G-protein subtypes that are less relevant to muscarinic M_2-receptor signaling. The conclusion to be drawn from these studies is that anesthetic agents may interfere with several components of the muscarinic signaling pathway. However, the following should be kept in mind: (1) a mixture of muscarinic receptor subtypes was most commonly studied; (2) the anesthetic agents were administered in relatively high, and clinically unequal, concentrations; and (3) anesthetic effects on functional properties of the receptor–G-protein unit were not specifically addressed.

Magyar and Szabo,[96] using the patch-clamp technique, investigated the effects of halothane (0.9 mM) and isoflurane (0.8 mM) on ACh (10 μM)–induced activation of the muscarinic K^+ channel in frog atrial myocytes. These investigators found that if anesthetic and agonist agents were administered at the same time, a reduction in the peak K^+ current was observed, which was greater with halothane than with isoflurane. However, pretreatment with the anesthetic agent was found to have a significant, time-dependent, additional effect: 25-minute exposure to halothane restored the peak and significantly increased the steady-state current, whereas exposure to isoflurane decreased both. Because equilibration of the anesthetic agent with the direct signaling pathway should be complete within milliseconds to seconds, the prolonged time course of these effects appears to indicate that additional intracellular pathways (eg, PKC-mediated phosphorylation) are involved. Exposure of the membrane patches to the nonhydrolyzable GTP analogue GTPγS, thereby irreversibly activating G_K, prolonged the current. When single-channel measurements were performed, halothane was found to enhance the frequency of channel opening without significantly affecting the single-channel conductance. Isoflurane was without effect. Therefore halothane affects the signaling pathway downstream of the muscarinic receptor in this model. Whether this action is on the G protein or on the channel itself cannot be conclusively determined from these studies.

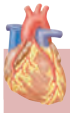
When time considerations are taken into account, it appears likely that the initial action of halothane on the system is inhibiting, whereas that of isoflurane is less so. After prolonged exposure, halothane is found to enhance signaling, whereas isoflurane inhibits it. These results probably reflect various effects of the anesthetic agents on intracellular systems that modify the signaling properties of the muscarinic pathway. In addition, halothane, but not isoflurane, has a direct activating effect downstream of the muscarinic receptor. This is consistent with findings of the effect of halothane on Ca^{2+} channels mentioned earlier.

Remote Ischemic Conditioning

Remote ischemic conditioning is the phenomenon by which brief periods of ischemia and reperfusion to one tissue bed or organ of the body (often induced by repeatedly inflating a blood pressure cuff on the arm) confer protection against ischemic injury in a remote organ such as the heart. This phenomenon appears to be a consequence of both neuronal and neurohumoral transfer of signals from the remote organ to the heart, the mechanisms of which are complex and still under investigation.[97] Multiple studies have explored the efficacy of remote ischemic preconditioning for mitigating adverse cardiac outcomes after cardiac surgical procedures. Most of these studies focused on patients undergoing coronary artery bypass graft operations, with the primary study end point being association with a reduction in myocardial injury biomarkers (ie, troponin I, troponin T, creatine kinase MB isoenzyme) 24 to 72 hours postoperatively.[97] Most of these studies were small, but slightly more than one-half of these studies demonstrated a significant reduction in levels of myocardial injury biomarkers in patients who underwent remote ischemic preconditioning induced by applied cycles of intermittent occlusion of blood flow to an upper or lower extremity.[97] The largest of these studies included more than 320 patients undergoing coronary artery bypass graft operations. This study identified a significant reduction in troponin I at 72 hours after the surgical procedure in the remote ischemic preconditioning intervention group as well as reduced all-cause mortality rates.[98] In addition to the need to understand the potential protective mechanisms of remote ischemic conditioning more clearly, additional large studies are needed to determine what timing and methods of invoking remote ischemic conditioning may incur the most myocardial protection during cardiac operations. Further studies are also needed to determine which concurrent anesthetic agents may potentiate or inhibit effects of remote ischemic conditioning.[97] One trial showed renal protection from remote preconditioning during cardiac surgical procedures, a finding suggesting that multiorgan protection conferred during cardiac operations should be evaluated for potential impact and translation into clinical practice.[99]

Genetic Cardiovascular Medicine

Considerable progress has been made in the identification and understanding of the genetic basis of cardiovascular disease. These disorders, spanning all aspects of cardiovascular disease and affecting all parts of the heart, can be divided into two groups (Box 8.6). *Monogenic disorders* are mendelian disorders for which changes in a single gene are implicated in the disease process and that usually exhibit characteristic inheritance patterns (ie, additive, dominant, or recessive genetic models). More than 40 cardiovascular disorders are known to be caused directly by single gene defects. Examples include familial hypercholesterolemia, hypertrophic cardiomyopathies (HCMs), DCMs, and the LQTSs.[100,101]



BOX 8.6 EXAMPLES OF IMPORTANT CARDIOVASCULAR DISORDERS WITH A GENETIC BASIS

Monogenic disorders
- Familial hypercholesterolemia
- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Long QT syndrome

Multigenic disorders
- Coronary artery disease
- Hypertension
- Atherosclerosis

More commonly, however, multiple genes influence the disease process by enhancing disease susceptibility or by augmenting the impact of environmental risk factors. The genetic component in those *multigenic disorders* comprises a collection of gene variants such as single nucleotide mutations, referred to as *single nucleotide polymorphisms* (SNPs). Each individual SNP may have a modest effect on the quantity or function of a translated protein product. However, when individual SNPs aggregate and interact with environmental risk factors, they may have a major impact on disease biology. Common complex diseases that appear to follow this paradigm include coronary artery disease (CAD), atherosclerosis, hypertension, and atrial fibrillation.[102–104]

This section discusses the current status of genetic diagnosis of monogenic and complex cardiovascular disorders, as well as the main techniques used to perform such diagnostic testing.

Monogenic Cardiovascular Disorders

Great progress has been made in the identification and characterization of the disease genes specific to mendelian cardiovascular diseases,[100,101,105] but several factors complicate these investigative efforts. *Locus heterogeneity* (many genes causing the same disease) is one of those factors.[106] The channelopathies, encompassing the LQTS, Brugada syndrome, and other genetic arrhythmogenic disorders, are accounted for by at least 30 genes.[35] Whereas HCM genes *MYH7, MYBPC3,* and *TNNT2* (encoding the β-myosin heavy chain, cardiac myosin-binding protein C, and cardiac troponin T genes, respectively) account for 70% to 80% of cases of HCM as diagnosed by molecular genetic approaches,[107] an additional 21 genes have been implicated to cause the HCM phenotype.[108] In addition, more than 40 genes have been implicated in DCM.[108] A second, related factor complicating genetic diagnosis of "monogenetic" disorders is *allelic heterogeneity* or the concept that multiple different mutations typically occur within a single culprit gene and may result in a certain cardiovascular phenotype such as HCM (ie, within the list of genes known to cause HCM, hundreds of pathogenic mutations have been identified, but many of them are rare variants). Furthermore, although the list of known disease-causing genetic variants is expanding rapidly, not all disease loci have been identified, and this information gap diminishes the sensitivity of molecular testing to screen for genetic susceptibility to disorders. Whereas investigators have estimated that a mutation causing LQTS can be identified in up to three-fourths of index patients, this is not true for other cardiovascular single-gene disorders. For example, only 30% to 60% of the genetic causes of HCM[109] and only 20% to 30% of the genetic causes of DCM have been identified.[105,106] As an example, *MYH7* consists of 40 exons encoding the β-myosin heavy chain protein, and 194 mutations in this structure have been reported to be associated with HCM. For diagnostic purposes, this necessitates sequencing the entire coding sequence and intron/exon boundaries of each gene. The advent and refinement of next-generation sequencing have made this an increasingly clinical viable approach (discussed further later).

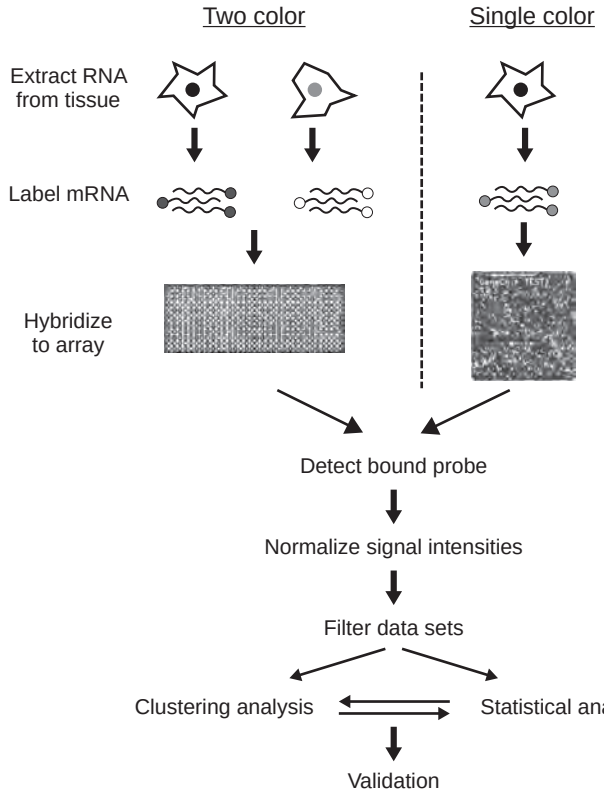


Fig. 8.11 Schematic representation of a microarray experiment. RNA is extracted from the tissues of interest, labeled, and then hybridized (competitively, two color arrays; noncompetitively, one color array) to the DNA microarray, where it binds complementary sequences. Bound sequences are identified by their position on the array. Signal intensities are normalized, allowing interarray comparisons. Normalized data sets are filtered and subjected to computational analysis. Finally, differentially regulated transcripts should be prospectively validated or confirmed using independent methods. *(From Cook SA, Rosenzweig A. DNA microarrays: implications for cardiovascular medicine.* Circ Res. *2002;91:559–564.)*

Methodologies for Identifying Mutations: Linkage Analysis, Sequencing, and Microarrays

Linkage analysis is a nonbiased and powerful approach for identifying causative genes underlying familial monogenetic and complex diseases.[110] The analysis is conducted after a priori identification of potential candidate genes or their chromosomal locations. It then looks for DNA markers that cosegregate with the disease phenotype between affected family members at a rate that is statistically greater than random chance. The chromosomal region containing the DNA markers can then be examined in further detail to look for potential candidate genes. Several successful studies have been performed using CAD as a model.[111–113]

Techniques for identifying gene sequences have evolved from the classic Southern blotting procedure into highly automated systems that can rapidly screen hundreds of thousands of gene sequences. Southern blotting, invented in the mid-1970s, is based on the transfer to nitrocellulose of DNA molecules separated on gels and their subsequent identification with DNA probes. It allows detection of small mutations, as well as large deletions, duplications, and gene rearrangements. The principle was expanded and automated in the development of DNA microarrays (Fig. 8.11), which consist of series of thousands of microscopic spots of DNA oligonucleotides, each containing tiny amounts of a specific DNA sequence. The arrays are

printed on a platform, usually a glass slide. A DNA probe, encoding a specific sequence, is then used to bind to and identify homologous nucleic acids, as detected by fluorophore-labeled targets whose signal is proportional to the relative abundance of nucleic acid sequences in the target. This technique makes it possible to examine for genetic variants with high density across large numbers of disease genes at the same time in large numbers of patients.

Sanger "first-generation" sequencing was the method of choice for several decades for determining a person's exact base-pair by base-pair genetic DNA sequence. Although Sanger sequencing is accurate, it is also slow (one patient at a time and one gene at a time) and expensive. Next-generation high-throughput sequencing platforms allow base-pair by base-pair simultaneous sequencing of multiple specific genes (ie, targeted sequencing), the whole exome, or the whole genome in a rapid and cost-effective fashion.[114] Multiple patients can undergo sequencing in a parallelized fashion by using next-generation sequencing techniques. The steps involved in next-generation sequencing platforms are shown in Fig. 8.12.[115] Next-generation sequencing has been useful for the discovery of novel (often rare) variants that cause monogenetic disorders. Next-generation sequencing also has enhanced genetic screening for monogenetic cardiovascular disorders, although some sequence variants of uncertain clinical significance that have been discovered create challenges for physicians who counsel and manage families susceptible to inherited cardiovascular disease.[115]

Clinical Applications

The ability of these techniques to identify diseases before they become clinically manifest allows preventive treatment (Table 8.2). For example, implantable cardioverter-defibrillators (ICDs) can prevent sudden cardiac death in patients with certain genetic cardiomyopathies and arrhythmias (Fig. 8.13).[116–118] Medical therapy may ameliorate the progression of genetic DCM. Prospective identification of those patients who are asymptomatic but at greater risk for development of the disease enables closer surveillance and early intervention. Knowledge of the LQTS genotype may be used to tailor the treatment plan (Fig. 8.14). For instance, patients with LQT3 benefit less from β-blockers,

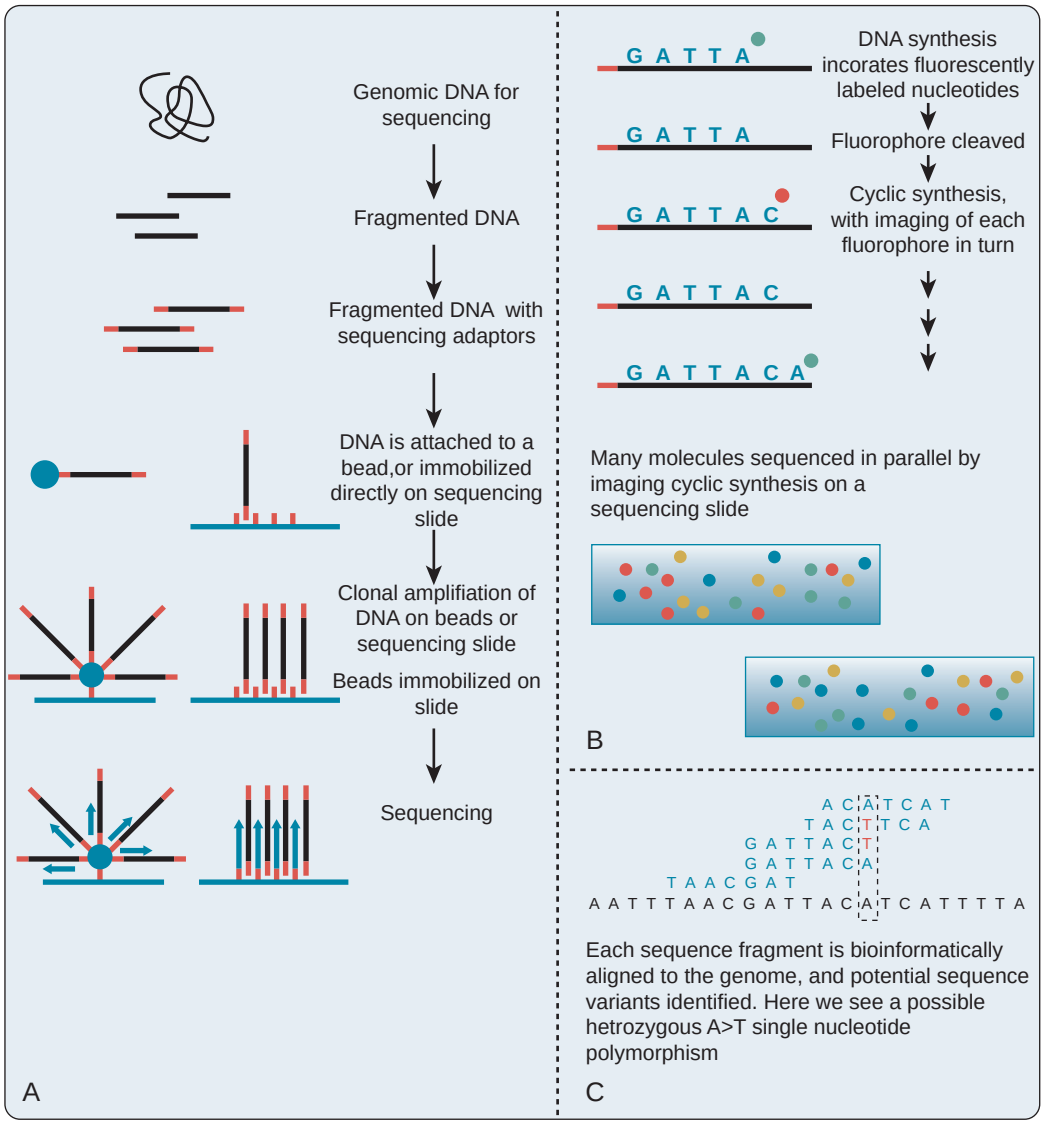


Fig. 8.12 A to C, Next-generation high-throughput sequencing is parallel sequencing process that is faster and less expensive than Sanger sequencing. *(From Mogensen J, van Tintelen JP, Fokstuen S, et al. The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics.* Eur Heart J. *2015;36:1367–1370.)*

so a lower threshold for ICD placement is advised in these patients.[119] In addition, the triggers for malignant arrhythmias have been found to differ based on the affected gene; for example, patients with LQT1 can be asked to avoid vigorous activities such as exercise and competitive sports.[120]

TABLE 8.2 Clinical Applicability of Genetic Testing in Monogenic Cardiac Diseases[a]

Disease	*Success Rate (%)*	*Identification of Silent Carriers/ Diagnosis*	*Reproductive Risk Assessment*	*Prognosis*	*Therapy*
HCM	60–65	+	+	±	–
DCM	NA	+	+	–	–
ARVC	<10	+	+	–	–
MFS	80–90	+	+	–	–
LQTS	60–65	+	+	+	+
BrS	20	+	+	–	–
CPVT	50	+	+	+	–
NS	40	+	+	–	–

[a]Only conditions for which consistent epidemiologic data are available have been listed.
+, Genetic testing can be used for this disorder; *±*, genetic testing might be used for this disorder but not validated; *–*, means the genetic test is not being used for this disorder; *ARVC,* arrhythmogenic right ventricular cardiomyopathy; *BrS,* Brugada syndrome; *CPVT,* catecholaminergic polymorphic ventricular tachycardia; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *LQTS,* long QT syndrome; *MFS,* Marfan syndrome; *NA,* not applicable; *NS,* Noonan syndrome.
From Camm AJ, Lüscher TF, Serruys PW. *The ESC Textbook of Cardiovascular Medicine.* 2nd ed. New York: Oxford University Press; 2009. By permission of Oxford University Press.

Common Complex Multigenic Cardiovascular Disorders

Identifying the gene variants associated with the development and progression of multigenic common complex cardiovascular diseases provides the potential for these variants to be used to better predict who will develop certain cardiovascular disorders, as well as to target preventive and treatment strategies more accurately and to develop novel treatments. The obvious challenges are to identify the genes and gene variants that collectively contribute to a cardiovascular disease such as CAD and to understand how these genetic variants interface with environmental insults to perpetuate cardiovascular disease. Several genomic technologies allow researchers to study the genetic components of multigenic disorders such as CAD.

State-of-the Art Methodologies for Multigenic Genetic Screening: Whole-Genome Association and Gene Expression Profiling

Genetic association studies are performed to determine whether a genetic variant is associated with a disease or trait; if association is present, a particular allele, genotype, or haplotype of a polymorphism or polymorphisms will be seen more often than expected by chance in a subject carrying the trait. Thus a person carrying one or two copies of a high-risk variant is at increased risk for development of the associated disease or having the associated trait. Using modern genomic technologies, researchers can now assay more than a million SNPs simultaneously in a single subject by using "SNP chips." The

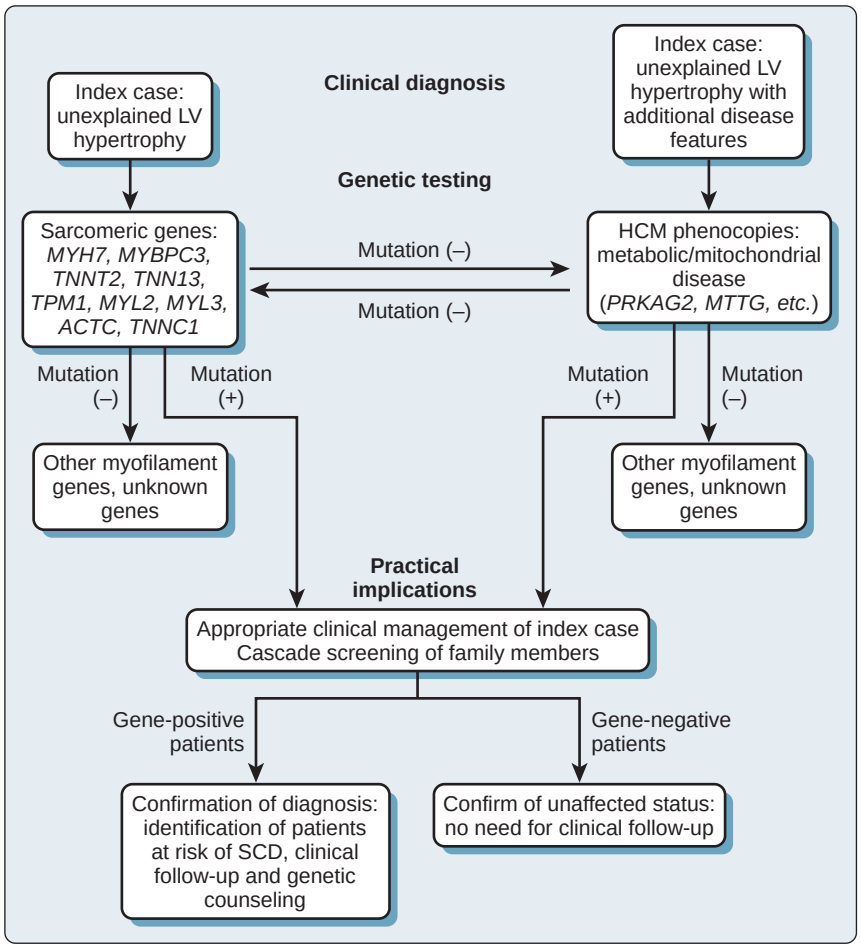


Fig. 8.13 Proposed sequence of genetic testing for patients with hypertrophic cardiomyopathy (*HCM*). *LV,* Left ventricular; *SCD,* sudden cardiac death. *(From Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression.* Nat Clin Pract Cardiovasc Med. *2008;5:158–168.)*

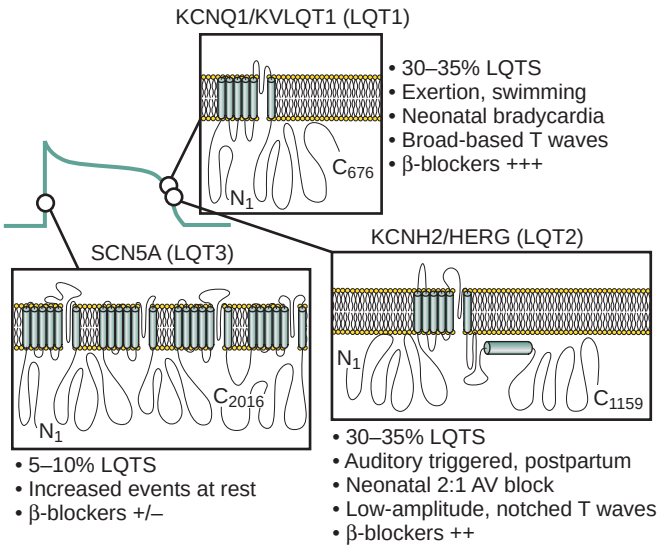


Fig. 8.14 Genotype-phenotype relations seen in long QT syndromes (LQTSs) LQT1, LQT2, and LQT3. The linear topologies for the three principal cardiac channels that account for two-thirds of LQTSs are superimposed on the cardiac action potential of a ventricular myocyte. The *inset* next to each channel summarizes some of the signature phenotypes associated with the three most common LQTS-causing genotypes. *AV,* Atrioventricular. *(From Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction?* Curr Opin Cardiol. *2005;20:175–181.)*

principle is the same as previously described for gene arrays. Studies have performed whole-genome association to identify SNPs associated with the development and progression of MIs.[121,122] Next-generation high-throughput sequencing technologies are also now being used to explore for genetic variants contributing to common complex diseases, particularly when using targeted and whole exome sequencing. Targeted next-generation sequencing may be used to explore for rare variants (SNPs and copy number variations) within genes where more frequent SNPs have been associated already with a certain cardiovascular phenotype (ie, this allows assessment of both common and rare genetic variants because SNP chips contain fewer low-frequency SNPs; <2% of the population).

Gene expression profiling (functional genomics) is another approach to identify genes and pathways that contribute to the development and progression of complex cardiovascular diseases such as coronary atherosclerosis. This approach analyzes disease in relevant tissues to look for changes in the abundance of transcribed genes mRNA that correlate with a disease state, clinical outcome, or therapeutic response.[123,124] Next-generation RNA sequencing techniques are now being used in research to provide an unbiased assessment of the transcriptome and its role in the biology of cardiovascular responses such as to myocardial ischemia. For example, next-generation RNA sequencing was used to examine changes in left ventricular myocardial gene expression before and after cold-blood cardioplegia–induced myocardial arrest and ischemia in 45 patients undergoing aortic valve replacement.[125]

Clinical Application

Knowledge of the multiple genetic variants associated with complex cardiovascular disease phenotypes such CAD could potentially be used to better define individual risk for developing these disorders beyond what can be assessed from currently available clinical knowledge and nongenetic tests. Discovery of novel genetic loci associated with common complex diseases such as CAD could also lead to understanding of new dimensions of the biology underlying CAD and consequently could lead to development of new medical treatments for CAD. Finally, knowledge of individual genetic profiles could allow enhanced selection of the most effective therapies to prevent or treat disorders such as CAD.

However, barriers remain to using genetics to enhance risk assessment for, prophylaxis of, and treatment of common complex diseases such as CAD. Unlike with monogenetic disorders, for multigenic disorders, each genetic variant identified is likely to contribute only very small percentages to increased risk.[104] The advent of whole-genome association studies conducted and assessed across multiple very large CAD cohorts has resulted in identification of 50 genetic variants that have been associated with development of sporadic CAD in communities.[104] A person who carries many of these risk variants is potentially at higher risk for developing CAD than a patient who is a carrier of fewer of these risk variants. If a validated genetic risk score could be established using an unweighted or weighted assessment of known genetic variants that are associated with CAD, then patients at identified higher genetic risk could receive more intensive preventive medical treatments to delay or prevent CAD development. However, just because a patient carries multiple genetic risk variants for a common complex disease such as CAD does not provide certainty that the patient will indeed develop CAD. Environmental risk factors in and of themselves, or the combination of certain environmental factors with specific genetic variants, may carry equal or more weight in determining CAD development.

Another study evaluated 45 genetic variations that have been associated in genome-wide association studies with CAD, ischemic heart disease, or MI. This study assessed more than 6000 Danish subjects to evaluate a risk score that added the number of risk alleles of the 45 SNPs that each subject carried and assessed for association with development of MI or CAD over a mean 11.6-year follow-up. The genetic risk score when assessed by allele was significantly associated with occurrence of MI but not with development of CAD, and the hazard ratio for Cox proportional hazards regression assessment for association MI revealed a statistically significant but small effect size (hazard ratio, 1.06; 95% confidence interval, 1.02 to1.11).[126] No association was found between genetic risk score and development of CAD. Furthermore, when the association between genetic risk score and MI was adjusted for EuroSCORE (European System for Cardiac Operative Risk Evaluation), the association was no longer significant.[126] This finding suggests that if a meaningful genetic risk score for predicting CAD is possibly to be developed in the future, the basis will need to be a strong understanding of the biology behind each of these whole-genome association study discovered SNP associations. Understanding of the biology of the variations that would include determining the interface between genetic variant and environment will be necessary to determine how the existence of these variants can be used to determine meaningful risk. Furthermore, a negative test result for genetic risk factors does not guarantee that the patient will not ultimately develop CAD secondary to environmental risk factors or even genetic risk variants that have yet to be identified. Approaches such as blood pressure reduction, augmented antiplatelet therapy, and aggressive cholesterol lowering have all been shown to reduce the risk for CAD substantially and are considered safe, but universal administration of these therapies is financially unfeasible and would lead to unavoidable side effects. Theoretically, with the use of more precise genomic information, it may be possible to identify disease-susceptible patients for whom intensive prevention is cost effective. However, this remains to be proven. Finally, even if future studies determine useful genetic risk panel assessments for multigenic diseases such as CAD, potentially problematic legal and ethical issues could complicate clinical genetic testing for complex diseases because these tests they may have potentially significant effects on health insurance premiums or employment. Another application of identifying the biology underlying genetic associations with multigenic disorders lies in the development of new therapeutic approaches. Most genetic variants discovered to be associated with CAD in whole-genome association studies act through biologic pathways that are not yet fully understood.[104] However, the discovery of significant associations between genetic variants in the gene encoding PCSK9 (proprotein convertase subtilisin/kexin type 9)

at chromosomal location 1p32 and increased incidence of CAD has helped lead to the development of a therapeutic monoclonal antibody (evolocumab) to inhibit PCSK9 for purposes of lowering low-density lipoprotein cholesterol.[104,127] Use of evolocumab has been assessed in multiple phase II and phase III trials and in a randomized trial was shown over 1-year follow-up to be associated with significant decreases in low-density lipoprotein cholesterol as well as decreased adverse cardiovascular events (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78).[127] However, the evolocumab-treated group was noted to have significantly increased incidence of neurocognitive events, although these events occurred in fewer than 1% of patients.[127]

Finally, another way to translate genetic information into practice of clinical cardiovascular medicine is through better understanding of genetic responsiveness of patients to medications prescribed to address cardiovascular diseases and their sequelae. This concept that drug selection can be personalized to a person's genetic susceptibility is a straightforward idea. However, several hurdles must be overcome for this to become common practice in cardiovascular medicine. The primary problem is to provide convincing evidence that a gene contributes to disease development and progression. In gene association studies, an SNP associated with an outcome phenotype is not necessarily functionally relevant and may simply be tightly linked with the real (but unidentified) causal genetic variant. In some cases, the SNP identified in an SNP association study may not even lie within a known or putative gene. Additionally, for candidate genes identified by functional genomic studies, the difficulty is in determining whether gene expression levels are altered because the genes are contributing to disease biology or whether the genes are altered as a consequence of the disease process.

In some areas, however, knowledge of genetic variation has led to pharmacogenomic personalization of treatment in cardiovascular medications.[128] The pharmacogenomics of warfarin is an example. Warfarin is an anticoagulant administered to patients with prothrombotic risks such as chronic atrial fibrillation or the presence of a mechanical heart valve to prevent thrombosis and associated thromboembolic events. Warfarin also has a narrow therapeutic window, is metabolized by cytochrome P450, and shows large variations in dose requirements between patients. Patients with CYP2C9*2 and CYP2C9*3 allele variants (cytochrome P450 2C9 enzyme) and patients with the A haplotype of the *VKORC1* gene (vitamin K epoxide reductase complex subunit 1) seem to require lower doses of warfarin to achieve an optimal state of anticoagulation.[128–130] In 2005, the US Food and Drug Administration changed the label of warfarin to point out the potential relevance of genetic information to prescribing decisions.[131] However, randomized trials of pharmacogenetic algorithms that have used *CYP2C9* and *VKORC1* genotyping to guide warfarin dosing have had mixed results, and further studies are needed to determine how these genotypes may effectively guide initial dosing of warfarin as well as long-term monitoring of international normalized ratio.[132,133]

Perioperative Genomics in Cardiac Surgery

Despite advances in surgical, anesthetic, and cardioprotective strategies, the incidence of perioperative adverse events in cardiac surgical procedures continues to be significant and is associated with reduced short- and long-term survival.[134] Because all surgical patients are exposed to perturbations that potentially activate inflammation, coagulation, and other stress-related pathways, but only a subset of patients experience adverse perioperative events (even after controlling for coexistent disease), a genetic component is likely (Fig. 8.15).[135–137] The field of perioperative genomics uses gene association study approaches to identify novel genetic loci associated with adverse short- and long-term postoperative events, but it is also beginning to use functional genomic approaches to discover underlying biologic mechanisms that explain why similar patients have dramatically different postoperative outcomes.[138]

Gene association studies of cardiac surgical patients have identified genetic loci associated with adverse postoperative events such as myocardial ischemia or myocardial injury,[139,140] postoperative ventricular dysfunction,[141] postoperative atrial fibrillation,[142–144] vein graft restenosis,[139] renal compromise,[145] neurocognitive dysfunction,[146] stroke,[147] and death,[139] as well as other, in some cases more systemic, outcomes such as bleeding,[148] thrombosis,[149] inflammatory responses, and severe

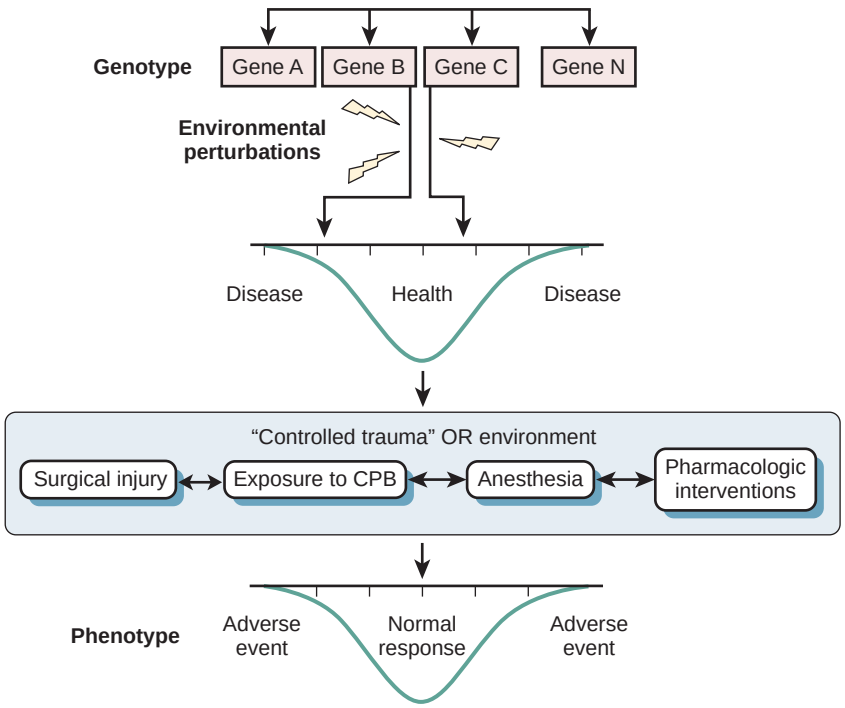


Fig. 8.15 The possible role of genetic factors combined with perioperative insults in adverse postoperative outcomes. *CPB*, Cardiopulmonary bypass; *OR*, operating room.

sepsis.[150–153] Just a few examples of perioperative genomics research resources within the United States are listed here:

- The Duke Perioperative Genomics investigative team initiated a single institution prospective study in 2001 (the Perioperative Genomics and Safety Study, US [PEGASUS]).
- Also in 2001, investigators at Texas Heart Institute, Houston, and Brigham and Women's Hospital, Boston, initiated a multiinstitution perioperative genomics research group now known as PeriGRen (Perioperative Genomics Research Network), which since added a third study site enrolling at the University of Texas Southwestern Medical Center in Dallas, Texas.
- Vanderbilt University Medical Center in Nashville, Tennessee created a DNA and data repository across their hospital system that allows for fruitful exploration of perioperative genomics research questions.

The overriding goals of the these large perioperative genomics research database and biobank projects is to identify genetic loci associated with adverse postoperative cardiovascular and renal events during the months and years following surgical procedures, to investigate the biology that underlies genetic contributions to adverse cardiovascular events, to determine how to alter clinical management of surgical patients based on knowledge of patent genetics, and finally to explore overlap between genetic contributions to adverse cardiovascular events in the postoperative setting and similar phenotypes that occur in nonsurgical patients (ie, ambulatory heart failure, atrial fibrillation).

Will genetic or genomic studies result in practical information capable of facilitating therapeutic interventions designed to improve outcome after cardiovascular operations? This has yet to be determined because perioperative genomics is still in its early phases. Cardiac surgical study cohorts with data and biobanks are just becoming large enough to allow for powerful multiinstitution collaborations. Such collaboration is vital to being able to replicate genetic associations. These collaborations will also be essential for pooling data in large enough numbers to be able to leverage fully the large amount of potential information provided by whole-genome genotyping but allow adequate statistical power to detect modest but biologically relevant effect sizes. The 4q25 locus, which has been identified by whole-genome association studies of ambulatory patients as containing SNPs associated with atrial fibrillation,[154] is also associated with increased incidence of atrial fibrillation after cardiac operations.[143] The 9p21 locus, which has been associated in whole-genome association studies with CAD[122] and MI[121] in ambulatory cohorts, contains a variant also associated with postoperative myocardial injury after coronary artery bypass graft operations.[140] The key will be to understand the biology that underlies these associations to best design perioperative interventions to prevent these postoperative outcomes in all patients, but particularly those patients identified at highest genetic risk. Advances in gene expression techniques and analyses as well as proteomics should expand meaningful assessment of functional genomics for applicability to cardiac surgical patients.

Gene Therapy

Although molecular diagnostic techniques have advanced rapidly, gene therapy is still just tantalizingly out of the scope of routine clinical practice for treating cardiovascular disorders. One overriding concept of gene therapy is to correct a faulty genetic sequence by using an affected cell's molecular workings. Another gene therapy objective is the targeting of drug delivery to specific organs by using molecular techniques. The focus of this discussion is on studies of gene therapy designed to address heart failure in human patients.

Gene therapies are designed to modify expression of genetic material. Although myriad approaches have been suggested, these all fall into three basic strategies: (1) gene transfer to restore or increase gene expression, (2) gene silencing to inhibit gene expression selectively, and (3) gene editing to "correct" DNA.[37] Each gene therapy strategy requires a vector (usually a modified virus) to carry a therapeutic genetic component such as complementary DNA, small interfering RNA, microRNA (miRNA), or small hairpin RNA into a target cell for the purpose of generating altered protein synthesis.[37] Cardiac gene transfer is now a routine technique in laboratory cell cultures and can be performed with reasonable ease in animal models such as transgenic animals. However, application in the clinical setting has been slow, to ensure gene therapy techniques that appropriately target cardiac myocytes while minimizing expression of the delivered gene in nontarget organs

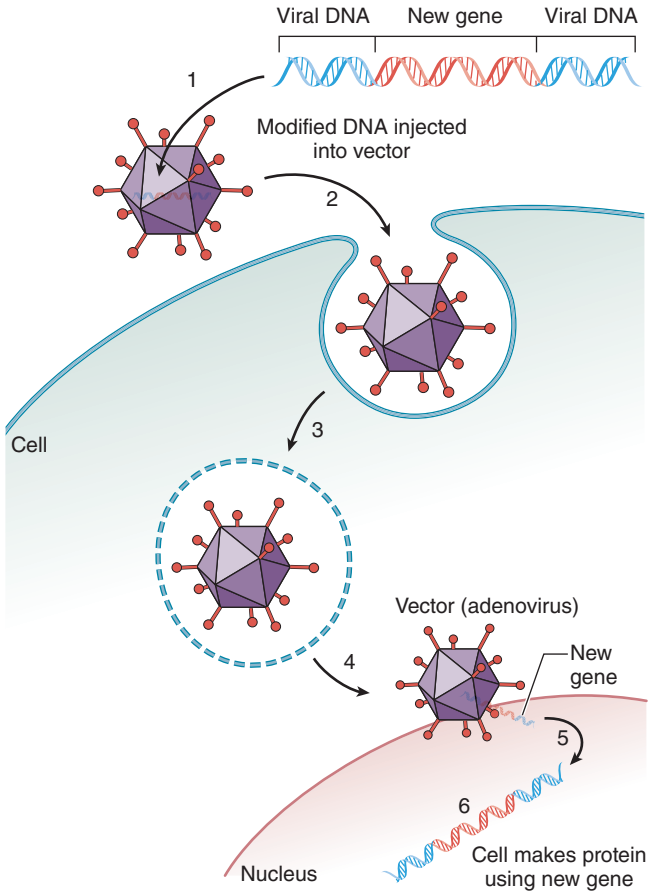


Fig. 8.16 Gene transfer in gene therapy. *Top left* in *1*, the new gene attaches to the viral DNA. In *2*, the vector binds to the cardiomyocyte's membrane and enters the cell. In *3* and *4*, it traverses the cytoplasm. In *5*, it docks on the nuclear membrane, and in *6*, the gene is incorporated into the host cell's DNA. *(From National Library of Medicine. In: Braunwald E. The war against heart failure: the Lancet lecture.* Lancet. *2015;385:814.)*

Fig. 8.16 is a schematic of gene transfer using a viral vector. Recombinant adenoassociated viruses (AAVs) are cardiotropic and thus are potentially good vectors in gene transfer therapies designed to treat heart failure.[155] Sarcoplasmic-endoplasmic reticulum ATPase (SERCA2a) plays an important role in intracellular Ca^{2+} handling and cardiomyocyte relaxation. Impaired SERCA2a activity has been reported in patients with heart failure.[155] After a large series of preclinical studies, SERCA2 cDNA was the first cardiac gene transfer to be tested in humans. The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) trial was a phase I/II trial that provided a single intracoronary gene therapy infusion of AAV1/SERCA2a in nine patients who had systolic heart failure (left ventricular ejection fraction ≤30%; New York Heart Association functional class III to IV).[156] Two of these patients had anti-AAV1 antibodies and did not respond to therapy.[37,156] This possibility is a disadvantage of using viral vectors for gene transfer therapy.[155] Six patients showed some improvement in heart failure assessments during the 6 months after gene therapy.[156]

This study was followed by the CUPID 2 trial, which was a double-blind, placebo-controlled phase II trial that enrolled 39 patients with systolic heart failure. Patients in the intervention group received intracoronary gene therapy infusion of AAV1/SERCA2a cDNA (some received lower dose, some medium dose, some high dose). At 6 months after infusion, subjects in the intervention group had significantly better simultaneous assessments of heart failure symptoms, functional status, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) heart failure biomarker, and left ventricular ejection fraction.[157] At 12 months and 3 years after infusion, patients in the intervention group had experienced significantly decreased frequency of cardiovascular events, and no adverse effects of the intervention were noted.[157,158] Evidence of long-term transgene presence was observed in the patients who received high-dose AAV1/SERCA2a cDNA therapy.[158] A 200-patient multicenter, multinational, double-blind randomized placebo-controlled phase IIb trial is currently being undertaken, and the results of this trial may move this gene transfer therapy to clinical practice.[159]

Inhibition of gene expression by antisense treatment is similarly full of promise.[160–162] The basis of this technique is that mRNA can no longer be translated efficiently into protein when it is bound to a complementary strand of nucleic acid, a so-called antisense strand. Thus by introducing specific antisense DNA into cells, expression of a selected gene product can be inhibited. The problem here again is efficient targeting of the tissue of interest. Remarkably, cells are able to take up antisense material from the extracellular environment without degrading it, but the material still must be brought in contact with the tissue of interest. A second technical problem involves the stability of the antisense DNA. Because most diseases for which this technique seems suitable require constant inhibition of gene expression over long periods, the antisense construct must be highly stable, and this degree of stability has not yet been consistently achieved.

MicroRNAs and Antagomir Therapy

Micro-RNAs (miRNAs) are short, noncoding RNA gene products that silence mRNA by pairing with mRNA messenger sites and preventing protein translation. Preclinical research on miRNA identified that these molecules play an integral role in development of heart failure and other diseases. Thus the potential exists to manipulate miRNAs to treat cardiovascular diseases. The potential also exists to use circulating miRNAs for biomarker assessment of severity of clinical phenotypes such as heart failure.[155] Antagomirs are single-stranded mRNA analogues designed to be complementary to and thus silence specific miRNAs. Antagomir therapy (miravirsen; a locked nucleic acid modified DNA phosphorothioate antisense oligonucleotide that sequesters mature miRNA122) was shown in a phase IIa trial to treat hepatitis C successfully in human patients.[155,163] Although antagomir therapy has not yet been tested in human subjects to address cardiovascular phenotypes such as heart failure, some antagomirs have been administered in animal studies with corresponding improvement in cardiac function.[155]

Thus molecular therapy for cardiovascular disease seems feasible but is not yet quite ready for the clinic. Nonetheless, the concepts appear sound, and they have been proved in animal models. It appears to be only a matter of time before patients will be treated with these methods.

Cell Therapy

Cell therapy is primarily being investigated in cardiovascular medicine for the purpose of regenerating damaged myocardium.[155] Stem cells are undifferentiated precursor cells that can differentiate into specialized cells including cardiomyocytes. Embryonic stem cells derived from cryogenically preserved human embryos have been differentiated into cardiomyocytes that have been used to regenerate myocardium in infarcted primate hearts. However, certain disadvantages hinder moving the use of allogeneic embryonic stem cells into clinical practice for myocardial regeneration. These include ethical concerns about use of cells from human embryos, the need for immunosuppression to avoid rejection of allogenic cells, and the risk for teratoma formation.

As an alternative to embryonic stem cell therapy, research has focused on induced pluripotent stem cells that can be derived from autologous adult somatic cells and then differentiated into cardiomyocytes. Although the use of induced pluripotent stem cells avoids the need for immunosuppression, concerns remain regarding teratoma formation, and no clinical trials conducted thus far have used induced pluripotent stem cells in human subjects.[155]

Other types of adult stem cells are more limited in their ability to differentiate into different tissue cell types (multipotent stem cells), but they have shown promise in treatment of myocardial injury and heart failure.[40,155,164] Bone marrow contains a variety of stem cells, and unfractionated autologous bone marrow–derived mononuclear cells (BMMNCs) have been studied in multiple clinical trials to treat heart failure and post-MI injury.[155] BMMNCs do not differentiate into cardiomyocytes, but they may potentiate myocardial function and recovery through paracrine effects that involve secretion of cytokines and chemokines and induction of angiogenesis.[155,164] A metaanalysis of 50 clinical trials of adult bone marrow cell therapy administered by intracoronary or intramyocardial routes to treat ischemic heart disease (n = 2625 patients) found that patients treated with bone marrow cells (BMCs) or BMMNCs had significantly increased left ventricular ejection fractions (3.96%; 95% confidence interval, 2.90% to 5.02%), smaller infarct size, and lower end-diastolic left ventricular volume ($P < 0.0001$). Mortality rates were also significantly lower in the BMC/BMMNC-treated patients.[165] Although these results appear promising, the efficacy of BMC/BMMC treatment remains controversial in that that several studies within the metaanalysis group did not show a clinically significant impact.[155] The BAMI Trial (Effect of Intracoronary Reinfusion of BMMNC on All-Cause Mortality in Acute Myocardial Infarction Trial; NCT01569178) is an ongoing multinational, multicenter randomized trial that is scheduled to enroll 3000 patients with systolic left ventricular dysfunction through May 2017; it should provide greater clarity regarding the efficacy of this mode of cell therapy.[155]

Studies of mesenchymal stem cells in swine suggest that these cells also can differentiate into cardiomyocytes and have paracrine effects that may reduce myocardial fibrosis.[155,166] Mesenchymal stem cells may be hypoimmunogenic, so the potential exists not only for effective autologous treatment but also for possible allogeneic treatment without the need for immunosuppressive therapy.[155] Adipose tissue–derived stem cells have also been studied for efficacy in cardiac regeneration and appear to be able to differentiate into cardiomyocytes; these cells had promising results in the PRECISE trial (n = 36; NCT00426868) of subjects with ischemic heart failure.[155,167] A multisite, phase II international placebo-controlled, blinded trial of the efficacy of intracoronary injection of adipose derived regenerative cells in the setting of acute ST-segment elevation MI is under way (ADVANCE Trial; NCT01216995).[155]

The final two categories of cell therapy currently being investigated for treatment of ischemic cardiomyopathy are transplantation of autologous cardiac stem cells and intracoronary infusion of cardiospheres. The Autologous Human Cardiac-Derived Stem Cell to Treat Ischemic Cardiopathy (ALCADIA; NCT00981006) trial is investigating the effectiveness of administering autologous multipotent cardiac stem cells in addition to fibroblastic growth factor in patients with heart failure and ischemic cardiomyopathy.[155] Cardiospheres are a mixture of cardiac stem cells, mesenchymal cells, and endothelial cells that are adherent to one another and can be harvested from the human heart by percutaneous endomyocardial biopsy.[155] The Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS; NCT 00893360) trial was a phase I trial that assessed the efficacy of intracoronary infusion of autologous cardiospheres and found a reduction of myocardial scar and an increase in myocardial viability and regional myocardial function in the treatment versus control group in patients who had reduced left ventricular ejection fraction 1.5 to 3 months after acute MI.[168] Like mesenchymal stem cells, cardiospheres may also be hypoimmunogenic and may not require immunosuppression to be used for allogeneic treatment.[155]

This concept is important because some research suggests that autologous stem cell therapy in older patients is less effective than autologous treatment in younger patients. This suggests the question whether allogeneic treatment with certain types of adult stem cells from younger patients to older patients could be more effective than autologous treatment if it could be accomplished without immunosuppression.[164] Efficacy of allogeneic cardiosphere treatment of patients after MI who have reduced left ventricular ejection fraction is being studied in the phase II and then phase II multicenter trial Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration (ALLSTAR; NCT01458405). Although clinical trials are bringing cell therapy closer to reality for routine treatment of clinical heart failure, future research will need to identify which forms of cell therapy are most effective in which patients and with what timing of therapy and by what route of administration.

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9 Systemic Inflammation

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KEY POINTS

1. Mortality and morbidity are relatively common after major surgical procedures.
2. Postoperative morbidity often involves multiple organ systems, and this implies a systemic process.
3. Excessive systemic inflammation is proposed to be a cause of postoperative organ dysfunction.
4. No interventions that attenuate systemic inflammation have been proved in large, randomized clinical trials to protect patients from morbidity and mortality.

Numerous advances in perioperative care have allowed increasingly high-risk patients to undergo cardiac surgical procedures safely. Although mortality rates of 1% are quoted for "low-risk" cardiac operations, results from large series of patients older than 65 years of age suggest that mortality rates are actually more substantial.[1] For example, Birkmeyer and colleagues[1] reviewed a large number (N = 474,108) of "all-comers" undergoing coronary artery bypass graft (CABG) procedures or aortic valve surgical procedures who were in the Medicare Claims Database. Notably, the 30-day all-cause mortality rate was in the range of 4.0% to 5.4% after CABG and 6.5% to 9.1% after aortic valve replacement. The patient population studied, although older (age >65 years), would not be considered to be particularly high risk by today's standards. These data do not point to the cause of death. Nevertheless, they indicate that the outcome after routine cardiac surgical procedures is poor for many patients. The outcome after these procedures is even worse if the extent of postoperative complications is considered. Postoperative morbidity is common,[2] and complications include atrial fibrillation, poor ventricular function requiring inotropic agents, and non–cardiac-related causes such as infection, gastrointestinal dysfunction, acute lung injury, stroke, and renal dysfunction. For example, in the report by Rady and associates[3] of large series of patients who were 75 years of age or older and who underwent cardiac surgical procedures (N = 1157), the mortality rate was 8%. The rate of serious complications, however, exceeded 50%.

An exaggerated systemic proinflammatory response to surgical trauma is a proposed cause of many postoperative complications ranging from organ dysfunction to death.[4–6] However, the cause and clinical relevance of systemic inflammation after cardiac operations are poorly understood. Systemic inflammation is a multifactorial process and has profound secondary effects on both injured and normal tissues. Proinflammatory mediators can have beneficial as well as deleterious effects on multiple organ systems. According to most theories, tissue injury, endotoxemia, and contact of blood with the foreign surface of the cardiopulmonary bypass (CPB) circuit are some of the major factors postulated to initiate a systemic inflammatory response. Nevertheless, controversy surrounds the cause and pathogenesis of inflammation in the perioperative period.

Terminology

The terminology of inflammation is confusing and has hampered effective communication among scientists and clinicians. Despite attempts to standardize this terminology, variation in usage still exists in the scientific literature, as well as the clinical setting.[7] Much of the confusion relates to the term *inflammation*, defined as "a fundamental pathologic process consisting of a dynamic complex of cytologic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biologic agent, including (1) the local reactions and resulting morphologic changes, (2) the destruction or removal of the injurious material, and (3) the responses that lead to repair and healing."[8] This definition acknowledges the potential role of noninfectious causative factors (ie, infection is not a prerequisite for the development of inflammation). The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference developed definitions for terms related to inflammation (Box 9.1). Fig. 9.1 demonstrates the possible interrelationships among many of these terms.

In particular, the *systemic inflammatory response syndrome* (SIRS) refers to an inflammatory process that can arise from infection or in its absence. A viewpoint consistent with the recommended terminology is that systemic inflammation is a spectrum from mild systemic inflammation without organ dysfunction to a more severe form characterized by multisystem organ failure and death. Many clinicians do not routinely think of systemic inflammation as a clinical entity, for three reasons: (1) no universally accepted tests (eg, physical diagnosis or laboratory assays) are available to measure the degree of systemic inflammation reliably and accurately; (2) even if such a test existed and it was known that a patient had "severe" SIRS, the clinician still would not be able to predict (a) whether organs would fail, (b) which organs would fail, and (c) when organs would fail; and (3) even if SIRS could be diagnosed accurately, currently no therapies in widespread clinical use improve clinical outcomes through the prevention or treatment of systemic inflammation.

In surgical patients, the use of the phrase SIRS and the definition of SIRS have generated some controversy.[9] The reason is that almost all patients after major surgical procedures fulfill the criteria for SIRS. Most patients, however, clearly do not develop clinically significant organ dysfunction from systemic inflammation. Critics may argue that the use of the term *SIRS* in cardiac surgical patients is therefore meaningless because it does not differentiate patients who will have a benign course from those with a complicated postoperative course. For these reasons, *SIRS* is used more commonly by investigators than by practicing physicians. Nevertheless, the use of this term has the benefit of increasing awareness regarding the many noninfectious causes of inflammation.

The distinction between systemic and local inflammation is important. Local inflammation has several beneficial purposes. Invasion of the injured or infected tissue by inflammatory cells (ie, neutrophils and macrophages) results in high concentrations of cells involved in host defense. Local mediator-induced edema and clotting of lymphatics by fibrinogen result in the effective "walling off" of the injured area. In contrast, systemic inflammation is not limited to the initial

BOX 9.1 DEFINITIONS RELATED TO INFLAMMATION

Infection: microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms

Bacteremia: presence of viable bacteria in the blood

Systemic inflammatory response syndrome (SIRS): systemic inflammatory response to a variety of severe clinical insults that is manifested by two or more of the following conditions: (1) temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or $PaCO_2$<32 mm Hg; and (4) white blood cell count >12,000/mm^3, <4000/mm^3, or >10% immature (band) forms

Sepsis: systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats/min; (3) respiratory rate >20 breaths/min or $PaCO_2$<32 mm Hg; and white blood cell count >12,000/mm^3, <4000/mm^3, or >10% immune (band) forms

Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock: sepsis-induced with hypotension despite adequate fluid resuscitation together with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Sepsis-induced hypotension: systolic blood pressure <90 mm Hg or reduction of ≥40 mm Hg from baseline in the absence of other causes of hypotension

Multiple organ dysfunction syndrome (MODS): presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

$PaCO_2$, Arterial partial pressure of carbon dioxide.
From Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: ACCP/SCCM consensus conference. *Chest.* 1992;101:1644–1655.

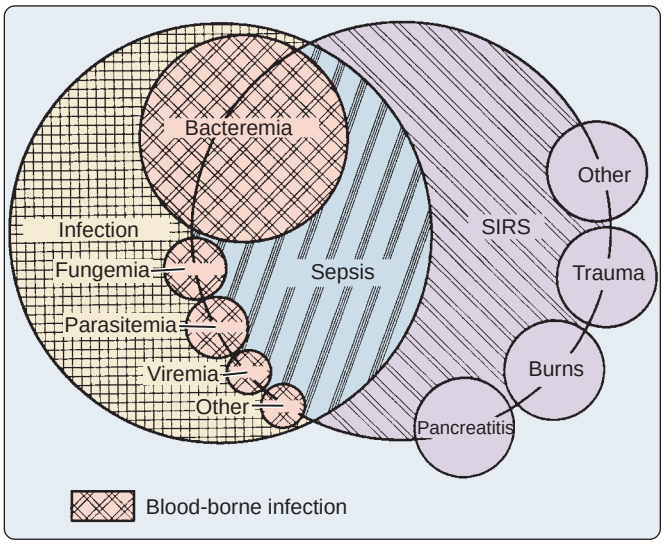

Fig. 9.1 The interrelations among systemic inflammatory response syndrome *(SIRS)*, sepsis, and infection. *(From Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis: ACCP/SCCM Consensus Conference.* Chest. *192;101:1644–1655.)*

area of infection or injury. The systemic elaboration of inflammatory mediators may be beneficial by heightening the host's general defenses. However, it may also lead to "autodestruction" of the host through secondary damage to tissues and organs not originally affected by the primary injury or infection.

The *acute-phase response* to tissue injury and infection is characterized by leukocytosis, fever, increased vascular permeability, a negative nitrogen balance, changes in plasma steroid and metal concentrations, and increased synthesis of hepatic acute-phase proteins. Examples of these proteins include haptoglobin, fibrinogen, C-reactive protein (CRP), complement factors (C3, factor B), serum amyloid A, α_1-acid glycoprotein, and α_1-antichymotrypsin.[10] The terms *acute-phase response* and *systemic inflammation* often are used interchangeably.

A common misconception relates to the terms *bacteremia* and *endotoxemia*. Whereas *bacteremia* refers to the presence of viable bacteria in the blood, *endotoxemia* refers to the presence of endotoxin in the blood. Endotoxin, also known as lipopolysaccharide (LPS), is a component of the cell membranes of gram-negative bacteria, and hence its presence does not require the existence of viable organisms. In fact, investigators have clearly established that cardiac surgical patients have a high incidence of intraoperative endotoxemia despite simultaneously exhibiting a low incidence of culture-proven bacteremia. This observation is consistent with the finding that "sterile" instruments and solutions, including intravenous fluids and the CPB circuit, may be contaminated with endotoxin.[11]

Systemic Inflammation and Cardiac Surgical Procedures

The systemic inflammatory response after cardiac operations is multifactorial. As described earlier, the term *SIRS* is not particularly helpful in clarifying the pathophysiology of inflammation in cardiac surgical procedures.[9] A schematic of the inflammatory process is depicted in Fig. 9.2. Clinicians generally agree that all these processes may happen and may be associated with complications in cardiac surgical patients.

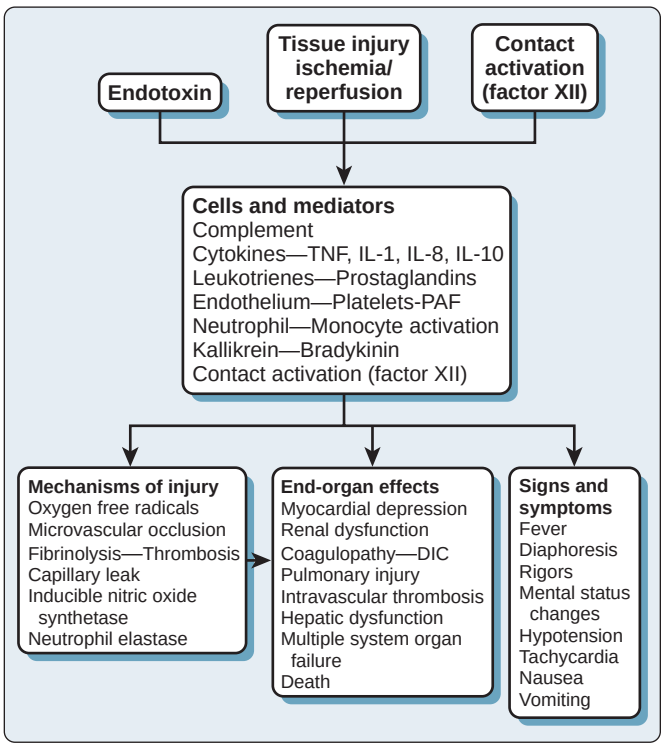

Fig. 9.2 Overview of inflammation. *DIC,* Disseminated intravascular coagulation; *IL,* interleukin; *PAF,* platelet-activating factor; *TNF,* tumor necrosis factor.

Tissue injury, endotoxemia, and contact of blood with the foreign surface of the CPB circuit are thought to initiate a systemic inflammatory response after cardiac surgical procedures. What is least understood and most controversial is the issue of which of these many processes is the most clinically relevant. It appears as if major surgical procedures comprise an important cause of systemic inflammation, and CPB further exacerbates the elaboration of proinflammatory mediators. Various causes and mediators of inflammation are reviewed in the subsequent sections.

Mechanisms of Inflammation-Mediated Injury

It is not entirely clear how inflammation ultimately damages cells and organ systems. Activation of neutrophils and other leukocytes is central to most theories of inflammation-induced injury.[6,12–15] Neutrophil activation leads to the release of oxygen radicals, intracellular proteases, and fatty acid (ie, arachidonic acid) metabolites. These products, as well as those from activated macrophages and platelets, can cause or exacerbate tissue injury.

In localized areas of infection, oxygen free radicals liberated by activated neutrophils aid in the destruction of pathogens.[16] Complement, in particular, C5a, results in activation of leukocytes and oxygen free radical formation.[17] These activated neutrophils liberate toxic amounts of oxygen free radicals such as hydrogen peroxide, hydroxyl radicals, and superoxide anion. Oxygen free radicals are thought to cause cellular injury, ultimately through damage to the lipid membrane.[18–20] Increased levels of lipid peroxidation products (ie, products of oxidation of membrane lipids such as malondialdehyde) are thought to reflect the severity of free radical cellular damage.[21] Consistent with this model of injury, Royston and colleagues[22] demonstrated increased levels of peroxidation products in cardiac surgical patients. In another study, oxygen free radicals were found to be increased in 21 patients undergoing cardiac operations; however, the clinical relevance of these changes was not studied.[21]

A related mechanism of injury results from the degranulation of neutrophils. Activated neutrophils release granules that contain myeloperoxidase, as well as other toxic digestive enzymes such as neutrophil elastase, lactoferrin, β-glucuronidase, and *N*-acetyl-β-glucosaminidase.[23–26] Release of these intracellular enzymes not only causes tissue damage but also reduces the number of cells that can participate in bacterial destruction. In one study, cardiac surgical patients who developed splanchnic hypoperfusion, a possible cause of inflammation, had increased neutrophil degranulation and increased plasma neutrophil elastase concentrations.[26]

Another mechanism of inflammation-mediated injury involves microvascular occlusion. Activation of neutrophils leads to adhesion of leukocytes to endothelium and formation of clumps of inflammatory cells (ie, microaggregates).[14,27] Activated leukocytes have less deformable cell membranes, and this affects their ability to pass through capillaries.[28] Microaggregates can cause organ dysfunction through microvascular occlusion and reductions in blood flow and oxygen at the local level.[22,28,29] After the disappearance of these microaggregates and restoration of microvascular flow, reperfusion injury may occur.

Finally, activated leukocytes release leukotrienes such as leukotriene B_4. Leukotrienes are arachidonic acid metabolites generated by the lipoxygenase pathway. They markedly increase vascular permeability and are potent arteriolar vasoconstrictors. These leukotriene-mediated effects account for some of the clinical signs of systemic inflammation, in particular, generalized edema, as well as "third-space losses." Prostaglandins, generated from arachidonic acid through the cyclooxygenase pathway, also act as mediators of the inflammatory process.

Physiologic Mediators of Inflammation

Cytokines

Cytokines are believed to play a pivotal role in the pathophysiology of acute inflammation associated with cardiac surgical procedures.[30,31] Cytokines are proteins released from activated macrophages, monocytes, fibroblasts, and endothelial cells that have far-reaching regulatory effects on cells.[32] They are small proteins that exert their effects by binding to specific cell-surface receptors. Many of these proteins are called *interleukins* because they aid in the communication between white blood cells (leukocytes).

Cytokines are important components of the acute-phase response to injury or infection. The acute-phase response is the host's physiologic response to tissue injury or infection and is intended to fight infection, as well as contain areas of diseased or injured tissue. Cytokines mediate this attraction of immune system cells to local areas of injury or infection. They also help the host through activation of the immune system, thus providing for an improved defense against pathogens. For example, cytokines enhance the function of both B and T lymphocytes, therefore improving both humoral and cell-mediated immunity. Most cytokines are proinflammatory, whereas others appear to exert an antiinflammatory effect, suggesting a complex feedback system designed to limit the amount of inflammation. Excessive levels of cytokines, however, may result in an exaggerated degree of systemic inflammation that may lead to greater secondary injury. Numerous cytokines (tumor necrosis factor [TNF], interleukin-1 [IL-1] to IL-16), as well as other protein mediators (eg, transforming growth factors, macrophage inflammatory proteins), have been described and may play an important role in the pathogenesis of postoperative systemic inflammation. The cytokines that have received the most attention related to cardiac surgical procedures include TNF, IL-1, IL-1 receptor antagonist (IL-1ra), IL-6, IL-8, and IL-10.

Tumor Necrosis Factor

TNF is one of the earliest cytokines detected in the blood after the activation of macrophages and other proinflammatory cells. One factor complicating studies of TNF is that TNF has two similar forms, TNF-α and TNF-β, as well as two distinct receptors, TNFR-I and TNFR-II. TNF appears to be pivotal in initiating the complex inflammatory cascade. Endotoxin is a potent stimulus for TNF production.

Endotoxemia unequivocally results in initiation of proinflammatory pathways, most likely through stimulation of TNF.[33–36] Michie and associates[33] administered endotoxin intravenously to human volunteers and detected peak levels of TNF 90 to 180 minutes later. Peak concentrations of TNF correlated with increased temperature and heart rate (HR), as well as circulating levels of adrenocorticotropic hormone and epinephrine. In this and other studies, TNF levels soon appeared after a proinflammatory stimulus and disappeared quickly, thus helping explain a common finding from clinical studies. TNF levels are often not increased when they are measured in patients with systemic inflammation, probably because test samples are obtained long after exposure to the primary inflammatory stimulus. This issue of sampling time may partially account for the finding that some cardiac surgical studies have detected increased TNF levels, whereas others have not.[37–53]

Interleukins

After the appearance of TNF, levels of IL-1 increase in cardiac surgical patients.[47,50,52,54] Measured levels are low and may peak within several hours after CPB.[54] Other studies have demonstrated maximum levels 1 day after cardiac surgical procedures, and this may explain the inability of some investigators to detect IL-1 during the intraoperative period.[50] IL-1 may decrease systemic vascular resistance after CPB through induction of nitric oxide synthesis in vascular endothelial cells.[55] Although IL-1 appears to be important in the initiation and propagation of the inflammatory cascade, it is not clear whether IL-1 levels cause deleterious effects or even serve as a marker for patients who will develop organ dysfunction after cardiac operations. Some of the reported effects of IL-1 may instead be caused by other cytokines, in particular, TNF, which are detected at the same time.

IL-8 is also believed to be an important component of the proinflammatory cascade. It is a potent chemoattractant of neutrophils to the site of injury or infection. IL-8 also is responsible for the activation, priming, and degranulation of neutrophils.[56,57] The relevance of

increases in IL-8 levels to outcome after cardiac surgical procedures has not been established.[42–44,46,47,51,53,58,59] Rothenburger and colleagues[60,61] observed a significant association between prolonged mechanical ventilation and postoperative IL-8 levels but not IL-6 levels.

IL-6 levels have been shown to increase in the setting of cardiac surgical procedures, although this finding is not universal.[10,42,43,45–48,51–54,58,62–65] Peak levels of this cytokine appear after maximum values for TNF and IL-1. For example, Steinberg and associates[54] measured plasma cytokine levels in 29 patients undergoing CPB. IL-6 levels peaked at 3 hours after separation from CPB and remained increased 24 hours postoperatively. No association was found between IL-6 levels and hemodynamic parameters or postoperative pulmonary function.

Antiinflammatory Cytokines

The regulation of inflammation is complex and involves a balance between proinflammatory and antiinflammatory cytokines. IL-10 is a potent inhibitor of the synthesis of TNF, IL-1, IL-6, and IL-8, and it increases in the perioperative period.[44,66–68] McBride and colleagues[68] obtained blood samples perioperatively from 20 patients undergoing cardiac surgical procedures. Before and during CPB, increases were observed in the proinflammatory cytokines TNF, IL-1, and IL-8. At the same time that proinflammatory cytokine levels began to decrease, increases in the antiinflammatory cytokines IL-10 and IL-1ra were observed. These investigators suggested that the balancing effects of these two types of cytokines may determine whether a patient suffers from the effects of excessive systemic inflammation (ie, postoperative organ dysfunction) or the effects of inadequate immune system enhancement (ie, postoperative infection and poor wound healing). Using this theory to improve outcome has not been translated yet into a clinical trial involving surgical patients. One concern related to potentially deleterious effects of inhibiting proinflammatory mediators has been borne out in sepsis trials in which mortality rates were increased in the group given an antiinflammatory agent.[69] An understanding of the interaction between proinflammatory and antiinflammatory mediators may result in the development of an effective and safe approach to reducing complications related to excessive systemic inflammation.

Complement System

The complement system describes at least 20 plasma proteins and is involved in the chemoattraction, activation, opsonization, and lysis of cells. Complement also is involved in blood clotting, fibrinolysis, and kinin formation. These proteins are found in the plasma, as well as in the interstitial spaces, mostly in the form of enzymatic precursors.

The complement cascade, illustrated in Fig. 9.3, can be triggered by either the *classic pathway* or the *alternate pathway*. In the alternate pathway, C3 is activated by contact of complement factors B and D with complex polysaccharides, endotoxin, or exposure of blood to foreign substances such as the CPB circuit. *Contact activation* describes contact of blood with a foreign surface with resulting adherence of platelets and activation of factor XII (Hageman factor) (Fig. 9.4). Activated factor XII has numerous effects, including initiation of the coagulation cascade through factor XI and conversion of prekallikrein to kallikrein. Kallikrein leads to generation of plasmin, which is known to activate the complement and the fibrinolytic systems. Kallikrein generation also activates the kinin-bradykinin system.

The classic pathway involves the activation of C1 by antibody-antigen complexes. In the case of cardiac surgery, two mechanisms for the activation of the classic pathway are likely. Endotoxin can be detected in the serum of almost all patients undergoing cardiac surgical procedures. Endotoxin forms an antigen-antibody complex with anti-endotoxin antibodies normally found in serum that can then activate C1. The administration of protamine after separation from CPB has been reported to result in heparin-protamine complexes, which also can activate the classic pathway[70,71] (see Chapters 31 through 36). Other investigators, however, have not observed this effect.[72] Contact activation leads to activation of factor XII, which results in the generation of

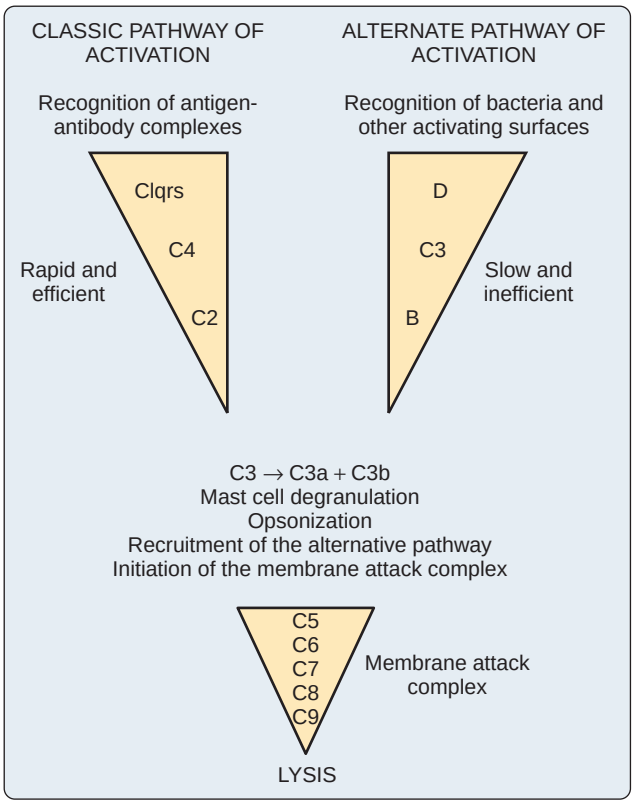

Fig. 9.3 Simplified components of the complement system. *(From Haynes BF, Fauci AS. Introduction to clinical immunology. In: Braunwald E, Isselbacher KJ, Petersdorf RG, et al., eds.* Harrison's Principles of Internal Medicine. *11th ed. New York: McGraw-Hill; 1987:328–337.)*

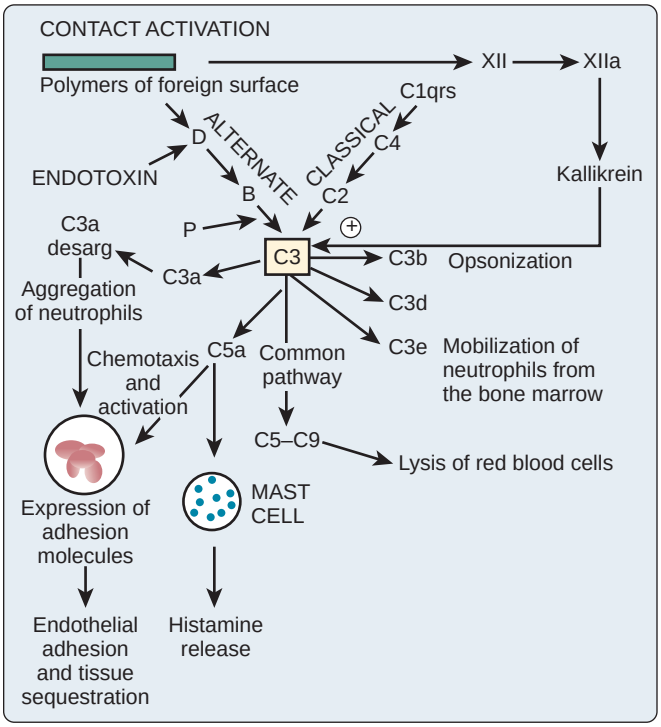

Fig. 9.4 Contact activation of the complement cascade during cardiopulmonary bypass. Activation of complement occurs primarily through the alternate pathway. *(From Ohri SK. The effects of cardiopulmonary bypass on the immune system.* Perfusion. *1993;8:121.)*

plasmin. Plasmin is capable of activating complement factors C1 and C3. Table 9.1 is a summary of the physiologic effects of the complement system.

Activated C3 and other complement factors downstream in the cascade have several actions. The effects of activated complement fragments on mast cells and their circulating counterparts, the basophil cells, may be relevant to the development of postoperative complications potentially attributable to complement activation. Fragments C3a and C5a (also called *anaphylatoxins*) lead to the release of numerous mediators including histamine, leukotriene B_4, platelet-activating factor, prostaglandins, thromboxanes, and TNF. These mediators, when released from mast cells, result in endothelial leak, interstitial edema, and increased tissue blood flow. Complement factors such as C5a and C3b complexed to microbes stimulate macrophages to secrete inflammatory mediators such as TNF. C3b activates neutrophils and macrophages and enhances their ability to phagocytose bacteria. The lytic complex, composed of complement factors C5b, C6, C7, C8, and C9, is capable of directly lysing cells. Activated complement factors make invading cells "sticky," such that they bind to one another (ie, agglutinate). The complement-mediated process of capillary dilation, leakage of plasma proteins and fluid, and accumulation and activation of neutrophils makes up part of the acute inflammatory response.

Although some elements of complement activation have been elucidated, clinicians are continuing to learn about the clinical relevance of this process to patients undergoing cardiac operations.

TABLE 9.1 Biologically Significant Effects of the Various Complement-Split Products

Biologic Effect	*Complement-Split Products*
Mast cell degranulation, contraction of smooth muscle, increased vascular permeability	C3a, C5a
Chemotaxis of neutrophils	C5a, C5a des Arg
Neutrophil aggregation	C5a, C5a des Arg
Lysosomal enzyme release	C5a, C3b
Leukocytosis	C3e
Immune adherence/opsonization	C3b, C4b
Membrane lysis	C5b-9 (membrane attack complex)

From Knudsen F, Andersen LW. Immunological aspects of cardiopulmonary bypass. *J Cardiothorac Anesth.* 1990;4:245.

Several studies reported increased complement levels during cardiac surgery.[38,58,73–78] Chenoweth and associates[73] measured plasma C3a and C5a levels at different time points in 15 adults undergoing cardiac surgical procedures with CPB. Although C3a levels were not affected by surgical stimulation, complement activation increased significantly during CPB. This and other studies did not test the association between increased complement levels and adverse postoperative outcome. Thus the studies do not provide any evidence that complement activation causes clinically significant systemic inflammation. Kirklin and colleagues[75] measured plasma C3a levels in 116 patients undergoing cardiac operations with CPB and in 12 patients undergoing operations without CPB. In this study, an increase of complement activation during CPB was associated with postoperative morbidity, although this study has significant limitations. Patients undergoing procedures without CPB did not demonstrate increases in complement. This result suggests that a factor unique to CPB causes activation of complement.

In several large, randomized clinical trials, complement activation was selectively blocked.[79–81] These studies indicated that attenuation of complement activation results in less myocardial injury; however, it did not appear to have an impact on complications such as pulmonary and renal dysfunction and severe vasodilation. These results suggest that complement activation may not play as large a role in the development of systemic inflammation-mediated morbidity as previously thought. These trials are discussed in more detail later in this chapter.

Endotoxin

Endotoxin, also called *LPS,* is a component of the cell membrane of gram-negative bacteria. It is a potent activator of complement and cytokines, and it appears to be one of the initial triggers of systemic inflammation, as summarized in Fig. 9.2.[12,82–84] Although the LPS constituent varies from one bacterial species to another, it generally may be described with reference to Fig. 9.5 as consisting of three structural regions: lipid A, core, and O-polysaccharide outer region. The lipid region of lipid A is embedded in the outer leaflet of the outer membrane. The oligosaccharide core region is positioned between lipid A and the O-polysaccharide outer region. Lipid A has the same basic structure in practically all gram-negative bacteria and is the toxic component of endotoxin. The LPS core region shows a high degree of similarity among various bacteria. It usually consists of a limited number of sugars. For example, the inner core region consists of heptose and 3-deoxy-D-*manno*-2-octulosonate (KDO) residues, whereas the outer core region comprises galactose, glucose, or *N*-acetyl-D-glucosamine residues displayed in various manners depending on the strain.

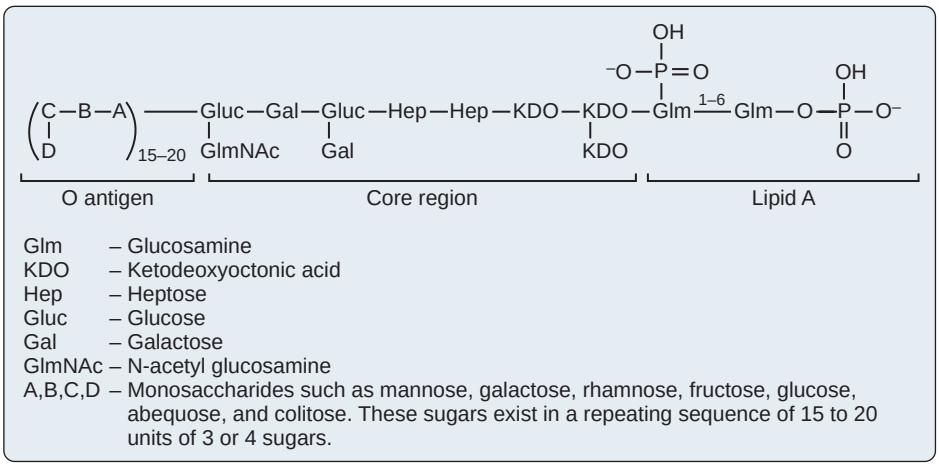

Fig. 9.5 Schematic structure of one unit of *Salmonella* cell wall lipopolysaccharide (*LPS;* endotoxin). The structure of the cell wall LPS may vary slightly from one genus of gram-negative organism to another, but as far as is known, all contain three general regions, as shown. Although not shown here, all free hydroxyl groups of the glucosamines in lipid A are esterified with fatty acids. The serologic differences among different strains within a genus lie in the kinds of sugars and their linkages that exist in the O-antigen region. *(From Volk WA, Benjamin DC, Kadner RJ, Parsons JT, eds.* Essentials of Medical Microbiology. *3rd ed. Philadelphia: Lippincott; 1986:399.)*

The O-polysaccharide outer region (also called *O-specific antigen* or *O-specific side chain*) is highly variable and is composed of one or more oligosaccharide repeating units characteristic of the serotype.

Endotoxemia

Endotoxemia refers to the presence of endotoxin in the blood. This disorder is common in cardiac surgical patients.[10,11,38,41,60,64,65,85–95] It is not surprising that some investigators have failed to detect endotoxemia during cardiac surgical procedures given its transient and intermittent nature, although differences in endotoxin-assaying techniques used also may contribute to this discrepancy.[51,52,96,97] Andersen and associates[11] measured circulating endotoxin levels in 10 patients undergoing cardiac operations. All preoperative blood samples were free of endotoxin; however, substantial levels of endotoxin were detected intraoperatively. Blood endotoxin levels from eight typical patients undergoing cardiac operations are presented in Fig. 9.6.[85] Although endotoxin can be found in sterile fluids administered to patients, it is believed that the majority of endotoxin arises through a patient's impaired gut barrier.[11] Rothenburger and colleagues[60] studied the association of endotoxin levels with prolonged mechanical ventilation in 78 cardiac surgical patients. Endotoxin levels were three times greater in patients with a postoperative mechanical ventilation time longer than 24 hours (n = 13) compared with patients with ventilator time less than 24 hours.

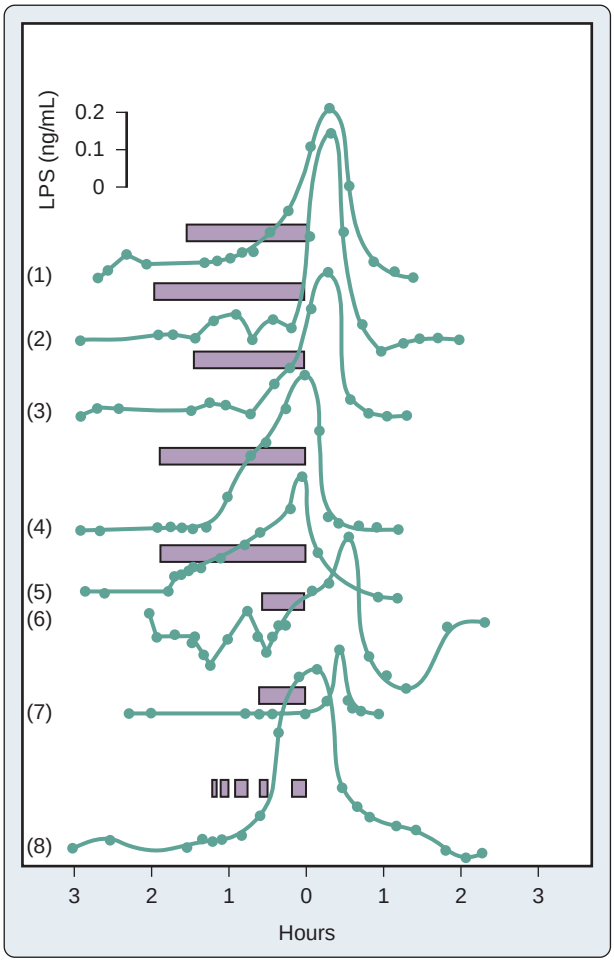

Fig. 9.6 Time course of plasma lipopolysaccharide *(LPS)* concentrations during cardiopulmonary bypass procedures for patients 1 to 8. *Hatched boxes* indicate the period of aortic cross-clamping. For clarity, records were offset and aligned at the time of removal of the aortic clamp. *(From Rocke DA, Gaffin SL, Wells MT, et al. Endotoxemia associated with cardiopulmonary bypass.* J Thorac Cardiovasc Surg. *1987;93:832.)*

Normally, intestinal flora contain a large amount of endotoxin from gram-negative microorganisms.[98] The average human colon contains approximately 25 billion nanograms of endotoxin, which is an enormous quantity when 300 ng endotoxin is toxic to humans.[33,34] The leakage of live bacterial cells into the bloodstream can result in infection as these viable bacteria multiply.[99] However, many of the bacteria in the intestine are dead, and thus endotoxin also can enter the bloodstream contained within cell membrane fragments of dead bacteria. In this case, infection per se does not develop. Instead, endotoxin may initiate a systemic inflammatory response through potent activation of macrophages and other proinflammatory cells.[100] A plasma endotoxin concentration of only 1 ng/mL has been reported to be lethal in humans.[101]

On entry to the bloodstream, endotoxin forms complexes with numerous intravascular compounds including high-density lipoprotein, LPS-binding protein, and endotoxin-specific immunoglobulins. Endotoxin has been linked to dysfunction in every organ system of the body and may be the key initiating factor in the development of systemic inflammation.[12,82–84,93]

Normal Host Defenses Against Endotoxemia

Early Tolerance

If endotoxemia is deleterious to patients, it would be logical to assume that patients have defense mechanisms against this ubiquitous toxin. Tolerance to endotoxin was studied extensively by Greisman and Hornick in the early 1970s.[102] Two distinct types of tolerance to endotoxin exist and are classified as *early tolerance* and *late tolerance.*[102] Early tolerance to endotoxin represents a reduction in the proinflammatory effects of LPS when it is administered several hours after an earlier infusion of LPS.[103] It appears to result from an LPS-induced refractory state of macrophages in which they release less TNF in response to endotoxin. This early refractive state shows no LPS specificity and can be overcome with increased doses of endotoxin. The degree of this tolerance is directly proportional to the dose and hence the intensity of the initial LPS-induced inflammatory state. Early tolerance begins within hours of LPS exposure and decreases almost to baseline within 2 days. It cannot be transferred with plasma. Early tolerance may protect the host from lethal systemic inflammation after an overwhelming exposure of LPS.

Late Tolerance

Late tolerance to endotoxin is caused by the synthesis of immunoglobulins (ie, antibodies) directed against the offending LPS.[102] Late tolerance begins approximately 72 hours after exposure to LPS, timing that correlates with the appearance of the early-appearing immunoglobulin M (IgM) class of antibodies. This form of tolerance persists for at least 2 weeks and correlates with the presence of serum immunoglobulins. In contrast to early tolerance, the late response is not proportional to the intensity of the initial LPS-induced inflammatory response but is related to the immunogenicity of the initial LPS. Furthermore, late tolerance does not generally protect against a subsequent challenge with a dissimilar type of LPS. In other words, late tolerance is most pronounced when the same (ie, homologous) LPS serotype is used for both the initial and the subsequent challenge. It is not definitively understood how antiendotoxin antibodies responsible for late tolerance confer protection from LPS-induced systemic inflammation. Proposed mechanisms include increased clearance of endotoxin into the reticuloendothelial system, as well as direct neutralization through binding.

Understanding of the host's normal humoral defense against endotoxin is further complicated by the numerous serotypes of endotoxin.[98] Serotype-specific antibodies (ie, antibodies synthesized in response to a particular LPS) exhibit high-affinity binding to and protection from the specific serotype of endotoxin. These serotype (O-specific) antiendotoxin antibodies, however, do not recognize the many possible

variations of endotoxin O-polysaccharide side chains and thus are ineffective at conferring protection against the numerous serotypes of endotoxin likely to be encountered in the clinical setting. Conversely, antibodies directed against the well-conserved inner core structure of endotoxin should theoretically be cross-reactive against many clinically relevant serotypes of endotoxin. Cardiac surgical patients are exposed to a wide variety of endotoxin types. For example, at least 164 O-antigens exist for *Escherichia coli,* the gram-negative bacteria most commonly isolated in high-risk surgical patients and patients in the intensive care unit (ICU).[104,105]

Criticisms of Endotoxin as a Causative Factor

Several criticisms of the theory that endotoxemia is an important cause of postoperative morbidity have been expressed. A common criticism relates to the low incidence of culture-proven bacteremia in surgical and ICU patients.[106–109] Endotoxemia, however, is clearly prevalent in these patients and usually exists in the setting of negative blood culture results.[10,11,24,38,41,64,65,85–95] In fact, studies attempting to detect endotoxemia probably underestimate its incidence given its intermittent nature.

The failure of two antilipid A monoclonal antibodies (HA-1A, Centocor, Malvern, Pennsylvania; and E5, Xoma, Berkeley, California) to improve outcome on an "intention-to-treat" basis in ICU patients with established sepsis also has been used to suggest that endotoxemia is not clinically relevant.[110,111] These monoclonal antibodies may not bind to endotoxin with high affinity, and this may partly explain their lack of demonstrable efficacy.[112] In addition, these antibodies were tested in patients with established sepsis and organ failure, which comprise an entirely different setting from that of elective surgical patients, who are more likely to benefit from prophylaxis with endotoxin-neutralizing drugs. Arguing against the clinical relevance of endotoxin is the negative result of a trial of prophylactic administration of a lipid A antagonist (E5564) in cardiac surgical procedures.[113]

Splanchnic Perfusion

Splanchnic hypoperfusion appears to be an important cause of systemic inflammation.[114–117] The gut is one of the most susceptible organs to hypoperfusion during conditions of trauma or stress.[117–119] In the 1960s, Price and associates[118] removed 15% of the blood volume from healthy volunteers and caused a 40% reduction in splanchnic blood volume. In this study, cardiac output (CO), blood pressure (BP), and HR did not change from baseline. A study was conducted by Hamilton-Davies and colleagues[120] in which 25% of the blood volume was removed from six healthy volunteers. Gastric mucosal perfusion, as measured by saline tonometry, was the first variable to decline (in five of the six subjects). Stroke volume also decreased; however, routinely measured cardiovascular variables such as HR, BP, and CO did not change significantly enough from baseline values to cause suspicion of a hypovolemic state. Based on these types of studies, the Advanced Trauma Life Support (ATLS) course teaches that a 15% blood loss (class I hemorrhage) rarely results in changes in HR, BP, or urine output.[121] Significant decreases in systolic BP are late signs of shock, which typically occurs after class III hemorrhage (30–40% blood loss).

These studies suggest that during periods of hypovolemia, the gut vasoconstricts, thus shunting blood toward "more vital organs" such as the heart and brain.[117–119] In addition to hypovolemia, endogenously released vasoconstrictors during CPB, such as angiotensin II, thromboxane A_2, and vasopressin, also may result in decreased splanchnic perfusion.[122–125] Vasoconstrictors, such as phenylephrine, are routinely administered by anesthesiologists and perfusionists to increase BP and are likely to reduce gut perfusion further. Oudemans-van Straaten and associates[89] measured intestinal permeability and endotoxin levels in 23 patients during cardiac surgical procedure. Intestinal leak was measured by the amount of orally administered cellobiose present in the patients' urine. Intestinal permeability increased during the surgical procedures and correlated with circulating endotoxin levels. Administration of ephedrine, low central venous pressures, and less fluid balance during the operations also were associated with intestinal permeability; this finding confirms the theory that gut perfusion is reduced by vasoconstrictors, as well as by hypovolemia. Evidence also indicates that systemic endotoxemia may worsen intestinal permeability, thus exacerbating splanchnic hypoperfusion and initiating a vicious cycle.[126]

Several studies observed a high incidence of splanchnic hypoperfusion during cardiac operations, and some of these studies showed an association between abnormal gut perfusion during cardiac surgical procedures and postoperative complications.[10,87,88,127–130] Fiddian-Green and Baker[127] used saline tonometry to measure gastric mucosal perfusion in 85 cardiac surgical patients. Half (49%) of these patients developed evidence of abnormal perfusion, and all serious postoperative complications (eight patients, including five deaths) developed in this group. Gastric tonometry was shown in this and in two other studies to be a more sensitive predictor of adverse postoperative outcome compared with more routinely used global measures such as CO, BP, HR, and urine output.[128,130] A study using air tonometry demonstrated an increased gastric mucosal partial pressure of carbon dioxide in 52% of cardiac surgical patients. Thirty-five percent of these patients with abnormal perfusion developed postoperative complications, in contrast to 5% in the group without evidence of hypoperfusion.[130]

Studies that have failed to demonstrate an association between splanchnic hypoperfusion and adverse postoperative outcome are limited, in part, by small sample size, insensitive measures of postoperative morbidity, and deviation from validated methodology of tonometry.[87,88] Tonometric measurements of gastric mucosal perfusion during hypothermic CPB have not been validated in terms of their ability to predict postoperative morbidity.

Postoperative Complications Attributable to Inflammation

Types of Complications

Many postoperative complications are attributed to an exaggerated systemic proinflammatory response to surgical trauma. A common misunderstanding relates to the types of postoperative complications that may be attributable to systemic inflammation and, in particular, splanchnic hypoperfusion. Many of the complications that are thought to be linked to splanchnic hypoperfusion do not involve the gastrointestinal system. Because splanchnic hypoperfusion may cause injury through a systemic inflammatory response, it would be expected that every organ system of the body potentially would be involved.[131] For example, endotoxin has been reported to have adverse effects on the pulmonary, renal, cardiac, and vascular systems.[41,46,83,84,132–135] It affects the coagulation system and may be both antihemostatic, thus potentially explaining bleeding, and prothrombotic.[83,132,136] Prothrombotic effects may account for some cases of postoperative stroke, deep vein thrombosis, and pulmonary emboli. Circumstantial evidence also indicates that systemic inflammation may worsen neurologic injury.[137] Activation of inflammatory cascades has been shown to worsen neurologic injury in numerous animal models.

Infections are common after cardiac surgical procedures and increase hospital length of stay and cost.[107,138,139] Infecting bacteria may arise from translocation across the patient's gastrointestinal tract.[107,114,116] Surgical wounds (sternum and lower extremity) and the respiratory tract are common sources of postoperative infection.[140] Infections of prosthetic heart valves are less common but represent a devastating complication.[141] Infections are probably not caused by the direct effects of inflammation, but rather secondary effects on host immunity may predispose to this complication.[142]

Widespread activation of the complement system results in depletion of complement factors, which are crucial to the effective opsonization of bacterial pathogens.[143,144] Systemic activation and degranulation of neutrophils render these cells less capable of destroying bacteria by phagocytosis. CPB leads to reductions in immunoglobulin levels through denaturation of these and other proteins.[144–148] Antibody

production by B lymphocytes (plasma cells) is depressed after cardiac surgical procedures.[149] Cell-mediated immunity, revealed by decreased T-lymphocyte function, appears to be impaired after cardiac operations.[150] Thus reduced antibody levels, as well as reduced B- and T-cell function in the post-CPB period, may lead to increased infection rates after cardiac surgical procedures.

Incidence of Complications

The "low" mortality rate after cardiac surgical procedures also has been cited as evidence that splanchnic hypoperfusion, endotoxemia, and systemic inflammation result in only "rare" complications. As discussed earlier, it is clear that death[1] and morbidity[3,151] are still significant problems after cardiac operations. In addition, many studies report only frank organ failures or catastrophes and do not take into account less severe forms of organ dysfunction that do not lead to admission to an ICU but nevertheless cause suffering and increase hospital length of stay.

For example, a series by Huddy and colleagues[152] of 4473 cases involving CPB demonstrated a very low incidence rate (0.78%) of "gastrointestinal complications." In a series of 3129 patients, Christenson and associates[153] reported an incidence rate of 2.3% for major gastrointestinal complications after CABG procedures. The low incidence of major gastrointestinal complications (ie, perforation, necrotic bowel, major gastrointestinal bleeding) is often used to call into question the clinical relevance of splanchnic hypoperfusion. Growing evidence, however, indicates that less severe forms of splanchnic dysfunction (eg, ileus, nausea, anorexia, and abdominal distention) are clinically relevant and increase hospital length of stay.

Some series of postoperative complications have broadened their scope. In a series of 572 patients, Corwin and colleagues[154] reported the incidence of renal failure requiring dialysis (1%), as well as the incidence of renal dysfunction not requiring dialysis (6.3%). This study demonstrates that organ dysfunction is common postoperatively, despite a low incidence of organ failure.

Similarly, the incidence rate of acute respiratory distress syndrome after cardiac operations was reported to be very low (<2%) in several series.[155,156] The incidence of less severe pulmonary dysfunction appears to be much greater, however, as many as 7% of patients require supplemental oxygen 11 days postoperatively (Bennett-Guerrero E, unpublished data). Furthermore, a high incidence of postoperative pulmonary dysfunction, as measured by diagnostic tests, gives further support to the hypothesis that many patients have abnormal pulmonary physiology potentially attributable to systemic inflammation.[157–159]

Potential Therapies for the Prevention of Inflammation-Related Complications

Numerous strategies and pharmacologic agents have been demonstrated to reduce laboratory indices of complement activation and cytokinemia. Many of these studies, however, have been too small to detect improvements in clinically meaningful postoperative outcomes. All interventions that have been tested in large phase III trials have failed to demonstrate meaningful clinical improvement, as discussed in following sections. Currently, no therapies in widespread clinical use are available to prevent or treat organ dysfunction resulting from systemic inflammation; however, several approaches are discussed.

Steroid Administration

Steroids have been demonstrated to attenuate the release of proinflammatory cytokines, mitigate complement activation, and increase antiinflammatory mediators during cardiac surgical procedures.[37,86,160–169] The effect of steroids on the SIRS response during cardiac operations is among the most thoroughly studied of all interventions. No less than 3 metaanalyses focused on this intervention have been published, with more than 50 trials included.[170–172] Each metaanalysis suggested a trend toward benefit of steroids on morbidity and possibly mortality and called for large definitive trials to be undertaken.

The first large randomized controlled trial published in this area was the Dexamethasone for Cardiac Surgery Study (DECS).[173] This trial randomized 4494 adult patients to dexamethasone or placebo in 8 centers in the Netherlands. The DECS demonstrated that dexamethasone had no effect on the primary outcome of death, myocardial infarction, stroke, new renal failure, or respiratory failure (risk ratio [RR] for dexamethasone, 0.83; 95% confidence interval [CI], 0.67 to 1.01). However, a prespecified subgroup analysis suggested a benefit of steroids on the primary outcome in the subgroup of high-risk patients, defined as patients with a European System for Cardiac Operative Risk Evaluation score (EuroSCORE) of 5 or higher (RR, 0.77; 95% CI, 0.61 to 0.98). Further publications from the DECS group also demonstrated no impact on postpericardiotomy syndrome, new-onset atrial fibrillation, or postoperative cognitive decline.[174–176]

The Steroids in Cardiac Surgery trial followed on the heels of the DECS and randomized 7507 high-risk patients (EuroSCORE ≥6) to methylprednisolone or placebo. The dosing protocol used in the Steroids in Cardiac Surgery trial had been demonstrated to attenuate the biomarkers of inflammation in a published pilot study.[169] In fact, unpublished data from the group demonstrated what was thought to be a more favorable balance across a broad selection of proinflammatory and antiinflammatory mediators measured, with lower levels of IL-6, IL-8, TNF-α and increased levels of IL-10 (Fig. 9.7). The Steroids in Cardiac Surgery trial results were presented at the 2014 American College of Cardiology Conference, and publication is pending. The Steroids in Cardiac Surgery trial failed to demonstrate benefit of methylprednisolone on the risk of death (RR for methylprednisolone, 0.87; 95% CI, 0.70 to 1.07) or on the composite of death, myocardial injury, stroke, renal failure, and respiratory failure (RR, 1.03; 95% CI, 0.95 to 1.11) in patients with an elevated EuroSCORE.[177]

With both the DECS and the Steroids in Cardiac Surgery trial demonstrating no benefit of steroid prophylaxis on important clinical outcomes, the use of steroids in the field will likely disappear, and broader questions regarding the clinical relevance of the systemic inflammation are raised.

Role of Cardiopulmonary Bypass Technique

Although heparin-coated circuits have many theoretic advantages, evidence that their use during cardiac operations results in fewer clinically significant adverse complications is scant. Steinberg and associates[54] found no difference in cytokine levels or markers of complement activation between patients randomized to a heparin-coated circuit and patients randomized to a traditional circuit. Borowiec and colleagues,[25] however, observed lower levels of myeloperoxidase and lactoferrin (markers of inflammation) in patients undergoing CPB with a heparin-coated circuit. Other investigators reported reduced plasma levels of cytokines or neutrophil proteases in patients subjected to CPB using heparin-coated circuits; however, no improvement in outcome was observed in these small studies[23,53,178,179] (see Chapters 31 and 32). A metaanalysis involving 3434 patients from 41 randomized trials demonstrated reductions in blood transfusion and durations of mechanical ventilation, ICU stay, and hospital length of stay, findings that provide some support for this intervention.[180]

Centrifugal vortex blood pumping has been shown to result in reduced complement and neutrophil activation, as well as reduced hemolysis during cardiac surgical procedures compared with standard roller blood pumping.[181,182] Centrifugal vortex blood pumping, however, did not significantly prevent increases in cytokines in 17 pediatric patients randomized to this bypass technique.[58]

A randomized study of 15 patients suggested that pulsatile-flow CPB may result in less endotoxemia than CPB involving nonpulsatile flow.[94] Levine and associates[125] randomized 20 patients to pulsatile versus nonpulsatile flow and observed a less marked increase in vasopressin levels (an endogenous vasoconstrictor) in patients perfused with pulsatile flow. Taylor and colleagues[122] demonstrated increased levels of the endogenously produced vasoconstrictor angiotensin II in patients (n = 24) randomized to nonpulsatile flow CPB as compared with pulsatile flow. Watkins and associates[124] observed fewer marked

alterations in thromboxane B_2 and prostacyclin levels in patients (n = 16) randomized to pulsatile CPB. These studies evaluating pulsatile flow suggest that splanchnic perfusion may be better preserved with pulsatile flow because of less endogenously mediated vasoconstriction. Quigley and colleagues,[52] however, reported a lack of endotoxemia and pathologic cytokinemia in an uncontrolled study of patients who underwent nonpulsatile CPB. These investigators claimed that the use of "adequate flow and perfusion pressures" during CPB accounted for their findings.

The role of membrane oxygenators as a means of reducing systemic inflammation-related complications also is controversial. Less complement activation has been observed with the use of membrane oxygenators; however, other studies found no difference.[62,74,161,183–187] The use of membrane oxygenators was associated with better pulmonary function as compared with the use of a bubble oxygenator, although whether the difference observed reflected reduced systemic inflammation in the protocol group is unclear.[185] Butler and associates[62] randomized 20 patients undergoing cardiac surgical procedures to either a membrane oxygenator or a bubble oxygenator. IL-6 levels peaked 4 hours postoperatively, yet no significant differences were observed between groups in IL-1 or IL-6 levels or in intrapulmonary shunting. This study failed to show a difference in postoperative outcome, possibly because of short CPB durations (<1 hour), as well as the small sample size, which makes detecting a clinically significant difference in postoperative complications unlikely. Host defenses may be better maintained with the use of membrane oxygenators.[186]

Whether hypothermia during CPB affects systemic inflammation is also controversial.[40,51,76,188–190] Hypothermia has been shown to reduce

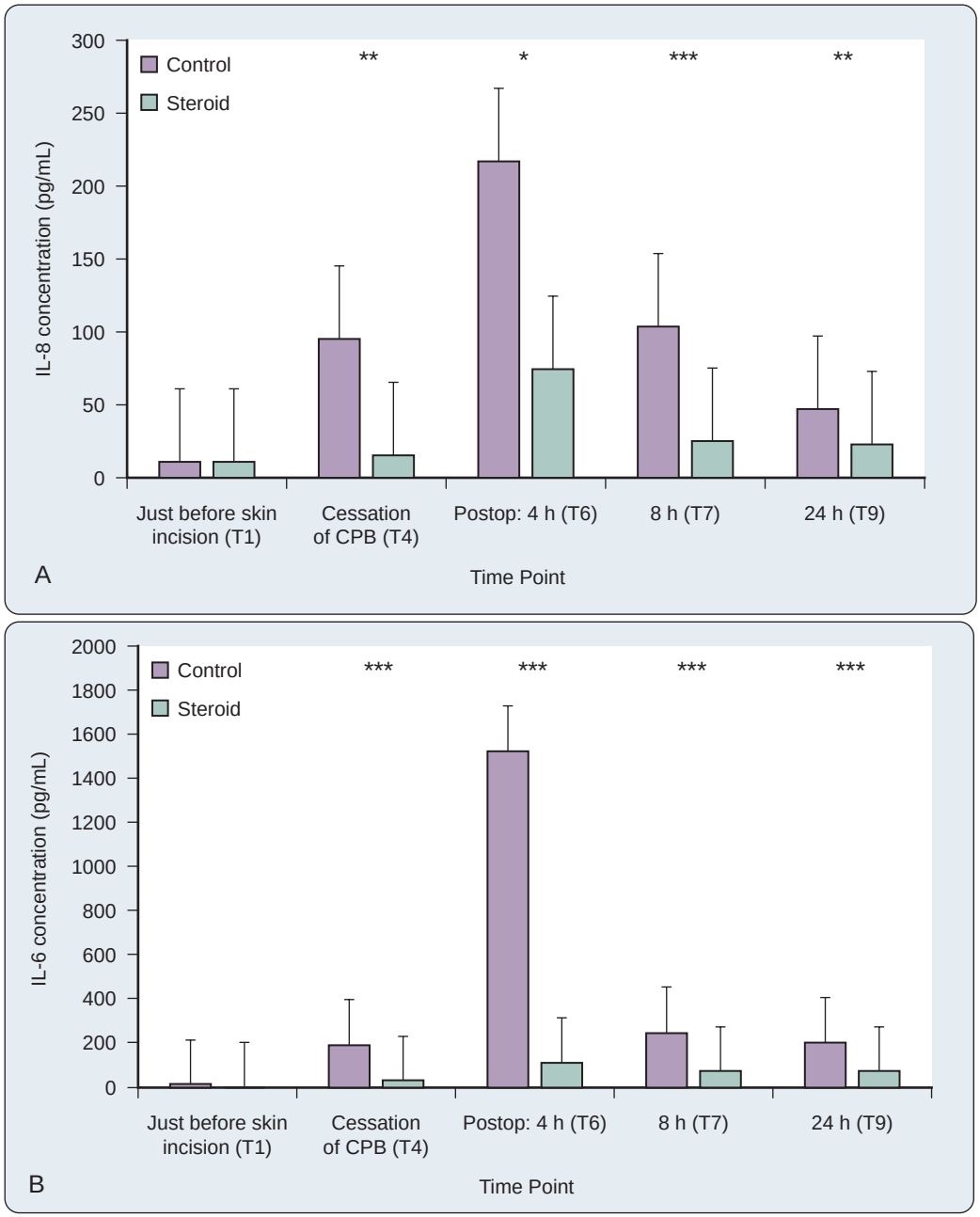

Fig. 9.7 Impact of methylprednisolone on (A) interleukin-6 *(IL-6),* (B) IL-8, (C) tumor necrosis factor-alpha *(TNF-alpha),* and (D) IL-10, from Randox's Evidence Investigator Platform9.8. *CPB,* Cardiopulmonary bypass; *$P < .05$; **$P < .01$; ***$P < .005$. *(Data from Dr. Richard Whitlock.)*

Continued

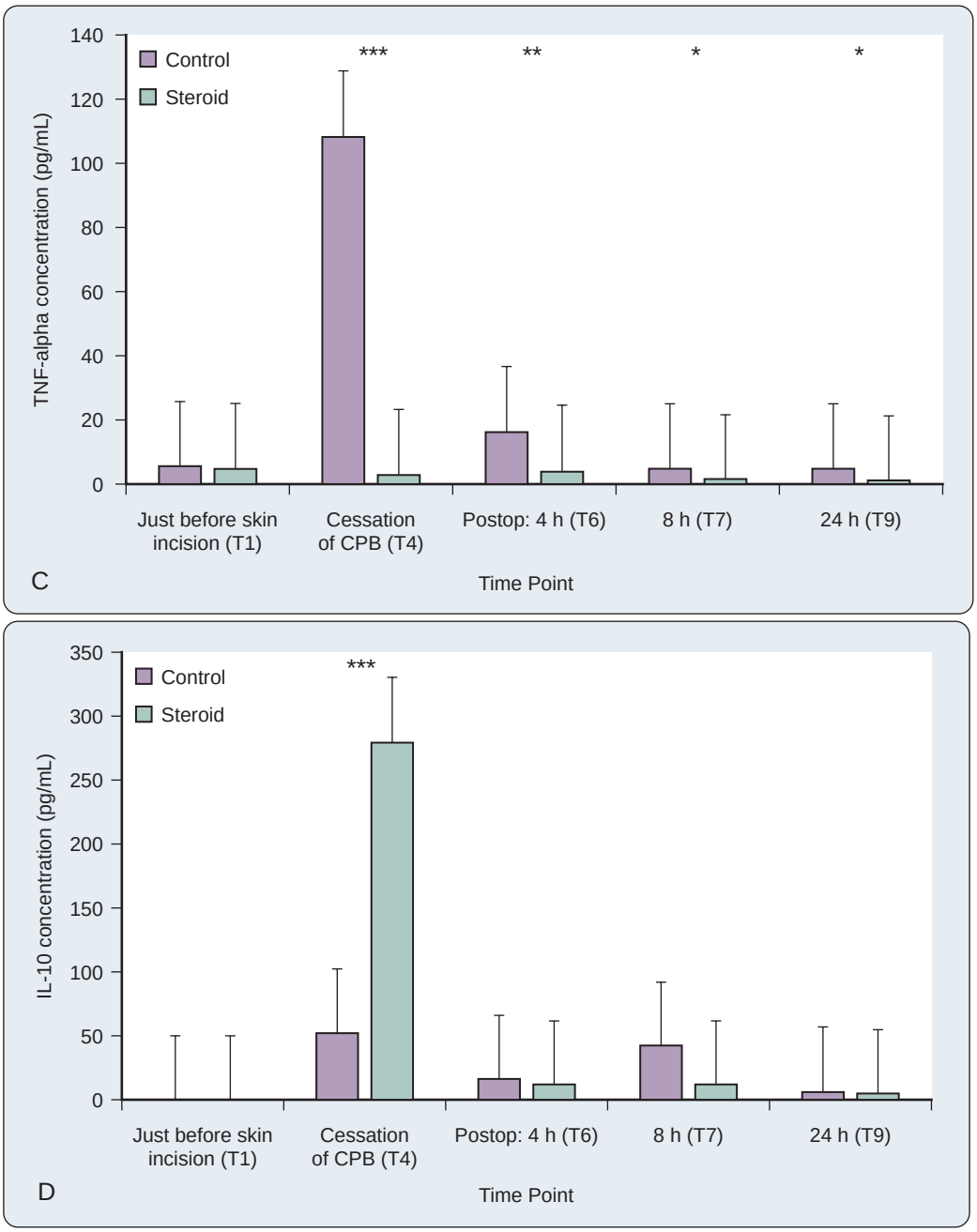

Fig. 9.7, cont'd

markers of complement activation.[76] Another study demonstrated reduced markers of inflammation, such as TNF and IL-6, as well as decreased neutrophil activation in the hypothermia group.[189] In contrast, another study randomized 30 cardiac surgical patients to either normothermic or hypothermic CPB.[40] These investigators found no association between CPB temperature and plasma TNF levels at any time point in the perioperative period, a finding suggesting a limited role for temperature as an independent cause of proinflammatory cytokine release. In one of the largest randomized trials to date, 300 elective CABG-treated patients were randomized to either normothermic (35.5–36.5°C) or hypothermic (28–30°C) CPB.[191] No differences were seen in either short-term or longer term outcome, thus suggesting no benefit to intraoperative hypothermia. However, evidence indicates that perioperative hyperthermia may be detrimental to the brain.[192] These investigators also observed an association between greater levels of the proinflammatory cytokine IL-6 and postoperative hyperthermia, a finding suggesting a potential role of inflammation in the increases in temperature commonly observed after major operations.

Finally, current data suggest that use of CPB for cardiac surgical procedures may not itself be more deleterious than not using CPB for these operations. Results from initial randomized clinical trials did not suggest that outcomes were substantially different in patients undergoing on-pump versus off-pump CABG procedures.[193–197] Given the importance of this question, two large randomized trials were performed to assess the potential benefits of off-pump CABG. The first trial included 2203 cardiac surgical patients at 18 Veterans Affairs medical centers from 2002 to 2008 and randomized these patients to either on-pump or off-pump CABG. No benefit was found with regard to outcomes such as duration of mechanical ventilation, lengths of stay in the ICU or hospital, renal failure, or a composite end point of complications.[198] The second trial randomized 4752 patients who were to undergo CABG procedures to either off-pump or on-pump

technique. No benefit was demonstrated for the primary outcome of death, nonfatal stroke, nonfatal myocardial infarction, or new renal failure (HR for the off-pump group, 0.95; 95% CI, 0.79 to 1.14).[199] Systemic inflammation was not specifically studied in these trials, but these data suggest that systemic inflammation attributable to CPB may have a more modest role in determining clinical outcome than previously thought.

Complement Inhibition

The results from several large, randomized clinical trials in which complement activation is selectively blocked have become available.[79–81] For example, in the largest randomized, double-blind clinical trial conducted to date, 3099 adults undergoing CABG procedures at 205 hospitals in North America and Western Europe were enrolled.[80] Patients were randomized to placebo or to a 24-hour infusion of pexelizumab, which is a recombinant, humanized, single-chain antibody fragment that binds to human C5 complement and prevents its activation. The administration of pexelizumab resulted in rapid and complete inhibition of complement activation. The primary outcome variable (death or myocardial infarction within 30 days) did not achieve statistical significance ($P = .07$). The subset of patients undergoing CABG plus valve did demonstrate a statistically significant difference ($P = .03$) in this outcome. This finding is somewhat contradictory to that of the previous phase IIb trial (n = 914), which enrolled patients undergoing CABG or valve operations, or both, and did not show a significant difference with regard to the end point of death or myocardial infarction.[79] This previous trial did achieve significance in the subset of patients undergoing isolated CABG, which was the apparent justification for studying isolated CABG operations in the larger phase III trial. These results suggest that complement activation may not play as large a role in the development of systemic inflammation-mediated morbidity as previously thought.

Ultrafiltration

Removal of excess fluid with ultrafiltration has been proposed as a method for eliminating proinflammatory mediators during cardiac surgical procedures, particularly in the pediatric population.[46,200] It is unclear in studies performed thus far whether the beneficial effects of ultrafiltration are caused by one or some combination of the following factors: prevention of initiation of inflammation, removal of inflammatory mediators, or removal of excessive fluid alone. In one study, Journois and colleagues[201] randomized 20 pediatric cardiac surgical patients to either a control group or high-volume, zero-fluid balance ultrafiltration. Measured TNF, IL-1, IL-10, myeloperoxidase, and C3a levels were lower in the protocol group compared with the control group. These investigators suggested that hemofiltration may have some beneficial effects that are not the result of water removal alone. Patients in the ultrafiltration group had less postoperative fever, reduced perioperative blood loss, a shorter time to extubation, and a lower postoperative alveolar-arterial oxygen gradient, findings suggesting, but not proving, a causal relationship between proinflammatory cytokinemia and several clinically meaningful end points. The small sample size of this study precludes any conclusions from being made regarding other outcomes such as the incidence of multiple organ dysfunction syndrome or hospital length of stay.

In an interesting study, 192 cardiac surgical patients were randomized to placebo (no steroids or ultrafiltration), steroid administration without ultrafiltration, or hemofiltration without steroids.[202] The study arm randomized to ultrafiltration without steroids showed a reduction in time to extubation; however, steroid administration was not effective compared with placebo. These data are promising, but the small number of subjects per arm of the study and the limited number of positive outcomes reported make it unclear whether ultrafiltration should be used more routinely.

Leukocyte Depletion

Removal of leukocytes during CPB with an inline leukocyte filter has been proposed as a method for reducing the concentration of activated leukocytes. This, in turn, may prevent inflammatory-mediated postoperative complications. This technology was well reviewed by Warren and associates,[203] who, in their review of 63 studies, concluded that this procedure may have some modest benefits, but the low quality of evidence from the predominantly small trials precluded any definitive conclusions on this matter. For example, patients randomized to leukocyte depletion (n = 20) had better oxygenation after CPB; however, no differences were noted in other outcomes measured.[204] A prospective randomized study of patients (N = 50) receiving inline leukocyte filtration demonstrated decreased leukocytes; however, postoperative arterial blood gases, pulmonary vascular resistance, ventilator time, and hospital length of stay were no different between groups.[205] Another study demonstrated no difference in postoperative complications or in the plasma levels of neutrophil proteases in patients undergoing leukocyte depletion with an inline filter.[206]

Davies and colleagues[207] used another method of leukocyte depletion in which they removed platelets and leukocytes by plasmapheresis from patients before cardiac operations. These patients, compared with the control group, demonstrated reduced postoperative thoracic drainage, decreased allogeneic blood product administration, and improved pulmonary function. This technique is not in widespread clinical use because of a lack of studies confirming its findings, as well as the time and cost involved in performing plasmapheresis.

The techniques described earlier differ from the issue of administration of leukocyte-reduced packed red blood cells. This method of minimizing a patient's exposure to leukocytes involves filtering collected blood either at the time of donation (fresh filtered) or before its release by the blood bank (stored filtered).[208] Van de Watering and colleagues[209] reported results from a large (N = 914) randomized clinical trial in which patients undergoing cardiac surgical procedures were randomized to receive allogeneic red cells without buffy coat, fresh-filtered allogeneic red cells, or stored filtered units. Patients randomized to either filtration group experienced a significant reduction in postoperative mortality ($P = .015$); however, this effect was most robust in patients administered more than three transfusions. The differences among groups in the incidence of infection did not achieve statistical significance ($P = .13$). No differences among groups were found in ICU or hospital length of stay in those patients in the overall study population or in the subset administered more than three units. These data are from a randomized trial and therefore should be more heavily weighted. Data from some retrospective cohort studies have shown no benefit of leukocyte reduction.[210,211]

Aprotinin and Other Serine Protease Inhibitors

Aprotinin, a 58–amino acid serine protease inhibitor isolated from bovine lung, has been shown in numerous studies to decrease bleeding associated with cardiac surgical procedures. It antagonizes numerous proteolytic enzymes including plasmin and kallikrein, and it may have some antiinflammatory effects,[14,212] although a metaanalysis found no beneficial effect of aprotinin on systemic markers of inflammation.[213] The blood-sparing effects of aprotinin were apparently discovered serendipitously while it was being evaluated as an antiinflammatory agent in cardiac surgical patients. Despite more than 45 randomized clinical trials conducted to date, few data support the hypothesis that aprotinin administration reduces postoperative complications attributable to excessive systemic inflammation. In these trials, numerous surrogate markers of postoperative morbidity, such as the duration of postoperative tracheal intubation, ICU stay, and hospital length of stay, were not reported to be improved in aprotinin-treated patients. One large trial was completed in 2331 cardiac surgical patients at 19 Canadian centers.[214] Patients were randomized to aprotinin, aminocaproic acid, or tranexamic acid. No benefit of aprotinin was observed with regard to complications such as respiratory failure, renal failure, or multisystem organ failure, and the study was terminated early because of an increase in mortality rates in aprotinin-treated patients (RR for aprotinin, 1.53; 95% CI, 1.06 to 2.22). The findings from this trial, as well as from several previous observational studies, led to market withdrawal of aprotinin.

Tumor Necrosis Factor Antagonists

Soluble TNF receptor proteins antagonize the toxic effects of LPS-induced lethality in mice.[215] These agents are ineffective in the treatment of sepsis or septic shock but have not been tested in the setting of cardiac surgery.[216] Anti-TNF monoclonal antibodies have also been studied in ICU patients with sepsis; however, these antibodies have not yet been tested prophylactically in cardiac surgical patients.[69] A study involving prophylactic administration would allow for the antibody to be present before the TNF and thus determine whether TNF has overall harmful or beneficial effects. If TNF and other cytokines are essential to the healing process, complete inhibition of their effects may result in worse, rather than improved, postoperative outcomes. Well-designed, large clinical trials could resolve these controversial issues.

E5564

E5564 is a synthetically derived lipid A analogue that is a potent Toll-like receptor 4–directed endotoxin antagonist.[217] It does not have lipid A agonist properties, and even in high doses it does not cause signs or symptoms of endotoxemia or systemic inflammation in humans and animals. Healthy volunteers were administered E5564 before a standard challenge dose of reference endotoxin (4 ng/kg). Single E5564 doses of 50 to 250 μg blocked or attenuated all the effects of LPS in a dose-dependent manner. All E5564 dose groups had statistically significant reductions in increased temperature, HR, CRP levels, white blood cell count, and cytokine levels (TNF-α and IL-6) compared with placebo ($P < .01$).[217] This drug has shown promising results in critically ill patients with sepsis; however, results from a phase II trial in cardiac surgical patients were disappointing.[113] In this trial, 152 cardiac surgical patients at 9 centers in the United States were randomized to receive placebo or ascending doses of E5564. Blocking lipid A with eritoran did not result in any overt beneficial effects on markers of systemic inflammation (IL-6, IL-8, or CRP) or measures of organ injury. These results call into question the potential clinical relevance of lipid A in this setting.

Pentoxifylline

Pentoxifylline is a nonspecific phosphodiesterase inhibitor similar in chemical structure to theophylline, a common antiinflammatory used to treat asthma. Pentoxifylline has multiple rheologic and antiinflammatory properties, but the exact mechanism of its pharmacologic effects is poorly understood. Clinically, pentoxifylline is approved by the US Food and Drug Administration to treat intermittent claudication, presumably by increasing red cell deformability, which may improve oxygen delivery to ischemic tissues. Animal studies showed that treatment with pentoxifylline significantly attenuates endothelial damage and the formation of oxygen radicals after ischemia/reperfusion, prevents fever after the administration of LPS, and prevents leakage of bacteria from the gut during hemorrhagic shock. Clinical research studies using pentoxifylline have been performed in the setting of lung transplantation, cardiac surgery, and anemia requiring red blood cell transfusion.

In an initial study, Hoffman and associates[218] randomized 40 patients with an Acute Physiology and Chronic Health Enquiry (APACHE) II score of 19 or higher after cardiac surgical procedures to placebo or pentoxifylline (1.5 mg/kg per hour for 48 hours). In this study, patients administered pentoxifylline had significantly fewer days on mechanical ventilation, less need for hemofiltration, and a shorter ICU length of stay. In a historic control study, Thabut and colleagues[219] administered pentoxifylline to 23 consecutive patients undergoing lung transplantation. Compared with historic controls, patients administered pentoxifylline experienced less allograft dysfunction, and a significant reduction in 60-day mortality rates was noted. Other small studies also suggested possible benefit[220,221]; however, these results have not been confirmed in a large, multicenter trial.

Ethyl Pyruvate

Ethyl pyruvate is a novel antiinflammatory agent.[222,223] It was shown to protect the intestinal mucosa from mesenteric ischemia and reperfusion in rats and improve survival in murine models of acute endotoxemia and bacterial peritonitis. Results from a phase II trial in cardiac surgical patients were disappointing.[224] In this trial, 102 high-risk cardiac surgical patients were randomized to receive placebo or ethyl pyruvate at 13 centers in the United States. Administration of ethyl pyruvate did not result in any overt beneficial effects on markers of systemic inflammation (TNF-α, IL-6, or CRP) or measures of organ injury.

Statins

Statins are routinely used to reduce cholesterol levels in patients at risk for cardiovascular disease; however, the antiinflammatory effects of these drugs have received significant attention.[225] Investigators have speculated that prophylactic statin administration before surgical procedures may have beneficial effects. One trial randomized 497 vascular surgical patients to placebo or fluvastatin daily from randomization to 30 days postoperatively.[226] Patients randomized to the statin exhibited lower levels of the inflammatory markers IL-6 and CRP, and they also had reduced myocardial ischemia ($P = .01$). All-cause mortality rates were lower in the statin-treated patients (2.4% vs 4.9%); however, this difference did not achieve statistical significance ($P = .14$). No similar large trials have been conducted in cardiac surgery, but a metaanalysis was completed of 8 trials involving a total of 638 such patients.[227] This analysis showed that statin use decreased levels of IL-6, IL-8, CRP, and TNF-α, although no improvement in clinical outcomes was reported. At this point, the use of statins in cardiac surgery must be investigational until additional data are obtained to support this indication.

N-*Acetylcysteine*

This agents is used to prevent radiocontrast-induced nephropathy and as an antidote for acetaminophen overdose. Its antiinflammatory and antioxidant properties have been studied in the ICU setting and in cardiac surgical patients, with mixed results. A metaanalysis of *N*-acetylcysteine to ameliorate postoperative morbidity included 1338 patients from 13 trials.[228] This analysis suggested that *N*-acetylcysteine may have a beneficial effect with regard to postoperative atrial fibrillation, but the agent did not appear to be beneficial with regard to other postoperative complications.

Other Potential Antiendotoxin or Antiinflammatory Agents

Other potential approaches to preventing endotoxin-related complications involve the use of either synthetic or naturally occurring antiendotoxin compounds. *Bactericidal/permeability-increasing protein (BPI)* is a neutrophil granule protein that has been shown to have endotoxin-neutralizing and bactericidal activity in animal models. A human recombinant version, $rBPI_{21}$, neutralized endotoxin-mediated toxicity in humans.

A recombinant version of an antiendotoxin factor, *endotoxin-neutralizing protein,* is another agent that has been shown to protect animals from endotoxin-mediated toxicity.[229] Reconstituted high-density lipoprotein neutralized some of the toxic effects of endotoxin during an experimental model of human endotoxemia.[230]

Polymyxin B neutralizes the toxic effects of endotoxin, although toxicity has prevented prophylactic intravenous use.[231] *Dextran-polymyxin B* is a variation of polymyxin B that has been reported to have antiendotoxin properties, as well as minimal toxicity in animal models.

Soluble TNF receptor proteins antagonize the toxic effects of LPS-induced lethality in mice. This agent was not effective in the treatment of sepsis or septic shock but has not been tested in the setting of cardiac surgery.[215]

Role of Anesthetic Agents and Vasoactive Agents

Anesthetic agents, defined here as drugs that induce hypnosis, amnesia, muscle relaxation, or regional anesthesia, have not been shown to result in clinically meaningful reductions in systemic inflammation after cardiac surgical procedures. Numerous studies have evaluated the effect of these agents on the immune system, with varied results;

however, no studies have reported a difference in outcome with one technique versus another. Ketamine is a promising agent that has been studied largely as an adjunct to reduce postoperative pain in noncardiac operations. In an initial study in cardiac surgical procedures, administration of a low dose (0.25 mg/kg) of ketamine before CPB prevented an increase in IL-6 for 7 days postoperatively.[232] In addition, ketamine administration inhibited TNF production and leukocyte adherence in animal models and suppressed oxygen radical production in vitro. These results were confirmed in another small study of patients undergoing CPB.[233] However, no outcome data exist from large outcome trials, so it is unknown whether this intervention reduces clinically relevant complications.

All general anesthetic agents can reduce splanchnic perfusion indirectly through a depression of myocardial function and a reduction in CO and hence oxygen delivery to the splanchnic mucosa.[234,235] Isoflurane theoretically may be better than halothane, enflurane, or propofol because of its vasodilating properties, which may preserve splanchnic blood flow and blood volume.[234–237] A prospective randomized study of cardiac surgical patients demonstrated better splanchnic perfusion in patients with anesthesia maintained with isoflurane in contrast to patients with anesthesia with propofol or enflurane.[238]

Although not definitively supported yet, evidence indicates that splanchnic hypoperfusion and endotoxin-induced inflammation can be prevented in the operating room by strategies familiar to clinicians. Strategies involve the use of fluid loading to maximize stroke volume,[129] as well as the use of adequate levels of vasodilating volatile anesthetic agents. Inodilating agents, such as milrinone, amrinone, dopexamine, and dobutamine, may be more protective of splanchnic perfusion than inoconstricting agents, such as epinephrine, norepinephrine, and dopamine. Patients randomized to enoximone administration during cardiac surgical procedures demonstrated lower endotoxin levels, a finding suggesting a beneficial effect on the barrier function of the gut.[91] Endotoxemia is probably a more sensitive marker of loss of barrier function than gastric mucosal hypoperfusion because these patients still had decreases in calculated gastric mucosal pH (pHi). When tested in vitro, amrinone was a potent inhibitor of endotoxin-induced TNF production at clinically relevant drug concentrations, thus suggesting an additional advantage to the use of this phosphodiesterase inhibitor.[239] Dopamine is often touted as preserving splanchnic blood flow; however, responses to this agent are unpredictable, with vascular resistance increasing in some patients at low doses (3 to 5 μg/kg per minute).

Selective Digestive Decontamination

Selective digestive decontamination represents a possible approach to limiting the incidence and severity of systemic inflammation. The technique attempts to reduce the total amount of endotoxin exposure by reducing the reservoir of endotoxin normally contained within the gut. Martinez-Pellús and associates[65] conducted a prospective, open, randomized, controlled trial in 80 cardiac surgical patients. Patients were randomized to either a control group or up to 3 days of preoperative selective digestive decontamination accomplished with the administration of oral nonabsorbable antibiotics (polymyxin E, tobramycin, amphotericin B). Patients in the protocol group demonstrated much lower gut bacterial counts, as well as lower blood levels of endotoxin and the proinflammatory cytokine IL-6 in the operating room and the postoperative unit. The study was not designed with sufficient power to determine whether this technique affects outcomes such as mortality and morbidity. Nevertheless, a trend toward improved outcome (mortality, hospital length of stay) was observed in the protocol group. In contrast, Bouter and colleagues[240] found no beneficial effects of selective digestive decontamination on clinical outcome or blood levels of TNF-α, IL-6, or IL-10 in 78 cardiac surgical patients.

Summary

A large body of circumstantial evidence strongly suggests that systemic inflammation is an important cause of mortality and morbidity after cardiac surgical procedures. However, all therapies that have been shown to alter the inflammatory milieu of patients to what investigators perceive as a more favorable state have failed to demonstrate clinical benefit in large clinical trials. At this point, the need exists to question whether ongoing efforts to improve outcomes through suppression of inflammation are wise, at least until the pathophysiology is better understood.

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10

Pharmacology of Anesthetic Drugs

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KEY POINTS

1. In patients, the observed acute effect of a specific anesthetic agent on the cardiovascular system represents the net effect on the myocardium, coronary blood flow, and vasculature; electrophysiologic behavior; and neurohormonal reflex function. Anesthetic agents within the same class may differ from one another quantitatively and qualitatively. The acute response to an anesthetic agent may be modulated by the patient's underlying pathology or pharmacologic treatment, or both.
2. Volatile agents cause dose-dependent decreases in systemic blood pressure. For halothane and enflurane, this mainly results from depression of contractile function, and for isoflurane, desflurane, and sevoflurane, pressure changes result from decreases in systemic vascular responses. Volatile anesthetics cause dose-dependent depression of contractile function that is mediated at a cellular level by attenuating calcium currents and decreasing calcium sensitivity. Decreases in systemic vascular responses reflect various effects on endothelium-dependent and endothelium-independent mechanisms.
3. Volatile agents determine coronary blood flow by their effect on systemic hemodynamics, myocardial metabolism, and coronary vasculature. When these variables were controlled in studies, the anesthetics exerted only mild direct vasodilatory effects on the coronary vasculature.
4. In addition to causing acute coronary syndromes, myocardial ischemia can manifest as myocardial stunning, preconditioning, or hibernating myocardium. Volatile anesthetics can attenuate myocardial ischemia development through mechanisms that are independent of myocardial oxygen supply and demand and can facilitate functional recovery of stunned myocardium. Volatile agents also can simulate ischemic preconditioning, a phenomenon described as anesthetic preconditioning; the mechanisms of which are similar but not identical.
5. Intravenous induction agents (ie, hypnotics) belong to various drug classes, including barbiturates, benzodiazepines, *N*-methyl-D-aspartate receptor antagonists, and α_2-adrenergic receptor agonists. Although they all induce hypnosis, their sites of action and molecular targets are different, and their cardiovascular effects partially depend on the class to which they belong.
6. Studies of isolated cardiac myocytes, cardiac muscle tissue, and vascular tissue have demonstrated that induction agents inhibit cardiac contractility and relax vascular tone by inhibiting the mechanisms that increase intracellular calcium ion (Ca^{2+}) concentration. This may be offset by mechanisms that increase myofilament Ca^{2+} sensitivity in the cardiac myocyte and vascular smooth muscle, which can modulate cardiovascular changes. However, the cumulative effects of induction agents on contractility, vascular resistance, and vascular capacitance are mediated predominantly by their sympatholytic effects. Induction agents should be used judiciously and with extreme caution in patients with shock, heart failure, or other pathophysiologic circumstances in which the sympathetic nervous system is paramount in maintaining myocardial contractility and arterial and venous tone.
7. Opioids have diverse chemical structures, but all retain an essential T-shaped component necessary stereochemically for the activation of the μ-, κ-, and δ-opioid receptors. These receptors are not confined to the nervous system and have been identified in the myocardium and blood vessels where endogenous opioid proteins can be synthesized.
8. Acute exogenous opioid administration modulates many determinants of central and peripheral cardiovascular regulation. However, the predominant clinical effect is mediated by attenuation of central sympathetic outflow.
9. Activation of the δ-opioid receptor can elicit preconditioning, which is mediated by signaling pathways that involve G-protein–coupled protein kinases, caspases, nitric oxide, and other chemicals. In contrast with ischemia in homeotherms, hibernation is well tolerated in certain species. This phenomenon may partially depend on mechanisms that are activated by opioids or opioid-like molecules.

An enormous body of literature has described the protean effects of different anesthetic agents on the heart and the pulmonary and systemic regional vascular beds. More publications have been spawned by the great interest in anesthesia-induced preconditioning (APC). However, the prodigious literature detailing the influence of anesthetic agents on the myocardium has not always been consistent[1–3] because of the challenges inherent in quantitating the direct effects of volatile agents on the myocyte and myocardium and because of confounding variables such as the effects on coronary blood flow (CBF), the systemic vasculature, and the baroreceptor reflex arc.

In this chapter, volatile agents, intravenous anesthetics (ie, fixed agents), and opioids (ie, narcotics) are discussed in terms of their acute

BOX 10.1 VOLATILE ANESTHETIC AGENTS

- All volatile anesthetic agents cause dose-dependent decreases in systemic blood pressure, which for halothane and enflurane predominantly result from attenuation of myocardial contractile function and which for isoflurane, desflurane, and sevoflurane predominantly result from decreases in systemic vascular resistance.
- Volatile agents obtund all components of the baroreceptor reflex arc.
- The effects of volatile agents on myocardial diastolic function are not well characterized and await the application of emerging technologies that have the sensitivity to quantitate indices of diastolic function.
- Volatile anesthetics lower the arrhythmogenic threshold to catecholamines. However, the underlying molecular mechanisms are not well understood.
- When confounding variables are controlled (eg, systemic blood pressure), isoflurane does not cause coronary steal by a direct effect on coronary vasculature.
- The effects of volatile agents on systemic regional vascular beds and on the pulmonary vasculature are complex and depend on many variables, including the specific anesthetic, precise vascular bed, and vessel size and whether endothelial-dependent or endothelial-independent mechanisms are being investigated.

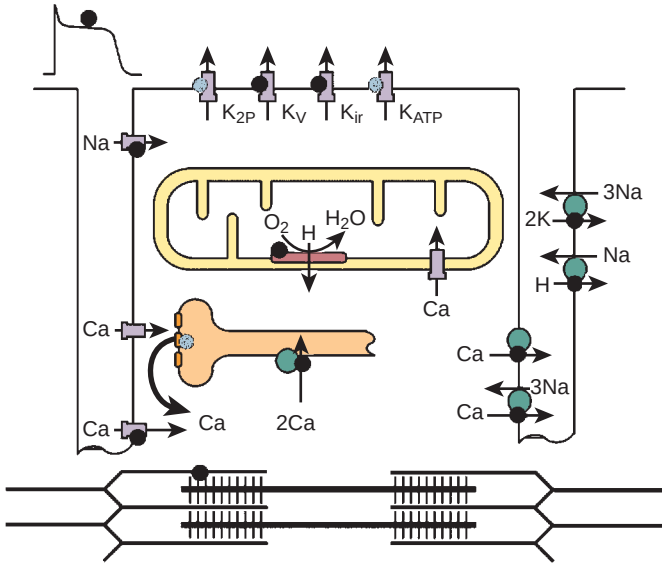


Fig. 10.1 Sites of action of volatile anesthetics in a ventricular myocyte. *Black circles* indicate inhibitory actions; *small green circles* indicate stimulatory actions. *(From Hanley PJ, ter Keurs HEDJ, Cannell MB, Excitation-contraction in the heart and the negative inotropic action of volatile anesthetics.* Anesthesiology. *2004;101:999.)*

and delayed effects on the cardiovascular system (CVS). The acute effects on myocardial function, electrophysiology, coronary vasoregulation, systemic and pulmonary vasoregulation, and the baroreceptor reflex are described. Discussion of the delayed effects focuses on APC.

Volatile Agents

Acute Effects

Myocardial Function

The influence of volatile anesthetics on contractile function has been investigated extensively in several animal species and in humans using various in vitro and in vivo models.[4–11] It is widely agreed that volatile agents cause dose-dependent depression of contractile function (Box 10.1). Different volatile agents are not identical in this regard, and the preponderance of information indicates that halothane and enflurane exert equal but more potent myocardial depression than isoflurane, desflurane, or sevoflurane, in part because of reflex sympathetic activation with the latter agents. In the setting of preexisting myocardial depression, volatile agents have a greater effect than in normal myocardium.[12,13] Early studies indicating that volatile agents did not have a deleterious effect on function in the setting of acute myocardial infarction (AMI) likely reflected the fact that the limited infarction did not compromise overall myocardial function.[14,15]

At the cellular level, volatile anesthetics exert their negative inotropic effects mainly by modulating sarcolemmal L-type Ca^{2+} channels, the sarcoplasmic reticulum (SR), and contractile proteins. L-type Ca^{2+} currents are decreased, and SR Ca^{2+} release is secondarily depressed (Figs. 10.1 and 10.2).[16] The contractile response to lower Ca^{2+} levels is further attenuated in the presence of volatile agents. The response is decreased by volatile agents at any given Ca^{2+} level because volatile agents decrease Ca^{2+} sensitivity (Fig. 10.3).[16]

The mechanisms by which anesthetic agents modify ion channels are not completely understood. Ion channels usually are studied in ex vivo circumstances in which they may be altered by multiple modulating influences. Moreover, the studies frequently used nonhuman tissue, and well-recognized species differences make extrapolation to humans difficult.[17] Nitrous oxide directly causes mild myocardial depression and sympathetic activation.[18]

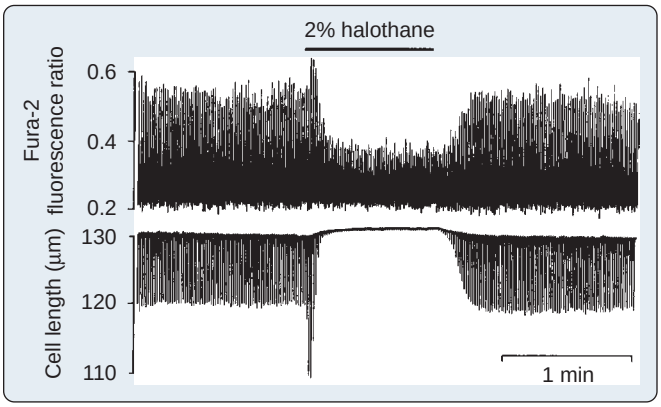


Fig. 10.2 Fura-2 fluorescence *(top trace)*, a ratiometric fluorescent dye that binds to free intracellular calcium and provides an index of calcium ion (Ca^{2+}) concentration, and cell length *(bottom trace)*, an index of contraction, were measured simultaneously in an electrically stimulated rat ventricular myocyte. Application of halothane initially induced a transient increase in the Ca^{2+} transient amplitude and twitch force before the Ca^{2+} signals and contraction decreased. *(From Harrison SM, Robinson M, Davies LA, et al. Mechanisms underlying the inotropic action of halothane on intact rat ventricular myocytes.* Br J Anaesth. *1999;82:609.)*

Even in the setting of normal systolic function, diastolic dysfunction occurs with increasing frequency in the elderly, and it is an important cause of congestive heart failure (CHF).[19–25] Diastolic dysfunction and its more severe clinical counterpart, diastolic heart failure, have protean causative factors and can be mechanistically complex[23] (Box 10.2). The mechanisms underlying these conditions can be categorized as those involving alterations in myocardial relaxation (eg, SR Ca^{2+} handling, phospholamban), those related to intrinsic properties of myocardial tissue (eg, myocyte cytoskeletal elements), and those that are extramyocardial (eg, loading conditions).

Indices of diastolic function were not readily and reliably measured noninvasively in the past, but there has been a relatively recent recognition of diastolic dysfunction and diastolic heart failure compared

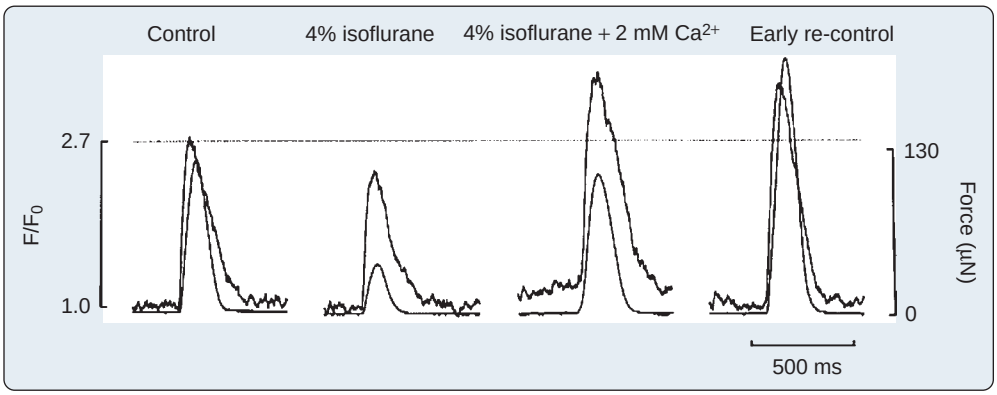


Fig. 10.3 Simultaneous measurement of force (*F*) and normalized fluo-3 fluorescence signals F/F_0, a fluorescence indicator of intracellular Ca^{2+}, in a rat cardiac trabecula. Application of isoflurane decreased force and Ca^{2+}. Restoration of the Ca^{2+} transient amplitude by an increase in external Ca^{2+} did not recover force, indicating that the anesthetic decreased Ca^{2+} responsiveness of the contractile proteins in addition to decreasing Ca^{2+} availability. *(From Hanley PJ, Loiselle DS. Mechanisms of force inhibition of halothane and isoflurane in intact rat cardiac muscle.* J Physiol. *1998;506:231.)*

BOX 10.2 MECHANISMS AND CAUSES OF DIASTOLIC HEART FAILURE

Abnormalities of Myocardial Relaxation
Ischemia
Hypertrophy
Hypertension
Valvular heart disease

Abnormalities of Myocardial Compliance
Aging
Fibrosis
Hypertrophy
Diabetes mellitus
Metabolic syndrome
Infiltrative disorders (eg, amyloidosis)
Cardiomyopathies
Constrictive pericarditis

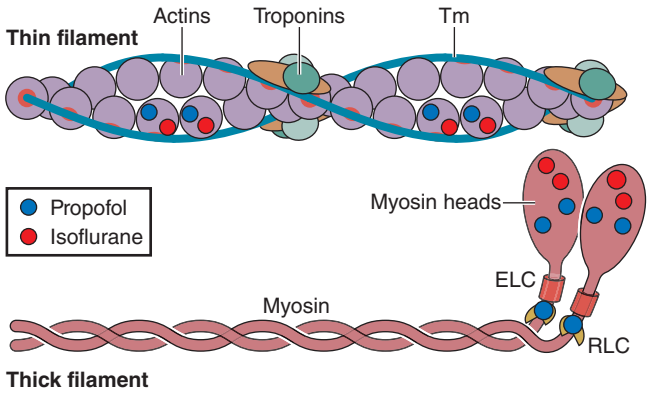


Fig. 10.4 Multiple binding sites are shown for isoflurane and propofol on actin and myosin. The direct actions on myofilaments result in myocardial depression that is independent of calcium concentration. Identification of specific binding sites for volatile and intravenous anesthetics may lead to development of agents that produce less myocardial depression. *ELC*, Essential light chain; *RLC*, regulatory light chain; *Tm*, tropomysin. *(Courtesy of Gao WD, Meng T, Bu W, et al.* Molecular mechanism of anesthetic-induced depression of myocardial contraction. FASEB J. *2016;30(8):2915–2925.)*

with perturbations in systolic function. This likely explains the relative paucity of literature detailing the modulating effects of volatile agents on diastolic function. There is reasonable agreement in the literature that volatile agents prolong isovolumic relaxation in a dose-dependent manner.[21,22,26–30]

The effects of volatile agents on chamber stiffness are more controversial. For example, halothane has been reported to decrease compliance and have no effect on myocardial stiffness.[21,22,26,28–31] The effect of nitrous oxide on diastolic function has not been investigated in a manner that critically rules out confounding variables. At a molecular level, alterations in relaxation likely reflect modulation of Ca^{2+} currents, including SR Ca^{2+} reuptake mechanisms. Paradoxically, in the setting of reperfusion injury and Ca^{2+} overload, the volatile agent sevoflurane improves indices of diastolic relaxation and attenuates myoplasmic Ca^{2+} overload.[32]

Further studies may illuminate the specific binding sites and mechanisms by which volatile anesthetics exert their negative inotropic and lusitropic effects. Ongoing work by Wei Dong Gao and colleagues suggests that isoflurane and the intravenous agent propofol bind directly to the myofilaments actin and myosin, resulting in myocardial depression that is independent of calcium concentration (Fig. 10.4).[33]

Cardiac Electrophysiology

Volatile anesthetics reduce the arrhythmogenic threshold for epinephrine. For volatile agents, the order of sensitization is halothane > enflurane > sevoflurane > isoflurane = desflurane.

The molecular mechanisms underlying the effect of volatile anesthetics are poorly understood. Anesthetic-induced modulation of ion channels is important mechanistically in excitation-contraction coupling (discussed earlier), in preconditioning (discussed later), and in modulating automaticity and arrhythmia generation[17] (Table 10.1). Although the effects of a particular volatile agent on a specific cardiac ion channel may be characterized, the information often cannot be extrapolated for use in clinical situations. This partly reflects issues such as species differences and ex vivo studies, but it also recognizes the impossibility of predicting the arrhythmogenic effect that can ensue after modulation with a particular volatile agent. This is one of the lessons garnered from experience with antiarrhythmic drugs such as encainide and flecainide.[34] Even in the clinical setting, not all volatile agents have the same effect.[35]

Coronary Vasoregulation

Volatile anesthetics modulate several determinants of myocardial oxygen supply and demand. They also directly modulate the myocyte's response to ischemia. Studies investigating the effects of volatile agents on coronary vasoregulation should be interpreted in this context.

TABLE 10.1 Effects of Volatile Anesthetics

Anesthetic Gas	*Target*	*Effect*	*Cardiac Side Effects*
Halothane, isoflurane, sevoflurane	L-type Ca^{2+} current	Inhibition	Reduced contractility,[a] shortened AP and refractory time
Halothane	β-Adrenergic regulation of L-type Ca^{2+} current	Complex interference	Enhanced proarrhythmicity compared with sevoflurane (?)
Halothane, isoflurane, xenon	Voltage-dependent transient outward K^+ current	Inhibition	Shortened AP duration, AP duration mismatch within the heart
Halothane, isoflurane, sevoflurane	Voltage-dependent sustained outward K^+ current	Inhibition	Delayed repolarization, mismatch of AP duration[a]
Isoflurane, sevoflurane	ATP-dependent K^+ current	Enhancement	Myocardial preconditioning
Halothane, isoflurane, sevoflurane	Fast Na^+ current	Inhibition	Slowed conduction,[a] induction of tachyarrhythmias (?)

[a]Effects of paramount importance.
AP, Action potential; *ATP*, adenosine triphosphate.
From Huneke R, Fassl J, Rossaint R, et al. Effects of volatile anesthetics on cardiac ion channels. *Acta Anaesthesiol Scand.* 2004;48:547.

Animal studies indicate that halothane has little direct effect on the coronary vasculature.[36–38] Clinical studies investigating the effect of halothane also indicate that it has minimal or mild coronary vasodilator effects.[39–42] The effect of isoflurane on coronary vessels was controversial and dominated much of the relevant literature in the 1980s and early 1990s. Current assessments of the effects of isoflurane have been succinctly detailed by Tanaka and colleagues.[43] Several reports indicated that it caused direct coronary arteriolar vasodilatation in vessels with diameters of 100 µm or less and that isoflurane could cause coronary steal in patients with steal-prone coronary anatomy. The patients had significant coronary stenosis in a vessel serving a region of ischemic myocardium, in which vessels were presumably maximally dilated because of local metabolic autoregulation, and had isoflurane-induced vasodilatation in adjacent vessels in nonischemic zones that reduced flow through collateral vessels, diverting coronary flow away from the ischemic region.[44,45] Several animal and human studies in which potential confounding variables were controlled found that isoflurane did not cause coronary steal.[46–52] Studies of sevoflurane and desflurane showed similar results that were consistent with a mild direct coronary vasodilator effect of these agents.[53,54]

Ultimately, CBF in the setting of normal systemic hemodynamics is controlled by coronary vascular smooth muscle tone, which can be modulated directly (ie, endothelium independent) or indirectly through the endothelium (ie, endothelium dependent). Teleologically, it can be predicted that in vital organs, control of blood flow is predominantly local, acting through endothelium-dependent or endothelium-independent mechanisms.

Volatile agents can modulate mechanisms underlying vascular tone. Halothane and isoflurane have been shown to attenuate endothelial-dependent tone by receptor-dependent and receptor-dependent plus -independent mechanisms, respectively, in coronary microvessels.[55] Several volatile agents cause coronary vasodilation through mechanisms that depend on ATP-sensitive K^+ (K^+_{ATP}) channels.[55–58] Sevoflurane-induced K^+ and Ca^{2+} channel–mediated increases coronary collateral blood flow.[59] The effects in vivo typically are modest because local control mechanisms are likely to predominate.

Systemic Regional and Pulmonary Vascular Effects

Volatile agents can modulate vascular tone. The specific result, however, can be influenced by the agent under study, the vascular bed being investigated, the vessel size and type within the vascular bed, the level of preexisting vascular tone, patient age, and indirect effects of the agents, such as anesthesia-induced hypotension and reflex autonomic nervous system (ANS) activation.

All volatile anesthetics decrease systemic blood pressure (BP) in a dose-dependent manner. With halothane and enflurane, the decrease in systemic BP primarily results from decreases in stroke volume (SV) and cardiac output (CO), whereas isoflurane, sevoflurane, and desflurane decrease overall systemic vascular resistance (SVR) while maintaining CO. However, these overall effects belie the multiple effects in the various regional vascular beds. Within the systemic noncoronary vasculature, aortic and mesenteric vessels have been the best studied.

Reversible inhibition of endothelium-dependent relaxation in aortic and femoral vessels was first demonstrated for halothane and then was demonstrated for enflurane, isoflurane, and sevoflurane in capacitance and resistance vessels.[55,60–64] However, these observations mask the differential effects of volatile agents on underlying endothelium-dependent mechanisms. Halothane and enflurane decrease agonist- (ie, bradykinin-) and ATP-induced Ca^{2+} increases in bovine endothelial cells, whereas isoflurane does not.[65] In contrast, isoflurane does attenuate histamine-induced Ca^{2+} influx into human endothelial cells.[66]

Alterations in endothelium-dependent mechanisms by volatile agents are not confined to attenuation of agonist-dependent and -independent activation of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) release but also may extend to other mechanisms. For example, the effects of sevoflurane on endothelial cell function may be partially because of sevoflurane-induced changes in endothelin 1 (ET1) production and in the redox milieu of the endothelial cells (ie, increased superoxide anion production).[67]

The effect of volatile agents on vascular smooth muscle mechanisms is equally complex and varies among agents. In endothelial cell–denuded aortic rings, halothane decreases sarcolemmal Ca^{2+} influx through voltage-dependent calcium channels and SR Ca^{2+} release, but sevoflurane does not.[68] Sevoflurane also inhibits angiotensin II–induced vascular smooth muscle contraction in aortic rings.[69] In mesenteric vessels, sevoflurane accentuates endothelium-dependent mechanisms and attenuates endothelium-independent mechanisms in the presence of norepinephrine.[70] Studies of the influence of volatile agents on vascular smooth muscle Ca^{2+} currents indicate that halothane and enflurane stimulate SR release and reuptake from the caffeine-sensitive pool. In contrast, halothane, enflurane, and isoflurane increase calcium-induced calcium release (CICR) mechanisms, but sevoflurane decreases CICR mechanisms.[71] Volatile agents also modulate Ca^{2+} sensitivity. In mesenteric vessels, halothane relaxation is largely mediated by Ca^{2+} and myosin light-chain desensitizing mechanisms.[72]

The pulmonary circulation has unique features that must be taken into account when interpreting studies of this vascular bed. In addition to issues that also apply to systemic vascular beds (eg, vessel size), the pulmonary vasculature is a low-resistance bed (ie, requires preconstriction to access vasoactive effects), is not rectilinear (ie, changes in flow can change certain parameters used to calculate resistance), is contained within the chest and subject to extravascular pressures (ie, that are not atmospheric and change during the respiratory cycle), and exhibits the unique vascular phenomenon of hypoxia-induced vasoconstriction. Volatile agents modulate the baseline pulmonary vasculature and multiple vasoactive mechanisms that control pulmonary vascular tone.

The effect of volatile anesthetics is agent specific. For example, halothane causes flow-independent pulmonary vasoconstriction.[73] In contrast, the hypoxic pulmonary vasoconstrictor response does not appear to be altered by sevoflurane and desflurane.[74] The pulmonary vascular endothelial response appears to be impaired by the volatile agents halothane and isoflurane.[75,76]

Pulmonary vascular smooth muscle regulatory mechanisms also can be modified by volatile agents. Halothane, enflurane, and isoflurane attenuate pulmonary vasodilation induced by K^+_{ATP} channel activation.[77,78] Although the effects of various volatile agents on K^+_{ATP} channel activation are similar, β-adrenergic receptor–induced pulmonary vasodilatation is differently modulated. Halothane and isoflurane potentiate the vasodilatory response, but enflurane has no effect.[79]

Baroreceptor Reflex

All volatile agents attenuate the baroreceptor reflex. Baroreceptor reflex inhibition by halothane and enflurane is more potent than that observed with isoflurane, desflurane, or sevoflurane, each of which has a similar effect.[80,81] Each component of the baroreceptor reflex arc (eg, afferent nerve activity, central processing, efferent nerve activity) is inhibited by volatile agents. Inhibition of afferent nerve traffic in part results from baroreceptor sensitization,[82,83] whereas attenuation of efferent activity in part results from ganglionic inhibition as manifested by differential preganglionic and postganglionic nerve activity.[82–84]

Delayed Effects

Reversible Myocardial Ischemia

Prolonged ischemia results in irreversible myocardial damage and necrosis (Box 10.3). Depending on the duration and sequence of ischemic insults, shorter durations of myocardial ischemia can lead to preconditioning or myocardial stunning (Fig. 10.5).[85] Stunning, first described in 1975, occurs after brief ischemia and is characterized by myocardial dysfunction in the setting of normal restored blood flow and by an absence of myocardial necrosis.[86] Ischemic preconditioning (IPC) was first described by Murry and coworkers[87] in 1986 and is characterized by an attenuation of infarct size after sustained ischemia if the period of sustained ischemia is preceded by a period of brief ischemia (Fig. 10.6). This effect is independent of collateral flow. Short periods of ischemia followed by reperfusion can lead to stunning or preconditioning with a reduction in infarct size (Fig. 10.7).[85]

Work in the 1970s indicated that volatile anesthetic agents attenuated ST-segment elevations in the setting of short-duration ischemia and limited infarct size and lactate production after prolonged ischemia.[88,89] The effects seemed to be independent of the main determinants of myocardial oxygen supply and demand, suggesting that the volatile agents might be exerting a beneficial effect at the level of the myocyte.

On resolution of the isoflurane coronary steal controversy, the first description of the salutary effects of volatile agents on the consequences of brief ischemia was published in 1988. Warltier and coworkers[90] described the beneficial effects of halothane and isoflurane in facilitating recovery of contractile function in stunned myocardium (Fig. 10.8). It was almost a decade later before the effects of volatile agents on preconditioning were outlined[2,3] and the term *APC* was used[1] (Fig. 10.9).

BOX 10.3 VOLATILE AGENTS AND MYOCARDIAL ISCHEMIA

- Volatile anesthetic agents can attenuate the effects of myocardial ischemia (ie, acute coronary syndromes).
- Nonacute manifestations of myocardial ischemia include hibernating myocardium, stunning, and preconditioning.
- Halothane and isoflurane facilitate the recovery of stunned myocardium.
- Preconditioning, an important adaptive and protective mechanism in biologic tissues, can be provoked by protean nonlethal stresses, including ischemia.
- Volatile anesthetic agents can mimic preconditioning (ie, anesthetic preconditioning), which can have important clinical implications and provide insight into the cellular mechanisms of action of these volatile agents.

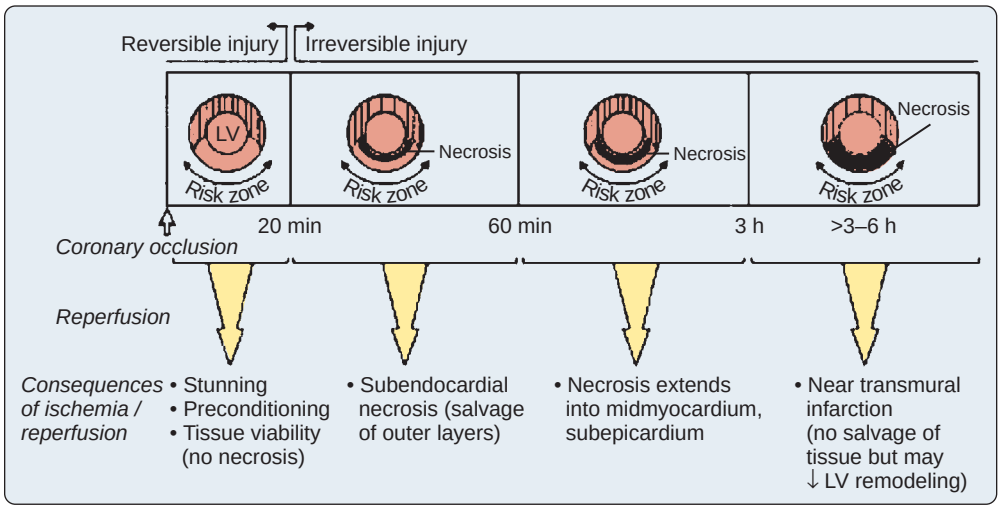


Fig. 10.5 Effects of ischemia and reperfusion on the heart based on studies using an anesthetized canine model of proximal coronary artery occlusion. Periods of ischemia of less than 20 minutes followed by reperfusion are not associated with development of necrosis (ie, reversible injury). Brief ischemia and reperfusion results in stunning and preconditioning. If the duration of coronary occlusion is extended beyond 20 minutes, necrosis develops from the subendocardium to subepicardium over time. Reperfusion before 3 hours of ischemia salvages ischemic but viable tissue. Salvaged tissue may demonstrate stunning. Reperfusion beyond 3 to 6 hours in this model does not reduce myocardial infarct size. Late reperfusion may still have a beneficial effect on reducing or preventing myocardial infarct expansion and left ventricular *(LV)* remodeling. *(From Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications, part I.* Circulation. *2001;104:2981.)*

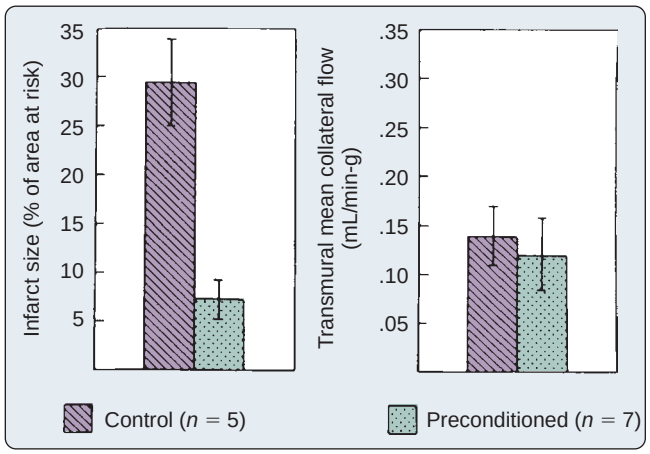


Fig. 10.6 Infarct size and collateral blood flow in a 40-minute study. Infarct size as a percentage of the anatomic area at risk in the control *(purple)* and preconditioned *(green)* hearts *(left)*. Infarct size in control animals averaged 29.4% of the area at risk. Infarct size in preconditioned hearts averaged only 7.3% of the area at risk (preconditioned vs control, $P < .001$). Transmural mean collateral blood flow *(right)* was not significantly different in the two groups. The protective effect of preconditioning was independent of the two major baseline predictors of infarct size: area at risk and collateral blood flow. *Bars* represent the group mean ± standard error of the mean. *(From Warltier DC, al-Wathiqui MH, Kampine JP, et al. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane.* Anesthesiology. *1988;69:552.)*

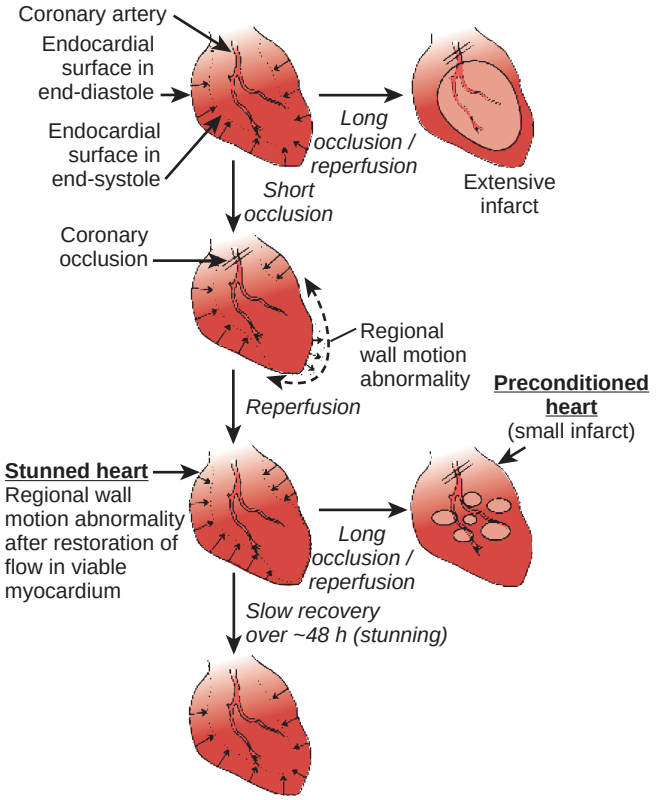


Fig. 10.7 Short coronary artery occlusions result in stunning, in which the regional wall motion abnormality is prolonged despite reperfusion and viable myocardial cells. Brief episodes of ischemia and reperfusion precondition the heart. When the heart is then exposed to a longer duration of ischemia and reperfusion, myocardial infarct size is reduced. *(From Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications, part I.* Circulation. *2001;104:2981.)*

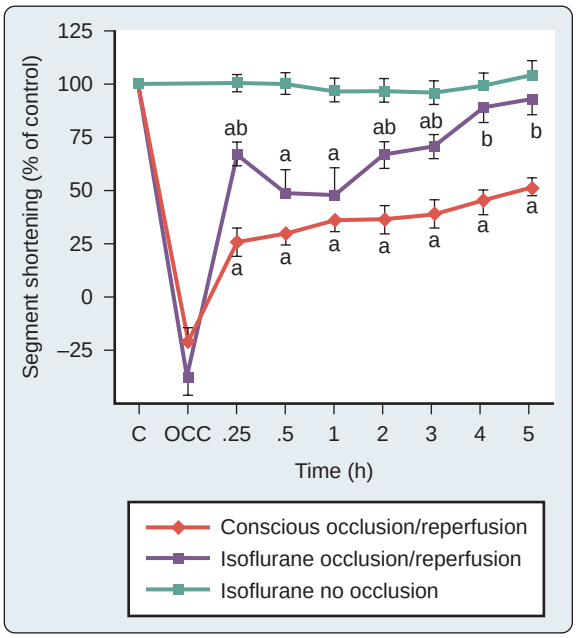


Fig. 10.8 Segment shortening data are expressed as a percentage of the control mean ± standard error of the mean during coronary artery occlusion *(OCC)* and at various times after reperfusion in conscious dogs *(red)* and in dogs anesthetized with isoflurane *(purple)*. Comparisons are made at various time points with animals anesthetized with isoflurane but not undergoing coronary artery occlusion and reperfusion *(green)*. A significant ($P < .05$) difference *(a)* was found for dogs anesthetized without occlusion *(green)* versus those undergoing conscious occlusion *(red)* or those undergoing occlusion during anesthesia *(purple)*. A significant ($P < 9.95$) difference *(b)* was found for dogs undergoing conscious occlusion *(red)* versus those undergoing occlusion during anesthesia (*purple*). The control state *(C)* indicates the awake, unsedated state *(red)* or a stable hemodynamic state after 2 hours of isoflurane anesthesia (*black* and *green*). *(From Warltier DC, al-Wathiqui MH, Kampine JP, et al. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane.* Anesthesiology. *1988;69:552.)*

The phenomenon of and the mechanisms underlying IPC are the focus of extensive investigation. IPC has the following characteristics:

- It results in two periods (ie, windows) of protection. The first (ie, early or classic) occurs at 1 to 3 hours, and the second (ie, late or delayed) occurs 24 to 96 hours after the preconditioning stimulus.
- It also occurs in noncardiac tissue (eg, brain, kidney).
- It is ubiquitous across species.
- It is most pronounced in larger species with lower metabolism and slower heart rates (HRs).
- It seems to be important clinically because angina within the 24-hour period preceding an AMI is associated with an improved outcome (Fig. 10.10).[91]
- It is mediated by multiple endogenous signaling pathways[92,93] (Fig. 10.11).

As might be predicted from the time frame of delayed IPC, it is in part mediated by transcriptional and posttranslational mechanisms[92] (Fig. 10.12). Preconditioning also can be triggered by events other than ischemia (eg, cellular stressors, pharmacologic agonists, anesthetic agents) (see Fig. 10.12).[92]

The benefits of IPC are not necessarily confined to and may not include limitation of infarct size. They depend on the specific trigger, the species under study, and the type (ie, classic or delayed) of IPC. For example, rapid pacing affords protection against arrhythmias but not against infarct evolution. In contrast, cytokine-induced IPC limits infarct size but has no effect on arrhythmias.[92] Although there are fundamental mechanisms common to various triggers of IPC, the

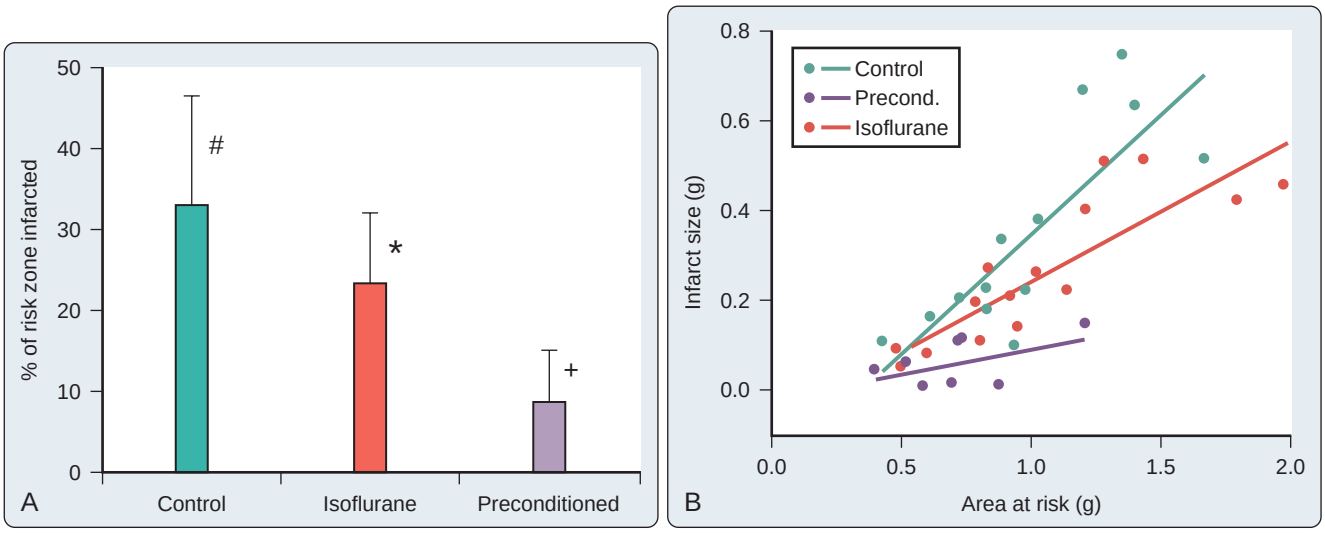


Fig. 10.9 (A) Infarct size (mean ± standard deviation) is expressed as a percentage of the area at risk in rabbit hearts that were not pretreated (control group: $n = 13$), exposed to 5 minutes of preconditioning (ischemic preconditioned group: $n = 8$), or exposed to 15 minutes of 1.1% isoflurane (isoflurane group: $n = 15$) before 30 minutes of anterolateral coronary occlusion. Statistical analysis of the groups ($^{\#},^{*},^{+}$) showed that the relationship between infarct size and area at risk was different in each group ($P < .05$). (B) Relationship between infarct size and myocardium at risk for the three groups in grams (g). This was a statistically significant difference in line elevation but not in slope. *(From Cason BA, Gamperi AK, Slocum RE, et al. Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits.* Anesthesiology. *1997;87:1182.)*

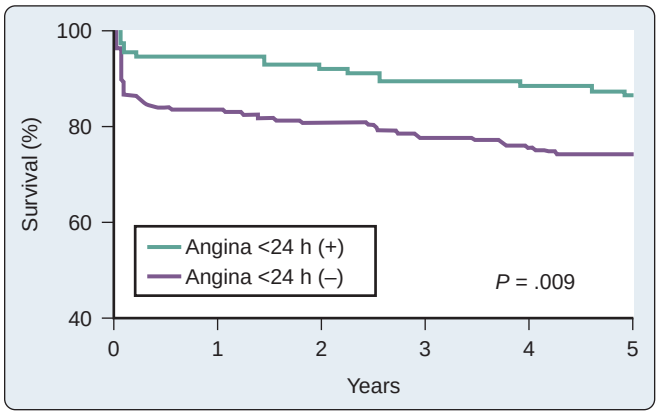


Fig. 10.10 Five-year survival curves for patients with *(green)* and those without *(purple)* prodromal angina in the 24 hours before infarction. *(From Ishihara M, Sato K, Tateishi H, et al. Implications of prodromal angina pectoris in anterior wall acute myocardial infarction: acute angiographic findings and long-term prognosis.* J Am Coll Cardiol. *1997;30:970.)*

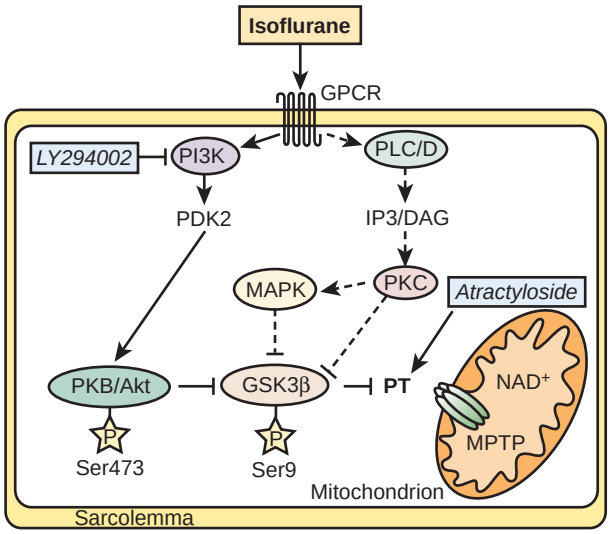


Fig. 10.11 Investigated signaling pathways *(solid lines)*. During early reperfusion, multiple signaling cascades inhibit the master switch kinase, glycogen synthase kinase 3β *(GSK3β)*, which converges the prosurvival pathways and prevents permeability transition *(PT)* in mitochondria. In addition to other kinases, protein kinase B *(PKB)/Akt* represents a key enzyme in the reperfusion injury salvage kinase cascade requiring phosphorylation at *Ser473* for full activation. Phosphorylated PKB/Akt subsequently inactivates its downstream target GSK3β by phosphorylation at *Ser9*. *LY294002* inhibits phosphatidylinositol 3-kinase *(PI3K)*. *Atractyloside* induces opening of the mitochondrial permeability transition pore *(MPTP)*. *Arrows* indicate positive activity; *lines with blunted ends* indicate inhibition. *DAG*, Diacylglycerol; *GPCR*, G-protein–coupled receptor; *IP3*, inositol 1,4,5-triphosphate; *MAPK*, mitogen-activated protein kinase; *NAD^+*, nicotinamide adenine dinucleotide; *PDK2*, phosphatidylinositol-dependent kinase 2 (ie, Ser473 kinase); *PKC*, protein kinase C; *PLC/D*, phospholipase C/D. *(From Feng J, Lucchinetti E, Ahuja P, et al. Isoflurane postconditioning prevents opening of the mitochondrial permeability transition pore through inhibition of glycogen synthase kinase 3β.* Anesthesiology. *2005;103:987–995.)*

different triggers of IPC modulating different end points suggest that there also exist mechanistic differences across triggers. APC may not be identical to IPC mechanistically.

Induced ischemia in a region of the body away from the heart (ie, remote ischemic preconditioning [RIPC]) has myocardium-protective effects in animals and has shown promising results in humans.[94–96] A randomized, controlled trial of RIPC (ie, three cycles of 5 minutes of an inflated BP cuff to 200 mm Hg on the upper extremity followed by 5 minutes of reperfusion with the cuff deflated) enrolling patients undergoing coronary artery bypass grafting (CABG) showed a mortality benefit with the intervention.[95] Metaanalyses show mixed results, with some showing insufficient evidence and others suggesting benefit.[94,97,98]

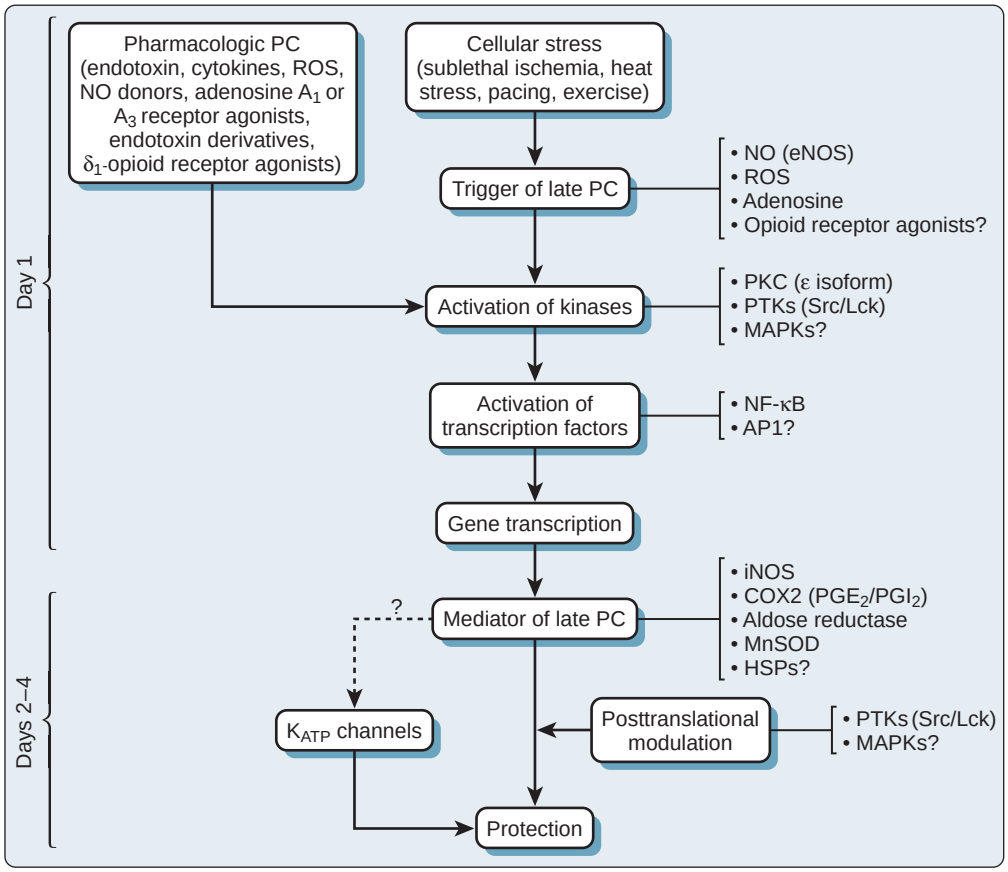


Fig. 10.12 Schematic representation of the cellular mechanisms underlying late preconditioning *(PC)*. A nonlethal cellular stress (eg, reversible ischemia, heat stress, ventricular pacing, exercise) causes release of chemical signals (eg, nitric oxide *[NO]*, reactive oxygen species *[ROS]*, adenosine, opioid receptor agonists) that serve as triggers for the development of late PC. These substances activate a complex signal transduction cascade that includes the ε isoform of protein kinase C *(PKC)*, Src or Lck protein tyrosine kinases *(PTKs)*, and probably other kinases. Similar activation of PKC and downstream kinases can be elicited pharmacologically by a wide variety of agents, including naturally occurring and often noxious substances (eg, endotoxin, interleukin-1, tumor necrosis factor-α or -β, leukemia inhibitor factor, or ROS) and clinically applicable drugs (eg, NO donors, adenosine A_1 or A_3 receptor agonists, endotoxin derivatives, or δ_1-opioid receptor agonists). Recruitment of PKC and distal kinases leads to activation of nuclear factor-κB *(NF-κB)* and almost certainly other transcription factors, resulting in increased transcription of multiple cardioprotective genes and synthesis of many cardioprotective proteins that serve as comediators of protection 2 to 4 days after the PC stimulus. The mediators of late PC include inducible nitric oxide synthase *(iNOS)*, cyclooxygenase 2 *(COX2)*, aldose reductase, and manganese superoxide dismutase *(MnSOD)*. Among the products of COX2, prostaglandin E_2 and I_2 (*PGE_2* and *PGI_2*) appear to be the most likely effectors of COX2-dependent protection. Increased synthesis of heat shock proteins *(HSPs)* is unlikely to be a mechanism of late PC, although the role of posttranslational modification of preexisting HSPs remains to be determined. The occurrence of cardioprotection on days 2 to 4 requires the activity of PTKs and possibly p38 mitogen-activated protein kinases *(MAPKs)*, potentially because iNOS and other mediators need to undergo posttranslational modulation to confer protection against ischemia. Opening of K^+_{ATP} channels is also essential for the protection against infarction (but not against stunning) to occur. The exact relationships among iNOS, COX2, aldose reductase, MnSOD, and K^+_{ATP} channels are unknown, although evidence suggests that COX2 may be downstream of iNOS (ie, COX2 is activated by NO). *AP1*, Activator protein 1; *PTK*, protein tyrosine kinases. *(From Bolli R. The late phase of preconditioning.* Circ Res. *2000;87:972.)*

The endogenous cannabinoids and the cannabinoid receptors, identified as the sites of action of Δ^9-tetrahydrocannabinol (THC) and other compounds found in marijuana, contribute to IPC and RIPC in animals. In a rat model, antagonism at the CB_2 receptor, but not the CB_1 receptor, reversed the cardioprotective effects of RIPC.[99] In a mouse model of ischemia and reperfusion, agonism at the CB_2 receptor was cardioprotective.[100] It is unknown whether cannabinoid signaling is involved in volatile anesthetic–induced IPC. Future investigations of the cannabinoid system and the CB_2 receptor in particular should elucidate whether they are pharmacologic targets for activating IPC.

Preconditioning and Postconditioning Anesthetic Agents

Preconditioning and postconditioning anesthetics is an area of intense investigation, as reflected in two issues of *Anesthesiology* that were predominantly devoted to the subject.[101,102] After the initial description of APC,[1–3] subsequent investigations indicated that volatile agents could elicit delayed (ie, late) and classic (ie, early) preconditioning.[103,104] APC is dose dependent,[105–107] exhibits synergy with ischemia in affording protection,[108,109] and perhaps not surprisingly in view of the differential uptake and distribution of volatile agents, requires different time intervals between exposure and the maintenance of a subsequent benefit that is agent dependent.[43]

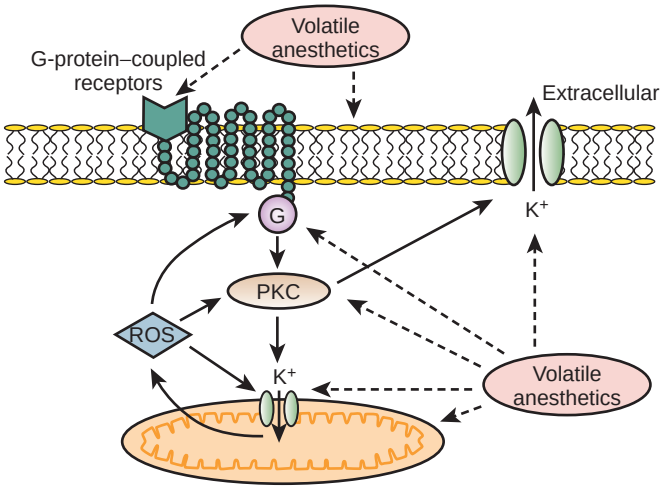


Fig. 10.13 Multiple endogenous signaling pathways mediate volatile anesthetic–induced myocardial activation of an end-effector that promotes resistance against ischemic injury. Mitochondrial K^+_{ATP} channels have been implicated as the end-effector in this protective scheme, but sarcolemmal K^+_{ATP} channels may also be involved. A trigger initiates a cascade of signal transduction events, resulting in protection. Volatile anesthetics signal through adenosine and opioid receptors, modulate G proteins *(G)*, stimulate protein kinase C *(PKC)* and other intracellular kinases, or directly stimulate mitochondria to generate reactive oxygen species *(ROS)* that ultimately enhance K^+_{ATP} channel activity. Volatile anesthetics may also directly facilitate K^+_{ATP} channel opening. *Dotted arrows* delineate the intracellular targets that may be regulated by volatile anesthetics; *solid arrows* represent potential signaling cascades. *(From Tanaka K, Ludwig LM, Kersten JR, et al. Mechanisms of cardioprotection by volatile anesthetics.* Anesthesiology. *2004;100:707.)*

The contributions of sarcolemmal and mitochondrial K^+_{ATP} channels in IPC have been extensively investigated, demonstrating that mitochondrial K^+_{ATP} channels play a critical role in this process. Volatile agents that exhibit APC activate mitochondrial K^+_{ATP} channels, and specific mitochondrial K^+_{ATP} channel antagonists block this effect. The precise contributions of sarcolemmal versus mitochondrial K^+_{ATP} channel activation to APC remain to be elucidated (Fig. 10.13).[43]

The original descriptions of APC indicated that volatile agents could trigger preconditioning without concurrent ischemia during the triggering period[1–3] (see Fig. 10.9). However, studies of mitochondrial activation (through mitochondrial K^+_{ATP} channels), indicate that volatile agents on their own do not activate mitochondria but do potentiate the effects of direct mitochondrial K^+_{ATP} channel openers[107] (Fig. 10.14). These apparent inconsistencies are likely explained by the presence of multiple parallel and redundant pathways activated during APC and IPC[104] (see Fig. 10.13). For example, the adenosine A_1 and δ_1-opioid G-coupled receptors can trigger IPC. Pharmacologic blockade of these receptors attenuates the positive effects of volatile agents.[106,110] Protein kinase C (PKC) and the nuclear signaling pathway (ie, mitogen-activated protein kinase [MAPK]) are important signaling pathways in preconditioning, and volatile agents have been shown to modulate PKC translocation.[111]

Oxidant stress is a central feature of reperfusion. Depending on the specific moiety, the enzymatic source, and most importantly, the oxidant stress load, it may trigger preconditioning or mediate reperfusion injury. Indirect and direct evidence indicate that volatile agents can increase oxidant stress to levels that trigger preconditioning.[112–114]

Activation of eNOS also plays a role, as does depolarization of the mitochondrial internal membrane.[115] It may prevent opening of the mitochondrial permeability transition pore (MPTP) and inhibit Na^+/H^+ exchange, attenuating Ca^{+2} overload and cell edema.[115] Inhibition of mitochondrial permeability by APC may decrease myocyte death, and PKC appears to play a role in IPC-induced delay of MPTP opening.[116,117] One study demonstrated that isoflurane activated PKC-dependent signaling pathways, resulting in the delay of MPTP opening,[118] suggesting a possible mechanism for isoflurane in APC. Ge and colleagues[119] demonstrated that NO could act as a trigger of preconditioning and a mediator for isoflurane-induced cardiac protection in mouse hearts. The finding implies that an eNOS-dependent mechanism prevents the opening of the MPTP, although other pathways, including glycogen synthase kinase-3β, have been implicated (Fig. 10.15).[93,119]

Mitochondrial activation attenuates ischemia-induced oxidant stress, favorably modulates mitochondrial energetics, decreases cytochrome *c* egress into the cytoplasm, and attenuates mitochondrial and cytoplasmic Ca^{2+} overload. Mitochondrial cytochrome *c* release is an important mechanism underlying caspase activation and the apoptotic process[120] (Fig. 10.16). Whether by Ca^{2+}-mediated or apoptotic mechanisms, or both, volatile agents attenuate cell death in models of APC[109] (Fig. 10.17). Although the mechanisms of mitochondrial activation have been aggressively studied, they remain incompletely understood. These salutary effects of volatile agents seem to have a clinical correlate[109] (Fig. 10.18).

The use of volatile anesthetics can alter outcomes after cardiac surgery. A metaanalysis by Landoni and associates[121] demonstrated a significant reduction in postoperative myocardial infarction after cardiac surgery and significant advantages with respect to postoperative cardiac troponin release, inotrope requirements, time to extubation, intensive care unit stay, hospital stay, and survival. Another metaanalysis by Bignami and colleagues[122] demonstrated that the use of volatile anesthetics was beneficial in terms of mortality rates after cardiac surgery. The duration of the volatile anesthetic exposure seemed to have an impact; the longer the exposure, the greater the effect. De Hert and coworkers[123] demonstrated the cardioprotective effects of volatile anesthetics if used throughout the surgical procedure rather than only before and after cardiopulmonary bypass (CPB).

Further studies are necessary to delineate the role of the anesthetic regimen on outcomes after cardiac surgery and elucidate the mechanisms behind this protection. Whether it involves mechanisms that are associated with APC remains unclear.

Intravenous Induction Agents

The drugs discussed in this section are induction agents and hypnotics. The drugs belong to different classes (ie, barbiturates, benzodiazepines, *N*-methyl-D-aspartate [NMDA] receptor antagonists, and α_2-adrenergic receptor agonists). Their effects on the CVS depend on the class to which they belong. These effects have been studied at a cellular, tissue, organ, and whole-animal level. Although a detailed discussion of the molecular mechanisms underlying each agent is beyond the scope of this chapter, a focused appraisal of well-established effects of specific drugs is given. Although sophisticated pharmacologic studies dissecting the signal transduction pathways can provide insights into mechanisms, they cannot fully predict the response of an intact organism. Because propofol is the most common induction agent, literature for this agent is used as the paradigm for discussing mechanisms by which cardiovascular regulation is altered by intravenous agents. A summary of the cardiovascular effects of each induction agent is provided later in the chapter.

Unlike the inhalation anesthetic agents that augment IPC, there is no good evidence that intravenous hypnotic agents demonstrate these protective effects. There is, however, emerging evidence that propofol, the mainstay of induction agents, may enhance antioxidant activity in the heart and may prevent lipid peroxidation after ischemia and reperfusion, offering a potential protection of the heart.[124]

Acute Cardiac Effects

Myocardial Contractility

To understand the effect of intravenous anesthetics on integrated cardiovascular responses is to understand the effect on the various factors that regulate the force of contraction of the heart. If the heart in

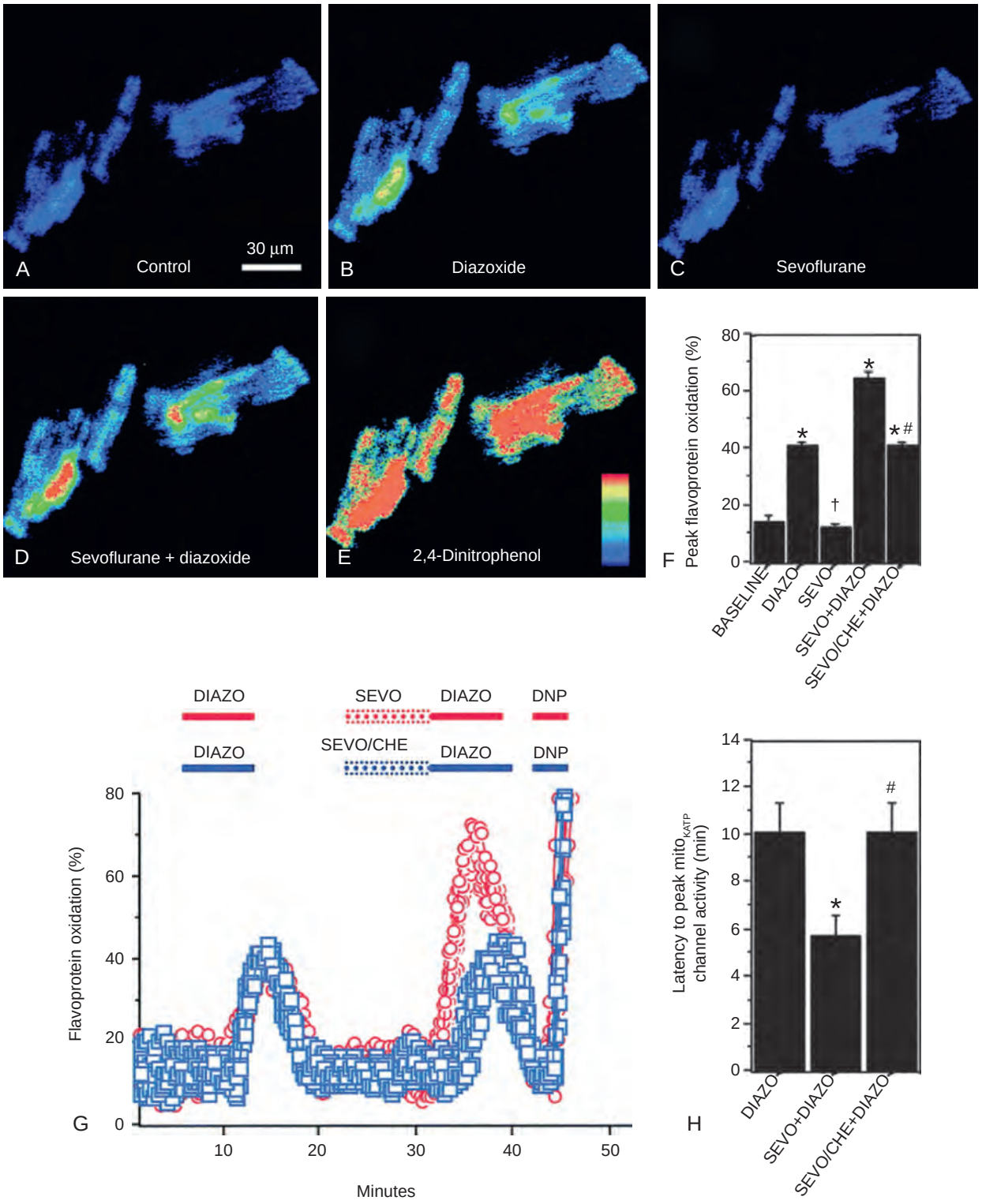


Fig. 10.14 Effect of sevoflurane (*SEVO*; 2.8% [vol/vol]) on diazoxide *(DIAZO)*–induced flavoprotein oxidation in myocytes excited at 480 nm. Similar results were obtained for isoflurane. An artificial color scale was used to visualize the relative intensity of emitted fluorescence at 530 nm; *blue* indicates reduced flavoproteins, and *red* indicates fully oxidized flavoproteins. (A) At baseline. (B) At 100 µm for DIAZO (same cells). (C) At 2 minimal alveolar concentration (MAC) of SEVO. (D) At 100 µm for DIAZO preceded by 2 MAC of SEVO. *Red* indicates intense local oxidation by mitochondrial clusters. (E) At 100 µm for 2,4-dinitrophenol *(DNP)*. (F) Mean percentages of peak flavoprotein fluorescence depending on the drugs exposed to myocytes. $*P < .0001$ versus baseline or SEVO + DIAZO versus DIAZO alone. $^{\#}P$ value is not significantly different from DIAZO; $^{\dagger}P$ value is not significantly different from baseline. SEVO/CHE indicates concomitant treatment of myocytes with SEVO and chelerythrine (CHE) at 2 µm before exposure to DIAZO. (G) Time-lapse analysis of alterations in fluorescence intensity in individual myocytes expressed as percentage of DNP-induced fluorescence. *Blue squares* and *red circles* indicate values from eight different experiments. (H) Latency to peak activation of mitochondrial K^{+}_{ATP} ($mitoK^{+}_{ATP}$) channels in response to the various treatment regimens. $*P < .001$ versus DIAZO; $^{\#}P$ value is not significant versus DIAZO. Data are mean ± standard deviation. *(From Zaugg M, Lucchinetti E, Spahn DR, et al. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial KATP channels via multiple signaling pathways.* Anesthesiology. *2002;97:4.)*

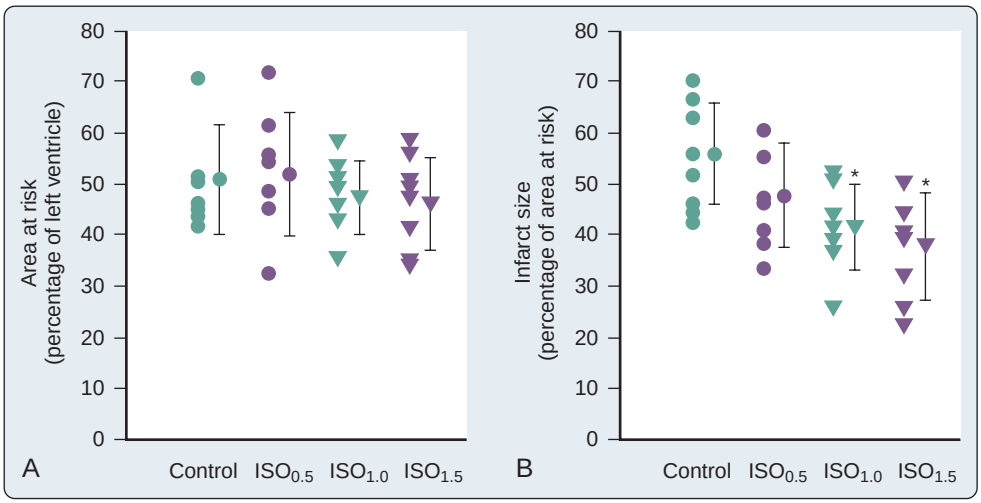


Fig. 10.15 Concentration-dependent decreases in myocardial infarct size by isoflurane *(ISO)* postconditioning in wild-type mice subjected to 30 minutes of coronary occlusion followed by 2 hours of reperfusion. (A) Area at risk expressed as a percentage of left ventricle area. (B) Myocardial infarct size expressed as a percentage of area at risk. Isoflurane postconditioning was produced by 0.5, 1.0, or 1.5 minimum alveolar concentrations of isoflurane ($ISO_{0.5}$, $ISO_{1.0}$, or $ISO_{1.5}$) administered during the last 5 minutes of ischemia and first 3 minutes of reperfusion. *$P < 0.05$ versus control ($n = 8–10$ mice/group). *(From Ge Z, Pravdic D, Bienengraeber M, et al. Isoflurane postconditioning protects against reperfusion injury by preventing mitochondrial permeability transition by an endothelial nitric oxide synthase-dependent mechanism.* Anesthesiology. *2010;112:73–85.)*

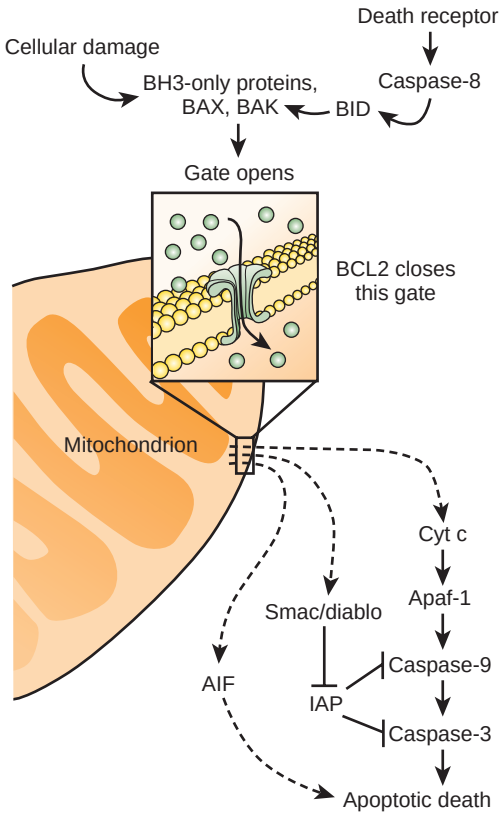


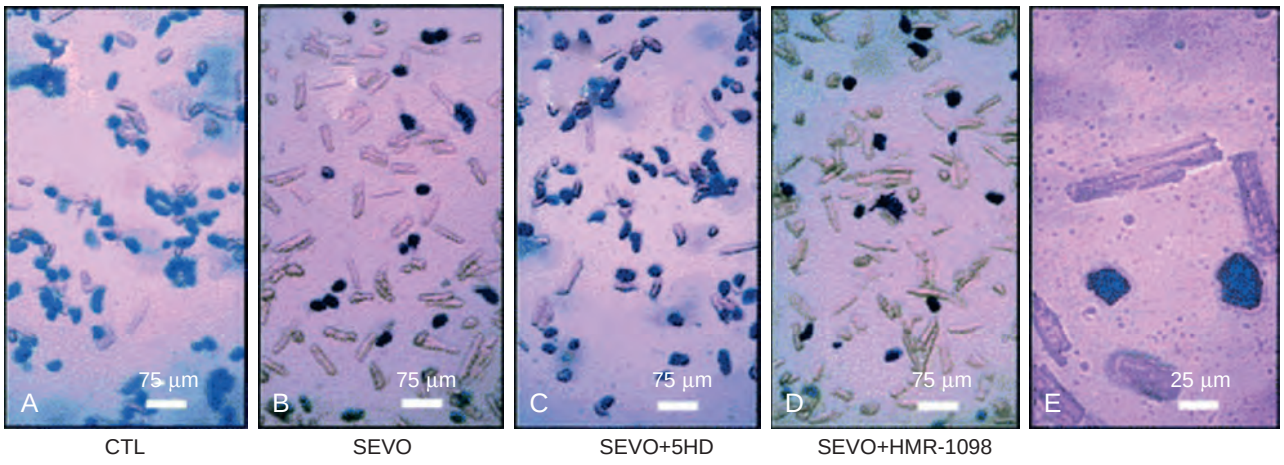
Fig. 10.16 Mitochondrion center stage in apoptosis. In this view, numerous cell death stimuli work through mitochondria. They cause proapoptotic members of the *BCL2* family, such as *BAX* and *BAK*, to open new pores or modify existing channels in the mitochondrial membrane, releasing cytochrome *c (Cyt c)* and other proteins that lead to caspase activation and cell death. BCL2, which is antiapoptotic, blocks the pore or channel opening. *AIF*, Apoptosis-inducing factor; *IAP*, inhibitors of apoptosis. *(From Finkel E. The mitochondrion: is it central to apoptosis?* Science. *2001;292(5517):624–626.)*

isolation is considered (ie, not coupled to the vasculature and not regulated by the autonomic system), the best methodologies for examining the effects of anesthetic agents involve using isolated myocytes and muscle tissue preparations in which the effect of the anesthetic drugs on contractile force or tension or on myocyte or sarcomere shortening can be determined.

The studies of propofol remain controversial about whether there is a direct effect on myocardial contractile function at clinically relevant concentrations. The weight of evidence, however, suggests that the drug has a modest negative inotropic effect, which may be mediated by inhibition of L-type Ca^{2+} channels or modulation of Ca^{2+} release from the SR. The effect of propofol may be mediated at multiple sites in the cardiac myocytes (see Fig. 10.4).

Effects of the agents may be species dependent, further confounding the literature regarding mechanisms. For instance, van Klarenbosch and colleagues[125] demonstrated that in contrast with use in rats, propofol directly depresses myocardial contractility in isolated muscle preparations from guinea pigs, probably by decreasing transsarcolemmal Ca^{2+} influx. However, there was little influence of propofol on Ca^{2+} handling by the SR or on the contractile proteins in rats. In one of the few human studies using isolated atrial muscle tissue (Fig. 10.19), no inhibition of myocardial contractility was found in the clinical concentration ranges of propofol, midazolam, and etomidate. Thiopental showed strong negative inotropic properties, whereas ketamine showed slight negative inotropic properties (Fig. 10.20). Negative inotropic effects may partially explain the cardiovascular depression on induction of anesthesia with thiopental but not with propofol, midazolam, and etomidate. Improvement of hemodynamics after induction of anesthesia with ketamine cannot therefore be explained by intrinsic cardiac stimulation but is a function of sympathoexcitation.[126]

The effect of drugs such as propofol may be affected by the underlying myocardial pathology.[127,128] For instance, Sprung and coworkers[128] determined the direct effects of propofol on the contractility of human nonfailing atrial and failing atrial and ventricular muscles obtained from the failing human hearts of transplant recipients or from nonfailing hearts of patients undergoing CABG. They concluded that propofol exerted a direct negative inotropic effect in nonfailing



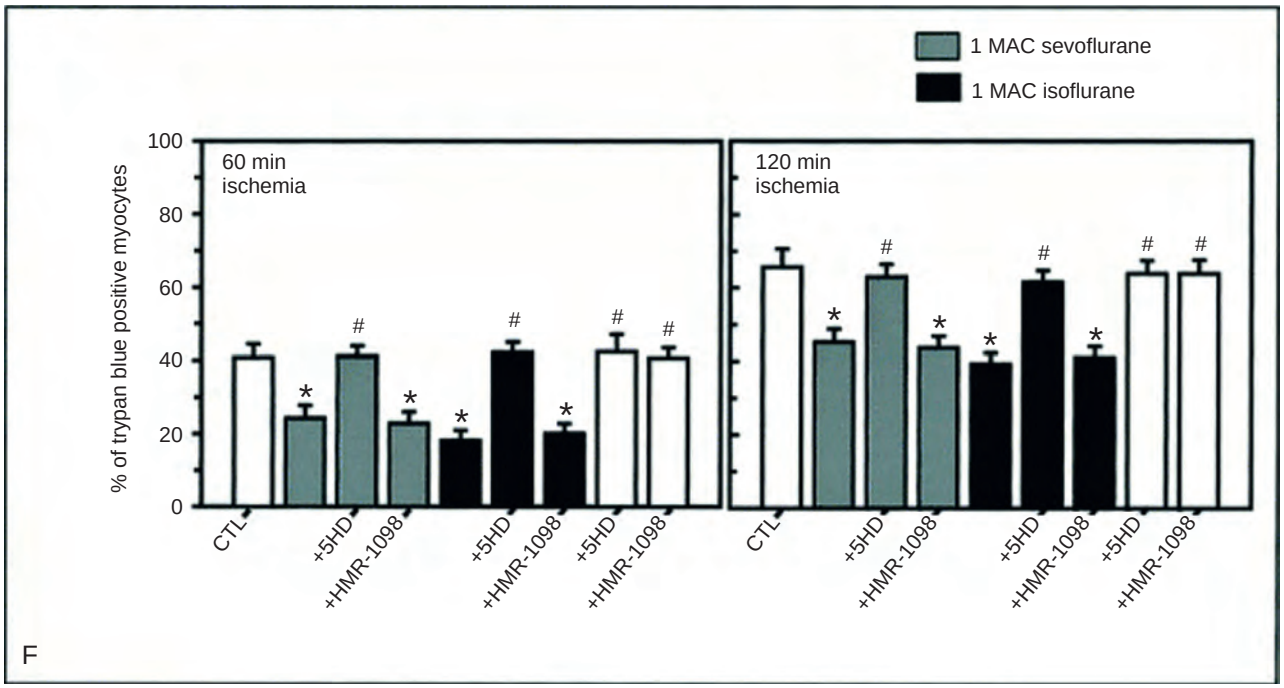


Fig. 10.17 Effects of the specific mitochondrial K^+_{ATP} (mitoK^+_{ATP}) channel blocker 5-hydroxy-decanoate *(5HD)* and the specific sarcolemmal K^+_{ATP} (sarcK^+_{ATP}) channel blocker *HMR-1098* on sevoflurane *(SEVO)*– and isoflurane *(ISO)*–mediated protection at 1 minimal alveolar concentration *(MAC)* against 60 or 120 minutes of ischemia in myocytes as assessed by trypan blue staining. (A) Control *(CTL)* myocytes after 60 minutes of ischemia. Myocytes stained *dark blue* indicate irreversible cell damage. (B) Myocytes exposed to SEVO before ischemia. Most myocytes retain their rod-shaped morphology. (C) Myocytes exposed to 5HD and SEVO before ischemia. The protective effect of SEVO is abolished. (D) Myocytes exposed to HMR-1098 and SEVO before ischemia. The protection by SEVO is unaffected. (E) Representative trypan blue–positive and –negative myocytes after exposure to ischemia seen at higher magnification. (F) Trypan blue–positive myocytes are indicated as a percentage of total viable myocytes before ischemia. The CTL group represents myocytes exposed to 60 or 120 minutes of ischemia alone. Data are mean ± standard deviation. $^*P < .0001$ versus respective CTL; $^\#P$ value is not significant versus respective CTL. *(From Zaugg M, Lucchinetti E, Spahn DR, et al. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways.* Anesthesiology. *2002;97:4.)*

and failing human myocardium, but only at concentrations larger than typical clinical concentrations.

Negative inotropic effects are reversible with β-adrenergic stimulation, suggesting that propofol does not alter the contractile reserve but may shift the dose responsiveness to adrenergic stimulation. The negative inotropic effect of propofol is at least partially mediated by decreased Ca^{2+} uptake into the SR, but the net effect of propofol on contractility is insignificant at clinical concentrations because of a simultaneous increase in the sensitivity of the myofilaments to activator Ca^{2+}.[128]

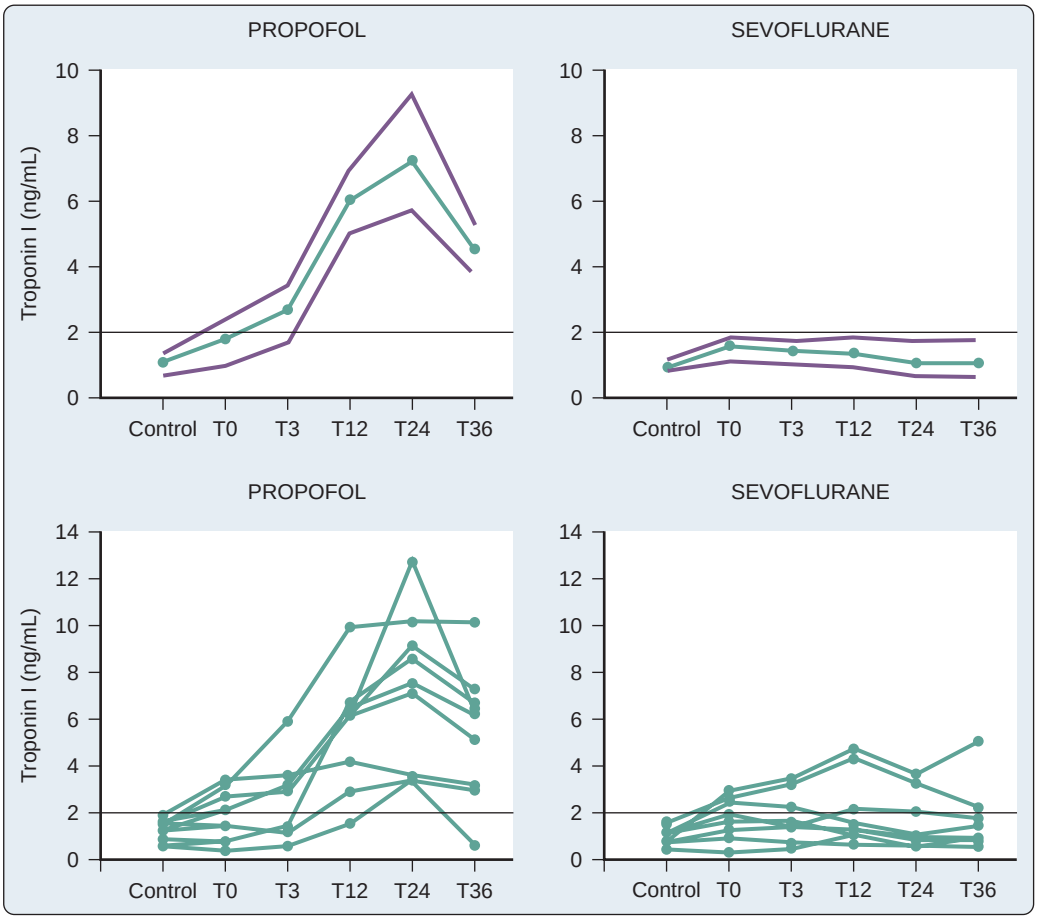


Fig. 10.18 Cardiac troponin I concentrations in the propofol and sevoflurane groups before surgery *(Control)*, at arrival in the intensive care unit *(T0)*, and after 3 *(T3)*, 12 *(T12)*, 24 *(T24)*, and 36 *(T36)* hours. *Top,* Median values *(green)* with 95% confidence intervals *(purple). Bottom,* Evolution of the individual values. Concentrations were significantly greater with propofol. In the propofol group, all patients had troponin concentrations greater than the cutoff value of 2 ng/mL *(gray line). (From de Hert S, ten Broecke PW, Mertens E, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients.* Anesthesiology. *2002;97:42.)*

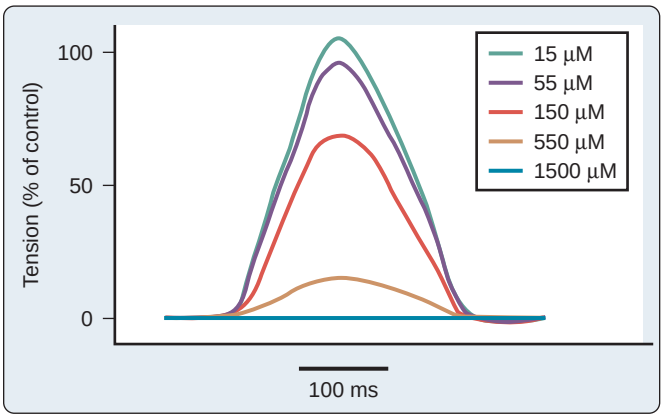


Fig. 10.19 Typical experiment shows the force traces of an isometric twitch of human atrial tissue during exposure to increasing concentrations of propofol (15 to 1500 µmol/L). *(From Gelissen HP, Epema AH, Henning RH, et al. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle.* Anesthesiology. *1996;84:397.)*

Molecular Mechanisms: Adrenergic Signaling, Ca^{2+} Influx, and Ca^{2+} Sensitivity

A drug such as propofol may alter cardiac contractility by several molecular mechanisms. Propofol may inhibit cardiac L-type calcium current by interacting with the dihydropyridine-binding site[129] (Fig. 10.21A), with resultant alteration in developed tension (see Fig. 10.21B). Propofol may alter adrenergic signaling in cardiac myocytes. Experiments using membranes and cardiac preparations isolated from rat heart demonstrate that relatively high concentrations of propofol (25 to 200 µmol/L) are required to antagonize β-adrenoceptor binding and tissue responsiveness.[130] Kurokawa and colleauges[131] observed that clinically relevant concentrations of propofol-attenuated β-adrenergic signal transduction in cardiac myocytes by inhibition of cyclic adenosine monophosphate (cAMP) production (Fig. 10.22). The inhibitory site of action of propofol appears to be upstream of adenylyl cyclase and involves activation of PKCα, an isoform of the enzyme that plays a role in regulating contractility.

Although propofol may decrease contractile response to adrenergic stimulation, there is emerging evidence that it may enhance myofilament sensitivity to Ca^{2+}. Propofol caused a leftward shift in the extracellular Ca^{2+}-shortening relationship, suggesting that propofol increases the sensitivity of myofibrillar actomyosin ATPase to Ca^{2+} (ie,

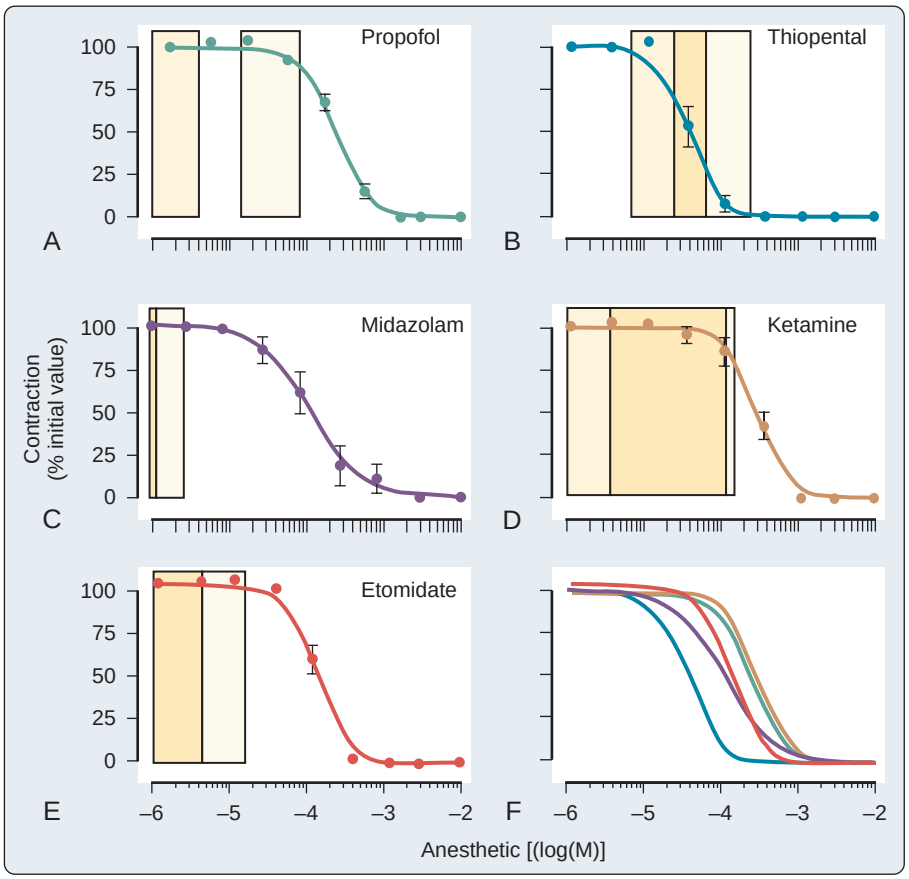


Fig. 10.20 Comparative effects of increasing concentrations of anesthetic on isometric contractions of human atrial tissue induced by field stimulation. Data are mean ± standard error of the mean. Curves were plotted using logistic regression. *Circles* indicate the clinical concentration range during anesthesia. Tan areas represent the total concentration and *white areas* show the free fraction. (A) Propofol ($n = 16$). (B) Thiopental ($n = 7$). (C) Midazolam ($n = 7$). (D) Ketamine ($n = 9$). (E) Etomidate ($n = 9$). (F) Combined plot shows the concentration–response curves of the five anesthetics. *(From Gelissen HP, Epema AH, Henning RH, et al. Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle.* Anesthesiology. *1996;84:397.)*

increases myofilament Ca^{2+} sensitivity) (Fig. 10.23). This is mediated in part by increasing pH through PKC-dependent activation of Na^+/H^+ exchange or by a PKC-dependent pathway involving the phosphorylation of myosin light chain 2 (MLC2).[132]

Integrated Cardiovascular Responses

The use of combined conductance-manometric catheters allows simultaneous measurement of pressure and volume in the ventricle and precise determination of the effects of anesthetic agents on integrated cardiovascular responses. Parameters include load-independent measures of contractility (eg, slope of the end-systolic pressure-volume relationship, end-systolic elastance [E_{es}]) and indices of ventricular-vascular coupling (eg, ratio of arterial elastance to ventricular elastance [E_a/E_{es}]) (see Chapters 6 and 13).

In one study, the effects of propofol and pentobarbital on integrated cardiovascular function were assessed in pigs at baseline and after an acute increase in ventricular afterload.[133] At baseline, E_{es} was lower during pentobarbital compared with propofol anesthesia, suggesting a greater negative inotropic effect for barbiturates than propofol (Fig. 10.24). However, the responses to ventricular afterload induced by aortic banding were maintained in the pentobarbital-anesthetized animals, whereas the responses were markedly attenuated in the propofol-anesthetized pigs, suggesting attenuation of the baroreflex responses with propofol. A decrease in arterial pressure with propofol is consistent with the drug acting as a vasodilator.

There is a question about what represents a clinically relevant dose of intravenous induction agents. Although coronary concentrations of propofol have been the major contributor to myocardial depression, they were a less significant contributor to the hypotension caused by this drug.[124]

Propofol affects ventricular and atrial function.[125] Propofol depresses contractility of the left atrial myocardium and reduces the active left atrial contribution to left ventricular filling in vivo. Compensatory decreases in chamber stiffness contribute to relative maintenance of left atrial reservoir function during the administration of propofol.

Oxidative Stress

Oxidative stress remains an important pathophysiologic mechanism for cellular injury in critically ill patients and represents an imbalance between the production of free radicals and the enzymatic defense system that removes them (Box 10.4). This has potential therapeutic implications because these agents are used routinely for sedation in the intensive care unit, in which disease processes associated with increased oxidative stress are treated.

Animal data suggest that propofol decreases postischemic myocardial mechanical dysfunction, infarct size, and histologic evidence of

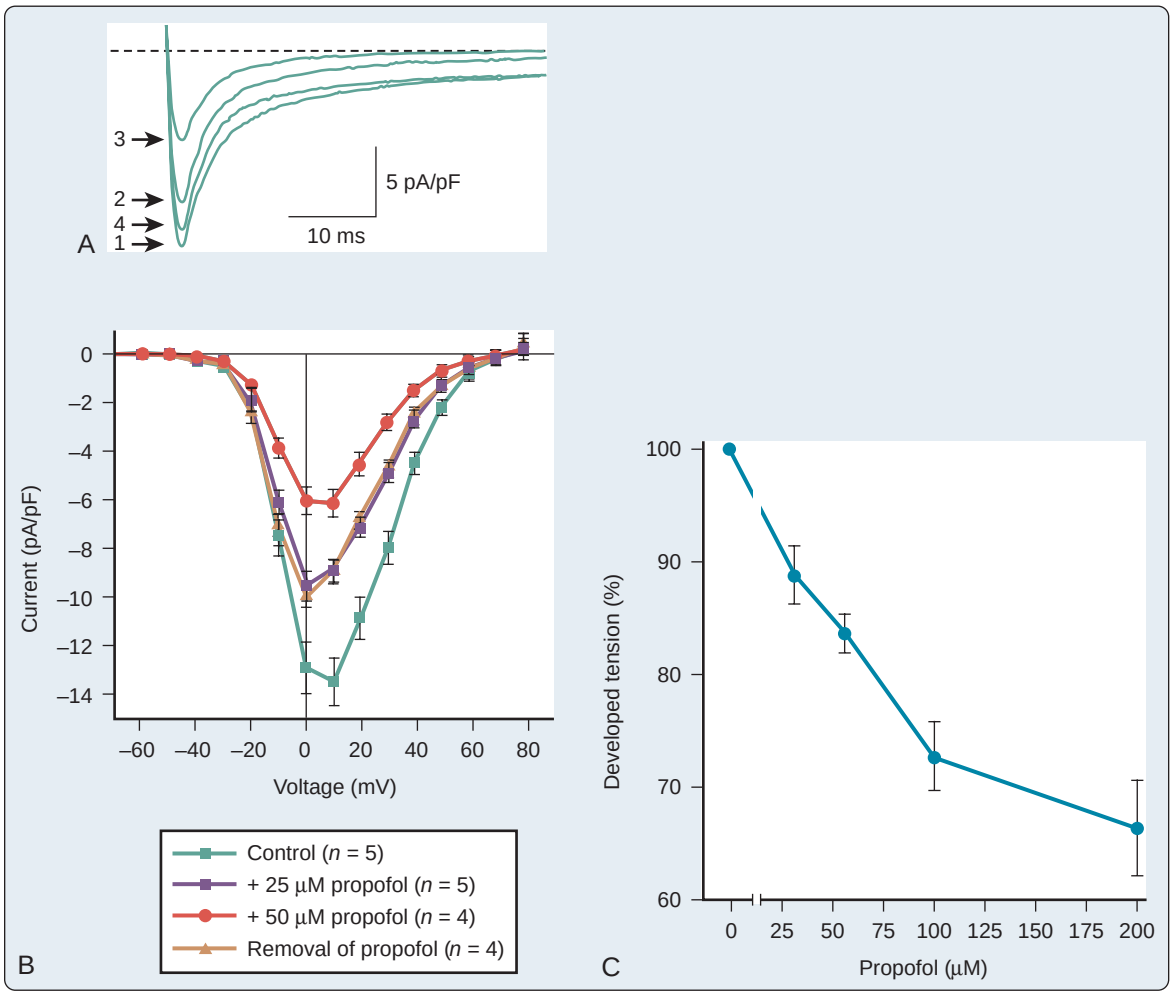


Fig. 10.21 (A) Current-voltage (I-V) relationship of peak cardiac L-type calcium current ($I_{Ca,L}$) as monitored before and during exposure to propofol. Cultured rat ventricular myocytes were clamped at –70 μV. $I_{Ca,L}$ was elicited by 200-ms pulses from the holding potential of –70 μV to potentials between –60 and +80 μV in 10-μV increments. Propofol dose-dependently decreased calcium current. (B) Representative current traces of $I_{Ca,L}$ by current density pA/pF in response to depolarizing pulses to 0 μmol/L from a holding potential of –70 μV. As shown in the legend below the graph, traces were obtained (1) before exposure to propofol, during treatment with (2) 25 μmol/L and (3) 50 μmol/L propofol, and (4) after recovery. (C) Effects of propofol on developed tension in papillary muscle isolated from the rat heart. Preparations (n = 4) were bathed in an oxygenated Krebs-Henseleit solution at 37°C and paced electrically at 1 Hz. The anesthetic was added to the bathing solution cumulatively. *Vertical bars* represent standard error of the mean. Values on the ordinate indicate the percentage of the developed tension recorded immediately before adding propofol (0.64 ± 0.15 g). Propofol dose-dependently decreases twitch tension. *(From Zhou W, Fontenot HJ, Liu S, et al. Modulation of cardiac calcium channels by propofol.* Anesthesiology. *1997;86:670.)*

BOX 10.4 INTRAVENOUS INDUCTION AGENTS

- Oxidative stress is an important pathophysiologic mechanism for cellular injury in critically ill patients and represents an imbalance between the production of free radicals and the enzymatic defense system that removes them.
- Propofol and midazolam act as free radical scavengers at near-therapeutic doses and suggest a role for propofol in modulating injury. This has therapeutic implications because the agents are used routinely for sedation in the intensive care unit, where patients with disease processes associated with increased oxidative stress are treated.
- Evidence does not support propofol or other induction agents as preconditioning-inducing agents.
- The effects of intravenous anesthetic agents may not be solely mediated by directly modulating vascular tone through alteration of the contractile state of the vascular smooth muscle. They also may alter vascular smooth muscle proliferation and modulate pathways that are important in angiogenesis.
- Administration of these anesthetic agents by the anesthesiologist may have effects that last long after the drugs have disappeared from the circulation.

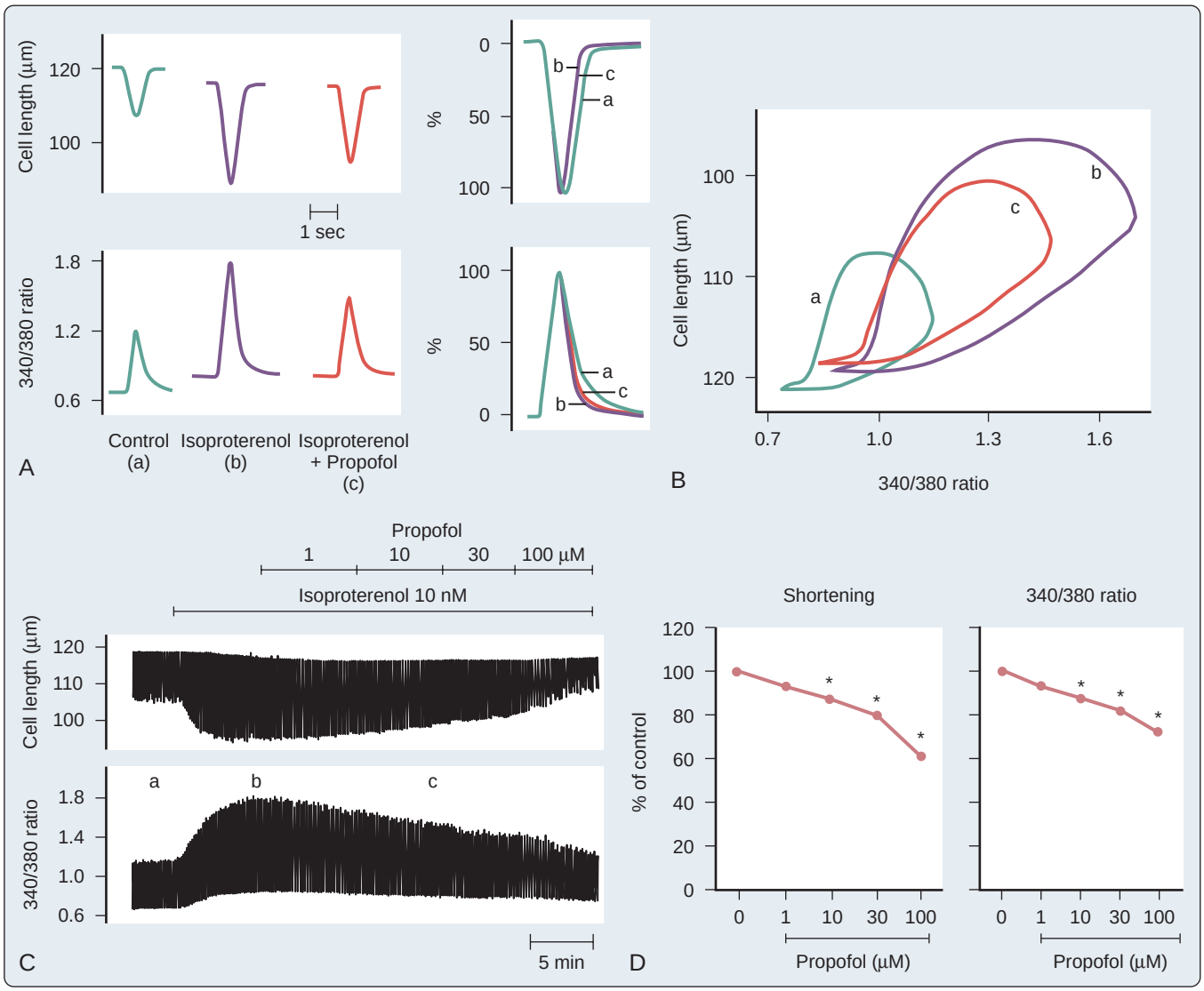


Fig. 10.22 (A and B) Original traces depict the dose-dependent effects of propofol on shortening and intracellular Ca^{2+} concentration, $[Ca^{2+}]_i$, after exposure to isoproterenol (10 nM) in a rat isolated ventricular myocyte. Calcium concentration was measured as the 340/380 ratio by dual wave spectrofurometry. (C and D) Summarized data for the effects of propofol on isoproterenol-stimulated increases in shortening and $[Ca^{2+}]_i$. Results are expressed as a percentage of the control. Propofol inhibits β-adrenergic–mediated contractility in a dose-dependent system. Significant changes (*) are shown. *(From Kurokawa H, Murray PA, Damron DS. Propofol attenuates beta-adrenoreceptor-mediated signal transduction via a protein kinase C-dependent pathway in cardiomyocytes.* Anesthesiology. *2002;96(3):688–698.)*

injury[134–140] (Fig. 10.25). Propofol has a chemical structure similar to that of phenol-based free radical scavengers (eg, vitamin E) and may therefore act as a free radical scavenger.[141,142] Studies by Tsuchiya and colleagues[143,144] demonstrated in vitro the potential for propofol and midazolam to act as free radical scavengers at near-therapeutic doses. Propofol also impairs the activity of neutrophils by inhibiting the oxidative burst and may modulate injury at the critical phase of reperfusion by reducing free radicals, Ca^{2+} influx, and neutrophil activity.[145]

Microsomes prepared from animals anesthetized with propofol demonstrate a significantly increased resistance to lipid peroxidation.[146] The evidence does not support propofol as an APC-inducing agent because protection was observed when the heart was treated with propofol solely during reperfusion rather than before or during the ischemic insult,[139] although the addition of glibenclamide, a K^+_{ATP} channel blocker, does not abolish the protection afforded by propofol.[140] There is little evidence for other intravenous induction agents having protective effects on the heart. Ketamine may block IPC[147–149] by deactivating sarcolemmal K^+_{ATP} channels.[150]

Vasculature

As with the heart, the physiologic actions of anesthetics in the vasculature represent a summation of their effects on the central ANS, direct effects on the vascular smooth muscle, and modulating effects on the underlying endothelium. An exhaustive review of the effects of each agent on isolated and integrated vascular function is beyond the scope of the chapter, but an overview of the effects of some commonly used agents on vasoregulation is presented.

Despite clear effects of anesthetics on vascular smooth muscle and endothelial function, controversy and diversity regarding mechanisms arise because of the species of animals studied, the vessel bed examined, and the drug dosage used. The effects may be significantly

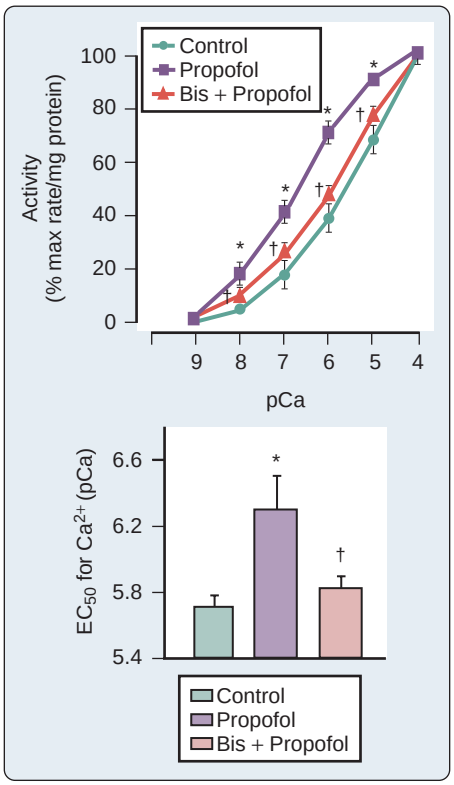


Fig. 10.23 *Top,* Summarized data depict the effects of bisindolylmaleimide I (Bis) or aprotinin kinase C inhibition on the propofol-induced leftward shift (30 μm) in actomyosin ATPase activity in isolated myofibrils. *Bottom,* Summarized data depict the increase (*$P < .05$ vs control) in the median effective concentration (EC_{50}) value for Ca^{2+} induced by propofol and inhibition of this effect (†$P < .05$ vs propofol) after pretreatment with Bis. Propofol increased myofilament Ca^{2+} sensitivity by a protein kinase C–dependent receptor. *(From Kanaya N, Gable B, Murray PA, et al. Propofol increases phosphorylation of troponin I and myosin light chain 2 via protein kinase C activation in cardiomyocytes.* Anesthesiology. *2003;98:1363.)*

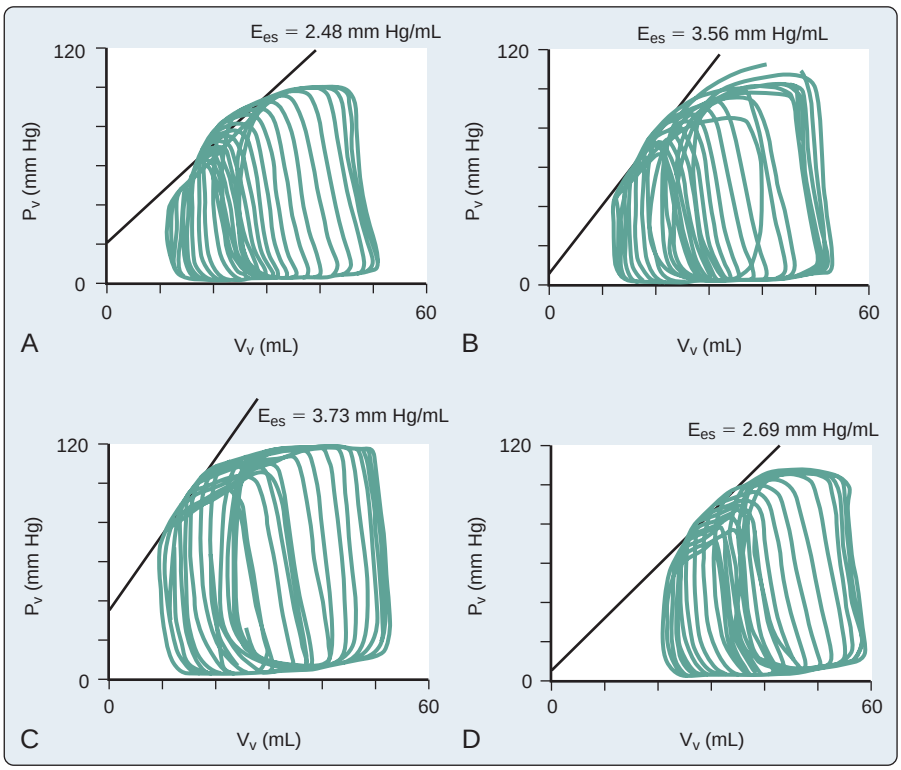


Fig. 10.24 Typical pressure-volume loop recordings under pentobarbital anesthesia at baseline (A) and during aortic banding (C), under propofol anesthesia at baseline (B), and during aortic banding (D). E_{es}, End-systolic elastance; V_v, ventricular volume. *(From Kolh P, Lambermont B, Ghuysen A, et al. Comparison of the effects of propofol and pentobarbital on left ventricular adaptation to an increased afterload.* J Cardiovasc Pharmacol. *2004;44:294.)*

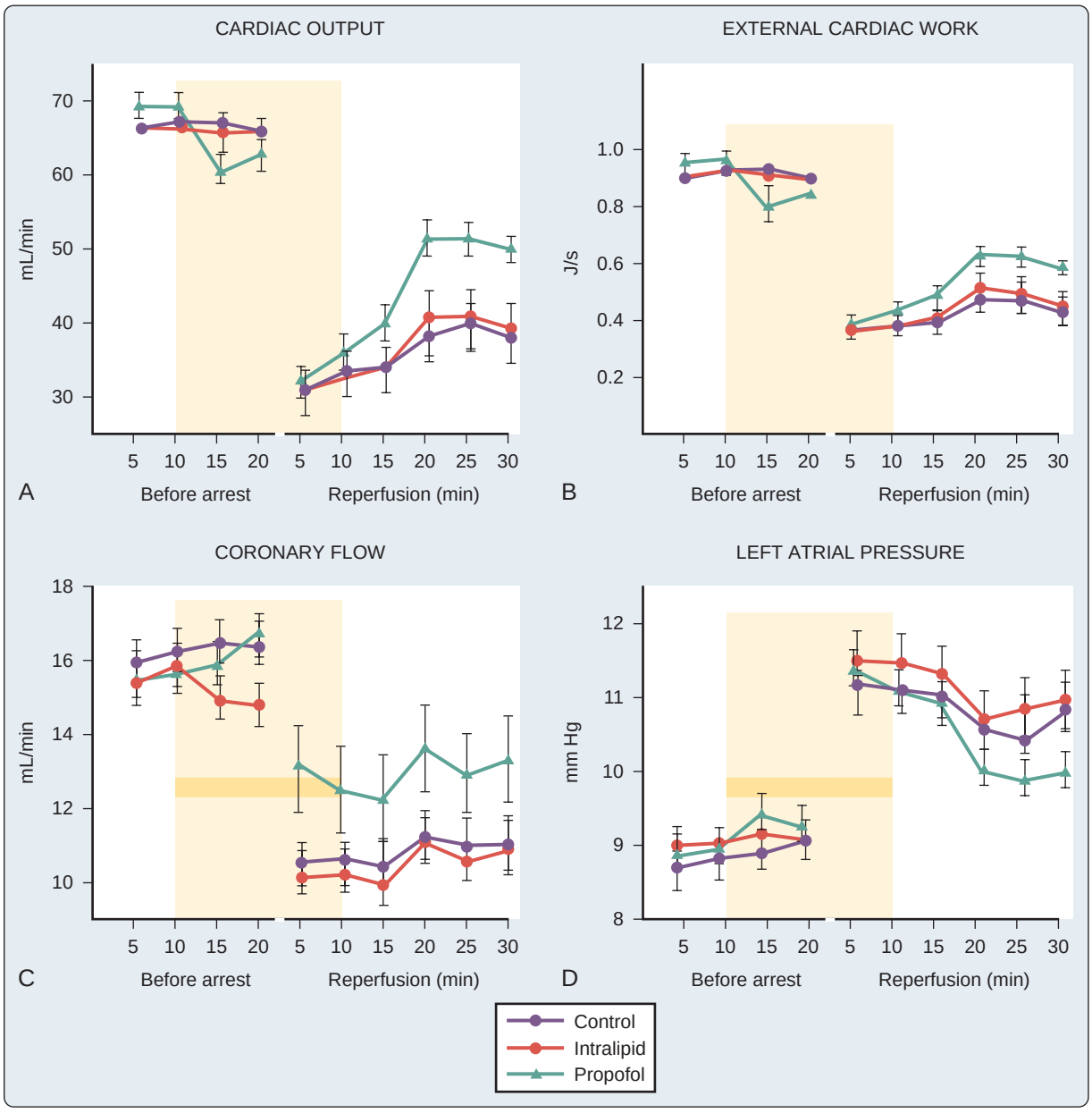


Fig. 10.25 Cardiac function of the isolated working rat heart subjected to cold cardioplegic arrest and subsequent reperfusion. (A) Cardiac output. (B) External cardiac work. (C) Coronary flow. (D) Left atrial pressure. Propofol (4 g/mL dissolved in intralipid emulsion) or intralipid alone was added 10 minutes after initiation of the working heart mode and washed out after 10 minutes into the working heart reperfusion. Data are plotted as mean ± standard error of the mean *(error bars)* for the separate heart preparations: control, intralipid, and propofol (n = 12, 12, and 14, respectively). *Shaded area* represents the period during which test agents were present. The break in the plots represents a 60-minute cold cardioplegic arrest and 10 minutes of initial Langendorff reperfusion. An increase in cardiac output (A) and a decrease in left atrial pressure (D) in propofol-perfused hearts demonstrate the protective effect of the drug. *(From Ko SH, Yu CW, Lee SK, et al. Propofol attenuates ischemia-reperfusion injury in the isolated rat heart.* Anesth Analg. *1997;85:719.)*

different in vessels from animals that develop disease phenotypes such as hypertension and diabetes. Although the effects of anesthetics on a variety of signal transduction pathways are invariably seen with high concentrations of the agents, their clinical relevance remains unclear.

Systemic Vasoregulation

Propofol decreases SVR in humans. This was demonstrated in a patient with an artificial heart in whom the CO remained fixed.[151] The effect is predominantly mediated by alterations in sympathetic tone, but in isolated arteries, propofol decreases vascular tone and agonist-induced contraction (discussed later). Propofol mediates these effects by inhibition of Ca^{2+} influx through voltage- or receptor-gated Ca^{2+} channels and inhibition of Ca^{2+} release from the intracellular Ca^{2+} stores regulated by the ryanodine receptor.[152–155]

Most of the experimental data obtained in isolated studies have focused on conduit arteries (eg, rat aorta), but some properties of the resistance arteries differ from the rat bioassay. Modulation of

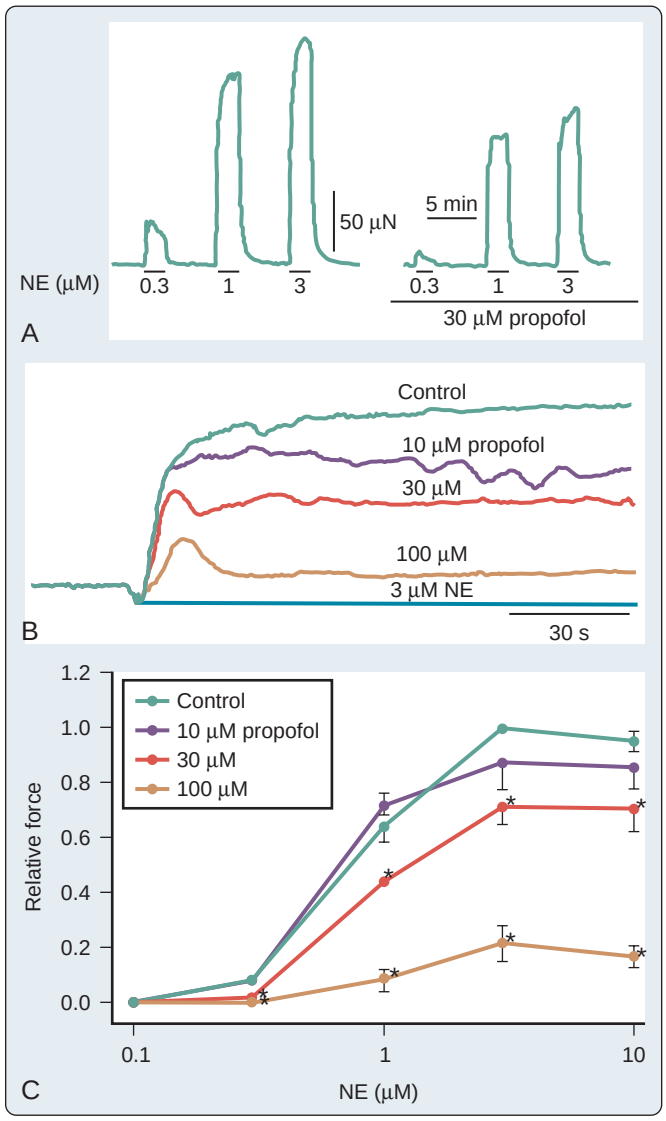


Fig. 10.26 (A–C) Effects of propofol on norepinephrine *(NE)*–induced increases in intracellular Ca^{2+} concentration and force in smooth muscle of the rabbit mesenteric resistance artery. *(From Imura N, Shiraishi Y, Katsuya H, et al. Effect of propofol on norepinephrine-induced increases in [Ca^{2+}] and force in smooth muscle of the rabbit mesenteric resistance artery.* Anesthesiology. *1998;88:1566.)*

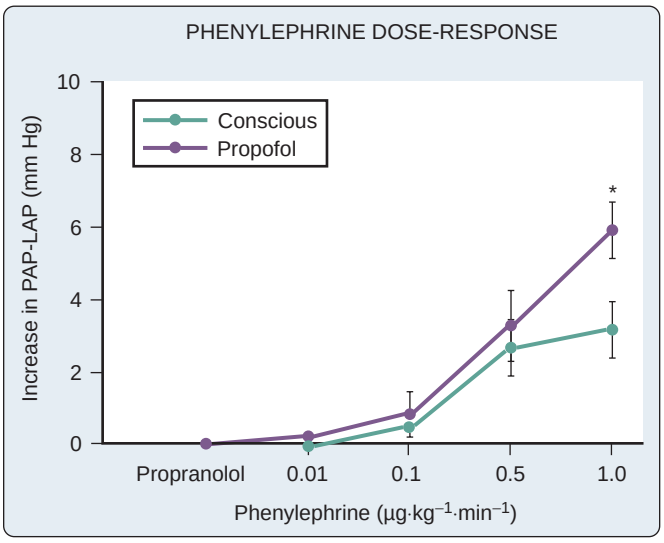


Fig. 10.27 Pulmonary vascular effects of propofol at baseline, during elevated vasomotor tone, and in response to sympathetic and adrenoreceptor activation. *LAP*, Left atrial pressure; *PAP*, pulmonary artery pressure. *(From Kondo U, Kim SO, Nakayama M, et al. Pulmonary vascular effects of propofol at baseline, during elevated vasomotor tone, and in response to sympathetic alpha- and beta-adrenoreceptor activation.* Anesthesiology. *2001;94:815.)*

vasoconstriction by vascular smooth muscle may be mediated by an alteration in endothelium-independent vasodilation[153] or an alteration in the sensitivity of the myofilaments to Ca^{2+}, primarily mediated by Rho activation (ie, activation of Rho kinase). In an elegant study examining the effects of propofol on resistance arteries, Imura and coworkers[156] examined the effect of propofol on simultaneous measurements of force and in mesenteric resistance arteries. The investigators concluded that propofol attenuated norepinephrine-induced contraction through inhibition of Ca^{2+} release and Ca^{2+} influx through L-type Ca^{2+} channels, partially explaining the effects of propofol on vascular adrenergic signaling (Fig. 10.26). Propofol may modulate vascular tone by interfering with other signaling pathways involved in vasoregulation, such as ET1.[156,157] Propofol also may attenuate the myogenic tone or response in pressure-flow autoregulation.[158]

Pulmonary Vasoregulation

The effects of induction agents on pulmonary vasoregulation may have important implications for the management of patients whose primary pathologies involve the pulmonary circulation when they undergo cardiothoracic surgery (ie, primary pulmonary hypertension for lung transplantation and chronic thromboembolic disease for pulmonary endarterectomy). The effects may be important for patients with right ventricular failure.[159] In modulating hypoxic pulmonary vasoconstriction, induction agents may affect intraoperative alveolar-arterial (A-a) gradients, particularly during one-lung ventilation.

Murray and colleagues[160,161] systematically studied the effects of anesthetic agents on pulmonary vasoregulation. They found that propofol attenuated endothelium-dependent vasodilatation[160] through a mechanism involving NO and endothelium-dependent hyperpolarizing factor.[161] In vascular smooth muscle, the effect appears somewhat different in the pulmonary circulation. Rather than attenuate vasoconstriction and thereby decrease tone, propofol appears to increase the sensitivity of the contractile myofilaments to Ca^{2+},[154] and it potentiates the effect of catecholamines on pulmonary artery smooth muscle cells[162,163] (Fig. 10.27).

Endothelial Function

Propofol modulates the function of the endothelium, altering the underlying tone of the vessels. The data about the direction and mechanism underlying this effect are widely divergent and depend on the vascular bed, species, and experimental conditions. Early studies suggested that propofol-mediated vasodilatation was a function of stimulation of NO and vasodilator prostanoids from the endothelium.[148] Other studies demonstrated an inhibitory effect of propofol and ketamine, but not of midazolam, on endothelium-dependent relaxation.[164] The suppressive effect of ketamine on endothelium-dependent relaxation appears to be mediated by suppression of NO formation, whereas that of propofol may be mediated in part by suppression of NO function.

In a rabbit mesenteric resistance artery preparation, Yamashita and colleagues[165] demonstrated that propofol inhibits prostacyclin-mediated, endothelium-dependent vasodilatation by inhibition of vascular hyperpolarization (Fig. 10.28). The inhibition of hyperpolarization and inhibition of relaxation appear to be mediated by the blockade of ATP-sensitive K^+ channels. Although the clinical implications of these findings are unclear, it may be predicted based on the data that the effects of propofol on the vasculature may be significantly

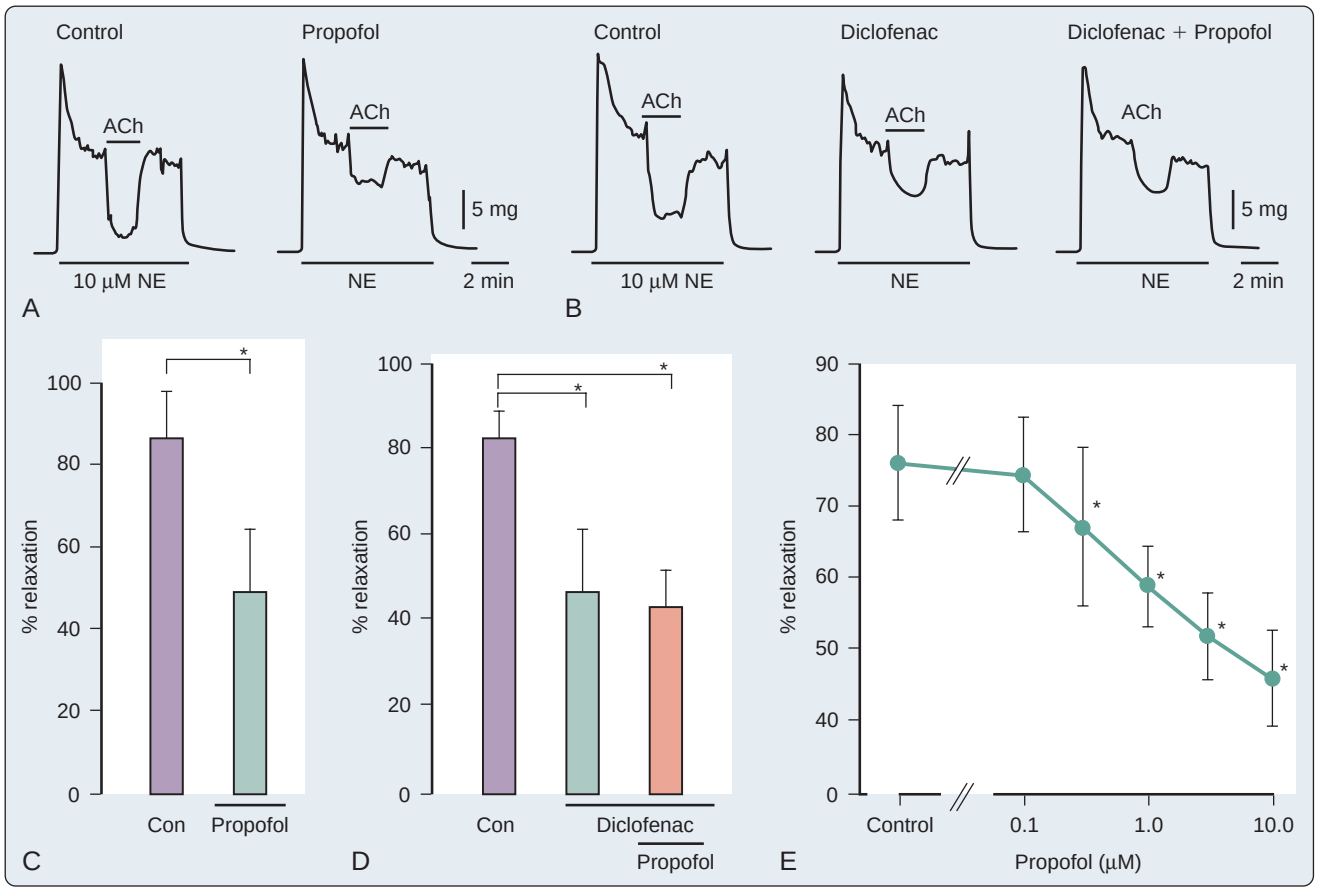


Fig. 10.28 (A–E) Inhibitory effects of propofol on acetylcholine *(ACh)*–induced, endothelium-dependent relaxation and prostacyclin synthesis in rabbit mesenteric resistance arteries. *Con*, Control; *NE*, norepinephrine; significant difference (*) from control ($P < .05$). *(From Yamashita A, Kajikuri J, Ohashi M, et al. Inhibitory effects of propofol on acetylcholine-induced, endothelium-dependent relaxation and prostacyclin synthesis in rabbit mesenteric resistance arteries.* Anesthesiology. *1999;91:1080.)*

different in patients in whom endothelial dysfunction, such as hypertension and atherosclerosis, is a significant factor.

Gursoy and associates[166] described the dose-dependent vasorelaxation produced by intravenous anesthetic agents on human radial artery grafts. The relaxant properties of thiopental and ketamine were more potent than those of etomidate and propofol. These observations may have implications for the perioperative management of coronary artery graft vasospasm.[166]

Sympathetic and Parasympathetic Nervous System

In human in vivo studies, it appears that the cumulative effects of propofol on peripheral arterial venous capacitance are mediated primarily by its effects on the sympathetic nervous system (SNS). In a well-designed study in which the effect of a local infusion of propofol into the brachial artery was compared with systemic intravenous administration with induction of anesthesia, direct brachial infusion had little effect on resistance and capacitance, whereas the effect of intravenous administration was similar to the effect observed with sympathectomy induced by stellate ganglion block (Fig. 10.29). The peripheral vascular effects of propofol appear to be mediated primarily by reduced sympathetic vasoconstrictor nerve activity.[167]

In another elegant study, Sellgren and coworkers[168] measured the effect of propofol on the SNS using percutaneous recordings of muscle sympathetic nerve activity. The researchers demonstrated a profound decrease in SNS activity with a reciprocal increase in blood flow (measured by laser Doppler) with propofol-induced anesthesia. Sympathetic baroreflex sensitivities were also depressed by propofol, highlighting the profound effect of this agent on central sympathetic modulation of integrated cardiovascular function. The precise locations of the central modulation by propofol were investigated by Yang and colleagues,[169,170] who demonstrated that propofol principally inhibited the vasomotor mechanism in the dorsomedial and ventrolateral medulla to effect its hypotensive actions.

The implications of these effects are significant in that sympathoinhibition is amplified in patients in whom the level of SNS activity is high. Caution is indicated in the administration of these agents to patients with shock, CHF, or other pathophysiologic conditions in which the SNS is paramount in maintaining arterial and venous tone.

Remodeling and Cell Proliferation

The literature suggests that the effects of intravenous anesthetic agents may not be solely mediated by direct modulation of vascular tone through alteration of the contractile state of the vascular smooth muscle. Some studies suggest that intravenous anesthetics may alter vascular smooth muscle proliferation and modulate pathways that are important in angiogenesis. For example, Shiga and associates[171] demonstrated the effect of ketamine (but not propofol) on inhibiting vascular smooth muscle proliferation through a PKC-dependent pathway. However, midazolam (but not ketamine) released vascular endothelial growth factor, a growth factor important in angiogenesis and cellular proliferation, from vascular smooth muscle cells.[172] The clinical importance of these findings remains unstudied and unclear, but they emphasize that the administration of these agents and others

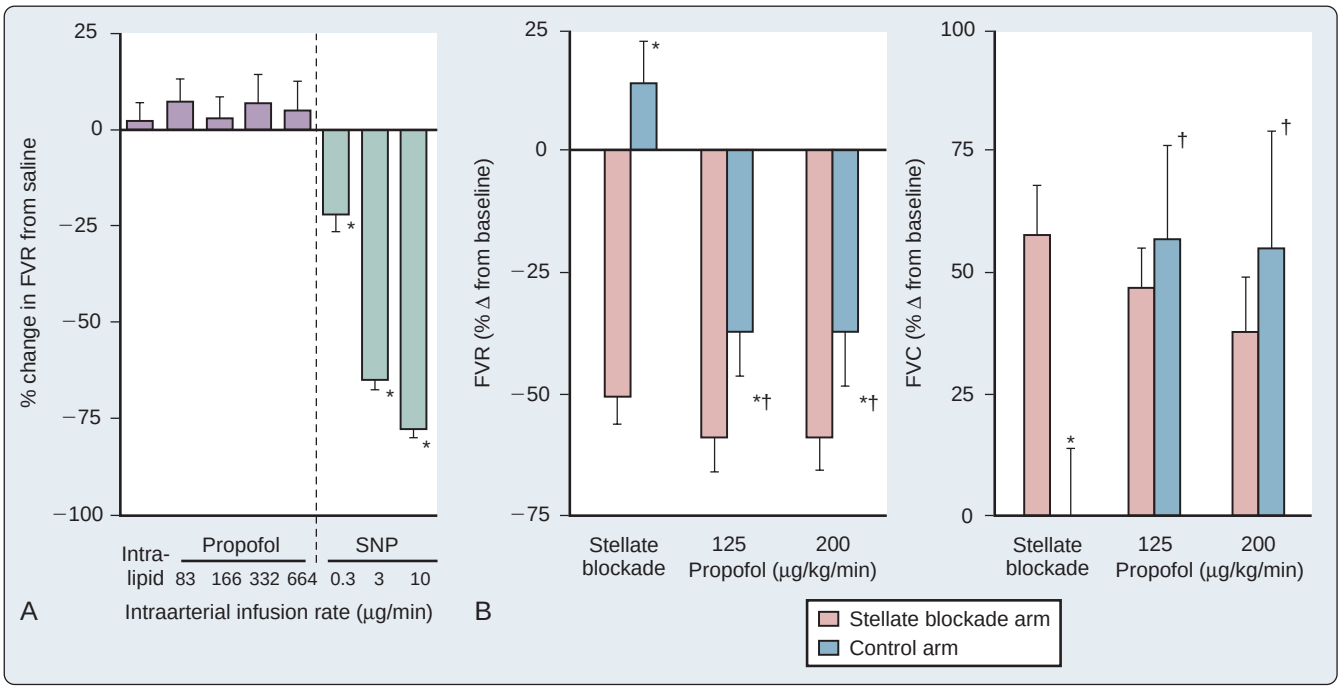


Fig. 10.29 (A) Change in forearm vascular resistance *(FVR)* during brachial artery infusions of intralipid, propofol, and sodium nitroprusside *(SNP)*. Intraarterial infusions of propofol did not change FVR, whereas intraarterial infusions of SNP significantly reduced FVR. Data are expressed as the percentage change from saline and are shown as the mean ± standard error of the mean (SEM). *$P < .05$ indicates a significant change from saline. (B) Percentage changes from awake baseline in FVR and forearm venous compliance *(FVC)* in the left arm after stellate blockade and in the control unblocked arm before and during propofol anesthesia. Stellate blockade decreased FVR and increased FVC on the side of the blockade. During propofol anesthesia, there was no further arterial or venous dilation in the sympathectomized arm, but significant dilation occurred in the unblocked control arm. Data are mean ± SEM. *$P < .05$ indicates a significant difference between arms; †$P < .05$ indicates a significant change from prepropofol baseline. *(From Robinson BJ, Ebert TJ, O'Brien TJ, et al. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation?* Anesthesiology. *1997;86:64.)*

by the anesthesiologist may have effects that last well after the drug has disappeared from the body.

Individual Agents

Thiopental

General Characteristics

Thiopental has survived the test of time as an intravenous anesthetic drug (Box 10.5). Since Lundy introduced it in 1934, thiopental remained the most widely used induction agent for decades because of the rapid hypnotic effect (ie, one arm-to-brain circulation time), highly predictable effect, lack of vascular irritation, and general overall safety.[173]

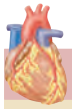
The induction dose of thiopental is less for older than for younger healthy patients.[174] Pharmacokinetic analyses[175–177] confirm the findings from the early classic studies of Brodie and Mark[178] relating the awakening from thiopental to rapid redistribution. Thiopental has a distribution half-life ($t_{½}\alpha$) of 2.5 to 8.5 minutes, and the total body clearance varies according to sampling times and techniques from 0.15 to 0.26 L/kg per hour.[167–169,171,172] The elimination half-life ($t_{½}\beta$) varies from 5 to 12 hours.[176,177,179,180]

Barbiturates[181] and drugs such as propofol[182] have increased volumes of distribution (V_d) when used during CPB. Young (<13 years) patients seem to have a greater total clearance and quicker plasma thiopental clearance than do adults, which theoretically might result in earlier awakening, especially after multiple doses.[183] Because of the affinity of fat for this drug, its relatively large V_d, and its low rate of hepatic clearance, thiopental can accumulate in tissues, especially if given in large doses over a prolonged period.

Cardiovascular Effects

The hemodynamic changes produced by thiopental have been studied in healthy patients[174,184–190] and in patients with cardiac disease (Table 10.2).[191–196] The principal effect is a decrease in contractility,[188,189,197] which results from reduced availability of calcium to the myofibrils.[198] There is also an increase in HR.[174,185,187–189,194–197] The cardiac index (CI) is unchanged[185,193–196] or reduced,[184,186,189] and the mean arterial pressure (MAP) is maintained[185,195,196,199] or slightly reduced.[186,187,193–195] In the dose range studied, no relationship between plasma thiopental and hemodynamic effect was found.[174] Early hemodynamic investigations demonstrated that thiopental (100 to 400 mg) significantly decreased CO (24%) and systemic BP (10%), presumably by reducing venous return because of an increase in venous capacitance.[186,200]

Mechanisms for the decrease in CO include direct negative inotropic action; decreased ventricular filling, resulting from increased venous capacitance; and transiently decreased sympathetic outflow from the central nervous system (CNS). The 10% to 36% increase in HR that accompanies thiopental administration probably results from the baroreceptor-mediated sympathetic reflex stimulation of the heart. Thiopental produces dose-related negative inotropic effects that appear to result from a decrease in calcium influx into the cells and a resultant diminished amount of calcium at sarcolemma sites.[201,202] Patients who had compensated heart disease and received 4 mg/kg of thiopental had a greater (18%) BP decline than did other patients without heart disease. The 11% to 36% increase in HR encountered



BOX 10.5 INTRAVENOUS ANESTHETICS

Thiopental
- Thiopental decreases cardiac output by
  - A direct negative inotropic action
  - Decreased ventricular filling resulting from increased venous capacitance
  - Transiently decreasing sympathetic outflow from the central nervous system
- Because of these effects, caution should be used when thiopental is given to patients who have left or right ventricular failure, cardiac tamponade, or hypovolemia.

Midazolam
- Small hemodynamic changes occur after the intravenous administration of midazolam.

Etomidate
- Etomidate is the drug that changes hemodynamic variables the least. Studies in noncardiac patients and those who have heart disease document remarkable hemodynamic stability after administration of etomidate.
- Patients who have hypovolemia, cardiac tamponade, or low cardiac output probably represent the population for whom etomidate is better than other induction drugs, with the possible exception of ketamine.

Ketamine
- A unique feature of ketamine is stimulation of the cardiovascular system with the most prominent hemodynamic changes, including significant increases in heart rate, cardiac index, systemic vascular resistance, pulmonary artery pressure, and systemic artery pressure. These circulatory changes increase myocardial oxygen consumption with an appropriate increase in coronary blood flow.
- Studies have demonstrated the safety and efficacy of induction with ketamine in hemodynamically unstable patients, and it is the induction drug of choice for patients with cardiac tamponade physiology.

Dexmedetomidine
- Dexmedetomidine is a highly selective, specific, and potent adrenoreceptor agonist.
- α_2-Adrenergic agonists can safely reduce anesthetic requirements and improve hemodynamic stability. They can enhance sedation and analgesia without producing respiratory depression or prolonging the recovery period.

in patients with coronary artery disease (CAD) who were anesthetized with thiopental (1 to 4 mg/kg) is potentially deleterious because of the obligatory increase in myocardial oxygen consumption ($M\dot{V}o_2$).

Despite the well-known potential for cardiovascular depression when thiopental is given rapidly in large doses, the drug has minimal hemodynamic effects in healthy patients and in those who have heart disease when it is given slowly or by infusion. Significant reductions in cardiovascular parameters occur in patients who have impaired ventricular function. When thiopental is given to patients with hypovolemia, there is a significant reduction in CO (69%) and a large decrease in BP, which indicate that patients without adequate compensatory mechanisms may have serious hemodynamic depression with a thiopental induction.[203] Thiopental produces greater changes in BP and HR than midazolam when used for induction of American Society of Anesthesiologists (ASA) class III (ie, severe systemic disease) and class IV (ie, severe systemic disease that is life-threatening) patients.

Uses in Cardiac Anesthesia

Thiopental can be used safely for the induction of anesthesia in normal patients and in those who have compensated cardiac disease. Because of the negative inotropic effects, increase in venous capacitance, and dose-related decrease in CO, caution should be used when thiopental is given to patients who have left or right ventricular failure, cardiac tamponade, or hypovolemia. The development of tachycardia is a potential problem in patients with ischemic heart disease.

A controversial additional use for thiopental infusion is for putative cerebral protection during CPB in patients undergoing selected cardiac operations.[204] However, the cerebral protective effect of thiopental during CPB has been challenged by Zaidan and coworkers,[205] who demonstrated no differences in outcome between thiopental and control patients undergoing hypothermic CPB for CABG. Although the administration of a barbiturate during CPB may result in myocardial depression necessitating additional inotropic support, the study by Ito and associates[206] suggested beneficial effects of a thiopental infusion during CPB in maintaining peripheral perfusion, which allowed more uniform warming, decreased base deficit, and decreased requirements for postoperative pressor support.

Midazolam

General Characteristics

Midazolam, a water-soluble benzodiazepine, was synthesized in the United States in 1975, in contrast to most new anesthetic drugs, which are synthesized and first tested in European countries. It is unique

TABLE 10.2 Induction Agents and Hemodynamic Changes

Parameter	*Thiopental (%)*	*Midazolam (%)*	*Etomidate (%)*	*Propofol (%)*	*Ketamine (%)*
Heart rate	0 to 36	−14 to +21	0 to +22	−6 to +12	0 to +59
MAP	−18 to +8	−12 to −26	0 to −20	0 to −47	0 to +40
Systemic vascular resistance	0 to +19	0 to −20	0 to −17	−9 to −25	0 to +33
Pulmonary artery pressure	Unchanged	Unchanged	0 to −17	−4 to +8	+44 to +47
Pulmonary vascular resistance	Unchanged	Unchanged	0 to +27	—	0 to +33
LAP or PAOP	Unchanged	0 to −25	—	—	—
Left ventricular end-diastolic pressure or PAOP	—	—	0 to −11	+13	Unchanged
Right atrial pressure	0 to +33	Unchanged	Unchanged	−8 to −21	+15 to +33
Cardiac index	0 to +24	0 to −25	0 to +14	−6 to −26	0 to +42
Stroke volume	−12 to −35	0 to −18	0 to −15	−8 to −18	0 to −21
Left ventricular stroke work index	0 to −26	−28 to −42	0 to −27	−15 to −40	0 to +27
Right ventricular stroke work index	NR	−41 to −57	—	—	—
dP/dt	−14	0 to −12	0 to −18	—	Unchanged
$1/PEP^2$	−18 to −28	—	—	—	—
Systolic time interval	—	—	Unchanged	—	NR

dP/dt, Rate of left ventricular pressure rise in early systole; *LAP*, left atrial pressure; *MAP*, mean arterial pressure; *NR*, not reported; *PAOP*, pulmonary artery occlusion pressure; *PEP*, pre-ejection period.

among benzodiazepines because of its rapid onset, short duration of action, and relatively rapid plasma clearance.[207] Although controversial, the dose for induction of general anesthesia is between 0.05 and 0.2 mg/kg and depends on the premedication and speed of injection.[208–211]

The pharmacokinetic variables of midazolam reveal that it is cleared significantly more rapidly than diazepam and lorazepam. The rapid redistribution of midazolam and high rate of liver clearance account for its relatively short hypnotic and hemodynamic effects. The $t_{1/2}\beta$ is about 2 hours, which is at least tenfold less than for diazepam.[212–216]

Cardiovascular Effects

The hemodynamic effects of midazolam have been investigated in healthy subjects,[187,217,218] in ASA class III patients,[219] and in patients who have ischemic[200–227] and valvular[219] heart disease (VHD). Table 10.2 summarizes the hemodynamic changes after induction of anesthesia with midazolam. Only small hemodynamic changes occur after intravenous administration of midazolam (0.2 mg/kg) in premedicated patients who have CAD.[223,225] Potentially important changes include a decrease in MAP of 20% (ie, 102 to 81 mm Hg) and an increase in HR of 15% (ie, 55 to 64 beats/min).[223] The CI is maintained.[223,225] Filling pressures are unchanged or decreased in patients who have normal ventricular function,[223,225] but they are significantly decreased in patients who have an increased pulmonary capillary wedge pressure (PCWP = 18 mm Hg).[224] There seems to be little effect of different doses on hemodynamics: 0.2,[225] 0.25,[222] and 0.3 mg/kg[227] all produce similar effects.

Sedation with midazolam (0.05 mg/kg) in patients undergoing cardiac catheterization is devoid of any hemodynamic effect.[220] Marty and colleagues[221] showed that induction with 0.2 mg/kg produced a 24% reduction in CBF and a 26% reduction in MVo_2 in patients with CAD. As in patients with ischemic heart disease, the induction of anesthesia in patients with VHD is associated with minimal changes in CI, HR, and MAP after midazolam.[220] When intubation follows anesthesia induction with midazolam, significant increases in HR and BP occur, because midazolam is not an analgesic.[187,225–227] Adjuvant analgesic drugs are required to block the response to noxious stimuli.

Midazolam appears to affect the capacitance vessels more than diazepam does, at least during CPB, when decreases in venous reservoir volume of the pump are greater with midazolam than with diazepam. Diazepam decreases SVR more than midazolam during CPB.[228]

Midazolam (0.15 mg/kg) and ketamine (1.5 mg/kg) have proved to be a safe and useful combination for rapid-sequence induction for emergency surgery.[190] This combination was superior to thiopental alone because it caused less cardiovascular depression, more amnesia, and less postoperative somnolence. If midazolam is given to patients who have received fentanyl, significant hypotension may occur, as seen with diazepam and fentanyl.[229] However, midazolam routinely is combined with fentanyl for induction and maintenance of general anesthesia during cardiac surgery without adverse hemodynamic sequelae.[230,231]

Uses

Midazolam is distinctly different from the other benzodiazepines because of its rapid onset, short duration, water solubility, and failure to produce significant thrombophlebitis. It is therefore one of the mainstays of anesthesia in the cardiac operating room.

Etomidate

General Characteristics

Etomidate is a carboxylated imidazole derivative that was synthesized by Godefroi and coworkers in 1965.[232] In animal experiments, it was found that etomidate had a safety margin four times greater than that of thiopental.[233] The recommended induction dose of 0.3 mg/kg has pronounced hypnotic effects. Etomidate is moderately lipid soluble[234] and has a rapid onset (ie, 10 to 12 seconds) and a brief duration of action.[235–237] It is hydrolyzed primarily in the liver and in the blood.[238]

The administration of etomidate in a buffered solution was accompanied by a burning sensation in about 40% of cases and myoclonic movements in about 40% to 50%.[237] The myoclonic movements were not associated with an epileptiform pattern on the electroencephalogram.[234]

Etomidate infusion and single injections directly suppress adrenocortical function, which interferes with the normal stress response.[237–239] Blockade of 11β-hydroxylation mediated by the imidazole radical of etomidate results in decreased biosynthesis of cortisol and aldosterone.[240–242] The clinical significance of etomidate-induced adrenal suppression remains undetermined.

Cardiovascular Effects

In comparative studies with other anesthetic drugs, etomidate is usually described as the drug that changes hemodynamic variables the least.[243–249] Studies of noncardiac patients[245,248,250] and those who have heart disease[195,243,246,247,251,252] document the remarkable hemodynamic stability after administration of etomidate (see Table 10.2). In healthy subjects or patients who have compensated ischemic heart disease, HR, pulmonary artery pressure (PAP), PCWP, left ventricular end-diastolic pressure, right atrial pressure (RAP), CI, SVR, pulmonary vascular resistance (PVR), rate of left ventricular pressure rise in early systole (dP/dt), and systolic time intervals are not significantly changed after doses of 0.15 to 0.30 mg/kg.[195,243,244,252] Compared with other anesthetics, etomidate produces the least change in the balance of myocardial oxygen demand and supply. Systemic BP remains unchanged in most series[243,244,246,249] but may be decreased 10% to 19%[247,251,253] in patients who have VHD.

Dose-related changes have been demonstrated in the dog and were attributed to three possible causes: decreased CNS sympathetic stimulation, autoregulation due to decreased regional O_2 consumption, and decreased SV due to reduced venous return.[254]

A dose-dependent direct negative inotropic effect of etomidate was demonstrated in dogs, although at equianesthetic doses, it was one-half as pronounced as that of thiopental.[201] Determining the effects of anesthetic agents on myocardial contractility is difficult in vivo because of concomitant changes in HR, preload, and afterload. The effects may be evaluated in vitro, although this does not accurately represent what is occurring in the myocardium as a whole. Riou and associates[255] studied the effect of etomidate on intrinsic myocardial contractility using left ventricular papillary muscle and an electromagnetic lever system. Etomidate induced a slightly positive inotropic effect, as manifested by increased maximum shortening velocity. It appears, however, that propylene glycol, the solvent in which etomidate is available, may result in SR dysfunction with a slight negative inotropic effect in some clinical conditions.

Intravenous etomidate (0.3 mg/kg), used to induce general anesthesia in patients with AMI undergoing percutaneous coronary angioplasty, did not alter the HR, MAP, and rate-pressure product, demonstrating the remarkable hemodynamic stability of this agent.[256,257] However, VHD may influence the hemodynamic responses to etomidate. Whereas most patients can maintain their BP, patients with aortic and mitral VHD had significant decreases of 17% to 19% in systolic and diastolic BP[247,251] and had decreases of 11% and 17% in PAP and PCWP, respectively.[251] CI in patients who had VHD and received 0.3 mg/kg remained unchanged[194,247] or decreased 13%.[251] There was no difference in response to etomidate between patients who had aortic valve disease and those who had mitral valve disease.[251]

Wauquier[257] anticipated the widespread clinical use of etomidate in their investigation, in which they compared the effects of etomidate and thiopental in hypovolemic dogs. In a hemorrhagic shock model, dogs were bled to an MAP of 40 to 45 mm Hg and then given etomidate (1 mg/kg) or thiopental (10 mg/kg). There was significantly more hemodynamic depression in the thiopental group and increased

survival for the etomidate group. Whether this is true in humans is not known, but clinical evidence suggests that etomidate is useful in patients with hypovolemia.

Uses

In certain situations, the advantages of etomidate outweigh the disadvantages. Emergency uses include situations in which rapid induction is essential. Patients who have hypovolemia, cardiac tamponade, or low CO probably represent the population for whom etomidate is better than other drugs, with the possible exception of ketamine. The brief hypnotic effect means that additional analgesic or hypnotic drugs, or both, must be administered. Etomidate offers no real advantage over most other induction drugs for patients undergoing elective surgical procedures.

Ketamine

General Characteristics

Ketamine is a phencyclidine derivative whose anesthetic actions differ so markedly from barbiturates and other CNS depressants that Corssen and Domino[258] labeled its effect *dissociative anesthesia.* The properties of ketamine and its use in anesthesia have been completely reviewed.[199] Although ketamine produces rapid hypnosis and profound analgesia, respiratory and cardiovascular functions are not depressed as much as with most other induction agents.

Disturbing psychotomimetic activity (ie, vivid dreams, hallucinations, or emergence phenomena) remains a problem. Preliminary data suggest the possibility of a protective effect against postoperative cognitive dysfunction in patients undergoing cardiac surgery, and a study conducted by Hudetz and colleagues[259] suggested that ketamine attenuated the postoperative delirium seen in cardiac surgical patients after surgery.

Cardiovascular Effects

The hemodynamic effects of ketamine have been examined in noncardiac patients,[247,260–265] critically ill patients,[266] geriatric patients,[267] and patients who have a variety of heart diseases.[262,268–270,272–278] Table 10.2 contains the range of hemodynamic responses to ketamine. A unique feature of ketamine is stimulation of the CVS. The most prominent hemodynamic changes are significant increases in HR, CI, SVR, PAP, and systemic artery pressure. These circulatory changes increase $M\dot{V}o_2$ with an apparently appropriate increase in CBF.[268,277] Although global increases in $M\dot{V}o_2$ occur, there is some evidence that the increased work may be borne primarily by the right ventricle because of significantly greater increases in PVR than SVR[279]; however, both ventricles demonstrate increased work.

The hemodynamic changes observed with ketamine are not dose related in the relatively small dose ranges examined; there is no significant difference between changes after intravenous administration of 0.5 and 1.5 mg/kg.[280] A second dose of ketamine produces hemodynamic effects opposite to those of the first.[276] The cardiovascular stimulation seen after ketamine induction of anesthesia (2 mg/kg) in a patient who has VHD is not observed with the second administration, which is accompanied instead by decreases in the BP, PCWP, and CI.

Ketamine produces similar hemodynamic changes in healthy patients and those who have ischemic heart disease.[264] In patients who have increased PAP (eg, mitral valvular disease), ketamine appears to cause a more pronounced increase in PVR than in SVR. Marked tachycardia after administration of ketamine and pancuronium also can complicate the induction of anesthesia in patients who have CAD or VHD with atrial fibrillation.[281] In a study of patients undergoing elective CABG, the use of S-(+)-ketamine did not lead to increased cardiac troponin T levels after surgery when used in combination with propofol.[282]

The mechanism responsible for ketamine's stimulation of the circulatory system remains enigmatic. The direct effects of ketamine on the myocardium remain controversial. Riou and associates[283] demonstrated that ketamine has a dual opposing action on the myocardium: a positive inotropic effect, probably due to increased Ca^{2+} influx, and an impairment of SR function. The impairment is significant only at supratherapeutic ketamine concentrations or in cardiomyopathic myocardium,[284] and it overcomes this positive inotropic effect only under these circumstances. Myocardial depression has been demonstrated in isolated rabbit hearts,[285] intact dogs, and isolated dog heart preparations.[286,287] Although the precise site of cardiovascular stimulation is unknown, Ivankovich and colleagues[288] showed that small doses of ketamine injected directly into the CNS result in immediate hemodynamic stimulation. Ketamine also causes the sympathoneuronal release of norepinephrine, which can be measured in venous blood.[268,280,289] Blockade of the effect is possible with barbiturates, benzodiazepines,[280,288–290] and droperidol.[269]

Animal work supports the hypothesis that the primary hemodynamic effect of ketamine is central and not peripheral.[291–298] The role of ketamine's cocaine-like neuronal inhibition of norepinephrine reuptake has not been defined in its overall influence on the CVS.[299,300] It also is unknown whether ketamine exerts the same effect centrally, preventing reuptake of norepinephrine in the brain.

One of the most common and successful approaches to blocking ketamine-induced hypertension and tachycardia is prior administration of benzodiazepines. Diazepam, flunitrazepam, and midazolam successfully attenuate the hemodynamic effects of ketamine.[190,270,273,290,301–303] For example, in a study involving 16 patients with VHD, ketamine (2 mg/kg) did not produce significant hemodynamic changes when preceded by diazepam (0.4 mg/kg).[270] The HR, MAP, and rate-pressure product were unchanged, but there was a slight but significant decrease in CI.[270]

Hatano and associates[302] reported their experience with 200 cardiac surgical patients in whom the administration of diazepam (0.3 to 0.5 mg/kg) and then a ketamine infusion (0.7 mg/kg per hour) provided a stable hemodynamic course during induction, intubation, and incision. The combination of diazepam and ketamine rivals the high-dose fentanyl technique with regard to hemodynamic stability. No patient had hallucinations, although 2% had dreams and 1% had recall of events in the operating room.[302]

Levanen and colleagues[304] suggested that premedication with 2.5 μg/kg of intramuscular dexmedetomidine before ketamine-based anesthesia was as effective as midazolam in blocking the hemodynamic effects of ketamine and was more effective in reducing adverse CNS effects. Because of the propensity of dexmedetomidine to produce bradycardia, concomitant use of an anticholinergic agent was suggested.

Studies have demonstrated the safety and efficacy of induction with ketamine (2 mg/kg) in hemodynamically unstable patients who required emergency operations.[266,305,306] Most patients were hypovolemic because of trauma or massive hemorrhage. Ketamine induction was accompanied in most patients by the maintenance of BP and presumably of CO.[266,305] In patients who have an accumulation of pericardial fluid with or without constrictive pericarditis, induction with ketamine (2 mg/kg) maintains CI and increases BP, SVR, and RAP.[307,308] The HR in this group of patients was unchanged by ketamine, probably because cardiac tamponade already produced a compensatory tachycardia.

Uses

In adults, ketamine is probably the safest and most efficacious drug for patients who have decreased blood volume or cardiac tamponade. Undesired tachycardia, hypertension, and emergence delirium may be attenuated with benzodiazepines.

Propofol

Propofol was introduced into clinical practice in 1986. It is an alkylphenol with hypnotic properties. The pharmacokinetics of propofol has been evaluated by numerous investigators and been described by two-compartment[309,310] and three-compartment[311,312] models.

Cardiovascular Effects

The hemodynamic effects of propofol have been investigated in ASA class I (ie, normal and healthy) and class II (ie, mild systemic disease) patients,[313] elderly patients,[314,315] patients with CAD and good left ventricular function,[316,317] and patients with impaired left ventricular function (see Table 10.2). Numerous studies have compared the cardiovascular effects of propofol with the most commonly used induction drugs, including the thiobarbiturates and etomidate.[318–322] However comparison of the study findings is difficult because of variations in anesthetic techniques, drug dosages, and techniques for measuring data. It is clear that systolic arterial pressure declines 15% to 40% after intravenous induction with 2 mg/kg and maintenance infusion with 100 µg/kg per minute of propofol. Similar changes are seen in diastolic arterial pressure and MAP.

The effect of propofol on HR varies. Most studies have demonstrated significant reductions in SVR (ie, 9% to 30%), CI, SV, and LVSWI after propofol. Although controversial, the evidence points to a dose-dependent decrease in myocardial contractility. In a double-blind, randomized, controlled trial, Bendel and associates[323] compared the effects of propofol and etomidate in patients undergoing elective aortic valve surgery for aortic stenosis. They concluded that propofol was twice as likely to result in hypotension during the induction of patients with severe aortic stenosis compared with etomidate.[323]

It has been suggested that propofol increases triglyceride levels.[324–326] In 2007, Oztekin and coworkers[327] conducted a study evaluating the effect of propofol and midazolam on lipid levels early in the postoperative period in patients undergoing CABG surgery. Serum triglyceride levels and very-low-density lipoproteins were significantly increased in patients receiving intraoperative propofol infusions 4 hours after surgery. It remains to be seen what effect this increase has on clinical outcomes and postoperative course.[327]

Uses

In a study of the cerebral physiologic effects of propofol during CPB, Newman and colleagues[328] found that when given during nonpulsatile CPB, propofol produced statistically significant reductions in cerebral blood flow and cerebral metabolic rate in a coupled manner without adverse effects on the cerebral arteriovenous oxygen content difference or jugular bulb venous saturation. The coupled reductions in cerebral blood flow and cerebral metabolic rate suggest the potential for propofol to reduce cerebral exposure to emboli during CPB.

The effect of propofol on hypoxic pulmonary vasoconstriction was minimal in thoracic surgical patients undergoing one-lung ventilation. Compared with isoflurane, maintenance of anesthesia with propofol resulted in a lower CI and right ventricular ejection fraction but avoided the threefold increase in shunt fraction observed with isoflurane on commencement of one-lung ventilation.[329]

Dexmedetomidine

Dexmedetomidine, the pharmacologically active D-isomer of medetomidine, is a highly selective, specific, and potent adrenoreceptor agonist. Medetomidine has a considerably greater α_2/α_1 selectivity ratio than does the classic prototype α_2-adrenergic agonist clonidine in receptor-binding experiments. Compared with clonidine, it is more efficacious as an α_2-adrenoreceptor agonist. It has effectively reduced volatile anesthetic requirements in experimental animals as measured by the minimal alveolar concentration (MAC), and it can be a complete anesthetic in sufficiently high doses. The exact mechanisms of function and reduced anesthetic requirement are unknown but are thought to involve actions at presynaptic and postsynaptic α_2-adrenoreceptors in the CNS.

Cardiovascular Effects

The cardiovascular effects of dexmedetomidine are dose related. Furst and Weinger[330] demonstrated that an increase in systemic BP was associated with the pretreatment of rats with high-dose dexmedetomidine and that dexmedetomidine had little effect on arterial blood gases in spontaneously ventilating rats, consistent with minimal respiratory depression. Canine studies with medetomidine in doses of 30 µg/kg given intravenously or 80 µg/kg given intramuscularly showed decreases in HR and CO with increased SVR after drug administration. The intravenous administration of 5 to 10 µg/kg of medetomidine to anesthetized, autonomically blocked dogs suggested that the decline in CO was not mediated by decreased contractility but rather by the effects of increased vascular resistance and decreased HR. At high doses, the increase in SVR most likely results from the activation of peripheral postsynaptic α_2-adrenoreceptors in vascular smooth muscle.

In human studies, ASA class I women who received low-dose premedication with 0.5 µg/kg of dexmedetomidine demonstrated modest decreases in BP and HR. Intramuscular dexmedetomidine in a dose of 2.5 µg/kg administered 45 minutes before induction of a ketamine-N_2O-oxygen anesthetic resulted in effective attenuation of the cardiostimulatory effects of ketamine but also in increased intraoperative and postoperative bradycardia.[304] The use of perioperative intravenous infusions of low-dose dexmedetomidine in vascular patients at risk for CAD produced lower preoperative HR and systolic BP and less postoperative tachycardia, but it also resulted in a greater intraoperative requirement for pharmacologic intervention to support BP and HR. The precise cause of this effect is unknown, but it may reflect the attenuation of sympathetic outflow from the CNS.

Some controversy exists about whether the hemodynamic effects of dexmedetomidine are influenced by the background anesthetic. In conscious animals, the hypotensive effect of the drug dominates, but with the addition of potent inhalation anesthetics, MAP remains unchanged or increased, which implies a different mechanism of interaction of inhalation agents for this class of anesthetics. Dexmedetomidine has little effect on respiration, with minimal increase in arterial carbon dioxide tension ($PaCO_2$) after administration to spontaneously ventilating dogs. It has a potential advantage over other respiratory depressant anesthetics. Antinociceptive effects of medetomidine are mediated by suppression of responses of the pain-relay neurons in the dorsal horn of the spinal cord.

Uses

Clinical studies have suggested that α_2-adrenergic agonists can safely reduce anesthetic requirements and improve hemodynamic stability. These agents may enhance sedation and analgesia without producing respiratory depression or prolonging the recovery period. Barletta and associates[331] compared postoperative opioid requirements in patients undergoing cardiac surgery who received intraoperative propofol with those receiving dexmedetomidine. Although dexmedetomidine resulted in lower opioid use compared with propofol, it did not translate to a shorter duration of mechanical ventilation, but it did result in significantly greater sedation-related costs.[331]

Levanen and coworkers[304] suggested that dexmedetomidine might be an effective alternative to benzodiazepines in attenuating the postanesthetic delirium effects of ketamine. Because α_2-adrenergic agonists potentially inhibit opiate-induced rigidity, they may be of use as adjuvants with high-dose opioid anesthetics for cardiac surgery. In contrast with other anesthetic adjuvants such as the benzodiazepines, the α_2-adrenoreceptor agonist dexmedetomidine does not further compromise cardiovascular or respiratory status in the presence of high-dose opioids.

The use of dexmedetomidine as a sedative adjunct in the management of patients after surgery in the intensive care unit is becoming increasingly popular.[332] The idea that the type and amount of agent used intraoperatively can influence the postoperative course, specifically neuropsychologic events, is emerging as an important paradigm.[333] The management of patients after surgery is covered extensively in Chapters 37, 38, and 39. In summary, pharmacologic evidence suggests dexmedetomidine may be useful as an adjuvant in cardiac anesthesia.

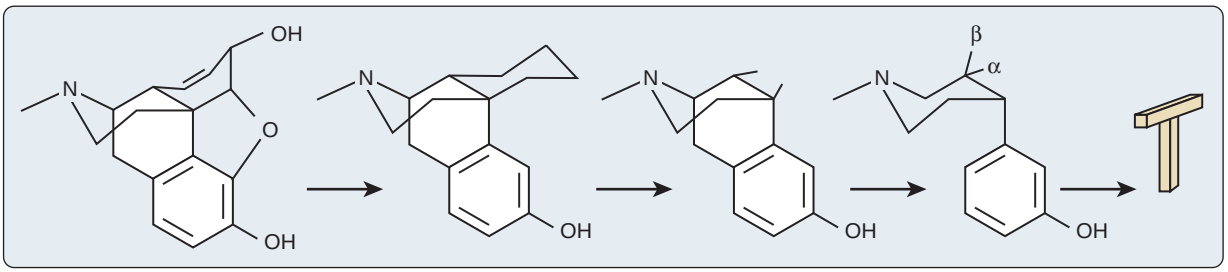


Fig. 10.30 Synthetic opioids are produced by successive removal of ring structures from the five-ring phenanthrene structure of morphine. A common core, envisaged as a T shape, is shared by all opioids. A piperidine ring (which is thought to confer opioid-like properties to a compound) forms the crossbar, and a hydroxylated phenyl group forms the vertical axis. *(From Ferrante FM. Opioids. In: Ferrante FM, VadeBoncouer TR, eds.* Postoperative Pain Management. *New York: Churchill Livingstone; 1992:149.)*

Opioids in Cardiac Anesthesia

Terminology and Classification

Various terms are commonly used to describe morphine-like drugs that are potent analgesics. The word *narcotic* is derived from the Greek word for "stupor" and refers to any drug that produces sleep. In legal terminology, it refers to any substance that produces addiction and physical dependence. Its use to describe morphine or morphine-like drugs is misleading and should be discouraged.

Opiates refer to alkaloids and related synthetic and semisynthetic drugs that interact stereospecifically with one or more of the opioid receptors to produce a pharmacologic effect. The more encompassing term, *opioid,* also includes the endogenous opioids and is used in this chapter. Opioids may be agonists, partial agonists, or antagonists.

A wide diversity in chemical structure exists among the naturally occurring, semisynthetic, and synthetic opioids. Opium contains several important alkaloid constituents, which may vary markedly in their pharmacologic actions. The five major alkaloid constituents of opium can be separated into two groups based on differences in their chemical structure. The phenanthrene derivatives include morphine, codeine, and the convulsogenic compound thebaine, which is used as a chemical precursor in the development of many clinically useful semisynthetic opioid compounds such as oxycodone. The benzylisoquinoline derivatives of opium include the phosphodiesterase inhibitor, smooth muscle relaxant papaverine, and the antitussive compound noscapine.

Modification of the morphine molecule, although simultaneously preserving the basic five-ring structure, results in semisynthetic compounds that also exhibit analgesic effects (eg, hydromorphone, heroin). Progressive removal of the rings results in synthetic opioids. As long as the common core or T shape is retained stereochemically and is shared by these synthetic derivatives, opioid properties are retained. The piperidine ring forms the crossbar and the hydroxyl phenyl group forms the vertical axis of the T shape (Fig. 10.30).

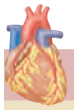
Opioid Receptors

The idea of opioid receptors was stated in the pioneering work of Beckett and Casy,[334] which in 1965 allowed Portoghese[335] to postulate the existence of separate opioid receptors by correlating analgesic activity with the chemical structure of many opioid compounds (Box 10.6). The concept of multiple opioid receptors is accepted, and several subtypes of each class of opioid receptors have been identified. Through biochemical and pharmacologic methods, the μ, δ, and κ receptors have been characterized.[336–338] Pharmacologically, the δ-opioid receptors consist of two subtypes: δ_1 and δ_2.[339–342] Table 10.3 lists the opioid receptors and their associated agonists and antagonists.

The μ-, κ-, and δ-opioid receptors have been cloned, and experimental data indicate that they belong to the family of G-protein–coupled receptors.[343–346] Three steps have been identified in the opioid-induced transmembrane signaling process: recognition by the receptor of the extracellular opioid agonist, signal transduction mediated by the G protein, and altered production of an intracellular second messenger (Fig. 10.31). The opioid receptors preferentially couple to a pertussis toxin–sensitive G protein (ie, G_i/G_o subunits) to influence one or more of three second-messenger pathways: cytoplasmic-free Ca^{2+} $[Ca^{2+}]_i$, the phosphatidylinositol-$[Ca^{2+}]_i$ system, and the cyclic nucleotide cAMP.

The actions of opioids are primarily inhibitory. Opioids close N-type, voltage-operated Ca^{2+} channels and open Ca^{2+}-dependent inwardly rectifying K^+ channels. This results in hyperpolarization and a reduction in neuronal excitability.[347] The κ receptors may act only on Ca^{2+} channels.[348] Evidence indicates that P/Q-type Ca^{2+} channels may be inhibited by μ-opioid but not δ-opioid receptors.[349] These effects may be mediated through direct coupling between the G protein and ion channels or indirectly through changes in intracellular Ca^{2+} levels. The Ca^{2+} fluxes and their consequences, such as calmodulin activation, are altered by opioids. Ca^{2+} ions are essential in nociception, and Ca^{2+} channel blockers potentiate opioid analgesia[350,351] and reduce fentanyl requirements during cardiac surgery.[352] Opioid-induced inhibition of adenylyl cyclase and the resultant decrease in the concentration of cAMP may be responsible for modulation of neurotransmitter release (eg, substance P).

Opioids have excitatory effects that involve disinhibition of interneurons and direct excitation of neurons. Nanomolar concentrations acting through G proteins stimulate adenylyl cyclase activity in certain neurons.[353] Another important stimulatory effect is a transient increase in cytoplasm-free Ca^{2+} due to Ca^{2+} influx through L-type Ca^{2+} channel



BOX 10.6 OPIOIDS

- The μ-, κ-, and δ-opioid receptors and endogenous opioid precursors have been identified in cardiac and vascular tissue.
- The functional roles of opioid precursors and opioid receptors in the cardiovascular system of persons with pathophysiologic conditions (eg, congestive heart failure, arrhythmia) are areas of ongoing investigation.
- The predominant cardiovascular effect of exogenously administered opioids is attenuation of central sympathetic outflow.
- Endogenous opioids and opioid receptors (especially the δ_1-opioid receptor) are likely important contributors to early and delayed preconditioning in the heart.
- Plasma drug concentrations are profoundly altered by cardiopulmonary bypass as a result of hemodilution, altered plasma protein binding, hypothermia, exclusion of the lungs from the circulation, and altered hemodynamics that likely modulate hepatic and renal blood flow. The specific effects are drug dependent.

TABLE 10.3 Agonist and Antagonist Drugs for μ-, κ-, and δ-Opioid Receptors

Opioid Receptor	*Agonists*	*Antagonists*
μ	Morphine Fentanyl Levorphanol Methadone	Naloxone Naltrexone β-Funaltrexamine (β-FNA)[a] Nalbuphine[b]
κ	U-50,488H Ethylketocyclazocine (EKC) Spiradoline (U-62,066E) U-69,593	Nor-binaltorphimine (nor-BNI) MR-2266 Naloxone
δ	(−)TAN-67 7-Spiroindinooxymorphone (SIOM) (+)-4-[((αR)- α (2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxy-benzyl]-*N*,*N*-diethylbenzamide chloride (SNC 80)	Naltrindole 7-Benzylidene-naltrexone (BNTX) Naltriben

[a]β-FNA is an irreversible opioid receptor antagonist.
[b]Nalbuphine is an opioid receptor antagonist with partial agonist properties.

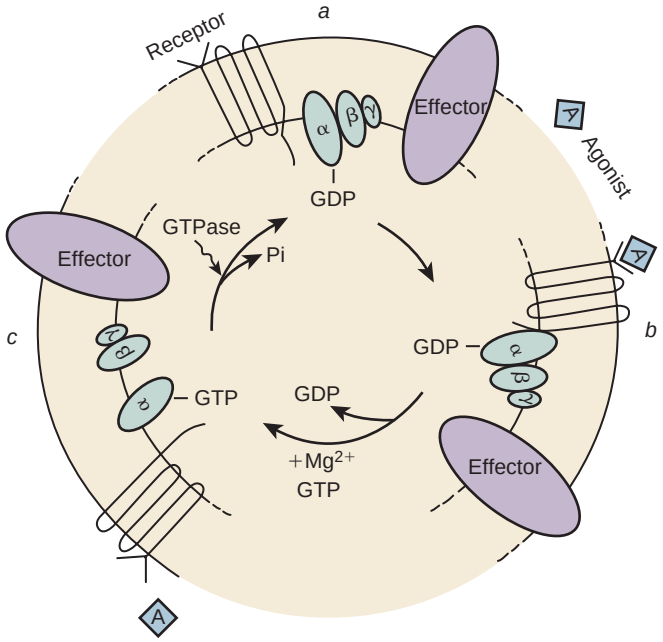


Fig. 10.31 Simple scheme for G-protein signal transduction. From the unliganded state (*a*), receptor binds agonist A (eg, epinephrine, acetylcholine), which produces a change (*b*) in the receptor and G protein interaction, allowing guanosine triphosphate *(GTP)* in the presence of Mg^{2+} to replace guanosine diphosphate *(GDP)* on the α subunit. The activated GTP α subunit and the βγ subunits dissociate, and one or both interact with effectors (eg, adenylyl cyclase, K^+ channel). Alternatively, free βγ may bind other α subunits. The intrinsic *GTPase* activity of the α subunit hydrolyzes GTP to GDP, releasing inorganic phosphate *(Pi)*, and α-GDP recombines with βγ (*c*), ending the activation cycle. Nonhydrolyzable analogues of GTP, such as Gpp(NH)p or GTP-γS, produce persistent activation of α subunits and persistent dissociations of α from βγ because activation cannot be reversed by hydrolysis of these nucleotide analogues to GDP.

openings and mobilization of Ca^{2+} from inositol triphosphate–sensitive intracellular stores.[354] The μ agonists also may stimulate Ca^{2+} entry into neurons through G-protein–coupled activation of phospholipase C to increase inositol 1,4,5-triphosphate formation due to Ca^{2+} influx through L-type Ca^{2+} channel openings.[354–356]

TABLE 10.4 Endogenous Opioid Peptide Precursors and Opioid Peptide Products Involved in Cardiovascular Regulation and Function

Precursor	*Opioid Peptide*	*Receptor*[a]
Proenkephalin[b]	Met-enkephalin Leu-enkephalin	δ > μ ≫> κ
POMC[c]	β-Endorphin	μ ≈ δ ≫ κ
Prodynorphin[d]	Dynorphin A Dynorphin $A_{(1–8)}$ Dynorphin B	κ ≫> μ > δ κ ≫ μ > δ κ ≫> μ > δ
Pronociception	Nociception	ORL1

ORL1, Opioid receptor-like 1; *POMC*, proopiomelanocortin.
[a]The affinity of the opioid peptide for its receptor is qualitatively described in this table for the μ-, κ-, and δ-opioid receptor subtypes found in the central nervous system.[544]
[b]An additional opioid peptide product from this precursor that exhibits relevant cardiovascular actions in MERF.[545]
[c]An additional POMC peptide cleavage product is adrenocorticotropic hormone, which is converted to α-melanocyte–stimulating hormone–related peptides in cardiac tissue.[546]
[d]Additional active peptides include leumorphin, α-neoendorphin, and β-neoendorphin.[544]

Opioid receptors involved in regulating the CVS have been localized centrally to the cardiovascular and respiratory centers of the hypothalamus and brainstem and peripherally to cardiac myocytes, blood vessels, nerve terminals, and the adrenal medulla. Opioid receptors are differentially distributed between atria and ventricles. The highest specific receptor density for binding of κ-opioid agonists is in the right atrium and least in the left ventricle.[357,358] As with the κ-opioid receptor, distribution of the δ-opioid receptor favors atrial tissue and the right side of the heart more than the left.[359] Data confirming the presence of the μ-opioid receptor subtype in the heart are less conclusive, and most researchers think that this receptor subtype is not present in cardiac tissue.[357,358,360,361]

Whether the differences in receptor location are important cannot be determined because it has not been shown whether the receptors are differentially located in cardiac muscle or cardiac nerves or are expressed on immunomodulatory cells within the heart. Based on these studies, the ability of opioid agonists to produce cardioprotection is most likely the effect of δ- and κ-opioid receptor stimulation, and studies appear to support a role for the δ-opioid receptor as the primary receptor responsible for IPC.

Endogenous Opioids in the Heart

Myocardial cells can synthesize, store, and release opioid-receptor peptides.[362] Opioid-receptor peptides may be secreted from nerves that innervate the heart or produced in myocardial tissue. Regardless of the manner of production, the peptides are devoid of activity until they undergo enzymatic proteolysis of the precursor by convertases into one or more active peptide products. The large stores of endogenous opioid peptide (EOP) precursors, which reside in the myocardial tissue, include proenkephalin, proendorphin, and prodynorphin.

The EOP system consists of the peptides endorphin, dynorphin, and enkephalin and their associated μ-, δ-, and κ-opioid receptors (Table 10.4). These opioid peptides and receptors are widely distributed in the body, and all have complex actions. In the heart, κ- and δ-receptor agonists inhibit ventricular contractility without altering atrial function.[359] A study of the actions of peptides on electrical and mechanical properties of the isolated rat heart showed that δ- and κ-opioid receptor agonists could directly depress cardiac function.[363] The rate of vagal firing is regulated by opioid peptides.[364] Vagal bradycardia is inhibited by the administration of the intrinsic cardiac opioid heptapeptide Met-enkephalin-Arg-Phe (MERF), presumably by the activation of δ-opioid receptors on prejunctional cardiac vagal nerves or parasympathetic ganglia, reducing acetylcholine release.[365] EOPs therefore mediate direct and indirect actions in various regions of the heart. In addition to complex differences in the general tissue

distribution of opioid receptors, cardiac opioid peptide function is complicated by the fact that receptor expression is modulated by physiologic states and disease.

Several investigators have demonstrated that certain opioid peptides are released during stressful situations into the peripheral circulation.[366,367–369] The peptides can modulate the ANS.[370] In the heart, opioid peptides (Leu- and Met-enkephalins) have been shown to increase with age[371–373] and disease.[374–377] EOPs are involved in the modulation of hypertension and other cardiovascular conditions such as CHF and appear to be involved in arrhythmogenesis.[378] Myocardial ischemia and reperfusion can induce synthesis and release of opioid peptides.[377,379–384] Several studies have demonstrated that levels of circulating β-endorphins are greater in patients with acute myocardial ischemia or those undergoing angioplasty.[379,382,383,385]

Although κ-receptor agonists have no effect on cardiovascular indices in healthy humans,[386] activation of δ and κ receptors during CHF decreases myocardial mechanical performance and alters regional blood flow distribution.[380] The mechanism for the negative inotropic effects is thought to be an increase of intracellular free Ca^{2+} by increasing the mobilization of calcium from intracellular stores due to increased production of inositol 1,4,5-triphosphate. The increase in Ca^{2+} concentration may manifest in cardiac arrhythmias, whereas depletion of Ca^{2+} from intracellular stores is responsible for a reduction in contractility.[380,387]

In patients with acute heart failure, concentrations of EOPs are increased,[388] whereas concentrations are decreased in patients with chronic heart failure. This has been interpreted as exhaustion of the opioid system.[389] Many studies suggest that EOPs mediate depression of myocardial function in CHF states.[367,388,390,391] Clinically, increased levels of EOPs (ie, β-endorphin, Met-enkephalin, and dynorphin) have been found in CHF patients, and they may correlate with severity. Naloxone administration to CHF patients increased BP and HR, suggesting a homeostatic regulatory role for EOPs.

Not all clinical studies suggest that inhibition of opioid peptides benefits patients with acute and chronic heart failure.[389] Oldroyd and colleagues[392] found that plasma levels of β-endorphins were normal in patients with acute and chronic heart failure and did not correlate with the severity of heart failure observed in their study.[392] They also found that naloxone administration did not alter cardiopulmonary exercise in these patients and suggested that EOP inhibition was not likely to have any therapeutic potential.

Cardiac Effects of Opioids

At clinically relevant doses, the cardiovascular actions of opioid analgesics are limited. The role that endogenously or exogenously administered opioids play in the regulation of the CVS is difficult to interpret because the physiologic effects they impart depend on pharmacologic variables such as dose, site, and route of administration; receptor specificity; and species. The actions opioids exhibit are mediated by opioid receptors located centrally in specific areas of the brain and nuclei that regulate the control of cardiovascular function and peripherally by tissue-associated opioid receptors. Opioids exhibit a variety of complex pharmacologic actions on the CVS[367] (Fig. 10.32).

Most of the hemodynamic effects of opioids in humans can be related to their influence on sympathetic outflow from the CNS. Evidence shows that sympathetic overactivity favors the genesis of life-threatening ventricular tachyarrhythmias, and its control has protective effects during acute myocardial ischemia.[393] Imbalance of the ANS, characterized by increased sympathetic activity and reduced vagal activity, results in myocardial electrical instability and promotes ischemic events. Pharmacologic modulation of the sympathetic activity by centrally or peripherally acting drugs elicits cardioprotective effects. Opioid-receptor agonists such as fentanyl exhibit significant central sympathoinhibitory effects.[394]

Fentanyl and sufentanil enhance the calcium current that occurs during the plateau phase (ie, phase 2) of the cardiac action potential and depress the outward potassium current responsible for terminal

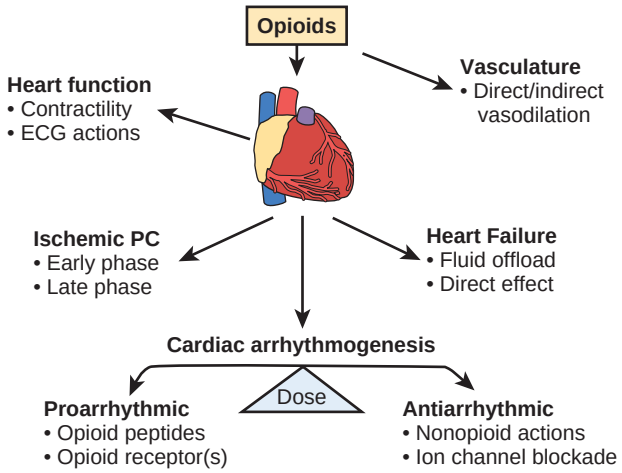


Fig. 10.32 Actions of opioids on the heart and cardiovascular system. Actions may involve direct opioid receptor–mediated actions, such as the involvement of the δ-opioid receptor in ischemic preconditioning *(PC)*, or indirect, dose-dependent, nonopioid-receptor–mediated actions, such as ion channel blockade associated with the antiarrhythmic actions of opioids. *ECG*, Electrocardiogram.

repolarization,[395] resulting in a significant prolongation of the duration of the action potential. Blair and coworkers[396] suggested that the cardiac electrophysiologic effects of fentanyl and sufentanil represented a direct membrane effect resembling that produced by class III antiarrhythmic drugs. In patients, large doses of opioids prolong the QT interval of the electrocardiogram.[395] Although generally proarrhythmic, this effect has been cited to explain the antiarrhythmic properties of opioids, particularly in the setting of myocardial ischemia.[292] Fentanyl (60 μg/kg) and sufentanil (10 μg/kg) significantly increased the ventricular fibrillation threshold in dogs after coronary artery occlusion.[397]

With the exception of meperidine, all opioids produce bradycardia, although morphine given to unpremedicated, healthy persons may cause tachycardia. The mechanism of opioid-induced bradycardia is central vagal stimulation. Premedication with atropine can minimize but not totally eliminate opioid-induced bradycardia, especially in patients taking β-adrenoceptor antagonists. Although severe bradycardia should be avoided, moderate slowing of the HR may be beneficial in patients with CAD by decreasing myocardial oxygen consumption.

Isolated heart or heart muscle studies have demonstrated dose-related inotropic effects for morphine, meperidine, fentanyl, and alfentanil.[398–401] However, these effects occurred at concentrations a hundred to several thousand times those found clinically. In canine hearts, the direct intracoronary injection of fentanyl in concentrations up to 240 ng/mL produced no changes in myocardial mechanical functions.[402]

Morphine produced dose-related decreases in the contractility of atria obtained from nonfailing and failing human hearts, but the concentration-response curve was significantly shifted to the right for preparations from failing hearts[403] (Fig. 10.33). The negative inotropic effects induced by morphine in failing and nonfailing preparations were not antagonized by naloxone, indicating that opioid receptors do not play a part in this cardiac effect of morphine. One explanation may be an interaction with β-adrenoceptors, unrelated to the binding of opioids to opioid receptors. Opioids inhibit β-adrenoceptor–sensitive adenylyl cyclase.[404]

Hypotension can occur after even small doses of morphine and is primarily related to decreases in SVR. The most important mechanism responsible for these changes is histamine release. The amount of histamine release is reduced by slow administration (<10 mg/min). Pretreatment with a histamine H_1 or H_2 antagonist does not block these reactions, but they are significantly attenuated by combined H_1

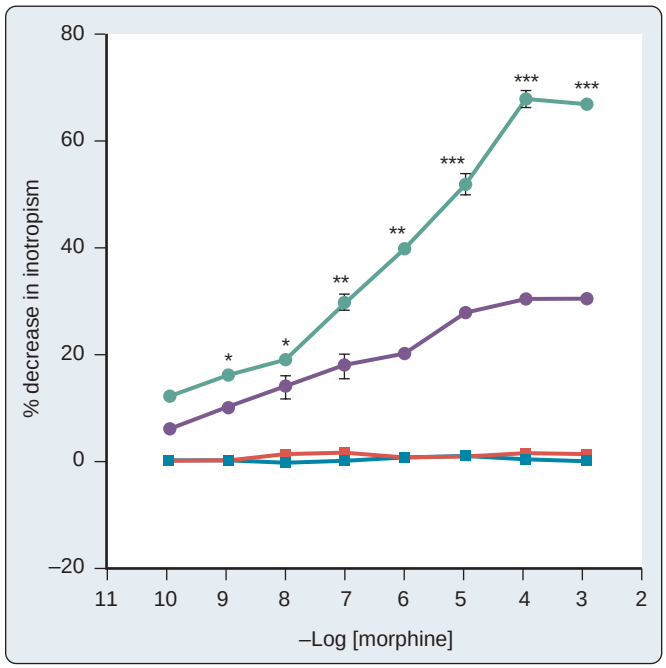


Fig. 10.33 Concentration-response curves for morphine *(circles)* in isolated electrically stimulated human right atrial strips from nonfailing *(green circles)* and failing *(purple circles)* hearts (*squares* indicate control). Average auricular inotropism (mean ± standard error of the mean [SEM)]) was 0.90 ± 0.05 g for nonfailing hearts and 0.89 ± 0.02 g for failing hearts. *$P < .05$; **$P < .01$; ***$P < .001$ versus failing heart. Each point represents the mean ± SEM of eight experiments for each experimental group.

TABLE 10.5 Effects of Arylacetamide κ-Opioid Agonists on Heart Rate, Blood Pressure, and Electrocardiographic Measures

Drug[a]	*Heart Rate*	*Blood Pressure*	*PR*	*QRS*	*RSh*	*QT*
U-50,488H	1.5	>32	20	>32	16	32
U-62,066E	4.0	8.0	15	25	2.0	10
PD117,302	5.5	0.50	3.0	7.5	1.0	6.0

[a]The nonopioid actions of structurally related arylacetamide κ-opioid receptor agonists were examined in pentobarbital-anesthetized rats. Heart rate, blood pressure, and electrocardiographic (ECG) measures (in milliseconds) were determined as D_{25}, the intravenous dose (μmol/kg/min) producing a 25% change in the given response. This measure allowed determination of the differential actions of the arylacetamides on ECG measures, an index of drug action on cardiac ion channels ($n = 6$). The drug dose produced a 25% change from controls in intact animals for six determinations per measure. All drugs consistently reduced the heart rate but had various D_{25} doses for blood pressure reduction. PD117,302 {(±)-*N*-methyl-*N*-[2-(1-pyrrolidinyl) cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride} produced evidence of sodium channel blockade (ie, changes in the PR, QRS, and RSh measures) and potassium channel blockade (ie, changes in the QT interval) at lower D_{25} values than either of the other two drugs.

and H_2 antagonist pretreatment.[405] Neither morphine nor fentanyl in clinically relevant concentrations blocks α-adrenergic receptors in isolated vascular tissue studies.[406,407]

Opioids may directly act on vascular smooth muscle, independent of histamine release. In the isolated hind limbs of dogs anesthetized with halothane, high doses of alfentanil (500 μg/kg), fentanyl (50 μg/kg), and sufentanil (6 μg/kg) caused decreases in SVR of 48%, 48%, and 44%, respectively. Neither pretreatment with naloxone nor denervation changed the responses, and it was concluded that the three opioids produced vasodilation by a direct action on vascular smooth muscle.[408] Although fentanyl-induced relaxation in the rat aorta may be mediated by α-adrenergic receptors, this effect occurs only at concentrations several hundred times greater than those encountered clinically.[409]

The effects of κ-agonists on BP have been examined[410] and shown to be dose, species, and route dependent.[410,411] U-50,488H, for example, displays a markedly different cardiovascular profile when injected intravenously compared with direct injection into the CNS. In anesthetized dogs, κ-agonists produce dose-related decreases in BP, HR, peak systolic pressure, and cardiac contractility when administered intravenously. The cardiovascular responses to both opioid agonists were abolished by previous administration of naloxone.[412] In addition to reducing BP, κ-opioid agonist dose-dependently reduced the HR in anesthetized rats.[410] This suggests an effect on the reflex mechanisms that regulate the HR during hypotension or direct action on the electrical or mechanical properties responsible for normal cardiac contractility. The κ-opioid agonists slightly depress the HR and BP at low doses and are not inhibited by naloxone, suggesting a lack of involvement of opioid receptors and a possible direct effect on cardiac muscle.[411] In anesthetized rats, the cardiovascular responses to κ-opioid agonists in the presence of opioid antagonists were not changed.[411,413,414] It was concluded from these studies and others[415] that because opioid receptor antagonists did not block these responses, they were not mediated by opioid receptors.

Opioid-receptor agonists and antagonists block ion channels that constitute the genesis of the action potential in neurons. Voltage-gated Na^+ channels are responsible for the initiation of membrane depolarization and conduction of action potentials in electrically excitable cells, resulting in contraction of the heart or transmission of electrical impulses in nerves. K^+ channels are responsible for repolarization of the cell membrane and cessation of action potentials in excitable cells. Morphine and naloxone block the propagation of action potentials in many nerve and cardiac muscle preparations by directly inhibiting voltage-dependent Na^+ and K^+ currents.

In addition to the opioid receptor–independent actions of U-50,488H and related κ-opioid agonists on BP and HR (ie, actions not blocked by opioid-receptor antagonists), these drugs produce changes in the electrocardiogram indicative of a drug interaction with cardiac ion channels.[410,416] Table 10.5 summarizes the action of several κ-opioid agonists and their actions on BP, HR, and the PR, QRS, RSh, and QT intervals on rat electrocardiograms. The electrocardiographic changes, including PR interval prolongation, QRS widening, and increased amplitude of the RSh, are indicative of cardiac Na^+ channel blockade. Widening of the QT interval, an index of cardiac repolarization, suggests K^+ channel blockade.

The results of studies of opioid drugs such as sufentanil[395] and morphine[417] corroborate the suggestion of interaction of κ-opioids with cardiac K^+ channels. However, the opioid receptor–independent nature of the ion channel blockade may not be isolated to Na^+ and K^+ channels and may include L-type Ca^+ channels found in cardiac muscle. The use of Ca^{2+} fluorescent techniques for measurement of cardiac myocyte contractility suggested that the negative inotropic actions of κ-opioid agonists also may result from inhibition of L-type Ca^{2+} currents.[418,419] While investigating the possible cardiotoxic effects produced by opioids in human poisoning, Wu and colleagues[420] found that opioids such as meperidine and dextropropoxyphene exert negative inotropic actions in cardiac muscle by blockade of Ca^{2+} currents in myocytes in the presence of naloxone.

Ischemic Preconditioning

Myocardial IPC is a phenomenon that occurs in cardiac muscle in which brief periods of ischemia (usually <5 minutes) render the muscle tolerant to tissue damage that occurs during a subsequent period of ischemia after an interlude of perfusion[94] (Fig. 10.34). The phenomenon occurs in many species and is mediated by a well-defined intracellular cascade.[421] The intercellular mediator or IPC-induction trigger appears to be diverse and involves opioids and other substances.

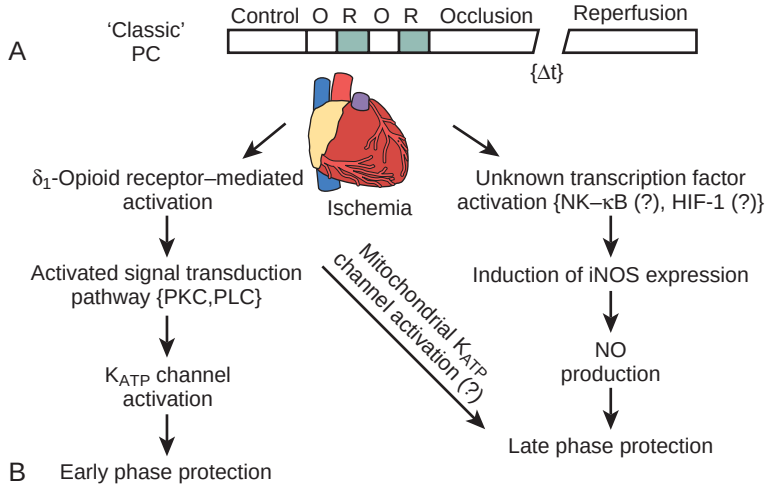


Fig. 10.34 (A) Typical protocol bar that may be used in experiments that investigate the effects of agents on ischemic preconditioning *(PC)* in the heart. Similar protocols have been used to study opioid receptor–mediated cardioprotective mechanisms in the rat and other mammalian species. Studies may investigate the effects of ischemic PC on ischemia or reperfusion arrhythmias of various durations in length (Δt). Ischemic PC usually involves a sequence of coronary artery occlusion *(O)* followed by reperfusion *(R)* cycles. Two cycles are depicted before coronary artery occlusion followed by reperfusion. This type of protocol may be easily amenable to modification; the protocol shown is a simplified protocol bar. (B) The schematic diagram shows the molecular pathways involved in the protective effects of ischemic PC in the heart. Brief periods of ischemia provide an early and late phase of protection to the heart from subsequent episodes of prolonged or permanent ischemia. Activation of G-protein–coupled δ_1-opioid receptors is involved in both protective phases. Activation of the δ_1-opioid receptor activates intracellular signal transduction pathways, including protein kinase C *(PKC)*, phospholipase C *(PLC)*, and related kinase pathways. Activation of these pathways results in phosphorylation of proteins such as the K^+_{ATP} channel on the myocyte cell surface and the myocyte mitochondrial cell surface. Opening of these ion channels mediates the early phase of cardioprotection that lasts 2 to 3 hours after the ischemic episode. The late phase of cardioprotection that results from the brief episodes of ischemia may be mediated by activation of oxygen-sensitive transcription factors such as nuclear factor-κB *(NF-κB)* and hypoxia-inducible factor 1 *(HIF-1)*. These factors subsequently induce the expression of inducible nitric oxide synthase *(iNOS)* and the production of nitric oxide *(NO)*, the putative mediator of the protective effect on the heart observed 24 to 48 hours after the ischemic episode. δ_1-Opioid receptor stimulation also may produce a late cardioprotective effect that may result from activation of mitochondrial K^+_{ATP} channels. *(From Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium.* Circulation. *1986;74:1124.)*

The nature of IPC may not be consistent among the species examined despite a common end result.

In vivo studies show that IPC can reduce the size of an infarct resulting from prolonged ischemia.[422] There also is a reduction in damage to myocardial intracellular structure, a decrease in the dysfunction of the cardiac contractile machinery, and a direct reduction in arrhythmias associated with IPC.[422,423] The ability of IPC to limit myocardial damage occurs chronologically in two distinct phases. The first or early phase provides a window of protection to the heart muscle that occurs soon after IPC and declines with time during the first 3 hours of reperfusion. The late or delayed phase of IPC provides a second window of protection to heart muscle that emerges after 24 hours of reperfusion and may last up to 72 hours[424–426] (see Chapter 7).

Importance of Opioid Receptors in Early Preconditioning

The involvement of opioids in IPC resulted from recognition of their value at increasing survival time and tissue preservation before surgical transplantation and their possible role in enhancing tolerance to hypoxia.[427,428] The first evidence demonstrating a role for opioids in early IPC was published by Schultz and associates[429] in the intact, blood-perfused rat heart. The investigators demonstrated that the nonselective opioid receptor antagonist naloxone completely antagonized the ability of IPC to reduce infarct size whether administered before the IPC stimulus or after the IPC stimulus just before the index ischemia. The results suggested that endogenous opioids served as a trigger and end-effector of IPC in rat hearts (Fig. 10.35). Chien and Van Winkle[430] found similar results in the rabbit heart with the use of the active enantiomer (−)naloxone. Schulz and coworkers[431] also determined the role of endogenous opioids in mediating IPC and myocardial hibernation in pig hearts and observed that naloxone blocked IPC but not the effects of short-term hibernation. The data suggest that an opioid receptor mediates the effect of endogenous opioids to elicit IPC in the rat, rabbit, and pig.

Takashi and colleagues[432] performed a study in isolated adult rabbit cardiomyocytes to determine the EOPs responsible for the cardioprotective effect observed during and after IPC. They found that Met-enkephalin, Leu-enkephalin, and Met-enkephalin-Ang-Phe (MEAP) reduced the incidence of cell death, suggesting that the enkephalins are the most likely candidates for triggers and distal effectors of IPC in the rabbit heart. Huang and associates[433,434] studied the role of δ-opioid receptor activation in reducing myocardial infarct size in human and rat hearts. Their studies indicated that endogenous adrenergic receptor activation and downstream signaling were important mediators in attenuating infarct size.[433,434]

Cardioprotective Effects of Exogenous Opioid Agonists

In 1996, Schultz and colleagues[435] were the first to demonstrate that an opioid could attenuate ischemia-reperfusion damage in the heart.

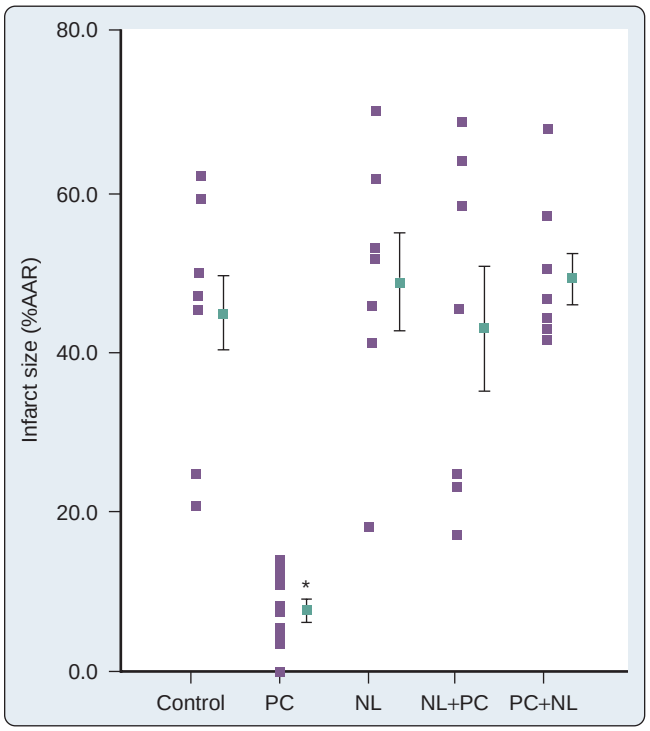


Fig. 10.35 Infarct size is expressed as a percentage of the area at risk *(AAR)* in intact rat hearts subjected to vehicle *(Control)*, ischemic preconditioning *(PC)*, naloxone *(NL)* in the absence of PC, NL treatment before PC *(NL+PC)*, and NL treatment after PC *(PC+NL)* before the index ischemic period. Green squares indicate the mean ± standard error of the mean for each group. *$P < .05$ versus the control group. *(From Schultz JJ, Rose E, Yao Z, et al. Evidence for involvement of opioid receptors in ischemic preconditioning in rat heart.* Am J Physiol. *1995;268:157.)*

Morphine at the dose of 300 µg/kg was given before left anterior descending coronary artery occlusion for 30 minutes in rats in vivo. The infarct area or area at risk was diminished from 54% to 12% by this treatment. The infarct-reducing effect of morphine has been shown in hearts in situ, isolated hearts, and cardiomyocytes.[432,436,437] Morphine also improved postischemic contractility.[438] It is now accepted that morphine provides protection against ischemia-reperfusion injury.

Gross and coworkers[439] reported a significant reduction in infarct development in rats after administration of morphine or a selective δ-opioid receptor ligand at reperfusion. The effects are mediated through glycogen synthase kinase-β and the phosphatidylinositol 3-kinase pathway.[439] There is also evidence to suggest that remifentanil, when added to a standard anesthetic regimen, may reduce myocardial damage after CABG (Fig. 10.36).[440]

Fentanyl has been studied in a limited fashion and has had mixed results as far as its ability to protect the myocardium.[438,441,442] This may be because of differences in species studied or fentanyl concentrations, or both. Pentazocine and buprenorphine improved postischemic contractility in rabbits in vitro.[438] Overall, the effects of opioids other than morphine have not been sufficiently investigated to allow conclusions to be drawn.

Schultz and colleagues[443] showed that IPC's reduction of infarct size was mediated by the δ_1-opioid receptor but not the δ_2-, µ-, or κ-opioid receptor. The effects of IPC were blunted by the selective δ_1-opioid receptor antagonist 7-benzylidenenaltrexone (BNTX) but not the δ_2-opioid receptor antagonist naltriben. They also showed that cardioprotection was not induced by the administration of the selective µ-opioid receptor agonist [D-Ala2, *N*-methyl-Phe4, Gly5-ol]enkephalin (DAMGO) and that PC was not attenuated by the µ-opioid receptor antagonist β-funaltrexamine (β-FNA).[443] In the same study, they excluded involvement of the κ-opioid receptor because a κ-selective antagonist could not reverse the effects of IPC to reduce infarct size. These data suggest that the δ_1-opioid receptor is the primary opioid receptor involved in IPC in the intact rat heart.

Although exogenous activation of the δ-opioid receptor subtype by highly specific agonists before ischemia reduces infarct size in several species, including rats,[443] rabbits,[444] and swine,[445] the role of κ-opioid receptors in preconditioning has been a subject of much controversy. Cao and associates[446,447] found that the cardioprotective effects caused by κ-opioid receptor stimulation were abolished with a calcium-activated potassium channel (K_{Ca}) blocker. This is consistent with reports that the protective effects of the κ-opioid receptor are mediated through a K_{Ca} channel pathway as seen in IPC.[446,447]

Preischemic administration of selective κ-opioid receptor agonists can reduce infarct size and ischemia-induced arrhythmias in the isolated rat heart. Conversely, specific activation of the κ-opioid receptor before ischemia can increase infarct size[427] and arrhythmias[448] and induce an antipreconditioning-like state in rats. It has been proposed that the κ-opioid receptor agonists exert a biphasic effect on the myocardium, producing proarrhythmic and antiarrhythmic effects in the rat.[393] It is unclear whether selective or nonselective activation of the κ-opioid receptor subtype is beneficial during preconditioning, and although conflicting information exists for the rat, the role of opioid receptor subtypes in IPC and pharmacologic preconditioning in other species is even more limited. Further studies are needed to address the role of the κ-opioid receptor in arrhythmias.

Signaling Pathways Involved in Opioid-Induced Cardioprotection

Opioid-induced cardioprotection and IPC appear to share a common pathway. The δ-opioid receptor and the mitochondrial K^+_{ATP} channel appear to be involved in the beneficial effects observed. Additional studies show that the cardioprotective effect of IPC and δ_1-opioid receptor activation are mediated through a G_i-protein–coupled receptor and may involve NO.[443,449,450] G-protein–coupled receptors have an established role in the attenuation of ischemia-reperfusion injury, mainly by activation of κ- and δ-opioid receptors.[451,452] The mechanisms underlying this effect include apoptotic pathways and restriction of internucleosomal DNA fragmentation.[453]

While investigating signaling pathways involved in opioid-induced protection, it was observed that morphine produced a cardioprotective effect in isolated rabbit hearts that was blocked by pretreatment with a nonselective PKC inhibitor. Jang and coworkers[449] demonstrated the activation of δ-opioid receptors and their role in postconditioning. This effect occurs by modulation of the MPTP and signaling through an NO- and PKC-mediated pathway (Fig. 10.37). The beneficial effects were eliminated by a G_i-protein inhibitor, a PKC inhibitor,[437,441,454,455] and a selective mitochondrial K^+_{ATP} channel blocker.[436,441,454,456,457] Studies also have demonstrated the role of inducible nitric oxide synthase (iNOS) as an upstream mediator of cyclooxygenase 2 (COX2). In iNOS gene *(NOS2)* knockout mice, morphine-mediated cardioprotection is attenuated, and some reports suggest iNOS and COX2 are required only during the mediation phase and not in the trigger phase.[458,459] Fig. 10.38 is a schematic summary of the major pathways involved in acute opioid-induced cardioprotection.

Role of Opioids in Delayed Preconditioning

It appears that opioid receptors are involved in delayed cardioprotection through activation of the δ- and κ-opioid receptors. Fryer and colleagues[460] demonstrated that TAN-67, a δ_1-opioid agonist, also induced cardioprotection during the second window of IPC. They found no protective effect to reduce infarct size 12 hours after administration of the selective δ_1-opioid receptor agonist, but it produced a marked cardioprotective effect at 24 to 48 hours after drug administration, which disappeared at 72 hours (Fig. 10.39). The cardioprotective effects were blocked by pretreatment with a selective δ_1-opioid receptor antagonist, a nonselective K^+_{ATP} channel antagonist, and a mitochondrial-selective K^+_{ATP} channel blocker. These results suggest that δ_1-opioid receptor

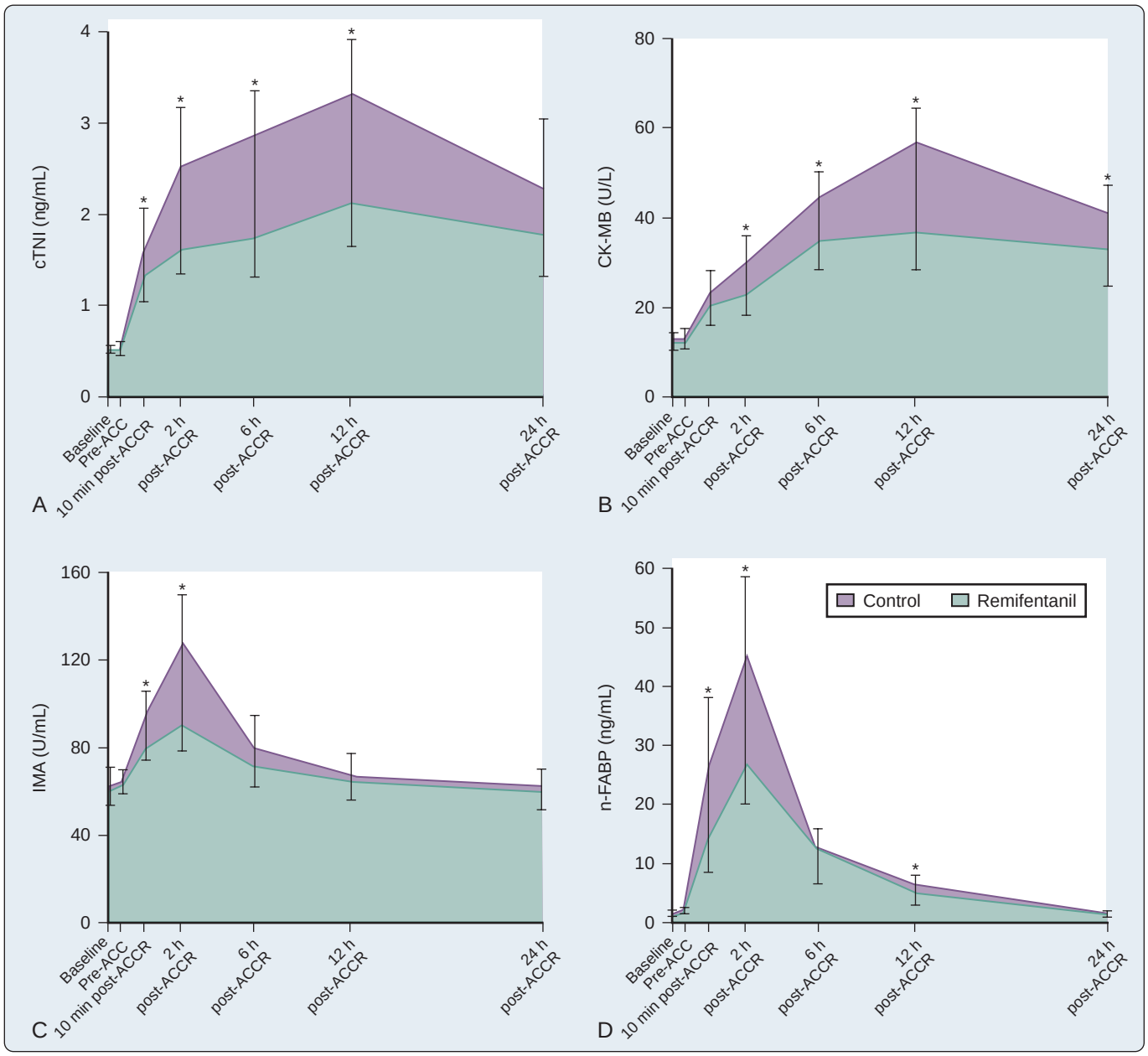


Fig. 10.36 Blood levels of biochemical markers over time. (A) Cardiac troponin 1 *(cTNI)*. (B) Creatinine kinase-MB fraction *(CK-MB)*. (C) Ischemia-modified albumin *(IMA)*. (D) Heart-type fatty acid bonding protein *(n-FABP)*. Values are plotted as medians (*error bars* indicate the interquartile range); *$P < .05$. *ACCR*, Aortic cross-clamp release; *post-ACC*, period after aortic cross-clamp was applied; *pre-ACC*, period before aortic cross-clamp was applied. *(From Wong GT, Huang Z, Ji S, et al. Remifentanil reduces the release of biochemical markers of myocardial damage after coronary artery bypass surgery: a randomized trial.* J Cardiothorac Vasc Anesth. *2010;24:790–796.)*

activation 24 to 48 hours before an ischemic insult results in a delayed cardioprotective effect that appears to be mediated by the mitochondrial K^+_{ATP} channel.

Wu and colleagues[461] demonstrated that κ-opioid receptor–induced cardioprotection occurred in two phases. The first window occurred about 1 hour after receptor activation, and the second developed 16 to 20 hours after administration in isolated ventricular myocytes.

Opioids and Cardioprotection in Humans

Although the animal and cell work reviewed imply a cardioprotective effect by opioid receptor activation, it is important to demonstrate that a similar system exists in humans and whether the studies can be extrapolated to the clinical world. Tomai and associates[462] demonstrated that naloxone abolished the reduction in ST-segment elevation normally observed during a second balloon inflation during coronary angioplasty. In naloxone-treated patients, the severity of cardiac pain and time to onset at the end of the second balloon inflation were similar to those of the first inflation, whereas in the placebo-treated patients, the severity of cardiac pain during the second inflation was reduced, and the time to onset of pain was lengthened compared with the first inflation. The findings suggest a preconditioning-like effect in humans undergoing coronary angioplasty that may be attenuated by the opioid antagonist naloxone.

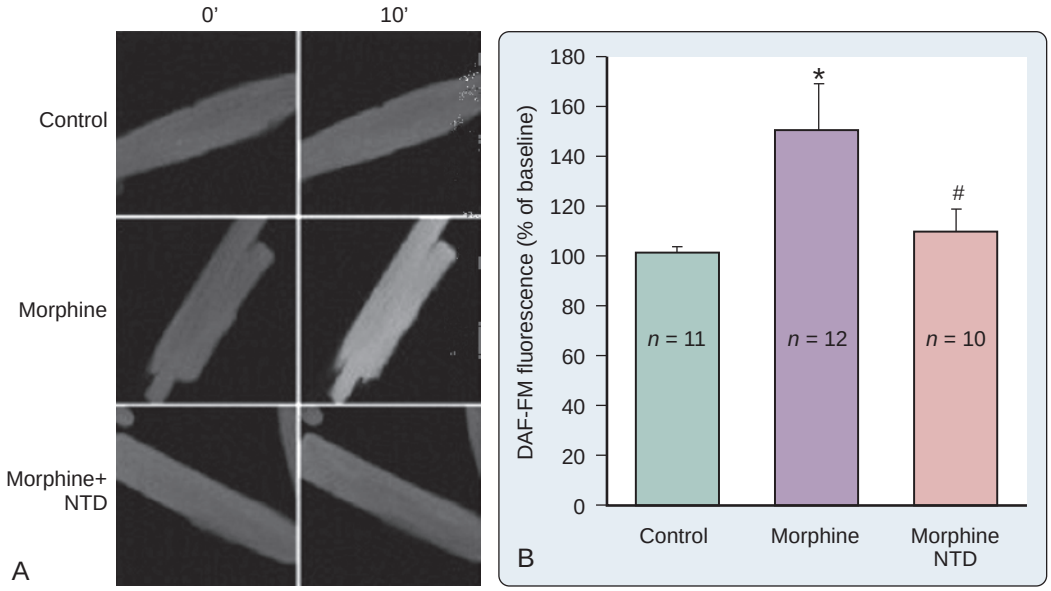


Fig. 10.37 (A) Confocal fluorescence images of 4-amino-5-methylamino-2′,7′-difluorofluorescein diacetate *(DAF-FM)* at baseline and 10 minutes after exposure to morphine in rat cardiomyocytes. Morphine (1 μm) increased nitric oxide production in cardiomyocytes, which was blocked by naltrindole (*NTD*, 5 μm). (B) Summarized data for DAF-FM fluorescence intensity 10 minutes after exposure to morphine are expressed as a percentage of the baseline. *$P < .05$ versus control; #$P < .05$ versus morphine. *(From Jang Y, Xi J, Wang H, et al. Postconditioning prevents reperfusion injury by activating delta-opioid receptors.* Anesthesiology. *2008;108:243–250.)*

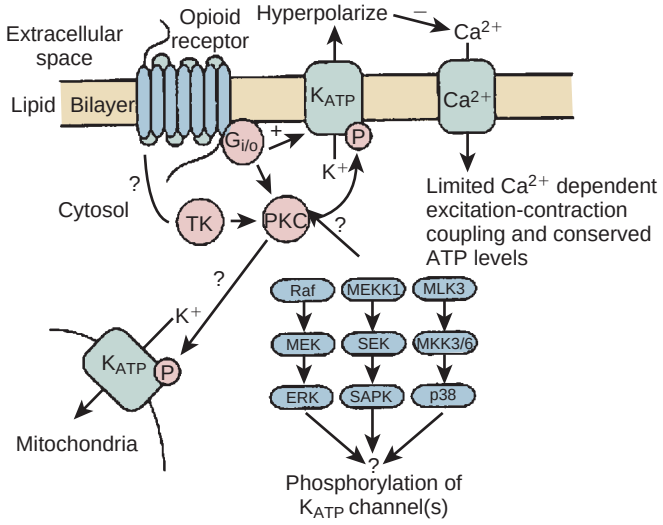


Fig. 10.38 Schematic diagram of major pathways thought to be involved in acute opioid-induced cardioprotection. Signaling cascades that involve mitogen-activated protein kinases (eg, *MEKK1, MLK3, ERK*) are shown. *G*, G protein; *PKC*, protein kinase C; *TK*, tyrosine kinase. *(From Schultz J, Gross GJ. Opioids and cardiac protection.* Pharmacol Ther. *2001;89:123–137.)*

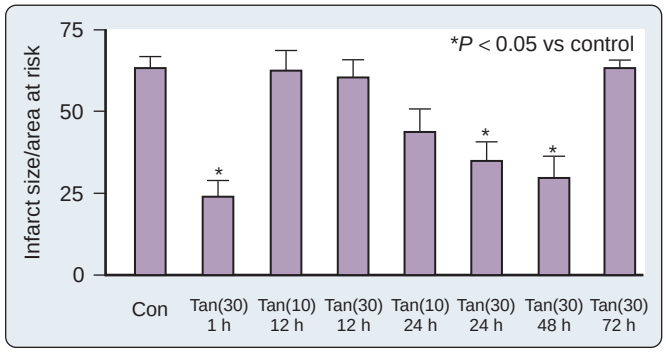


Fig. 10.39 Infarct size is expressed as a percentage of the area at risk in rats administered 10 or 30 mg/kg of TAN-67 1, 12, 24, 48, or 72 hours before 30 minutes of ischemia and 2 hours of reperfusion. A 1-hour pretreatment with TAN-67 produced a significant reduction in infarct size or area at risk. Pretreatment with both doses of TAN-67 12 hours before ischemia and reperfusion or low-dose TAN-67 24 hours before ischemia and reperfusion had no significant effect on infarct size or area at risk. However, pretreatment with the large dose of TAN-67 24 to 48 hours before ischemia and reperfusion significantly reduced the infarct size or area at risk. This cardioprotective effect was lost after 72 hours of pretreatment. All values are the mean ± standard error of the mean. *(From Fryer RM, Hsu AK, Ells JT, et al. Opioid-induced second window of cardioprotection. Potential role of mitochondrial KATP channels.* Circ Res. *1999;84:846.)*

Xenopoulos and coworkers[463] similarly showed that intracoronary morphine (15 μg/kg) mimics IPC as assessed by changes in ST-segment shifts in humans undergoing percutaneous transluminal coronary angioplasty. Bell and colleagues[456] demonstrated that δ-opioid receptor stimulation mimics IPC in human atrial trabeculae by K^+_{ATP} channel activation. These results are encouraging and suggest a possible clinical use for opioids in the therapy of acute or chronic myocardial ischemia.[456]

Cardioplegia and hypothermia provide considerable myocardial protection against the induced ischemia of cardiac surgery. However, in certain high-risk subgroups and to some extent in all patients, current methods of cardioprotection are still suboptimal, and there continues to be poor myocardial tolerance to ischemia. Myocardial ischemia often is evidenced by perioperative ventricular dysfunction, myocardial stunning, and poor functional recovery after an ischemic episode, which may lead to a poor surgical outcome (see Chapters 36 and 38). Postsurgical myocardial ischemic changes include hypothermia, intracellular acidosis, hypoxia, depletion of energy stores, and cellular volume shifts, all of which adversely affect myocardial

contractility. Hibernating animals demonstrate cellular and molecular cardiac changes during hibernation that closely parallel those seen in hypothermic cardioplegic arrest. However, the changes are well tolerated in the myocardium of the hibernating mammals for months at a time, whereas the duration of induced ischemia tolerated surgically is limited. This process is induced by a hibernation-induction trigger molecule, which has an opioid basis.[464] Opioid peptides can induce mammalian hibernation and may provide protection against the adverse effects of hypothermic myocardial ischemia, providing potential therapeutic applications during CPB and protection of organs for heart transplantation.

Bolling and associates[465,466] showed in animal studies the δ-opioid receptor agonist [D-Ala2, D-Leu5]enkephalin (DADLE) protected hearts that were subjected to 18 hours of cold storage at 4°C or 2 hours of global ischemia in the presence of a standard cardioplegic solution. Another study[467] provided evidence that pentazocine, a δ-opioid agonist, enhanced the myocardial protection of standard cardioplegia at temperatures ranging from 0°C to 34°C. Subsequently, Kevelaitis and colleagues[468] showed that stimulation of δ-opioid receptors improved recovery of cold-stored rat hearts to a state similar to IPC. The investigators showed that opioid-induced cardioprotection was mediated through K^+_{ATP} channel activation.[468]

Although the initial success of cardiopulmonary resuscitation (CPR) is on average 39% (range, 13% to 59%), most victims die within 72 hours, primarily because of heart failure or recurrent ventricular fibrillation, or both. CPR therefore yields a functional survival rate of only 1.4% to 5%.[469–471] Myocardial function is substantially impaired after successful resuscitation from cardiac arrest, prompting investigation of the use of opioid-receptor agonists to improve functional outcome. Fang and colleagues[472] demonstrated that pharmacologic activation of δ-opioid receptors significantly reduced $M\dot{V}o_2$ during the global myocardial ischemia of cardiac arrest. A follow-up study in rats demonstrated that the nonselective δ-opioid receptor agonist pentazocine strikingly reduced the severity of postresuscitation myocardial dysfunction and increased the duration of postresuscitation survival.[472]

Opioid analgesics are used widely for the treatment of pain. Although these agents are predominantly agonists of μ-opioid receptors, crosstalk with δ-opioid receptors has been demonstrated. However, the US Food and Drug Administration has not approved these drugs for use in patients with unstable angina or who are predisposed to myocardial infarction, probably due to the limited research in humans on the importance of opioid receptors in the myocardium and the high potential for dependence, abuse, and respiratory depression. Future avenues of research should focus on the identification of orally active compounds with high affinity for δ-opioid receptors to be used as cardioprotective agents because these drugs are currently lacking.

Opioids in Cardiac Anesthesia

A technique of anesthesia for cardiac surgery involving high doses of morphine was developed in the late 1960s and early 1970s. The technique was based on the observation by Lowenstein and colleagues[473] that patients requiring mechanical ventilation after surgery for end-stage VHD tolerated large doses of morphine for sedation without discernible circulatory effects. When they attempted to administer equivalent doses of morphine as the anesthetic for patients undergoing cardiac surgery, they discovered serious disadvantages, including inadequate anesthesia (even at doses of 8 to 11 mg/kg), episodes of hypotension related to histamine release, and increased intraoperative and postoperative blood and fluid requirements. Attempts to overcome these problems by combining lower doses of morphine with a variety of supplements (eg, N_2O, halothane, diazepam) proved unsatisfactory, resulting in significant myocardial depression, with decreases in CO and hypotension.[474]

However, Murphy and coworkers[475] demonstrated that morphine resulted in better myocardial function after CABG surgery than using fentanyl. For the protective effects mediated by IPC, it appears that morphine may have some benefit over fentanyl,[475] but the use of morphine has to be weighed against the multitude of other deleterious effects during the management of cardiac surgical patients.

Because of the problems associated with the use of morphine, other opioids were investigated in an attempt to find a suitable alternative. The use of fentanyl in cardiac anesthesia was first reported by Stanley and Webster in 1978.[476] Since then, there have been extensive investigations of fentanyl, sufentanil, and alfentanil in cardiac surgery. The fentanyl group of opioids has proved to be the most reliable and effective for producing anesthesia for patients with valvular disorders and CABG (see Chapters 20 and 21).

A major advantage of fentanyl and its analogues for patients undergoing cardiac surgery is their lack of cardiovascular depression, which is important during anesthesia induction, when episodes of hypotension can be critical. Cardiovascular stability may be less evident during surgery; in particular, the period of sternotomy, pericardiectomy, and aortic root dissection may be associated with significant hypertension and tachycardia. During and after sternotomy, arterial hypertension increases in SVR and decreases in CO frequently occur.[477,478] Variability in hemodynamic responses to surgical stimulation, even with similar doses of fentanyl, probably reflects differences in the patient populations studied by different investigators. One factor is the influence of β-blocking agents. In patients anesthetized with fentanyl while undergoing CABG, 86% of those not taking β-blockers became hypertensive during sternal spread compared with only 33% of those who were taking β-blockers.[479]

The opioids may produce different degrees of hemodynamic stability during surgery. One study concluded that fentanyl and sufentanil provided similar hemodynamic stability during induction, whereas alfentanil caused hemodynamic instability and myocardial ischemia.[480] Alfentanil also may be less effective in suppressing reflex sympathetic and hemodynamic responses to stimuli than fentanyl or sufentanil.[481] In patients undergoing valvular surgery, all three opioids provided satisfactory anesthesia.[482] However, controversy still surrounds the best choice of anesthetic, at least for CABG. Two studies involving more than 2000 patients anesthetized with inhalation agents (ie, fentanyl or sufentanil) came to the conclusion that the choice of anesthetic did not significantly influence the outcome after CABG, although the type of anesthetic continues to remain a topic of controversy with respect to postoperative outcomes.[121–123,483,484]

The degree of myocardial impairment influences the response. Critically ill patients or patients with significant myocardial dysfunction appear to require lower doses of opioid for anesthesia. This may reflect altered pharmacokinetics in the patients. A decrease in liver blood flow resulting from decreased CO and CHF reduces plasma clearance. Patients with poor left ventricular function may develop greater plasma and brain concentrations for a given loading dose or infusion rate than patients with good left ventricular function. Patients with depressed myocardial function may lack the ability to respond to surgical stress by increasing CO in the face of progressive increases in SVR.[485]

An infusion of alfentanil (125-μg/kg bolus followed by 0.5 mg/kg per hour) has been compared with fentanyl (100 μg/kg) or sufentanil (20 μg/kg) by bolus injection as the sole anesthetic for patients undergoing valvular surgery.[482] No differences in hemodynamic effects were found in the study, and it was concluded that all three opioids could provide satisfactory anesthesia for valve replacement surgery (see Chapter 19).

Sufentanil appears to offer more stable anesthesia with less hemodynamic disturbance than fentanyl,[486] and it has been used successfully for cardiac transplantation.[487,488] In patients undergoing mitral or aortic valve surgery, sufentanil (total dose, 9.0 ± 0.4 μg/kg) resulted in less need for supplements and vasodilators than fentanyl (113 ± 11 μg/kg), but sufentanil produced more hypotension during induction.[489] Howie and associates[490] compared a fentanyl/isoflurane/propofol regimen with remifentanil/isoflurane/propofol for fast-track anesthesia. Significantly more patients in the fentanyl regimen experienced hypertension during skin incision and maximal sternal spread compared with patients in the remifentanil regimen. There was no

difference between the groups in time to extubation, discharge from the intensive care unit, electrocardiographic changes, catecholamine levels, or cardiac enzymes. The remifentanil-based anesthetic (ie, bolus followed by continuous infusion) resulted in less need for anesthetic interventions compared with the fentanyl regimen.[490]

Samuelson and colleagues[491] compared hemodynamic and stress responses in patients with CAD anesthetized with sufentanil/oxygen or enflurane/nitrous oxide and oxygen. Both techniques were satisfactory and resulted in stable hemodynamics, but considerable fine-tuning was required when enflurane was administered. The postoperative hemodynamic effects were compared in patients who received sufentanil (25 µg/kg) or fentanyl (100 µg/kg) for anesthesia for CABG.[492] Patients who received sufentanil had a more stable course, with higher CO, lower SVR, and a lower incidence of hypertension. The two groups had similar values for time to awakening, response to verbal commands, and extubation.

Collard and coworkers[493] compared the intraoperative hemodynamic profiles and recovery characteristics of propofol/alfentanil with those of fentanyl/midazolam in elective coronary artery surgery. Cardiovascular parameters and time to extubation were recorded. Throughout surgery, hemodynamic profiles were comparable between groups except after intubation, when the MAP was significantly lower in the propofol/alfentanil group. This group also required less inotropic support, and extubation was performed earlier.

Murphy and associates[494] compared the long-acting opioid methadone with fentanyl in a randomized, double-blind clinical trial and showed improved pain scores, decreased morphine requirements, and enhanced patient-perceived quality of pain management with methadone. Previous studies in rats have shown methadone to have myocardial protective effects similar to morphine.[495] With increased emphasis on patient satisfaction, more frequent use of methadone in cardiac surgery is possible.

Effects of Cardiopulmonary Bypass on Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of drugs in cardiac anesthesia is well covered by Wood.[496] This section focuses on the effects of CPB on pharmacokinetics as the most relevant area for the cardiac anesthesiologist.

Institution of CPB has profound effects on the plasma concentration, distribution, and elimination of administered drugs. The major factors responsible are hemodilution and altered plasma protein binding, hypotension, hypothermia, pulsatile versus nonpulsatile flow, isolation of the lungs from the circulation, and uptake of anesthetic drugs by the bypass circuit. These changes result in altered blood concentrations, which also depend on the particular pharmacokinetics of the drug administered (Table 10.6).

TABLE 10.6 Effects of Cardiopulmonary Bypass on Drug Disposition

Pharmacokinetic Process	*Pathophysiology*	*Pharmacokinetic Sequelae*
Absorption	Hypotension and alterations in regional blood flow or perfusion	Reduced oral or intramuscular absorption
Distribution	Lung sequestration	Decreased volume of distribution
	Decreased pulmonary blood flow	Decreased pulmonary drug distribution and increased systemic drug levels
	Hypotension, altered regional blood flow	Decreased volume of distribution
	Decreased protein binding	Increased volume of distribution
	Hemodilution Dilution of binding proteins	
	Postoperative increased α_1-acid glycoprotein	Decreased volume of distribution
	Postoperative increased protein binding	Interpretation of postoperative drug levels difficult
Elimination	Decreased hepatic blood flow	Decreased drug clearance
	Hypothermia	Decreased intrinsic clearance (decreased hepatic metabolism)
	Decreased renal blood flow and hypothermia	Decreased renal function

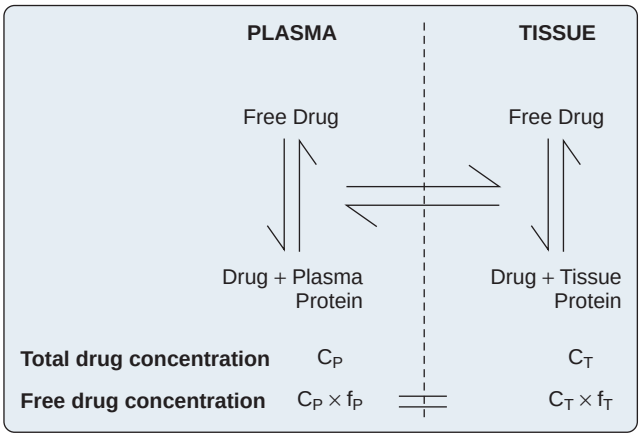


Fig. 10.40 Relationship between free drug concentration in plasma and tissue. The free concentration in plasma equals the total concentration (C_P) × the free fraction in plasma (f_P). The free concentration in tissue equals the total concentration in tissue (C_T) × the free fraction in tissue (f_t).

Hemodilution

At the onset of CPB, the circuit priming fluid is mixed with the patient's blood. In adults, the priming volume is 1.5 to 2 L, and the prime may be crystalloid or crystalloid combined with blood or colloid. The overall result is a reduction in the patient's hematocrit to approximately 25% with an increase in plasma volume of 40% to 50%. This decreases the total blood concentration of any free drug in the blood. When CPB is initiated, there is an immediate reduction in the levels of circulating proteins such as albumin and α_1-acid glycoprotein. This affects the protein binding of drugs because of alteration in the ratio of bound-to-free drug in the circulation. Introduction of retrograde autologous priming and low-volume CPB circuits has decreased these effects.

In the blood, free (ie, unbound) drug exists in equilibrium with bound (ie, bound to plasma proteins) drug. The free drug interacts with the receptor to produce the drug effect (Fig. 10.40). Drugs primarily are bound to the plasma protein albumin and α_1-acid glycoprotein. Changes in protein binding are of clinical significance only for drugs that are highly protein bound. The degree of drug-protein binding depends on the total drug concentration, the affinity of the protein for the drug, and other substances that may compete with the drug or alter the drug's binding site. If the drug has a high degree of plasma protein binding, hemodilution results in a relatively larger increase in the free fraction than for a drug with a low affinity for plasma protein binding.

The effect of heparin administration on plasma protein binding is important. Heparin results in lipoprotein lipase and hepatic lipase release, which hydrolyzes plasma triglycerides into nonesterified fatty acids. They can bind competitively to plasma proteins and result in displacement of bound drug, increasing the concentration of the unbound fraction.[496]

The consequences of acute hemodilution by the pump prime on drug disposition can be summarized as follows:

1. Because plasma drug concentration is reduced without any change in the amount of drug in the body, the apparent V_d increases acutely but by a relatively small amount.
2. After acute hemodilution, drug redistribution from tissues may occur to bring free drug concentrations in plasma and tissues back into equilibrium. The magnitude of this flux of drug depends on the relative amounts in tissues and plasma and on the degree of protein binding change.
3. Focus on total drug concentration of the free fraction and free concentration change may give misleading information on the expected change in the drug effect.
4. For drugs whose plasma and red cell partitioning is not equal, blood and plasma clearance no longer bears the same relation to each other after hemodilution and must be distinguished.
5. Heparin has an effect on the measurement of drug protein binding.

There may be marked changes in acid-base balance during CPB, resulting in changes in ionized and unionized drug concentrations, which affect drug binding. CPB may be conducted using pH-stat or alpha-stat blood gas management. The change in pH with either management scheme may affect organ blood flow.[497,498] pH management may affect the degree of ionization and protein binding of certain drugs, leading to increased or decreased free (active) drug concentrations.

Blood Flow

Hepatic, renal, cerebral, and skeletal perfusion is reduced during CPB, and the use of vasodilators and vasoconstrictor agents to regulate arterial pressure may further change regional blood flow. Alterations in regional blood flow distribution have implications for drug distribution and metabolism. The combination of hypotension, hypothermia, and nonpulsatile blood flow significantly affects distribution of the circulation, with a marked reduction in peripheral flow and relative preservation of the central circulation.[499,500]

CPB may be conducted with or without pulsatile perfusion. Nonpulsatile perfusion is associated with altered tissue perfusion.[501] Nonpulsatile flow and decreased peripheral perfusion from CPB, hypothermia, and administration of vasoconstrictors may result in cellular hypoxia and probable intracellular acidosis. This may affect the tissue distribution of drugs whose tissue binding is sensitive to pH. On reperfusion, rewarming, and reestablishment of normal cardiac (pulsatile) function, redistribution of drugs from poorly perfused tissue is likely to add to the systemic plasma concentration because basic drugs have been trapped in acidic tissue. The degree to which pulsatile perfusion altars drug pharmacokinetics is not well studied.

Hypothermia

Hypothermia commonly is used and can reduce hepatic and possibly renal enzyme function.[502] Hypothermia depresses metabolism by inhibiting enzyme function and reduces tissue perfusion by increasing blood viscosity and activation of autonomic and endocrine reflexes to produce vasoconstriction. Hepatic enzymatic activity is decreased during hypothermia, and there is marked intrahepatic redistribution of blood flow with the development of significant intrahepatic shunting. Hypothermia reduces metabolic drug clearance and has been shown to reduce the metabolism of propranolol and verapamil.

Altered renal drug excretion occurs as a result of decreased renal perfusion, glomerular filtration rate, and tubular secretion. In dogs, glomerular filtration rate is decreased by 65% at 25°C.[503]

Sequestration

When normothermia is reestablished, reperfusion of tissue may lead to washout of drug sequestered during the hypothermic CPB period, which may explain the increase in opioid plasma levels during the rewarming period.[504–506]

Many drugs bind to components of the CPB circuit, and their distribution may be affected by changes in circuit design, such as the use of oxygenators (ie, gas exchange devices) from different manufacturers. In vitro, various oxygenators bind lipophilic agents such as volatile anesthetic agents, propofol, opioids, and barbiturates[498,507–511] This phenomenon has never been demonstrated to be important in vivo, likely because any drug removed by the circuit is replaced from the much larger tissue reservoir.

During CPB, the lungs are isolated from the circulation with the pulmonary artery blood flow being interrupted. Basic drugs (eg, lidocaine, propranolol, fentanyl) that are taken up by the lungs are sequestered during CPB, and the lungs can serve as a reservoir for drug release when systemic reperfusion is established.[504] After the onset of CPB, plasma fentanyl concentrations decrease acutely and then plateau. However, when mechanical ventilation of the lungs is instituted before separation from CPB, plasma fentanyl concentrations increase. During CPB, pulmonary artery fentanyl concentrations exceed radial artery levels, but when mechanical ventilation resumes, the pulmonary artery-to-radial ratio is reversed, suggesting that fentanyl is being washed out from the lungs.

Specific Agents

Opioids

The total drug concentration of all opioids decreases on commencing CPB (Table 10.7). The degree of decrease is greater with fentanyl, because a significant proportion of the drug adheres to the surface of the CPB circuit.[408,509,512] Inadequate anesthesia has been described when fentanyl was used as the major anesthetic agent.[513] There is high first-pass uptake of fentanyl by the lungs,[500,514] and reperfusion of the lungs at the end of CPB results in increased fentanyl concentrations (Figs. 10.41 and 10.42).

Total drug concentration is decreased least with opioids that have a high V_d, when the addition of the prime volume is less important, and for drugs that can equilibrate rapidly to minimize the dilutional effect. In this respect, sufentanil, which has the most stable total drug concentrations, may offer advantages. Free alfentanil concentrations remain relatively stable throughout CPB, and the pharmacologically active concentrations remain unchanged. The bound concentration changes, reflecting concentration changes in albumin and α_1-acid glycoprotein, to which alfentanil is predominantly bound.[515–517] Elimination of fentanyl and alfentanil was prolonged by CPB, whereas that of morphine was unchanged. Data on the elimination of sufentanil after

TABLE 10.7 Effect of Cardiopulmonary Bypass on Opioid Disposition

	Concentration				
Opioid	*Start of CPB*	*During CPB*	*Clearance*	*Half-Life*	*Volume of Distribution*
Fentanyl	Decreased	Relatively stable or increased near end of CPB	—	Increased	—
Alfentanil	Decreased total alfentanil concentration; no change in free concentration	Gradual increase in total concentration near end of CPB	Unchanged	Increased	Increased
Sufentanil	Decreased	Gradual increase	—	—	—

CPB, Cardiopulmonary bypass.
Data from Buylaert WA, Herregods LL, Mortier EP, Bogaert MG. Cardiopulmonary bypass and the pharmacokinetics of drugs, *Clin Pharmacokinet.* 1989;17:10.

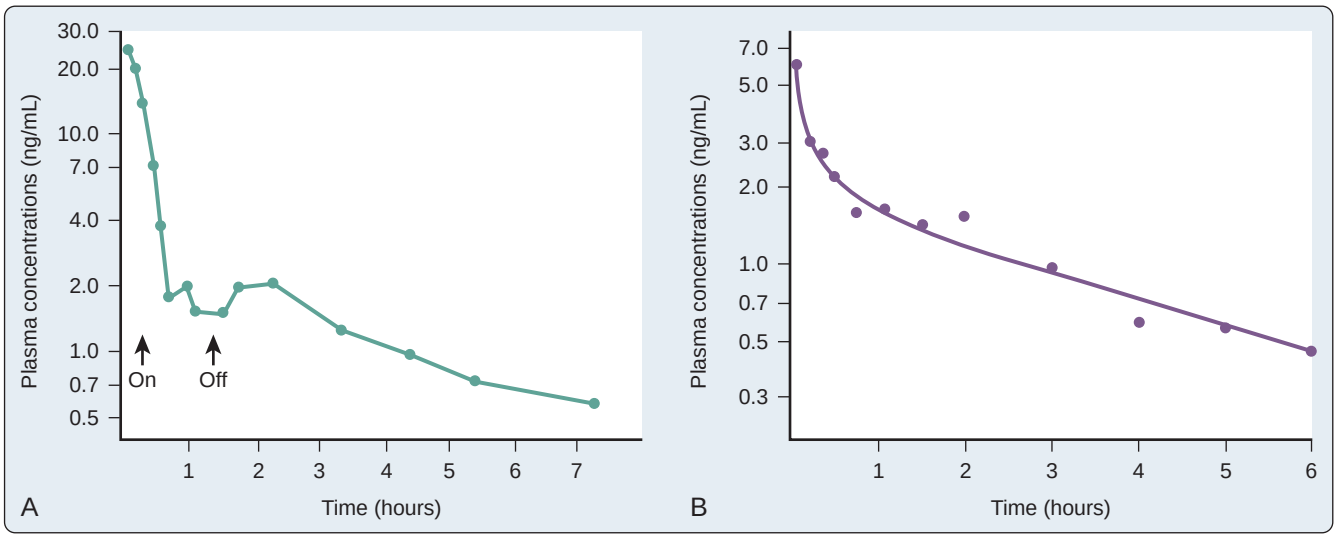


Fig. 10.41 Effect of cardiopulmonary bypass (CPB) on the disposition of a single bolus injection of fentanyl. The time course of plasma fentanyl concentrations is shown after injection of a 500-µg intravenous bolus at time zero. (A) Data from a cardiac surgery patient. Times of CPB are indicated by *arrows*. (B) Data from a vascular surgery control patient. *(From Koska AJ, Romagnole A, Karmer WG. Effect of cardiopulmonary bypass on fentanyl distribution and elimination.* Clin Pharmacol Ther. *29:100, 1981.)*

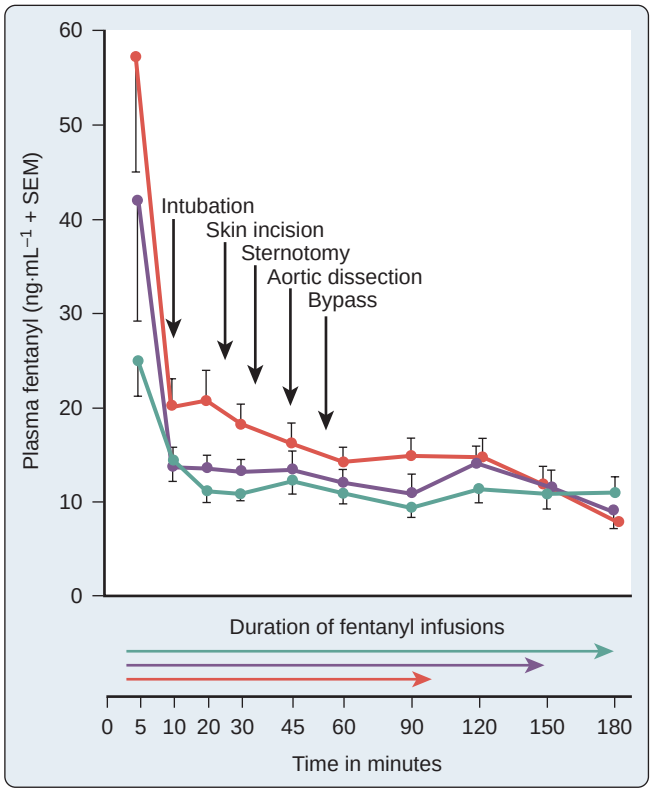


Fig. 10.42 Effect of cardiopulmonary bypass (CPB) on plasma fentanyl concentrations when fentanyl is administered at various constant-rate infusions for aortocoronary surgery. Plasma fentanyl concentrations and durations of fentanyl infusion are shown for three groups of patients: those given 30 µg/kg followed by 0.3 µg/kg per minute *(green)*; those given 40 µg/kg followed by 0.4 µg/kg/min *(purple)*; and those given 50 µg/kg followed by 0.5 µg/kg/min *(red)*. *SEM*, Standard error of the mean. *(From Sprigge JS, Wynands JE, Whalley DG, et al. Fentanyl infusion anesthesia for aortocoronary bypass surgery: plasma levels and hemodynamic response.* Anesth Analg. *1982;61:972.)*

CPB are inadequate. Based on the available pharmacokinetic information, alfentanil may be the most suitable opioid for CPB because free concentrations are stable during CPB and its half-life is much less prolonged than that of fentanyl.

Benzodiazepines

The total concentration of benzodiazepines decreases on commencing CPB. Because the drugs are more than 90% protein bound, changes in free concentrations are greatly influenced by changes in protein concentrations or factors such as acid-base balance that influence protein binding. This is particularly pertinent in the context of CPB, but no studies have commented on free versus total concentrations of benzodiazepines.

Diazepam has a very long elimination half-life, even in non-CPB patients, and it is cumulative after CPB.[518] Midazolam has a shorter elimination half-life. It increases with age and is significantly longer for CPB patients than for patients undergoing other types of major surgery (Fig. 10.43). The elimination half-life is prolonged in 6% of patients.[519,520] However, the half-life of midazolam is shorter than that of the other benzodiazepines; and in small doses, elimination is rapid in most patients. It is the suitable benzodiazepine for use by repeated boluses or infusion. The elimination half-life of lorazepam is unchanged by CPB but is longer than that of midazolam.

Intravenous Anesthetic Agents

Total drug concentrations of thiopental and methohexital decrease on commencing CPB, but the active free concentrations are remarkably stable[516,521] (Fig. 10.44). Clearance of thiopental is halved during CPB, but its elimination half-life after CPB is unknown. Elimination of methohexital remains unchanged after CPB. Conflicting results have been obtained for propofol[522,523] (Fig. 10.45). The total concentration of propofol may decrease on commencing CPB with an increase in the free fraction, or the total concentration may remain unchanged. A prolonged elimination half-life was demonstrated in one study,[522] but the redistribution half-life was short, concentrations decreased rapidly after stopping the drug, and patients made a rapid recovery. The free active concentrations of these drugs usually remain unchanged, but their actions may be prolonged.

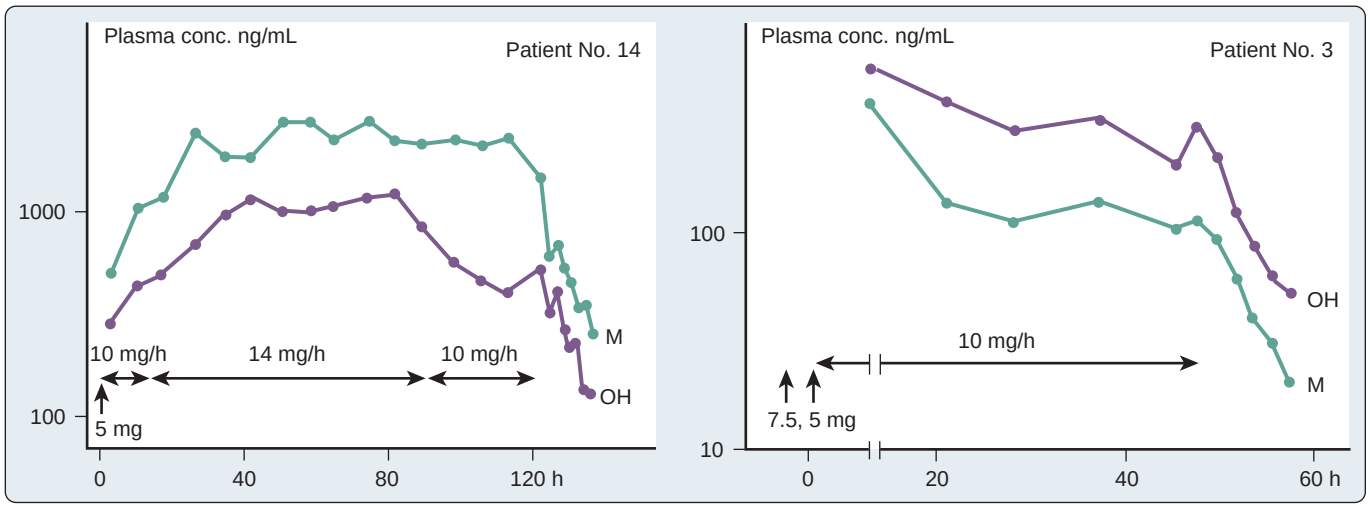


Fig. 10.43 Variations of concentrations of midazolam and its metabolite in the intensive care unit. Notice the difference in the two scales for concentration for the panels. *Left,* Concentrations of midazolam *(M)* are slightly higher than those of its metabolite *(OH). Right,* Midazolam concentrations are lower than those of the metabolite. *(From Vree TB, Shimoda M, Driessen JJ, et al. Decreased plasma albumin concentration results in increased volume of distribution and increased elimination of midazolam in intensive care patients.* Clin Pharmacol Ther. *1989;46:537.)*

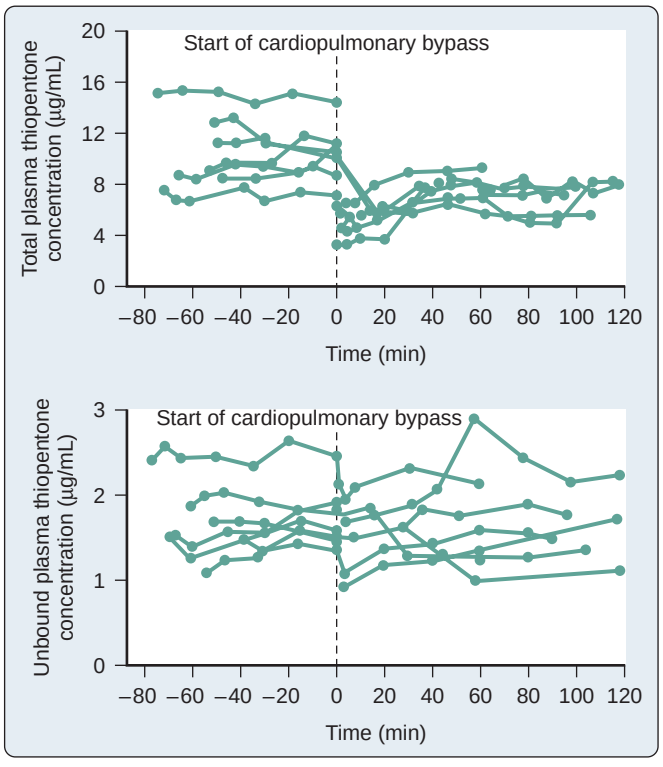


Fig. 10.44 Effect of cardiopulmonary bypass on plasma thiopental concentrations during continuous infusion. *Top,* Total plasma thiopental concentrations. *Bottom,* Unbound (free) plasma thiopental concentrations. The zero time point is considered the start of bypass. *(From Morgan DJ, Crankshaw DP, Prideaux PR, et al. Thiopentone levels during cardiopulmonary bypass: changes in plasma protein binding during continuous infusion.* Anaesthesia. *1986;41:4.)*

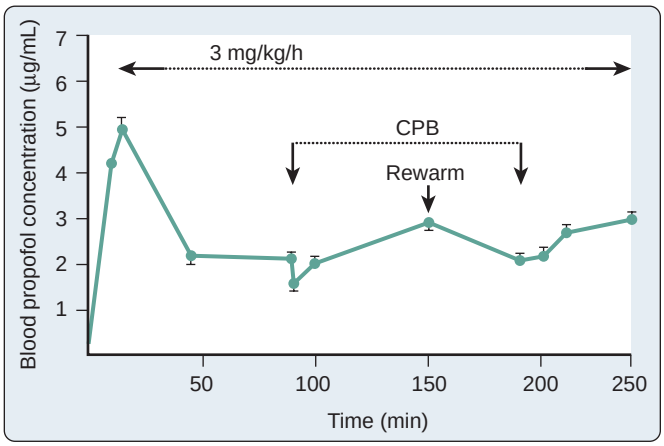


Fig. 10.45 Blood propofol concentrations during coronary artery surgery and cardiopulmonary bypass *(CPB).* A two-stage propofol infusion (10 mg/kg/h for 30 minutes followed by 3 mg/kg/h thereafter) was administered. Time scale shows the mean time taken to specific events such as the onset of CPB, induced hypothermia (25–27°C), and the end of bypass. *Bars* represent mean concentrations ± standard error of the mean. *(From Russell GN, Wright EL, Fox MA, et al. Propofol-fentanyl anaesthesia for coronary artery surgery and cardiopulmonary bypass.* Anaesthesia. *1989;44:205.)*

Volatile Anesthetic Agents

The effect of CPB on MAC remains uncertain. Some researchers have shown that CPB reduces the MAC of enflurane by as much as 30% in animal studies, whereas others have failed to demonstrate any reduction.[521–526] Several groups have shown variation in MAC with temperature and found reduced volatile concentrations were required at lower temperatures.[525,527–529]

The effect of CPB with cooling on the uptake of volatile anesthetics administered to the oxygenator depends on three factors: the blood/gas solubility of the agent and opposing effects of cooling in increasing blood/gas solubility of blood compared with hemodilution, which decreases the solubility of volatile anesthetics[530]; the increased solubility in tissue of volatile anesthetics due to hypothermia; and uptake by the oxygenator.[531] CPB produces changes in the blood/gas partition coefficient that depend on the prime used and the temperature. The coefficient is the ratio of the concentration of an inhaled anesthetic in blood to the concentration in gas that is in contact with the blood when the partial pressure in both compartments is equal.

Factors that alter the solubility of volatile anesthetics in blood and other tissues include lipid concentration, osmolarity, and hematocrit.

The changes in blood composition after the addition of a crystalloid prime tend to decrease blood solubility, favoring a more rapid attainment of steady state and a lower blood concentration of volatile agent for a given inspired concentration. However, hemodilution with a plasma prime increases solubility because volatile agents are more soluble in albumin than red blood cells.[532] Blood solubility also is inversely proportional to temperature. This relationship is linear but different for individual agents, with a range of 4% to 4.9% per 1°C decrease in body temperature.[533] Hemodilution with a crystalloid prime and hypothermia have opposite effects on the blood/gas partition coefficient. The predicted net change in solubility for isoflurane when the hematocrit is reduced from 40% to 20% and temperature is reduced from 37°C to 28°C is 2%.[534]

Volatile agents can bind to a variety of plastics,[535] which may account for some of the decrease in concentrations on commencing CPB. A volatile agent started during hypothermic CPB takes longer to equilibrate, and agents already in use need to equilibrate, potentially changing the depth of anesthesia, until equilibration is complete. Because these agents are metabolized to a small degree and washout is fast, the duration of action is not prolonged after CPB.[536,537]

Neuromuscular Blockers

CPB influences the concentrations and response relationships of neuromuscular blockers during hypothermia.[538] The requirements for neuromuscular blockade are significantly reduced as a result of several pharmacokinetic and pharmacodynamic effects. Cooling influences nerve conduction in the mobilization of acetylcholine from the nerve vesicles[539] and modifies cholinergic receptors. Cooling affects cholinesterase enzyme activity, which is temperature dependent. The most important effect of cooling is decreased mobilization of acetylcholine, which has been demonstrated in vitro and in animal models.[540,541] During hypothermia, less muscle relaxant is needed to obtain the same amount of muscle relaxation obtained in normothermic conditions. Cooling alters the mechanical properties of the muscle and has potentially significant effects on electrolytes, which modulate the contractile response.

CPB causes hemodilution, which may result in an initial decrease in the free drug concentration. The albumin concentration is also decreased during CPB, and although the total drug concentration may be decreased as a result of hemodilution, the free drug concentration may be increased if the drug is partially bound to albumin. This phenomenon may occur with neuromuscular blockers such as rocuronium.[542]

Hypothermia inhibits the hepatic clearance of steroidal neuromuscular blocking agents, although it seems to promote renal clearance. This may explain why the durations of action of steroidal neuromuscular blocking agents such as rocuronium and vecuronium, which depend on liver clearance, are more prolonged under hypothermic conditions than the durations of agents that depend on renal clearance (eg, pancuronium and pipecuronium).[543]

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11 Cardiovascular Pharmacology

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KEY POINTS

1. Ischemia during the perioperative period demands immediate attention by the anesthesiologist. The impact of ischemia may be acute (ie, impending infarction or hemodynamic compromise) and chronic (ie, marker of previously unknown cardiac disease or prognostic indicator of poor outcome).
2. Nitroglycerin is indicated in most cases of perioperative myocardial ischemia. Mechanisms of action include coronary vasodilation and favorable alterations in preload and afterload. Nitroglycerin is contraindicated in cases of hypotension.
3. Perioperative β-blockade may reduce the incidence of perioperative myocardial ischemia by several mechanisms when initiated at an appropriate time in the preoperative period. Favorable hemodynamic changes associated with β-blockade include blunting of the stress response and reduced heart rate, blood pressure, and contractility. All of these conditions improve myocardial oxygen supply-to-demand ratios.
4. Calcium channel blockers reduce myocardial oxygen demand by depression of contractility, reduction of heart rate, and decrease in arterial blood pressure. Calcium channel blockers are often administered in the perioperative period for long-term antianginal symptomatic control.
5. Current guidelines suggest seeking a target blood pressure of less than 150/90 mm Hg in patients 60 years of age or older to minimize the long-term risk of adverse cardiovascular morbidity and mortality.
6. For patients younger than 60 years age or those with diabetes or chronic kidney disease, blood pressures lower than 140/90 mm Hg are recommended.
7. Mild or moderate hypertension does not represent an independent risk factor for perioperative complications, but a diagnosis of hypertension necessitates preoperative assessment for target organ damage.
8. Patients with poorly controlled preoperative hypertension experience more labile blood pressures in the perioperative setting with a greater potential for hypertensive and hypotensive episodes.
9. The signs, symptoms, and treatment of chronic heart failure are related to the neurohormonal response and underlying ventricular dysfunction.
10. Treatments for chronic heart failure are aimed at prolonging survival, along with relief of symptoms.
11. The pathophysiology, treatment, and prognosis of low cardiac output syndrome seen after cardiac surgery are different from those of chronic heart failure, with which it is sometimes compared.
12. Physicians must be cautious in administering antiarrhythmic drugs because their proarrhythmic effects can increase mortality for certain subgroups of patients.
13. Amiodarone has become a popular intravenous antiarrhythmic drug for use in the operating room and critical care areas because it has a broad range of effects for ventricular and supraventricular arrhythmias.
14. β-Receptor antagonists are effective but underused antiarrhythmics in the perioperative period because many arrhythmias are adrenergically mediated due to the stress of surgery and critical illness.
15. Managing electrolyte abnormalities and treating underlying disease processes such as hypervolemia and myocardial ischemia are critical treatment steps before the administration of any antiarrhythmic agent.

Antiischemic Drug Therapy

Perioperative myocardial ischemia is an anesthetic emergency that should be treated promptly with appropriate therapy. The treatment of ischemia during anesthesia is complicated by the ongoing stress of surgery, blood loss, concurrent organ ischemia, and the patient's inability to interact with the anesthesiologist. Nonetheless, the fundamental principles of treatment remain the same as in the unanesthetized state.

All events of myocardial ischemia involve an alteration in the oxygen supply-to-demand balance (Table 11.1). The American College of Cardiology and American Heart Association (ACC/AHA) Guidelines on the Management and Treatment of Patients with Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction provide an excellent framework for the treatment of patients with ongoing myocardial ischemia.[1] The guidelines detail the initial evaluation, management, hospital care, and coronary revascularization strategies for the patient with an acute coronary syndrome. For the anesthetized patient with evidence of myocardial ischemia, initiation of antiischemic drug therapy is the primary intervention until definitive therapy, if needed, can be obtained. This section reviews the common agents used for this purpose (see Chapter 20).

Nitroglycerin

Nitroglycerin (NTG) is clinically indicated as initial therapy for most types of myocardial ischemia.[2] Chronic exertional angina, de novo angina, unstable angina, Prinzmetal angina (ie, vasospasm), and silent

ischemia respond to NTG administration.[2–6] NTG therapy decreases the incidence of anginal attacks and improves exercise tolerance before angina symptoms occur.[7] During therapy with intravenous NTG, if blood pressure (BP) drops and ischemia is not relieved, the addition of phenylephrine allows coronary perfusion pressure to be maintained while allowing higher doses of NTG to be used for ischemia relief.[8] If reflex increases in heart rate and contractility occur, combination therapy with β-adrenergic blockers may be indicated to blunt the undesired increase in heart rate. Combination therapy with nitrates and calcium channel blockers may be an effective antiischemic regimen in selected patients, but excessive hypotension and reflex tachycardia may be a problem, especially when a dihydropyridine (DHP) calcium antagonist is used.[9]

Mechanism of Action

NTG enhances myocardial oxygen delivery and reduces myocardial oxygen demand. NTG is a smooth muscle relaxant that causes vasculature dilation. Nitrate-mediated vasodilation occurs with or without intact vascular endothelium.[10] Nitrites, organic nitrites, nitroso compounds, and other nitrogen oxide–containing substances (eg, nitroprusside) enter the smooth muscle cell and are converted to reactive nitric oxide (NO) or *S*-nitrosothiols, which stimulate guanylate cyclase metabolism to produce cyclic guanosine monophosphate (cGMP)[11–13] (Fig. 11.1). A cGMP-dependent protein kinase is stimulated with resultant protein phosphorylation in the smooth muscle. This leads to a dephosphorylation of the myosin light chain and smooth muscle relaxation.[14,15]

Vasodilation is also associated with a reduction of intracellular calcium.[16] Sulfhydryl (SH) groups are required for formation of NO and the stimulation of guanylate cyclase. When excessive amounts of SH groups are metabolized by prolonged exposure to NTG, vascular tolerance occurs.[17] The addition of *N*-acetylcysteine, an SH donor, reverses NTG tolerance.[18] The mechanism by which NTG compounds are uniquely better venodilators, especially at lower serum concentrations, is unknown but may be related to increased uptake of NTG by veins compared with arteries.[19]

TABLE 11.1 Myocardial Ischemia: Factors Governing Oxygen Supply and Demand

Oxygen Supply	*Oxygen Demand*
Heart rate[a]	Heart rate[a]
O_2 content	Contractility
Hgb, SAT%, PaO_2	Wall tension
Coronary blood flow	Afterload
CPP = DP − LVEDP[a]	Preload (LVEDP)[a]
CVR	

[a]Affects supply and demand.

CPP, Coronary perfusion pressure; *CVR*, coronary vascular resistance; *DP*, diastolic blood pressure; *Hgb*, hemoglobin; *LVEDP*, left ventricular end-diastolic pressure; PaO_2, partial pressure of oxygen; *SAT*, percent oxygen saturation.

Modified from Royster RL. Intraoperative administration of inotropes in cardiac surgery patients. *J Cardiothorac Anesth.* 6(suppl 5):17, 1990.

Physiologic Effects

Two important physiologic effects of NTG are systemic and regional venous dilation (Fig. 11.2). Venodilation can markedly reduce venous pressure, venous return to the heart, and cardiac filling pressures. Prominent venodilation occurs at lower doses and does not increase further as the NTG dose increases.[20] Venodilation results primarily in pooling of blood in the splanchnic capacitance system.[21] Mesenteric blood volume increases as ventricular size, ventricular pressures, and intrapericardial pressure decrease.[21]

NTG increases the distensibility and conductance of large arteries without changing systemic vascular resistance (SVR) at low doses.[22] Improved compliance of the large arteries does not necessarily imply afterload reduction. At higher doses, NTG dilates smaller arterioles and resistance vessels, reducing afterload and BP (see Fig. 11.2).[23] Reductions in cardiac dimension and pressure reduce myocardial oxygen consumption ($M\dot{V}O_2$) and improve myocardial ischemia[24] (Fig. 11.3). NTG may preferentially reduce cardiac preload while maintaining systemic perfusion pressure, an important hemodynamic effect in myocardial ischemia. However, in hypovolemic states, higher doses of NTG may reduce systemic BP to dangerous levels. A reflex increase in heart rate may occur at arterial vasodilating doses.

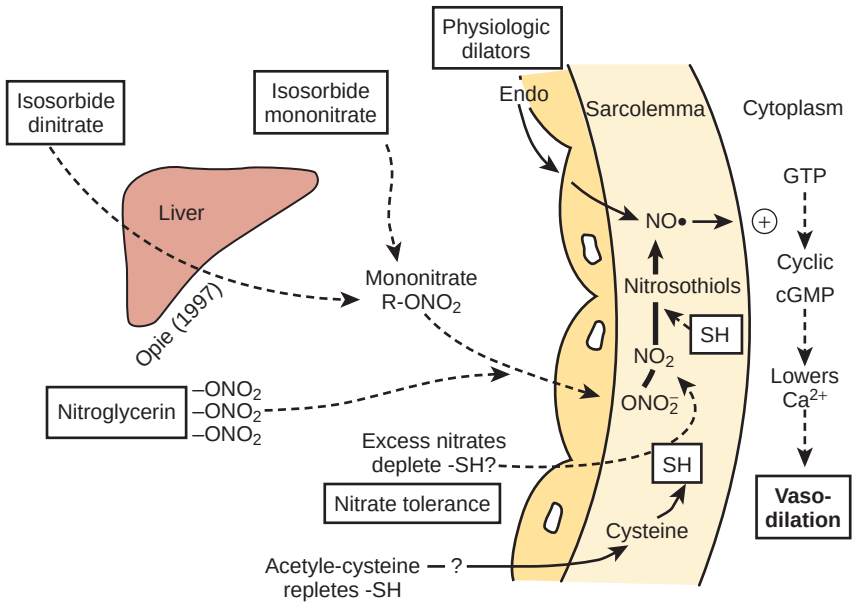


Fig. 11.1 Mechanisms of nitrates *(ONO_2)* in the generation of the free radical nitric oxide (NO•) and stimulation of guanylate cyclase cyclic guanosine monophosphate *(cGMP)*, which mediates vasodilation. Sulfhydryl *(SH)* groups are required for the formation of NO• and stimulation of guanylate cyclase. Isosorbide dinitrate is metabolized by the liver, whereas this route of metabolism is bypassed by the mononitrates. *Endo*, Endothelium; *GTP*, guanosine triphosphate. *(Modified from Opie LH.* Drugs for the Heart. *4th ed. Philadelphia: Saunders; 1995:33.)*

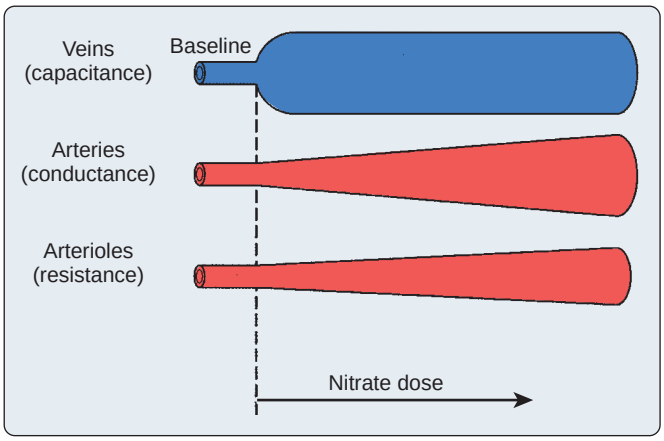


Fig. 11.2 Actions of organic nitrates on the major vascular beds and relation of vasodilation to the size of the administered dose. The venous capacitance system dilates maximally with very low doses of organic nitrates. Increasing the amount of drug does not cause appreciable additional venodilation. Arterial dilation and enhanced arterial conductance begin at low doses of nitrates, with further vasodilation as the dosage is increased. With high plasma concentrations of nitrates, the arteriolar resistance vessels dilate, decreasing systemic and regional vascular resistance. *(Modified from Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates.* Am Heart J. *1985;110(pt 2):216; Abrams J. Nitrates. In: Chatterjee K, Cheitlin MD, Karliner J, et al, eds.* Cardiology: An Illustrated Text/Reference. *Vol 1. Philadelphia: Lippincott; 1991:275–290.)*

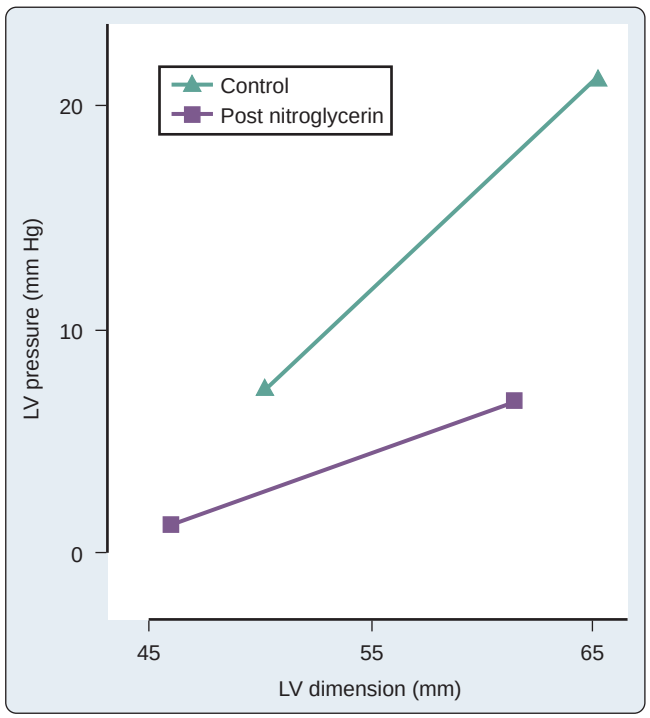
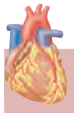


Fig. 11.3 Effect of sublingual nitroglycerin on the left ventricular *(LV)* diastolic pressure-dimension relationship in a patient with chronic aortic regurgitation. Dimensions (from an echocardiogram) and pressure data points were obtained in early diastole (ie, minimal pressure) and at end-diastole (ie, peak of QRS). After the administration of nitroglycerin, the pressure-dimension curve is shifted to the left. *(From Smith ER, Smiseth OA, Kingma I, et al. Mechanism of action of nitrates. Role of changes in venous capacitance and in the left ventricular diastolic pressure-volume relation.* Am J Med. *1984;76:14.)*



BOX 11.1 EFFECTS OF NITROGLYCERIN AND ORGANIC NITRATES ON THE CORONARY CIRCULATION

- Epicardial coronary artery dilation: small arteries dilate proportionately more than larger arteries
- Increased coronary collateral vessel diameter and enhanced collateral flow
- Improved subendocardial blood flow
- Dilation of coronary atherosclerotic stenoses
- Initial short-lived increase in coronary blood flow; later reduction in coronary blood flow as myocardial oxygen consumption decreases
- Reversal and prevention of coronary vasospasm and vasoconstriction

Modified from Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates. *Am Heart J.* 1985;110(pt 2):216.

NTG causes vasodilation of pulmonary arteries and veins and predictably decreases right atrial, pulmonary artery, and pulmonary capillary wedge pressures (PCWP).[23] Pulmonary artery hypertension may be reduced by NTG in various disease states and in congenital heart disease.[25,26] Renal arteries, cerebral arteries, and cutaneous vessels also dilate with NTG.[27] Blood flow to the kidney and brain may decrease if adequate renal and cerebral perfusion pressures are not maintained.

NTG has several important effects on the coronary circulation (Box 11.1). It is a potent epicardial coronary artery vasodilator in normal and diseased vessels. Stenotic lesions dilate with NTG, reducing the resistance to coronary blood flow (CBF) and improving myocardial ischemia.[28,29] Smaller coronary arteries may dilate relatively more than larger coronary vessels, but the degree of dilation may depend on the baseline tone of the vessel.[30] NTG effectively reverses or prevents coronary artery vasospasm.[31]

Total CBF may initially increase but eventually decreases with NTG despite coronary vasodilation[32] (Fig. 11.4). Autoregulatory mechanisms probably decrease total flow as a result of reductions in wall tension and $M\dot{V}O_2$.[23] However, regional myocardial blood flow may improve by vasodilation of intercoronary collateral vessels or reduction of subendocardial compressive forces[33] (Fig. 11.5). Coronary arteriographic studies in humans demonstrate that coronary collateral vessels increase in size after NTG administration.[34] This effect may be especially important when epicardial vessels have subtotal or total occlusive disease.[35] Improvement in collateral flow can also be protective in situations in which coronary artery steal may occur with other potent coronary vasodilator agents. The improvement in blood flow to the subendocardium, the area most vulnerable to development of ischemia, results from improvement in collateral flow and reductions in left ventricular end-diastolic pressure (LVEDP), which reduce subendocardial resistance to blood flow.[36]

With the maintenance of an adequate coronary perfusion pressure (eg, with administration of phenylephrine), NTG can maximize subendocardial blood flow[8] (see Figs. 11.4 and 11.5). The ratio of endocardial to epicardial blood in transmural segments is enhanced with NTG.[36] Inhibition of platelet aggregation also occurs with NTG, but the clinical significance of this action is unknown.[37]

Pharmacology

Organic nitrates are biotransformed by reduction hydrolysis catalyzed by the hepatic enzyme glutathione–organic nitrate reductase.[15] The rate of hepatic denitrification is characteristic of each nitrate and further depends on hepatic blood flow or presence of hepatic disease.[15] Common organic nitrates for clinical use are shown in Table 11.2.

Sublingual Nitroglycerin

Sublingual NTG (0.15- to 0.6-mg tablets) achieves blood levels adequate to cause hemodynamic changes within several minutes; the

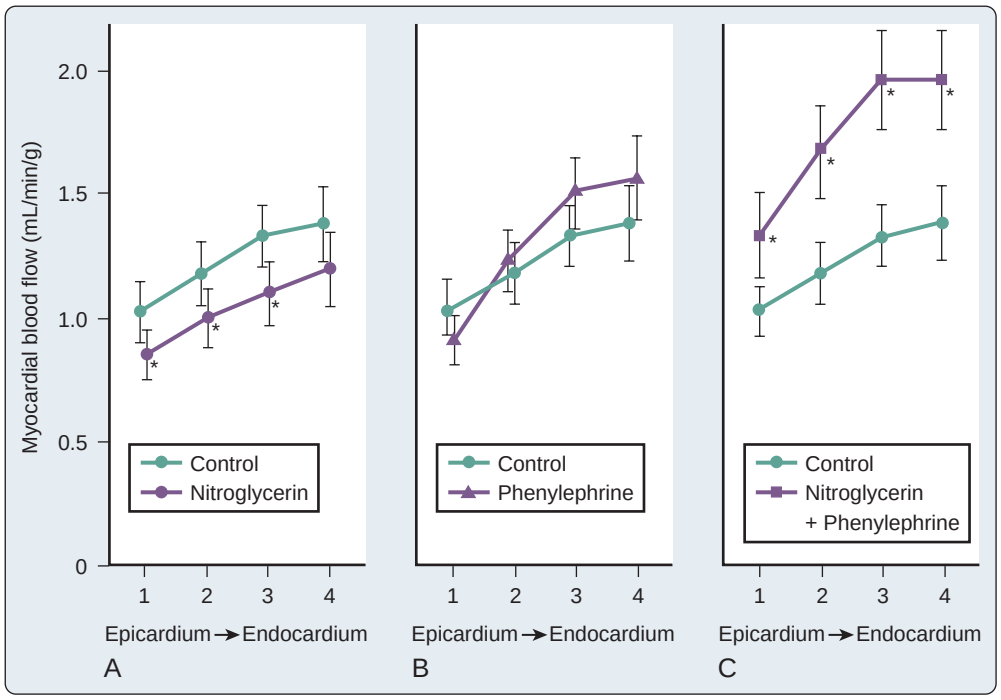


Fig. 11.4 Mean blood flow (mL/min per gram) ± SE to four transmural layers of anterior nonischemic myocardium during occlusion of the circumflex coronary artery in animals. Data are reported during control conditions, during infusion of nitroglycerin (0.015 mg/kg per minute) (A), during administration of phenylephrine to increase mean arterial pressure to 153 ± 6 mm Hg (B), and during simultaneous administration of nitroglycerin and phenylephrine (C). Nitroglycerin decreases blood flow, and phenylephrine usually increases blood flow in normal myocardium. The combination markedly augments flow; *$P < .05$ compared with control measurements. *(A–C, From Bache RJ. Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog.* Circulation. *1978;57:557.)*

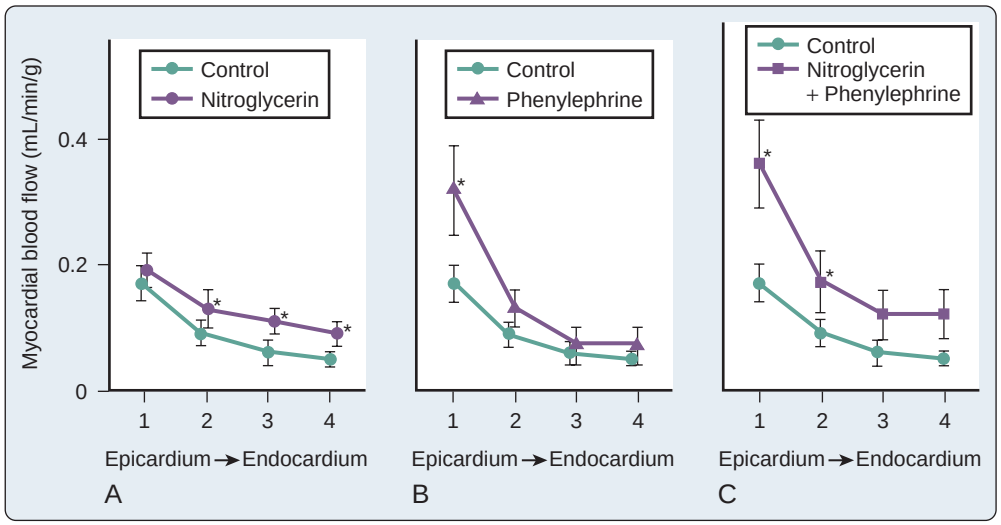


Fig. 11.5 Mean blood flow (mL/min per gram) ± SE to four transmural layers of the central ischemic zone during occlusion of the circumflex coronary artery in animals. Data are reported during control conditions, during infusion of nitroglycerin (0.015 mg/kg per minute) (A), during administration of phenylephrine to increase mean arterial pressure to 153 ± 6 mm Hg (B), and during simultaneous administration of nitroglycerin and phenylephrine (C). Coronary blood flow to all layers of ischemic myocardium is enhanced with the combination; *$P < .05$ compared with control measurements. *(A–C, From Bache RJ. Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog.* Circulation. *1978;57:557.)*

TABLE 11.2 Nitroglycerin and Nitrates Used for Angina

Compound	*Route*	*Dosage*	*Duration of Effect*
Nitroglycerin	Sublingual tablets Spray Transdermal Intravenous	0.3–0.6 mg up to 1.5 mg 0.4 mg as needed 0.2–0.8 mg/h every 12 h 5–200 µg/min	1–7 minutes Similar to sublingual tablets 8–12 h during intermittent therapy Tolerance in 7–8 h
Isosorbide dinitrate	Oral Oral, slow release	5–80 mg 2 or 3 times daily 40 mg 1 or 2 times daily	Up to 8 h Up to 8 h
Isosorbide mononitrate	Oral Oral, slow release	20 mg twice daily 60–240 mg once daily	12–24 h
Pentaerythritol tetranitrate	Sublingual	10 mg as needed	Unknown
Erythritol tetranitrate	Sublingual Oral	5–10 mg as needed 10–30 mg 3 times daily	Unknown Unknown

Modified from Gibbons RJ, Chatterjee K, Daley J, Douglas JS. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol.* 1999;33:2092–2197.

physiologic effects last 30 to 45 minutes.[38] Sublingual bioavailability is approximately 80% and bypasses the high (90%) first-pass biodegradation in the liver by nitrate reductase to glycerol dinitrate and nitrite, which are renally excreted. Plasma half-life of sublingual NTG is 4 to 7 minutes.

NTG spray has pharmacokinetics and pharmacodynamics equivalent to those of a 0.4-mg sublingual tablet, but it has a longer shelf half-life compared with the tablets, which decompose in air and warm temperatures.[39] A tablet that adheres to the buccal area between the upper lip and teeth has a rapid onset and has the advantage of a longer half-life than sublingual tablets.[40] Although NTG is readily absorbed through the gastric mucosa, the high rate of liver metabolism makes oral administration highly unpredictable.

Nitroglycerin Ointment and Patches

NTG ointment (2%) is readily absorbed through the skin, and this method of administration provides longer-lasting effects.[41] Adequate NTG blood levels are reached within 20 to 30 minutes, and the duration of action is 4 to 6 hours.[41] Ointment (ie, nitro paste) is administered in inches (15 mg/inch), but the surface area of application, not the amount administered, determines the blood level achieved. NTG ointment is messy, requires application four times each day, and is most appropriate for nursing administration in an inpatient setting.[42]

NTG patches contain liquid NTG or NTG bonded to a polymer gel and slowly released to the skin through a semipermeable membrane.[43] The pharmacokinetics approach that of a consistent intravenous infusion.[43] Blood levels are reached within 20 to 30 minutes, and a steady state is reached within 2 hours. Blood levels may be maintained up to 24 hours and are largely determined by patch size. Patches or disks contain an NTG concentration per square centimeter, and doses of 0.2 to 0.8 mg/h are usually required for relief of myocardial ischemia. Although convenient for patients, tolerance may be a problem with sustained-release preparations.[41] Intermittent therapy is recommended to avoid tolerance.[44]

Intravenous Nitroglycerin

NTG has been available since the early 1980s as a parenteral drug with a stable shelf half-life in a 400-µg/mL solution of 5% dextrose in water (D_5W). Blood levels are achieved instantaneously, and arterial dilating doses with resulting hypotension may quickly occur. If the volume status of the patient is unknown, initial doses of 5 to 10 µg/min are recommended. The dose necessary for relieving myocardial ischemia may vary from patient to patient, but relief is usually achieved with 75 to 150 µg/min. In a clinical study of 20 patients with rest angina, a mean dose of 72 µg/min reduced or abolished ischemic episodes in 85% of patients.[45] However, doses as high as 500 to 600 µg/min may be necessary for ischemic relief in some patients. Arterial dilation becomes clinically apparent at doses around 150 µg/min. Drug offset after discontinuation of an infusion is rapid (2–5 minutes). The dosage of NTG available is less when administered in plastic bags and polyvinylchloride tubing because of NTG absorption by the bag and tubing, although this is not a significant clinical problem because the drug is titrated to effect.[46]

Adverse Effects

The metabolism of NTG by liver nitrate reductase produces a nitrite that oxidizes the ferrous iron of hemoglobin to the ferric form of methemoglobin. The ferric iron does not bind or release oxygen.[47] Methemoglobin is formed normally and is reduced by enzyme systems within the red blood cell.[48] Normally, methemoglobin levels do not exceed 1%, but they may increase when direct oxidants (eg, nitrates, sulfonamides, aniline dye derivates) are present in the serum. Methemoglobinemia with levels up to 20% is not a clinical problem. Documented increases in methemoglobin blood levels occur with intravenous NTG, averaging 1.5% in one study of 50 patients receiving NTG for longer than 48 hours.[49] NTG doses of 5 mg/kg per day and higher should be avoided to prevent significant methemoglobinemia.[50] However, rare instances of smaller doses causing clinically significant problems have been reported.[51] Nitrates are effective in producing methemoglobin to bind cyanide in sodium nitroprusside toxicity.

Several mechanisms of nitrate tolerance have been proposed, including a depletion of SH groups, neurohumoral activation, volume expansion, and downregulation of nitrate receptors.[52–57] Tolerance may occur with all forms of nitrate administration that maintain continuous blood levels of the drug.[17,58–61] Discontinuation of the drug after prolonged exposure may result in a rebound phenomenon, possibly resulting in coronary vasospasm and myocardial ischemia or infarction.[62] Tolerance to NTG does not occur in all patients.[63] If tolerance develops after prolonged exposure, physiologic responsiveness may be achieved with higher doses of NTG, an important observation during NTG administration in cardiac surgery.[64] Intermittent dosing with a nitrate-free interval each day or night can maintain NTG responsiveness.[44,65]

NTG interferes with platelet aggregation.[66] The ability of the platelet to adhere to damaged intima is reduced.[67] Primary and secondary wave aggregation of platelets is also attenuated.[68] Previously formed platelet plugs are disaggregated.[69] A clinical study of 10 patients with coronary artery disease (CAD) demonstrated that a mean dose of NTG (1.19 µg/kg per minute) inhibited platelet aggregation by 50%, with a return to baseline platelet aggregation 15 minutes after the infusion was discontinued[70] (Fig. 11.6). NO production increases cGMP, which modulates intracellular platelet calcium and reduces platelet secretion of proaggregatory factors.[71] The clinical significance of these actions remains unclear. As with other potent vasodilators, NTG may increase intrapulmonary shunting of blood and reduce arterial oxygen tension.

NTG may induce resistance to the anticoagulant effects of heparin.[72] During simultaneous infusions of NTG and heparin, an increase in the NTG infusion caused the activated partial thromboplastin time to decrease.[73] Becker and colleagues[74] reported NTG-induced heparin resistance at NTG infusion rates greater than 350 µg/min.

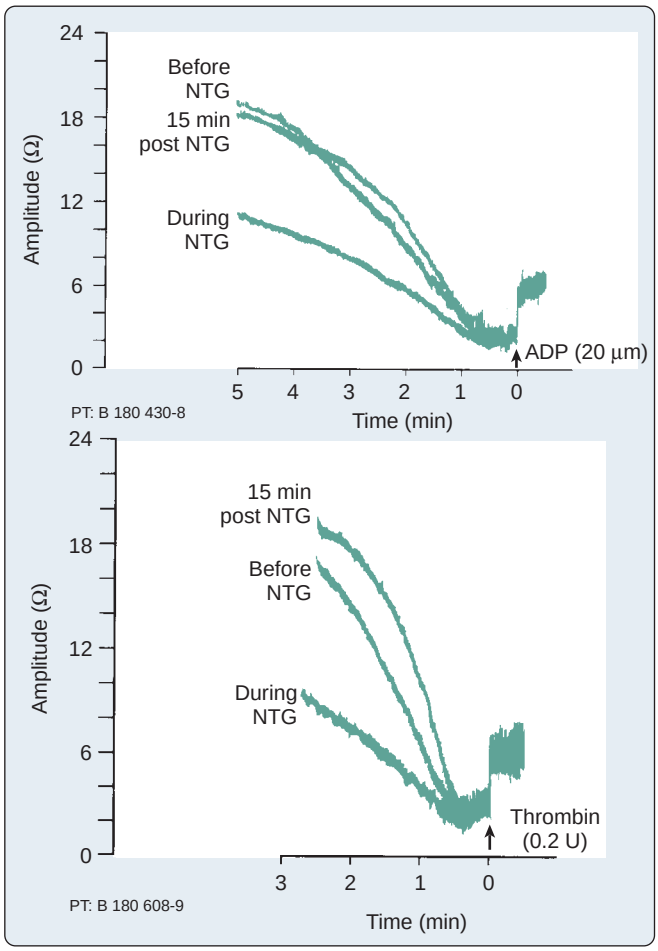


Fig. 11.6 Typical examples of aggregation responses to adenosine diphosphate *(ADP) (top)* and to thrombin *(bottom)* before, during, and after infusion of nitroglycerin *(NTG)* in patients with coronary artery disease. The amplitude of the curve is calibrated in ohms *(Ω)* using a dual-channel impedance aggregometer. NTG inhibits platelet aggregation to both reagents, and the effect is rapidly reversible after discontinuation of the drug. *(Modified from Diodati J, Theroux P, Latour JG, et al. Effects of nitroglycerin at therapeutic doses on platelet aggregation in unstable angina pectoris and acute myocardial infarction.* Am J Cardiol. *1990;66:683.)*

They suggested a qualitative problem with antithrombin III (AT III), because AT III levels did not decrease. Others have suggested that NTG interferes with AT III binding to heparin by *N*-desulfation of the heparin molecule at the AT III binding sites.[75] *N*-Desulfation of heparin reduces its anticoagulant activity.[76]

NTG is contraindicated in patients who have used sildenafil, vardenafil, or tadalafil and in patients who are hypotensive. The drugs for erectile dysfunction inhibit phosphodiesterase type 5 (PDE5), an enzyme that degrades cGMP, which mediates vascular smooth muscle relaxation by NO. NTG-mediated vasodilation is markedly enhanced and prolonged, resulting in cases of profound hypotension, myocardial infarction (MI), and death.[77] Guidelines suggest at least 24 hours between the last dose of sildenafil and vardenafil and nitrate administration and 48 hours for tadalfil.[1,78–80]

Summary

NTG remains a first-line agent for the treatment of myocardial ischemia. Special care must be taken in patients with signs of hypovolemia or hypotension because vasodilating effects of the drug may worsen the clinical condition (Box 11.2). The 2014 ACC/AHA guidelines address the prophylactic intraoperative use of NTG and state there is no benefit in preventing myocardial ischemia and cardiac morbidity in high-risk patients undergoing noncardiac surgery and that NTG use could be harmful.[1]

BOX 11.2 ACC/AHA GUIDELINES FOR EARLY USE OF NITROGLYCERIN AFTER STEMI

Class I

1. Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin (level of evidence [LOE] C).
2. Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion (LOE C).

Class III

1. Nitrates should not be administered to patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (<50 beats/min), tachycardia (>100 beats/min), or suspected right ventricular infarction (LOE C).
2. Nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hours (48 hours for tadalafil) (LOE B).

ACC, American College of Cardiology; *AHA*, American Heart Association; *STEMI*, ST-segment elevation myocardial infarction.

BOX 11.3 EFFECTS OF β-ADRENERGIC BLOCKERS ON MYOCARDIAL ISCHEMIA

- Reductions in myocardial oxygen consumption
- Improvements in coronary blood flow
- Prolonged diastolic perfusion period
- Improved collateral flow
- Increased flow to ischemic areas
- Overall improvement in the supply-to-demand ratio
- Stabilization of cellular membranes
- Improved oxygen dissociation from hemoglobin
- Inhibition of platelet aggregation
- Reduced mortality rate after myocardial infarction

β-Adrenergic Blockers

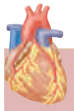
β-Adrenergic blockers have multiple favorable effects in treating the ischemic heart during anesthesia (Box 11.3). β-Adrenergic blockers reduce oxygen consumption by decreasing heart rate, BP, and myocardial contractility. Heart rate reduction increases diastolic CBF. Increased collateral blood flow and redistribution of blood to ischemic areas may occur with β-blockers. Microcirculatory oxygen delivery improves, and oxygen dissociates more easily from hemoglobin after β-adrenergic blockade. Platelet aggregation is inhibited.

β-Blockers should be started early in ischemic patients in the absence of contraindications. If hemodynamics prevent concomitant NTG and β-blockers use, β-blockers should receive precedence.[1] Many patients at high risk for perioperative cardiac morbidity should be started on β-blockers before surgery and continued for up to 30 days after surgery.[81–83] Although the choice of β-blocker for an individual patient is based on clinician familiarity and desired pharmacologic profile, adequate time in initiating β-blocker therapy should be allowed to adjust dosing before surgical procedures. There is no evidence that one specific agent is superior to another, but β-blockers

without intrinsic sympathomimetic activity (ISA) are preferable when treating acute myocardial ischemia.

β-Blockers administered during MI reduce myocardial infarct size.[84] Morbidity has been reduced by acute intravenous metoprolol administration during MI.[84] Similar findings with reductions in mortality extending up to 3 years after MI have been shown in numerous trials with β-adrenergic blockers.[85,86] The mechanisms for mortality reduction are unclear. In the absence of contraindications, β-blockers should be a routine part of care of patients with all forms of CAD, including unstable angina and recent MI.

Data confirm the important role of β-blockade in treating patients after acute MI and in reducing mortality in high-risk populations. Immediate β-blockade after thrombolytic therapy for patients with acute MI significantly decreased recurrent early myocardial ischemia and reinfarction.[87] Early β-blockade is indicated in the treatment of MI[88,89] (Box 11.4). β-Blocker therapy after MI may be greatly underused in patients older than 65 years.[90]



BOX 11.4 ACC/AHA GUIDELINES FOR EARLY THERAPEUTIC USE OF β-ADRENOCEPTOR BLOCKING AGENTS AFTER STEMI

Class I[a]

1. Oral β-blocker therapy should be initiated in the first 24 hours for patients who do not have any of the following: (1) signs of heart failure, (2) evidence of low output state, (3) increased risk[a] of cardiogenic shock, or (4) other relative contraindications to β-blockade (PR interval > 0.24 s), second- or third-degree heart block, active asthma, or reactive airway disease) (level of evidence [LOE] B).
2. Patients with contraindications within the first 24 hours of STEMI should be reevaluated for candidacy for β-blocker therapy as secondary prevention (LOE C).
3. Patients with moderate or severe left ventricular failure should receive β-blocker therapy as secondary prevention with a gradual titration scheme (LOE B).

Class IIa

1. It is reasonable to administer an intravenous β-blocker at the time of presentation to STEMI patients who are hypertensive and who do not have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk[a] for cardiogenic shock, or (4) other relative contraindications to β-blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) (LOE B).

Class III

1. Intravenous β-blockers should not be administered to STEMI patients who have any of the following: (1) signs of heart failure, (2) evidence of a low-output state, (3) increased risk[a] of cardiogenic shock, or (4) other relative contraindications to β-blockade (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) (LOE A).

[a]Risk factors for cardiogenic shock (the greater the number of risk factors, the higher the risk of developing cardiogenic shock) are age older than 70 years, systolic blood pressure less than 120 mm Hg, sinus tachycardia greater than 110 beats/min or heart rate less than 60 beats/min, and increased time since the onset of symptoms of STEMI.

ACC, American College of Cardiology; *AHA*, American Heart Association; *STEMI*, ST-segment elevation myocardial infarction.

From Antman EM, Hand M, Armstrong PW, et al. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 writing group to review new evidence and update the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction, writing on behalf of the 2004 Writing Committee. *Circulation*. 2008;117:296.)

Atenolol can reduce ischemia and adverse outcomes for patients with mildly symptomatic ischemia.[91] Many studies have shown that perioperative administration of β-adrenergic blockers reduces mortality and morbidity when given to patients at high risk for CAD who must undergo noncardiac surgery.[81–83,92,93] These data suggest that intermediate- and high-risk patients undergoing noncardiac surgery should receive perioperative β-adrenergic blockade to reduce postoperative cardiac mortality and morbidity. However, in the POISE trial, the use of higher-dose metoprolol started in patients on the day of noncardiac surgery was associated with an increased risk of severe stroke and a higher total mortality rate.[94] The POISE trial findings have been replicated, and combined with concerns about the validity of the results of the DECREASE trials, they have led to increased scrutiny of perioperative β-blockade usage due to higher rates of stroke, bradycardia, hypotension, and death perioperatively when starting β-blockers in the immediate preoperative period.[92,95]

β-Receptor

The β-receptor was conceptualized by Ahlquist, who divided the various physiologic effects of catecholamine stimulation into α- and β-responses.[96] The β-receptor has been identified biochemically as a polypeptide chain of approximately 50,000 to 60,000 kDa.[97] The receptor's structure is common to most receptor proteins that have been identified: seven transmembrane crossings with two extramembranous terminal ends[98] (Fig. 11.7). All receptors that transduce a signal through G-proteins share this basic structure.[99] Three extracellular and intracellular loops connect the intramembranous portion of the receptor.[98] Agonist-antagonist binding occurs at the intramembranous portion, and the intracellular loops modulate interaction with the G-protein complex.[100,101] The terminal intracellular end contains amino acid residues that undergo phosphorylation, which is related to desensitization and downregulation of the receptor.[102]

Receptor stimulation activates a G-protein, which stimulates adenylyl cyclase. The G-protein complex is composed of stimulatory (G_s) and inhibitory (G_i) intermediary proteins.[99] Adenylyl cyclase converts ATP to cyclic AMP (cAMP) which phosphorylates a protein kinase and produces the appropriate cellular response. A typical cascade of this sequence leading to increases in myocardial contractility from β-receptor stimulation is illustrated in Fig. 11.8.

β-Receptor numbers in any tissue may decrease with chronic stimulation (ie, downregulation) or increase with chronic blockade (ie, upregulation). The process of desensitization of the adrenergic response in chronic stimulation (ie, congestive heart failure [CHF]) may involve downregulation of the receptors and may involve the G-protein complex or adenylyl cyclase. Desensitization may occur very quickly, whereas downregulation with internalization of the receptor within the cell may take days to weeks.[103]

Myocardial ischemia increases β-receptor density, although it remains controversial whether upregulation results in greater adrenergic response.[104] Several studies have demonstrated that high-affinity β-receptors in nonischemic tissue were shifted to a low-affinity state during ischemia.[105,106] The levels and activity of G_s also are reduced during myocardial ischemia.[107] However, stimulation of these receptors with isoproterenol during ischemia does increase cAMP production.[104,108]

β-Receptors have a multitude of responses[109] (Table 11.3). The β_1- and β_2-receptor forms of stimulation primarily involve cardiac function (Fig. 11.9). Responses of isolated human atrial tissue demonstrated greater inotropic response to β_1-receptor stimulation than to β_2-receptor stimulation.[110] Endogenous norepinephrine produces inotropic responses in human atrial appendages and ventricular papillary muscle by β_1-receptor stimulation; epinephrine produces its maximal inotropic effects on the atria by β_2-receptor stimulation and up to 50% of its maximal inotropic response in the ventricle by β_2-receptor stimulation.[111,112] The sinus node, atrioventricular (AV) node, left and right bundle branches, and Purkinje system contain higher densities of β_2-receptors.[113] Both receptor subtypes have cardiac inotropic, chronotropic, and dromotropic properties.

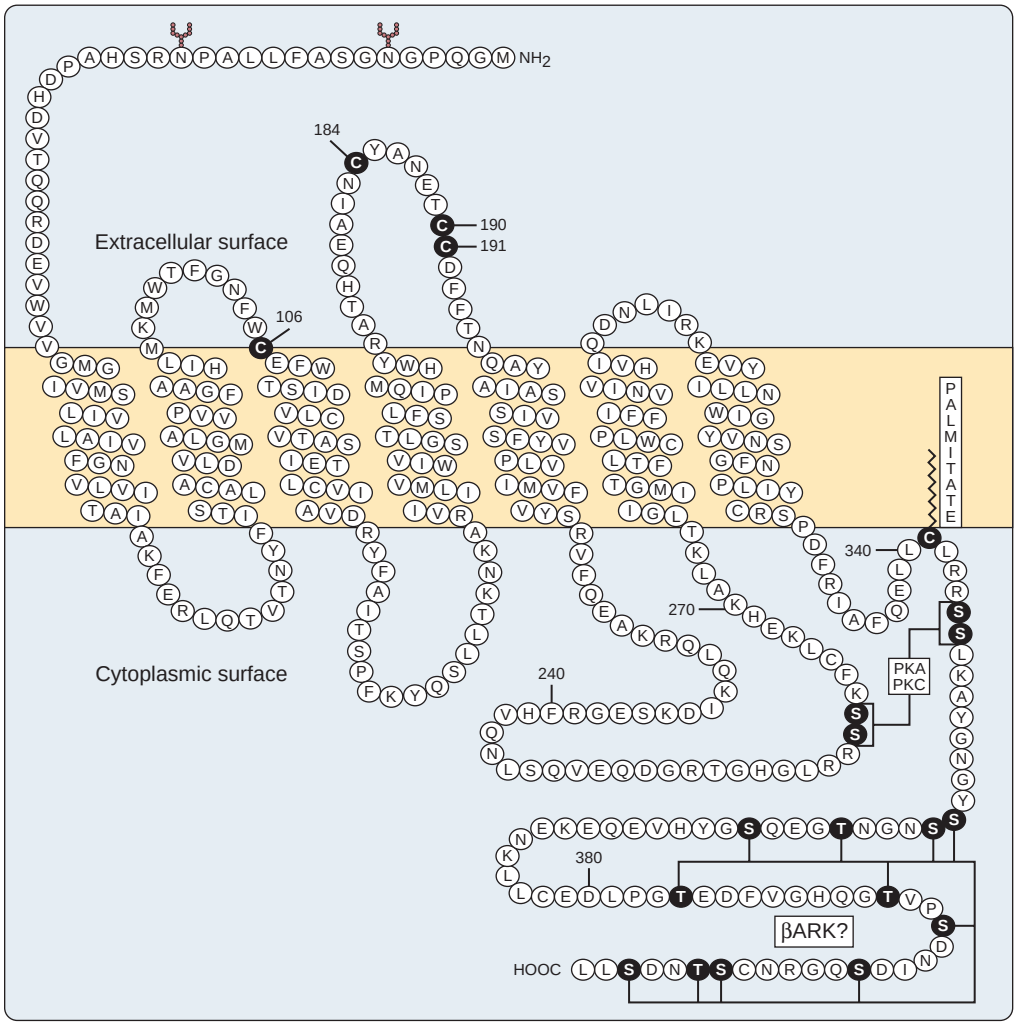


Fig. 11.7 The human β_2-adrenergic receptor (*tan area* represents the cell membrane). Depicted are two sites of extracellular *N*-linked glycosylation (Asn5, 16), four cysteine *(C)* residues that may participate in disulfide bonds (Cys106, 184, 190, 191), an intracellular cysteine residue (Cys341) that may serve as a site of attachment for a palmitate membrane anchor, and multiple threonine *(T)* and serine *(S)* residues located in C-III and the cytoplasmic carboxyl terminus, which are potential sites of phosphorylation by protein kinase A *(PKA)*, protein kinase C *(PKC)*, or β-adrenergic receptor kinase (βARK). *(From Raymond JR, Hnatowich M, Lefkowitz RJ, Caron MG. Adrenergic receptors. Models for regulation of signal transduction processes.* Hypertension. *1990;15:119.)*

β_2-Adrenoceptors comprise 93% of the total population of β-receptors in arterioles and 100% of receptors in the epicardium, vena cava, aorta, and pulmonary artery.[112] β_2-Receptors are found on the intimal surface of human internal mammary artery but not on the saphenous vein,[114] the two vessels most commonly used for coronary artery bypass graft (CABG) surgery β_2-Stimulation results in vascular smooth muscle relaxation and vasodilation.

β_1-Receptor stimulation increases plasma renin production and aqueous humor production. β_2-Receptor stimulation relaxes smooth muscle and produces bronchodilation and uterine relaxation. β_2-Stimulation also increases insulin secretion, glycogenolysis, and lipolysis and shifts extracellular potassium to intracellular sites. β_3-Adrenoreceptors are found on visceral adipocytes, the gallbladder, and colon. Stimulation of β_3-receptors is thought to mediate lipolytic and thermic responses in brown and white adipose tissue.[115]

Physiologic Effects

Antiischemic Effects

β-Blockade on the ischemic heart may result in a favorable shift in the oxygen supply-to-demand ratio (see Table 11.1). Reductions in the force of contraction and heart rate reduce $M\dot{V}O_2$ and result in autoregulatory decreases in myocardial blood flow. Several studies have shown that blood flow to ischemic regions with propranolol is maintained, but this probably results from maintenance of α-vasoconstrictor tone of epicardial vessels and of a pressure gradient to the vasodilated endocardial areas of ischemia.[116,117]

Reductions in blood flow in some patients with vasospastic angina may worsen with the administration of propranolol.[118] Intracoronary infusion of propranolol does not worsen stenotic lesions and increases the luminal size of the stenosis at rest and during exercise.[119]

Antihypertensive Effects

The exact mechanisms involved in BP reduction are not clear. Both β_1- and β_2-receptor blockers inhibit myocardial contractility and reduce heart rate; both effects should reduce BP. No acute decrease in BP occurs during acute administration of propranolol.[120] However, chronic BP reduction has been attributed to a chronic reduction in cardiac output (CO).[121]

Reductions in high levels of plasma renin have been suggested as effective therapy for controlling essential hypertension.[122] However, the

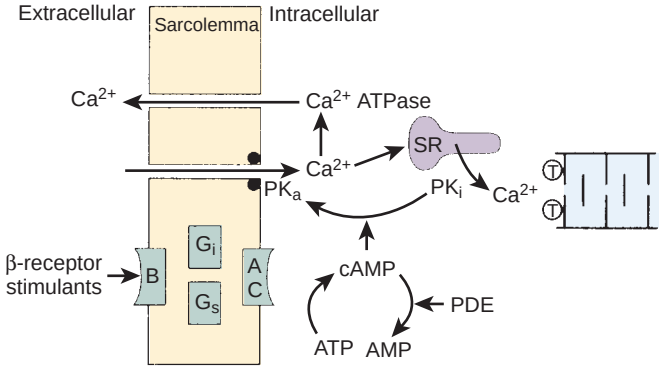


Fig. 11.8 The β-receptor, G-protein, adenylyl cyclase system. With β-receptor stimulation *(B)*, dynamic changes occur in the inhibitory G_i and stimulatory G_s regulatory proteins. Ultimately, G_s stimulates adenylyl cyclase *(AC)* to convert adenosine triphosphate *(ATP)* to cyclic adenosine monophosphate *(cAMP)*, which is metabolized by phosphodiesterase enzyme *(PDE)*. An inactive protein kinase *(PK_i)* is activated *(PK_a)* by cAMP, which opens an energy-dependent receptor-operated calcium channel, allowing calcium entry into the cell. Calcium cycling occurs with calcium actively pumped out of the cell by Ca^{2+} adenosine triphosphatase *(ATPase)*. Calcium cycling causes a release of calcium from the sarcoplasmic reticulum *(SR)*, allowing calcium to bind to troponin C *(T)*, with subsequent activation of the actin-myosin complex. *AMP*, Adenosine monophosphate. *(Modified from Royster RL. Intraoperative administration of inotropes in cardiac surgery patients.* J Cardiothorac Anesth. *1990;4:17.)*

TABLE 11.3 Physiologic Effects of β_1- and β_2-Receptor Stimulation

Physiologic Effect	β_1 *Response*	β_2 *Response*
Cardiovascular Effects		
Increased heart rate	++	++
Increased contractility		
Atrium	+	++
Ventricle	++	++
Increased automaticity and conduction velocity		
Nodal tissue	++	++
His-Purkinje	++	++
Arterial relaxation	—	
Coronary	—	++
Skeletal muscle	—	++
Pulmonary	—	+
Abdominal	—	+
Renal	+	+
Venous relaxation	—	++
Smooth Muscle Relaxation		
Trachea and bronchi	—	+
Gastrointestinal system	—	+
Bladder	—	+
Uterus	—	+
Splenic capsule	—	+
Ciliary muscle	—	+
Metabolic Effects		
Renin release	++	—
Lipolysis	++	+
Insulin secretion	—	+
Glycogenolysis, gluconeogenesis	—	++
Cellular K^+ uptake	—	+
ADH secretion (pituitary)	+	—

ADH, Antidiuretic hormone; +, response; ++, greater response; —, no response.
Modified from Lefkowitz RJ, Hoffman BB, Taylor P. Neurohumoral transmission: the autonomic and somatic motor nervous systems. In: Gilman AG, Rall TW, Niew AS, Taylor P, eds. *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. New York: Pergamon Press; 1990:84–121.

relationship between renin levels and hypertension is not established, and the decrease in BP has no relation to the change in renin levels in patients.[123,124]

Stimulation of prejunctional β-receptors results in norepinephrine release from postganglionic sympathetic fibers and increases in vascular tone to most major organ systems.[125] Prejunctional β-blockade reduces norepinephrine release, sympathetic nerve traffic, and vascular tone.[125]

Electrophysiologic Effects

Several β-blockers have potent local anesthetic effects at higher serum levels because of sodium channel blocking activity and result in depression of phase 0 of the cardiac action potential.[126] However, the membrane-stabilizing or quinidine-like effect is of questionable clinical relevance because it is observed at concentrations far exceeding therapeutic levels.[127] Generalized slowing of cardiac depolarization results from reducing the rate of diastolic depolarization (ie, phase 4). Action potential duration (APD) and the QT interval may shorten with β-adrenergic blockers.[126] The ventricular fibrillation (VF) threshold is increased with β-blockers.[128] These antiarrhythmic actions of β-blockers are enhanced in settings of catecholamine excess as in pheochromocytoma, acute MI, the perioperative period, and hyperthyroidism.

Metabolic Effects

Although β_2-blockers are reported to reduce insulin release, the clinical significance of the reduction is questionable.[129] Catecholamines, however, promote glycogenolysis and mobilization of glucose in response to hypoglycemia. In the diabetic patient, nonselective β-blockade may impede this process, worsening recovery from a hypoglycemic episode. The usual hypoglycemic symptoms of tachycardia and anxiety may be suppressed when taking β-blockers, delaying detection. Bradycardia and hypertension are documented side effects of hypoglycemia in diabetic patients receiving propranolol because of unopposed β-receptor stimulation with catecholamine release.[130]

Stimulation of β_2-receptors increases the movement of potassium into skeletal muscle cells, reduces aldosterone secretion, and increases renal potassium loss, effects that reduce serum potassium levels. β_2-Receptor blockers aid in the maintenance of serum potassium levels by blocking the adrenergic-stimulated movement of potassium intracellularly.[131] β_2-Receptor blockers may cause mild elevations in serum potassium, which may be significant in patients with renal insufficiency.[132]

Inhibition of catecholamine-stimulated lipolysis may occur with β-blockers, which reduces the availability of free fatty acids to activate contracting muscle such as the heart.[133] β-Adrenergic blockers increase serum levels of triglycerides, decrease high-density lipoprotein cholesterol, and cause little change in low-density lipoprotein cholesterol. A proposed mechanism is an increase in the relative ratio of α- to β-receptor activity.[134] Increases in β-receptor activity result in increases in lipoprotein lipase and triglyceride levels.[135] These effects on blood lipids are concerns for patients receiving chronic therapy. However, animal studies have revealed that β-blockers have a retarding effect on the development of atherosclerosis.[136] β-Blockers with ISA produce the smallest changes in the lipid profile.[137]

Intrinsic Sympathomimetic Activity

Several β-blockers (eg, acebutolol, carteolol, penbutolol, pindolol) have agonist and antagonist properties and are characterized as having ISA.[138] These agents are agonists that elicit a submaximal response and block the effects of endogenous catecholamines in a competitive fashion.[138] CO and heart rate are reduced less with ISA drugs.[139] Peripheral blood flow is reduced less, making ISA agents attractive in patients with peripheral vascular disease.[140] ISA drugs also cause less bronchoconstriction and are advantageous in chronic obstructive pulmonary disease. Theoretically, changes in β-receptor density should differ with ISA. The ISA drugs reduce β-receptor density (similar to pure agonists), whereas non-ISA agents increase β-receptor density.[141]

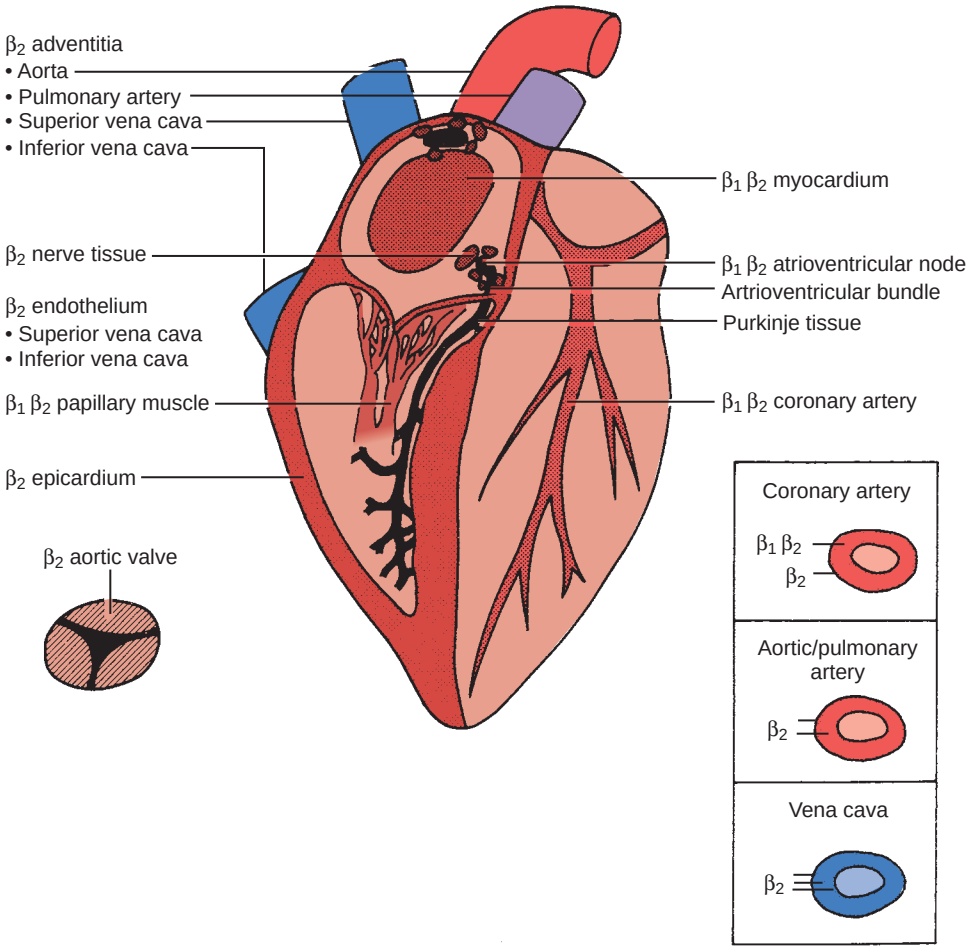


Fig. 11.9 Locations of β_1- and β_2-adrenoceptors in rat, guinea pig, dog, and human hearts determined by autoradiography. The β_1- and β_2-adrenoceptors are located on myocardium and specialized conducting tissue. A greater density of β_2-adrenoceptors is found on the atrioventricular node, bundle of His, and left and right bundle branches compared with surrounding myocardium in guinea pig. The β_2-adrenoceptors are located on blood vessels, nerve tissue, epicardium, and the aortic valve. In large canine coronary arteries (0.5 to 2 mm in diameter), β_1-adrenoceptors account for 85% of the total population of β-adrenoceptors; in small arterioles (16 to 55 μm), β_2-adrenoceptors comprise 93% of the total population. *(Modified from Summers RJ, Molenaar P, Stephenson JA. Autoradiographic localization of receptors in the cardiovascular system.* Trends Pharmacol Sci. *1987;8:272; Jones CR. New views of human cardiac β-adrenoceptors.* J Mol Cell Cardiol. *1989;21:519.)*

Although controversial, ISA drugs appear to have a role in mortality reduction after MI, similar to non-ISA β-blockers.[142]

General Pharmacology

Lipid-soluble β-blockers (eg, propranolol, labetalol, metoprolol) are well absorbed after oral administration and attain high concentrations in the brain.[143] Lipid-soluble agents produce a high incidence of central nervous system (CNS) side effects, such as depression, sleep disturbances, and impotence. The rate of first-pass hepatic metabolism after oral ingestion can be very high but varies from patient to patient and affects daily dosing schedules.[144] Cirrhosis, CHF, and cigarette smoking may reduce hepatic metabolism.[145] Lipophilic agents are highly protein bound. The hepatic metabolism of lipophilic agents is independent of protein binding, which is different from most drugs, for which hepatic metabolism occurs only with the unbound drug.[146]

Lipid-insoluble or water-soluble agents (eg, atenolol, nadolol, acebutolol, sotalol) are less well absorbed orally but are not hepatically metabolized. They are almost entirely eliminated by renal excretion and must be used cautiously in renal insufficiency. The incidence of CNS side effects is low because of lipid insolubility.

Pindolol and timolol have intermediate lipid solubility properties and are metabolized partially by the liver (50%) and excreted through the kidneys (50%). Information on the available oral and intravenous β-adrenergic blockers for treatment of myocardial ischemia is provided in Table 11.4. Some β-blockers with other indications, such as carvedilol (for CHF) and sotalol (for arrhythmias), are covered later in this chapter.

Pharmacology of Intravenous β-Adrenergic Blockers

Propranolol

Propranolol has an equal affinity for β_1- and β_2-receptors, lacks ISA, and has no β-adrenergic receptor activity. It is the most lipid-soluble β-blocker and has the most CNS side effects. Because the rate of first-pass liver metabolism is very high (90%), it requires much higher oral doses than intravenous doses for pharmacodynamic effect.[147] Although propranolol has an active metabolite (ie, 4-hydroxypropranolol), the metabolite's half-life is much shorter and does not add to the clinical effect.[148] Serum half-life of the drug after intravenous dosing is 3 to 4 hours.[149]

TABLE 11.4 Properties of β-Blockers in Clinical Use

Drug	*Selectivity*	*Partial Agonist Activity*	*Usual Dose for Angina*
Propranolol	None	No	20–80 mg bid
Metoprolol	β_1	No	50–200 mg bid
Atenolol	β_1	No	50–200 mg/d
Nadolol	None	No	40–80 mg/d
Timolol	None	No	10 mg bid
Acebutolol	β_1	Yes	200–600 mg bid
Betaxolol	β_1	No	10–20 mg/d
Bisoprolol	β_1	No	10 mg/d
Esmolol (infusion)	β_1	No	50–300 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Labetalol[a]	None	Yes	200–600 mg tid
Pindolol	None	Yes	2.5–7.5 mg tid

[a]Labetalol is a combined α- and β-blocker.

Modified from Gibbons RJ, Chatterjee K, Daley J, Douglas JS. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol.* 1999;33:2092–2197.

Because of the high rate of hepatic extraction of propranolol, factors that affect hepatic blood flow markedly affect propranolol plasma levels. Because propranolol reduces hepatic blood flow, it can reduce its own metabolism and the metabolism of other drugs.[150] This must be taken into consideration during anesthetic procedures in patients with liver disease, reduced CO states, and right ventricular heart failure (HF).

Propranolol serum levels of 100 ng/mL produce a maximal β-blocking effect for reducing exercise-induced tachycardia.[144] Propranolol still produces a 50% reduction of exercise-induced tachycardia at serum levels of 12 ng/mL.[151] Reductions in heart rate with propranolol occur at lower serum levels than depression of myocardial contractility.[152] As drug levels decrease after discontinuation of therapy, reductions in the chronotropic response last much longer than reductions in inotropy.[152] This is an important concept in treating tachycardias in patients with significant ventricular dysfunction and CHF.

The usual intravenous dose of propranolol initially is 0.5 to 1.0 mg titrated to effect. A titrated dose resulting in maximal pharmacologic serum levels is 0.1 mg/kg. The use of continuous infusions of propranolol has been reported after noncardiac surgery in patients with cardiac disease.[153] A continuous infusion of 1 to 3 mg/h can prevent tachycardia and hypertension but must be used cautiously because of the potential of cumulative effects.

Metoprolol

Metoprolol was the first clinically used cardioselective β-blocker. Its affinity for β_1-receptors is 30 times higher than its affinity for β_2-receptors as demonstrated by radioligand binding.[154] Metoprolol is lipid soluble, with 50% of the drug metabolized during first-pass hepatic metabolism and with only 3% excreted renally.[155] Protein binding is less than 10%. Metoprolol's serum half-life is 3 to 4 hours. Because of its lipophilic properties, metoprolol has been shown in animal studies to diffuse into ischemic tissue better than atenolol, a hydrophilic β-receptor blocker.[154]

As with any cardioselective β-blocker, higher serum levels may result in greater incidence of β_2-blocking effects. Metoprolol is administered intravenously in 1- to 2-mg doses, titrated to effect. The potency of metoprolol is approximately one-half that of propranolol. Maximal β-blocker effect is achieved with 0.2 mg/kg given intravenously.

Esmolol

Esmolol's chemical structure is similar to that of metoprolol and propranolol, except that it has a methylester group in the *para*-position of the phenyl ring, making it susceptible to rapid hydrolysis by red blood cell esterases (ie, 9-minute half-life).[156] Esmolol is not metabolized by plasma cholinesterase. Hydrolysis results in an acid metabolite and methanol with clinically insignificant levels.[157] Ninety percent of the drug is eliminated in the form of the acid metabolite, normally within 24 hours.[157] A loading dose of 500 μg/kg given intravenously followed by a 50 to 300 μg/kg per minute infusion reaches steady-state concentrations within 5 minutes. Without the loading dose, steady-state concentrations are reached in 30 minutes.[157]

Esmolol is cardioselective, blocking primarily β_1-receptors. It lacks ISA and membrane-stabilizing effects and is mildly lipid soluble. Esmolol produced significant reductions in BP, heart rate, and the cardiac index after a loading dose of 500 μg/kg and an infusion of 300 μg/kg per minute in patients with CAD, and the effects were completely reversed 30 minutes after discontinuation of the infusion.[158] Initial therapy during anesthesia may require significant reductions in the loading and infusion doses.

Hypotension is a common side effect of intravenous esmolol. The incidence of hypotension was higher with esmolol (36%) than with propranolol (6%) at equal therapeutic end points.[159] The cardioselective drugs may cause more hypotension because of β_1-induced myocardial depression and the failure to block β_2 peripheral vasodilation. Esmolol appears safe in patients with bronchospastic disease. In another comparative study with propranolol, esmolol and placebo did not change airway resistance, and 50% of patients treated with propranolol developed clinically significant bronchospasm.[160] Phlebitis may occur at the site of intravenous administration after prolonged infusion.[161]

Esmolol inhibits human plasma cholinesterase during in vitro studies, in which clinically insignificant prolongation of duration of succinylcholine action by esmolol was reported.[162] Digoxin levels may increase slightly with concomitant esmolol administration.[163] Esmolol and landiolol, a short-acting β_1-receptor blocker, suppress the bispectral index during general anesthesia.[164]

Labetalol

Labetalol is an equal mixture of four stereoisomers with various α- and β-blocking properties. Labetalol provides selective α_1-receptor blockade and nonselective β_1- and β_2-blockade. The potency of β-adrenergic blockade is 5- to 10-fold greater than α_1-adrenergic blockade.[15,164] Labetalol has partial β_2-agonist effects that promote vasodilation.[165] It is moderately lipid soluble and is completely absorbed after oral administration.[166] First-pass hepatic metabolism is significant, with production of inactive metabolites.[166] Renal excretion of the unchanged drug is minimal. Elimination half-life is approximately 6 hours.[166]

In contrast to other β-blockers, labetalol should be considered a peripheral vasodilator that does not cause a reflex tachycardia. BP and systolic vascular resistance decrease after an intravenous dose.[167] Stroke volume (SV) and CO remain unchanged, with the heart rate decreasing slightly.[168] The reduction in BP is dose related, and acutely hypertensive patients usually respond within 3 to 5 minutes after a bolus dose of 100 to 250 μg/kg.[169] However, the more critically ill or anesthetized patients should have their BP titrated beginning with 5- to 10-mg intravenous increments. The BP reduction may last as long as 6 hours after intravenous dosing.

Significant Adverse Effects

CHF can be precipitated by β-adrenergic blockers, especially when used with other cardiac drugs with myocardial depressant properties, such as calcium blockers and disopyramide. β-Blockers used with other depressant agents blunt the usual reflex in sympathetic activity.[170] The effects on the conduction system are additive, and heart block can occur. Propranolol reduces the clearance of many drugs that depend on hepatic metabolism by reducing hepatic blood flow (eg, lidocaine).[171]

β_2-Blockers can cause bronchospasm and peripheral vasoconstriction, which can exacerbate symptoms in patients with chronic pulmonary disease and peripheral vascular disease. Impotence is a problem in some patients. The lipophilic agents cause many CNS side effects such as depression, sleep disturbances, and fatigue. Hypoglycemia is a significant problem for diabetics.

Sudden withdrawal of β-adrenergic blockers can precipitate a state of enhanced adrenergic activity, resulting in tachycardia, hypertension, arrhythmias, myocardial ischemia, and infarction.[172] Most studies indicate that this period of hypersensitivity occurs 2 to 6 days after withdrawal of β-blockade and corresponds to an increase in human lymphocyte β-receptors. Continuing β-receptor blockers before cardiac surgery results in a more stable anesthetic induction, intubation, and sternotomy sequence than performing anesthesia and surgery during a period of withdrawal hypersensitivity.[82,173] Reinstitution of small doses of β-adrenergic blockade after cardiac surgery smoothes the postoperative course and reduces the incidence of tachyarrhythmias.[174]

Summary

β-Adrenergic blockers are first-line agents in the treatment of myocardial ischemia. These agents effectively reduce myocardial work and oxygen demand. Although perioperative β-blockers may decrease perioperative cardiovascular events in noncardiac surgery, the benefit may come at an increased short-term risk for severe complications, including stroke and death if started too close to the time of surgery.[175]

Calcium Channel Blockers

Calcium channel blockers reduce myocardial oxygen demands by depression of contractility, heart rate, and arterial BP.[176] Myocardial oxygen supply may be improved by dilation of coronary and collateral vessels. Calcium channel blockers are used primarily for symptom control in patients with stable angina pectoris. In an acute ischemic situation, calcium channel blockers (ie, verapamil and diltiazem) may be used for rate control when β-blockers cannot be used.

The most important effects of calcium channel blockers may be the treatment of variant angina. These drugs can attenuate ergonovine-induced coronary vasoconstriction in patients with variant angina, suggesting protection by coronary dilation.[177] Most episodes of silent myocardial ischemia, which may account for 70% of all transient ischemic episodes, are not related to increases in myocardial oxygen demands (ie, heart rate and BP); instead, intermittent obstruction of coronary flow is likely caused by coronary vasoconstriction or spasm.[178] All calcium channel blockers are effective at reversing coronary spasm, reducing ischemic episodes, and reducing NTG consumption in patients with variant or Prinzmetal angina.[179]

Combinations of NTG and calcium channel blockers, which also effectively relieve and possibly prevent coronary spasm, are rational therapy for variant angina. β-Blockers may aggravate anginal episodes in some patients with vasospastic angina and should be used with caution.[180] Preservation of CBF with calcium channel blockers is a significant difference from the predominant β-blocker antiischemic effects of reducing $M\dot{V}O_2$.

Calcium channel blockers have proved effective for treating of stable angina in controlled trials.[181–184] However, rapid-acting DHPs such as nifedipine may cause a reflex tachycardia, especially during initial therapy, and exacerbate anginal symptoms. These proischemic effects probably explain why the short-acting DHP nifedipine in high doses produces adverse effects in patients with unstable angina. The introduction of long-acting DHPs, such as extended-release nifedipine, amlodipine, felodipine, isradipine, nicardipine, and nisoldipine, has led to fewer adverse events. These agents should be used in combination with β-blockers. Some patients may have symptomatic relief improved more with calcium channel blockers than with β-blocker therapy; although it is difficult to predict which patients respond better by other than empiric observation.

The causes of unstable angina may involve coronary vasospasm, an accelerated atherosclerotic process, or enhanced platelet aggregation with fibrin clot formation. Calcium channel blockers have favorable effects in all three of the processes and are effective in the relief of symptoms of unstable angina.[185] There are no significant clinical differences in the response of patients with unstable angina to β-adrenergic blockers and calcium channel blockers.[186]

Calcium Channel

Calcium channels are functional pores in membranes through which calcium flows down an electrochemical gradient when the channels are open. Calcium channels exist in cardiac muscle, smooth muscle, and probably many other cellular membranes. These channels are also found in cellular organelle membranes such as the sarcoplasmic reticulum (SR) and mitochondria. Calcium functions as a primary generator of the cardiac action potential and an intracellular second messenger to regulate various intracellular events.[187]

Calcium enters cellular membranes through voltage-dependent channels or receptor-operated channels. The voltage-dependent channels depend on a transmembrane potential for activation (ie, opening). Receptor-operated channels are linked to a voltage-dependent channel after receptor stimulation or directly allow calcium passage through cell or organelle membranes independent of transmembrane potentials.

There are three types of voltage-dependent channels: the transient (T), long-lasting (L), and neuronal (N) channels.[188] The T and L channels are located in cardiac and smooth muscle tissue, whereas the N channels are located only in neural tissue. The T channel is activated at low voltages (−50 mV) in cardiac tissue, plays a major role in cardiac depolarization (ie, phase 0), and is not blocked by calcium antagonists.[189,190] The L channels are the classic slow channels, are activated at higher voltages (−30 mV), and are responsible for phase 2 of the cardiac action potential. These channels are blocked by calcium antagonists.[189,190]

Receptor-operated channels regulate calcium entry through voltage-regulated channels or through channels regulated by the receptor system. The β-adrenergic receptor operates an L-type voltage-dependent channel, which is activated by phosphorylation of a protein kinase by cAMP generated by the β-adrenergic receptor.[190] α_1-Receptor stimulation activates a G-protein, which causes phospholipase C to hydrolyze phosphatidylinositol diphosphate to diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3).[191] DAG activates protein kinase C that likely phosphorylates an L-type channel allowing calcium entry, whereas IP3 is a second messenger that interacts with the SR and directly promotes calcium release from the SR through an intracellular calcium channel.[192] A receptor-operated channel may also increase calcium entry stimulated directly by a G-protein. Both α_2-receptor and β-receptor stimulation may activate G-protein–regulated channels, which are not voltage dependent[193,194] (see Chapter 8).

Calcium channel blockers interact with the L-type calcium channel and are composed of drugs from four classes: the 1,4-DHP derivatives (eg, nifedipine, nimodipine, nicardipine, isradipine, amlodipine, felodipine); the phenylalkyl amines, (eg, verapamil); the benzothiazepines (eg, diltiazem); and a diarylaminopropylamine ether (ie, bepridil).[15] The L-type calcium channel has specific receptors that bind to each of the different chemical classes of calcium channel blockers.[195] Binding to calcium blocker receptors by DHP derivatives (eg, nifedipine) is voltage dependent.[196]

Calcium channels transform from a closed resting form that can potentially open, to an activated open form, to an inactive conformation that cannot open, and then back to the closed resting form. Nifedipine binds preferentially to the inactive receptor that has recently undergone activation and cannot open. Nifedipine essentially acts as a plug to block the channel. Verapamil binds to the L-type channel preferentially when it is active or open.[197] The greater the period of activation of the channel, the more effective is the blockade (ie, use dependent). Any repetitive activity, such as cardiac pacemaker activity, is sensitive to use-dependent agents.

Physiologic Effects

Hemodynamic Effects

Systemic hemodynamic effects of calcium channel blockers in vivo represent a complex interaction among myocardial depression, vasodilation, and reflex activation of the autonomic nervous system (Table 11.5).

TABLE 11.5 Calcium Channel Blocker Vasodilator Potency and Inotropic, Chronotropic, and Dromotropic Effects on the Heart

Characteristic	*Amlodipine*	*Diltiazem*	*Nifedipine*	*Verapamil*
Heart rate	↑/0	↓	↑/0	↓
Sinoatrial node conduction	0	↓↓	0	↓
Atrioventricular node conduction	0	↓	0	↓
Myocardial contractility	↓/0	↓	↓/0	↓↓
Neurohormonal activation	↑/0	↑	↑	↑
Vascular dilatation	↑↑	↑	↑↑	↑
Coronary flow	↑	↑	↑	↑

0, No effect.
From Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. *Am J Med.* 2004;116:35–43.

TABLE 11.6 Hemodynamic Effects of Intravenous Verapamil in 20 Patients With Coronary Artery Disease

Characteristic	*Before Verapamil*[a]	*After Verapamil*[a]	*Significance* (P)
Heart rate (beats/min)	74 ± 12	75 ± 12	NS
Mean arterial pressure (mm Hg)	94 ± 17	82 ± 13	<.0005
Right ventricular end-diastolic pressure (mm Hg)	4 ± 2	7 ± 2	<.0005
Left ventricular end-diastolic pressure (mm Hg)	12 ± 4	14 ± 4	<.25
Cardiac index (L/min/m^2)	2.8 ± 0.6	3.1 ± 0.7	<.0005
Stroke volume index (mL/m^2)	57 ± 12	63 ± 13	<.025
Systemic vascular resistance (dyne·sec·cm^{-5})	1413 ± 429	1069 ± 235	<.0005
Ejection fraction (%)	55 ± 16	61 ± 18	<.01

[a]Values are mean ± standard deviation.
NS, Not significant
From Ferlinz J, Easthope JL, Aronow WS. Effects of verapamil on myocardial performance in coronary disease. *Circulation.* 1979;59:313.

Nifedipine, like all DHPs is a potent arterial dilator with few venodilating effects.[198] Reflex activation of the sympathetic nervous system (SNS) may increase heart rate. The intrinsic negative inotropic effect of nifedipine is offset by potent arterial dilation, which lowers BP and increases CO in patients.[199] DHPs are excellent antihypertensive agents because of their arterial vasodilatory effects. Antianginal effects result from reduced myocardial oxygen requirements due to the afterload-reducing effect and to coronary vascular dilation resulting in improved myocardial oxygen delivery.

Verapamil is a less potent arterial dilator than the DHPs and results in less reflex sympathetic activation. In vivo, verapamil usually results in moderate vasodilation without significant changes in heart rate, CO, or SV[200] (Table 11.6). Intravenous administration of verapamil in the catheterization laboratory causes increases in right ventricular pressure and LVEDP, decreases in SVR, improvement of the ejection fraction (EF), and little change in pulmonary artery pressure.[201] Verapamil can significantly depress myocardial function in patients with preexisting ventricular dysfunction.[202]

Diltiazem is a less potent vasodilator and has fewer negative inotropic effects compared with verapamil. Clinical studies reveal reductions in SVR and BP, with increases in CO, pulmonary arterial wedge pressure, and EF[203] (Fig. 11.10). Diltiazem attenuates baroreflex increases in heart rate due to NTG and decreases in heart rate due to phenylephrine.[204] Regional blood flow to the brain and kidney increases, whereas skeletal muscle flow does not change.[205] In contrast to verapamil, diltiazem is not as likely to aggravate CHF, although it should be used carefully in these patients.[206]

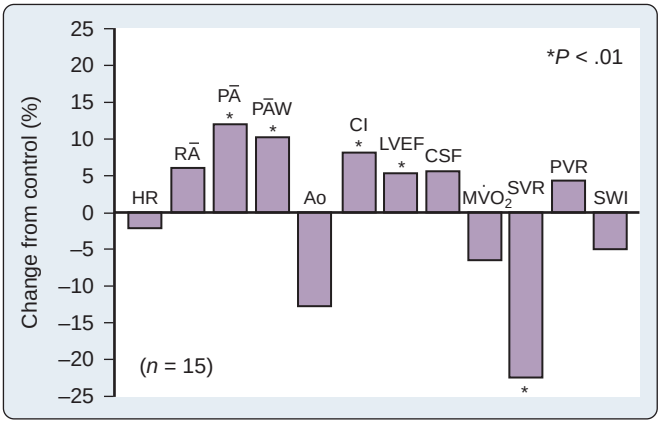


Fig. 11.10 Effects of intravenous diltiazem on systemic and coronary hemodynamics and LVEF in patients with coronary artery disease. *Ao*, Mean aortic pressure; *CI*, cardiac index; *CSF*, coronary sinus flow; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *MV̇O$_2$*, myocardial oxygen consumption; *PĀ*, mean pulmonary artery pressure; *PĀW*, mean pulmonary capillary wedge pressure; *PVR*, pulmonary vascular resistance; *RĀ*, mean right atrial pressure; *SVR*, systemic vascular resistance; *SWI*, stroke work index. *(Modified from Josephson MA, Singh BN. Use of calcium antagonists for ventricular dysfunction.* Am J Cardiol. *1985;55:81B; Abrams J. Nitrates. In: Chatterjee K, Cheitlin MD, Karliner J, et al, eds.* Cardiology. An Illustrated Text/Reference. *Vol 1. Philadelphia: Lippincott; 1991:2.75–2.90.)*

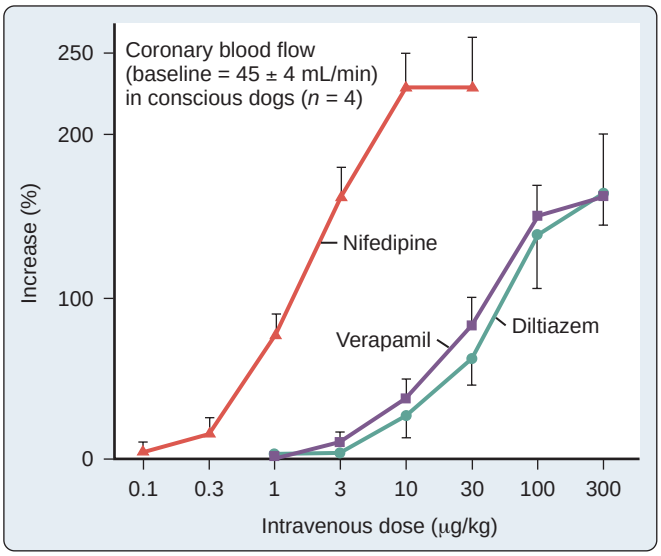


Fig. 11.11 Coronary blood flow responses to intravenous diltiazem, nifedipine, and verapamil in the conscious normal dog. In contrast to nitroglycerin and β-blockers, calcium channel blockers increase total coronary flow. Data are mean values ± SE (*n* = 4). *(From Millard RW, Grupp G, Grupp IL, et al. Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. A comparative study of physiological responses and membrane receptor activity.* Circ Res. *1983;52[suppl I]:29.)*

Coronary Blood Flow

Coronary artery dilation occurs with the calcium channel blockers, along with increases in total CBF (Fig. 11.11). Nifedipine is the most potent coronary vasodilator, especially in epicardial vessels, which are prone to coronary vasospasm. Diltiazem is effective in blocking coronary artery vasoconstriction caused by a variety of agents, including α-agonists, serotonin, prostaglandin, and acetylcholine.[177,207,208]

Calcium channel blockers may dilate the coronary artery at the stenotic site, reducing the pressure gradient across the coronary lesion.[177]

Diltiazem preferentially dilates coronary arteries compared with other peripheral vessels.[209] Animal studies demonstrate that nifedipine, verapamil, and diltiazem increase coronary collateral flow distal to coronary ligation in animals and improve subendocardial flow relative to subepicardial flow[210–213] (Fig. 11.12).

Electrophysiologic Effects

Calcium channel blockers exert their primary electrophysiologic effects on tissue of the conducting system that depends on calcium for generation of the action potential, primarily at the sinoatrial (SA) and AV nodes. They do not alter the effective refractory period (ERP) of atrial, ventricular, or His-Purkinje tissue. Diltiazem and verapamil exert these electrophysiologic effects in vivo and in vitro, whereas the DHPs' (eg, nifedipine) electrophysiologic depression is completely attenuated by reflex sympathetic activation. Nifedipine can enhance SA and AV node conduction, whereas verapamil and diltiazem slow conduction velocity and prolong refractoriness of nodal tissue.[214–216]

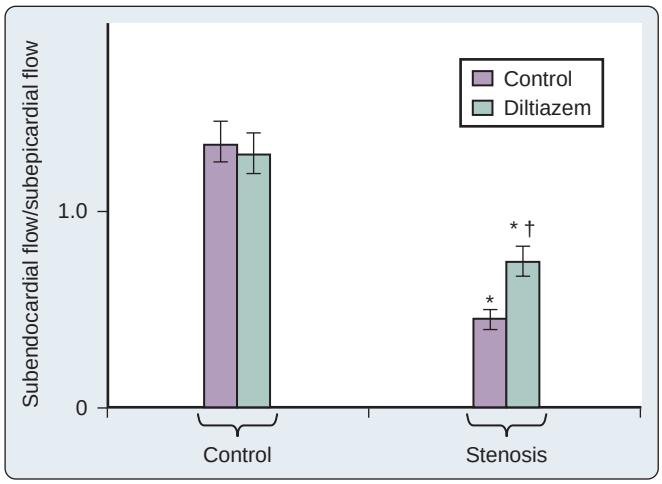


Fig. 11.12 The ratio of subendocardial to subepicardial blood flow during resting control conditions and in the setting of proximal stenosis, which prevented arterial inflow from increasing above the preocclusion control after a 10-second coronary artery occlusion in animals. Diltiazem increased subendocardial to subepicardial blood flow ratio in the ischemic area. Values are mean ± SEM. *$P < .05$ compared with measurements during control conditions with unimpeded arterial inflow. †$P < .05$ compared with the control stenosis. *(From Bache RJ, Dymek DJ. Effect of diltiazem on myocardial blood flow.* Circulation. *1982;65[suppl I]:1.)*

Atherosclerosis

Calcium is involved in the generation of atherosclerotic plaque and in damaged atherosclerotic tissue (ie, calcification).[217] Verapamil and nifedipine have antiatherogenic effects.[217] Nifedipine can retard angiographic progression of CAD in humans.[218] Diltiazem may also reduce atherosclerotic progression after heart transplantation.[219] Diltiazem suppresses aortic atherosclerosis (but not that of coronary arteries), inhibits spontaneous calcinosis in hypertensive rats, and prevents vitamin D–induced calcinosis in arterial elastic tissue.[220–222] Diltiazem also suppresses necrosis of aortic smooth muscle cells by hyperlipidemia serum[223] and intimal thickening in rabbit carotid arteries.[224]

Platelet Aggregation

Calcium antagonists, nitrates, and β-adrenergic blockers inhibit platelet aggregation. This may be the most important effect of all antiischemic drugs, especially in the treatment of chronic disease. Calcium is a mediator involved in the release of platelet aggregatory factors, such as adenosine diphosphate, and verapamil inhibits calcium-induced release of these factors.[225] Diltiazem inhibition of platelet aggregation correlates with changes in intracellular calcium levels.[226] In vivo, diltiazem inhibits platelet aggregation after 24 hours in healthy volunteers.[227] Similar antiaggregatory effects of diltiazem were seen in patients with unstable angina, but no inhibitory effect of platelet aggregation was found with verapamil. Diltiazem metabolites are even more effective in inhibiting platelet aggregation than diltiazem.[228]

Metabolic Effects

Nifedipine may be associated with decreases in serum glucose levels in diabetics, but glucose levels in normal volunteers usually rise slightly with nifedipine and in hypertensive patients with diltiazem.[229,230] Diltiazem reportedly has no effect on insulin, glucagon, growth hormone, or cortisol levels.[231,232] However, nifedipine apparently delays insulin release in diabetic patients.[232]

Pharmacology

Table 11.7 illustrates the pharmacokinetic parameters of the US Food and Drug Administration (FDA)–approved antiischemic calcium channel blockers.

TABLE 11.7 Properties of Calcium Antagonists in Clinical Use

Drug	*Usual Dosage*	*Duration of Action (Half-Life)*	*Side Effects*
Dihydropyridines			
Nifedipine	Immediate release: 30–90 mg qd Slow release: 30–180 mg	Short (0.2–1 h) Long (24 h)	Hypotension, dizziness, flushing, nausea, constipation, edema Hypotension, dizziness, flushing, nausea, constipation, edema
Amlodipine	5–10 mg qd	Very long (30–50 h)	Headache, edema
Felodipine	5–10 mg qd	Long (11–16 h)	Headache, edema
Isradipine	2.5–10 mg qd	Medium (8–12 h)	Headache, fatigue
Nicardipine	Immediate release: 20–40 mg tid Slow release: 30–60 mg bid	Short (6–8 h) Medium (8–12 h)	Headache, dizziness, flushing, edema
Nisoldipine	20–40 mg qd	Short (7–12 h)	Hypotension, dizziness, flushing, nausea, constipation, edema
Nitrendipine	20 mg qd or bid	Long (12–24 h)	Hypotension, dizziness, flushing, nausea, constipation, edema
Miscellaneous			
Bepridil	200–400 mg qd	Very long (3 0–40 h)	Arrhythmias, dizziness, nausea
Benzothiazepines			
Diltiazem	Immediate release: 30–90 mg qd Slow release: 120–480 mg qd	Short (6–8 h) Long (12–24 h)	Hypotension, dizziness, flushing, bradycardia, edema Hypotension, dizziness, flushing, bradycardia, edema
Phenylalkylamines			
Verapamil	Immediate release: 80–160 mg tid Slow release: 120–480 mg qd	Short (6–8 h) Long (12–24 h)	Hypotension, heart failure, myocardial depression, edema, bradycardia Hypotension, heart failure, myocardial depression, edema, bradycardia

From Gibbons RJ, Chatterjee K, Daley J, Douglas JS. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol.* 1999;33:2092–2197.

Nifedipine

Nifedipine was the first dihydropyridine derivative to be used clinically. Other dihydropyridines available for clinical use include nicardipine, isradipine, amlodipine, felodipine, and nimodipine.[233] In contrast to the other calcium channel blockers, nimodipine is highly lipid soluble and penetrates the blood-brain barrier. It is indicated for vascular spasm after intracerebral bleeding.

Nifedipine's oral bioavailability is approximately 70%, with peak plasma levels occurring within 30 to 45 minutes. The rate of protein binding is 95%, and the elimination half-life is approximately 5 hours. Nifedipine is available for oral administration in capsular form. The compound degenerates in the presence of light and moisture, preventing commercially available intravenous preparations. Puncture of the capsule and sublingual administration provide an onset of effects in 2 to 3 minutes. Nifedipine GITS (GastroIntestinal Therapeutic System, Procardia XL), a long-acting, controlled-release delivery system, is available for single daily dosing and has become the preferred preparation. It has an onset of action of 20 minutes, with steady-state plasma levels being reached in 48 hours.

Nicardipine

Nicardipine is a dihydropyridine agent with a longer half-life than nifedipine and with vascular selectivity for coronary and cerebrovascular beds. Nicardipine may be the most potent overall relaxant of vascular smooth muscle among the dihydropyridines.[234] Peak plasma levels are reached 1 hour after oral administration, with bioavailability of 35%.[235] Plasma half-life is approximately 8 to 9 hours. Although the drug undergoes extensive hepatic metabolism with less than 1% of the drug excreted renally, greater renal elimination occurs in some patients.[236] Plasma levels may increase in patients with renal failure, and reduction of the dose is recommended in these patients.[235]

Nicardipine is a potent cerebrovascular vasodilator that has prevented ischemia-related neuronal necrosis in animal studies.[237,238] Marked improvements in CBF occur with nicardipine.[239] Although coronary vasodilation is one explanation, positive inotropic effects with phosphodiesterase activity or calcium channel agonist (and antagonist) activity resulting in autoregulatory increases in blood flow may be an additional mechanism.[240]

Verapamil

Verapamil's structure is similar to that of papaverine. Verapamil exhibits significant first-pass hepatic metabolism, with a bioavailability of only 10% to 20%.[241] One hepatic metabolite, norverapamil, is active and has a potency approximately 20% of that of verapamil.[241] Peak plasma levels are reached within 30 minutes. Bioavailability markedly increases in hepatic insufficiency, mandating reduced doses.[241] Intravenous verapamil achieves hemodynamic and dromotropic effects within minutes, peaking at 15 minutes and lasting up to 6 hours. Accumulation of the drug occurs with prolonged half-life during long-term oral administration.[242]

Verapamil's metabolism depends on hepatic blood flow and may decrease in the presence of H_2-receptor blockers. Increased metabolism may occur when hepatic enzyme-inducible agents such as phenobarbital are given concomitantly. Seventy percent of verapamil's metabolites are recovered in the urine and 15% in feces.

Diltiazem

After oral dosing, the bioavailability of diltiazem is greater than verapamil's, varying between 25% to 50%.[243] Peak plasma concentration is achieved between 30 to 60 minutes, and the elimination half-life is 2 to 6 hours.[243] Protein binding is approximately 80%. As with verapamil, hepatic clearance is flow dependent, and major hepatic metabolism occurs, with metabolites having 40% of the clinical activity of diltiazem.[244,245] Hepatic disease may require decreased dosing, whereas renal failure does not affect dosing.[246]

Clevidipine

Clevidipine is a dihydropyridine agent with a unique chemical structure that renders it inactive by cleavage of an ester linkage by nonspecific esterases in the blood and in tissues. This unique property renders it extremely short acting, similar to other drugs (eg, esmolol) that are metabolized through this pathway. Its initial phase half-life is 1 minute, with 90% of the drug eliminated. Its clinical effects are fully reversed in 5 to 15 minutes for most patients after discontinuing the infusion.[247]

Clevidipine is a potent arterial vasodilator whose primary use is as a parenteral antihypertensive agent. A reflexive tachycardia may be seen with its use in healthy volunteers and patients with essential hypertension that combined with possible hypotension would limit its role in treating ongoing myocardial ischemia.[248] In studies looking at perioperative and postoperative cardiac surgical patients, clevidipine was effective in decreasing mean arterial pressure but did not effect heart rate or filling pressures.[249]

Significant Adverse Effects

Most significant adverse hemodynamic effects can be predicted from calcium channel blockers' primary effects of vasodilation and negative inotropy, chronotropy, and dromotropy. Hypotension, HF, bradycardia, asystole, and AV nodal block have occurred with calcium channel blockers.[250] These side effects are more likely to occur with combination therapy with β-blockers or digoxin in the setting of hypokalemia.[250]

Verapamil increases digoxin levels, diltiazem has variable effects, and nifedipine has no effect on digoxin levels.[251–253] Cimetidine and ranitidine increase calcium blockers' serum levels by liver enzyme induction or reductions of hepatic blood flow.[254] The physiologic effects of calcium blockers may be additive to those of anesthetic agents in animal studies, but clinically significant effects vary.[255,256] The cautious use of intravenous verapamil with a β-adrenergic receptor antagonist is necessary because of the increased risk of AV block or severe myocardial depression.

Paradoxical aggravation of myocardial ischemia may be seen with the short-acting dihydropyridines (eg, nifedipine).[257] This may result from decreased coronary perfusion pressure with associated hypotension, selective vasodilation in the nonischemic region (ie, coronary steal), or increased oxygen demand as a result of reflex sympathetic stimulation and tachycardia.

Case reports of a withdrawal syndrome similar to β-blocker withdrawal have been presented. Five of 143 patients had significant ST-segment changes after diltiazem or verapamil withdrawal.[258] MI and coronary spasm have been reported after diltiazem withdrawal.[259,260] One study comparing propranolol with verapamil withdrawal in patients with stable angina found that 2 of 20 patients had severe exacerbation of their angina with propranolol withdrawal, and no patients had hemodynamic or symptomatic evidence of a withdrawal phenomenon with verapamil.[261]

Summary

Calcium antagonists provide excellent symptom control in patients with unstable angina. In the absence of β-adrenergic blockade, the short-acting dihydropyridine nifedipine may increase the risk of MI or recurrent angina. When β-adrenergic blockers cannot be used and heart rate slowing is indicated, verapamil and diltiazem may offer an alternative.

Drug Therapy for Systemic Hypertension

Systemic hypertension, long recognized as a leading cause of cardiovascular morbidity and mortality, accounts for enormous health-related expenditures. Almost one-fourth of the US population has hypertensive vascular disease, but 30% of these individuals are unaware of their condition, and another 30% to 50% are inadequately treated.[262,263] On a worldwide basis, almost 1 billion individuals are hypertensive.[264] Based on data from the Framingham Heart study, normotensive patients at age 55 can expect a 90% lifetime risk for subsequent development of hypertension.[265] Hypertension management comprises the most common reason underlying adult visits to primary care physicians, and antihypertensive drugs are the most prescribed medication class.[262]

Despite the asymptomatic nature of hypertensive disease, with symptom onset delayed 20 to 30 years after development of systemic hypertension, substantial and incontrovertible evidence demonstrates a direct association between systemic hypertension and increased morbidity and mortality. The World Health Organization (WHO) estimates that hypertension underlies one in eight deaths worldwide, making elevated BP the third leading cause of mortality.[261]

Hypertension is the single most treatable risk factor for MI, stroke, peripheral vascular disease, CHF, renal failure, and aortic dissection.[262] In prospective, randomized trials, over the course of adult lifetimes, successful treatment of hypertension has been associated with a 35% to 40% reduction in the incidence of stroke, 50% reduction in CHF, and 25% reduction in MIs.[261,262] Improved treatment of hypertension has been credited with the major reductions in stroke and cardiovascular mortality occurring in the United States during the past 30 years.

Pathophysiologic mechanisms underlying predisposition to hypertension remain unclear. Undoubtedly, genetic and environmental factors play contributory roles.[266] Concordance for hypertension is greater between monozygotic or dizygotic twins and even siblings within a single family than that observed between unrelated individuals, supporting a genetic component. However, by some estimates, genetic predeterminants account for only 30% to 40% of hypertensive disease.[266] A direct association between body mass index and hypertension has been reported, and dietary sodium intake has been associated with a long-term risk of hypertension.[267,268]

In most cases, no single reversible mechanism underlying systemic hypertensive disease can be identified for *primary* or *essential hypertension*. In about 5% of hypertensive patients, a distinct cause promoting systemic hypertension can be identified. The most common cause underlying *secondary hypertension* is renal insufficiency. Less common mechanisms include pheochromocytoma, renal artery stenosis, and hypertension resulting from adrenal cortical abnormalities such as primary aldosteronism or Cushing syndrome. Diagnostic clues for secondary hypertension include hypertensive disease refractory to medical therapy, unusually abrupt onset with severe associated symptoms, or occurrence of hypertension at a particularly young age.

Definitions for hypertension are somewhat arbitrary, although derived from clinical trials suggesting systemic pressures at which the benefits of treatment outweigh the risk for adverse effects related to antihypertensive therapy. BP varies with normal distribution across the population at large, and aging is associated with progressive increases in systolic pressure. After 50 years of age, reductions in diastolic pressure and widening pulse pressure prove common. Published evidence suggests that systolic and pulse pressures are better predictors for morbidity and mortality than diastolic pressure.[262]

The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) provided significant modifications to prior recommendations for the management of high BP. In contrast to prior guidelines, JNC8 recommendations are derived from evidence-based guidelines drawn only from randomized, controlled trials (RCTs). Specific recommendations emanating from the new guidelines include lifestyle interventions and pharmacologic treatment as needed to attain systolic BPs less than 150 mm Hg and diastolic BPs less than 90 mm Hg for adults 60 years of age and older. For younger patients and those with diabetes or chronic kidney disease, treatment goals include systolic BPs less than 140 mm Hg and diastolic BPs less than 90 mm Hg.[262,269]

Although antihypertensive drug therapy is widely regarded as essential for BPs greater than 150/90 mm Hg, evidence suggests benefits to more aggressive BP reduction for certain patient subsets. The association between systemic BP and cardiovascular risk has been described as a J curve, with progressive cardiovascular risk reductions accompanying BP reductions until a critical threshold, after which the potential for myocardial ischemia and other organ injury increases.[270] Risk for cardiovascular disease appears to increase at BPs greater than 115/75 mm Hg, with a doubling in risk associated with each 20/10-mm Hg increment in systemic pressure.[262]

Medical Treatment for Hypertension

Almost 80 distinct medications are marketed for the treatment of hypertension (Table 11.8).[262] Combined therapy with two or more classes of antihypertensive medications is often needed to achieve treatment goals (Table 11.9).[271] Although the specific drug selected for initial therapy is deemed less important than in the past, recognition that specific antihypertensive drug classes alleviate end-organ damage beyond that associated with reductions in systemic BP has led to targeted selection of antihypertensive drug combinations on the basis of coexisting risk factors such as recent MI, chronic renal insufficiency, or diabetes.

Diuretics

Thiazide diuretic therapy comprises the cornerstone of most antihypertensive regimens.[272,273] Three classes of diuretics have proved efficacious in reducing systemic BP: the thiazide and related sulfonamide compounds, loop diuretics, and potassium-sparing agents. All classes of diuretics initially reduce BP by increasing urinary excretion of sodium, with resultant reductions in plasma volume and CO. However, over a period of 6 to 8 weeks, diuretic therapy leads to reductions in SVR, which is hypothesized to activate vascular endothelial potassium channels.

Thiazide diuretics remain the first choice for most patients with hypertension.[274] Although the natriuretic effect achieved by blockade of sodium and chloride transport in the distal convoluted tubule is relatively weak, thiazide diuretics usually produce 10-mm Hg reductions in BP and have proved efficacious in numerous randomized trials to reduce morbidity and mortality related to hypertensive vascular disease.[262,271]

Loop diuretics, the most potent natriuretics of this class, block sodium, potassium, and chloride transport in the thick ascending loop of Henle. Loop diuretics typically are reserved for patients with renal insufficiency (ie, serum creatinine >2 mg/dL or creatinine clearance <25 mL/min) or CHF, conditions for which thiazide diuretics prove relatively ineffective. The short duration of action of loop diuretics (eg, 4 to 6 hours for furosemide) and greater likelihood for adverse effects limit more widespread application.

Potassium-sparing and aldosterone receptor–blocking diuretics are among the weakest natriuretics of this class. These drugs act by a variety of mechanisms to inhibit sodium reabsorption from the distal collecting duct while simultaneously reducing urinary potassium excretion. These drugs most commonly are administered in combination with a thiazide diuretic to reduce the incidence of hypokalemia or for their salutary effects in chronic HF.

Low doses of diuretics are well tolerated, but common adverse effects of this drug class include hypokalemia (due to renal potassium wasting), impaired glucose tolerance and insulin resistance, hyperuricemia, hypercalcemia, hyperlipidemia, and hyponatremia (rare). The potassium-sparing and aldosterone receptor–blocking drugs are relatively contraindicated for patients at risk for hyperkalemia, particularly those with renal insufficiency.

β-Adrenergic Receptor Blockers

β-Adrenergic receptor blockers, which reduce sympathetic stimulation of the heart and vasculature, comprise another common antihypertensive therapy, particularly in settings of CAD or CHF.[275–279] The β-blockers inhibit myocardial and peripheral β_1-adrenergic receptors to reduce CO. β-Blockers reduce renin release from renal juxtaglomerular cells and norepinephrine release by inhibition of prejunctional β_2-adrenergic receptors in the peripheral vasculature.

β-Blockers traditionally are classified on the basis of cardioselectivity, lipid solubility, and intrinsic sympathetic activity. First-generation agents such as propranolol nonselectively block both β_1- and β_2-adrenergic receptors. Second-generation agents (eg, metoprolol, atenolol) exhibit a relatively cardioselective preference for β_1-adrenergic receptor blockade at low doses. Pindolol, a novel β-blocker with ISA, stimulates vasodilation by activation of β_2-adrenergic receptors. Combination agents such as labetalol provide mixed β- and

TABLE 11.8 Oral Antihypertensive Drugs

Drug (Trade Name)	*Usual Dose Range (mg/d)*[a]	*Usual Frequency*
Thiazide Diuretics		
Chlorothiazide (Diuril)	125–500	qd or bid
Chlorthalidone (generic)	12.5–25	qd
Hydrochlorothiazide (Microzide, HydroDIURIL)[b]	12.5–50	qd
Polythiazide (Renese)	2–4	qd
Indapamide (Lozol)[b]	1.25–2.5	qd
Metolazone (Mykrox)	0.5–1.0	qd
Metolazone (Zaroxolyn)	2.5–5	qd
Loop Diuretics		
Bumetanide (Bumex)[b]	0.5–2	bid
Furosemide (Lasix)[b]	20–80	bid
Torsemide (Demadex)[b]	2.5–10	qd
Potassium-Sparing Diuretics		
Amiloride (Midamor)[b]	5–10	qd or bid
Triamterene (Dyrenium)	50–100	qd or bid
Aldosterone Receptor Blockers		
Eplerenone (Inspra)	50–100	qd
Spironolactone (Aldactone)[b]	25–50	qd
β-Blockers		
Atenolol (Tenormin)[b]	25–100	qd
Betaxolol (Kerlone)[b]	5–20	qd
Bisoprolol (Zebeta)[b]	2.5–10	qd
Metoprolol (Lopressor)[b]	50–100	qd or bid
Metoprolol extended release (Toprol XL)	50–100	qd
Nadolol (Corgard)[b]	40–120	qd
Propranolol (Inderal)[b]	40–160	bid
Propranolol long acting (Inderal LA)[b]	60–180	qd
Timolol (Blocadren)[b]	20–40	bid
β-Blockers with Intrinsic Sympathomimetic Activity		
Acebutolol (Sectral)[b]	200–800	bid
Penbutolol (Levatol)	10–40	qd
Pindolol (generic)	10–40	bid
β-Blockers with Vasodilating Nitric Oxide–Mediated Activity		
Nebivol (Bystolic)	5–40	qd
Combined α-Blockers and β-Blockers		
Carvedilol (Coreg)	12.5–50	bid
Labetalol (Normodyne, Trandate)[b]	200–800	bid
Angiotensin-Converting Enzyme Inhibitors		
Benazepril (Lotensin)[b]	10–40	qd
Captopril (Capoten)[b]	25–100	bid
Enalapril (Vasotec)[b]	5–40	qd or bid
Fosinopril (Monopril)	10–40	qd
Lisinopril (Prinivil, Zestril)[b]	10–40	qd
Moexipril (Univasc)	7.5–30	qd
Perindopril (Aceon)	4–8	qd
Quinapril (Accupril)	10–80	qd
Ramipril (Altace)	2.5–20	qd
Trandolapril (Mavik)	1–4	qd
Angiotensin Receptor Blockers		
Azilsartan (Edarbi)	80	qd
Candesartan (Atacand)	8–32	qd
Eprosartan (Teveten)	400–800	qd or bid
Irbesartan (Avapro)	150–300	qd
Losartan (Cozaar)	25–100	qd or bid
Olmesartan (Benicar)	20–40	qd
Telmisartan (Micardis)	20–80	qd
Valsartan (Diovan)	80–320	qd or bid
Direct Renin Inhibitor		
Aliskiren (Tekturna)	150–300	qd
Nondihydropyridine Calcium Channel Blockers		
Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac)[b]	180–420	qd
Diltiazem extended release (Cardizem LA)	120–540	qd
Verapamil immediate release (Calan, Isoptin)[b]	80–320	bid
Verapamil long acting (Calan SR, Isoptin SR)[b]	120–480	qd or bid
Verapamil (Coer, Covera HS, Verelan PM)	120–360	qd
Dihydropyridine Calcium Channel Blockers		
Amlodipine (Norvasc)	2.5–10	qd
Felodipine (Plendil)	2.5–20	qd
Isradipine (Cynacirc CR)	2.5–10	bid
Nicardipine sustained release (Cardene SR)	60–120	bid
Nifedipine long acting (Adalat CC, Procardia XL)	30–60	qd
Nisoldipine (Sular)	17–34	qd
α_1-Blockers		
Doxazosin (Cardura)	1–16	qd
Prazosin (Minipress)[b]	2–20	bid or tid
Terazosin (Hytrin)	1–20	qd or bid
Central α_2-Agonists and Other Centrally Acting Drugs		
Clonidine (Catapres)[b]	0.1–0.8	bid
Clonidine patch (Catapres-TTS)	0.1–0.3	qwk
Methyldopa (Aldomet)[b]	250–1000	bid
Reserpine (generic)	0.1–0.25	qd
Guanfacine (Tenex)[b]	0.5–2	qd
Direct Vasodilators		
Hydralazine (Apresoline)[b]	25–100	bid
Minoxidil (Loniten)[b]	2.5–80	qd or bid

[a]In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (ie, trough effect). Blood pressure should be measured just before dosing to determine whether satisfactory control is obtained, and an increase in dosage or frequency may be needed. Dosages may vary from those listed in the *Physicians' Desk Reference* (PDR), 5th ed.

[b]Available now or soon to become available in generic preparations.

Modified from Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206.)

α_1-adrenergic blocking properties, resulting in inhibition of sympathetic activity and direct vasodilatory effects.

As with the diuretics, β-blockers typically are well tolerated at low doses, but nonselective blockade of β-adrenergic receptors may result in bronchospasm, Raynaud phenomenon, depression, and HF or heart block. β-Blockers are relatively contraindicated for patients with asthma or reactive airways disease, heart block, or depression. Rapid withdrawal of β-blockers may be associated with rebound adrenergic stimulation and potential for exacerbating myocardial and peripheral vascular ischemia; β-blocker discontinuation must occur by gradual, stepped dose reductions.

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors reduce peripheral vascular resistance by inhibiting conversion of angiotensin I (Ang I) to the highly vasoconstrictive angiotensin II (Ang II).[280] Evidence suggests that much of the long-term antihypertensive effect of ACE inhibitors is derived from protective effects on bradykinin degradation. Bradykinin, a potent vasodilator under normal conditions, undergoes degradation by the action of ACE. ACE inhibition results in increased plasma and tissue concentrations of bradykinin.

Persistent, dry cough accounts for the most common adverse effect associated with ACE inhibitor administration. Attributed to

TABLE 11.9 Combination Drugs for Hypertension

Fixed-Dose Combinations[a] *(mg)*	*Trade Names*
Angiotensin-Converting Enzyme Inhibitor/Calcium Channel Blocker	
Amlodipine/benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
Enalapril/felodipine (5/5)	Lexxel
Trandolapril/verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
Angiotensin-Converting Enzyme Inhibitor/Diuretic	
Benazepril/hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
Captopril/hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
Enalapril/hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
Fosinopril/hydrochlorothiazide (10/12.5, 20/12.5)	Monopril HCT
Lisinopril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
Moexipril/hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
Quinapril/hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
Angiotensin II Receptor Blocker/Diuretics	
Candesartan/hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
Eprosartan/hydrochlorothiazide (600/12.5, 600/25)	Teveten HCT
Irbesartan/hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
Losartan/hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
Olmesartan medoxomil/hydrochlorothiazide (20/12.5, 40/12.5, 40/25)	Benicar HCT
Telmisartan/hydrochlorothiazide (40/12.5, 80/12.5)	Micardis HCT
Valsartan/hydrochlorothiazide (80/12.5, 160/12.5, 160/25)	Diovan HCT
β-Blocker/Diuretic	
Atenolol/chlorthalidone (50/25, 100/25)	Tenoretic
Bisoprolol/hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
Metoprolol/hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
Nadolol/bendroflumethiazide (40/5, 80/5)	Corzide
Propranolol LA/hydrochlorothiazide (40/25, 80/25)	Inderide LA
Timolol/hydrochlorothiazide (10/25)	Timolide
Centrally Acting Drug/Diuretic	
Methyldopa/hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
Reserpine/chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton
Reserpine/chlorothiazide (0.125/250, 0.25/500)	Diupres
Reserpine/hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic/Diuretic	
Amiloride/hydrochlorothiazide (5/50)	Moduretic
Spironolactone/hydrochlorothiazide (25/25, 50/50)	Aldactazide
Triamterene/hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide
Triple Drug Combinations	
Aliskiren/amlodipine/hydrochlorothiazide	Amturnide
Valsartan/amlodipine/hydrochlorothiazide	Exforge HCT
Olmesartan/amlodipine/hydrochlorothiazide	Tribenzor

[a]Some drug combinations are available in multiple fixed doses, which are reported in milligrams. Modified from Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206.

elevated concentrations of bradykinin, this side effect frequently leads to discontinuation of therapy. Angioedema, also attributable to elevated bradykinin concentrations, occurs less commonly. Angioedema may occur at any time during therapy, occurs most frequently in African Americans, and may prove fatal due to airway compromise. Increased potential for hyperkalemia occurs in patients with renal insufficiency and those receiving potassium supplements or potassium-sparing diuretics. ACE inhibitors can induce renal failure in patients with bilateral renal artery stenosis and may potentiate severe, intractable hypotension in patients with particularly elevated renin activity (eg, decompensated HF, intravascular volume depletion). ACE inhibitors pose a teratogenic risk and are therefore contraindicated in pregnancy.

Angiotensin II Antagonists

Ang II antagonists (ie, angiotensin receptor blockers) may be the best tolerated of all current antihypertensive therapies and are increasingly a favored drug therapy for management of hypertensive vascular disease.[280] Ang II antagonists bind and competitively inhibit Ang II AT_1 receptors, directly inhibiting the vasoconstrictive effects of Ang II.[281]

Similar concerns to those for ACE inhibitors exist with regard to administration of Ang II antagonists in the settings of bilateral renal artery stenosis or hypovolemia, but Ang II antagonists typically are not associated with cough and are rarely implicated in angioedema. Ang II antagonists are contraindicated in pregnancy.

Calcium Channel Blockers

Calcium channel blockers, commonly classified as dihydropyridines or nondihydropyridines, share a common mechanism of action in binding various sites on the α_1 subunit of the L-type voltage-dependent calcium channel to partially inhibit calcium entry into cells. Although all calcium channel blockers induce arterial vasodilation, the dihydropyridines more frequently induce reflex tachycardia, whereas the nondihydropyridines (eg, diltiazem, verapamil) more commonly impair cardiac conduction and contractility.[282]

Common side effects reported with calcium channel blockers and relating to arterial vasodilation include ankle edema, flushing, and headaches. Nondihydropyridines are relatively contraindicated in patients with preexisting HF or cardiac conduction defects due to the potential for precipitating HF and heart block. Controversy surrounding the safety of calcium channel blockers has been somewhat negated by prospective, randomized trials demonstrating the safety and efficacy of long-acting calcium channel blockers for the treatment of hypertensive cardiovascular disease.[283–285] Administration of short-acting dihydropyridines (eg, nifedipine) for rapid control of hypertension has been associated with an increased incidence of acute coronary events and is contraindicated in the acute treatment of severe hypertension.

α_1-Adrenergic Receptor Blockers

α_1-Adrenergic blockers competitively inhibit binding of norepinephrine to α_1-adrenergic receptors in the peripheral vasculature to produce vasodilation and BP reductions. Prazosin and its congeners selectively block postsynaptic α_1-adrenergic receptors. Continued activity of the presynaptic α_1-receptors allows for downregulation of norepinephrine release, limits development of tolerance, and reduces the incidence of compensatory tachycardia. In contrast, phenoxybenzamine, commonly used in the preoperative management of pheochromocytoma, blocks both presynaptic and postsynaptic α_1-adrenergic receptors.

Adverse effects associated with α_1-blockers include orthostatic hypotension, fluid retention, and reflex tachycardia.[286] Although rarely administered as monotherapy, α_1-blockers continue to prove useful in combination with other antihypertensives due to their lack of metabolic side effects and propensity to dilate urethral smooth muscle to alleviate symptoms of prostatism.[262]

Central α_2-Adrenergic Receptor Agonists and Other Centrally Acting Drugs

Centrally acting antihypertensive agents (eg, clonidine, methyldopa) stimulate α_2-adrenergic and imidazoline receptors within the CNS to reduce sympathetic outflow and SVR. In the case of clonidine, activation of presynaptic α-adrenergic receptors inhibits norepinephrine release and subsequent catecholamine generation.[287] Reserpine differs from the α_2-agonists in that it inhibits reuptake of norepinephrine by storage vesicles in the postganglionic adrenergic neurons, depleting norepinephrine. As opposed to the α_2-agonists, reserpine's peripheral effects predominate over central activity.

More widespread use of centrally acting antihypertensives has been limited by CNS-mediated adverse effects, including sedation, depression, and dry mouth. Autoimmune hemolytic anemia has been reported with methyldopa. Abrupt discontinuation of clonidine frequently results in rebound hypertension, but this effect may be

alleviated with transdermal clonidine patches or the longer-acting oral agent guanfacine. All centrally acting antihypertensives are contraindicated in the setting of depression.

Direct Vasodilators

Hydralazine and minoxidil produce potent direct arterial vasodilation mediated by activation of ATP-sensitive potassium channels within the arterial vasculature. The relative lack of effect by direct vasodilators on venous capacitance vessels reduces the potential for orthostatic hypotension. The potency and propensity for adverse effects limit applications to hypertensive disease resistant to standard pharmacologic approaches, most often in the setting of severe hypertension associated with chronic renal failure.

Hydralazine and minoxidil promote peripheral edema formation and profound reflex sympathetic activation manifested as tachycardia, headaches, and flushing. Minoxidil, a more potent antihypertensive than hydralazine, frequently is associated with hirsutism. Reflex sympathetic responses to direct vasodilators necessitate concomitant administration of diuretics and β-adrenergic blockers to alleviate potential for fluid retention and myocardial ischemia.

Novel Approaches to Antihypertensive Therapy

Despite the array of antihypertensive medications available, the heterogeneity of treatment effect and adverse effects of current drugs on quality of life measures suggest the need for alternative approaches to antihypertensive therapy.[288] Promising approaches include aldosterone receptor blockers and renin inhibitors. With the exception of the potential for hyperkalemia, aldosterone receptor inhibitors have been well tolerated, and renin inhibitors administered in concert with Ang II inhibitors have alleviated the compensatory rise in plasma renin activity. Third-generation β-blockers incorporating vasodilatory activity offer particular promise for treating hypertension in the setting of concomitant HF. Further modifications to endothelin receptor antagonists and dual vasopeptidase inhibitors may offer novel antihypertensive approaches for the future. Several interventional approaches for control of pharmacologically resistant hypertension have been reported, including renal sympathetic denervation, targeted baroreflex stimulation, and percutaneous device placement to create a central iliac arteriovenous fistula—thereby mitigating arterial stiffness.[289–291] Lack of appropriate control groups limit conclusions about the efficacy of these treatments. The interventional nature of the procedures poses novel risks for morbidity and mortality.

Ultimately, gene therapy may prove the definitive solution to essential hypertension. It appears likely that environmental factors interacting with multiple genetic polymorphisms contribute to overall risk for hypertension. Gene therapy offers a viable approach to long-term management of hypertension but requires further identification of target genes, improvements in gene transfer efficiency, and development of safer transfer vectors. Advances in personalized medicine offer the potential for testing DNA polymorphisms to identify antihypertensive drugs most likely to benefit specific patients.[292]

Management of Severe Hypertension

Severe hypertension may be characterized as a *hypertensive emergency,* with target organ injury (eg, myocardial ischemia, stroke, pulmonary edema), or as *hypertensive urgency,* with severe elevations in BP not yet associated with target organ damage. Specific BPs associated with these conditions prove somewhat arbitrary, but BPs exceeding 220/125 mm Hg pose an immediate risk for life-threatening end organ damage. Chronic elevations in BP, even when severe, do not necessarily require urgent intervention and often may be managed with oral antihypertensive therapy on an outpatient basis. In contrast, a hypertensive emergency necessitates immediate therapeutic intervention, most often with intravenous antihypertensive therapy and invasive arterial BP monitoring. In the most extreme cases of *malignant hypertension*, severe elevations in BP may be associated with retinal hemorrhages, papilledema, and evidence of encephalopathy, which may include headache, vomiting, seizure, and coma. Progressive renal failure and cardiac decompensation may characterize the most severe hypertensive urgencies.

A common therapeutic approach to hypertensive urgency includes a limited reduction in BP (about 10%) over the initial 1 to 2 hours of therapy, followed by further modest reductions in diastolic BP during the next 12 hours. Further reductions in BP to acceptable target levels should proceed over a period of days to minimize potential for ischemic injury in the setting of altered autoregulatory flow to target organ vascular beds.[262,293]

Sodium nitroprusside, long favored as a parenteral treatment for hypertensive urgencies in intraoperative settings[262] (Table 11.10), acts as an NO donor to induce arterial and venous dilation. A rapid physiologic response and relatively predictable titratable effect prove useful for intraoperative settings. However, the potency of sodium nitroprusside and the potential for prolonged administration to be associated with cyanide or thiocyanate toxicity have provided an opportunity for newer parenteral antihypertensive drugs.

Nicardipine and clevidipine, parenteral dihydropyridine calcium channel blockers, have proved particularly applicable for hypertensive urgencies in perioperative settings (see Table 11.10). Although less potent and predictable than sodium nitroprusside, NTG, another NO donor, may be preferable in the setting of myocardial ischemia or after CABG surgery. NTG preferentially dilates venous capacitance beds rather than arterioles. However, rapid onset of tolerance limits the efficacy of sustained infusions to maintain BP control. Fenoldopam, a selective dopamine D_1-receptor antagonist, has been promoted for hypertensive control in the setting of chronic kidney disease.

Several drugs remain available for intermittent parenteral administration in hypertensive emergencies or urgencies. Enalaprilat, an intravenous ACE inhibitor, has been administered in settings of severe hypertension complicated by HF. Hydralazine, labetalol, and esmolol provide additional therapeutic options for intermittent parenteral injection for hypertensive control. In most cases of emergent or severe hypertension, a diuretic is required to maintain prolonged natriuresis to sustain an antihypertensive response. In settings of renal insufficiency or failure, minoxidil and acute dialysis may be necessary for BP control.

Indications for Specific Antihypertensive Drug Selection

Despite compelling evidence supporting the preferential administration of thiazide diuretics as agents of choice for treatment of hypertension, most patients require addition of a second nondiuretic antihypertensive drug to achieve desired target BPs.[262] Selection of a complementary antihypertensive agent necessitates a thorough understanding of the mechanisms of action to optimize the additive effect of combined therapy. For example, β-blockers, ACE inhibitors, and Ang II antagonists inhibit renin release. Combinations of these agents are unlikely to achieve a maximal additive antihypertensive response. Similarly, diuretics and dihydropyridine calcium channel blockers produce peripheral vasodilation, and combination with other antihypertensive drug classes may prove more efficacious.

Data derived from ongoing outcomes-based trials of antihypertensive therapy for patients with coexisting diseases suggest that specific antihypertensive drugs reduce morbidity beyond that expected for BP reduction alone (Table 11.11).[262] For example, in patients with ischemic heart disease and especially a recent MI, β-blockers have reduced mortality and morbidity related to subsequent cardiac events.[277,279,294,295] Although precise mechanisms remain unclear, reductions in overall sympathetic stimulation and antiarrhythmic effects presumably play contributory roles. In the setting of renal insufficiency, ACE inhibitors and Ang II antagonists delay progression of diabetes- and nondiabetes-associated renal disease.[295–298] Calcium channel blockers have proved efficacious in the setting of peripheral vascular

TABLE 11.10 Parenteral Drugs for Treating Hypertensive Emergencies[a]

Drug	*Dose*	*Onset of Action*	*Duration of Action*	*Adverse Effects*[b]	*Special Indications*
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Clevidipine	1–2 mg/h IV	2–4 min	5–15 min	Headache, nausea, vomiting, soy and egg allergy cross-reactivities	Most hypertensive emergencies except severe aortic stenosis
Sodium nitroprusside	0.25–10 µg/kg per minute as IV infusion[c]	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Fenoldopam mesylate	0.1–0.3 µg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 µg/min as IV infusion	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 h IV	15–30 min	6–12 h	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV 10–40 mg IM	10–20 min IV 20–30 min IM	1–4 h IV 4–6 h IM	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min 0.5–2.0 mg/min IV infusion	5–10 min	3–6 h	Vomiting, scalp tingling, dizziness, nausea, heart block, orthostatic hypotension, bronchoconstriction	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 µg/kg per minute IV bolus, then 50–100 µg/kg per minute by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min	1–2 min	10–30 min	Hypotension, nausea, asthma, first-degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

[a]Doses may vary from those in the *Physicians Desk Reference* (PDR).
[b]Hypotension may occur with all agents.
[c]Requires special delivery system.
IM, Intramuscular route; *IV*, intravenous route.
Modified from Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206.

TABLE 11.11 Compelling Indications for Individual Drug Classes According to Clinical Trials and Guidelines

	Recommended Drugs						
Compelling Indication[a]	*DRTC*	*BBl*	*ACEI*	*ARB*	*CCB*	*AA*	*Basis for Recommenations*[b]
Heart failure	R	R	R	R		R	ACC/AHA Heart Failure Guideline,[273] MERIT-HF,[276] COPERNICUS,[289] CIBIS,[278] SOLVD,[290] AIRE,[291] TRACE,[292] ValHEFT,[293] RALES,[294] CHARM[295]
Post-MI		R	R			R	ACC/AHA Post-MI Guideline,[296] BHAT,[86] SAVE,[297] CAPRICORN,[275] EPHESUS(TS40)[319]
High coronary disease risk	R	R	R		R		ALLHAT,[283] HOPE,[299] ANBP2,[300] LIFE,[301] CONVINCE,[302] EUROPA,[303] INVEST,[304]
Diabetes	R	R	R	R	R		NKF-ADA guideline,[305,306] UKPDS,[307] ALLHAT[283]
Chronic kidney disease			R	R			NKF guideline,[305] Captopril trial,[308] RENAAL,[309] IDNT,[310] REIN,[311] AASK[312]
Recurrent stroke prevention	R		R				PROGRESS[313]

[a]Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines. The compelling indication is managed in parallel with the blood pressure.
[b]Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve blood pressure goals according to test outcomes.
AA, Aldosterone antagonist; *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *BB*, β-blocker; *CCB*, calcium channel blocker; *DRTC*, diuretic; *MI*, myocardial infarction; *R*, recommended.
From Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206.)

diseases (eg, Raynaud syndrome), and α_1-blockers favorably influence symptoms of prostatism.

Hypertension in the setting of pregnancy continues to pose challenges given concerns about drug effects on the fetus. Historically, methyldopa and hydralazine were mainstay approaches for the management of hypertension complicating pregnancy.[262]

Perioperative Implications of Hypertension

There is little evidence to suggest that mild or moderate degrees of hypertension significantly impact perioperative morbidity and mortality. The ACC/AHA guidelines state that mild or moderate hypertension does not represent an independent risk factor for perioperative cardiovascular complications.[299] However, given the strong association between hypertension and vascular or kidney diseases, a preoperative diagnosis of hypertension necessitates assessment for evidence of target organ damage such as cardiovascular disease, chronic kidney disease (ie, nephrosclerosis), cerebrovascular disease and dementia, and atherosclerotic vascular disease.[300] In contrast to isolated mild hypertension, secondary cardiovascular diseases in many cases do pose an increased risk of perioperative morbidity and mortality. In patients with a preoperative diagnosis of hypertension, an electrocardiogram

is performed to assess for evidence of ischemia, prior MI, or left ventricular (LV) hypertrophy, and serum electrolyte and glucose levels may be used to assess for concomitant kidney disease or diabetes. Specific antihypertensive therapies may necessitate additional evaluations, such as assessment of plasma potassium and sodium levels in patients taking diuretics.

In cases of mild to moderate hypertension, few controlled trials assessing the association between preoperative hypertension and perioperative morbidity and mortality are available. Most investigations are observational and fail to account adequately for confounding variables. In many cases, the number of study participants proves inadequate to ensure statistical power to assess for relevant associations between outcomes and a preoperative diagnosis of hypertension. Howell and colleagues[293] published a metaanalysis summarizing 30 studies that included more than 12,995 patients for whom an association between hypertension and perioperative complications could be assessed. The investigators calculated an odds ratio of 1.31, suggesting a slightly increased risk for perioperative cardiovascular complications in patients with preexisting hypertension. However, given the limitations of the dataset, they further concluded that such a small odds ratio in the setting of a "low perioperative event rate" likely represented a clinically insignificant association between preexisting hypertension and cardiac risk. Other investigators have reported similar small associations between isolated systolic hypertension preoperatively and subsequent perioperative morbidity.

In contrast, cases of severe hypertension (ie, diastolic BP >110 mm Hg) frequently lead to questions about whether elective surgery should be postponed to allow for titration of antihypertensive therapy to acceptable systemic BPs. There are no data to support conclusive recommendations regarding acceptable preoperative BPs or the time period needed to attain a new steady-state systemic pressure. Patients with poorly controlled BP experience more labile BP responses in the perioperative setting, with a greater potential for hypertensive or hypotensive episodes.[300–302] Guidelines published by the ACC/AHA suggest that systemic BPs exceeding 180 mm Hg systolic or 110 mm Hg diastolic should be controlled before surgery.[299] In a review, Howell and colleagues[301] concluded that surgery need not be cancelled in the setting of severe hypertension. However, careful preoperative assessment for target organ damage (ie, cardiovascular, renal, and cerebrovascular disease) should be performed preoperatively, and intraoperative arterial pressures should be maintained within 20% of preoperative BPs.[288] At a minimum, invasive monitoring of arterial pressure with strict control of perioperative BPs continuing into the postoperative setting, appears justified for patients with severe hypertension, Given the predilection for CAD in these patients, perioperative therapy with β-blockers may be indicated.[93,303]

Pharmacotherapy for Acute and Chronic Heart Failure

Chronic HF is a major cardiovascular disorder that continues to increase in incidence and prevalence in the United States and worldwide. It affects almost 5.7 million persons in the United States, with 870,000 new cases annually among those 55 years of age or older.[304,305] Currently, 1% to 2% of those between 40 and 59 years of age and 11% to 14% of individuals older than 80 years have HF.[304] Because HF is primarily a disease of the elderly, its prevalence is projected to increase 46% from 2012 to 2030, resulting in more than 8 million people with HF, paralleling the substantial increase in growth of this population sector.[306] The disease also affects the black population disproportionately compared with whites.[307,308]

The increasingly prolonged survival of patients with various cardiovascular disorders that culminate in ventricular dysfunction (eg, patients with CAD are living longer rather than dying acutely with MI), and the greater diagnostic awareness further compound the HF epidemic. By age 40, the lifetime risk of developing HF for men and women is one in five, and this risk remains constant into the 80s, even in the face of a much shorter life expectancy.[305] Despite improvements in the understanding of the neurohormonal mechanisms underlying its pathophysiology and remarkable advances made in pharmacologic therapy, HF continues to cost the United States an estimated $31 billion annually in medical expenditures,[305] and it is projected to increase 127% (almost $70 million) by 2030.[306]

More importantly, functional capacity is impaired in HF, causing a significant decline in the individual's quality of life.[309] Given the public health impact of the disease and the rapid pace of therapeutic advances, it is essential that the perioperative physician remain aware of contemporary clinical practice for the benefit of patients with chronic HF presenting to the operating room or intensive care unit.

The pharmacologic management of HF was revised in the 2013 guidelines published by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA).[304] The focus is primarily on chronic HF with a reduced ejection fraction (HFrEF) and HF with a preserved ejection fraction (HFpEF), although acute HF is also discussed. For each drug commonly used in clinical practice, the general format includes whether it alters the progression of myocardial damage (for agents administered chronically), its mechanisms of action, clinical data on trials of its use for HF, and its current place in the treatment of HF. New pharmacologic options in HF management are also reviewed.

Level of Evidence

To gain the best understanding of the guidelines for the management of HF, it is important to review definitions of terms, class of recommendation (COR), and level of evidence (LOE). The COR is a statement of the strength of the recommendation. The COR ranges from class I, in which case treatments or procedures should be administered or performed, to class III, in which case treatments or procedures have no benefit (ie, a treatment strategy is no better than with the control) or may be harmful to the person (ie, outcomes were worse with the intervention than with the control).

Class I is the strongest recommendation; the benefit is substantially better than the risk. Class II is based on whether the treatment or procedure's benefit outweighs the risk to the individual. Class II is divided into IIa (ie, it is reasonable to perform the treatment or procedure, with intermediate strength that the benefit is somewhat greater than risk) and class IIb (ie, performing the treatment or procedure may be considered, or marginal benefit-risk ratios exist).

The LOE describes the certainty or precision of the information supporting the recommendation and is based on the type and quality of the evidence. Level A evidence is derived from multiple RCTs or a metaanalysis based on high-quality RCTs. Level B evidence is derived from single randomized or nonrandomized trials, and level C evidence is based on expert opinions, case studies, or standards of care.

The term *guideline-directed medical therapy* (GDMT) has been designated in the revised guidelines to represent optimal medical therapy, which is primarily a class I, LOE A recommendation (Fig. 11.13). Adherence to GDMT for HF improves outcomes through reductions in morbidity, hospitalizations, and mortality (Fig. 11.14).

Heart Failure Terms

EF is important in classifying patients with HF because of different patient demographics, comorbid conditions, prognoses, and therapies and because most clinical trials select patients according to EF. Although EF measurement has been used to differentiate between systolic and diastolic dysfunction, the 2013 guidelines use the terms HFrEF and HFpEF to differentiate systolic from diastolic HF. HFrEF is based on a clinical diagnosis of HF combined with an EF of 40% or less. HFpEF classification includes the following: those with an EF of 50% or greater; those with an EF between 41% and 49% (ie, HFpEF, borderline); and those who had improved HFpEF of greater than 40%.

Several criteria have been proposed to define the syndrome of HFpEF, including clinical signs or symptoms of HF, evidence of preserved or normal left ventricular ejection fraction (LVEF), and

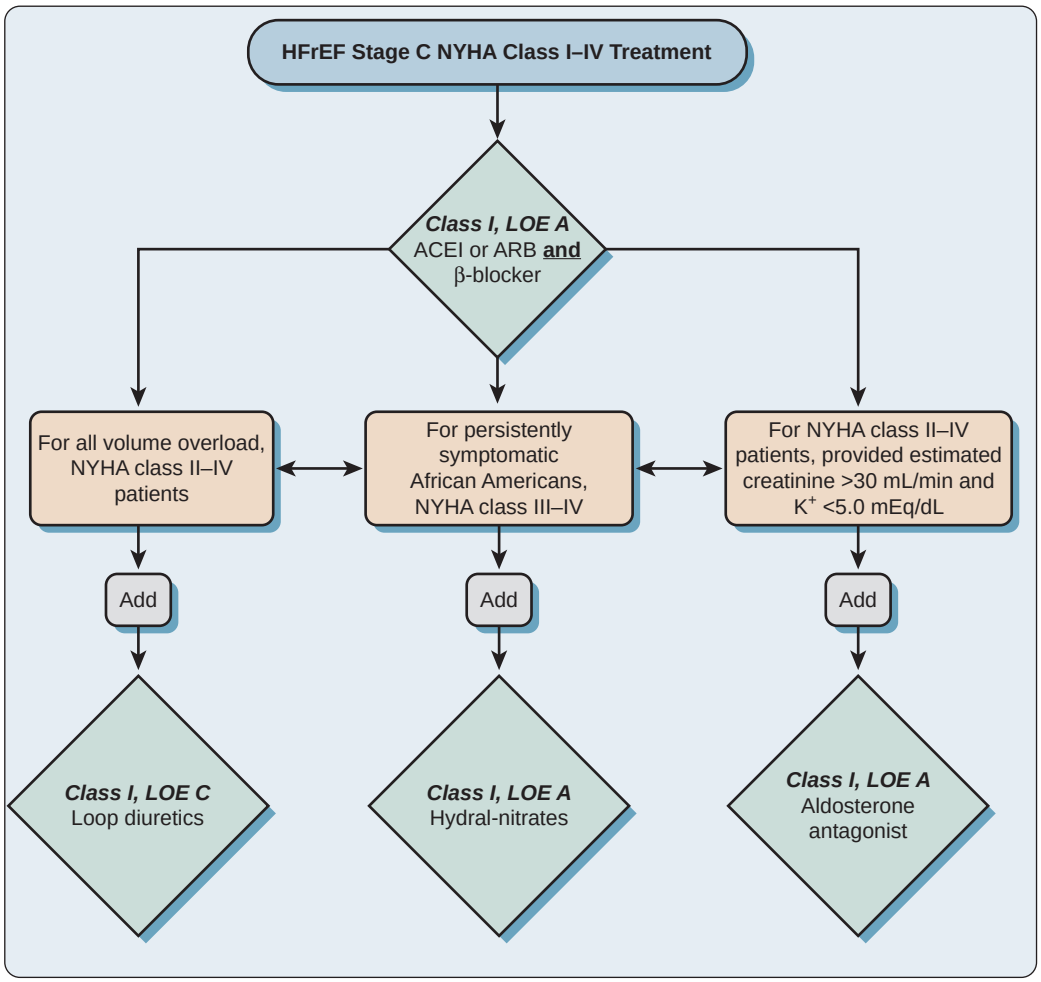


Fig. 11.13 Guideline-directed medical therapy algorithm for stage C heart failure with reduced ejection fraction (HFrEF). *ACEI*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin-receptor blocker; *Hydral-nitrates*, hydralazine and isosorbide dinitrate; *LOE*, level of evidence; *NYHA*, New York Heart Association. *(From Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation. *2013;128:e240.)*

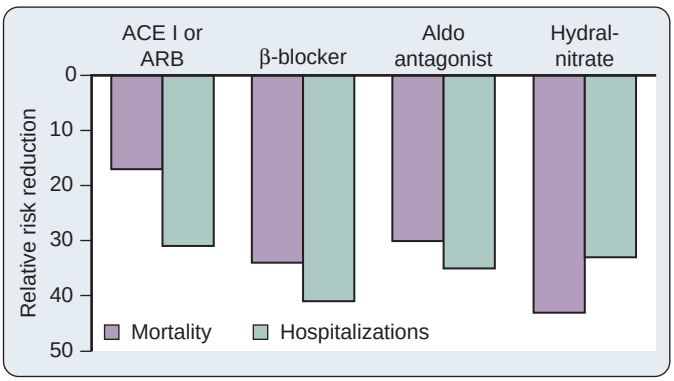


Fig. 11.14 Guideline-directed medical therapy improves outcomes. Class I, level of evidence A recommendations for the treatment of heart failure with reduced ejection fraction has been shown to reduce mortality and hospitalizations for heart failure in various trials, including SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS-II, and EMPHASIS-HF. *ACE I*, angiotensin-converting enzyme inhibitor; *aldo*, aldosterone; *ARB*, angiotensin-receptor blocker; *hydral-nitrate*, hydralazine and isosorbide dinitrate.

evidence of abnormal LV diastolic dysfunction that can be determined by Doppler echocardiography or cardiac catheterization. Patients who previously had a reduced EF but had improvement or recovery in the EF are categorized as *HFpEF improved*. The diagnosis of HFpEF is more challenging than the diagnosis of HFrEF because it is largely one of excluding other noncardiac causes of symptoms that suggest HF.

Heart Failure Classification

The ACCF/AHA guidelines for evaluating and managing HF include the four-stage classification system, which emphasizes the evolution and progression of the disease (Fig. 11.15), and the New York Heart Association (NYHA) classification (Table 11.12), which focuses on exercise capacity and symptomatic severity of the disease.[304] The four-stage classification system calls attention to patients with preclinical stages of HF to focus on halting disease progression. By recognizing its progressive course and identifying those who are at risk (ie, the first two stages, A and B, are clearly not HF), it reinforces the importance of determining the optimal strategy for neurohormonal antagonism in an attempt to improve the natural history of the syndrome.

The NYHA classification focuses on exercise capacity and symptomatic status of the disease, which correlate with quality of life and survival.[304] It is subjective and can change frequently over short

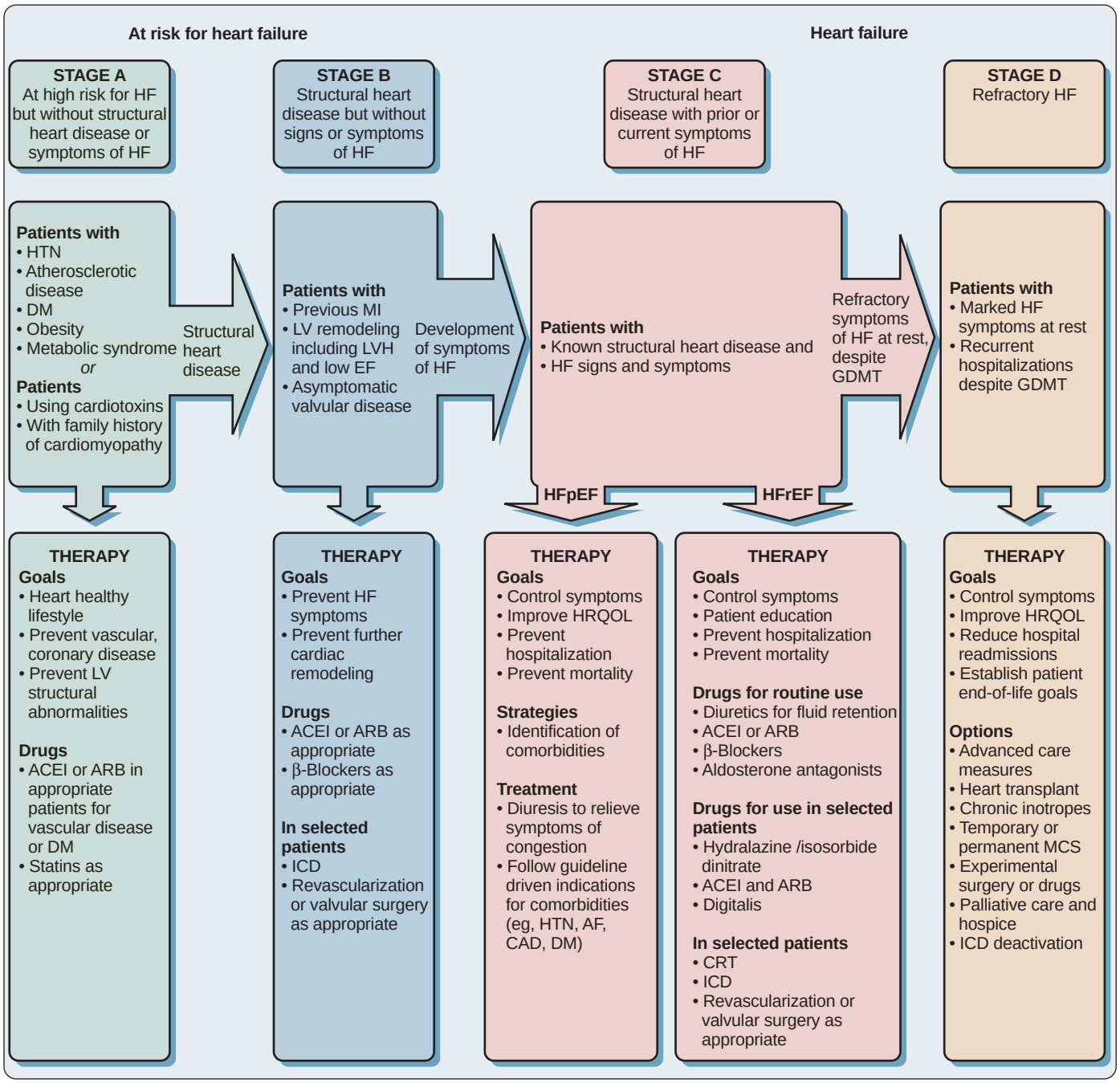


Fig. 11.15 Stages in the development of heart failure *(HF)* and recommended therapy by stage. *ACEI*, Angiotensin-converting enzyme inhibitor; *AF*, atrial fibrillation; *ARB*, angiotensin-receptor blocker; *CAD*, coronary artery disease; *CRT*, cardiac resynchronization therapy; *DM*, diabetes mellitus; *EJ*, ejection fraction; *GDMT*, guideline-directed medical therapy; *HFpEF*, heart failure with preserved ejection fraction; *HFrEF*, heart failure with reduced ejection fraction; *HRQOL*, heart-related quality of life; *HTN*, hypertension; *ICD*, implantable cardioverter-defibrillator; *LV*, left ventricular; *LVH*, left ventricular hypertrophy; *MCS*, mechanical circulatory system; *MI*, mycoardial infarction. *(From Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:e240.)*

periods, whereas the stages of HF are progressive and inviolate; after a patient moves to a higher stage, regression to an earlier stage of HF is not observed. In comparing the NYHA classification with HF staging (see Table 11.12), notice that there is no classification for stage A and that stage B correlates with NYHA class I (ie, no limitation of physical activity). For stage C HF, the classification ranges from no limitation to class IV (ie, unable to carry on any physical activity without symptoms of HF or symptoms of HF at rest). Stage D HF correlates with NYHA class IV symptoms even at rest. The two classifications are complementary in nature.

TABLE 11.12 Comparison of ACCF/AHA Stages of Heart Failure and New York Heart Association (NYHA) Functional Classifications

ACCF/AHA Stages of Heart Failure		NYHA Functional Classification	
Stage	*Definition*	*Class*	*Definition*
A	At high risk for HF but without structural heart disease or symptoms of HF	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity; ordinary physical activity does not cause HF symptoms
C	Structural heart disease with prior or current HF symptoms	I	No limitation of physical activity; ordinary physical activity does not cause HF symptoms
		II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in HF symptoms
		III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes HF symptoms
		IV	Unable to carry on any physical activity without HF symptoms or symptoms of HF at rest
D	Refractory HF requiring specialized interventions		Unable to carry on any physical activity without HF symptoms or symptoms of HF at rest

ACCF/AHA, American College of Cardiology Foundation/American Heart Association; *HF*, heart failure; *NYHA*, New York Heart Association.
From From Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:e240.

TABLE 11.13 Neurohormonal Effects of Impaired Cardiac Performance on the Circulation

Response	*Short-Term Effects*	*Long-Term Effects*
Salt and water retention	Augments preload	Pulmonary congestion, anasarca
Vasoconstriction	Maintains blood pressure for perfusion of vital organs (eg, brain, heart)	Exacerbates pump dysfunction (ie, excessive afterload), increases cardiac energy expenditure
Sympathetic stimulation	Increases heart rate and ejection	Increases energy expenditure

Overview of Heart Failure Pathophysiology

Although the pathophysiology of HF has been addressed elsewhere, it is important to mention key concepts as the basis of current pharmacologic therapy. HF is a complex clinical syndrome resulting from any structural and functional abnormalities in ventricular filling or ejection of blood that causes cardinal symptoms of dyspnea and fatigue, which may limit exercise tolerance and cause fluid retention, leading to congestion and edema. HF remains the final common pathway for CAD, hypertension, valvular heart disease, and cardiomyopathy, in which the natural history results in symptomatic or asymptomatic LV dysfunction (specifically, LV systolic dysfunction for the purposes of this discussion).

The neurohormonal responses to impaired cardiac performance (eg, salt and water retention, vasoconstriction, sympathetic stimulation) are initially adaptive, but if sustained, they become maladaptive, resulting in pulmonary congestion and excessive afterload. This leads to a vicious cycle of increases in cardiac energy expenditure and worsening of pump function and tissue perfusion (Table 11.13). Although the cardiorenal and cardiocirculatory branches of this neurohormonal hypothesis of HF were the original foundation for the use of diuretics, vasodilators, and inotropes, seminal information in the early 1990s emerged from large, randomized clinical trials that showed ACE inhibitors[310,311] and angiotensin receptor blockers,[312,313] but not most other vasodilators,[314] prolonged survival of patients with HF. In a similar fashion, the use of β-blockers, despite their negative inotropic effects, improved morbidity and mortality in RCTs.[315–317]

The finding that low-dose aldosterone antagonists added to conventional therapy for HF reduce mortality in patients with severe HF suggests that there is more to the neurohormonal hypothesis of drug efficacy than cardiorenal and hemodynamic effects alone.[318,319] Taken together with evidence from basic investigations showing that Ang II is a growth factor and a vasoconstrictor,[320] the clinical data promoted a shift in focus from cardiorenal and cardiocirculatory processes toward cardiac remodeling as the central component in the progression of the neurohormone-mediated cardiac syndrome.[321] The renin-angiotensin-aldosterone system (RAAS), excess sympathetic activity, endothelin, and various cytokines have been implicated as stimuli of proliferative signaling that contribute to maladaptive cardiac growth. Ventricular remodeling, or the structural alterations of the heart in the form of dilation and hypertrophy (Box 11.5), in addition to the counterregulatory hemodynamic responses, lead to progressive ventricular dysfunction and represent the target of current therapeutic interventions (Fig. 11.16).

BOX 11.5 MECHANICAL DISADVANTAGES CREATED BY LEFT VENTRICULAR REMODELING

- Increased wall stress (ie, afterload)
- Afterload mismatch
- Episodic subendocardial hypoperfusion
- Increased oxygen consumption
- Sustained hemodynamic overloading
- Worsening activation of compensatory mechanisms

From Mann DL. Mechanisms and models in heart failure: an approach. *Circulation*. 1999;100:999.

Pathophysiologic Role of the Renin-Angiotensin System in Heart Failure

The renin-angiotensin system (RAS) is one of several neuroendocrine systems that are activated in patients with HF. The RAS is also an important mediator in the progression of HF. In the short term, the juxtaglomerular cells of the kidney release the proteolytic enzyme renin in response to a decrease in BP or renal perfusion (eg, hemorrhage), generating Ang I from circulating angiotensinogen. ACE cleavage of Ang II from Ang I in the lung produces circulating Ang II. Acutely, Ang II acts as a potent arteriolar and venous vasoconstrictor to return BP and filling pressure to baseline, respectively. Ang II also stimulates the release of aldosterone from the adrenal cortex and antidiuretic hormone from the posterior pituitary. Both contribute to increases in blood volume through their effects on the kidney to promote salt and water reabsorption, respectively. In the long term, elevations in Ang II lead to sodium and fluid retention and increases in SVR, which contribute to symptoms of HF, pulmonary congestion, and hemodynamic decompensation (Fig. 11.17).

In addition to the cardiorenal and cardiocirculatory effects, most of the hormones and receptors of the RAS are expressed in the myocardium, where they contribute to maladaptive growth or remodeling,

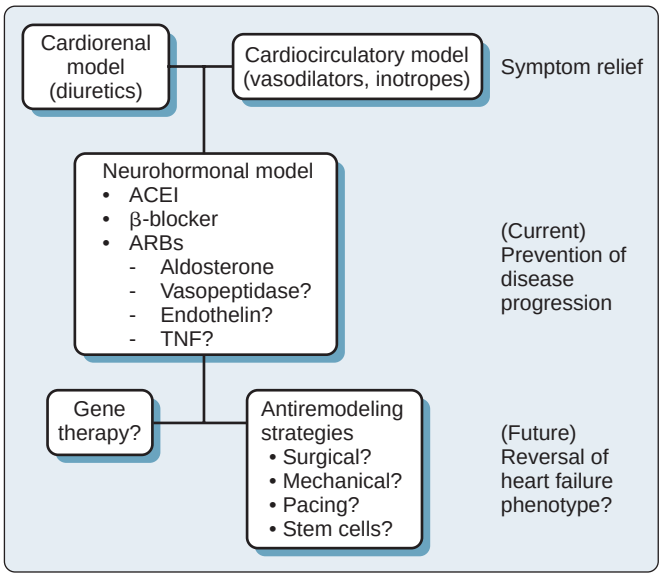


Fig. 11.16 Current and future treatments of heart failure. Current heart failure therapies are focused on prevention of disease progression with drugs that antagonize neurohormonal systems. Future therapies may involve antagonists of other biologically active systems (eg, endothelins, tumor necrosis factor *[TNF]*), and anti-remodeling strategies that may reverse the heart failure phenotype. *ACEI*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin-receptor blocker; *NEP*, neutral endopeptidase blocker. *(Modified from Mann DL. Mechanisms and model in heart failure: a combinatorial approach.* Circulation. *1999;100:999.)*

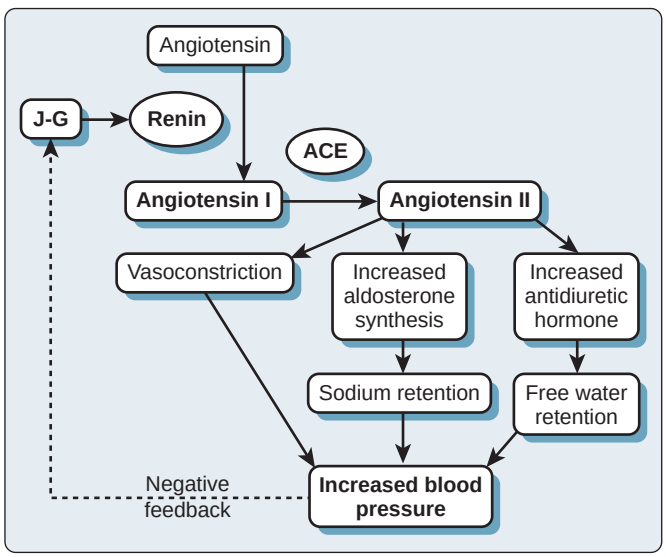


Fig. 11.17 Basic pathway of the renin-angiotensin-aldosterone system (RAAS). *ACE*, Angiotensin-converting enzyme; *J-G*, juxtaglomerular cells. *(From Jaski BE.* Basis of Heart Failure: a Problem Solving Approach. *Boston: Kluwer Academic Publishers; 2000.)*

a key factor in the progression of HF. Increased expression of mRNA for angiotensinogen, ACE, and Ang II has been identified in the failing human heart.[322] Increased coronary sinus Ang II concentrations were measured in patients with dilated and ischemic cardiomyopathy, signifying a paracrine or autocrine action of the RAS. Moreover, progressive increases in coronary sinus Ang II production correlated with increases in NYHA functional classification of HF.[322] These data

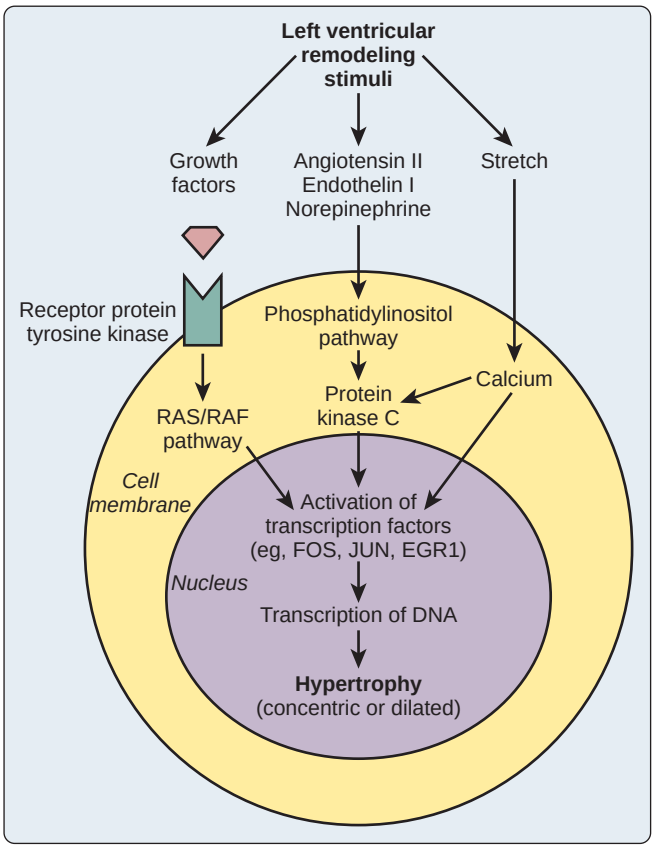


Fig. 11.18 Left ventricular remodeling stimuli.

TABLE 11.14 Cellular and Physiologic Effects of AT_1 and AT_2 Receptor Stimulation Leading to Tissue Remodeling

AT_1 Receptor	*AT_2 Receptor*
Vasoconstriction	Vasodilation
Cell growth and proliferation	Cell growth inhibition or apoptosis
Positive inotropy	Negative chronotropy
Aldosterone secretion	Natriuresis
Catecholamine release	Bradykinin release

provide evidence that intracardiac RAS is involved in the evolution of the disease process.

The effects of Ang II on its AT_1 and AT_2 receptors are well known. The AT_1 receptor is involved in several effects that lead to adverse cardiovascular outcomes. Activation of AT_1 receptors promotes aldosterone and vasopressin secretion with concomitant increases in salt and water reabsorption through the kidneys, vasoconstriction, catecholamine release, and cell growth and proliferation of cardiovascular tissue (Table 11.14). Stimulation of AT_2 receptors results in natriuresis, vasodilation, release of bradykinin and NO, and cell growth inhibition or apoptosis.

The Ang II that is formed locally in the heart acts primarily through AT_1 receptors located on myocytes and fibroblasts, where it participates in the regulation of cardiac remodeling. Through complex cascades of intracellular signal transduction that activate protein transcription factors within the nucleus initiating the creation of RNA transcripts, the long-term effects of intracardiac Ang II on the AT_1 receptor result in cardiomyocyte hypertrophy, fibroblast proliferation, and extracellular matrix deposition[323] (Fig. 11.18). These processes contribute to progressive LV remodeling and LV dysfunction characteristic of HF.

TABLE 11.15 Selected Clinical Trials of ACE Inhibitors in Heart Failure

Patient Subset	*Heart Failure Stage*	*Drug*	*Trial*
Heart Failure			
NYHA class II and III	C	Enalapril	SOLVD (treatment); V-HeFT II
NYHA class IV	D	Enalapril	CONSENSUS
Asymptomatic Left Ventricular Dysfunction			
EF <35%	B	Enalapril	SOLVD (prevention)
Post-MI (EF <40%)	B	Captopril	SAVE
Acute MI	B	Captopril Lisinopril	GISSI ISIS-4
Asymptomatic High Risk			
History of DM, PVD, and coronary risk factors	A	Ramipril	HOPE

ACE, Angiotensin-converting enzyme; *DM*, diabetes mellitus; *EF*, ejection fraction; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *PVD*, pulmonary vascular disease.

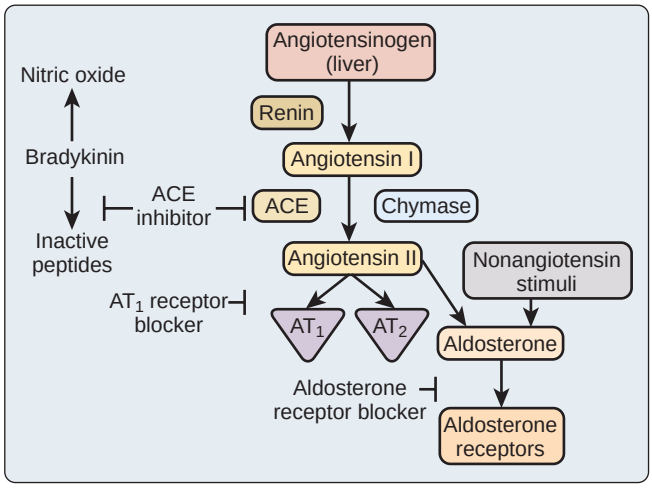


Fig. 11.19 Activation of the renin-angiotensin-aldosterone system (RAAS). *ACE*, Angiotensin-converting enzyme; AT_1, angiotensin I receptor; AT_2, angiotensin II receptor. *(Modified from Mann DL. Heart Therapy: A Companion to Braunwald's Heart Disease. Philadelphia: Saunders; 2004.)*

Angiotensin-Converting Enzyme Inhibitors

Clinical Evidence

Evidence supporting the beneficial use of ACE inhibitors in HF patients comes from various randomized, placebo-controlled clinical trials (Table 11.15). Initially, this class of drugs was evaluated for treatment of symptomatic HF (ie, SOLVD, V-HeFT, and CONSENSUS trials). Patients with NYHA class II to IV HF treated with ACE inhibitors had reductions in mortality ranging from 16% to 31%. ACE inhibitors were also found to improve outcomes for asymptomatic patients with LV systolic dysfunction in the following categories: patients with EFs less than 35% due to cardiomyopathy,[323] patients within 2 weeks after MI with EFs less than 40%,[324] and patients within the first 24 hours of MI regardless of EF.[325]

Results from the Heart Outcomes Prevention Evaluation (HOPE) study further expanded the indications for this class of agents to include asymptomatic, high-risk patients to prevent new-onset HF.[326] In patients with diabetes or peripheral vascular disease and an additional atherosclerotic risk factor but without clinical HF or systolic dysfunction, ramipril (10 mg/day) reduced the HF risk by 23%. The PEACE trial evaluated the use of ACE inhibitors in addition to modern conventional therapy in patients with stable CAD with preserved LV function. The results of this trial did not reveal any decrease in mortality from cardiovascular causes or nonfatal MI compared with placebo.[327]

The use of ACE inhibitors should be considered only in stage A patients who have diabetes or vascular disease and for controlling standard risk factors. In stage B patients or those with reduced EF with or without symptoms, ACE inhibitors are considered first-line therapy (COR 1, LOE A). Since the commencement of these trials, the rationale for the use of ACE inhibitors has expanded from a reduction in the progression of clinical HF through ACE inhibitor–mediated vasodilatory action to acknowledgment that ACE inhibitors also directly affect the cellular mechanisms responsible for progressive myocardial pathology.

Mechanisms of Action

ACE inhibitors act by inhibiting one of several proteases responsible for cleaving the decapeptide Ang I to form the octapeptide Ang II. Because ACE is also the enzyme that degrades bradykinin, ACE inhibitors increase circulating and tissue levels of bradykinin (Fig. 11.19).

ACE inhibitors have several useful effects in chronic HF. They are potent vasodilators through decreasing Ang II and norepinephrine and increasing bradykinin, NO, and prostacyclin. By reducing the secretion of aldosterone and antidiuretic hormone. ACE inhibitors also reduce salt and water reabsorption from the kidney. ACE inhibitors reduce release of norepinephrine from sympathetic nerves by acting on AT_1 receptors at the nerve terminal. In tissue, ACE inhibitors inhibit Ang II production and attenuate Ang II–mediated cardiomyocyte hypertrophy and fibroblast hyperplasia.[328,329]

Clinical evidence supporting an ACE inhibitor–mediated role in cardiac remodeling comes from comparative studies of enalapril versus placebo (ie, SOLVD trial) and enalapril versus hydralazine isosorbide dinitrate (ie, V-HeFT II trial).[330,331] In a subset of the SOLVD study,[330] the placebo group exhibited LV dilation, whereas the enalapril group exhibited a decrease in chamber size for a given LV pressure. In the V-HeFT II trial, survival was better with enalapril than hydralazine/isosorbide dinitrate despite improvements in exercise capacity in the latter group, suggesting that mechanisms other than vasodilation contribute to improved survival with ACE inhibitors.[330]

Chymase also catalyzes the production of Ang II from Ang I within myocardial tissue. The serine protease has an almost 20-fold greater affinity for Ang I than ACE, and it is not influenced by ACE inhibitors.[332] Angiotensin II receptor blockers (ARBs) may add to the inhibition by ACE inhibitors of angiotensin-promoted progression of HF.

ACE inhibitors attenuate insulin resistance, a common metabolic abnormality in HF patients, independent of Ang II activity. Ang II receptor antagonists do not attenuate insulin resistance.[333] ACE inhibitors and ARBs reduce proteinuria (ie, common comorbidity in HF patients) and slow the progression to renal failure in hypertensive patients.[297,334]

Drug Selection and Strategy for Clinical Practice

Treatment guidelines for the use of ACE inhibitors, including appropriate starting and target doses and common side effects, are shown in Table 11.16. Adherence to target doses of ACE inhibitors increases the likelihood of reproducing benefits demonstrated in large-scale HF trials (see Table 11.15).

According to the AHA/ACCF guidelines (see Fig. 11.15), it is reasonable to initiate ACE inhibitor therapy in high-risk patients (stage A), such as those with diabetes or peripheral vascular disease, although the committee acknowledges that further objective studies are needed for this patient group. ACE inhibitor therapy should be initiated in all stage B patients with a recent or remote history of MI and reduced EF to prevent symptomatic HF and reduce mortality and in all stage C HFrEP patients (COR I, LOE A).

Relative contraindications for the use of ACE inhibitors include (1) a history of intolerance or adverse reactions (eg, cough, angioedema, neutropenia, rash); (2) persistent hyperkalemia (>5.5 mEq/L) that cannot be reduced by diet or diuretic adjustment; (3) symptomatic

hypotension; and (4) history of bilateral renal artery stenosis. Small doses of an agent with a short plasma half-life (eg, captopril) are advocated when initiating therapy in patients with marginal BP (ie, systolic BP <90 mm Hg) or reduced renal function (ie, baseline creatinine >2.0 mg/dL).

After it is demonstrated that a patient tolerates inhibition of the RAS, dosing should be adjusted to target doses of a longer-acting agent. In the ATLAS trial, lisinopril in a dose of 32.5 to 35 mg/day had greater efficacy than 2.5 to 5.0 mg/day in patients with symptomatic HF and LV systolic dysfunction (EF <35%).[335] Patients receiving target doses of ACE inhibitors are less frequently hospitalized than those receiving reduced doses.[336] The importance of differences in tissue binding among the various ACE inhibitors remains unclear.

Angiotensin II Receptor Blockers for Heart Failure

Pathophysiology and Mechanism of Action

Although ACE inhibitors reduce mortality, many patients do not tolerate their side effects. ACE inhibitors incompletely antagonize Ang II. These factors have prompted the development of specific Ang II receptor blockers for the pharmacologic treatment of HF[337] (see Fig. 11.19). Non–ACE-generated Ang II within the myocardium contributes to LV remodeling and HF progression through AT_1 receptor effects (see Table 11.14). Selective AT_1 blockers prevent Ang II from acting on the cell, preventing vasoconstriction, sodium retention, release of norepinephrine, and delaying or preventing LV hypertrophy and fibrosis.[338] AT_2 receptors remain unaffected, and their actions, including NO release, remain intact.

Clinical Evidence

Outcome benefits from ARBs were first demonstrated in the ELITE I trial, which showed as a secondary end point a significantly reduced risk of sudden death with losartan (4.8%) compared with captopril (8.7%),[339] despite no between-group differences in the primary end points, renal dysfunction, and hypotension. The follow-up ELITE II trial (Table 11.17), although having greater statistical power than ELITE I, failed to confirm that losartan was superior to captopril in reducing mortality in older patients with HF.[340] In subgroup analyses, the ELITE II trial patients on preexisting β-blockers tended to have less favorable outcomes with losartan than with captopril.

The Valsartan in Heart Failure (Val-HeFT) and Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM) trials were designed to evaluate whether ARBs plus conventional therapy (including β-blockers, ACE inhibitors, and diuretics) for symptomatic HF provide additional clinical benefit. Although the findings from the Val-HeFT support the use of ARBs in patients with chronic HF who are intolerant to ACE inhibitors, the patients already on ACE inhibitors and β-blockers (93% of their patient population) showed a trend toward an increased risk of death or hospitalization when valsartan was added to their treatment regimen.[313]

In contrast, the CHARM-added trial[341] showed safety for the use of candesartan in combination with ACE inhibitors and β-blockers (ie, 15% relative risk reduction in cardiovascular-related mortality or hospitalization), and in patients intolerant to ACE (ie, alternative group), the relative risk reduction in mortality or hospitalization was 23%. Patients with EFs greater than 40% not receiving ACE inhibition (ie, preserved group) showed no difference in cardiovascular mortality and only a small reduction in HF hospitalizations.[342,343] In the CHARM-overall trial, cardiovascular-related death and hospitalizations were significantly reduced with candesartan use; the relative risk reduction for cardiovascular death was 16%.[312]

Clinical Practice

ARBs are used as alternatives to ACE inhibitors (class I, LOE A) for the treatment of patients with symptomatic HF if there are side effects to ACE inhibitors (eg, persistent cough, angioedema, hyperkalemia, worsening renal dysfunction). An ARB may be used as an alternative to an ACE inhibitor in patients who are already taking an ARB for another reason, such as hypertension, and who subsequently develop HF (class IIa, LOE A). Because ARBs do not affect bradykinin levels, cough and angioedema are rare side effects. Doses and dosing intervals for ARBs studied in large-scale trials are shown in Table 11.18.

Similar to ACE inhibition, ARBs produce dose-dependent decreases in right atrial pressure, PCWP, and SVR. Unlike long-term ACE inhibition,[344] the hemodynamic effects and associated increases in cardiac index are sustained while the plasma levels of Ang II remain suppressed with ARB therapy. Although trials have shown that the addition of an ARB to an ACE inhibitor may further reduce mortality and hospitalization for patients with HFrEF (ie, CHARM-added and V-HeFT trials),[330,341] significant increases in hypotension and renal impairment occurred in the treatment arm. The adverse effects of combining these

TABLE 11.16 ACE Inhibitors Proven Effective in Heart Failure or Left Ventricular Dysfunction

Drug	*Half-life (h)*	*Dosing Interval*	*Start Dose (mg)*	*Target Dose (mg)*	*Relative Tissue Binding*
Captopril	3	tid	6.25	50	+
Enalapril	11	bid	2.5–5	10	+
Lisinopril	12	qd	5	20	+
Ramipril	9–18	bid	2.5	5	++
Quinapril	2 (25)[a]	bid	5	20	+++
Trandolapril	6	bid	1	1–2	NA

[a]Elimination half-life in plasma of approximately 2 hours and a prolonged terminal phase with a half-life of 25 hours.
ACE, Angiotensin-converting enzyme; *NA*, not applicable.

TABLE 11.17 Trials of Angiotensin Receptor Blockers for Heart Failure

Trial	*Agent*	*Population*	*Outcome*
ELITE II	Losartan, 50 mg qd	Age ≥60 NYHA II–IV EF ≤40%	Losartan was not better than captopril No difference in mortality Losartan was better tolerated Losartan plus β-blocker had worse outcome
Val-HeFT	Valsartan, 160 mg bid or placebo plus open-label ACEI (93%)	NYHA II–IV EF <40%	No difference in all-cause mortality Significant difference of 13% for combined morbidity and mortality HF-related hospitalizations decreased by 27% Most benefit observed in ACEI-intolerant patients (7% of study group), with 45% reduction in combined primary end points
CHARM	Candesartan, 32 mg qd vs placebo with or without open-label ACEI	NYHA II–IV	
	Added	EF ≤40%	Relative risk reduction of 15% in all-cause mortality
	Preserved	EF >40%	Mild reduction in HF-related hospitalizations
	Alternative	EF ≤40%, ACEI intolerant	Relative risk reduction of 23% in HF-related mortality or hospitalization
	Overall		Significant difference in all-cause mortality

ACEI, Angiotensin-converting enzyme inhibitor; *EF*, ejection fraction; *HF*, heart failure; *NYHA*, New York Heart Association.

two drug classes has been underscored in a systematic, large metaanalysis of patients with symptomatic LV dysfunction.[345] Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is not recommended and is potentially harmful.[304]

Aldosterone Receptor Antagonists

Aldosterone, a mineralocorticoid, is another important component of the neurohormonal hypothesis of HF. Although it was previously assumed that treatment with an ACE inhibitor (or ARB) would block the production of aldosterone in patients with HF, elevated levels of aldosterone have been measured despite inhibition of Ang II[346] (see Fig. 11.19).

Adverse effects of elevated aldosterone levels on the cardiovascular system include sodium retention, potassium and magnesium loss, ventricular remodeling (eg, collagen production, myocyte growth, hypertrophy), myocardial norepinephrine release, and endothelial dysfunction[347] (Fig. 11.20). Non-Ang II–mediated aldosterone production may in part result from the hypomagnesemia commonly seen in HF patients.[348] Low extracellular Mg^{2+}, common in chronic illness and as a result of loop diuretics, becomes a stimulus for adrenal aldosterone secretion.[349] Extraadrenal production of aldosterone in myocardial and vascular tissue may also contribute to oxidative, proinflammatory, and prothrombotic signaling pathways (eg, nuclear factor-κB [NF-κB], activator protein 1 [AP-1], plasminogen activator inhibitor 1 [PAI-1]), and maladaptive processes such as LV dilation, perivascular fibrosis, and atherosclerosis.[350–352] Aldosterone produced in the brain increases SNS activity, a central finding in HF.[353]

Given the multiple endocrine and autocrine or paracrine contributions of aldosterone to the neurohormonal hypothesis of HF, the possibility that aldosterone receptor antagonism might halt disease progression became an increasingly attractive hypothesis. Besides the traditional mechanisms of mineralocorticoid receptor blockade, including natriuresis, diuresis, and kaliuresis,[348,354] beneficial nonrenal effects of aldosterone antagonism include decreased myocardial collagen formation,[355] increased myocardial norepinephrine uptake and decreased circulating norepinephrine levels,[355] normalization of baroreceptor function, increased heart rate variability,[356,357] and improved endothelial vasodilator dysfunction and basal NO bioactivity at the vascular level.[358]

TABLE 11.18 Angiotensin Receptor Blockers Evaluated in Large-Scale Trials

Agent	*Half-life (h)*	*Dosing Interval*	*Initial Dose (mg)*	*Target Dose (mg)*
Losartan	6–9	qd	25	50
Valsartan	9	bid	40	160
Irbesartan	11–15	qd	75	150
Candesartan	3.5–4	qd	4	32

Clinical Evidence

Three large-scale trials demonstrated improved outcomes with aldosterone receptor antagonism in chronic HF. The Randomized Aldactone Evaluation Study (RALES), which enrolled more than 1600 symptomatic HF (eg, stage C, NYHA III or IV) patients, showed the efficacy of spironolactone (26 mg/day) in combination with standard therapy (ie, ACE inhibitor, loop diuretic with or without digoxin, and a β-blocker). Regardless of age, gender, and HF cause, the treatment group experienced a 30% reduction in risk for all-cause mortality and in cardiovascular-related mortality compared with standard therapy[318] (Fig. 11.21).

Because β-blockers were used infrequently in this study (10–20%), the role of spironolactone in contemporary management of HF remains unclear. Studies have reported marked increases in hospital admission and death related to hyperkalemia after widespread use of spironolactone.[359] It has been speculated that the K^+-sparing effect of spironolactone and its ability to reduce circulating norepinephrine[360]

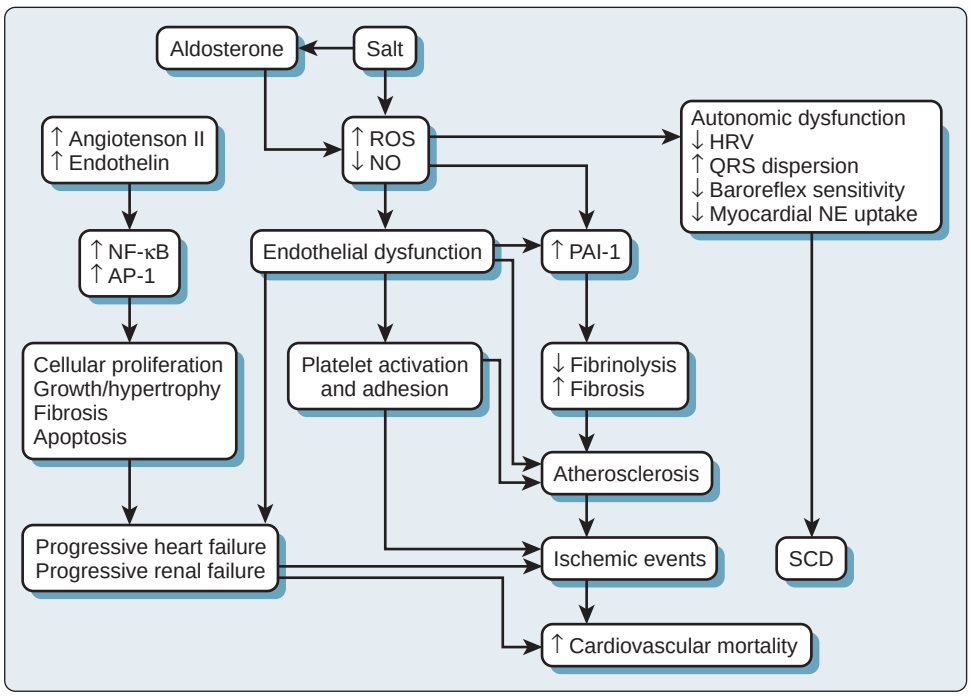
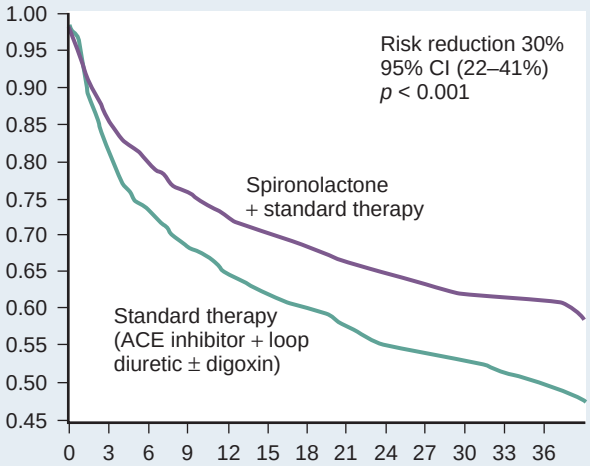


Fig. 11.20 Adverse effects of aldosterone and salt on the cardiovascular system. *AP-1*, Activator protein 1; *HRV*, heart rate variability. *NE*, norepinephrine; *NF-κB*, nuclear factor-κB; *NO*, nitric oxide; *PAI-1*, plasminogen activator inhibitor 1; *ROS*, reactive oxygen species; *SCD*, sudden cardiac death; ↑, increased; ↓,decreased. *(From Pitt B, Rajagopalan S. The role of mineralocorticoid receptor blocking agents in patients with heart failure and cardiovascular disease. In: McMurray JJV, Pfeffer MA, eds.* Heart Failure Updates. *London: Martin Dunitz; 2003:129.)*



	Risk reduction (95% CI)	*p value*
Cardiac mortality	31% (18–42%)	< 0.001
Progression of heart failure	36% (20–49%)	< 0.001
Sudden cardiac death	29% (5–46%)	0.02
Total mortality	30% (18–40%)	< 0.001

Fig. 11.21 The effect of spironolactone on morbidity and mortality of patients with severe heart failure in the Randomized Aldactone Evaluation Study. *ACE*, Angiotensin-converting enzyme; *CI*, confidence interval. *(From Pitt B, Rajagopalan S. The role of mineralocorticoid receptor blocking agents in patients with heart failure and cardiovascular disease. In: McMurray JJV, Pfeffer MA, eds.* Heart Failure Updates. *London: Martin Dunitz; 2003:118.)*

and increase NO availability[358] might have reduced the propensity for digitalis-related arrhythmias and the subsequent risk of sudden cardiac death reported in the digitalis trial.[361]

Eplerenone is an aldosterone antagonist that lacks some of spironolactone's common side effects.[362] The Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), enrolling more than 6600 patients with symptomatic HF within 3 to 14 days after MI, showed that eplerenone (25–50 mg/day) in combination with an ACE inhibitor, loop diuretic, and β-blocker reduced all-cause mortality ($P = .008$), death from cardiovascular causes ($P = .0002$), and hospitalization for cardiovascular events.[319]

In the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study, Zannad and coworkers[363] addressed the important question of whether aldosterone blockade is clinically useful in patients with mild systolic HF. In a double-blind trial, 2737 patients with NYHA class II HF and an EF of 35% or less were randomized to receive eplerenone (up to 50 mg daily) or placebo in addition to recommended therapy. The trial was stopped prematurely at a mean follow-up of 21 months due to improved benefits in the treatment arm. The primary outcome (ie, composite of death from cardiovascular causes or hospitalization for HF) occurred for 18.3% of patients in the eplerenone group compared with 25.9% in the placebo group (hazard ratio, [HR] =0.63; 95% confidence interval [CI], 0.54 to 0.74; $P < .001$). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (HR = 0.76; 95% CI, 0.62 to 0.93; $P = 0.008$); 10.8% and 13.5%, respectively, died of cardiovascular causes (HR = 0.76; 95% CI, 0.61 to 0.94; $P = .01$). Hospitalizations for HF and for any cause were also reduced with eplerenone.

Because of these findings, the use of aldosterone receptor blockade has been broadened to include patients with mild or moderate systolic HF (NYHA II or III) who have prior cardiovascular hospitalization or elevated levels of B-type natriuretic peptide (BNP), unless contraindicated.[304] The benefits of aldosterone inhibition in these less severe HF patients may be through improvements in endothelial function,[364] exercise tolerance, EF,[365] and attenuation of collagen formation. Successful use of aldosterone antagonists mandates close attention to blood potassium concentrations.[364] Based on these data and the favorable effects of aldosterone antagonism in animal models of infarction,[350] it seems reasonable to expect that aldosterone receptor blockers may find value even in patients with asymptomatic systolic LV dysfunction.

Clinical Practice

Evidence supports aldosterone antagonists for patients with symptomatic HF and patients with LV dysfunction after MI.[319] Aldosterone receptor antagonists should be considered in addition to standard therapy (including ACE inhibitors and β-blockers) in patients with NYHA II disease who have prior cardiovascular hospitalization or elevated BNP levels and those with NYHA IV HF and an EF of 35% or less, unless contraindicated. Class I recommendations also pertain to patients after an acute MI with an EF of 40% or less who develop HF symptoms or who have a history of diabetes, unless contraindicated.[304]

Spironolactone should be initiated at 12.5 to 25 mg/day. Patients should have a normal serum K^+ level (<5.0 mEq/L) and adequate renal function (creatinine ≤2.5 mg/dL in men, creatinine ≤2.0 mg/dL in women, and creatinine clearance >30 mL/min). Regular measurement of electrolytes is mandatory to avoid hyperkalemia. Dosages and dosing intervals should be reduced during episodes of potential dehydration (eg, vomiting, diarrhea) and with concomitant use of pharmacologic agents that may predispose to impairments in renal function (eg, steroidal antiinflammatory agents). In the RALES trial, there was no significant increase in the incidence of severe hyperkalemia (K^+ ≥6.0 mEq/L), and only one death related to hyperkalemia (in the placebo arm).[318] This is in marked contrast to a Canadian time-series analysis that showed an abrupt increase in hyperkalemia-associated morbidity and mortality in association with the publication of the RALES data.[359]

Spironolactone can occupy androgen receptors, leaving unopposed estrogen receptors and predisposing to estrogen-like effects such as painful gynecomastia and menstrual disorders. Because digoxin has estrogen-like properties, its use in combination with spironolactone can also predispose to gynecomastia.[366] This usually does not pose a problem in men because they do not have biologically significant amounts of estrogen. From the EPHESUS data, it appears that the newer aldosterone receptor antagonist, eplerenone, has a lower incidence of hyperkalemia and no evidence of unopposed estrogen receptor-like properties. Unfortunately, eplerenone is many times more expensive than spironolactone.

Renin Inhibition

Although RAAS inhibitors improve prognosis for HFrEF, HF-associated morbidity and mortality remain high. The effect of RAAS blockade may be limited due to the loss of an inhibitory feedback of angiotensin II on renin production. Suppression of Ang II and aldosterone generation by ACE inhibitors or ARBs does not result in persistently decreased ANG II and aldosterone plasma levels.[367] One reason for the reduced effectiveness of RAAS blockers may be the compensatory increase in renin and Ang I levels in response to interruption of the negative feedback activity of Ang II signaling.

Sustained elevations in renin levels after RAAS inhibitors have been associated with worse outcomes.[368,369] Evidence also suggests that these increases in renin may have additional, non-RAAS–dependent effects through activation of the (pro-) renin receptor and its subsequent activation of an intracellular postreceptor cascade that leads to enhanced synthesis of DNA, plasminogen activator inhibitor 1, collagen type I, fibronectin, and transforming growth factor-β_1.[370]

Clinical Evidence

Because ACE inhibitors and ARBs increase renin levels due to the loss of negative feedback of Ang II on renin release and the clinical clues suggesting that high plasma renin levels may ultimately influence the progression of cardiac disease, direct renin inhibitors have been considered in the treatment of HF. The most recently studied renin inhibitor is aliskiren. However, the reputed neurohormonal benefits[371,372] of adding this drug to standard therapy have not translated to improved outcomes in HF patients.

The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) trial[373] investigated whether aliskiren, when added to standard therapy, would reduce the rate of cardiovascular death or HF rehospitalization at 6 or 12 months of patients with acute decompensated HF. A total of 1639 patients were randomized to aliskiren or placebo. At 6 months, 24.9% of the aliskiren group (77 cardiovascular deaths, 153 HF rehospitalizations) and 26.5% of the placebo group (85 cardiovascular deaths, 166 HF rehospitalizations) experienced the primary end point (HR = 0.92; 95% CI, 0.76 t0 1.12; $P = .41$). At 12 months, the event rates were 35.0% for the aliskiren group (126 cardiovascular deaths, 212 HF rehospitalizations) and 37.3% for the placebo group (137 cardiovascular deaths, 224 HF rehospitalizations) (HR = 0.93; 95% CI, 0.79 to 1.09; $P = .36$). The rates of hyperkalemia, hypotension, and renal failure were higher in the aliskiren group compared with the placebo group. Among patients hospitalized for HF with reduced LVEF, initiation of aliskiren in addition to standard therapy did not reduce cardiovascular death or HF rehospitalization at 6 months or 12 months after discharge.

An interaction between treatment and diabetes was found. In diabetic patients, aliskiren was associated with greater incidence of cardiovascular death or HF rehospitalization (HR = 1.16; 95% CI, 0.91 to 1.47) and all-cause mortality (HR = 1.64; 95% CI, 1.15 to 2.33), whereas in nondiabetics, an opposite result was found (HR = 0.80; 95% CI, 0.64 to 0.99 and HR = 0.69; 95% CI, 0.50 to 0.94, respectively).[374]

Results from the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure (ATMOSPHERE) study, the other trial that is testing the safety and efficacy of aliskiren, are expected soon.[375] In this trial, patients with class II to IV systolic failure (EF <35%) and an elevated BNP or N-terminal pro BNP (NT-pro-BNP) concentration were randomized in equal proportions to receive enalapril (10 mg twice daily), aliskiren (300 mg once daily), or a combination of both drugs. The primary end point is delayed time to first occurrence of cardiovascular death or HF hospitalization. Although the development of renin inhibitors has increased our arsenal for modulating the RAAS, their widespread use in HFrEF patients, particularly those with concomitant diabetes, has not been advocated.

Combination Approaches With Renin-Angiotensin System Inhibition

Angiotensin receptor–neprilysin inhibitors (ARNIs) offer treatment for HF that involves neprilysin inhibition and AT_1 receptor blockade. ARNIs can modulate two counterregulatory neurohormonal systems in HF: the RAAS and natriuretic peptide system (Fig. 11.22).[376] Drugs that inhibit the RAAS have been foundational to cardiovascular drug therapy for almost 3 decades. RAAS inhibitors moderate

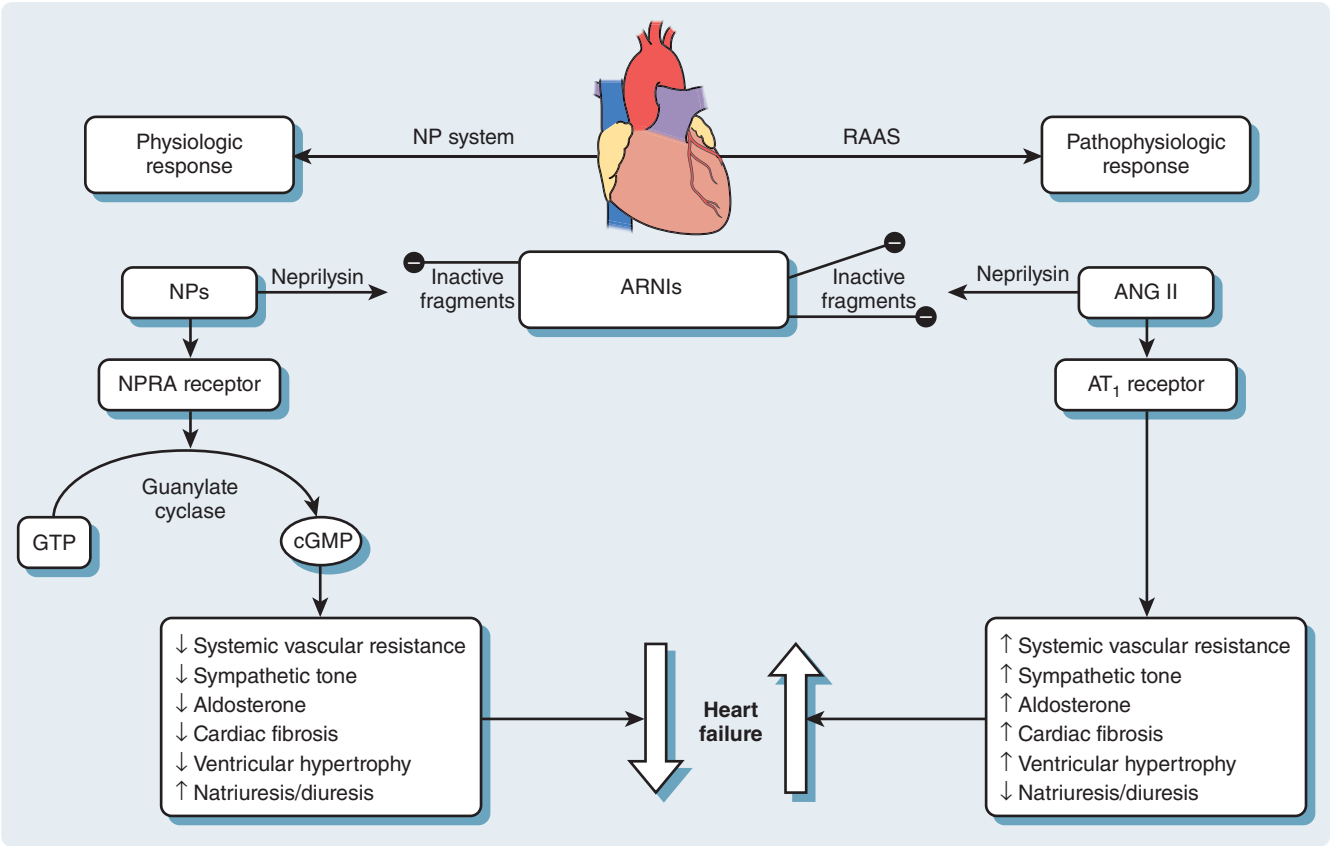


Fig. 11.22 Angiotensin receptor neprilysin inhibitors *(ARNIs)* can modulate two counterregulatory neurohormonal systems in heart failure: the renin-angiotensin-aldosterone system *(RAAS)* and the natriuretic peptide *(NP)* system (eg, atrial NP, B-type NP). *ANG,* angiotensin; *AT_1,* angiotensin I receptor; *cGMP,* cyclic guanosine monophosphate; *GTP,* guanosine-5′-triphosphate; *NPRA,* natriuretic peptide receptor A; ↑, increased; ↓,decreased. *(From Langenickel TH. Angiotensin receptor-neprilysin inhibition with LCZ696: a novel approach for the treatment of heart failure.* Drug Discov Today Ther Strateg. *2012;9:e131.)*

vasoconstriction, myocyte hypertrophy, and myocardial fibrosis, an effect that has translated into clinically meaningful improvements in functional status and survival. Natriuretic peptides, which include atrial natriuretic peptide, BNP, and urodilatin, are secreted by the heart, vasculature, kidney, and CNS in response to increased cardiac wall stress and other stimuli. Natriuretic peptides have potent natriuretic and vasodilatory properties, inhibit the RAAS, reduce sympathetic drive, and have antiproliferative and antihypertrophic effects. Neprilysin inhibition results in an increased concentration of natriuretic peptides. The beneficial effects of RAAS inhibition are likely to be augmented by the enhancement of natriuretic peptide activity.[376]

LCZ696 is the first and most clinically developed agent in the new class of ARNI compounds. The chemical entity comprises anionic moieties of the neprilysin inhibitor prodrug AHU377 and the ARB valsartan in a fixed-dose combination in a 1:1 ratio.[376] In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, which involved 8399 patients with NYHA class II, III, or IV HF, McMurray and associates[377] reported that LCZ696 was more effective than enalapril in reducing the risks of cardiovascular death (by an incremental 20%), HF hospitalization (by an incremental 21%), and all-cause mortality (by an incremental 16%). Patients' quality of life, as measured on the Kansas City Cardiomyopathy Questionnaire, was significantly improved with ARNI when compared with an ACE inhibitor. LCZ696 was also better tolerated than enalapril, with less likelihood for cough, hyperkalemia, or renal impairment.

Due to the overwhelmingly statistically advantageous effects, the PARADIGM-HF trial was stopped early for the benefit of the HF patients, and in July 2015, the FDA approved the combination valsartan/sacubitril tablet for the treatment of patients with stage C HF with reduced EF (ie, NYHA class II or IV). The drug formerly known as LCZ696 was given the name Entresto.

The recommended starting dose is 49 mg/51 mg given orally twice daily, and the target maintenance dose is 97 mg/103 mg given orally twice daily within 2 to 4 weeks as tolerated. A reduced starting dose of 24 mg/26 mg given twice daily is recommended for patients who are naïve to ACE inhibitors or ARBs or who previously were taking low doses of these RAS inhibitors. The ARNI combination is contraindicated with concomitant use of an ACE inhibitor, and a 36-hour washout period is recommended when switching from an ACE inhibitor to the ARNI drug. Although it can be administered in conjunction with other HF therapies in place of an ACE inhibitor or other ARB, it is contraindicated for patients with diabetes who are taking aliskiren. Among the adverse side effects associated with Entresto, the risk for hypotension and hyperkalemia may be as high as 18% and 12%, respectively.

β-Adrenergic Receptor Antagonists

Sympathetic Nervous System Activation and Its Role in the Pathogenesis of Heart Failure

Activation of the SNS (eg, after MI, for long-standing hypertension), much like increases in RAS activity, contributes to the pathophysiology of HF. SNS activation leads to pathologic LV growth and remodeling. Myocytes thicken and elongate, with eccentric hypertrophy and increases in sphericity. Wall stress is increased by this architecture, promoting subendocardial ischemia, cell death, and contractile dysfunction. Persistent SNS activation leads to altered gene expression, with a shift to a fetal-like phenotype (ie, downregulation of cardiac α-actin and α-myosin heavy chain and upregulation of fetal forms of β-myosin heavy chain). There is downregulation of calcium regulatory proteins, including SR Ca^{2+}-ATPase, and impairment of contractility and relaxation. The activated SNS can also harm myocytes directly through programmed cell death. As myocytes are replaced by fibroblasts, heart function deteriorates from this remodeling.[378] The threshold for arrhythmias may also be lowered, contributing in a deteriorating cycle.

β-Adrenergic Receptor Blockers' Influence on Heart Failure Pathophysiology

In chronic HF, the beneficial effects of long-term β-blockade include improved systolic function and myocardial energetics and reversal of pathologic remodeling. A shift in substrate use from free fatty acids to glucose, a more efficient fuel in the face of myocardial ischemia, may partly explain the improved energetics and mechanics in the failing heart treated with β-blockade.[379] Heart rate, a major determinant of $M\dot{V}O_2$, is reduced by β_1-receptor blockade. β-Blockade is also associated with a change in the molecular phenotype of the heart. Systolic dysfunction of individual myocytes is associated with upregulation of gene expression of natriuretic peptides and fetal-like β-myosin heavy chain and increased expression of SERCA2 (ie, intracellular pump in the SR of muscle) and α-myosin heavy chain (ie, the more efficient, faster, adult isoform).[378] β-Blockade reverses the changes in gene expression with concurrent improvements in LV function.[380] In a dog model of HF, β-blockade also reduced myocyte apoptosis.[381] Chronic β-blockade reduces the harmful effects of excessive SNS activation of the heart and can reverse LV remodeling.

β-Adrenergic blockade can limit the disturbance of excitation-contraction coupling and predisposition to ventricular arrhythmias associated with HF. In the normal heart, the fight or flight response activates the SNS. This stimulates a β-adrenergic receptor signaling pathway in the myocyte that increases phosphorylation of three key components of excitation-contraction coupling: the voltage-gated Ca^{2+} channel (VGCC), the SR Ca^{2+} release channel (ie, ryanodine receptor 2 [RYR2] channel), and the Ca^{2+} uptake pathway (ie, phosphorylation of phospholamban reduces inhibition of the Ca^{2+}-ATPase SERCA2a), ultimately resulting in increased contractility.[382]

In the low-CO failing heart, the SNS is chronically activated. In this hyperadrenergically stimulated heart, excitation-contraction coupling becomes maladaptive due to leaky Ca^{2+} from the SR. This is caused by protein kinase A (PKA)–hyperphosphorylated RYR2 channels that produce a diastolic SR Ca^{2+} leak that conspires with reduced SERCA2a-mediated SR Ca^{2+} uptake (due in part to PKA-hypophosphorylated phospholamban that inhibits SERCA2a) to deplete SR Ca^{2+} and contribute to contractile dysfunction of cardiac muscle (Fig. 11.23).[383,384] Depletion of SR Ca^{2+} stores underlies the reduced contractility of failing cardiac muscle.

Leaky Ca^{2+} may also explain the predisposition to ventricular arrhythmias thought to be initiated by delayed afterdepolarizations.[385] The cardiac RyR2 has a large cytoplasmic structure that serves as a scaffold for modulatory proteins that regulate the function of the channel. PKA phosphorylation of RYR2 dissociates the regulatory protein FKBP 12.6 and regulates the open probability of the channel. In failing hearts, RYR2 is PKA-hyperphosphorylated, resulting in defective channel function due to increased sensitivity of Ca^{2+}-induced activation.

Studies using animal models of HF show that chronic β-blockade may reverse the PKA hyperphosphorylated state and restore the structure and function of the RYR2 Ca^{2+} release channel.[386,387] Another potential benefit of β-adrenergic receptor blockade in the failing heart may be normalization of excitation-contraction coupling, potentially reducing the propensity for arrhythmias.

An evolving concept in the pathophysiology of HF incorporates the negative inotropic action of catecholamines and specifically the role of β_3-adrenoreceptors. The failing heart is resistant to exogenous inotropic stimulation compared with hearts that are not failing. This has been attributed to downregulation of β_1- and β_2-adrenoreceptors due to a hyperadrenergic state.[388,389] However, β_3-adrenoreceptors have been identified in the failing and nonfailing hearts of humans and other mammalian species.[390–392] Unlike the case for β_1- and β_2-adrenoreceptors, β_3-adrenoreceptors are upregulated in HF.[392–394] β_3-Activation decreases contractility. In contrast to the G_s-protein–coupled adenylyl cyclase activation and cAMP-dependent pathway of the β_1- and β_2-adrenoreceptors, the negative inotropy that results from stimulation of β_3-adrenoreceptors appears to result from activation of an NO pathway and an increased intracellular level of cGMP.[395] However, an understanding of the role of β_3-receptors in

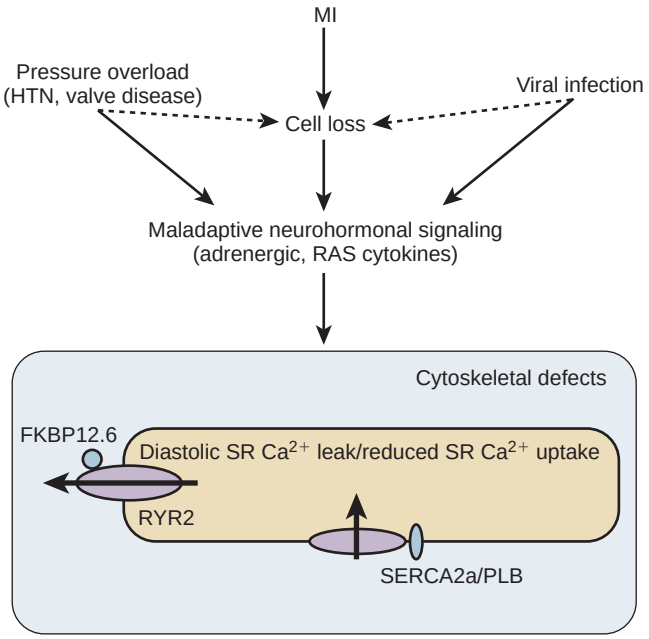


Fig. 11.23 The maladaptive response to cardiac muscle damage from myocardial infarction *(MI)*, viral infection, or pressure overload due to hypertension *(HTN)* or valve disease activates signaling pathways, including the adrenergic, renin-angiotensin *(RAS)*, and cytokine systems, in response to stress. Chronic activation of these pathways in heart failure causes defects in excitation-contraction coupling, including protein kinase A hyperphosphorylation of the cardiac ryanodine receptor *(RYR2)* that results in depletion of the enzyme *FKBP12.6* (which helps to keep the channel closed in diastole) from the channel macromolecular complex, causing a diastolic Ca^{2+} leak that depletes sarcoplasmic reticulum *(SR)* Ca^{2+} and reduces SR Ca^{2+} reuptake by means of *SERCA2a* (ie, intracellular calcium pump). Other defects in the maladaptive response to heart failure include alterations in the cytoskeleton and extracellular matrix (eg, imbalance between matrix metalloproteinases [MMPs] and tissue inhibitors of metalloproteinases [TIMPs]). *PLB*, Phospholamban. *(Modified from Marks AR. A guide for the perplexed: towards an understanding of the molecular basis of heart failure [editorial].* Circulation. *2003;107:1456.)*

the treatment and pathophysiology of HF awaits the arrival of specific β_3-adrenoceptor antagonists.

Clinical Evidence

The use of β-blockers in patients with HF was initially accepted with skepticism because of the perceived risk of decompensation from transient negative inotropic effects. However, data from human and animal studies have shown that β-blockers improve energetics and ventricular function and reverse pathologic chamber remodeling. Although this beneficial biologic process takes 3 months or more to manifest (Fig. 11.24), it translates into improved outcomes (ie, reduced deaths and hospitalizations) for patients with HF. Randomized trials show that metoprolol CR/XL, bisoprolol, and carvedilol (in conjunction with ACE inhibitors) reduce morbidity (ie, hospitalizations) in symptomatic, stage C and D (ie, not in cardiogenic shock) HF patients (ie, NYHA II to IV class) (Table 11.19).[316,317,396,397] Although β-blocker therapy is recommended for asymptomatic HF patients (ie, those with previous MI and reduced EF), evidence from randomized trials is lacking (class I, LOE B).[398]

β-Blockers are classified as being first-, second-, or third-generation drugs based on specific pharmacologic properties. First-generation agents, such as propranolol and timolol, block β_1- and β_2-adrenoreceptors, are considered nonselective, and have no ancillary properties. Second-generation agents, such as metoprolol, bisoprolol, and atenolol, are specific for the β_1-adrenoreceptor subtype but lack additional mechanisms of cardiovascular activity. Third-generation agents, such as bucindolol, carvedilol, and labetalol, block β_1- and β_2-adrenoreceptors and possess vasodilatory and other ancillary properties. Labetalol and carvedilol produce vasodilation by β_1-adrenoreceptor antagonism, whereas bucindolol produces mild vasodilation through a cGMP-mediated mechanism. Carvedilol increases insulin sensitivity,[399] possesses antioxidant effects,[400] and has β_3-adrenoreceptor selectivity.[401,402]

Although it is not clear whether the ancillary properties of third-generation β-blockers translate into better outcomes compared with the second-generation agents, findings from the Carvedilol or Metoprolol European Trial (COMET) suggest that the beneficial effect from β-blockers is not a drug class effect. The study compared carvedilol (25 mg twice daily) with metoprolol tartrate (50 mg twice daily) in symptomatic patients with EFs of 35% or less for 58

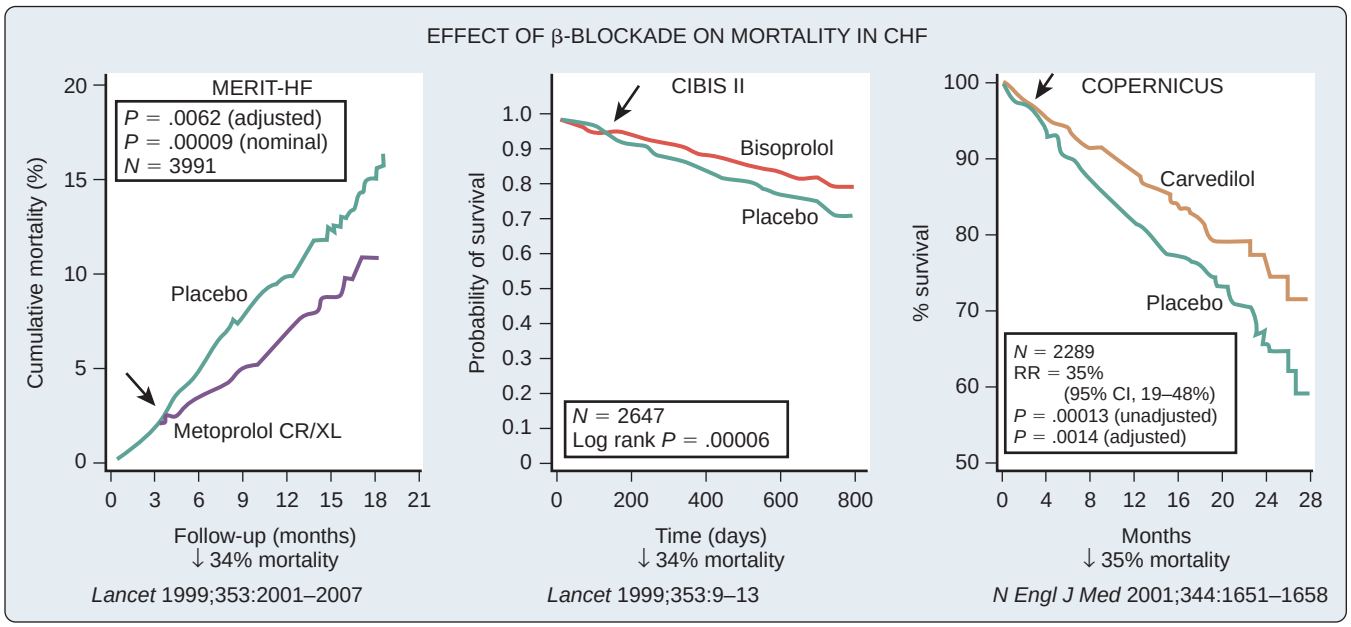


Fig. 11.24 Kaplan-Meier analysis of the probability of survival among patients in the placebo and β-blocker groups in the CIBIS-2, MERIT-HF, and COPERNICUS trials. *Arrows* denote the 3-month lag phase of the β-blocker benefit. CHF, Congestive heart failure; ↓, decreased. *(From Mann DL.* Heart Failure: A Companion to Braunwald's Heart Disease. *Philadelphia: Saunders; 2004.)*

TABLE 11.19 Large-Scale Placebo-Controlled Mortality Trials of β-Blockade in Heart Failure

					Effect on All-Cause	
Trial	*Agent*	*Heart Failure Severity*	*Patients* (N)	*Target Dose (mg)*	*Mortality*	*Hospitalization*
US Carvedilol	Carvedilol	NYHA II–III	1094	6.25–50 bid	↓ 65%	↓ 27%
CIBIS-II	Bisoprolol	EF ≤35; NYHA III–IV	2647	10 qd	↓ 34%	↓ 20%
MERIT-HF	Metoprolol CR/XL	EF ≤40; NYHA II–IV	3991	200 qd	↓ 34%	↓ 18%
BEST	Bucindolol	EF ≤35; NYHA III–IV	2708	50–100 bid	NS	↓ 8%
COPERNICUS	Carvedilol	EF ≤25; NYHA IV	2289	25 bid	↓ 35%	↓ 20%

EF, ejection fraction; *NS*, not significant; *NYHA*, New York Heart Association; ↓, reduced by.

TABLE 11.20 Effective β-Blockers for Heart Failure

Agent	*Receptor Selectivity*	*Starting Dose*	*Target Dose*
Metoprolol CR/XL	β_1	12.5 mg qd	200 mg qd
Bisoprolol	β_1	1.25 mg qd	5–10 mg qd
Carvedilol	β_1, β_2, β_3, α_2	3.125 mg qd	25–50 mg qd

months and demonstrated that carvedilol reduced the risk of death significantly more than metoprolol tartrate (all-cause mortality risk reduction: 17%, $P = .0017$; cardiovascular death risk reduction: 20%, $P = .00004$).[403] The superiority of carvedilol over metoprolol may reflect the importance of carvedilol's ancillary effects and pharmacodynamic (half-life) differences.[404]

Findings from the BEST trial confirm that not all β-blockers improve outcomes for patents with HF and suggest that the added benefit from carvedilol may not be a β_2-antagonistic effect because there was no improvement with bucindolol compared with placebo.[397] Whether the selective β_1-specific agents bisoprolol and metoprolol CR/XL exert clinical benefits similar to carvedilol will require additional study. Nonetheless, based on the results of COMET, carvedilol is preferred to conventional metoprolol (not metoprolol CR/XL) for HF treatment.

A metaregression analysis of β-blocker HF trials demonstrated that the magnitude of survival benefit seen with β-blockers was statistically significantly associated with the magnitude of heart rate reduction achieved but not the dosage of β-blocker administered. However, until HF trials randomly assign participants who receive β-blockers to different target heart rates, the optimal heart rate (with target heart rate reduction) remains unknown.[405]

Clinical Practice

Evidence suggests that β-blockers should be given to all HF patients with reduced EFs (<0.40) who are on ACE inhibitors or ARBs unless there is a contraindication. This recommendation is endorsed by the ACC/AHA[398] and the European Society of Cardiology.[406] Patients with ongoing decompensation (ie, requiring intravenous inotropic or vasodilator therapy), overt fluid retention, or symptomatic hypotension should not receive β-blockers. There is no apparent decline in safety or efficacy when β-blockers are given to diabetics with HF. The long-term benefit of β-blocker therapy in patients with coexisting chronic obstructive pulmonary disease is uncertain because they have been excluded from the major clinical trials.

The three agents with clinical trial evidence for improved morbidity and mortality for patients with HF are carvedilol, metoprolol CR/XL, and bisoprolol. Starting doses of β-blockers should be small to minimize worsening of HF symptoms, hypotension, and bradycardia. The dose should be doubled every 1 to 2 weeks, as tolerated, until the target doses shown to be effective in large trials are achieved (Table 11.20). Although it is recommended that β-blocker therapy be continued indefinitely in patients with HF, if it is to be electively stopped, a slow titration period is preferred. Acute withdrawal of β-blocker therapy in the face of high adrenergic tone may result in sudden cardiac death.[407]

The adverse effects of β-blocker therapy include fatigue, dizziness, hypotension, and bradycardia. Because the absolute risk of adverse events is small compared with the overall risk reduction of cardiovascular death, few patients have been withdrawn from β-blocker therapy.[408]

A practical guide to the use of β-blockers in HF patients has been published by McMurray and colleagues[409] All stage C HFrEF patients should be treated with one of the three β-blockers—bisoprolol, immediate- or extended release carvedilol, or sustained-release metoprolol—unless contraindicated,

Hydralazine–Isosorbide Dinitrate

Combination vasodilator therapy with hydralazine and isosorbide dinitrate can interfere with the mechanisms responsible for the progression of HF, particularly that which involves oxidative stress.[410] In addition to biochemical and molecular benefits, the hydralazine–isosorbide dinitrate combination reduces preload and afterload, decreases mitral regurgitation, improves exercise capacity, increases LVEF, and prolongs survival in selected HF populations.[411]

Clinical Evidence

Three major clinical studies have examined the effects of combination therapy with hydralazine and nitrates in the management of HF. In the first Vasodilator–Heart Failure Trial (V-HeFT I), combination vasodilator therapy with hydralazine and isosorbide dinitrate given to male patients with mild to severe HF improved survival compared with the ACE inhibitor prazosin or placebo.[412] However, in V-HeFT II, enalapril had a major benefit on survival in NYHA class II or III patients compared with the combination vasodilator therapy.[331]

Because subanalyses of these studies showed that hydralazine–isosorbide dinitrate produced a marked risk reduction in black patients,[413] the African Americans Heart Failure Trial (AheFT) was designed to prospectively examine the efficacy of this vasodilator combination. The AheFT randomized 1040 self-described African Americans with HF and an abnormal LVEF (only 23% with ischemic heart disease) treated with diuretics, ACE inhibitors, and β-blockers to isosorbide dinitrate (40 mg three times daily) plus hydralazine (75 mg three times daily) or to placebo.[414] Because a significant reduction in mortality rate was observed in isosorbide dinitrate plus hydralazine-treated patients compared with placebo treatment (6% vs 10%, respectively; HR = 0.52; $P = .02$), the study was terminated early, and ACCF/AHA recommendations were initiated.[414]

Clinical Practice

The combination of hydralazine and isosorbide dinitrate should be administered (class I) to improve outcomes for patients self-described as African Americans with moderate or severe symptoms on optimal therapy with ACE inhibitors, β-blockers, and diuretics.[398] The benefit is presumed to be related to an increase in NO bioavailability. The addition of hydralazine and isosorbide dinitrate can be useful in current or prior symptomatic HFrEF patients who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated (class IIa).[304]

The initial dose of oral isosorbide dinitrate is 20 mg three times daily, with subsequent titration up to a maximal dose of 40 mg three

times daily. Nitrates should be given no more than three times daily, with daily nitrate washout intervals of 12 hours to prevent nitrate tolerance from developing. The initial dose of oral hydralazine in patients with HF is 25 mg three times daily, with subsequent titration up to a maximal dose of 100 mg three times daily. The recommendation for initiation of the fixed combination is 20 mg of isosorbide dinitrate and 37.5 mg of hydralazine hydrochloride given three times daily, with subsequent maximal dosing at 40 mg of isosorbide dinitrate and 75 mg of hydralazine hydrochloride.

Adjunctive Drugs

In addition to ACE inhibitors and β-blockers, diuretics and digoxin are often prescribed for patients with LV systolic dysfunction and symptomatic HF.

Diuretics

For most patients, volume status should be optimized before introduction of β-blockers and ACE inhibitors. Patients with pulmonary congestion often require a loop diuretic in addition to standard therapy. Diuretics relieve dyspnea, decrease heart size and wall stress, and correct hyponatremia from volume overload. However, overly aggressive and especially unmonitored diuretic therapy can lead to metabolic abnormalities, intravascular depletion, hypotension, and neurohormonal activation. Loop diuretics inhibit tubular reabsorption of sodium along the ascending limb of the loop of Henle. Furosemide also reduces preload by increasing vascular capacity.

Diuretics continue to have a role in the management of chronic HF and are usually added to ACE inhibitors, β-blockers, and aldosterone antagonists. However, no RCT has shown a survival benefit for the use of diuretics in HF. Rates of hospitalization or death from worsening HF were significantly greater for HF patients receiving diuretics (other than aldosterone antagonists) than for those not receiving diuretics (relative risk = 1.31, 95% CI, 1.09 to 1.57) in a large post hoc review of data from SOLVD.[415]

Dosing recommendations and kinetic data for the commonly used loop diuretics are provided in Table 11.21. Common side effects of loop diuretics include electrolyte depletion (eg, Na^+, K^+, Mg^+, Ca^{2+}, Cl^-), prolonged action of nondepolarizing muscle relaxants, hyperglycemia, and insulin resistance. Less common side effects include rash, hyperuricemia, and ototoxicity.

Digoxin

Digoxin continues to be useful for patients with symptomatic HF and LV systolic dysfunction despite receiving ACE inhibitor, β-blocker, and diuretic therapy. Digoxin is the only positive inotropic drug approved for the management of chronic HF.

Its indirect mechanism of positive inotropy begins with inhibition of the myocardial sarcolemmal Na^+/K^+-ATPase, resulting in increased intracellular Na^+. This prompts the Na^+/Ca^+ exchanger to extrude Na^+ from the cell, increasing the intracellular concentration of Ca^{2+}. The increased Ca^{2+} available to the contractile proteins increases contractile function.[416]

Besides its inotropic effects, digoxin has important vagotonic and sympatholytic effects. The inhibition of $Na^{+/}K^+$-ATPase in the kidney also decreases sodium reabsorption in the renal tubules.[398] In atrial fibrillation (AF), digoxin slows the rate of conduction at the AV node. In HF patients, it reduces sympathetic efferent nerve activity to the heart and peripheral circulation through direct effects on the carotid sinus baroreceptors.[417] Digoxin increases heart rate variability, an additional beneficial action on autonomic function in the HF patient.[418]

Although these properties are beneficial in controlling the ventricular rate in AF, digoxin has a narrow therapeutic-to-toxicity ratio. Digoxin toxicity is dose dependent and modified by concurrent medications (eg, non–potassium-sparing diuretics) or conditions (eg, renal insufficiency, myocardial ischemia). Ventricular arrhythmias consequent to digoxin toxicity may be caused by calcium-dependent afterpotentials. In patients with intoxication and life-threatening arrhythmias, purified antidigoxin FAB fragments from digoxin-specific antisera provide a specific antidote.[416]

The efficacy of digoxin for symptomatic HF was shown in RCTs. The Digitalis Investigators Group (DIG) trial, enrolling more than 6500 patients with an average follow-up of 37 months, showed that digoxin reduced the incidence of HF exacerbations. Although the study showed no difference in survival in patients with EFs less than 45% receiving digoxin or placebo, the combined end point of death or hospitalization for HF was significantly reduced in patients who received digoxin (27% vs 35%; relative risk = 0.72; 95% CI, 0.66 to 0.79).[361] However, this study revealed a higher incidence of suspected digoxin toxicity in the treatment group.

Efficacy of digoxin in patients with mildly symptomatic HF was shown in pooled results from the Prospective Randomized Study of Ventricular Function (PROVED) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trials. Patients randomized to digoxin withdrawal had an increased likelihood of treatment failure compared with those who continued to receive digoxin, suggesting that patients with LV systolic dysfunction benefit from digoxin (or at least do not benefit from digoxin withdrawal), even when they have only mild symptoms.[419,420]

Taken together with its narrow therapeutic window, digoxin is deemed reasonable to add to treatment for HF patients with reduced EF who remain symptomatic despite optimal therapy (class IIa). Ideally, serum digoxin concentration should remain between 0.7 and 1.1 ng/mL. In the elderly patient with renal insufficiency, severe conduction abnormalities, or acute coronary syndromes, even a low dose of 0.125 mg/day should be used with extra caution.

Anticoagulation

Patients with chronic HFrEF are at an increased risk for thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and in peripheral blood vessels and possibly due to increased activation of procoagulant factors.[304] Even so, there are no large-scale data to support the routine use of anticoagulants in a HFrEF patient without having AF, a prior thromboembolic event, or a cardioembolic source (class III). However, a class I recommendation does exist for its use in patients with HF who have permanent, persistent, or paroxysmal AF and an additional risk factor for cardiometabolic stroke, including a history of hypertension, diabetes, previous stroke or transient ischemic attack, or age of at least 75 years. The topic is reviewed by Gheorghiade and coworkers.[421]

Other Pharmacologic Therapies for Chronic Heart Failure Management

Vasopressin Receptor Antagonists

Arginine vasopressin (AVP) has been elucidated as one of the mediators involved in the progression of HF. Patients with HF have higher

TABLE 11.21 Loop Diuretics

Drug	*Equivalent Doses*	*Initial Dose*	*Maximal Dose*	*Onset (Intravenous)*	*Diuresis Peak*	*Duration*
Furosemide	40 mg	10–40 mg qd	240 mg bid	10–20 min	90 min	4–5 h
Bumetanide	1 mg	0.5–1.0 mg qd	10 mg qd	Within 10 min	75–95 min	4–5 h
Torsemide	20 mg	50 mg qd	200 mg bid	10 min	60 min	6–8 h
Ethacrynic acid	25 mg	100 mg bid	100 mg bid	10–20 min	90 min	4–5 h

levels of AVP than controls, and this has been shown to be a marker of increased cardiac-related mortality.[422]

The effects of AVP include vasoconstriction through the V_1 receptor and antidiuresis through the V_2 receptor in the kidney. The water retention that occurs in chronic HF due to the activation of the RAS is treated with diuretics, but diuretics are associated with numerous adverse effects (eg, electrolyte imbalance, renal insufficiency, RAS activation). Due their ability to decrease water retention without activating the RAS, vasopressin receptor antagonists are being investigated for use in patients with HF.

Studies of patients with stage C HF comparing Tolvaptan with placebo have revealed the drug's ability to decrease water retention, correct hyponatremia, improve patient-assessed clinical status, and decrease PCWP without causing renal injury (ie, EVEREST and ECLIPSE trials). Vasopressin receptor antagonists may ultimately replace the use of diuretics in patients with HF, but further studies are necessary to determine whether this class of medication can improve outcomes for HF patients.

Anticytokines

In addition to the RAAS and the SNS, other vasoactive mediators and growth factors have been implicated in the progression of HF. Production of inflammatory cytokines (eg, tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]) is increased in HF patients, and increased blood concentrations of these cytokines have been associated with poor short-term and long-term prognoses.[423]

The value of anti-TNF-α therapy with Etanercept, a TNF-α receptor fusion protein, has been studied in two trials: Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) and Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction (RECOVER) and in the combined analysis of the Randomized Etanercept Worldwide Evaluation (RENEWAL). However, the trials were terminated prematurely after an interim data analysis showed a lack of benefit. Etanercept had no effect on clinical status and had no effect on the death or HF-related hospitalization end points.[424] Inhibition of anti-proinflammatory cytokines remains only a potential therapy for HF.

Endothelin Receptor Antagonists

The endothelin system may contribute to the progression of HF. Plasma levels of endothelin 1 (ET1) are increased in patients with HF.[425] ET1 produces vasoconstriction of the systemic, renal, pulmonary, and coronary vasculature; remodeling of the myocardium (including myocardial and vascular fibrosis); and neurohormonal activation, and it has proarrhythmic and negative inotropic effects.

After the central role of endothelin in pathogenesis and the beneficial effect of endothelin antagonists in treating experimental HF were defined, clinical studies with endothelin antagonists began.[426,427] The clinical efficacy of endothelin receptor-antagonists (eg, bosentan, enrasentan, darusentan) has been investigated in four clinical trials: REACH-1, ENCOR, ENABLE, and EARTH.[428–430] However, in none of these trials was there a significant difference between endothelin receptor antagonists and placebo with regard to clinical status, all-cause mortality, or HF-related hospitalizations.

Vasopeptidase Inhibitors

In opposition to the endogenous vasoconstrictor systems (ie, Ang II, the adrenergic system, ET1, vasopressin, and aldosterone) are the endogenous vasodilator systems, including NO, endothelium-derived hyperpolarizing factor, prostaglandins, adrenomedullin, and natriuretic peptides. These vasodilating mediators reduce BP, improve sodium and water excretion, reduce growth and fibrosis, inhibit coagulation, and reduce inflammation. However, there is an imbalance that favors vasoconstriction in HF.

The concept of neutral endopeptidase inhibition (ie, major enzymatic pathway for degradation of natriuretic peptides) for the treatment of chronic HF led to two large-scale RCTs, OCTAVE and OVERTURE, that compared the use of omapatrilat with ACE inhibition.[431,432] Although there was no statistically significant advantage with omapatrilat regarding total mortality, the secondary end point of cardiovascular death or HF-related hospitalization was reduced in the omapatrilat group (HR = 0.91; 95% CI, 0.82 to 0.98; P = .012). Concerns regarding the side effect profile of omapatrilat (eg, angioedema), limit its use in HF treatment.

I_F Current Inhibitors

The funny current (I_F current) is the most important current for SA node depolarization. The inward current affects Na^+ and K^+ channels and has a significant effect on heart rate. Ivabradine is the first I_F current inhibitor available for oral use (usually 5 mg daily) in the United States. It has been approved by the FDA for treatment of angina pectoris as an adjunct to other drugs for patients with an increased heart rate, for those who have a contraindication to β-receptor blockers, and for CHF in patients with an increased heart rate.

In a study of 10,917 patients with CAD, EF less than 40%, and a heart rate greater than 70 beats/min, ivabradine administration compared with placebo did not impact mortality but did reduce the incidence of coronary events, MI, and the need for coronary revascularization.[433] In patients with stable coronary disease without HF but an increased heart rate, ivabradine did not reduce mortality or the incidence of nonfatal MI.[434] The drug appears to be well tolerated in patients taking β-blockers for angina pectoris. In patients with coronary stents or coronary revascularization who continue to have angina after the procedure, ivabradine appears to reduce angina episodes due to exercise.

Ivabradine appears to be very effective in patients with HF. In a study of 6558 patients with an EF less than 35% and heart rate greater than 70 beats/min, the drug compared with placebo significantly reduced the incidence of HF death and the readmission rate for HF treatment.[435] All patients were also receiving β-blocker treatment for HF. The most impressive responses were in patients who had the fastest heart rates. Heart rate is a marker for a bad outcome in HF, and reducing the heart rate appears to improve outcomes, likely by reducing ventricular loading conditions.[436] This results in reduced end-systolic and end-diastolic volumes and improved EF.[437]

The drug is well tolerated, with very few episodes of bradycardia or hypotension even when combined with β-blockers. The drug is contraindicated in patients requiring calcium channel blockers, patients with sick sinus syndrome or symptomatic bradycardia, and patients taking drugs that inhibit the CYP3A4 enzymes such as ketoconazole, macrolide antibiotics, cyclosporin, gestodene, and antiretroviral drugs. Heart block, dizziness, and headaches have been reported. The QT interval is not directly prolonged but may lengthen with slowing of the heart rate. An unusual side effect is visual brightness without field cuts, which occurs in a small number of patients and is totally reversible after the drug is discontinued.

Stem Cell Therapy

Stem cell therapy is a potential treatment for HF. Stem cell therapy has shown promise in the treatment for ischemic heart disease in the laboratory and in small clinical studies.[438,439] Autologous bone marrow and peripheral blood stem cells transplanted in patients with acute MI improved cardiac function.[440,441] Although fewer randomized trials of transplantation of blood- or bone marrow–derived stem cells have been performed in the setting of chronic CAD and chronic HF,[442–445] the results show promise, including improvements in regional and global LV function, perfusion, and relief of angina pectoris.[446,447]

The C-CURE clinical trial assessed cardiopoietic stem cell intervention as an adjunct to chronic HF management. This was the first application of guided stem cells for targeted regeneration of a failing organ. Lineage priming of bone marrow stem cells from patients with ischemic HF was shown to be feasible. Administration of derived

autologous cardiopoietic stem cells into the hibernating myocardium of patients with HF was safe. The study also demonstrated consistent improvements in LVEF at 6 months by cardiopoietic stem cell therapy compared with standard of care.[448] Applying findings to clinical care will require additional clinical trials.

Diet and Exercise Therapy

Guidelines highlight patient- and family-centered education on self-care management of HFrEF. Included are dietary restrictions and exercise. Sodium restriction remains important in delaying the progression to HF. The current guidelines recommend a sodium intake of 1500 mg/day by patients with stage A or B disease, but insufficient evidence exists for recommended sodium level restrictions for patients with stages C and D. Nonetheless, the guidelines recommend that some degree of restriction to less than 3000 mg daily is reasonable because most people consume at least 4000 mg of sodium daily.

Regular physical activity is recommended for HF patients who can participate. Cardiac rehabilitation is deemed to be useful for patients with stable HFrEF.[304]

Pharmacologic Treatment of Heart Failure With Preserved Ejection Fraction or Diastolic Heart Failure

Abnormal diastolic ventricular function is a common cause of clinical HF. The incidence of HF with a normal or near-normal EF (≥50%) includes up to 50% of the general HF population.[305] The risk of HFpEF increases with age, approaching 50% among patients older than 70 years.[449] HFpEF is also more common in women and in those with multiple comorbidities, such as hypertension, diabetes, vasculopathy, renal disease, AF, and metabolic syndrome.[450]

In terms of morbidity and mortality, the prognosis associated with the diagnosis of HFpEF is similar to that of HFrEF.[451–454] Because this syndrome carries substantial morbidity (eg, exercise intolerance, poor quality of life, frequent hospitalizations) and reduced survival and results in substantial annual health care expenditures, pharmacotherapy for HFpEF represents one of the current frontiers of clinical cardiovascular medicine.

In contrast to the large, randomized trials that led to the treatment guidelines for HFrEF, the randomized, double-blind, placebo-controlled, multicenter trials enrolling patients with diastolic HF have resulted in neutral results for primary outcomes. Consequently, the treatment of HFpEF remains empiric.

The general pharmacologic approach to treating HFpEF has three main components. First, treatment should reduce symptoms, primarily by lowering pulmonary venous pressure during rest and exercise by carefully reducing LV volume and maintaining atrial-ventricular synchrony or tachycardia control. Second, treatment should target the underlying diseases that cause HFpEF. Ventricular remodeling (eg, myocardial hypertrophy, fibrosis) should be reversed by controlling hypertension, treating ischemia, and controlling glycemia in diabetic patients. Third, treatment should attempt to target the underlying mechanisms that are altered by the disease processes. However, due to our lack of understanding of the pathogenesis of HFpEF, the third goal remains elusive.

Many of the drugs used to treat HFrEF are also used to treat HFpEF. However, the reason for their use and the doses used may be different for diastolic HF. For instance, in diastolic HF, β-blockers may be used to prevent tachycardia and thereby prolong diastolic filling and reduce left atrial pressure[455]; whereas in systolic HF, β-blockers (eg, carvedilol) are used to reverse heart remodeling. Metoprolol-CR/XL may be a better β-blocker choice than carvedilol for HFpEF because an excessively low a BP (as a consequence of carvedilol) may be detrimental for the diastolic HF patient. However, because β-blocker therapy for the treatment of HFpEF has been challenged by exercise metabolic testing data indicating that impaired chronotropic response to exercise contributes to observed exercise intolerance,[456] it is less likely to be chosen as a stand-alone treatment.

Similarly, doses of diuretics or venodilators such as nitrates are much smaller than for HFrEF because the patient who has LV diastolic dysfunction with a small, stiff left ventricle is particularly susceptible to excessive preload reduction, which can lead to LV underfilling, a fall in CO, and hypotension. In patients with severe LV hypertrophy due to hypertension or hypertrophic cardiomyopathy, excessive preload reduction can also create subaortic outflow obstruction. Careful attention is required for symptoms of ventricular underfilling such as weakness, dizziness, near-syncope, and syncope.

Although calcium channel blockers are not a part of the armamentarium for HFrEF patients, they may be beneficial in HFpEF through effects on heart rate, BP control, and purported benefits on lusitropic function. With the exception of rate control in chronic AF, digoxin is not recommended for HFpEF.

Class I recommendations for HFpEF patients include control of systolic and diastolic BP in accordance with clinical practice guidelines (see "Pharmacologic Management of Hypertension") and use of diuretics to relieve symptoms from pressure overload.[304] β-Blockers and ACE inhibitors or ARBs are considered reasonable to use to control BP. Coronary revascularization is considered reasonable in patients with CAD in whom angina or demonstrable myocardial ischemia has an adverse effect on symptomatic HFpEF despite optimal medical therapy. AF is managed according to clinical practice guidelines. The use of an ARB can be considered for these patients to decrease hospitalizations. The routine use of nutritional supplements is not recommended for HFpEF patients.[304]

Trials of Treatment for Heart Failure With Preserved Ejection Fraction

The pharmacologic trials for HFpEF have focused primarily on neurohormonal activation as the underlying pathophysiologic mechanism for the disease process (Table 11.22). However, unlike the benefits observed from blockade of the RAAS and SNS in HFrEF patients, results from the HFpEF trials suggest that neurohormonal stimulation may not be as sustained in patients with symptomatic diastolic dysfunction.

It has been proposed that HFpEF is an integrative physiology disorder for which hemodynamics and the control of blood volume and its distribution are more important than, for instance, the RAAS.[450] Increasingly, data show that skeletal muscle abnormalities may be critical in the disease process.[457–459] Future treatment that integrates multiple targets, such as neuromodulators or pleomorphic drugs with antiinflammatory actions (eg, HMG CoA reductase inhibitors) and exercise training,[460] may prove to be more effective than RAAS blockade in the management of HFpEF. Even so, we review some of the findings from the larger HFpEF trials that have focused on neurohormonal antagonists.

Of all the three large RCTs of ACE inhibitors or ARBs that studied HFpEF, only the CHARM-preserved study found marginal benefit for candesartan in reducing HF hospitalizations (HR = 0.86; 95% CI, 0.74 to 1.0; $P = .051$) over 3 years of follow-up, and none showed benefit for primary end points. In a study by Lund and associates, a modest reduction in the 1-year mortality rate for ACE inhibitor and ARB therapy (propensity score-adjusted HR = 0.90; 95% CI, 0.85 to 0.96; $P < .001$) was found among 16,216 HFpEF community dwellers who were taking ACE inhibitors or ARBs. The mortality reduction was observed particularly in those with an LVEF of 40% to 49%.[461]

The ALDO-DHF study tested the impact of an aldosterone antagonist, spironolactone, in HFpEF, with the primary end points of improved diastolic function and exercise capacity.[462] After 12 months of treatment, spironolactone reduced LV mass and the mitral E/e′ ratio (ratio of mitral inflow and annular early diastolic velocities), although these favorable echocardiographic findings were somewhat attenuated after adjusting for reductions in BP. There was no improvement in the 6-minute walk distance, nor did participants report improvements in quality of life.

TABLE 11.22 Trials of Interventions for Heart Failure With Preserved Ejection Fraction

	Trials							
Parameter	*Japanese DHF*	*ELANDD*	*I-PRESERVE*	*DIG-PEF*	*ALDO-DHF*	*RAAM-PEF*	*RELAX*	*TOPCAT*
Intervention	Carvedilol	Nebivolol	Irbesartan	Digoxin	Spironolactone	Eplerenone	Sildenafil	Spironolactone
Sample size	245	116	4128	988	422	44	216	3445
Inclusion criteria	LVEF >40%	LVEF >45%; diastolic dysfunction by Doppler echo; NYHA class II–III	LVEF>45%; NYHA II–IV; hospitalization for HF within past 6 mo	LVEF >45%; clinical signs/ symptoms of HF; normal sinus rhythm	LVEF >50%; NYHA II–III, evidence of diastolic dysfunction	LVEF >50%, NYHA II-III; elevated BNP	LVEF >50%; elevated NT-pro-BNP; reduced exercise capacity	LVEF >45%; controlled hypertension (SBP <140 or <160 mm Hg if on 3+ medication; serum potassium <5.0 mmol; history of hospitalization for HF in past 12 mo or elevated BNP/NT-pro-BNP)
Primary end point	Composite cardiovascular death and unplanned hospitalization for HF	Change in 6MWT	Composite cardiovascular death from any cause or hospitalization for cardiovascular cause	Combined HF hospitalization or HF mortality	Changes in diastolic function (E/e′) and maximum exercise capacity (peak $\dot{V}O_2$)	Change in 6MWT	Change in peak $\dot{V}O_2$	Composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF
Outcome	Negative	Negative	Negative	Negative	Improved diastolic function; did not improve exercise capacity	Negative	Negative	Negative; lower hospitalization for HF in spironolactone group
1-Year survival rate (%)	Placebo 90[a]; treatment 90[a]	—	Placebo 90[a]; treatment 90[a]	Placebo 77; treatment 77	Placebo 100; treatment >99	—	6-Mo survival rate: placebo 100; treatment 97	Placebo >90; treatment >90
Patient Characteristics								
Age (y)	73	67	72	67	67	72	68	69
Women (%)	43	65	59	42	52	5	43	52
White (%)	—	—	94	86	—	—	90	89
Black (%)	—	—	2	—	—	—	—	—
NYHA class (%)	I (18), II (69), III (11), IV (2)	II (77), III (21)	II (21), III (77), IV (3)	I (19), II (59), III (20), IV (1)	II (85), III (15)	II (67), III (33)	II (49), III (51)	I (3), II (63), III (33), IV (0.4)

Comorbidities								
Hypertension (%)	80	86	89	62	92	100	80	91
CAD (%)	28	17	38	50	43	67	42	59
Diabetes mellitus (%)	28	21	28	27	61	62	42	32
CKD (%)	—	—	31	48	—	—	56	39
LV hypertrophy (%)	—	—	—	—	—	—	48	—
Vital Signs								
SBP (mm Hg)	134	134	137	—	135	130	124 (median)	129
DBP (mm Hg)	75	81	79	—	79	71	—	76
BMI (kg/m^2)	24	30	30	—	29	30	33 (median)	32
Admission Data								
BNP (pg/mL)	219	—	—	—	—	255	—	234 (median)
NT-proBNP (pg/mL)	—	—	360	—	179 (median)		757 (median)	950 (median)
Serum creatinine (mg/dL)	1.0	—	1.0	—	—	1.6	1.3	1.1
LV mass (g/m^2) or LVMI (g/m^2)	126 g/m^2	—	—	—	108 g/m^2	49 g/m^2	77 g/m^2	—
Medications								
Diuretic (%)	63	49	82	82	55	95	88	82
ACEI (%)	24	75 (ACEI or ARB)	26	86	78	95 (ACEI or ARB)	65 (ACEI or ARB)	65
ARB (%)	51	—	—	—	—	—	—	20
β-Blocker (%)	—	—	59	—	69	76	77	78
Digoxin (%)	19	—	14	—	—	—	—	—
Aldosterone antagonist (%)	21	—	15	—	—	—	12	—
Statin (%)	—	46	32	—	53	—	63	53

[a]Estimated survival based on Kaplan-Meier curves.

ACEI, Angiotensin-converting enzyme inhibitor; *ALDO-DHF*, Effect of Spironolactone on diastolic function and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; *ARB*, angiotensin receptor blocker; BNP, B-type natriuretic peptide; *CAD*, coronary artery disease; *CKD*, chronic kidney disease; *DBP*, diastolic blood pressure; *DIG-PEF*, Digitalis Intervention Group=Preserved Ejection Fraction; *ELANDD*, Effects of Nevivolol on Clinical Symptoms, Exercise Capacity, and Left Ventricular Function in Diastolic Dysfunction; *HF*, heart failure; *I-PRESERVE*, Irbesartan in Heart Failure with Preserved Ejection Fraction; *Japanese DHF*, Japanese Diastolic Heart Failure; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *LVMI*, left ventricular mass index (LV mass/body surface area); *NT-proBNP*, N-terminal pro-B-type natriuretic peptide; *NYHA*, New York Heart Association; *RAAM-PEF*, Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; *RELAX*, Effect of Phosphodiesterase-5 Inhibition on Exercise Capacity and Clinical Status in Heart Failure with Preserved Ejection Fraction; *SBP*, systolic blood pressure; *TOPCAT*, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; $\dot{V}O_2$, oxygen consumption; 6MWT, 6-mile walk test.

From Sharma K, Kass DA. Heart failure with preserved ejection fraction: mechanisms, clinical features, and therapies. *Circ Res.* 2014;115:79.

In a propensity-matched analysis of hospitalized, older HFpEF patients from the Organized Program to Initiate Lifesaving Treatments in Hospitalized Patients with Heart Failure (OPTIMIZE) study, aldosterone antagonists had no effect on all-cause mortality or hospitalization.[463] Moreover, in the large Treatment of Preserved Cardiac Function with Aldosterone Antagonist (TOPCAT) study[464] involving 3445 participants, the primary end point (ie, cardiovascular mortality, aborted cardiac arrest, or hospitalization for HF) was not met. Similar to CHARM-preserved, there was a small but significant decline in hospitalizations.

Given the neutral outcomes from the RAAS antagonist trials, efforts to identify key pathophysiologic perturbations and novel targets in HFpEF continue. For example, the ARNI LCZ696 has been tested for safety and efficacy in HFpEF patients. Neprilysin inhibitors inhibit the breakdown of natriuretic peptides and help to promote myocardial relaxation, diuresis, natriuresis, and modest vasodilation. Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with ARB on Management of Heart Failure (PARAMOUNT) was a phase 2, randomized, double-blind trial that enrolled 301 patients with NYHA class II or III HF, LVEF of 45% or higher, and an NT-pro-BNP level of more than 400 pg/mL.[465] Compared with valsartan alone, patients randomized to LCZ696 had significantly lower NT-pro-BNP levels and at 36 weeks showed decreased left atrial size and a trend toward improved functional class. LCZ696 also appears to reduce TNF-α levels, which correlates with improvements in the cardiac features of HFpEF.[466] The therapeutic potential for ARNIs in the treatment of HFpEF remains promising.

Another pharmacologic intervention tested for HFpEF is PDE5 inhibition. PDE5 metabolizes NO and natriuretic peptide generated cGMP. Because PDE5 is activated in HFpEF, it is reasonable to suspect that it may limit the beneficial NO and natriuretic peptide actions in the heart, vasculature, and kidney.

Redfield and colleagues randomized 216 HFpEF patients to the PDE5 inhibitor sildenafil or placebo in the PhosphodiesterRase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) study to determine whether exercise capacity (ie, primary end point) improved after 24 weeks of chronic treatment.[467] The study result was neutral, reporting no benefit in the primary end point and no improvement in the 6-minute walk distance or quality of life compared with placebo. Sildenafil was associated with modest worsening of renal function and increases in neurohormonal levels.

Exercise as Treatment for Heart Failure With Preserved Ejection Fraction

Because exercise intolerance is a major symptom in HFpEF patients, interest has focused on the role of exercise training as a treatment modality. In a study involving 53 HFPEF patients randomized to 16 weeks (three times per week) of moderate-intensity aerobic exercise or intention control, Kitzman and coworkers observed increased peak exercise oxygen uptake, 6-minute walk distance, and quality of life scores in the treatment arm.[468] Similar findings were seen in a multicenter study of 40 HFpEF patients randomized to a 32-session, 3-month exercise protocol involving aerobic and resistance training.[469] Whether exercise training improves survival of HFpEF patients remains to be determined.

Acute Heart Failure With Preserved Ejection Fraction

Except in the setting of acute diastolic HF, positive inotropic and chronotropic agents should be avoided because they may worsen diastolic function by increasing contractile force and heart rate or by increasing calcium concentrations in diastole. However, in the short-term management of acute diastolic dysfunction or HF (eg, after cardiopulmonary bypass [CPB]), β-adrenergic agonists (eg, epinephrine) and phosphodiesterase inhibitors (eg, milrinone) enhance calcium sequestration by the SR and thereby promote a more rapid and complete myocardial relaxation between beats.[470,471]

Serelaxin is a synthetic version of the naturally occurring hormone relaxin, which occurs in small amounts in men and women. It is produced in large quantities during pregnancy, in which it is thought to improve blood vessel, kidney, and heart function. The beneficial effects in pregnancy provided the basis for studying serelaxin in patients with HF, in which there are abnormalities in these functions. RELAX-AHF was a randomized, double-blind, controlled trial that evaluated the effects of a 48-hour intravenous infusion of serelaxin on clinical outcomes in 1161 patients admitted to hospital for acute HF. Serelaxin induced similar dyspnea relief in HFpEF and HFrEF patients at day 5 but was more effective in the HFpEF group in the first 24 hours. There were no differences between HFpEF and HFrEF patients in the effect of serelaxin on the secondary end points. Serelaxin had similar benefits on mortality for patients with HFpEF or HFrEF.[472]

Management of Acute Exacerbations of Chronic Heart Failure

Despite good medical management, patients with chronic HF may experience episodes of pulmonary edema or other signs of acute volume overload.[473] Other patients may experience exacerbations of HF associated with acute myocardial ischemia or infarction, hypertension, arrhythmia, worsening valvular dysfunction, infections (including myocarditis), or failure to maintain an established drug or dietary regimen. These patients may require hospitalization for intensive management if initial treatments fail to relieve their symptoms.

Fonarow and associates[474] described a risk stratification system for in-hospital mortality among acutely decompensated hospitalized HF patients using data from a national registry. Low-, intermediate-, and high-risk patients with mortality rates ranging from 2.1% to 21.9% were identified using blood urea nitrogen (BUN), creatinine, and systolic BP levels on admission. These patients require all of the standard medications outlined in previous sections, need more intensive diuretic therapy, and may require infusions of vasodilators or positive inotropic drugs.

Vasodilators

In the absence of systemic hypotension, intravenous vasodilators may be used to treat dyspnea in patients with decompensated chronic HF. Vasodilators reduce ventricular filling pressures and SVR while increasing SV and CO. NTG is commonly used for this purpose and has been studied in numerous clinical trials.[473] It is primarily a venodilator, reducing preload and improving symptoms of pulmonary vascular congestion. It is often initially effective at relatively small doses (20–40 μg/min) but frequently requires progressively increasing doses to counteract tachyphylaxis. NTG is associated with dose-dependent arterial hypotension.[475]

Nitroprusside acts as a systemic venodilator and arteriodilator and a pulmonary vasodilator. Efficacy data are limited, and administration of nitroprusside requires frequent BP monitoring, preferably with an arterial line, because of its potential for producing marked hypotension.[304] Nitroprusside therapy also carries a small risk of thiocyanate toxicity, particularly in the setting of renal insufficiency.

Nesiritide

BNP is a 32–amino acid peptide that is mainly secreted from the cardiac ventricles.[476] In normal healthy subjects, BNP concentrations in blood increase with age and are greater in women than men. Physiologically, BNP functions as a natriuretic and diuretic. It also serves as a counterregulatory hormone to Ang II, norepinephrine, and endothelin by decreasing the synthesis of these agents and by direct vasodilation.

As the clinical severity of HF increases, the concentrations of BNP in blood also increase.[476] Measurements of BNP in blood have been used to evaluate new-onset dyspnea to distinguish between lung disease and HF. Because BNP concentrations in blood increase with decreasing LVEF, measurements of this mediator have been used to estimate prognosis. BNP concentrations decline in response to therapy with ACE inhibitors, Ang II antagonists, and aldosterone antagonists.

Nesiritide, a recombinant BNP, was approved in 2001 and is indicated for patients with acute HF and dyspnea with minimal activity. Nesiritide produces arterial and venous dilation through increasing cGMP levels. Nesiritide does not increase heart rate and has no effect on cardiac inotropy. It has a rapid onset of action and a short elimination half-life (ie, 15 minutes). Initial studies showed that nesiritide reduced dyspnea associated with acute decompensated HF similar to NTG but without development of acute tolerance and with fewer adverse events than NTG.[477,478] Compared with dobutamine, nesiritide was associated with fewer instances of ventricular tachycardia (VT) or cardiac arrest.[479]

In the ADHERE registry of more than 65,000 episodes of acute decompensated HF, treatment with nesiritide or a vasodilator was associated with a 0.59 odds ratio for mortality compared with milrinone or dobutamine.[480] However, subsequent metaanalyses suggested that nesiritide may not offer a compelling safety advantage but instead may be associated with an increased incidence of adverse side effects, including renal failure and death, when administered to patients with acutely decompensated chronic HF.[481,482] These data prompted the FDA to convene an expert panel that made several recommendations, including that nesiritide be used only for hospitalized patients with acute decompensated HF and that the agent not be used to enhance diuresis or protect the kidneys.[483]

Designed to examine efficacy and safety concerns, the ASCEND-HF trial was a multicenter, randomized, double-blind, placebo-controlled trial of nesiritide in addition to standard care for acute HF. Nesiritide had a small but statistically insignificant effect on dyspnea at 6 and 24 hours. It neither increased nor decreased mortality or rehospitalization. It was not associated with worsening renal function. It was associated with increased rates of hypotension.[484] Overall, nesiritide and the other nitrovasodilators may be considered as adjuvants to diuretic therapy to reduce dyspnea in patients with acute HF without systemic hypotension.

Inotropes

Positive inotropic drugs, principally dobutamine or milrinone, have long been used to treat decompensated HF despite the lack of data showing an outcome benefit for their use.[473] In the past, some chronic HF patients received intermittent infusions of positive inotropic drugs as part of their maintenance therapy. Small studies consistently demonstrate improved hemodynamic values and reduced symptoms after administration of these agents to patients with HF. Studies comparing dobutamine with milrinone for advanced decompensated HF showed large differences in drug costs, favoring dobutamine, and only small hemodynamic differences, favoring milrinone.[485]

Nevertheless, placebo-controlled studies suggest there may be no role for discretionary administration of positive inotropes to patients with chronic HF.[486] In one study, 951 hospitalized patients with decompensated chronic HF who did not require intravenous inotropic support were assigned to receive a 48-hour infusion of milrinone or saline. All patients received ACE inhibitors and diuretics as deemed necessary. Total hospital days did not differ between groups, but those receiving milrinone were significantly more likely to require intervention for hypotension or to have new atrial arrhythmias. A subanalysis of the results found that patients suffering from ischemic cardiomyopathy were particularly subject to adverse events from milrinone (42% incidence of death or rehospitalization vs 36% for placebo).[487]

Positive inotropic drug support can be recommended only when there is no alternative. Dobutamine and milrinone continue to be used to treat low CO in selected patients with decompensated HF.

Alternative Therapies

When drug treatment proves unsuccessful, HF patients may require invasive therapy, including ultrafiltration for diuresis, ventricular assist devices, biventricular pacing, coronary bypass with or without surgical remodeling, or cardiac orthotopic transplantation. These treatment options are beyond the scope of this chapter[304,488] (see Chapters 4, 5, 20, 25, 28, 32, and 33).

Low-Output Syndrome

Acute HF is a frequent concern of the cardiac anesthesiologist, particularly at the time of separation from CPB. New-onset ventricular dysfunction with a low CO after aortic clamping and reperfusion is a condition with more pathophysiologic similarity to cardiogenic shock than to chronic HF, and it is typically treated with positive inotropic drugs, vasopressors (or vasodilators) if needed, or mechanical assistance.[489,490] The latter more commonly takes the form of intraaortic balloon counterpulsation and less commonly includes one of the several available ventricular assist devices (see Chapters 28, 33, and 36).

Causes

Most patients undergoing cardiac surgery with CPB experience a temporary decline in ventricular function, with a recovery to normal function in roughly 24 hours. Pathophysiologic explanations must acknowledge the usually temporary nature of the low-output syndrome after CPB. It likely results from one of three processes, all related to inadequate oxygen delivery to the myocardium: acute ischemia, hibernation, or stunning. All three processes can be expected to improve with adequate revascularization and moderate doses of positive inotropic drugs, consistent with the typical progress of the cardiac surgery patient. All three processes can be expected to be more troublesome in patients with preexisting chronic HF, pulmonary hypertension, or arrhythmias.

Risk Factors for Low-Output Syndrome After Cardiopulmonary Bypass

The need for inotropic drug support after CPB can often be anticipated based on data available in the preoperative medical history, physical examination, and imaging studies. In a series of consecutive patients undergoing elective CABG, it was observed that increasing age, decreasing LVEF, female sex, cardiac enlargement on the chest radiograph, and prolonged duration of CPB were associated with an increased likelihood that the patient would be receiving positive inotropic drugs on arrival in the intensive care unit.[491] Similarly, in a study of patients undergoing mitral valve surgery, independent predictors of low-CO syndrome were urgency of the case, LVEF less than 40%, NYHA class IV, a body surface area of 1.7 m^2 or less, ischemic mitral valve pathology, and CPB time.[492]

Another study of patients undergoing aortic valve surgery identified renal failure, LVEF less than 40%, shock, female gender, and increasing age as independent risk factors.[493] Data from an intraoperative transesophageal echocardiographic examination may also help identify patients who are more likely to need inotropic support. Patients with a decreased wall motion score index or those with moderate or severe mitral regurgitation may need inotropic support.[494]

Drugs for Treating Low-Output Syndrome

Although all positive inotropic drugs increase the strength of contraction in noninfarcted myocardium, the mechanisms of action are different. The drugs can be divided into those that increase cAMP (directly or indirectly) as their mechanism of action and those that do not. The agents that do not depend on cAMP form a diverse group, including cardiac glycosides, calcium salts, calcium sensitizers, and thyroid hormone. In contrast to chronic HF, cardiac glycosides are not used for this indication due to their limited efficacy and narrow margin of safety. Calcium salts continue to be administered for ionized hypocalcemia and hyperkalemia, common occurrences during and after cardiac surgery. Increased Ca^{2+} concentrations in buffer solutions bathing cardiac muscle in vitro unquestionably increase inotropy. However, despite long-standing contrary opinions, studies suggest that doses of $CaCl_2$ of 5 to 10 mg/kg do not increase cardiac index in patients recovering from cardiac surgery.[495,496]

Levosimendan is an inodilator that increases cardiac contractility by calcium sensitization of troponin C. Because levosimendan does not increase the intracellular Ca^{2+} concentration, it does not impair

diastolic cardiac function. Peripheral and coronary vasodilatation due to its effects on ATP-sensitive K^+ channels provides afterload reduction and improved coronary perfusion. These combined effects result in improvement of myocardial contractility without an increase in $M\dot{V}O_2$.

Another attractive feature of this inotropic agent is that its effects are not diminished by β-blockade.[497] It is indicated for the short-term treatment of severe chronic HF when conventional therapy is not sufficient, but it is being increasingly studied in cardiac surgical settings with favorable results.[498]

There are conflicting reports regarding the effect of levosimendan on mortality rates for patients with acutely decompensated HF. Four major double-blind, randomized clinical trials have evaluated the ability of levosimendan to decrease mortality rates for these patients. Only two of the trials (ie, LIDO and RUSSLAN studies) have shown a clear decrease in mortality rates compared with a placebo or dobutamine.[497,499] In the REVIVE II study, there was a statistically insignificant higher mortality rate for the levosimendan group compared with placebo. In the SURVIVE study, there was no significant difference in survival between levosimendan and dobutamine.[500] In a metaanalysis, levosimendan significantly reduced mortality rates in cardiology and cardiac surgery settings compared with dobutamine and placebo.[501]

Levosimendan is an acceptable choice for patients with acutely decompensated HF after hypovolemia has been corrected. Suggested dosing includes an infusion with or without a loading dose of 6 to 12 μg/kg for 10 minutes, followed by 0.005 to 2 μg/kg per minute for no more than 24 hours. Loading doses are not recommended for patients with low-normal BP (eg, SBP <100 mm Hg). Without a loading dose, maximal effect of the drug occurs after 4 hours. Infusions should not continue for longer than 24 hours due to levosimendan's active metabolites, which can accumulate and produce refractory hypotension and tachycardia.

Intravenous thyroid hormone (liothyronine [T_3]) has been studied extensively as a positive inotrope in cardiac surgery. Multiple studies support the existence of euthyroid sick syndrome with persistent reduced concentrations of T_3 in blood after cardiac surgery in children and adults.[495] Data suggest that after ischemia and reperfusion, T_3 increases inotropy faster than and as potently as isoproterenol.[502] Nevertheless, RCTs have failed to show a clinical benefit for T_3 after CABG.[503,504]

cAMP-dependent agents are the mainstays of positive inotropic drug therapy after cardiac surgery. There are two main classes of agents: PDE inhibitors and β-adrenergic receptor agonists. PDEs in clinical use around the world include enoximone, inamrinone, milrinone, olprinone, and piroximone. Comparisons among the agents have failed to demonstrate important hemodynamic differences.[505] Reported differences are related to pharmacokinetics and rare side effects, typically observed with chronic oral administrations during clinical trials.

All members of the class produce rapid increases in contractile function and CO and decreases in SVR. The effect on BP depends on the pretreatment state of hydration and hemodynamics, but the typical response is a small decrease in BP. There is no effect on heart rate or a small increase.

Inamrinone and milrinone are effective, first-line agents in patients with reduced preoperative LV function.[506,507] One of the few studies in which outcome was assessed after use of positive inotropic agents confirmed that prophylactic use of milrinone in children undergoing correction of congenital heart disease improved outcomes in terms of length of stay and incidence of low-output syndrome.[508] Milrinone, the most commonly used member of the class, is most often dosed at a 50 μg/kg loading dose and 0.5 μg/kg per minute maintenance infusion. It is often given in combination with a β-adrenergic receptor agonist.

Among the many β-adrenergic receptor agonists, the agents most often given to patients recovering from cardiac surgery are dopamine, dobutamine, and epinephrine. Dopamine has long been assumed to have dose-defined receptor specificity. At small doses (0.5–3 μg/kg per minute), it is assumed to have an effect mostly on dopaminergic receptors. At intermediate doses, β-adrenergic effects are said to predominate, and at doses of 10 μg/kg per minute or greater, β-adrenergic receptor effects predominate. Nevertheless, the relationship between dose and blood concentration is poorly predictable, even in normal volunteers, as was shown by MacGregor and colleagues.[509] This makes it unlikely that the dose-response relationship is as consistent as has been described in textbooks for the past 20 years. Moreover, dopamine is a relatively weak inotrope that has a predominant effect on heart rate rather than on SV.[510]

Dobutamine is a selective β-adrenergic receptor agonist. Most studies suggest that it causes less tachycardia and hypotension than isoproterenol.[511,512] It has been frequently compared with dopamine, in which dobutamine's greater tendency for pulmonary and systemic vasodilation is evident.[510] Dobutamine has a predominant effect on heart rate compared with SV, and as the dose is increased more than 10 μg/kg per minute there are further increases in heart rate without changes in SV.[513]

Epinephrine is a powerful adrenergic agonist, and like dopamine, it demonstrates different effects depending on the dose. At small doses (10–30 ng/kg per minute), despite an almost pure β-adrenergic receptor stimulus, there is almost no increase in heart rate.[496,514] Clinicians have long assumed that epinephrine increases heart rate more than dobutamine administered at comparable doses. In patients recovering from cardiac surgery, the opposite is true; dobutamine increases heart rate more than epinephrine.[514]

Other β-adrenergic agonists are used in specific circumstances. For example, isoproterenol is often used after cardiac transplantation to exploit its powerful chronotropy and after correction of congenital heart defects to exploit its pulmonary vasodilatory effects.[515] Norepinephrine is used to counteract profound vasodilation.[516] Outside of North America, dopexamine, a weak dopaminergic and β-agonist with a pronounced tendency for tachycardia, is sometimes used.[517]

Left Atrial Drug Administration

Based on an appeal to common sense, clinicians faced with severe cardiac depression in a severely ill patient undergoing cardiac surgery sometimes administered potentially vasoconstricting agents (eg, epinephrine, norepinephrine) into the left heart circulation through a left atrial catheter to avoid adverse effects on the pulmonary vascular resistance. Fullerton and colleagues confirmed the usefulness of this approach by showing that left atrial administration of epinephrine produced greater CO and reduced pulmonary artery pressure more than the same dose of epinephrine administered into the right atrium.[518]

Assist Devices

A small fraction of patients undergoing cardiac surgery develop acute HF refractory to drug treatment. For these patients, available options include intraaortic balloon counterpulsation, extracorporeal membrane oxygenation (or extracorporeal carbon dioxide elimination), and right- or left-heart assist devices as destination therapy or as a bridge to transplantation[488] (see Chapters 25, 28, 33, and 36).

Pharmacotherapy for Cardiac Arrhythmias

Perhaps the most widely used electrophysiologic and pharmacologic classification of antiarrhythmic drugs is that proposed by Vaughan Williams (Table 11.23).[519] There is, however, substantial overlap in pharmacologic and electrophysiologic effects of specific agents among the classes, and the linkage between observed electrophysiologic effects and the clinical antiarrhythmic effect is often tenuous. Likewise, especially in class I, there may be considerable diversity within a single class. Other antiarrhythmic drugs are not included in this classification such as digitalis, the classic antiarrhythmic for chronic AF, or adenosine, a drug with potent antiarrhythmic effects mediated by a specific class of membrane receptors.[520,521]

The Cardiac Arrhythmia Suppression Trial (CAST) questions the appropriateness of treating arrhythmias with antiarrhythmic agents in

TABLE 11.23 Classification of Antiarrhythmic Drugs

	Type of Antiarrhythmic Drug			
Effects	*I (Membrane Stabilizers)*	*II (β-Adrenergic Receptor Antagonists)*	*III (Drugs Prolonging Repolarization)*	*IV (Calcium Antagonists)*
Pharmacologic	Fast channel (Na^+) blockade	β-Adrenergic receptor blockade	Uncertain: possible interference with Na^+ and Ca^{2+} exchange	Decreased slow–channel calcium conductance
Electrophysiologic	Decreased rate of V_{max}	Decreased V_{max}, increased APD, increased ERP, and increased ERP:APD ratio	Increased APD, increased ERP, increased ERP:ADP ratio	Decreased slow–channel depolarization; decreased ADP

APD, Action potential duration; *ERP*, effective refractory period; V_{max}, maximal rate of depolarization.

TABLE 11.24 Subgroup of Class I Antiarrhythmic Drugs

	Subgroup		
Electrophysiologic Activity	*IA*	*IB*	*IC*
Phase 0	Decreased	Slight effect	Marked decrease
Depolarization	Prolonged	Slight effect	Slight effect
Conduction	Decreased	Slight effect	Markedly slowed
ERP	Increased	Slight effect	Slight prolongation
APD	Increased	Decreased	Slight effect
ERP/APD ratio	Increased	Decreased	Slight effect
QRS duration	Increased	No effect during sinus rhythm	Marked increase
Prototype drugs	Quinidine, procainamide, disopyramide, diphenylhydantoin	Lidocaine, mexiletine, tocainide	Lorcainide, encainide, flecainide, aprinidine

APD, Action potential duration; *ERP*, effective refractory period.

certain groups of patients.[522] The CAST study was designed to test the hypothesis that suppression of ventricular ectopy seen after MI reduces the subsequent incidence of sudden death. Patients were eligible for the study if they had ventricular ectopy without sustained VT after MI. The study required documented suppression of the ventricular ectopy with the class IC drugs encainide and flecainide. The primary study end points were death or cardiac arrest caused by arrhythmia.

After 22 months of enrollment (of a planned 36 months), the Data and Safety Monitoring Board recommended discontinuation of the encainide and flecainide limbs of the study because of apparent excess mortality in those two treatment groups. Among the 1498 patients assigned to the encainide and flecainide groups, there were 89 deaths (63 in the active drug subgroups and 26 in the placebo subgroups; $P < .0001$). The mechanism of excess mortality was thought to be precipitation of proarrhythmia due to facilitation of reentry, especially during ischemic episodes. After this study, the use of sodium channel blockers was not recommended, especially for low-risk patients after MI. Encainide is no longer available, but flecainide still is used for supraventricular tachyarrhythmias and documented life-threatening ventricular arrhythmias.

Although the class I and especially subclass IC agents are most commonly known for their proarrhythmic effects, the other classes are not devoid of this side effect. Bretylium initially causes the release of norepinephrine, and an increased incidence of ventricular arrhythmias often is seen when therapy is initiated. In one study, the rate of arrhythmias was significant when different doses of bretylium were used.[523] For the first week after initiation of sotalol, a nonspecific β-adrenergic blocker that is considered a class III arrhythmic agent, there is an increased incidence of torsades de pointes. The proarrhythmic effects appear to be increased in the setting of hypokalemia, bradycardia, CHF, and a history of sustained ventricular dysfunction (Box 11.6).[524]

Chronic antiarrhythmic therapy should be initiated only after careful evaluation of the risks and benefits of the intervention. The appropriate use of intravenous antiarrhythmic agents with sudden-onset arrhythmias is not clear. Life-threatening ventricular arrhythmias must be treated. Patients at low risk for arrhythmic events may not benefit from therapy, and as learned from CAST, mortality rates may increase with some of these agents. High-risk patients may be treated more safely in some cases by implantation of internal cardioverter-defibrillators.[525]

BOX 11.6 DRUGS THAT CAN PRODUCE TORSADES DE POINTES

- Amiodarone
- Disopyramide
- Dofetilide
- Ibutilide
- Procainamide
- Quinidine
- Sotalol

Class I Antiarrhythmic Drugs: Sodium Channel Blockers

Class I drugs inhibit the fast inward depolarizing current carried by sodium ions. Because of the diversity of other effects of the class I drugs, a subgroup of the class has been proposed[526] (Table 11.24). Whether the depression of fast inward current of the sodium channel produces the primary antiarrhythmic effect of all class I drugs is controversial. Other proposed mechanisms involve abolishing reentry by improving conduction in the reentry pathway. However, shortening the APD in ventricular pathways and improving conduction of premature impulses by shortening the refractory period of the action potential also can decrease the likelihood for reentry.[527–529]

Class IA Drugs

Quinidine

In addition to the electrophysiologic effects summarized in Table 11.25, quinidine decreases the slope of phase 4 diastolic depolarization at low concentrations and increases threshold potential at high concentrations.[530] Quinidine depresses cardiac contractility, which in combination with an indirect α-adrenergic blockade can reduce arterial pressure. This hypotensive effect is the principal limitation to intravenous administration of quinidine.

Electrocardiographic (ECG) effects of quinidine include an increase in the sinus rate, which is perhaps a reflex response to vasodilation

TABLE 11.25 Diastolic Heart Failure Treatments

Goal	*Management Strategy*	*Recommended Doses*
Reduce the Congestive State		
Prevent fluid retention and reduce blood pressure	Salt restriction Diuretics (avoid reductions in cardiac output) ACE inhibitors Angiotensin II receptor blockers	Sodium, <2 g/day Furosemide, 10–120 mg Hydrochlorothiazide, 12.5–25 mg Enalapril, 2.5–40 mg Lisinopril, 10–40 mg Candesartan, 4–32 mg Losartan, 25–100 mg
Target Underlying Cause		
Control hypertension (<130/80 mm Hg)	Antihypertensive agents	β-Blockers, ACE inhibitors, all receptor blockers: dose according to published guidelines
Restore sinus rhythm	Atrioventricular sequential pacing	—
Prevent tachycardia	β-Blockers, calcium channel blockers	Atenolol, 12.5–100 mg Metoprolol, 25–100 mg Diltiazem, 120–540 mg
Treat aortic stenosis	Aortic valve replacement	—
Target Underlying Mechanisms		
Promote regression of hypertrophy and prevent myocardial fibrosis	Renin-angiotensin axis blockade (theoretical)	Enalapril, 2.5–40 mg Lisinopril, 10–40 mg Captopril, 25–150 mg Candesartan, 4–32 mg Losartan, 50–100 mg Spironolactone, 25–75 mg Eplerenone, 25–50 mg

ACE, Angiotensin-converting enzyme.

and cardiac depression. Conduction through the AV node may be enhanced or depressed, or it may not change, depending on the interplay of the direct slowing effect and the anticholinergic effect of quinidine. Infranodal conduction is slowed, and at high concentrations, bundle branch block, complete AV block, or asystole may result. The QT interval possibly is prolonged by sympathetic activation.[531]

Clinically, quinidine is used primarily in oral form to treat atrial and ventricular arrhythmias. However, quinidine may substantially accelerate the ventricular response rate in AF or flutter. Its use in these conditions should be preceded by β-blockade or digitalization. Acceleration of ventricular response rate is a function of the direct slowing of the atrial rate produced by quinidine and its indirect anticholinergic effects. The decreased frequency of atrial depolarization allows a greater percentage of impulses to be conducted through the AV node to depolarize the His bundle.

Quinidine may be administered orally or intramuscularly. The gastrointestinal absorption of quinidine is good, and plasma levels peak 1 to 2 hours after oral administration. Quinidine has an elimination half-life of 6 to 7 hours. A dose every 6 or 8 hours is appropriate, although shortening the dosage interval may maintain a stable plasma concentration more effectively than increasing the dosage. Typical maintenance doses are 300 to 600 mg, and therapeutic plasma concentrations range from 2 to 6 μg/mL.[532] Quinidine gluconate (200 mg given intramuscularly) is the preferred dose.

Quinidine is 70% to 80% protein bound in plasma, with much of that caused by hemoglobin. Administration of quinidine substantially increases the plasma concentrations of digoxin, probably by releasing the glycoside from protein-binding sites.[533] Elimination of quinidine is primarily by hepatic metabolism (ie, hydroxylation), although about 20% is excreted unchanged by the kidney. Renal excretion is achieved by glomerular filtration and tubular secretion, and it depends on urinary pH; excretion is decreased up to 50% when urine is alkaline.[534]

The most serious toxic effect of quinidine is cardiac and is largely a function of its conduction effects. Monitoring the QRS duration and QT interval is a useful guide to therapy; a 50% increment in either should prompt a reduction in dose. Various degrees of conduction block at the atrial and ventricular levels may occur, including asystole. Quinidine syncope probably is related to a proarrhythmia produced by QT-interval prolongation and may not be dose related.[535] Symptoms of tinnitus, visual disturbance, and gastrointestinal irritation progressing to severe CNS symptoms (eg, headache, diplopia, photophobia, confusion, psychosis) are part of the spectrum of cinchonism produced by quinidine, by other cinchona alkaloids such as quinine, and by salicylates. Thrombocytopenia may occur with quinidine, and hypersensitivity to quinidine may appear as fever, anaphylaxis, or bronchospasm, which can be severe.

Procainamide

Electrophysiologic effects of procainamide include decreased maximal velocity (V_{max}) and amplitude during phase 0, decreased rate of phase 4 depolarization, and prolonged ERP and APD.[536] Clinically, procainamide prolongs conduction and increases the ERP in atrial and His-Purkinje portions of the conduction system, which may prolong PR interval and QRS complex durations, but the QT interval is lengthened less than with quinidine. As with quinidine, AV nodal ERP may be decreased by indirect anticholinergic side effects.

Procainamide is used to treat ventricular arrhythmias and to suppress atrial premature beats to prevent the occurrence of AF and atrial flutter. It has been useful for chronic suppression of premature ventricular contractions (PVCs), but it may be supplanted for this use by class IB drugs such as mexiletine. Quinidine and procainamide reduce the frequency of the short-coupling interval (<400 ms) PVCs and thereby reduce the frequency of VT or VF created by the R-on-T phenomenon.[537]

Administered intravenously, procainamide is an effective emergency treatment for ventricular arrhythmias, especially after lidocaine failure, but amiodarone has become a more popular drug for intravenous suppression of ventricular arrhythmias. Dosage is 100 mg, or approximately 1.5 mg/kg given at 5-minute intervals until the therapeutic effect is obtained or a total dose of 1 g or 15 mg/kg is given (Boxes 11.7 and 11.8). Arterial pressure and the electrocardiogram should be monitored continuously during loading and administration stopped if significant hypotension occurs or if the QRS complex is prolonged by 50% or more. Maintenance infusion rates are 2 to 6 mg/min to maintain therapeutic plasma concentrations of 4 to 8 μg/mL.[536]

Oral administration of procainamide has a 75% to 95% absorption rate, and plasma levels peak after 1 to 2 hours.[538] The elimination half-life of procainamide is 3 to 4 hours, and the oral dosage interval is similar. Sustained-release preparations are available. Oral dose requirements are on the order of 50 mg/kg per 24 hours or 400 to 600 mg every 3 to 4 hours.[539] Decreasing the dosage interval rather than increasing the dose may be a better method of producing a stable increase in plasma concentrations without creating peak levels that are toxic. Sustained-release forms of procainamide are available.

Procainamide has hepatic and renal routes of elimination, with each route approximately equal in magnitude. Hepatic metabolism occurs by acetylation and may be fast or slow in individual patients as a result of genetic variations.[540] The primary metabolite, *N*-acetylprocainamide, has antiarrhythmic and toxic side effects, and it is excreted almost entirely by the kidney.[541] The clinical importance is that patients with impaired hepatic or renal function or with diminished perfusion of either organ, as in CHF, have markedly impaired elimination of procainamide. Recommended dosages for patients with renal impairment or CHF are a loading dose of 12 mg/kg given over 1 hour, with a maintenance dose of 1.4 mg/kg per hour.[542]

Toxic side effects of procainamide are related to dose and plasma concentration, a function of total dose and rate of administration during the loading technique. Serious cardiac toxicity usually requires plasma concentrations greater than 12 μg/ml. *N*-acetylprocainamide levels should be monitored. The likelihood of producing proarrhythmia as a result of QT_c prolongation is less with procainamide than with quinidine.[543] Procainamide also may produce gastrointestinal

BOX 11.7 INTRAVENOUS SUPRAVENTRICULAR ANTIARRHYTHMIC THERAPY

Class I Drugs

Procainamide (IA): converts acute atrial fibrillation, suppresses PACs and precipitation of atrial fibrillation or flutter, converts accessory pathway SVT; 100 mg IV loading dose every 5 minutes until arrhythmia subsides or total dose of 15 mg/kg (rarely needed) with continuous infusion of 2 to 6 mg/min.

Class II Drugs

Esmolol: converts or maintains slow ventricular response in acute atrial fibrillation; 0.5 to 1 mg/kg loading dose with each 50 μg/kg per minute increase in infusion, with infusions of 50 to 300 μg/kg per minute. Hypotension and bradycardia are limiting factors.

Class III Drugs

Amiodarone: converts acute atrial fibrillation to sinus rhythm; 5 mg/kg IV over 15 minutes.

Ibutilide (Convert): converts acute atrial fibrillation and flutter.
- Adults (>60 kg): 1 mg IV given over 10 minutes; may repeat once.
- Adults (<60 kg) and children: 0.01 mg/kg IV given over 10 minutes; may repeat once.

Vernakalant: 3 mg/kg over 10 minutes in acute-onset atrial fibrillation; if no conversion; wait 15 minutes and then repeat with 2 mg/kg over 10 minutes. Hypotension may occur in a few patients.

Class IV Drugs

Verapamil: slow ventricular response to acute atrial fibrillation; converts AV node reentry SVT; 75–150 μg/kg IV bolus.

Diltiazem: slow ventricular response in acute atrial fibrillation; converts AV node reentry SVT; 0.25 μg/kg bolus, then 100–300 μg/kg/h infusion.

Other Therapy

Adenosine: converts AV node reentry SVT and accessory pathway SVT; aids in diagnosis of atrial fibrillation and flutter. Increased dosage required with methylxanthines, decreased use required with dipyridamole.
- Adults: 3–6 mg IV bolus, repeat with 6–12 mg bolus.
- Children: 100 μg/kg bolus, repeat with 200 μg/kg bolus.

Digoxin: maintenance IV therapy for atrial fibrillation and flutter; slows ventricular response.
- Adults: 0.25 mg IV bolus followed by 0.125 mg every 1–2 hours until rate is controlled; not to exceed 10 μg/kg in 24 hours.
- Children (<10 years): 10–30 μg/kg load given in divided doses over 24 hours.
- Maintenance: 25% of loading dose.

AV, Atrioventricular; *IV*, intravenous; *PACs*, premature atrial contractions. *SVT*, supraventricular tachycardia.

BOX 11.8 INTRAVENOUS VENTRICULAR ANTIARRHYTHMIC THERAPY

Class I Drugs

Procainamide (IA): 100 mg IV loading dose every 5 minutes until arrhythmia subsides or total dose of 15 mg/kg (rarely needed) with continuous infusion of 2 to 6 mg/min.

Lidocaine (IB): 1.5 mg in divided doses given twice over 20 minutes with continuous infusion of 1 to 4 mg/min.

Class II Drugs

Propranolol: 0.5 to 1 mg given slowly up to a total β-blocking dose of 0.1 mg/kg; repeat bolus as needed.

Metoprolol: 2.5 mg given slowly up to a total β-blocking dose of 0.2 mg/kg; repeat bolus as needed.

Esmolol: 0.5 to 1.0 mg/kg loading dose with each 50 μg/kg/min increase in infusion, with infusions of 50 to 300 μg/kg/min. Hypotension and bradycardia are limiting factors.

Class III Drugs

Bretylium: 5 mg/kg loading dose given slowly with a continuous infusion of 1 to 5 mg/min. Hypotension may be a limiting factor.

Amiodarone: 150 mg over 10 minutes IV; then 1 mg/min for 6 hours; then 0.5 mg/min for the next 18 hours. Repeat bolus as needed.

Other Therapy

Magnesium: 2 g of $MgSO_4$ over 5 minutes; then continuous infusion of 1 g/h for 6–10 hours to restore intracellular magnesium levels.

From Royster RL. *Diagnosis and Management of Cardiac Disorders.* ASA Refresher Course Lectures. Park Ridge, IL: American Society of Anesthesiologists; 1996.

disturbances, CNS symptoms (ie, headache and sleep disturbance), rash, and agranulocytosis. Among patients receiving procainamide chronically, antinuclear antibodies develop in 50% to 70%, and approximately one-half have fever, myalgia, rash, pleuritis, or pericarditis similar to that seen with lupus erythematosus, although renal and CNS effects are rare.[544] They are more common among patients who are slow acetylators. After discontinuation of the drug, lupus-like symptoms resolve slowly.

Intramyocardial distribution of procainamide, especially during ischemia or infarction, is an important component of its therapeutic effect. In a canine infarction model, procainamide increased ERP more in ischemic than in nonischemic myocardium.[545] The pharmacokinetic profiles of procainamide are different for ischemic and nonischemic regions of myocardium; tissue concentrations of procainamide decline more rapidly in the latter.[546]

Disopyramide

Although disopyramide is chemically different from quinidine and procainamide, electrophysiologic effects of the three drugs are similar. Conduction through the AV node may be facilitated slightly by disopyramide because of its indirect vagolytic effect.[547] Accessory pathway conduction may be slowed in patients with Wolff-Parkinson-White syndrome.[548] Disopyramide is a potent negative inotropic drug, and after intravenous use, SVR reflexively increases.[549]

Disopyramide is therapeutically effective against supraventricular and ventricular tachyarrhythmias. However, as with quinidine and procainamide, disopyramide should not be used for ventricular tachyarrhythmias caused by prolonged QT syndrome. The marked negative inotropic and anticholinergic effects limit the usefulness of the drug.

When given orally, 80% of disopyramide is absorbed, and steady-state therapeutic plasma concentrations of 2 to 4 μg/mL can be achieved with 100 to 200 mg given orally every 6 hours.[550] The elimination half-life is approximately 7 hours, and elimination occurs equally by hepatic and renal mechanisms; hepatic or renal insufficiency may necessitate smaller doses.[551] Disopyramide is approximately 30% to 50% protein bound at plasma concentrations of 3 μg/mL.[547]

Toxicity of disopyramide is most frequently anticholinergic in origin, with symptoms of gastrointestinal upset, visual disturbance, and urinary tract obstruction, which may be marked in elderly men with prostatic hypertrophy. Unless there is LV failure, cardiovascular complications are infrequent, but recurrent CHF is seen in up to 50% of patients with a history of CHF.[549] Conduction system toxicity resembles that with quinidine.

Class IB Drugs

Lidocaine

First introduced as an antiarrhythmic drug in the 1950s, lidocaine has become the clinical standard for the acute intravenous treatment of

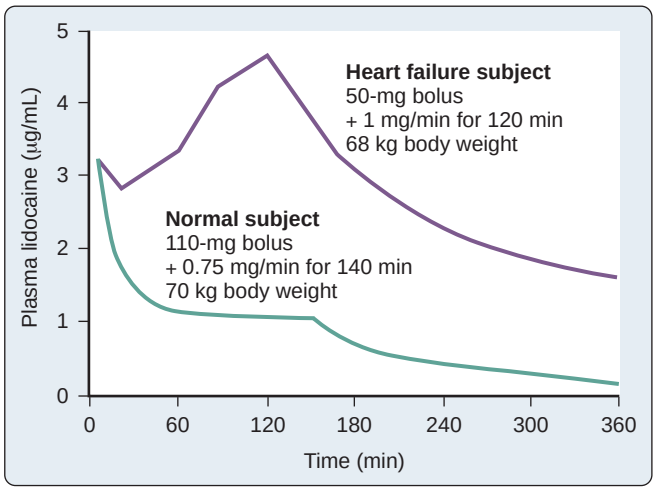


Fig. 11.25 Difference between plasma level responses to infused lidocaine in a normal person and a patient with heart failure. The accumulation of lidocaine in patients with depressed hepatic metabolism is dramatically illustrated. *(From American Heart Association.* Textbook of Advanced Cardiac Life Support. *Dallas, TX: American Heart Association; 1987.)*

ventricular arrhythmias except those precipitated by an abnormally prolonged QT interval.[552–555] Lidocaine may be one of the most useful drugs in clinical anesthesia because it has local and general anesthetic properties in addition to an antiarrhythmic effect.[556]

The direct electrophysiologic effects of lidocaine produce virtually all of its antiarrhythmic action. Lidocaine depresses the slope of phase 4 diastolic depolarization in Purkinje fibers and increases the VF threshold.[557] In Purkinje fibers, lidocaine increases transmembrane potassium conductance but does not affect resting membrane potential or threshold potential.[558] At less negative (partially depolarized) initial membrane potentials, lidocaine decreases fast-channel (Na^+) responses through an increase in background outward potassium flux, an effect directly related to extracellular potassium concentration.[559,560] Lidocaine may be ineffective in patients with hypokalemia.[561]

Conduction velocity is not affected by lidocaine in normal tissue, but it is significantly decreased in ischemic tissue.[562] The effects of lidocaine on APD vary by conduction system location. In atrial tissues, there is little or no effect. In Purkinje fibers, APD is markedly decreased, and the magnitude of the decrease is directly proportional to normal APD.[528] Because lidocaine decreases APD, its antiarrhythmic effect has been attributed to improved conduction in ectopic foci, which decreases the likelihood of reentry, but it has been shown that lidocaine slows conduction in these areas and decreases reentrant ventricular ectopy after experimental infarction.[533,563]

The clinical pharmacokinetics of lidocaine is well described. The distribution and elimination half-lives of lidocaine are short, approximately 60 seconds and 100 minutes, respectively.[564] Hepatic extraction of lidocaine is about 60% to 70%, and essentially all lidocaine is metabolized because the urine contains negligible amounts of unchanged lidocaine.[532] Hepatic metabolism produces monoethylglycine xylidide and glycine xylidide, both of which possess antiarrhythmic effects. Metabolic products are eliminated by the kidney, and accumulation of the monoethyl metabolite is related to the toxicity of intravenous lidocaine.[565–567] In patients with impaired hepatic function or blood flow (eg, those with CHF), the dose requirement is approximately 50% of that for healthy persons (Fig. 11.25 and Table 11.26; see Box 11.8).

Therapeutic plasma levels of lidocaine range from 1.5 to 5 μg/mL; signs of toxicity are common with concentrations greater than 9 μg/mL.[566] Various intravenous dosages can be used, but the important factor is to rapidly achieve steady-state therapeutic plasma concentrations. An initial bolus dose of 1 to 1.5 mg/kg should be followed immediately by a continuous infusion of 20 to 50 μg/kg per minute

TABLE 11.26 Potential Effects of Pathophysiologic Changes in Congestive Heart Failure on Drug Disposition

Pathology	*Pharmacokinetic Sequelae*
↓ Cardiac output and organ perfusion	↓ Hepatic and renal clearance
↑ Sympathetic activity	↓ Drug distribution
↑ Plasma norepinephrine Altered regional perfusion	↓ Intramuscular absorption
↓ Peripheral perfusion	Volume of distribution
Changes in extracellular fluid volume and protein binding	↑ or ↓
Visceral congestion	↓ Drug metabolism

↓, Decreased; ↑, increased.

to prevent the therapeutic hiatus produced by the rapid redistribution half-life of lidocaine. Infusion increments should be accompanied by additional bolus doses to immediately increase the plasma level.

The major toxic effect of lidocaine is associated with the CNS and manifests as drowsiness and disorientation, which progress to agitation, muscle twitching, and hearing abnormalities and culminate in seizures. Lidocaine can be an effective general anesthetic agent, and cases of coma with electroencephalographic silence similar to brain death patterns have been produced by an overdose of lidocaine and have resolved completely on discontinuation of the drug. The direct CNS effect of lidocaine and other local anesthetics is anticonvulsant.[568–570]

Local anesthetic–induced seizures do not produce permanent damage to the CNS as long as cardiovascular and respiratory complications of the seizure are prevented. Pharmacologically, benzodiazepines are superior to barbiturates (eg, thiopental) for stopping local anesthetic–induced seizure activity. Drug therapy alone is insufficient, and airway control, ventilation, and especially oxygenation are paramount to prevent CNS morbidity.

Mexiletine and Tocainide

Mexiletine and tocainide have electrophysiologic effects similar to those of lidocaine (ie, decreases in APD and ERP but little effect on conduction). Mexiletine has little effect on the QT interval. Hemodynamic effects are minor and consist primarily of small decreases of LV dP/dt and increases of LVEDP.[571] Small decreases of CO, SVR, and BP have been reported. However, even in patients with CAD, acute MI, or valvular heart disease, hemodynamic effects are clinically insignificant.[572–575]

The antiarrhythmic effects decrease the frequency of acute and chronic ventricular ectopy but not supraventricular arrhythmias. Mexiletine may decrease symptomatic ventricular arrhythmias in patients not responding to other therapy and may be more effective than lidocaine when used intravenously to suppress PVCs and VT in acute MI.[576–579] Administered orally, mexiletine also may be effective prophylaxis for PVCs and VT, but it may less effectively suppress closely coupled PVCs.[580–582] Mexiletine may be used in children and in patients with a long QT syndrome.

Pharmacokinetics of orally administered mexiletine reveals a bioavailability of 85%, with 70% of the drug protein bound. The volume of distribution of mexiletine is 2.5 times that for other antiarrhythmics.[583] Elimination half-life is 10 hours and is suitable for dosage regimens of two or three times per day.[584] Mexiletine is eliminated by hepatic metabolism, with less than 10% renally excreted unchanged in the urine. The hepatic metabolism is accelerated with microsomal enzyme induction and predictably decreased with hepatic disease, but overall metabolism is unaffected by renal failure.[585,586]

The usual dosage of mexiletine is 200 mg every 8 hours, which can be increased to 400 mg but should not exceed 1200 mg/day. Effective plasma levels of mexiletine range from 0.5 to 2 μg/mL, but there is wide individual variation of the dosage required to achieve that concentration.

Adverse effects of mexiletine include nausea, dysarthria, dizziness, paresthesia, tremor, vomiting, and sweating. Adverse reactions to

mexiletine are dose related and may occur at serum concentrations at the high end of the therapeutic range, which requires careful titration of the drug in patients. The incidence rate of minor reactions is 30%, and the incidence rate of severe reactions (ie, vomiting, confusion, and hypotension) is 19% when the plasma concentration is greater than 2 μg/mL.[587]

Diphenylhydantoin

Diphenylhydantoin (DPH) or phenytoin is unique among class IB drugs in that it has a potent central sympatholytic effect that decreases cardiac sympathetic efferent nerve activity.[588,589] Its electrophysiologic effect in many ways bridges the IA and IB classification. In normal conduction system cells, DPH decreases V_{max} and the amplitude of phase 0, but this effect is weaker than with other class IA drugs.[590] DPH does not decrease intraventricular conduction or prolong the QT interval, but it shortens APD.[591] DPH effectively can abolish the delayed afterpotentials associated with digitalis intoxication.[592,593] In cells partially depolarized from cold, hypoxia, or cardiac glycoside administration, DPH increases maximal diastolic potential, V_{max} of phase 0, and the conduction velocity.[594] DPH exerts its antiarrhythmic effect by increasing the ERP/APD ratio and by decreasing automaticity; both effects are enhanced in partially depolarized cells.

The drug is used to treat the atrial and ventricular arrhythmias produced by cardiac glycoside toxicity and in some patients with arrhythmias due to prolonged QT syndrome. It is less effective for other supraventricular arrhythmias and for suppressing chronic ventricular ectopy. The drug also is useful in children for preventing late postoperative arrhythmias after surgical correction of congenital heart disease such as junction ectopic tachycardia.[595]

Intravenous loading of DPH is accomplished in much the same way as with procainamide. Doses of 50 to 100 mg (0.5 to 1.5 mg/kg) are given at 5-minute intervals until therapeutic effects are obtained, up to a total dose of 1 g (15 mg/kg); the usual therapeutic plasma concentration is 8 to 10 μg/mL.[596] The drug undergoes primary hepatic metabolism, with urinary excretion of unchanged DPH accounting for only 5% of the total dose.[597] Patients with impaired hepatic or renal function should be expected to have greater plasma concentrations of DPH for a given dose, and the dose should be reduced to prevent toxicity.

With intravenous administration, a depressor effect is seen with depressed contractile function and a moderate increase of LVEDP.[598,599] These effects may in part result from the solvents used for the injectable preparation (ie, propylene glycol and ethyl alcohol).[600] Infusion rates greater than 50 mg/min in adults have produced cardiovascular collapse, VF, and death.[601] Other side effects include visual disturbances (ie, nystagmus and blurring), nausea, dysarthria, and cerebellar ataxia. Chronic DPH use produces gingival hyperplasia, macrocytic anemia, and dermatologic disorders.

Class IC Drugs

Flecainide

Flecainide depresses phase 0, delays repolarization in canine ventricular myocardium, and increases intracardiac monophasic APD in humans. The sodium channel depressant effects are slow onset and offset, and they are use dependent. Because it also can inhibit the slow calcium channel, the drug has properties of multiple classes.[602] Minimal changes occur in ventricular or atrial refractoriness, but the drug can markedly change accessory pathway refractoriness. The QT interval changes are also minimal.

This drug is indicated for life-threatening ventricular arrhythmias, supraventricular arrhythmias, and AF. It also is effective in patients with the Wolff-Parkinson-White syndrome. Chronic clinical studies have shown that PVCs and VT are effectively suppressed.[603] Flecainide is probably the most effective antiarrhythmic at eliminating premature depolarizations, but as CAST showed for certain patient populations, PVC suppression may not always be in the patient's best interest. Intravenous flecainide was effective in treating junctional ectopic tachycardia, converting all seven patients to sinus rhythm within 16 hours.[604]

Flecainide decreases LV dP/dt and CO experimentally.[605] Clinical studies have shown no effects of oral flecainide on BP, echocardiographic parameters, or exercise tolerance.[603,605,606] However, patients with depressed ventricular function may be more susceptible to the negative inotropic effects of flecainide.

Flecainide is well absorbed after oral administration, with a plasma half-life of 20 hours. The drug is 85% excreted renally in an unchanged form or as an inactive metabolite. Effective plasma concentrations range from 0.2 to 1.0 μg/mL. Dosages range from 100 to 200 mg given twice daily. The dose should be reduced in renal failure or HF. Flecainide increases serum digoxin and propranolol levels, whereas propranolol, quinidine, and amiodarone can increase flecainide levels.

Adverse effects are usually minor at doses that have a significant therapeutic effect, but the QT interval has been prolonged with induction of polymorphic VT, and the CAST study showed definite increases in mortality after MI.[607] Confusion and irritability rarely occur.

Propafenone

Propafenone blocks the fast sodium current in a use-dependent manner. It also has a slow offset like flecainide. Propafenone blocks β-receptors and is a weak potassium channel blocker.[608] This drug usually slows conduction and prolongs refractoriness of most cardiac conduction system tissue. Propafenone is indicated for life-threatening ventricular arrhythmias, various supraventricular arrhythmias, and AF. In one study, a single 600-mg oral dose of propafenone converted 76% of patients in AF.[609] Propafenone was more effective than placebo in preventing atrial tachyarrhythmias after cardiac surgery with combined intravenous and oral therapy.[610]

Propafenone is well absorbed orally and is highly protein bound, with an elimination half-life of 6 to 8 hours. Therapeutic serum levels are 0.2 to 1.5 μg/mL. The metabolites of propafenone are active and demonstrate significant action potential and β-blocking effects. A small percentage of patients poorly metabolize the drug, and the metabolites of these patients exhibit greater β-blocking properties.

The drug has fewer proarrhythmic problems than flecainide, likely because of the β-blocking effects, which tend to decrease arrhythmic traits of antiarrhythmic drugs. Worsening of bronchospastic lung disease has occurred, and in a small percentage of patients, dizziness, blurred vision, taste issues, and some gastrointestinal complaints may develop.

Moricizine

Moricizine is a potent sodium channel blocker with mild potassium-blocking effects. It prolongs AV node, His bundle–ventricular conduction time, and QRS duration. It has little effect on atrial tissue. The drug is indicated for life-threatening ventricular arrhythmias and is as effective as some of the other class I agents.

Moricizine is highly protein bound and its bioavailability is only 35%. Serum levels do not correlate with therapeutic activity. The elimination half-life is 1 to 3 hours, with the drug eliminated by hepatic and renal routes. Dosage is 300 mg every 8 hours. Dosage may be changed to every 12 hours for patients with hepatic or renal disease or patients with CHF.

Adverse effects include tremor, headache, vertigo, dizziness, and gastrointestinal side effects of nausea, vomiting, and diarrhea. Proarrhythmic episodes can occur in up to 15% of patients. In the CAST study, the moricizine limb was continued after the encainide and flecainide limbs were stopped, and analysis of the moricizine-treated patients showed an increase in mortality.[611]

Class II Drugs: β-Adrenergic Receptor Antagonists

β-Adrenergic receptor blockers are very effective antiarrhythmics in patients during the perioperative period or patients who are critically ill because many of their arrhythmias are adrenergically mediated.

Propranolol

Propranolol was the first major β-receptor-blocking drug to be used clinically. Propranolol is very potent but is nonselective for β_1- and β_2-receptor subtypes. It possesses essentially no ISA. Because it interferes with the bronchodilating actions of epinephrine and the sympathetic stimulating effects of hypoglycemia, propranolol is less useful in patients with diabetes or bronchospasm. These difficulties with propranolol stimulated the search for β-receptor—blocking drugs with receptor subtype specificity, such as metoprolol, esmolol, and atenolol.

The electrophysiologic effects of β-receptor antagonism are decreased automaticity, increased APD (primarily in ventricular muscle), and a substantially increased ERP in the AV node. β-Blockade decreases the rate of spontaneous (phase 4) depolarization in the SA node; the magnitude of this effect depends on the background sympathetic tone. Although resting heart rate is decreased by β-blockade, inhibition of the increase of heart rate in response to exercise or emotional stress is much more marked. Automaticity in the AV node and more distal portions of the conduction system is also depressed. β-Blockade affects VF threshold variably, but it consistently reverses the fibrillation threshold-lowering effect of catecholamines.

In addition to β-blockade, propranolol decreases the background outward current of potassium, and at greater concentrations, it inhibits inward sodium current. Because of similarity to class I activity, these effects have been called *membrane-stabilizing activity* or quinidine-like effects. In very high concentrations (1000–3000 ng/mL), this effect increases depolarization threshold in Purkinje fibers.[126] Although effective β-blockade is achieved at propranolol concentrations of 100 to 300 ng/mL, concentrations of 1000 ng/mL may be required to control ventricular arrhythmias.[612] Propranolol decreases intramyocardial impulse conduction in acutely ischemic myocardium but does not do so in normal myocardium.[613]

Pharmacokinetic results show that absorption after oral administration is virtually 100%, but bioavailability is impaired by first-pass hepatic metabolism, which accounts for approximately two thirds of the administered dose. The degree of hepatic extraction varies greatly, which probably accounts for the great variability of the plasma concentration produced by a given oral dose of propranolol. The hepatic extraction of propranolol is a saturable process, and bioavailability improves with increased oral dose or with chronic therapy.[614] Propranolol is 90% to 95% protein bound in plasma, which further confounds the use of plasma concentration as a guide to therapy.[615] Propranolol is metabolized before excretion; one product, 4-hydroxypropranolol, has a β-blocking potency similar to that of propranolol, but a short half-life prevents this metabolic product from contributing significantly to the therapeutic effect of propranolol.[616]

The elimination half-life of orally administered propranolol is 3 to 4 hours, but it is increased during chronic therapy as a result of saturation of hepatic metabolic processes.[617] CPB alters the kinetics of propranolol. Heparinization doubles the free fraction of propranolol, an effect that is reversed after protamine administration. This effect probably results from an increase of free fatty acid concentration produced by heparin, which decreases the protein binding of propranolol.[618]

Major toxic side effects of propranolol are related to β-blockade. Cardiac toxicity includes CHF (uncommon without other causes of ventricular dysfunction) and depressed AV conduction. Complete heart block and asystole have occurred in patients with preexisting AV nodal or intraventricular conduction abnormalities. Sudden discontinuation of β-blockade therapy may precipitate a withdrawal syndrome of excessive β-adrenergic activity as a result of the altered sensitivity associated with chronic blockade. Responses to normal levels of sympathetic activity are exaggerated as the β-blockade declines, likely because of increased receptor density or upregulation of the β receptor.[619,620] Increased airway resistance results from β_2-receptor blockade by propranolol, and this can precipitate severe pulmonary compromise in the asthmatic patient. The hypoglycemic action of insulin is accentuated by propranolol because the sympathomimetic effect of hypoglycemia is blocked. Adverse effects perhaps not related to β-receptor blockade include CNS disturbances such as insomnia, hallucinations, depression, and dizziness and minor allergic manifestations such as rash, fever, and purpura.

An appropriate intravenous dose for acute control of arrhythmias is 0.5 to 1.0 mg titrated to therapeutic effect up to a total of 0.1 to 0.15 mg/kg. Stable therapeutic plasma concentrations of propranolol can be obtained with a continuous intravenous infusion. An effective level of β-blockade may be obtained with a continuous infusion of approximately 3 mg/h in adult postoperative patients previously receiving chronic treatment. However, with the availability of esmolol, a propranolol infusion is no longer necessary.

Metoprolol

Metoprolol is a relatively selective β-receptor antagonist. The potency of metoprolol for β_1-receptor blockade is equal to that of propranolol, but metoprolol exhibits only 1% to 2% of the effect of propranolol at β_2-receptors.[621]

Like propranolol, metoprolol is rapidly and efficiently absorbed after oral administration, but its first-pass extraction by the liver is lower, and 40% of the administered dose reaches the systemic circulation. Plasma half-life after oral administration is approximately 3 hours. Metoprolol is 90% metabolized; hydroxylation and *O*-demethylation are the primary pathways. The metabolites lack β-receptor effects. As with acetylation of procainamide, the rate of hydroxylation of metoprolol is genetically determined. Slow hydroxylators have a markedly prolonged elimination of the parent drug and greater plasma concentrations.[622]

Toxicity of metoprolol is related primarily to its limited β_2-antagonist activity. Metoprolol increases airway resistance and decreases the forced expiratory volume in patients with asthma, although to a lesser extent than does propranolol at equipotent β_1-antagonist doses. In contrast to propranolol, metoprolol does not inhibit the bronchodilation of isoproterenol. Metoprolol impairs β-receptor–mediated insulin release, and the signs of hypoglycemia are masked as with propranolol. Other side effects of metoprolol are similar to those of propranolol.

Metoprolol is useful for treating supraventricular and ventricular arrhythmias that are adrenergically driven. The primary advantage of metoprolol is its relative lack of most of the bronchoconstrictive effects in patients with chronic obstructive pulmonary disease. Acute intravenous dosage is 1.0 mg titrated to therapeutic effect up to 0.1 to 0.2 mg/kg.

Intravenous therapy may be more effective than oral therapy in preventing AF after cardiac surgery.[623] Another study compared oral carvedilol and oral metoprolol and found carvedilol more effective in preventing AF after on-pump CABG surgery.[624]

Esmolol

Esmolol is a cardioselective β_1-receptor antagonist with an extremely brief duration of action.[625] In anesthetized dogs, esmolol infused at 50 μg/kg per minute produced a steady-state β-blockade that was completely reversed 20 minutes after stopping the infusion.[626] Esmolol has only minimal ISA and membrane-stabilizing activity, and in conscious dogs, it has no effect on LVEDP, BP, heart rate, CO, or SVR, but at 5 to 60 μg/kg per minute, it does decrease LV dP/dt. The decreased contractility fully resolves by 20 minutes after the infusion.

Electrophysiologic effects of esmolol are those of β-adrenergic receptor antagonism. In open-chest dogs, esmolol infused at 300 μg/kg per minute increased SA node recovery time and Atrial–His bundle (AH) conduction interval, but not the His bundle–ventricular (HV) interval. ERP was increased in the AV node, but this effect does not occur in vitro at β-blocking concentrations.

Esmolol is rapidly metabolized in blood by hydrolysis of its methyl ester linkage. Its half-life in whole blood is 12.5 to 27.1 minutes in dogs and humans, respectively. The acid metabolite possesses a slight degree (1500 times less than esmolol) of β-antagonism. Esmolol is not affected by plasma cholinesterase; the esterase responsible is located in erythrocytes and is not inhibited by cholinesterase inhibitors, but it is

deactivated by sodium fluoride. Of importance to clinical anesthesia, no metabolic interactions between esmolol and other ester molecules are known. Esmolol dosages up to 500 μg/kg per minute have not modified neuromuscular effects of succinylcholine.[627]

In patients with asthma, esmolol (300 μg/kg per minute) only slightly increases airway resistance. In patients with chronic obstructive pulmonary disease who received esmolol, no adverse pulmonary effects have occurred.[628] In a multicenter trial that compared esmolol with propranolol for the treatment of paroxysmal supraventricular tachyarrhythmia (PSVT), esmolol was equally efficacious and had the advantage of a much faster termination of the β-blockade.[629] Esmolol has become a useful agent in controlling sinus tachycardia in the perioperative period, a time when a titratable and brief β-blockade is highly desirable.

Dosing begins at 25 μg/kg per minute and is titrated to effect up to 250 μg/kg per minute. Doses greater than this may cause significant hypotension because of reduced CO in patients. Esmolol is especially effective in treating acute-onset AF or flutter perioperatively, and it results in acute control of the ventricular response and conversion of the arrhythmia to sinus rhythm.

Landiolol, an ultrashort-acting β-blocker, similar to esmolol but with greater cardioselectivity and a shorter half-life (4 minutes), is undergoing investigation.[630] The drug is efficacious in converting 89% of patients who developed AF or flutter to sinus rhythm.[631] Landiolol reduced the incidence of AF when given prophylactically after cardiac surgery.[632]

Class III Drugs: Potassium Channel Blockers and Agents That Prolong Repolarization

Amiodarone

Amiodarone is a benzofuran derivative that was initially introduced as an antianginal drug and was subsequently found to have antiarrhythmic effects. The drug has a wide spectrum of effectiveness, including supraventricular,[633] ventricular,[634,635] and preexcitation arrhythmias (see Boxes 11.7 and 11.8).[633–636] It also may be effective against VT and VF refractory to other treatment.[637] Amiodarone has been approved by the AHA as the first-line antiarrhythmic in cardiopulmonary resuscitation.[638] Amiodarone may be effective prophylactically in preventing AF after surgery.[633] It also can decrease the number of shocks in patients who have implantable cardioverter-defibrillators compared with other antiarrhythmic drugs.[639]

Amiodarone used in an isolated rabbit SA node preparation increased APD and decreased the slope of diastolic (phase 4) depolarization, which depressed SA node automaticity.[640] Amiodarone prolongs repolarization and refractoriness in the SA node, in atrial and ventricular myocardium, in the AV node, and in the His-Purkinje system.[641] Resting potential and myocardial automaticity are minimally affected, but ERP and absolute refractory period are prolonged.[642] Amiodarone blocks inactive sodium channels in Purkinje fibers, which significantly depresses phase 0.[641] In anesthetized dogs, amiodarone decreases AV junctional and SA nodal automaticity and prolongs intranodal conduction.[643]

There are substantial differences in the electrophysiologic effects of acute and chronic amiodarone administration. Acutely, the drug slightly increases ERP of the His-Purkinje system and ventricular myocardium. The QTc is not prolonged by acute intravenous administration despite myocardial concentrations similar to those with chronic oral therapy.[644] However, chronic oral administration significantly increases QTc.[645] Although AV nodal ERP increases with acute intravenous amiodarone therapy, the increase is greater after chronic use. In other cardiac tissue, there is little or no change in ERP after intravenous administration, but after chronic oral use, ERP is increased globally and the AH and HV conduction times are increased.[646]

The electrophysiologic effects of chronic amiodarone treatment mimic those of thyroid ablation.[647] Moreover, the repolarization effects of the drug are reversed by T_3 administration. This suggests that among the basic effects of amiodarone is the blockade of the cardiac effect of T_3. This mechanism has been proposed as an alternative to the active metabolite accumulation theory to account for the slow onset of the antiarrhythmic effect of amiodarone.[646]

Amiodarone increases the amount of electric current required to elicit VF (ie, increase in the VF threshold). In most patients, refractory VT is suppressed by acute intravenous use of amiodarone. This effect has been attributed to a selectively increased activity in diseased tissue, as has been seen with lidocaine.[648] Amiodarone also has an adrenergic-receptor (α and β) antagonistic effect produced by a noncompetitive mechanism; the contribution of this effect to the antiarrhythmic action of the drug is unknown.[649]

Hemodynamic effects of intravenous amiodarone (10 mg/kg) include decreased LV dP/dt, maximal negative dP/dt, mean aortic pressure, heart rate, and peak LV pressure after coronary artery occlusion in dogs. CO was increased despite the negative inotropic effect as a result of the more marked decrease in LV afterload.[650] Clinical effects are similar; a 5-mg/kg intravenous dose during cardiac catheterization decreased BP, LVEDP, and SVR and increased CO, but it did not affect heart rate. Chronic amiodarone therapy is not associated with clinically significant depression of ventricular function in patients without LV failure. Hemodynamic deterioration may occur in some patients with compensated CHF, perhaps because of the antiadrenergic effects of the drug.[651]

The pharmacokinetics of amiodarone is notable for the low bioavailability, very long elimination half-life, relatively low clearance, and large volume of distribution. Oral absorption of amiodarone is slow, with peak plasma levels occurring 3 to 7 hours after ingestion.[652] Bioavailability varies and is low, ranging from 22% to 50%. The hepatic extraction ratio is only 0.13, and the major limit to bioavailability may be incomplete absorption. Amiodarone has a large volume of distribution, estimated as 1.3 to 65.8 L/kg; plasma clearance rates range from 0.14 to 0.60 L/min.[653] Plasma half-life after chronic oral therapy is reported as 14 to 107 days; therapeutic and steady-state plasma concentrations are slowly achieved with maintenance oral administration at 9.5 to 30 days, respectively.[654]

Because steady-state plasma levels are achieved slowly, loading techniques have been developed. Patient-specific pharmacokinetic data have been used to prescribe loading infusion rates of 0.5 to 3.9 mg/min and maintenance rates of 0.5 to 1.0 mg/min to produce plasma levels of 0.5 to 2.5 μg/mL during maintenance infusion. This dosage reduced VT by 85%, paired PVCs by 74%, and isolated PVCs by 60%.[655] A comparison of onset of antiarrhythmic effect of oral loading (800 mg/day for 7 days, then 600 mg/day for 3 days) and intravenous (5 mg/kg for 30 minutes) plus oral (as for oral alone) administration demonstrated that the combined intravenous and oral loading technique had a more rapid therapeutic effect with a lower total amiodarone dose.[656] In acute situations with stable patients, a 150-mg intravenous bolus is followed by a 1.0-mg/min infusion for 6 hours and then 0.5 mg/min thereafter. In CPR, a 300-mg intravenous bolus is given and repeated with multiple boluses as needed if defibrillation is unsuccessful.

Adverse reactions to amiodarone are numerous. Photosensitivity of the skin occurs in 57% of patients without apparent relation to dose or plasma level.[657] Other skin manifestations include abnormal pigmentation (ie, slate gray) and an erythematous, pruritic rash. Corneal microdeposits occur in most patients taking amiodarone chronically, although visual symptoms are uncommon.

Pulmonary side effects are more severe.[658–661] Clinical features include exertional dyspnea, cough, and weight loss. Hypoxia may occur; pulmonary function studies show decreased total lung capacity and diffusion rate. Chest radiographic findings are diffuse bilateral interstitial infiltrates, which histologically may be fibrosing alveolitis. Pulmonary effects may resolve with discontinuation of treatment or with dose reduction. The pathophysiologic mechanism of these pulmonary effects is unknown but may be related to abnormal production of phospholipid. The overall incidence rate of pulmonary toxicity is up to 6%, with a mortality rate among affected patients of 20% to 25%. There are case reports of an increased risk for acute respiratory distress

syndrome when amiodarone is used before CPB, but this association has not been proved.

Thyroid abnormalities are associated with amiodarone. The frequencies of hyperthyroidism and hypothyroidism range from 1% to 5% and 1% to 2%, respectively.[649] Amiodarone contains two iodine atoms per molecule, or 75 mg of organic iodide per 200 mg of drug, and 10% of that amount may become free iodine. The iodine alone does not account for the thyroid abnormalities because intake of an amount of inorganic iodine equivalent to that ingested with chronic amiodarone intake does not have the same effect. Heart rate is not increased during hyperthyroidism associated with amiodarone, probably because of its antiadrenergic effects. Amiodarone therapy increases thyroxine (T_4) and reverse T_3, but it only slightly decreases T_3.[662,663]

Despite relatively widespread use of amiodarone, anesthetic complications infrequently have been reported. In two case reports, bradycardia and hypotension were prominent.[664,665] One of the reports described profound resistance to the vasoconstrictive effects of β-adrenergic agonists.[665] The slow decay of amiodarone in plasma and tissue makes such adverse reactions possible long after discontinuing its administration. Because T_3 can reverse electrophysiologic effects of amiodarone, T_3 possibly could be used to reverse hemodynamic abnormalities, such as those described in these two case reports, although this theory has not been tested. Epinephrine is more effective than dobutamine or isoproterenol in reversing amiodarone-induced cardiac depression.[666]

An RCT of amiodarone administered 6 days before and 6 days after cardiac surgery demonstrated significant reductions in atrial tachyarrhythmias and ventricular arrhythmias in patients of different ages and in different types of cardiac surgical procedures.[667] There were no differences in hospital mortality rates between groups.

A study in CABG surgery patients showed that amiodarone was more effective in converting AF than placebo.[668] All patients in this study received β-blockers. In children with postoperative junctional ectopic tachycardia, amiodarone was effective in converting or slowing the heart rate in all 18 study patients.[669] Prophylactic amiodarone has also reduced the incidence of AF in lung resection[670] but did not reduce the incidence of AF in cardiac valvular surgery.[671]

Bretylium

Bretylium has had supply problems over the past 5 years, and in 2011, the FDA placed it on a discontinued drug list. It was not discontinued due to safety issues and is still available in some countries outside the United States.

Bretylium is a quaternary ammonium compound that produces a biphasic cardiac response after acute intravenous administration. Initially, norepinephrine is displaced from adrenergic nerve endings, and there are attendant increases in BP, SVR, and cardiac automaticity. After 20 to 30 minutes, this response wanes, and the adrenergic-blocking effects of bretylium predominate.[672–674] The latter effects depend on uptake of bretylium by adrenergic neurons, but inhibition of its adrenergic-blocking effects does not impair the antiarrhythmic effect.

The direct electrophysiologic effect of bretylium is prolongation of the ventricular ERP. The electrophysiologic effect correlates with the myocardial rather than the plasma concentrations of bretylium.[675] Bretylium delays conduction of premature impulses from normal myocardium to the border of ischemic zones and decreases the disparity between the excitation thresholds of adjoining zones of ischemic and normal myocardium. Bretylium increases the electric current required to induce VF and may spontaneously convert VF to sinus rhythm.[676] The antiarrhythmic effect of bretylium is undiminished by cardiac denervation or chronic reserpine treatment, which indicates that the antiarrhythmic effects are dissociated from the antiadrenergic effects.[677,678] Bretylium also decreases the amount of electrical current required to produce defibrillation.[679]

Results of clinical trials of bretylium in acute cardiac arrest are inconsistent. In one study in which it was compared with lidocaine, bretylium did not have a better antiarrhythmic effect, improve resuscitation, or lower mortality rates.[680] In another study, bretylium (10 mg/kg) was used as a first-line treatment for out-of-hospital VF and significantly improved the outcome from resuscitation; lidocaine administered after bretylium also decreased the incidence of recurrent VF.[681] In the acute setting, bretylium is effective prophylaxis against VF.[642,682–685]

Clinical indications for bretylium include refractory VT or VF. For VF, bretylium is administered as a 5- to 10-mg/kg intravenous bolus, which can be repeated to a total dose of 30 mg/kg if VF persists. The antifibrillatory effect may require some time to develop, and full resuscitative efforts should continue for at least 20 to 30 minutes after bretylium has been administered. Administration for recurrent VT is similar to that for VF. Continuous infusion of 2 mg/min may be used to maintain plasma levels. As with VF, the effect of bretylium in VT may take 20 to 30 minutes to manifest.

Adverse reactions to bretylium include nausea and vomiting in conscious patients. During chronic therapy, postural hypotension may develop, but it is reduced by tricyclic drugs, which block uptake of bretylium by adrenergic neurons.

Sotalol

Sotalol is classified as a class III agent, but it also has class II β-adrenergic–blocking properties. Sotalol was first synthesized as a β-blocker and was initially used to treat angina and hypertension. The antiarrhythmic effect quickly was recognized, and the antiarrhythmic actions then were evaluated. Sotalol prolongs refractoriness in atrial and ventricular tissues because of blockade of the delayed rectifier potassium current. The β-blocking effects result in decreased heart rate and increased refractory periods at the atrial and ventricular levels.[686] It is indicated for life-threatening ventricular arrhythmias and AF.

Sotalol exists as a mixture of the D and L isomers, which have different mechanisms of action. Sotalol can be administered orally or intravenously. Oral bioavailability is greater than 90%. The drug is poorly bound to plasma protein and undergoes renal excretion with an elimination half-life of 12 hours when renal function is normal. The usual starting oral dose is 80 to 160 mg every 12 hours. Peak plasma concentration is seen within 4 hours.[687]

Sotalol has been used to treat supraventricular and ventricular tachyarrhythmias. Sotalol was found to be superior to class I agents in preventing the recurrence of ventricular arrhythmias.[688] To investigate the contribution of the β-blocking property to the efficacy of sotalol, class I agents with or without β-blocker were compared with sotalol.[689] Sotalol was more effective in preventing the recurrence of arrhythmias than class I agents with or without β-blockers. However, the mortality rates were similar when sotalol was compared with the combined class I drug and β-blocker regimen. Sotalol also is effective in the prevention of PSVTs.[690]

Sotalol administration is not without side effects. A large, prospective study of D-sotalol (not the mixture of D and L isomers) in patients with reduced LV function was terminated early because of an increased mortality rate in the treatment group.[691]

D-Sotalol lacks a significant β-adrenergic receptor–blocking property, which may explain the findings. Sotalol administration is associated with increased risk for torsades de pointes and QT-interval prolongation. Female patients and patients with renal failure are at increased risk for the proarrhythmic side effects.

Ibutilide

Ibutilide fumarate is a methanesulfonanilide antiarrhythmic agent that is approved for the conversion of atrial flutter and AF to sinus rhythm. Ibutilide prolongs the cardiac refractory period at the atrial and ventricular levels by activating a slow inward sodium current.[692] Ibutilide may cause the blockade of the rapid outward delayed rectifier potassium current, which also leads to prolongation of the cardiac refractory period.[693] In vitro and at high dose, ibutilide may shorten the action potential, although this effect has not been observed clinically. Ibutilide may also predispose to the formation of after depolarizations, which may be involved in the development of torsades de pointes.

Ibutilide is administered intravenously, is 40% protein bound, and undergoes hepatic metabolism. Of the eight metabolites, only one has slight antiarrhythmic activity. The pharmacokinetics of ibutilide is linear. Extravascular distribution is rapid, and systemic clearance is high, with the elimination half-life ranging from 2 to 6 hours.[694] The usual dose is 1 mg administered over 10 minutes. This may be followed by a second dose of 0.5 to 1 mg.

In one study, 0.015 mg/kg of ibutilide administered intravenously over 10 minutes resulted in conversion to sinus rhythm of about 45% of patients with atrial flutter longer than 3 hours in duration or AF 3 hours to 90 days in duration.[695] The arrhythmia was terminated in 3% of patients receiving placebo. The mean time to termination of arrhythmia was 19 minutes from the start of the infusion. In this study, termination of arrhythmias was unaffected by an enlarged left atrium, decreased EF, valvular heart disease, or use of concomitant medications such as β-blocking agents and digoxin.

In another study, the safety and efficacy of repeated intravenous doses were evaluated.[696] The investigators found a conversion rate similar to that in the previously described study. They found that efficacy was greater in atrial flutter than AF (63% vs 31%). In AF, conversion rates were greater in patients with shorter arrhythmia duration or a normal left atrial size. However, the duration of arrhythmias in all patients in this study was less than 45 days. Conversion rates of AF or flutter are enhanced with the concurrent use of magnesium.[697]

Cardiovascular side effects occur in about 25% of patients treated with ibutilide, compared with 7% for the placebo-treated group.[698] Torsades de pointes occurred in 4.3% of these patients. Most of the proarrhythmic activity was seen within 1 hour of termination of the infusion, reflecting the short half-life and lack of metabolites with significant antiarrhythmic properties. Bradycardia, low body weight, and a history of CHF predicted the occurrence of torsades de pointes. Electrolyte abnormalities and acquired prolonged QT interval should be corrected before ibutilide therapy.

Dofetilide

Dofetilide blocks the rapid component of the delayed rectifier potassium current of repolarization without slowing conduction. Similar to ibutilide, dofetilide has a profound effect on prolonging the QT interval. Atrial tissue is more affected by dofetilide's electrophysiologic effects than ventricular tissue. Dofetilide is indicated for acute conversion and chronic suppression of AF.[699]

Dofetilide is available only as an oral formulation and results in 90% bioavailability. About 50% of the drug is excreted in the urine, with an elimination half-life of 8 to 12 hours. Several drugs increase dofetilide serum concentrations, including verapamil, cimetidine, and ketoconazole. These drugs should be avoided or used with caution in combination with dofetilide.

Dosing is 0.125 to 0.5 mg twice daily and should be performed during ECG monitoring and measuring of the QT interval. QT prolongation with polymorphic VT can occur in up to 4% of patients. Electrolyte abnormalities should be corrected before administering this drug. Patients with prolonged QT intervals or a history of torsades de pointes should not receive chronic therapy. The concurrent use of magnesium enhanced the conversion of AF or atrial flutter with dofetilide and theoretically may reduce the incidence of QT prolongation.[700] No patients who received magnesium in this study developed torsades de pointes.

Dronedarone

Dronedarone was developed as an antiarrhythmic drug with a molecular structure and electrophysiologic effects similar to those of amiodarone but with more effect on atrial tissue and fewer side effects.[701] The main structural change is the replacement of iodine with a methane sulfonyl group that reduces the incidence of thyroid side effects and decreases the tissue accumulation, which should reduce the drug's half life, volume of distribution, and organ toxicity.

Dronedarone is available orally, is well absorbed, and has an elimination half life of 12 to 24 hours.[702] Oral dosing is 400 mg twice daily. First-pass metabolism in the liver accounts for 85%, and the drug is highly protein bound. Digoxin, statin, and cyclosporin levels increase with dronedarone and should be monitored. Grapefruit and verapamil may increase levels and should be avoided. The serum creatinine level may rise due to impaired tubular secretion. The drug may increase liver enzymes, and there have been several case reports of severe hepatotoxicity. Prolongation of the QT interval and proarrhythmias do not appear to be a problem.

Clinical trials have demonstrated that dronedarone maintains sinus rhythm and reduces the ventricular response in AF compared with placebo. The drug has also reduced mortality rates and reduced the incidence of stroke compared with placebo in AF. The reason for the reduced stroke rate was not clear. However, in patients with reduced LV function, dronedarone increased the risk of CHF and early death.[703] When compared with amiodarone, dronedarone had fewer adverse events that resulted in discontinuation of the drug, but amiodarone was more effective in maintaining sinus rhythm. In patients with permanent AF, dronedarone increased the risk of stroke, mortality, and hospitalization.[704] Dronedarone is not a first-line drug for AF and flutter and should not be used in patients with HF or in those with permanent AF.[705]

Vernakalant

Vernakalant is an antiarrhythmic drug approved for use in Europe but not in the United States for the acute conversion of AF but not atrial flutter.[706] The drug blocks atrial sodium and potassium channels and prolongs the atrial ERP duration. It is more effective at faster heart rates, which is different from other class III drugs.[707]

Vernakalant is available intravenously and orally. Intravenous drug is 89% metabolized by the liver, and 11% is renally excreted, with an elimination half-life of 3 hours.[706] The drug is not highly bound to proteins and does not appear to interact with other drugs, which typically could increase vernakalant serum levels.

An intravenous bolus dose of 3 mg/kg is given over 10 minutes, with a repeat dose of 2 mg/kg over 10 minutes given in 15 minutes if AF persists. [707] Significant side effects are rare, with hypotension occurring in only 6% of patients. Vernakalant does not appear to cause any significant clinical effects in the ventricular conducting system in humans, but in animal studies, there were mild sodium and potassium blocking effects in ventricular tissue. There appear to be no effects on QT prolongation, although in all clinical trials, patients with QT prolongation were excluded.

Clinical trials have demonstrated vernakalant to be extremely effective in the rapid conversion of acute-onset AF in nonsurgical and postoperative cardiac surgical patients.[708] Its speed of conversion is similar to that of ibutilide, but it has an acute safety profile similar to amiodarone (Table 11.27). More safety studies are needed before approval in the United States.[709]

Class IV Drugs: Calcium Channel Antagonists

Although the principal direct electrophysiologic effects of the three main chemical groups of calcium antagonists (ie, verapamil, a benzoacetonitrite; nifedipine, a dihydropyridine; and diltiazem, a benzothiazepine) are similar, verapamil and diltiazem are the primary antiarrhythmics.

As with other transmembrane ionic channels, the calcium channel is conceptualized as macromolecular protein that spans the ion-impermeable lipid bilayer of the membrane (Fig. 11.26). The channels exhibit selectivity for a particular ionic species and for specific transmembrane electrical potential ranges to control the permeability of the pore.[197] The decreased membrane potential produced by depolarization increases the permeability of the Ca^{2+} channel and permits Ca^{2+} to pass down its concentration gradient into the cell. Conversely, the gate closes on repolarization. This mechanism has been called the *voltage-dependent* or *voltage-gated* channel. In cardiac tissue, the Ca^{2+} channel is also controlled by membrane β-adrenergic receptors; activation of β_1 receptors recruits additional Ca^{2+} channels

TABLE 11.27 Comparison of Vernakalant and Ibutilide

Parameter	*Vernakalant*	*Ibutilide*
Vaughan-Williams class	Class III	Class III
Mechanism of action	Prolongation of refractoriness	Prolongation of refractoriness
Atrial selectivity	Yes	No
Effectiveness in acute AF	About 50% converted in 90 min	About 50% converted in 90 min
Effectiveness in AFI	No	Yes
Median time to conversion	11 min	30 min
Proarrhythmic effect	None to minimal	Risk of ventricular proarrhythmias (TdP, 1.7%)
Contraindications	SBP <100 mm Hg: severe aortic stenosis; heart failure (NYHA III or IV); ACS in the last 30 days; QTc prolongation	Heart failure (III or IV), recent ACS, QTc prolongation, coadministration with class I AADs and other QT-prolonging drugs, hypokalemia
Dosing regimen (intravenous)	3 mg/kg over 10 min followed by a second infusion of 2 mg/kg over 10 min if arrhythmia persists	1 mg over 10 min followed by a second infusion of 1 mg over 10 min if arrhythmia persists

AADs, antiarrhythmic drugs; *ACS*, acute coronary syndrome; *AF*, atrial fibrillation; *AFI*, atrial flutter; *NYHA*, New York Heart Association; *SBP*, systolic blood pressure; *TdP*, torsades de pointes.

Modified from Bronis K, Metaxa S, Koulouris S, Manolis AS. Vernakalant: review of a novel atrial selective antiarrhythmic agent and its place in current treatment of atrial fibrillation. *Hosp Chronicles.* 2012;7, 171.

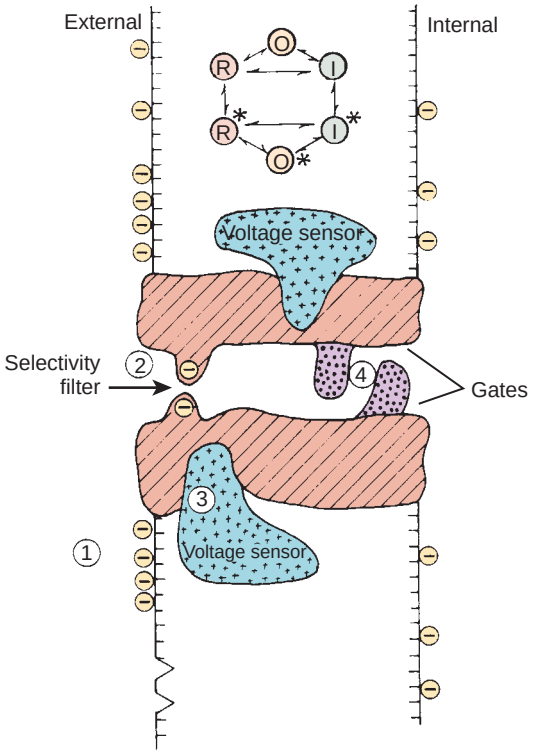


Fig. 11.26 Calcium channel depicted as a proteinaceous membrane pore. A selectivity filter *(2)* confers ion selectivity by specific molecular dimension and change density characteristics. Voltage sensor components *(3)* link membrane depolarization with channel opening and closing by the gating mechanism *(4)*. Negatively charged sites on the external surface serve as calcium binding sites *(1)*. *(From Triggle DJ. Biochemical pharmacology of calcium blockers. In: Flaim SF, Zelis R, eds.* Calcium Blockers: Mechanisms of Action and Clinical Applications. *Baltimore, MD: Urban & Schwarzenberg; 1982:121–134.)*

to the open or active state, and the channels are called *receptor-operated* channels.[710]

Based on studies with the sodium channels in the giant axons of squid, three activity states of the Ca^{2+} channel have been distinguished: resting, open, and inactive. The resting state of the Ca^{2+} channel is characterized by a closed activation *(d)* gate on the external surface of the membrane and an opened inactivation *(f)* gate on the internal surface (Fig. 11.27).[711] Depolarization triggers the open state when the *d* gate relaxes to permit Ca^{2+} influx and triggers the slower closure of the (*f*) gate, which when complete blocks further Ca^{2+} influx; the resulting inactive state persists until complete repolarization resets both gates. For the Ca^{2+} channel, the time constant for the transition from the resting to the open state is 520 ms, that from the open to the inactive state is 30 to 300 ms, and that from the inactive to the resting state is 30 to 300 ms.[712]

The use dependence seen with Ca^{2+} antagonists is the direct relation between the antagonist effect and the frequency of tissue activation. In cardiac tissue, the negative inotropic and Ca^{2+} channel blocking properties of verapamil depend on transmembrane potential and stimulation frequency; the inhibitory activity increases with increased frequency and with partial depolarization.[713] The findings may indicate that verapamil interacts primarily with the inactive (depolarized) state of the Ca^{2+} channel. The activation state of the membrane is less important for the inhibitory action of nifedipine.

The lipophilic nature of Ca^{2+} channel antagonists is important to their effect. In skinned cardiac cells, D600, a congener of verapamil, is ineffective, which appears to indicate a primary effect of the drug at the plasma membrane.[714] Likewise, quaternary ammonium derivatives of D600 and nifedipine, which are highly ionized and therefore less lipophilic, are also less effective Ca^{2+} channel antagonists.[713] The data indicate that perhaps the locus of activity of these Ca^{2+} channel antagonists is the internal surface of the channel or within the membrane itself.

The drugs commonly classified as Ca^{2+} channel antagonists, typified by verapamil, diltiazem, nifedipine, and nicardipine, exhibit specificity for vascular smooth muscle and cardiac tissues, but within the group, specificity for these tissues varies. Nifedipine and nicardipine (and other dihydropyridines) are more potent in smooth muscle than cardiac tissue, whereas verapamil and diltiazem are more potent in cardiac tissue.[715,716] Although Ca^{2+} channel antagonism is the dominant effect of these agents, at sufficiently high ($>10^{6}$ M) concentrations, other effects become notable. For example, verapamil and D600 at concentrations greater than 10^{6} M inhibit sodium channel activity and receptor binding at muscarinic, adrenergic, and opiate receptors.[717] The effects do not exhibit stereoselectivity, as does Ca^{2+} channel–specific action.[718]

Verapamil and Diltiazem

Verapamil and diltiazem have been used extensively in the treatment of supraventricular arrhythmias, AF, and atrial flutter. They are especially effective at preventing or terminating PSVT by blocking impulse transmission through the AV node by prolonging AV nodal conduction and refractoriness.[719] They are also useful in the treatment of AF and atrial flutter by slowing AV nodal conduction and decreasing the ventricular response. The effect on ventricular response is similar to that of the cardiac glycosides, although the onset is more rapid and acutely effective for control of tachycardia in patients.[720,721]

In the perioperative period, verapamil is a useful antiarrhythmic agent. In one study of anesthetized patients, it successfully controlled a variety of supraventricular and ventricular arrhythmias.[721] However, verapamil should be used with caution intraoperatively because significant cardiac depression may occur in conjunction with inhalation anesthetics.[722,723]

A significant precaution in the use of verapamil and diltiazem to treat PSVT involves preexcitation of the AV node in Wolff-Parkinson-White

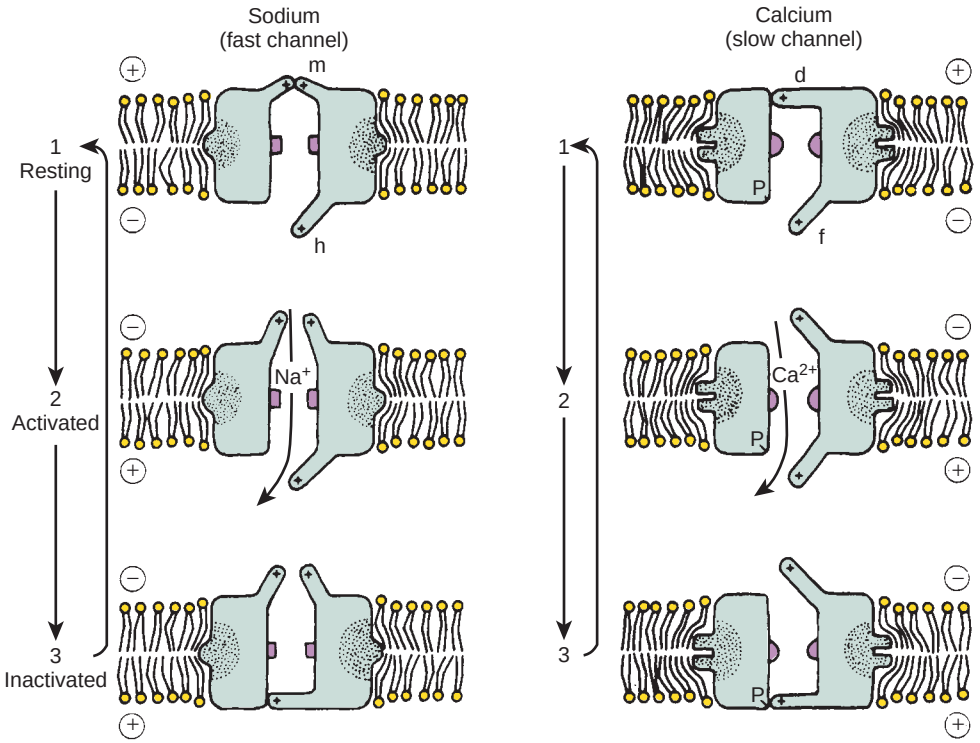


Fig. 11.27 Schematic depiction of the calcium channel in the sarcolemmal membrane. The upstroke (phase 0) of the action potential, which allows rapid entry of sodium into the cell, opens the activation gates *(m)* in the sodium channel. The resulting change in transmembrane potential closes the inactivation gate *(h),* which stops sodium influx but maintains a refractory state in the cell membrane until repolarization. Similar processes occur in the calcium channel activation gate *(d)* and inactivation gate *(f),* except that at least some of the steps in slow channel activation require phosphorylation *(P)* by a cyclic adenosine monophosphate protein kinase. Changes in the conformation of the channel proteins provide the three functional states of the channel: resting (ie, closed and able to open) *(1)*; activated (ie, open) *(2)*; and inactivated (ie, closed and unable to open in response to depolarization) *(3). (From Katz AM, Messineo FC. Lipids and membrane function: implications in arrhythmias.* Hosp Pract. *1981;16:49.)*

syndrome. If PSVT is orthodromic (ie, anterograde conduction through the AV node and retrograde over the accessory pathway) with a narrow or normal QRS complex, verapamil has a high success rate by blocking anterograde AV nodal conduction. If the PSVT is antidromic (ie, anterograde conduction through accessory pathway and retrograde over the AV node) with a widened QRS complex, successful blockade with verapamil is unlikely because it has little effect on refractoriness or conduction in accessory pathways.

Atrial flutter and AF also may occur in Wolff-Parkinson-White syndrome. In this setting, agents that shorten the ERP of the accessory pathway or increase the ERP in the AV node (eg, digitalis, verapamil) often increase the ventricular response and may precipitate VF.[724] Class I and III drugs (eg, procainamide, amiodarone) are more effective in slowing the ventricular response in AF with an accessory pathway (see Chapter 4).

Electrophysiologic effects of verapamil and diltiazem are seen predominantly in tissues in which phase 0 or 4 depolarization is largely calcium dependent (ie, SA and AV nodes). Discharge rate and recovery time in the SA, AV conduction time, and AV node ERP are prolonged. Clinically, the QRS complex and QT_c interval are not significantly affected, but AH (but not HV) conduction time is prolonged. Electrophysiologic effects of verapamil have been shown in anesthetized dogs to correlate with plasma concentration; the AH interval was prolonged at lower concentrations than were necessary to slow the SA node or to produce AV block.[725]

As with several other antiarrhythmic drugs, the pharmacokinetics of intravenously and orally administered verapamil differ. The hepatic extraction of orally administered verapamil is extensive; as a result, its bioavailability, which is normally low, is increased significantly by liver disease.[241] After intravenous administration of verapamil, plasma clearance approximates splanchnic blood flow rate, and because of its lipophilic nature, the apparent volume of distribution is large. Elimination half-life of verapamil is approximately 5 hours, but it may be longer with chronic administration, perhaps because of saturation of hepatic metabolic pathways. A principal metabolite, norverapamil, is biologically active, accumulates to concentrations equal to those of verapamil during chronic therapy, and has a longer half-life (8 to 13 hours).[726] Excretion of verapamil after metabolism is renal (65–70%), but 3% to 4% is excreted unchanged.[724] Metabolism involves *n*-dealkylation and *O*-demethylation with norverapamil (ie, one-eighth of the Ca^{2+} channel–blocking potency of verapamil) as the major metabolite.[715] Verapamil and metabolites are highly protein bound (90%).

Verapamil dosage for acute intravenous treatment of PSVT is 0.07 to 0.15 mg/kg over 1 minute, with the same dose repeated after 30 minutes if the initial response is inadequate (10 mg maximum). Because the cardiovascular depressant effects of the inhalation anesthetics involve inhibition of calcium-related intracellular processes, the interaction of verapamil and these anesthetics is synergistic. In one large clinical series, verapamil given during steady-state halothane anesthesia transiently decreased BP and produced a 4% incidence of PR-interval prolongation.[727] In laboratory studies, verapamil interacts similarly with halothane, enflurane, and isoflurane to mildly depress ventricular function and to slow AV conduction (ie, PR interval).[722] AV block can occur and may be refractory. AV block can occur when verapamil is combined with β-blockers.

Diltiazem in doses of 0.25 to 0.30 mg/kg administered intravenously and followed by a titratable intravenous infusion of 10 to 20 mg/h is rapid acting and efficacious in controlling ventricular response rate in new-onset AF and atrial flutter.[728,729] The prophylactic use of intravenous diltiazem can reduce the incidence of postoperative supraventricular arrhythmias after pneumonectomy and cardiac surgery.[730] Diltiazem also may have a role in treating ventricular arrhythmias. In an experimental model, diltiazem was protective against VF with acute cocaine toxicity.[731]

Another adverse effect of verapamil is the potentiation of neuromuscular blockade. In two laboratory studies, verapamil depressed twitch height response to indirect stimulation.[732,733] Although the exact presynaptic or postsynaptic site of the block was not determined, the qualitative similarity of the effect to that of pancuronium suggested an effect at the neuromuscular junction. At clinically relevant doses of verapamil, the effect is slight, but the clinical potential for synergistic interaction with residual muscle relaxants seems substantial. Cautious clinical attention to neuromuscular function is necessary to safely use verapamil in patients who are receiving or have recently received muscle relaxants.

Diltiazem proved equally as effective as amiodarone in managing postoperative AF occurring after lung resection surgery.[734] Another study of coronary artery surgery demonstrated that diltiazem prophylaxis reduced the incidence of AF when administered intravenously or orally.[735]

Other Antiarrhythmic Agents

Digoxin

The primary therapeutic use of digitalis drugs is to slow the ventricular response during AF or atrial flutter, which occurs because of a complex combination of direct and indirect actions on the AV node. The primary direct pharmacologic effect of digitalis is inhibition of the membrane-bound Na^+/K^+-ATPase. This enzyme provides the chemical energy necessary for the transport of sodium (out) and potassium (in) during repolarization. The glycosides bind to the enzyme in a specific saturable way that inhibits enzyme activity and impairs the active transport of sodium and potassium. The net result is a slight increase in intracellular sodium and a corresponding decrease in intracellular potassium concentration. The sodium exchanges for calcium, resulting in a relatively weak inotropic effect.

In Purkinje fibers, digoxin increases the slope of phase 4 depolarization and decreases resting potential or maximal diastolic potential so that the initiation of depolarization (phase 0) begins at a less negative potential; the V_{max} and the conduction velocity of the action potential are lower. The phase 4 effect is inversely related to extracellular potassium concentration. At low concentrations of potassium, the increased rate of phase 4 depolarization is augmented, and automaticity increases, which may partially explain the increased risk for digoxin-related toxicity during hypokalemia or pronounced potassium fluxes, such as during cardioversion or in the period immediately surrounding CPB. At concentrations approaching toxicity, digoxin produces delayed afterpotentials, which may be sufficient to reach threshold and trigger depolarization.[736–738] The direct action of therapeutic concentrations of digoxin in Purkinje fibers decreases conduction velocity and increases ERP.

In specialized conduction fibers in the SA and AV nodes, similar electrophysiologic effects occur; in both regions, however, the dominant effects are indirect and mediated by the autonomic nervous system. In atrial and ventricular muscle, direct effects resemble those in Purkinje fibers. The indirect effects of digitalis, notably a decreased APD, account for the decreased QT interval on the electrocardiogram. Effects of this drug during phases 2 and 3 of the action potential account for the characteristic downward convexity of the ST segment.[739]

Digoxin increases vagal efferent activity, the origin of which may correlate with increased sensitivity of arterial baroreceptors and increased carotid sinus nerve activity or be related to an effect on the central vagal nuclei.[740–743] SA node sensitivity to acetylcholine may be enhanced by digoxin. In high concentrations, digoxin may decrease SA and AV nodal sensitivities to catecholamines and sympathetic stimulation, although this may be because of increased sympathetic efferent activity produced by the CNS (ie, medulla) effects of digoxin and the inhibition of norepinephrine uptake at peripheral sympathetic nerve terminals.[741,742] The decreased sinus rate seen with digoxin in part results from increased vagal efferent activity and decreased sympathetic tone.

The AV node is the portion of the conduction system most strongly influenced by the direct and indirect effects of digoxin. Conduction through the AV node is slowed, and the ERP of the AV node is lengthened by digoxin. In toxic concentrations, digoxin can effectively block AV nodal transmission.

In atrial tissue, the direct and indirect (vagal) effects of digoxin are opposed. The direct effect is an increase in APD, but the indirect effect (mediated by acetylcholine release) is marked decreases in APD and ERP. At therapeutic concentrations, the indirect effect predominates, which makes the atria responsive to higher stimulation frequencies.[739] The frequency of atrial impulses arriving at the AV node usually is increased, which leads to frequent partial depolarization of the AV node (ie, concealed conduction). This effect and the increased AV nodal ERP produced by direct effects, vagal effects, and sympatholytic effects result in a net decrease in the frequency of impulses that successfully traverse the AV node to depolarize the His-Purkinje system.

The main preparation of cardiac glycosides available is digoxin. Digoxin reaches peak effects in 1.5 to 2 hours but has a significant effect within 5 to 30 minutes. For undigitalized patients, the initial dose is 0.5 to 0.75 mg of digoxin, with subsequent doses of 0.125 to 0.25 mg. The usual total digitalizing dose is 0.75 to 1.0 mg administered by the intravenous route. Digoxin is approximately 25% protein bound, and the therapeutic range of plasma concentrations is 0.5 to 2.0 ng/mL.

Adenosine

Adenosine is a virtually ubiquitous endogenous nucleoside that has potent electrophysiologic effects in addition to having a major physiologic role in regulation of vasomotor tone.[743] Adenosine is unique in that it is produced as an intermediate metabolite of adenosine monophosphate. It has an extremely short half-life in plasma (on the order of 1.5 to 2 seconds) because of metabolism by adenosine deaminase to inosine or by adenosine kinase to adenosine monophosphate. Both enzymes are contained within the intracellular cytosolic compartment, indicating a rapid transmembrane transport system for adenosine. Inhibition of this transport system by dipyridamole markedly enhances the cardiac effects of adenosine.

The important cardiac electrophysiologic effects of adenosine are mediated by the A_1 receptor and consist of negative chronotropic, dromotropic, and inotropic actions. Adenosine decreases SA node activity, AV node conductivity, and ventricular automaticity. In many ways, these effects mimic those of acetylcholine. The A_1 receptor is linked to the ionic channel for K^+ and Ca^{2+} and to adenylyl cyclase through the guanine nucleotide–binding inhibitory protein (G_i). Activation of the A_1 receptor in the SA and AV nodes activates the outward acetylcholine-adenosine–regulated potassium current. In ventricular myocardium, adenosine antagonizes the stimulation of the inward Ca^{2+} current produced by catecholamines. The primary antiarrhythmic effect of adenosine is to interrupt reentrant AV nodal tachycardia, and this effect most likely is related to the potassium current effects.

For clinical use, adenosine must be administered by a rapid intravenous bolus in a dose of 100 to 200 μg/kg, although continuous intravenous infusions of 150 to 300 μg/kg per minute have been used to produce controlled hypotension. For practical purposes, in adults, a dose of 3 to 6 mg is given by intravenous bolus followed by a second dose of 6 to 12 mg after 1 minute if the first dose was not effective. This therapy rapidly interrupts narrow-complex tachycardia caused by AV nodal reentry.[744]

Comparison with verapamil has shown adenosine to be equally effective as an antiarrhythmic, but with the advantages of fewer adverse hemodynamic effects, a faster onset of action, and a more rapid elimination so that undesired effects are short-lived.[745] The median effective close range (MD_{50}) of adenosine for reentrant supraventricular arrhythmias in children is 100 to 150 μg/kg.[746]

Potassium

Because of the close relationship between extracellular pH and potassium, the primary mechanism of pH-induced arrhythmias may be alteration of potassium concentration. Hypokalemia and hyperkalemia are associated with cardiac arrhythmias, but hypokalemia is more common perioperatively in cardiac surgical patients and is more often associated with arrhythmias.[747] Decreasing the extracellular potassium concentration increases the peak negative diastolic potential, which appears to decrease the likelihood of spontaneous depolarization. However, because the permeability of the myocardial cell membrane to potassium is directly related to extracellular potassium concentration, hypokalemia decreases cellular permeability to potassium. This prolongs the action potential by slowing repolarization, which slows conduction, increases the dispersion of recovery of excitability, and predisposes to the development of arrhythmias.

ECG correlates of hypokalemia include appearance of a U wave and increased P-wave amplitude.[748] The arrhythmias most commonly associated with hypokalemia are premature atrial contractions, atrial tachycardia, and supraventricular tachycardia. Hypokalemia also accentuates the toxicity of cardiac glycosides.

Moderate hyperkalemia, in contrast, increases membrane permeability to potassium, which increases the speed of repolarization and decreases APD, reducing the tendency to arrhythmias. An increased potassium concentration also affects pacemaker activity. The increased potassium permeability caused by hyperkalemia decreases the rate of spontaneous diastolic depolarization, which slows heart rate and, in the extreme case, can produce asystole. The repolarization abnormalities of hyperkalemia lead to the characteristic ECG findings of T-wave peaking, prolonged PR interval, decreased QRS amplitude, and a widened QRS complex.[749] AV and intraventricular conduction abnormalities result from the slowed conduction and uneven repolarization.

Treatment of hyperkalemia is based on its magnitude and on the clinical presentation. For life-threatening, hyperkalemia-induced arrhythmias, the principle is rapid reduction of extracellular potassium concentration, a treatment that does not acutely decrease total body potassium content. Calcium chloride (10 to 20 mg/kg given by intravenous infusion) directly antagonizes the effects of potassium on the cardiac cell membranes. Sodium bicarbonate in dose of 1 to 2 mEq/kg or a dose calculated from acid-base measurements to produce moderate alkalinity (pH ≈ 7.45 to 7.50) will shift potassium intracellularly. A change in pH of 0.1 unit produces a 0.5- to 1.5-mEq/L change of potassium concentration in the opposite direction. An intravenous infusion of glucose and insulin has a similar effect; glucose at a dose of 0.5 to 2.0 g/kg with insulin in the ratio of 1 unit to 4 g of glucose is appropriate. Sequential measurement of serum potassium levels is important with this treatment because marked hypokalemia can result. Loop diuretics and potassium-binding resins promote excretion of potassium, although the effects are less rapid than with the previously mentioned modalities.

With chronic potassium deficiency, the plasma level poorly reflects the total body deficit. Because only 2% of total body potassium is in plasma and total body potassium stores may be 2000 to 3000 mEq, a 25% decline in serum potassium from 4 to 3 mEq/L indicates an equilibrium total body deficiency of 500 to 800 mEq, replacement of which should be undertaken slowly.

Acute hypokalemia frequently occurs after CPB as a result of hemodilution, urinary losses, and intracellular shifts,[750] with the latter perhaps relating to abnormalities of the glucose-insulin system seen with nonpulsatile hypothermic CPB.[751] With frequent assessment of serum potassium concentrations and continuous ECG monitoring, potassium infusion at rates of up to 10 to 15 mEq/h may be administered to treat serious hypokalemia.

Magnesium

Magnesium deficiency is a relatively common electrolyte abnormality in critically ill patients, especially in chronic situations. Hypomagnesemia is associated with a variety of cardiovascular disturbances, including arrhythmias.[752,753] Sudden death from CAD, alcoholic cardiomyopathy, and CHF may involve magnesium deficiency.[752–754]

Functionally, magnesium is required for the membrane-bound Na^+/K^+-ATPase, which is the principal enzyme that maintains normal intracellular potassium concentration. Not surprisingly, the ECG findings seen with magnesium deficiency mimic those seen with hypokalemia: prolonged PR and QT intervals, increased QRS duration, and ST-segment abnormalities. As with hypokalemia, magnesium deficiency predisposes to the development of the arrhythmias produced by cardiac glycosides.[755,756] Magnesium is effective as an adjuvant in the treatment of patients with a prolonged QT syndrome and torsades de pointes.[757]

Arrhythmias induced by magnesium deficiency may be refractory to treatment with antiarrhythmic drugs and electrical cardioversion or defibrillation. Adjunctive treatment of refractory arrhythmias with magnesium has been advocated even when magnesium deficiency has not been documented.[758] Magnesium deficiency is common in cardiac surgery patients because of the diuretic agents these patients are often receiving and because magnesium levels decrease with CPB because of hemodilution of the pump. Magnesium lacks a counterregulatory hormone to increase magnesium levels during CPB, in contrast to the hypocalcemia that is corrected by parathyroid hormone. The results of magnesium administration trials involving CABG have been conflicting. Some studies have shown a benefit, and others have not in regard to reducing the incidence of postoperative arrhythmias.

Magnesium has been studied alone and in combination with other drugs in the prophylaxis and treatment of perioperative arrhythmias. In younger patients with good LV function, magnesium reduced the incidence of AF after CABG surgery.[759] Magnesium supplementation after CPB in which the serum magnesium level returned to normal reduced the incidence of AF.[760] A protocol using magnesium as first-line therapy and amiodarone as backup therapy appears effective in management of arrhythmias after surgery, as well as in critically ill patients.[761,762] Combination therapy with magnesium and sotalol after CABG reduced the incidence of AF.[763] A metaanalysis of 15 RCTs showed magnesium to be effective at preventing AF in coronary artery surgery.[764] However, magnesium added to oral β-blocker prophylaxis did not reduce the incidence of atrial arrhythmias.[765]

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12 Electrocardiographic Monitoring

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KEY POINTS

1. The electrocardiogram reflects differences in transmembrane voltages in myocardial cells that occur during depolarization and repolarization within each cycle.
2. Processing of the electrocardiogram occurs in a series of steps.
3. Where and how electrocardiographic (ECG) electrodes are placed on the body are critical determinants of the morphology of the ECG signal.
4. ECG signals must be amplified and filtered before display.
5. How accurately the clinician places ECG leads on the patient's torso is probably the single most important factor influencing clinical utility of the electrocardiogram.
6. The ST segment is the most important portion of the QRS complex for evaluating ischemia.
7. Use of inferior leads (II, III, aVF) allows superior discrimination of P-wave morphology and facilitates visual diagnosis of arrhythmias and conduction disorders.
8. Electrolyte abnormalities typically cause changes in repolarization (ST-T-U waves).

As late as 1970, the electrocardiographic (ECG) monitor was not considered an integral part of monitoring strategies in the perioperative period. As a matter of fact, luminaries in the specialty regarded the use of ECG monitoring as "questionable value because of possible iatrogenic problems." Concern was also expressed that the anesthesiologist's attention would be diverted from the patient.[1] Currently, monitoring the electrocardiogram is a fundamental standard of monitoring of the American Society of Anesthesiologists.[2] Despite the introduction of more sophisticated cardiovascular monitors such as the pulmonary artery catheter and echocardiography, the electrocardiogram (coupled with blood pressure measurement) serves as the foundation for guiding cardiovascular therapeutic interventions in the majority of anesthetic cases.[3] It is indispensable for diagnosing arrhythmias, acute coronary syndromes, and electrolyte abnormalities (particularly of serum potassium and calcium) and in the detection of some forms of genetically mediated electrical or structural cardiac abnormalities (eg, Brugada syndrome) (Box 12.1).[4]

One of the most important changes in electrocardiography is the widespread use of computerized systems for recording electrocardiograms. Bedside units are capable of recording diagnostic-quality 12-lead electrocardiograms that can be transmitted over a hospital network for storage and retrieval. Most of the electrocardiograms in the United States are recorded by digital, automated devices, equipped with software, that can measure ECG intervals and amplitudes and can provide virtually instantaneous interpretation. However, various automated systems may have different technical specifications that can result in significant differences in the measurement of amplitudes, intervals, and diagnostic statements.[5,6] The diagnostic specificity and sensitivity of the electrocardiogram to diagnose a particular abnormality are also not consistent. For example, finite limits are defined by the relationship between sensitivity and specificity (usually inversely related) for detecting obstructive coronary artery disease (CAD). During exercise testing, the 12-lead electrocardiogram has a mean sensitivity of only 68% and a specificity of 77%.[7,8] The resting 12-lead electrocardiogram is even less sensitive and specific.[8] In this chapter, the theory and the operating characteristics of ECG hardware used in the perioperative period are presented to facilitate proper use and interpretation of monitoring data. Sources of artifacts, changes associated with respirations, electrolyte disturbances, and medications are also discussed.

Historical Perspective

An extensive review of the history of electrocardiography is beyond the scope of this chapter. However, several excellent reviews were published in honor of the centennial of the first recording of the human electrocardiogram.[9–14] Willem Einthoven is universally considered the father of electrocardiography (for which he won the 1924 Nobel Prize for Medicine/Physiology). Many of the basic clinical abnormalities in electrocardiography were first described using the string galvanometer (eg, bundle branch block, delta waves, ST-T wave changes with angina). It was used until the 1930s, when it was replaced by a system using vacuum tube amplifiers and a cathode ray oscilloscope. With advances in electrical engineering technology, the devices became more compact, portable, and user friendly. In 1950s, a portable direct writing ECG cart was introduced. The first analog-to-digital (A/D) conversion systems for the electrocardiogram were introduced in the early 1960s, although their off-line use was impractical and restricted until the late 1970s. In the 1980s, microcomputer technology became widely available and is now standard for all diagnostic and monitoring systems. Further improvement in hardware and software design led to the development of automated ST-analysis algorithms and their use in routine clinical practice.

Basic Electrophysiology and Electrical Anatomy of the Heart

The electrocardiogram is the final result of a complex series of physiologic and technologic processes.[15] Physiologically, the electrocardiogram reflects differences in transmembrane voltages in myocardial cells that occur during depolarization and repolarization within each cycle. Ionic currents are generated as a result of ionic fluxes across cell membranes in myocardial cells during depolarization and repolarization. The cardiac cells are contiguous and electrically connected by ion channels (gap junctions), which allow the ion current to pass through the cells and spread depolarization.[16] Thus the membrane potential changes in the heart can be considered a single depolarization that propagates through the whole heart and assumes different forms along the way.[16] The pattern and sequence of depolarization that occur in the heart are depicted in Fig. 12.1. Many different types and subtypes of ion channels are involved in the synchronized generation of electrical

BOX 12.1 BASIC CLINICAL INFORMATION AVAILABLE FROM ELECTROCARDIOGRAPHY

Anatomy or Morphology
- Infection
- Ischemia
- Hypertrophy

Physiology
- Automaticity
- Arrhythmogenicity
- Conduction
- Ischemia
- Autonomic tone
- Electrolyte abnormalities
- Drug toxicity or effect

activity in the heart. Of note are the sodium, potassium, calcium, and chloride channels.[15–17] Detailed discussion of these channels is beyond the scope of this chapter.

At any point in time, the electrical activity of the heart is composed of differently directed electrical forces. However, these currents are synchronized by cardiac activation and recovery sequences to generate a cardiac electrical field in and around the heart that varies with time during the cardiac cycle. This cardiac electrical field passes through various internal structures such as lungs, blood, and skeletal muscles. The currents also reach the skin and are detected by the electrodes that are placed in specific locations on the body. The electrodes are uniquely configured to produce different ECG patterns or waveforms. The direction and strength of a lead vector depend on the geometry of the body and on the varying electric impedances of the tissues in the torso.[18,19] As expected, placement of electrodes on the torso is distinct from direct placement on the heart because the localized signal strength that occurs with direct electrode contact is markedly attenuated and altered by torso inhomogeneities that include thoracic tissue boundaries and variations in impedance of different tissues. The standard 12-lead electrocardiogram records potential differences (represented as change of voltage over time) among prescribed sites on the body surface that vary during the cardiac cycle.[4]

The first deflection noted on the electrocardiogram is caused by atrial depolarization and is called the P wave. Although the depolarization of the sinoatrial node precedes the atrial depolarization (see Fig. 12.1), the potentials from these pacemaker cells are too small to be detected on surface electrocardiogram. The width of the P wave reflects the time taken for the wave of depolarization to spread over both the right and left atria. In comparison with the ventricular action potential, the atrial action potential is narrower and has a less prominent plateau. The duration of atrial contraction is thus shorter, and this permits another action potential to occur sooner and makes the atria prone to a very high rate (atrial flutter). The repolarization atrial wave is rarely seen in the normal electrocardiogram because it is buried in the much larger QRS wave.

The electrocardiogram returns to its baseline between the end of atrial depolarization and the commencement of the QRS complex, which is the start of the QRS ventricular depolarization. This interval is called the PR interval. Although this period may seem electrically silent, it is a time of significant electrical activity. During this period the wave of depolarization that started in the sinoatrial node is propagated through the atrioventricular (AV) node, AV bundle, right and left bundle branches, and Purkinje fibers (see Fig. 12.1).

The QRS complex is generated by potential differences that originate from the rapid depolarization of the ventricular myocardium (phase 0). The duration of the QRS complex (ventricular depolarization) is very similar to that of the P wave (atrial depolarization). However, the amplitude of the QRS complex is significantly greater than that of the P wave because the ventricular mass is much larger than that of atria. The duration of the QRS complex can be increased

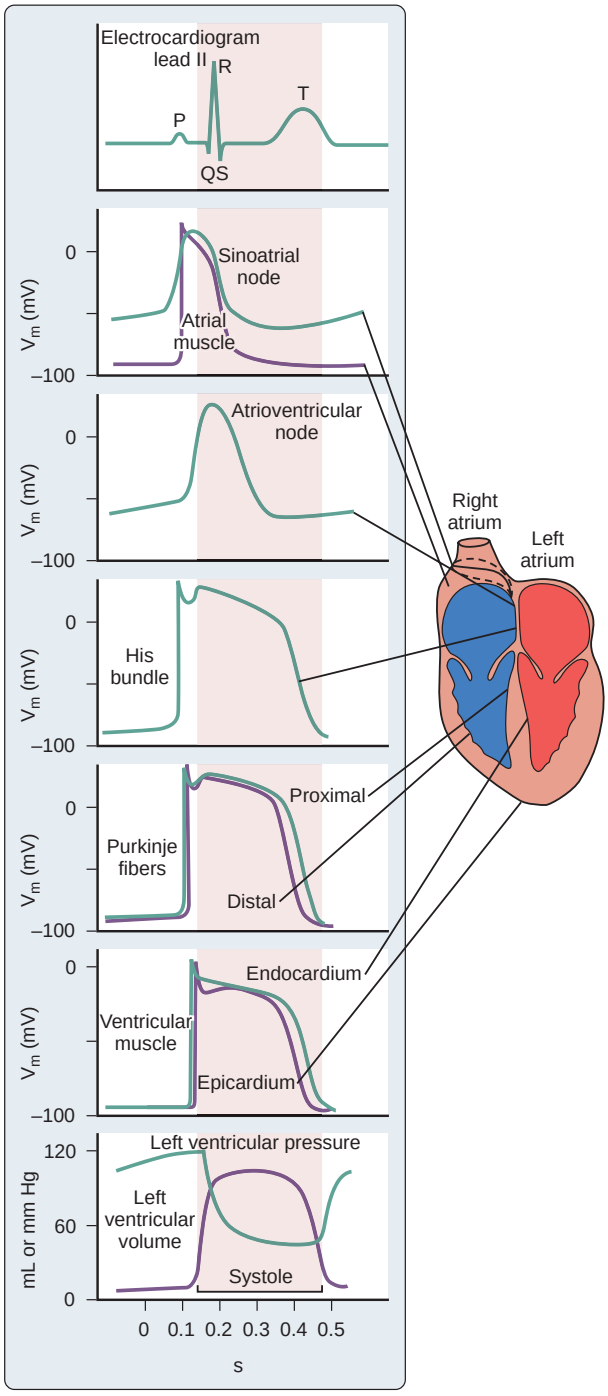

Fig. 12.1 The action potential of an automatic cell such as the sinoatrial node differs from that of the ventricular muscle cell in that the cell slowly depolarizes spontaneously during phase 4. The inward current If is responsible for diastolic depolarization. The action potential in a Purkinje cell has the fastest rate of depolarization, 400 to 800 V/s. When the cell is stimulated, an action potential results from a rapid influx of sodium ions (inward current) into the cell (phase 0). Phase 1 includes a notch caused by the "early outward current," Ito, which is a transient potassium (K) efflux, probably activated by an intracellular calcium increase. Phase 2 is the plateau of the action potential resulting principally from calcium entry (inward currents I_{CaL} and I_{CaT}) through the slow channel of the cell membrane. During phase 3, repolarization of the cell occurs (outward current IK1), whereas during phase 4, the sodium entering during phase 0 is actively pumped out of the cell. In a ventricular muscle cell, unlike in the automatic cells, no spontaneous phase 4 depolarization occurs. *(From Lynch C, Lake CL. Cardiovascular anatomy and physiology. In: Youngberg J, Lake C, Roizen M, et al, eds.* Cardiac, Vascular, and Thoracic Anesthesia. *Philadelphia: Churchill Livingstone; 2000:87.)*

when conduction through one of the bundle branches is blocked or a ventricle is depolarized by an ectopic focus that depolarizes one of the ventricles sooner than the other.

The QRS wave is followed by a period when the electrocardiogram returns to the baseline that is called the ST segment. It is a time when the ventricle is completely depolarized and is represented by phase 2 of the action potential (see Fig. 12.1). Even though the ventricles are depolarized, the electrocardiogram does not record any positive or negative waveforms because the whole ventricles are depolarized and no potential difference exists among sites. The electrocardiogram does not measure absolute level of membrane potential but records only the potential differences.[15] The same explanation also holds true for the T-P segment, which represents a time when the ventricles are fully repolarized; hence no significant potential difference is recorded on a surface electrocardiogram.

A T wave is generated by repolarization of the ventricles. Repolarization proceeds slowly and is not caused by a propagated wave; the T wave therefore is broad and of longer duration. The T wave is also a positive wave, although it represents repolarization. This is because the repolarization current is in the opposite direction from depolarization, moving from the epicardium to the endocardium. It is influenced by many local factors such as electrochemical potentials, temperature, adrenergic state, myocardial blood supply, myocardial hypertrophy, and scarring.[20]

The time between the onset of the QRS complex and the end of the T wave is called the QT interval and gives a useful measure of ventricular action potential duration. The duration of QT interval varies with heart rate and must be adjusted to improve detection of repolarization abnormalities. This "corrected" QT interval or QTc is usually less than 400 ms, and patients with a QTc interval greater than 450 ms are at risk for ventricular tachyarrhythmias.[21] Measurement of this interval can be used to evaluate for certain diseases or effects of certain medications on ventricular repolarization. QT-interval prolongation is very important clinically because delayed repolarization is a substrate for arrhythmias and sudden death.

Sometimes a small (0.5-mm) positive deflection can be seen after the T wave but before the next P wave. This is called a U wave. The source of the U wave is unknown. Three common theories regarding its origin are (1) delayed repolarization of Purkinje fibers, (2) prolonged repolarization of midmyocardial "M-cells" (specialized midmyocardial cells with prolonged action potentials), and (3) afterpotentials resulting from mechanical forces in the ventricular wall.[15]

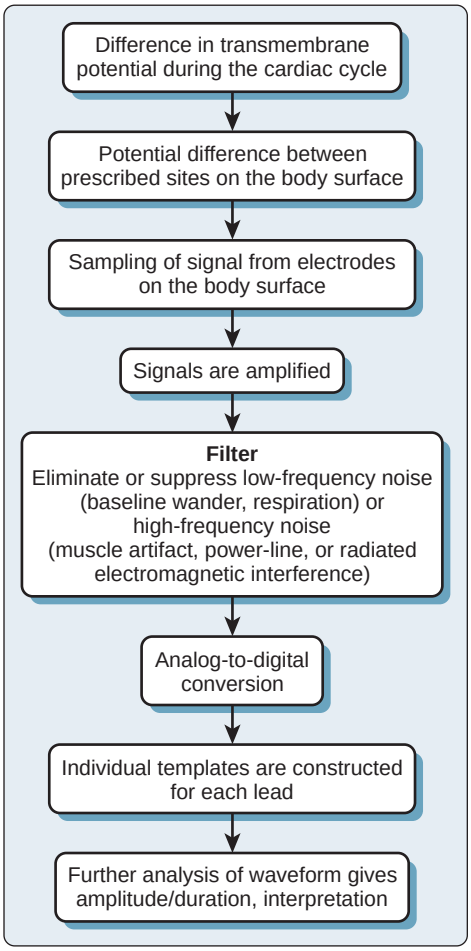

Fig. 12.2 Schematic representation of the processes resulting in recording of the electrocardiogram.

Technical Aspects of the Electrocardiogram

Most clinicians assume that the electrocardiogram is a relatively simple technical device. However, an extensive amount of advanced electrical theory underlies both the recording and display of the ECG signal. Digital signal processing (DSP) is now universally used, and the average ECG unit incorporates several microprocessors. Anesthesiologists should familiarize themselves with the theory behind ECG acquisition, to maximize rational clinical application and appreciate its clinical limitations. In this section, the basics of electrocardiography are presented, with brief consideration of the major components involved in the faithful rendition of the surface electrocardiogram, working from the skin and electrodes progressively to the final output on the screen. The reader is referred to technical reviews for more detail.[4,5,12,22–25]

Processing of the electrocardiogram occurs in a series of steps as shown in Fig. 12.2.[4] These steps include the following[4]:

1. Signal acquisition, including filtering
2. Data transformation, or rendition of data for further processing, including finding the complexes, classifying the complexes into "dominant" and "nondominant" (ectopic) types, and forming an average or median complex for each lead
3. Waveform recognition, which is the process for identification of the onset and offset of the diagnostic waves
4. Feature extraction, which is the measurement of intervals and amplitudes and is used for bedside 12-lead ECG machines
5. Diagnostic classification

Diagnostic classification may be heuristic (ie, deterministic, or based on experience-based rules) or statistical in approach.[26]

Signal Acquisition and Power Spectrum of the Electrocardiogram

To appreciate ECG signal acquisition it is relevant to consider an ECG signal in terms of its amplitude (or voltage) and its frequency components (generally called its phase). Voltage considerations differ depending on the signal source. Surface recording involves amplification of smaller voltages (on the order of 1 mV) at the recording sites closer to the heart beneath the electrically resistant layers of the skin (eg, endocardial, esophageal, and intratracheal leads). The "power spectrum" of the electrocardiogram (Fig. 12.3) is derived by Fourier transformation, in which a periodic waveform is mathematically decomposed to its harmonic components (sine waves of various amplitudes and frequencies).

The fundamental frequency for the QRS complex at the body surface is approximately 10 Hz, and most of the diagnostic information is contained at frequencies lower than 100 Hz in adults. Spectra representing some of the major sources of artifact must be eliminated during the processing and amplification of the QRS complex.[24] The frequency of each of these components can be equated to the slope of the component signal.[6] The R wave with its steep slope is a high-frequency component (100 Hz), whereas P and T waves have lesser slopes and are lower in frequency (1–2 Hz). The ST segment has the lowest frequency, not much different from the "underlying" electrical (ie, isoelectric) baseline of the electrocardiogram. Before the introduction of DSP, accurately displaying the ST segment presented significant

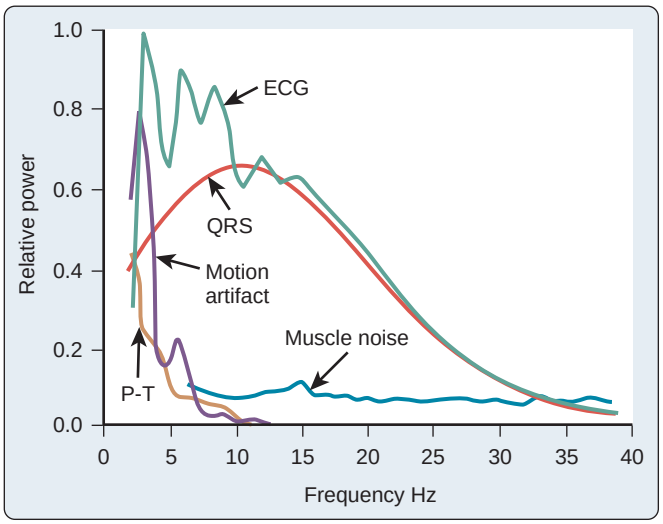

Fig. 12.3 The typical power spectrum of the electrocardiogram signal (obtained during ambulatory monitoring), including its subcomponents and common artifacts (ie, motion and muscle noise). The power of the P and T waves *(P-T)* is low frequency, and the QRS complex is concentrated in the midfrequency range, although residual power extends up to 100 Hz. *(From Thakor NV. From Holter monitors to automatic defibrillators: developments in ambulatory arrhythmia monitoring.* IEEE Trans Biomed Eng. *1984;31:770.)*

TABLE 12.1 Range of Signal Frequencies Included in Different Phases of Processing in an Electrocardiographic Monitor

Processing	*Frequency Range*
Display	0.5 (or 0.05)–40 Hz
QRS detection	5–30 Hz
Arrhythmia detection	0.05–60 Hz
ST-segment monitoring	0.05–60 Hz
Pacemaker detection	1.5–5 kHz

technical problems, particularly in the operating room and for ECG monitoring units in critical care units.

Although the overall frequency spectrum of the QRS complex does not appear to exceed 40 Hz, many components of the QRS complex, particularly the R wave, can exceed 100 Hz. The American Heart Association (AHA) recommended a bandwidth of 0.05 to 100 Hz for monitoring and detection of myocardial ischemia.[4] Very-high-frequency signals of particular clinical significance are pacemaker spikes. Their short duration and high amplitude present technical challenges for proper recognition and rejection to allow accurate determination of the heart rate. The frequencies of greatest importance for optimal ECG processing are presented in Table 12.1.[5]

Digital Signal Processing of the Electrocardiogram

Processing of the ECG signal by a digital electrocardiograph involves initial sampling of the signal from electrodes on the body surface. Nearly all current-generation ECG machines convert the analog ECG signal to digital form before further processing. The foundation of DSP is the A/D converter, which samples the incoming "continuous" analog signal (characterized by variable amplitude or voltage over time) at a very rapid rate, thus converting the sampled voltage into binary numbers, each of which has a precise time index or sequence. Higher sampling rates (10,000–15,000/s or higher) help detect pacemaker output reliably, which is typically less than 0.5 ms in duration. Several technical recommendations regarding low-frequency filtering and high-frequency filtering were published by the AHA.[4]

Computerized ECG processing has been adapted to all major clinical applications of the electrocardiogram. The earliest application of A/D signal processing occurred during exercise tolerance testing, in which significant motion artifact and electromyographic noise made acquisition of a "clean" ECG signal difficult. Outside the exercise treadmill laboratory, computer processing allows automated analysis of the diagnostic 12-lead electrocardiogram.[27] The reader is referred elsewhere for more detailed discussions of this technology, and to the reports of the scientific council of the AHA on standardization and specifications for automated electrocardiography and bedside monitors.[4,27–30]

Formation of a Representative Single-Lead Complex

After A/D conversion, the resultant data bits are inspected by a microprocessor using a form of mathematical construct to determine where reference points ("fiducial points") are located. A common method locates the point of most rapid change in amplitude (located on the down slope of the R wave). This process characterizes the baseline QRS complex (QRS recognition) and provides a "template" on which subsequent beats are overlaid (beat alignment) and averaged (signal averaging). This not only allows visual display of the QRS complex and quantification of its components, but also eliminates random electrical noise and wide complex beats that fail to meet criteria established by the fiducial points.

QRS waveform amplitudes and durations are subject to beat-to-beat variability and to respiratory variability between beats. Digital electrocardiograms can adjust for respiratory variability and decrease beat-to-beat noise to improve the measurement precision in individual leads by forming a representative complex for each lead. Signal averaging is a critical component of this process. By using this technique, noise is reduced proportionally by the square root of the number of beats averaged.[4] Thus a 10-fold reduction in noise is accomplished by averaging only 100 beats. Automated measurements are made from these representative templates, not from measurement of individual complexes. Average complex templates are formed from the average amplitude of each digital sampling point for selected complexes. Median complex templates are formed from the median amplitude at each digital sampling point. As a result, measurement accuracy strongly depends on the fidelity with which representative templates are formed.

Because of the proprietary nature of this technology (the specific algorithms used are patented), the methods used vary by manufacturer. Consequently, the processed QRS complexes may vary in the "quality" of representation (ie, if noise or aberrant beats are averaged into the complex, they will vary from the raw analog complex). The averaging process involves comparison of the voltages at a particular time point between the incoming complex and the template. Although the easiest method is to use the mean difference between voltages to update the "template," the most accurate method is to use the median (because it is less affected by outliers, such as aberrant beats or other signals that have escaped QRS matching)[4] (Fig. 12.4).

A feature incorporated into most monitors is a visual trend line from which deviations in the position of the ST segment can be rapidly detected, a feature that can aid online detection of ischemia. In addition, nearly all monitors display on-screen numeric values for the position of the ST segment used for ischemia detection (generally 60–80 ms after the J point), although the specific fiducial point used (based on heart rate), can be adjusted by the clinician (Fig. 12.5).

History and Description of the 12-Lead System

Where and how ECG electrodes are placed on the body are critical determinants of the morphology of the ECG signal. Lead systems have been developed based on theoretical considerations and references to anatomic landmarks that facilitate consistency among individual patients (eg, standard 12-lead system). Einthoven established electrocardiography using three extremities as references: the left arm (LA), right arm (RA), and left leg (LL). He recorded the difference in

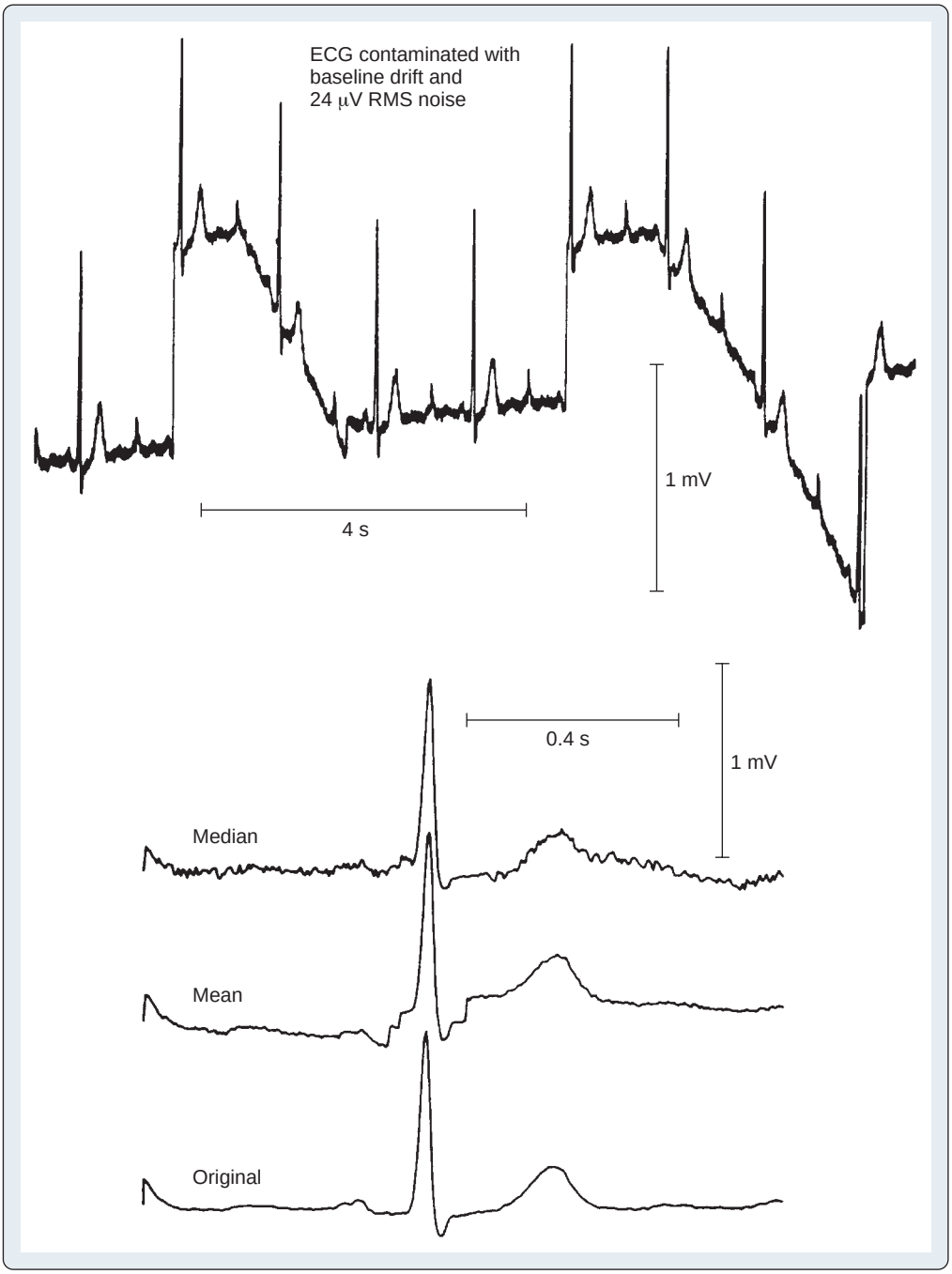

Fig. 12.4 Effects of averaging techniques on resolution of an electrocardiographic signal heavily contaminated with baseline and electrical noise. Despite a greater degree of baseline and electrical noise, median averaging results in a more accurate rendition of the original signal. Notice the abnormal J-point elevation in the mean averaged complex. *RMS,* Root mean square. *(From Froelicher VF. Special methods: computerized exercise ECG analysis. In:* Exercise and the Heart. *Chicago: Year Book; 1987:36.)*

potential between the LA and RA (lead I), between the RA and LL (lead II), and between the LA and LL (lead III) (Fig. 12.6). Because the signals recorded were differences between two electrodes, these leads were called bipolar. The RL served only as a reference electrode. Because the Kirchhoff loop equation states that the sum of the three voltage differential pairs must equal zero, the sum of leads I and III must equal lead II.[23]

The positive or negative polarity of each of the limbs was chosen by Einthoven to result in positive deflections of most of the waveforms and has no innate physiologic significance. He postulated that the three limbs defined an imaginary equilateral triangle with the heart at its center. Wilson refined and introduced the precordial leads into clinical practice. To implement these leads, he postulated a mechanism whereby the absolute level of electrical potential could be measured at the site of the exploring precordial electrode (the positive electrode). A negative pole with zero potential was formed by joining the three limb electrodes in a resistive network in which equally weighted signals cancel each other out. He called this the central terminal, and

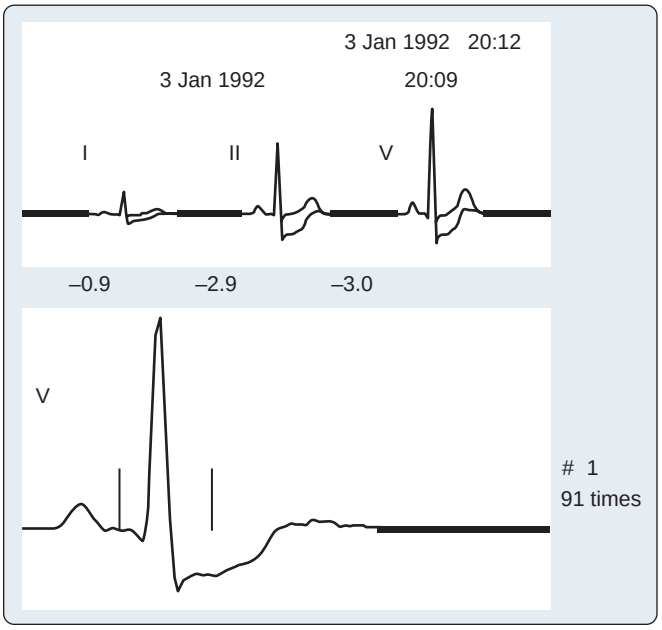

Fig. 12.5 The graphic output of the ST-segment adjustment window from a Marquette Electronics Series 7010 monitor (Milwaukee, WI) ST-segment analyzer. This software allows trending and display of three leads (ie, I, II, and any single V lead). In this window, the initial complex ("learned" when the program was activated) is displayed along with the current complex. Two complexes are superimposed with different intensities to facilitate comparison. ST-segment analysis is performed automatically at 80 ms after the J point, although the user can manually adjust this. The number of QRS complexes that are input to the monitor is displayed. *(From Reich DL, Mittnacht A, London M, Kaplan J. Monitoring of the heart and vascular system. In: Kaplan JA, Konstadt SN, Reich DL, eds.* Kaplan's Cardiac Anesthesia. *5th ed. Philadelphia: Saunders; 2006.)*

in a fashion similar to Einthoven's vector concepts, he postulated that it was located at the electrical center of the heart, representing the mean electrical potential of the body throughout the cardiac cycle. He described three additional limb leads (aVL, aVR, and aVF) (Fig. 12.7). These leads measured new vectors of activation, and in this way the hexaxial reference system for determination of the electrical axis was established. He subsequently introduced the six unipolar precordial V leads in 1935 (see Fig. 12.6).[31]

Six electrodes are placed on the chest in the following locations: V_1, fourth intercostal space at the right sternal border; V_2, fourth intercostal space at the left sternal border; V_3, midway between V_2 and V_4; V_4, fifth intercostal space in the midclavicular line; V_5, in the horizontal plane of V_4 at the anterior axillary line, or, if the anterior axillary line is ambiguous, midway between V_4 and V_6; and V_6, in the horizontal plane of V_4 at the midaxillary line[4] (see Fig. 12.6).

Clinical application of the unipolar limb leads was limited because of their significantly smaller amplitude relative to the bipolar limb leads from which they were derived. They were not clinically applied until Goldberger augmented their amplitude (by a factor of 1.5) by severing the connection between the central terminal and the lead extremity being studied (which he called augmented limb leads) in 1942. The limb leads, the precordial leads, and the augmented unipolar limb leads form what was accepted by the AHA as the conventional 12-lead ECG system.[32] Einthoven's law indicates that any one of the standard limb leads can be mathematically derived from the other 2 limb leads. Therefore, the "standard" 12-lead electrocardiogram actually contains 8 independent pieces of information: 2 measured potential differences from which the 4 remaining limb leads can be calculated and the 6 independent precordial leads.[4] In essence all leads are effectively "bipolar," and the differentiation between "bipolar" and "unipolar" in the description of the standard limb leads, the augmented limb leads, and the precordial leads is discouraged in the most recent statement by the AHA.[4]

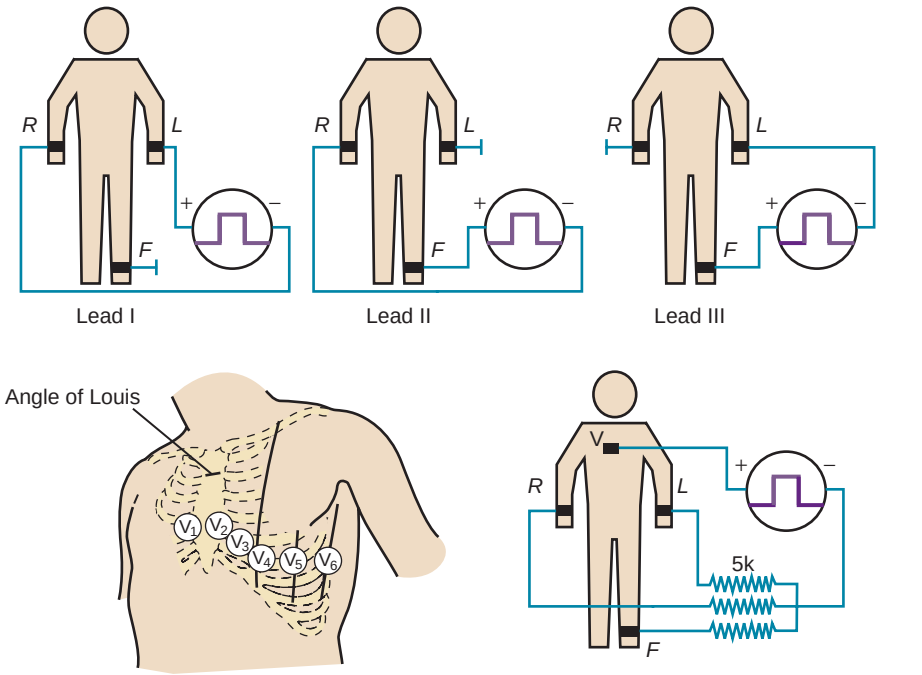

Fig. 12.6 *(Top)* Electrode connections for recording the three standard limb leads I, II, and III. *R, L,* and *F* indicate locations of electrodes on the right arm, the left arm, and the left foot, respectively. *(Bottom)* Electrode locations and electrical connections for recording a precordial lead. *(Left)* The positions of the exploring electrode (V) for the six precordial leads. *(Right)* Connections to form the Wilson central terminal for recording a precordial (V) lead. *(From Mirvis DM, Goldberger AL. Electrocardiography. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *8th ed. Philadelphia: Saunders; 2008:153.)*

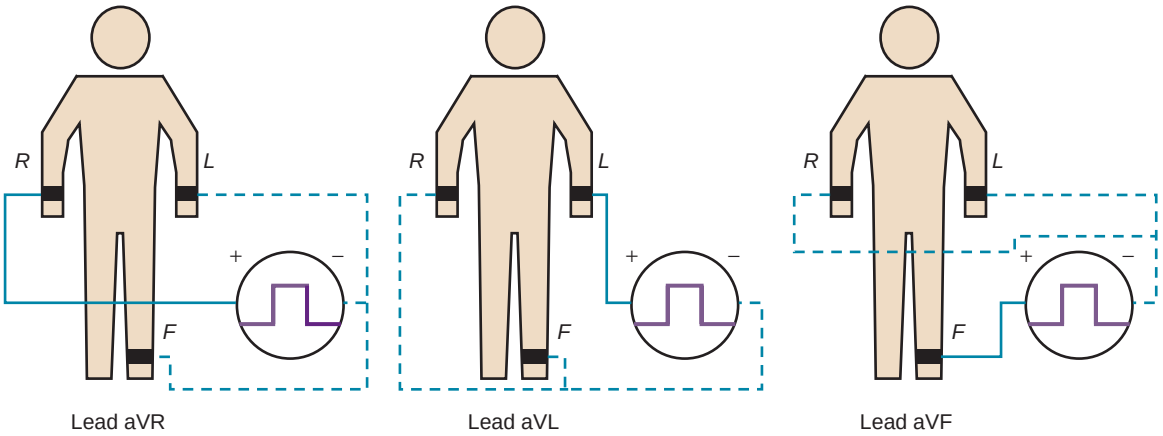

Fig. 12.7 Electrode locations and electrical connections for recording the three augmented limb leads aVR, aVL, and aVF. *R, L,* and *F* indicate locations of electrodes on the right arm, the left arm, and the left foot, respectively. Dashed lines indicate connections to generate the reference electrode potential. *(From Mirvis DM, Goldberger AL. Electrocardiography. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *8th ed. Philadelphia: Saunders; 2008:153.)*

Technical Aspects of Electrode Placement

Monitoring electrodes should preferentially be placed directly over bony prominences of the torso (eg, clavicular heads, iliac prominences) to minimize excursion of the electrode during respiration that could cause baseline wander. Electrode impedance must be optimized to avoid loss and alteration of the signal. By removing a portion of the stratum corneum (eg, gentle abrasion with a dry gauze pad that results in a minor amount of surface erythema works well), skin impedance can be reduced by a factor of 10 to 100. Optimal impedance is 5000 ohms or less. The electrode may be covered with a watertight dressing to prevent surgical scrub solutions from undermining electrode contact.

Intrinsic and Extrinsic Electrocardiographic Artifact

Intrinsic Sources

Skin Impedance

Motion artifact and "baseline wander" have several causes. Intrinsic to the body are electrical potentials generated by the skin.[33] Skin impedance has been shown to vary at different skin sites.

Electrodes

Direct current potentials are actually stored by the electrode itself (ie, offset potentials), and they vary with the type of electrode used. A striking example of an offset potential is the transient obliteration of the electrocardiogram that occurs immediately after electrical defibrillation. Poor electrode contact enhances pickup of alternating current power-line interference (60-Hz signals).

Motor Activity

Another major physiologic source of artifact is electromyographic noise produced by motor activity, either voluntary (ie, during treadmill testing or ambulatory ST-segment monitoring) or involuntary (ie, shivering or parkinsonian tremor). Electromyographic noise is similar in amplitude to the electrocardiogram, but it is generally of considerably higher frequency. Because it is a random signal, in contrast to the regular repetitive electrocardiogram, electromyographic noise is amenable to significant attenuation using routine DSP techniques (Fig. 12.8).[34]

Extrinsic Sources

Artifact also has extrinsic or nonphysiologic causes. An important cause is called common-mode rejection. The ECG signal is recorded as the difference in potential between two electrodes and is technically a differential signal. The body is not at absolute ground potential; this is why the right leg lead is used as a reference electrode.[24] This higher potential (over that of an absolute ground to earth) is called common-mode potential because it is common to both electrode inputs to the differential amplifier used to amplify the ECG signal. Common-mode potential must be rejected or it may alter the ECG signal.

Electrical Power-Line Interference

Electrical power-line interference (60 Hz) is a common environmental problem. Power lines and other electrical devices radiate energy that can enter the monitor by poor electrode contact or cracked or poorly shielded lead cables. Interference can also be induced electromagnetically as these signals radiate through the loop formed by the body, lead cables, and monitor.[33] This type of interference can be reduced by twisting the lead cables together (reducing the loop area) or by minimizing the distance between the lead cables. In current diagnostic ECG machines, A/D signal conversion occurs in an acquisition module close to the patient that effectively reduces the length of the lead cables and the amount of signal induction possible. A line frequency "notch" filter is often used to remove 60-Hz noise. Other means of mathematical manipulation and processing can also remove 60-Hz noise.[35]

Electrocautery

Electrocautery units generate radiofrequency currents at very high frequencies (800–2000 kHz) and high voltages (1 kV, which is 100 times greater than the ECG signal). Older units used a modulation frequency of 60 Hz, which spread substantial electrical noise into the QRS frequency range of the ECG signal. Newer units use a modulation frequency of 20 kHz, thus minimizing this problem[5]; however, case reports still exist of electrocautery as a cause of artifactual ST-segment changes in intraoperative electrocardiograms.[36,37] To minimize electrocautery artifact, the right leg reference electrode should be placed as close as possible to the return plate, and the ECG monitor should be plugged into a different power outlet from the electrosurgical unit.

Clinical Sources of Artifact

Clinical devices in physical contact with the patient, particularly through plastic tubing, may at times cause clinically significant ECG artifact.[38–41] Although the exact mechanism is uncertain, two leading explanations are either a piezoelectric effect secondary to mechanical deformation of the plastic or buildup of static electricity between two dissimilar materials, especially those materials in motion (as in the

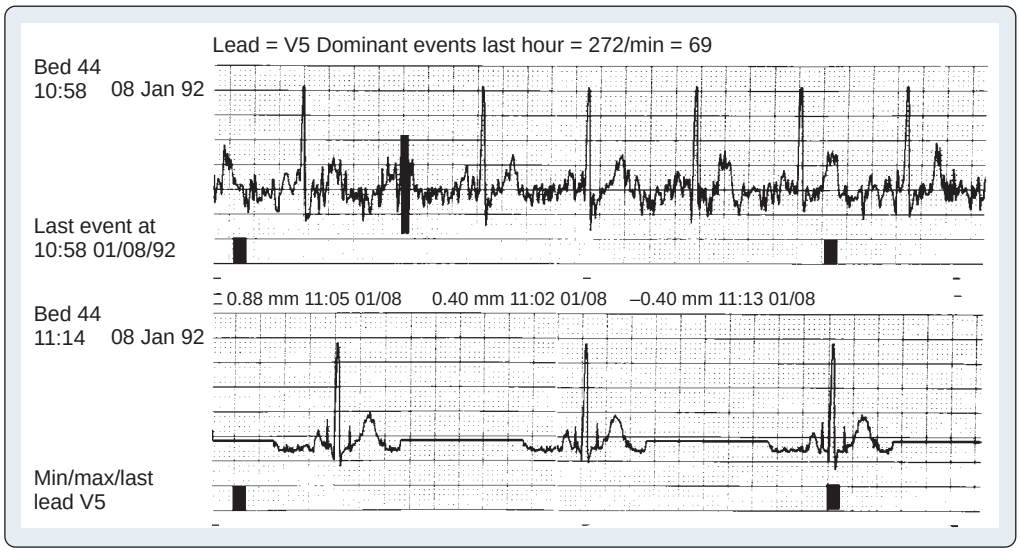

Fig. 12.8 Reduction of muscle artifact (simulated) by digital signal processing using signal averaging (PC2 Bedside Monitor, Spacelabs, Redmond, Wash). *(Top)* The initial learned complex (ie, dominant) on the left is followed by real-time complexes. *(Bottom)* Median complexes are smoothed by signal processing. Notice that the ST-segment position is isoelectric in the normal complex, but it does vary in accuracy with this degree of noise. The degree of noise reduction is proportional to the square root of the number of beats averaged. *(From Reich DL, Mittnacht A, London M, Kaplan J. Monitoring of the heart and vascular system. In: Kaplan JA, Konstadt SN, Reich DL, eds.* Kaplan's Cardiac Anesthesia. *5th ed. Philadelphia: Saunders; 2006.)*

case of cardiopulmonary bypass [CPB] tubing and the roller pump head described later). In this situation, the electricity generated in the pump flows into the patient through the tubing and is picked up by the electrodes. This artifact is not related to the electricity used to power the CPB pump because it has been reproduced by manually turning the pump heads.

Although ECG interference during CPB has been recognized for many years, Khambatta and colleagues[40] were the first to document it in the literature. It is manifested by marked irregularity of the baseline, similar to ventricular fibrillation, with a frequency of 1 to 4 Hz and a peak amplitude up to 5 mV. Uncorrected, it may make effective diagnosis of arrhythmias and conduction disturbances very difficult (Fig. 12.9), especially during the critical period of weaning from CPB, and it may also make accurate determination of asystolic arrest from the cardioplegia difficult. This artifact is more common in the winter than in the summer (56% vs 13% of patients), with low relative humidity (45–48% or less), and with room temperature lower than 18 to 20°C. Accumulation of static electricity is assumed to be the major etiologic factor, and Khambatta and colleagues recommended maintaining ambient temperature higher than 20°C. The current standard for operating room temperature is 20 to 24°C, in accordance with the American Society for Healthcare Engineering of the American Hospital Association.

ECG artifact often mimics arrhythmias, primarily atrial, because the baseline artifact may resemble flutter waves or atrial fibrillation. Kleinman and colleagues[41] (see the earlier discussion of pump artifact) reported the commonly observed "atrial flutter" artifact (see Fig. 12.9). Baseline artifact simulating flutter waves at 300/min occurred on an operating room monitor. The waves were observed to precisely track the pump head speed and to disappear when the pump was turned off. The artifact appears to have been caused by poor ECG electrode contact because these investigators the authors were able to produce it by undermining an ECG electrode with liquids. They pointed out that poor application of only one electrode could markedly impair the common-mode rejection capabilities of the ECG differential amplifier. This type of artifact has also been reported during noncardiac surgical procedures.[38] Other clinical devices associated with ECG interference, albeit rarely, include infusion pumps and blood warmers. Isolated

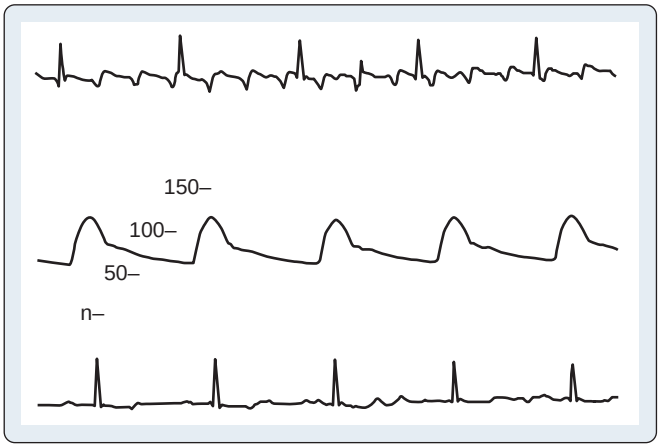

Fig. 12.9 *(Top)* Baseline artifact simulates atrial flutter in a cannulated patient. *(Middle)* This patient had stable arterial pressure just before institution of full cardiopulmonary bypass, similar to that described by Kleinman and associates.[41] *(Bottom)* The "pseudo-flutter waves" are corrected by application of the grounding cable. *(From London MJ, Kaplan JA. Advances in electrocardiographic monitoring. In: Kaplan JA, Reich DL, Konstadt SN, eds.* Cardiac Anesthesia. *4th ed. Philadelphia: Saunders; 1999.)*

power supply line isolation monitors have also been associated with 60-Hz interference. This can be diagnosed by removing the line isolation monitor fuses to see whether the artifact disappears.[42]

Frequency Response of Electrocardiographic Monitors: Monitoring and Diagnostic Modes

ECG signals must be amplified and filtered before display. To reproduce the component frequencies accurately, each must be amplified equally. The monitor must have a "flat amplitude response" over the wide range of frequencies present. Similarly, because the slight delay in a signal as it passes through a filter or amplifier may vary in duration with different

frequencies, all frequencies must be delayed equally. This is termed *linear phase response.* If the response is nonlinear, various components may appear temporally distorted *(phase shift)*. Given the importance of the electrocardiogram in diagnosing myocardial ischemia, it is important to realize that "significant" ST-segment depression or elevation can occur solely as a result of improper signal filtering in 12-lead ECG machines and bedside or ambulatory ST-segment monitors.[43–47] This artifact was a particular problem before the introduction of DSP. The AHA Committee on Electrocardiography Standardization addressed specific frequency requirements for monitoring in this setting.[6,28]

Nonlinear frequency response in the low-frequency range (0.5 Hz) can cause artifactual ST-segment depression, whereas phase delay in this range can cause ST-segment elevation.[6] The AHA recommended a bandwidth of 0.05 to 100 Hz (at 3 dB).[32] Although a completely linear response is desirable, with analog filters it is not generally possible. Because greater baseline noise is present when a 0.05-Hz cutoff is used, the 0.5Hz cutoff is often used to display a more stable signal. This is commonly referred to as the monitoring mode, and use of a 0.05-Hz low-frequency cutoff is known as the diagnostic mode.[48] The difference in ST-segment morphology at various low-frequency cutoffs is illustrated in Fig. 12.10. Because current monitors use signal averaging techniques that effectively eliminate most artifact even in the diagnostic mode, the clinician can usually (and should) avoid using the monitoring mode.

High-frequency response is less important clinically because the ST segment and T wave reside in the low-frequency spectrum. However, at the commonly used high-frequency cutoff of 40 Hz, the amplitude of the R and S waves may diminish significantly, thus making it difficult to diagnose ventricular hypertrophy.[44,49] Significant reduction in QRS amplitude may occur in the following circumstances: major decreases in left ventricular function, obesity, pericardial and pleural effusions, anasarca, and infiltrative or restrictive cardiac diseases.[50,51] Low QRS voltage is defined as peak-to-trough QRS amplitude of less than 5 mm in six limb leads and 10 mm or less in the precordial leads. Significant decrease in QRS voltage is more likely to be seen in the presence of a large pericardial effusion or fibrotic pericardial thickening. *Total electrical alternans* refers to the alternating high and low voltages of all ECG waveforms (P-QRS-T) between cardiac cycles within a given lead and is thought to result from swinging motion of the heart in a pericardial effusion at a frequency that is exactly one-half the heart rate. Total electrical alternans in addition to low voltage and widespread ST-segment elevation is pathognomic of significant pericardial effusion with cardiac tamponade.

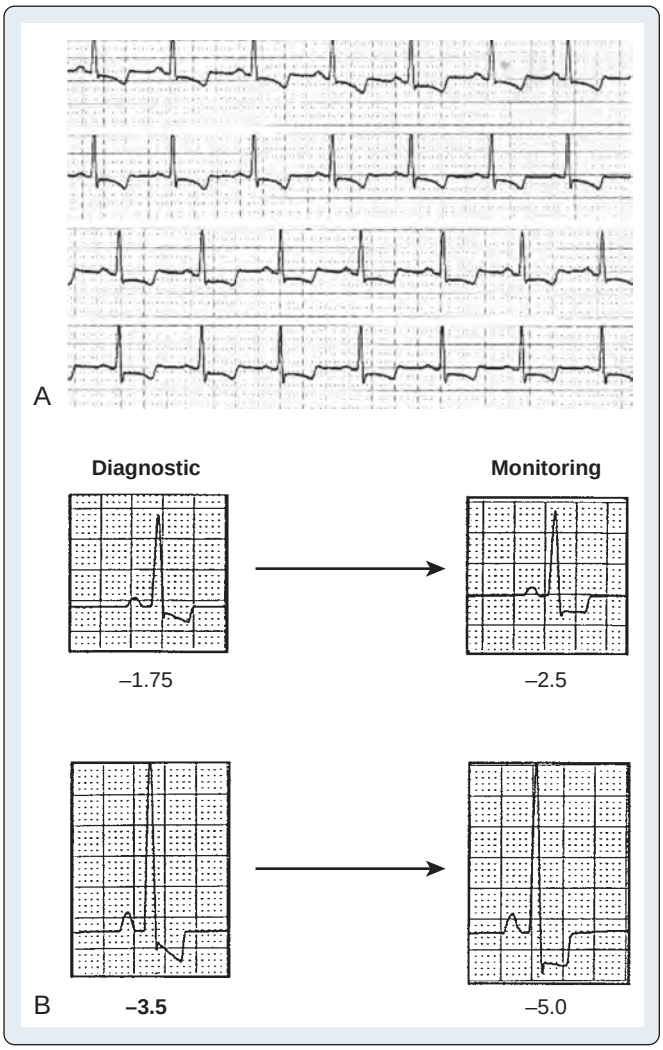

Fig. 12.10 (A) Monitoring versus diagnostic mode in *(top trace)* leads II and *(bottom trace)* V_5 in a patient undergoing coronary artery bypass grafting. Notice the straightening of the baseline with use of the monitoring mode, which is most notable in lead II. The degree of the PR and ST segments is exaggerated in both leads. (B) Effects of monitoring mode on ST-segment depth and morphology illustrated using a digital electrocardiographic simulator. A Spacelabs PC2 monitor (Redmond, WA) was switched from monitoring mode (0.5–40 Hz) to diagnostic mode (0.05–70 Hz). Notice the increase in the depth of ST-segment depression and the alteration of slope in both leads. *(From London MJ. Ischemia monitoring: ST segment analysis versus TEE. In: Kaplan JA, ed.* Cardiothoracic and Vascular Anesthesia Update. *Vol 3. Philadelphia: Saunders; 1993:1–20.)*

Electrocardiographic Changes With Myocardial Ischemia

Detection of Myocardial Ischemia

The ST segment is the most important portion of the QRS complex for evaluating ischemia.[52,53] It may come as a surprise that no gold standard criteria exist for the ECG diagnosis of myocardial ischemia. Many anesthesiologists, when evaluating an electrocardiogram for signs of ischemia, look for signs of repolarization or ST-segment abnormalities. Many other signs of myocardial ischemia may also be seen in the electrocardiogram, including T-wave inversion, QRS and T-wave axis alterations, R- or U-wave changes, or the development of previously undocumented arrhythmias or ventricular ectopy.[10] None of these, however, is as specific for ischemia as ST-segment depression or elevation. Depending on the location of the infarction, and the observed leads, the ST-segment changes are 84% to 100% specific and 12% to 66% sensitive for myocardial ischemia.[54]

The origin of the ST segment, at the J point, is easy to locate. However, J-point termination, which is generally accepted as the beginning of any change of slope of the T wave, is more difficult to determine. Physiologically normal persons may have no discernible ST segment because the T wave starts with a steady slope from the J point, especially at rapid heart rates. The TP segment has been used as the isoelectric baseline from which changes in the ST segment are evaluated, but with tachycardia, this segment is eliminated, and during exercise testing, the PR segment is used. The PR segment is used in all ST-segment analyzers.

Repolarization of the ventricle proceeds from the epicardium to the endocardium, opposite to the vector of depolarization. The ST segment reflects the midportion, or phase 2, of repolarization during little change in electrical potential occurs.[55] It is usually isoelectric. Ischemia causes a loss of intracellular potassium, resulting in a current of injury. The electrophysiologic mechanism accounting for ST-segment shifts (elevation or depression) remains controversial. The two major theories are based on a loss of resting potential as current flows from the uninjured to the injured area (ie, diastolic current) and on a true change in phase 2 potential as current flows from the injured to the uninjured area (ie, systolic current) (Fig. 12.11). With

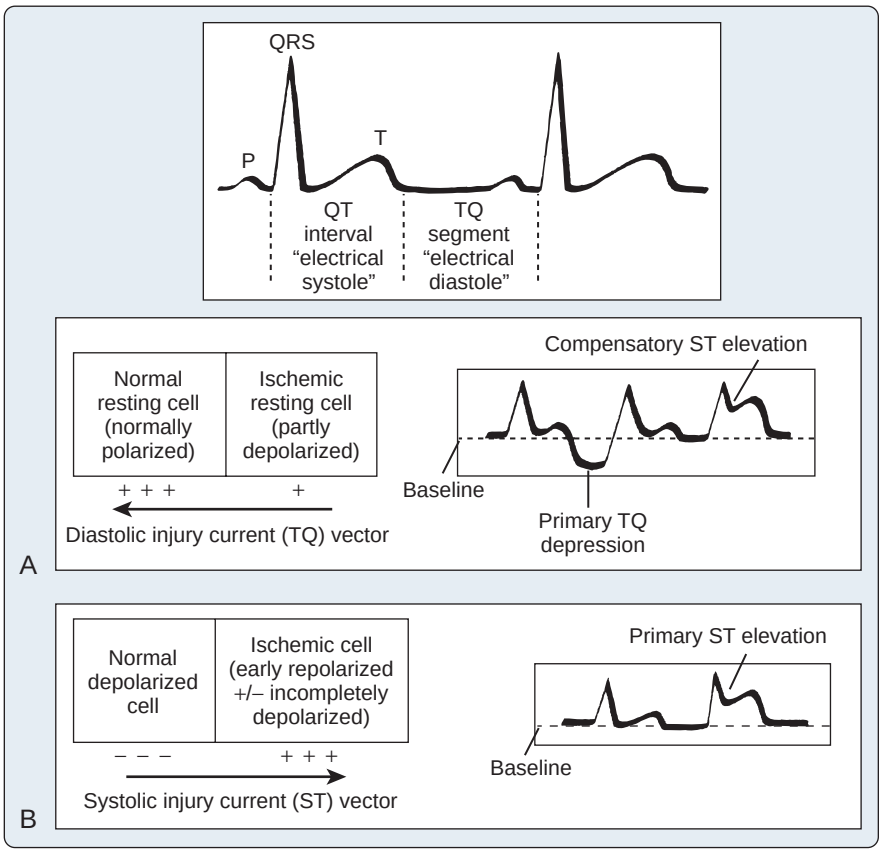

Fig. 12.11 Pathophysiology of ischemic ST-segment elevation. Two basic mechanisms have been advanced to explain the elevation seen with acute myocardial injury. (A) Diastolic current of injury. In this case (first QRS-T complex), the ST-segment vector is directed away from the relatively negative, partly depolarized, ischemic region during electrical diastole (TQ interval), and the result is primary TQ-interval depression. Conventional alternating current electrocardiograms compensate for the baseline shift, and an apparent ST-segment elevation (second QRS-T complex) results. (B) Systolic current of injury. In this case, the ischemic zone is relatively positive during electrical systole because the cells are repolarized early and the amplitude and upstroke velocity of their action potentials may be decreased. This injury current vector is oriented toward the electropositive zone, and the result is primary ST-segment elevation. *(From Mirvis DM, Goldberger AL. Electrocardiography. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *8th ed. Philadelphia: Saunders; 2008:174.)*

subendocardial injury, the ST segment is depressed in the surface leads. With epicardial or transmural injury, the ST segment is elevated (Fig. 12.12). When a lead is placed directly on the endocardium, the opposite patterns are recorded.

Although myocardial ischemia may manifest in PR-segment, QRS complex, ST-segment, or T-wave changes, the earliest ECG signs of ischemia are typically T-wave and ST-segment changes. Acute increases in T-wave amplitude, with prominent symmetric T waves in at least two contiguous leads, are early signs that may precede the elevation of the ST segment. Transient Q waves may be observed during an episode of acute ischemia or (rarely) during acute myocardial infarction (MI) with successful reperfusion.[56] With myocardial ischemia, repolarization is affected, resulting in downsloping or horizontal ST-segment depression. Various local effects and differences in vectors during repolarization result in different ST-segment morphologic features that are recorded by the different leads. It is generally accepted that ST-segment changes in multiple leads are associated with more severe degrees of CAD.

The criteria for MI are divided into two categories: ST-segment elevation MI (STEMI), and ST-segment depression/T-wave change MI (NSTEMI). The J point is located at the juncture of the QRS complex and the ST segment, and it is used to measure the magnitude of the ST-segment deflection as compared with the baseline of the ECG. A new J-point elevation of 0.1 mV or greater is required in all leads except V_2 and V_3 to meet the criteria for STEMI. J-point elevations of up to 0.25 mV may be seen in leads V_2 and V_3 in healthy men younger than 40 years of age; however, this finding decreases with age and is less prominent in women. For this reason, a range of J-point elevation criteria for MI are defined for V_2 and V_3 leads: 0.2 mV or greater for men 40 years old and older, 0.25 mV or greater for men younger than 40 years of age, and 0.15 mV or greater for women.[56] The J-point elevations must be seen in two or more contiguous leads for the satisfaction of ST-segment elevation criteria.[56] New horizontal or downsloping ST-segment depressions of 0.05 mV or greater or T-wave inversion of 0.1 mV or greater in two contiguous leads with an R-wave–to–S-wave ratio greater than 1 satisfy the criteria for NSTEMI. However, ST-segment elevations are more specific than ST-segment depressions and/or T-wave inversions for localizing the site of ischemia.[56] ST-segment elevation generally suggests greater degrees of myocardial damage than ST-segment depression or T-wave changes.[57] Previously inverted T waves may pseudonormalize during episodes of acute myocardial ischemia[56] (Appendix 12.1).

Nonspecific ST-segment depression can be related to drug use, particularly digoxin.[58] Interpretation of ST-segment changes in patients with left ventricular hypertrophy is particularly controversial given the tall R-wave baseline, J-point depression, and steep slope of the

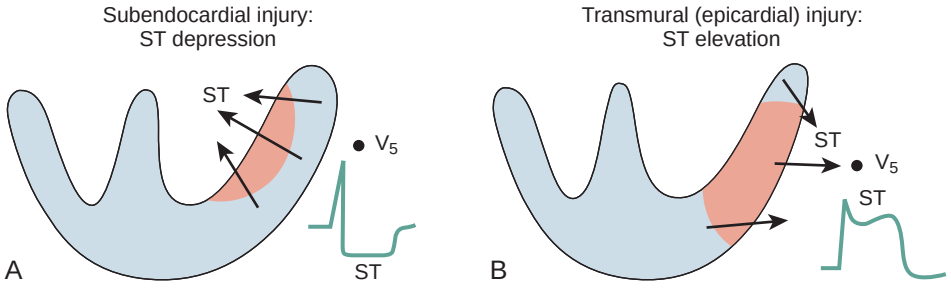

Fig. 12.12 Current of injury patterns with acute ischemia. (A) With predominant subendocardial ischemia the resultant ST-segment vector is directed toward the inner layer of the affected ventricle and the ventricular cavity. Overlying leads therefore record ST-segment depression. (B) With ischemia involving the outer ventricular layer (transmural or epicardial injury), the ST-segment vector is directed outward. Overlying leads record ST-segment elevation. Reciprocal ST-segment depression can appear in contralateral leads. *(From Mirvis DM, Goldberger AL. Electrocardiography. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *8th ed. Philadelphia: Saunders; 2008:174.)*

ST segment. Although some studies excluded such patients, others (including those using other modalities or epidemiologic studies) observed that left ventricular hypertrophy is a highly significant predictor of adverse cardiac outcome.[59] Occasionally, other conditions cause ECG changes that may confound diagnosing myocardial ischemia exclusively by electrocardiogram. For example, pulmonary embolism, intracranial bleeding, electrolyte abnormalities, hypothermia, and pericarditis may also result in ST-segment or T-wave abnormalities. The diagnosis of ischemia is more difficult in the presence of left bundle branch block and may require comparison with a previous electrocardiogram.[56] In contrast, patients with right bundle branch block often have ST-segment and T-wave abnormalities in leads $V_1$to V_3 that also confound the diagnosis of new ischemia. Ultimately, clinical suspicion should guide interpretation of the electrocardiogram.

The criteria for myocardial ischemia with ST-segment changes described previously are used in conjunction with clinical symptoms and confirmation with elevation of biomarkers to diagnose acute coronary syndromes.[60] These changes usually result from transmural ischemia, but they may potentially represent a reciprocal change in a lead oriented opposite to the primary vector with subendocardial ischemia (as may be seen in the reverse situation).[61,62] Perioperative ambulatory monitoring studies have also included more than 0.2 mV in any single lead as a criterion, but ST-segment elevation is rarely reported in the setting of noncardiac surgical procedures. It is commonly observed, however, during weaning from CPB in cardiac operations and during CABG procedures (on and off pump) with interruption of coronary flow in a native or graft vessel. ST-segment elevation in a lead with a Q wave should not be analyzed for acute ischemia, although it may indicate the presence of a ventricular aneurysm.

Although repolarization changes (eg, ST-T wave) are the focus of ischemia detection, computerized ECG analysis using signal averaging techniques has documented changes in depolarization with ischemia manifested by a reduction in high-frequency components of the QRS complex (150–250 Hz). Such changes are not visible on the standard electrocardiogram because they are in the range of only 10 to 20 mV and are measured quantitatively using the root mean square value (calculated by squaring the amplitude of each sample and determining the means of the squares and then the square root of that mean value). Absolute changes in the root mean square value greater than 0.6 mV or relative changes of more than 20% are considered clinically significant. This effect likely reflects slowing of conduction velocity in the ischemic region.[63]

One study documented higher sensitivity of this approach compared with 12-lead ST-segment analysis in the detection of acute coronary occlusion during percutaneous transluminal coronary angioplasty.[64] The overall sensitivity was 88%, compared with 71% using ST-segment elevation criteria or 79% by combining ST-segment elevation and depression. More recent studies suggested that high-frequency QRS analysis can be used in quantification of myocardial areas at risk of ischemia.[65]

Anatomic Localization of Ischemia With the Electrocardiogram

As noted earlier, ST-segment depression is a common manifestation of subendocardial ischemia. From a practical clinical standpoint, it has a single major strength and limitation. Its strength is that it is almost always present in one or more of the anterolateral precordial leads (V_4–V_6).[66] However, it fails to "localize" the offending coronary lesion and has little relation to underlying segmental asynergy.[67,68]

In contrast, ST-segment elevation correlates well with segmental asynergy and localizes the offending lesion relatively well.[67,69] Reciprocal ST-segment depression often is present in one or more of the other 12 leads. In patients with angiographically documented single-vessel disease, ST-segment elevation (as well as Q waves or inverted T waves) in leads I, aVL, or V_1 through V_4 is closely correlated with disease of the left anterior descending coronary artery, whereas similar findings in leads, I, III, and aVF indicate disease of the right coronary or left circumflex arteries (surprisingly, the latter two cannot be differentiated by ECG criteria).[69] A multivariate analysis suggested that ST-segment elevation, abnormal Q waves, and inverted T waves in leads I and aVL (with normal V_1 and V_6) can be used to differentiate isolated first diagonal branch occlusion from the more ominous proximal left anterior descending coronary artery occlusion.[70]

Clinical Lead Systems for Detecting Ischemia

Early clinical reports of intraoperative monitoring using the V_5 lead in high-risk patients were based on observations during exercise testing, in which bipolar configurations of V_5 demonstrated high sensitivity for myocardial ischemia detection (up to 90%). Subsequent studies using 12-lead monitoring (torso mounted for stability during exercise) confirmed the sensitivity of the lateral precordial leads.[71,72] Some studies, however, reported higher sensitivity for leads V_4 or V_6 compared with V_5, followed by the inferior leads (in which most false-positive responses were reported).[66,73–79]

The exact nature of perioperative MI (PMI) in noncardiac surgical procedures remains uncertain and is a subject of debate and controversy. The interaction between morphologic and functional factors is unpredictable. Some older pathologic and angiographic studies suggested that the cause of PMI resembles that in the nonsurgical setting (ie, plaque rupture in 50% of cases). However, newer analysis suggested that myocardial oxygen supply/demand imbalance predominates in the first 3 to 4 postoperative days, and patients suffer from demand

ischemia and injury. In PMI, the location and severity of underlying coronary artery stenosis do not necessarily predict the infarct territory. The high incidence of histologically confirmed transmural infarctions seems to be contradictory to the ECG finding of almost exclusively non–Q-wave PMIs. Conversely, the presence of subendocardial PMI is consistent with a myocardial oxygen supply/demand mismatch as the main trigger of myocardial injury.[80,81] Given the relatively low sensitivity and specificity of the electrocardiogram, echocardiographic imaging is now routinely used in addition to the electrocardiogram in cardiology evaluations.

With the widespread growth of percutaneous coronary interventions for acute MI and unstable angina, some investigators have reported the use of continuous ECG monitoring (3 or 12 leads) in this setting. These observations have extended the classic teaching on localization of sites of coronary artery occlusion. Horacek and Wagner[82] reviewed the complexities and controversies regarding vessel-specific ECG responses to acute myocardial ischemia in detail. In general, ST-segment elevation in leads V_2 and V_3 is most sensitive for occlusion of the left anterior descending coronary artery, and leads III and aVF are most sensitive for the right coronary artery. In contrast, circumflex artery occlusion results in variable responses, with primary elevation in the posterior precordial leads V_7 through V_9 (which are rarely monitored clinically) and reciprocal ST-segment depression in the standard precordial leads (V_2 or V_3).[83,84] For transmural ischemia, sensitivity is highest in the anterior rather than the lateral precordial leads. An international multidisciplinary working group specifically recommended continuous monitoring of leads III, V_3, and V_5 for all patients with acute coronary syndromes.[85]

Intraoperative Lead Systems

Detection of perioperative myocardial ischemia is an integral part of clinical monitoring and guides therapy. Many studies demonstrated associations of perioperative ischemia with adverse cardiac outcomes in adults undergoing a variety of cardiac and noncardiac surgical procedures, particularly major vascular operations.[86–91] Perhaps the greater challenge is interpreting minor ST-segment changes in the context of the overall risk profile of the patient to avoid inappropriate performance of costly diagnostic tests. Studies documented that transient myocardial ischemia occurs in the absence of significant CAD in unexpected patients, such as parturient women, particularly with significant hemodynamic stress or hemorrhage.[92] Although the precise cause of such changes is uncertain, significant troponin release has been documented in these patients, thus confirming the suspicion that these ECG changes are true ischemic responses (probably related to subendocardial ischemia secondary to global hypoperfusion).

How accurately the clinician places ECG leads on the patient's torso is probably the single most important factor influencing clinical utility of the electrocardiogram. Placement of the limb leads almost anywhere on the torso at or near the origin of the arms allows accurate rendition of lead II because both electrodes are farther than 12 cm from the heart (a distance considered to be the electrical infinity value beyond which amplitude of the QRS complex is unchanged).[93]

The cardiac anesthesiologist encounters a variety of ECG changes consistent with or pathognomonic for myocardial ischemia or infarction at many phases of the perioperative period in patients undergoing cardiac operations. In the majority of these patients (ie, those with known CAD), the sensitivity and specificity of the major signs described are high, and few false-positive or false-negative changes are encountered. However, the abnormal physiology of CPB, including acute changes in temperature, electrolyte concentrations, and catecholamine levels can significantly influence sensitivity and specificity. In addition, patients undergoing valve replacement, even those without coronary artery lesions, can develop significant subendocardial and transmural ischemia (ie, coronary artery embolus of valve calcification, vegetations, or air). Even neonates can develop myocardial ischemia[94](Fig. 12.13).

Detecting and recognizing the clinical significance of various ECG signs of ischemia or infarction and collaborating the findings with transesophageal echocardiography can enhance patient care in the acute setting, as in emergency treatment of coronary artery spasm or air embolus, or by alerting the surgeon that myocardial

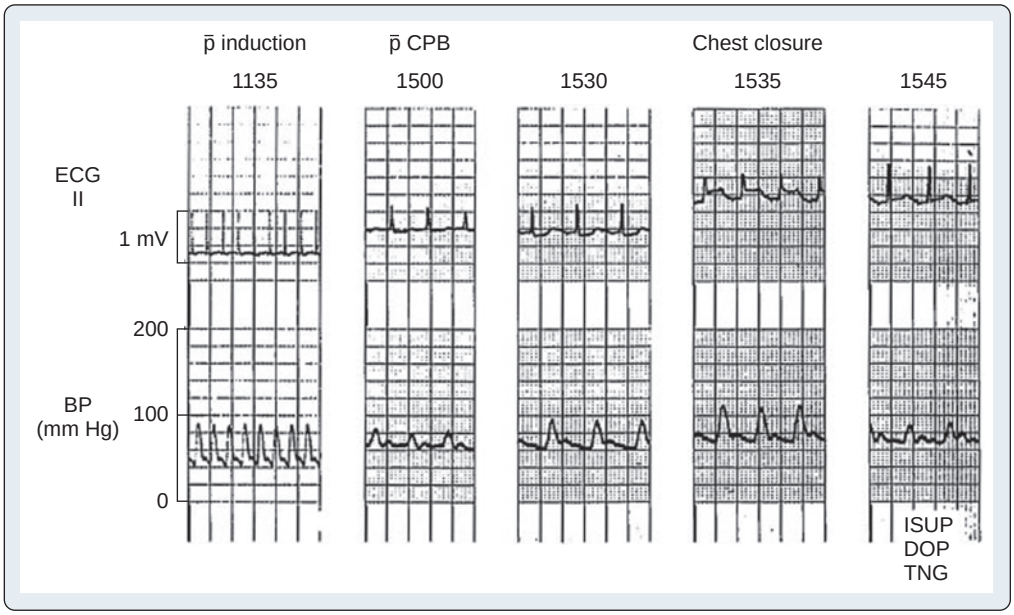

Fig. 12.13 In a 2-day-old, 3.5-kg male infant undergoing a Senning procedure, early ST-segment changes in lead II first noted immediately after cardiopulmonary bypass) (15:00 h) and 30 min later (15:30 h). Significant ST-segment elevation during chest closure (15:35 h) improved after administration of trinitroglycerin *(TNG)*, isoproterenol *(ISUP)*, and dopamine *(DOP)* at 15:45 h. *BP*, Blood pressure; *ECG*, electrocardiogram; p̄, after. *(Reproduced with permission from Bell C, Rimar S, Barash P. Intraoperative ST-segment changes consistent with myocardial ischemia in the neonate: a report of three cases.* Anesthesiology. *1989;71:601–604.)*

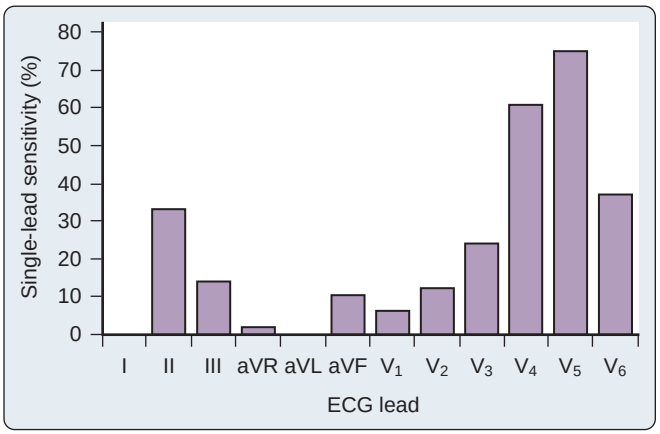

Fig. 12.14 Single-lead sensitivity for the intraoperative detection of ischemia based on 51 episodes detected in 25 patients undergoing noncardiac surgical procedures. Sensitivity was calculated by dividing the number of episodes detected in that electrocardiographic *(ECG)* lead by the total number of episodes. Sensitivity was greatest in lead V_5, and the lateral leads (I, aVL) were insensitive. *(Reproduced with permission from London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography.* Anesthesiology. *1988;69:232.)*

TABLE 12.2 Sensitivity for Different Electrocardiographic Lead Combinations

Number of Leads	*Combination*	*Sensitivity (%)*
1 lead	II	33
	V_4	61
	V_5	75
2 leads	II/V_5	80
	II/V_4	82
	V_4/V_5	90
3 leads	$V_3/V_4/V_5$	94
	$II/V_4/V_5$	96
4 leads	$II/V_2–V_5$	100

Data from London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology.* 1988;69:232.)

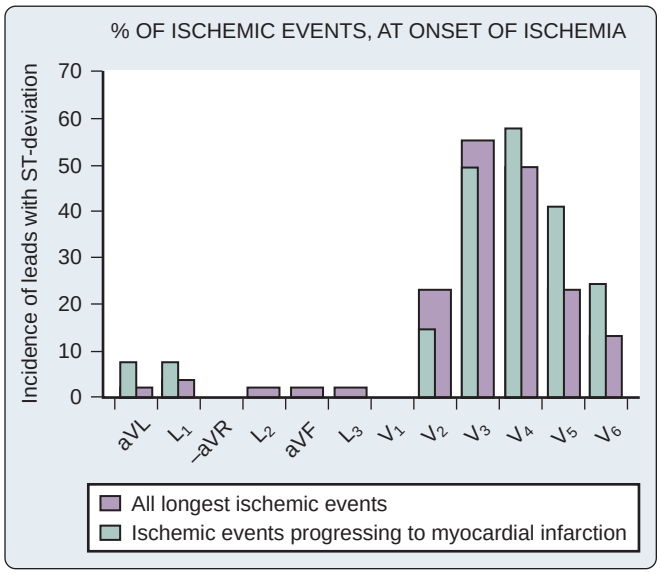

Fig. 12.15 Histogram showing the incidence in which prolonged ischemia was first noted by each lead at the onset of ischemia in all 38 longest ischemic events and in the 12 ischemic events that progressed to myocardial infarction. *(Reproduced with permission from Landesberg G, Mosseri M, Wolf Y, et al. Perioperative myocardial ischemia and infarction: identification by continuous 12-lead electrocardiogram with online ST-segment monitoring.* Anesthesiology. *2002;96:264–270.)*

revascularization may have been inadequate. This may lead to reexploration of a saphenous vein or internal mammary artery anastomosis, especially if the transesophageal echocardiographic data support the diagnosis of ischemia.

The early reports of Dalton[95] and Kaplan and King,[96] recommending routine intraoperative monitoring of V_5 in high-risk patients, cited exercise tolerance tests as the source of their recommendations. Subsequently, the recommended leads for intraoperative monitoring, based on several clinical studies, did not differ substantially from those used during exercise testing, although considerable controversy on the optimal leads persists in both clinical settings. The use of continuous ECG monitoring in the coronary care unit has received increasing attention.[97] A clinical study using continuous, computerized 12-lead ECG analysis in a mixed cohort (for vascular and other noncardiac procedures) by London and associates[98] reported that almost 90% of changes involved ST-segment depression alone (75% in V_5 and 61% in V_4). In approximately 70% of patients, significant changes were observed in multiple leads. The sensitivity of each of the 12 leads in that study is shown in Fig. 12.14. When considered in combination (as occurs clinically), the use of leads V_4 and V_5 increased sensitivity to 90%, whereas sensitivity for the standard clinical combination of leads II and V_5 was only 80%. Use of leads V_2 through V_5 and lead II captured all episodes (Table 12.2).

A larger clinical study by Landesberg and colleagues[99] of patients undergoing vascular operations using a longer period of monitoring (up to 72 hours) with more specific criteria for ischemia (>10-minute duration of episode) extended these observations. These investigators reported that V_3 was most sensitive lead for ischemia (87%) followed by V_4 (79%), whereas V_5 alone was only 66% sensitive (Fig. 12.15).[99] In the subgroup of patients whose prolonged ischemic episodes ultimately culminated in infarction, V_4 was most sensitive lead (83%). In this study, all MIs were non–Q-wave events detected by troponin elevation. The use of two precordial leads detected 97% to 100% of changes. Based on analysis of the resting isoelectric levels of each of the 12 leads (a unique component of this study), it was recommended that V_4 was the best single choice for monitoring a single precordial lead because it was most likely to be isoelectric relative to the resting 12-lead preoperative electrocardiogram. In contrast, the baseline ST-segment was more likely above isoelectric in V_1 through V_3 and below isoelectric in V_5 and V_6. Surprisingly, no episodes of ST-segment elevation occurred in this study, as opposed to 12% in the earlier study of London and associates,[98] in which such changes were detected in inferior and anteroseptal precordial leads.

Martinez and colleagues[100] evaluated a cohort of vascular surgical patients monitored in the intensive care unit for the first postoperative days with continuous 12-lead ECG monitoring using a threshold of 20 minutes for an ischemic episode. Eleven percent of 149 patients met the criteria, with ST-segment depression in 71% and ST-segment elevation alone in 18% (12% had both). Most changes were detected in V_2 (53%) and V_3 (65%). Using the standard two-lead system (II and V_5), only 41% of episodes would have been detected. Although these studies clearly support the value of precordial monitoring in patients at risk for subendocardial ischemia, clinicians must be vigilant for the rare patient with an acute Q-wave infarction (most commonly in the inferior leads). The studies previously cited were all conducted in patients undergoing noncardiac operations because it is not practical to conduct such studies in patients with open chests or extensive surgical dressings in the precordial region. However, no reason exists to assume that any significant differences would have been observed in the cardiac surgical patient. Sudden episodes of acute transmural ischemia (associated with ST-segment elevation) are much more likely in this setting from acute ischemia or infarction (eg, thrombotic occlusion) or from surgically induced reductions in coronary blood flow.

Abnormalities in T-wave morphology are probably the most common perioperative ECG abnormalities in the general surgical population. Breslow and associates[101] noted new T-wave abnormalities within 1 hour postoperatively in 18% of an unselected surgical population of 394 patients (excluding cardiac and neurosurgical procedures). Approximately two-thirds of the changes were limited to T-wave flattening, and the remainder had new inversions. The incidence was no different between patients with known CAD and those without it. Out of a battery of variables, the only one statistically associated with T-wave abnormalities was intraabdominal operation. The ECG changes were not associated with any clinical morbidity. This study illustrates the known relationship of T-wave changes with a variety of autonomic stimuli, including changes in serum glucose, elevated catecholamines, acute hyperventilation, and upper gastrointestinal disease. Similar analyses in patients undergoing cardiac surgical procedures are not available, and the specificity of the response would be expected to be much lower.

Electrocardiographic Changes With Pacemakers, Respirations, Electrolytes, and Medications

Use of the inferior leads (II, III, aVF) allows superior discrimination of P-wave morphology and facilitates the visual diagnosis of arrhythmias and conduction disorders. Although esophageal (and even intracardiac) leads allow the greatest sensitivity in detecting P waves, these leads are rarely used clinically. Nevertheless, they should be kept in mind for difficult diagnoses. With the increasing use of implantable defibrillators and automatic external defibrillators to treat ventricular fibrillation and ventricular tachycardia, considerable interest exists in the refinement of arrhythmia detection algorithms and their validation.[102] As expected, the accuracy of these devices for detecting ventricular arrhythmias is high, but it is much lower for detecting atrial arrhythmias. In the settings of critical care and ambulatory monitoring, various artifacts are common causes of false-positive responses.[102] Detection of pacemaker spikes may be complicated by very-low-amplitude signals related to bipolar pacing leads, amplitude varying with respiration, and total-body fluid accumulation.[102,103] Most critical care and ambulatory monitors incorporate pacemaker spike enhancement for small high-frequency signals (typically 5–500 mV with 0.5- to 2-ms pulse duration) to facilitate recognition. However, this can cause artifact if high-frequency noise is present within the lead system.

A promising application of the electrocardiogram is to correlate respiratory variation in wave amplitude with patients' volume responsiveness. The R wave, especially in lead II (RII), shows consistent respiratory amplitude variation during positive-pressure mechanical ventilation. This variation is likely caused by the "Brody effect," a theoretical analysis of left ventricular volume and electrical conductance.[104] RII-wave amplitude variation may be used as a dynamic index of volume responsiveness in a mechanically ventilated patient, similar to the use of arterial pulse contour analysis and esophageal Doppler monitoring to derive pulse-pressure and stroke volume variation as dynamic measures of fluid responsiveness.[105–107] Real-time, intraoperative RII-wave amplitude variation has the potential to become a truly noninvasive monitor for fluid responsiveness; however, at present, no commercially available intraoperative monitoring systems provide ECG R-wave amplitude variation measures.

Electrocardiographic Changes Resulting From Electrolyte Disorders

Cardiac myocytes exhibit a long action potential (200–400 ms) compared with neurons and skeletal muscle (1–5 ms). Multiple different channels are involved in cardiac muscle depolarization and repolarization. Sodium and calcium channels are the primary carriers of depolarizing current in both atria and ventricles. Inactivation of these currents and activation of potassium channels are predominantly involved in repolarizing the cardiac cells, thereby reestablishing the negative resting membrane potential. Thus it is not surprising that perturbations in the plasma concentrations of potassium and calcium ions lead to changes in the finely tuned cardiac electrical activity and the surface electrocardiogram. They typically cause changes in repolarization (ST-T-U waves) and can also lead to QRS complex prolongation.[108]

Hyperkalemia

Hyperkalemia is not an uncommon occurrence in patients undergoing cardiac surgical procedures with CPB. Hyperkalemia affects repolarization of cardiac cells. Although progressive changes in the surface electrocardiogram with increasing levels of potassium have been described, the correlation between serum potassium levels and ECG changes is not strong.[109] Typically, ECG changes start with narrowing and peaking of the T waves. Further elevation of extracellular potassium leads to prolongation of the QRS complex. The reason is delayed AV conduction, and an AV block may appear. These changes are typically followed by prolongation of the PR interval, flattening of the P waves, and loss of the P wave because the high potassium levels delay the spread of the cardiac activating impulse through the myocardium. Further increase in plasma potassium levels cause sine waves, which can progress to asystole or ventricular fibrillation. Hyperkalemia may also reduce the myocardial response to artificial pacemaker stimulation.

Hypokalemia

Because potassium channels and ions are significantly involved in cardiac repolarization, it is not surprising that hypokalemia prolongs ventricular repolarization. This results in characteristic reversal in the relative amplitudes of the T and U waves. T-wave flattening or inversion is noted, whereas U waves become more prominent. The U-wave prominence is caused by the prolongation of the recovery phase of the cardiac action potential. This can lead to the life-threatening torsades de pointes type of ventricular arrhythmia. Slight depression of the ST segment may also occur, as well as increased amplitude and width of the P waves with prolongation of the PR interval.

Hypocalcemia and Hypercalcemia

The ventricular recovery time, as represented on the electrocardiogram by the QTc interval, is altered by the extremes of serum calcium. Hypocalcemia can cause a prolonged QTc interval (ST portion), whereas hypercalcemia shortens the QTc interval. In hypocalcemia, the prolonged QT interval may be accompanied by terminal T-wave inversions. In extreme hypercalcemia, an increase in QRS complex, biphasic T waves, and Osborn waves have been described.

Medications

Many antiarrhythmic medications are used in the perioperative period in patients undergoing cardiac surgical procedures. Detailed discussion of each of these drugs is beyond the scope of this chapter (see Chapter 10). Generally, drugs that increase the duration of the cardiac action potential prolong the QT interval. These include class Ia and Ic antiarrhythmic drugs (eg, quinidine, procainamide), phenothiazines, antidepressants, haloperidol, and atypical antipsychotic agents. Intravenous amiodarone, commonly used in the management of perioperative arrhythmias, also causes QT-interval prolongation. Other class III antiarrhythmic drugs (eg, sotalol) cause QT-interval prolongation as well. Unlike class Ia and III antiarrhythmic drugs, digitalis glycosides shorten the QT interval and often cause "scooping" of the ST-T wave complex.

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APPENDIX
12.1

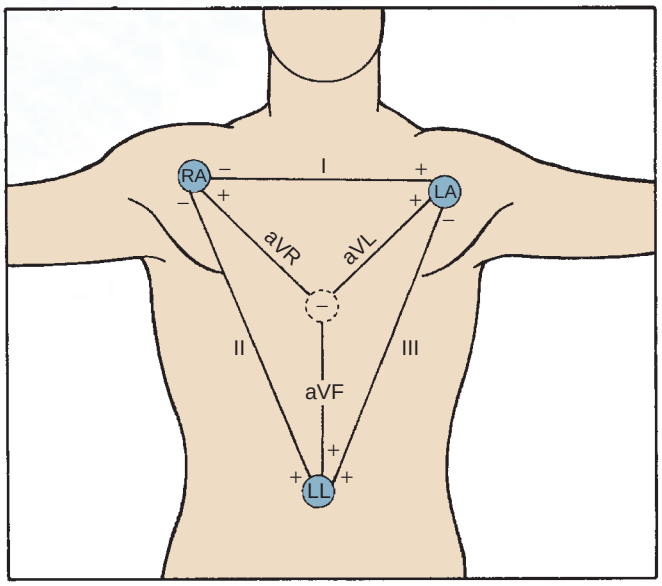
Electrocardiogram Atlas: A Summary of Important Changes on the Electrocardiogram

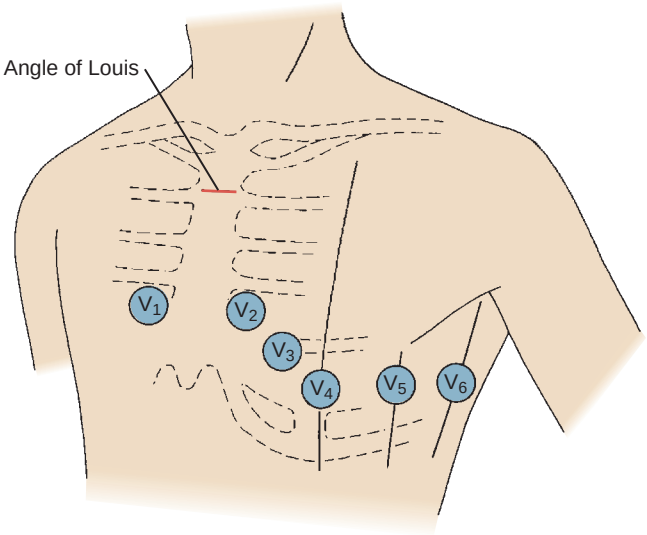
GINA C. BADESCU, MD | BENJAMIN SHERMAN, MD | JAMES R. ZAIDAN, MD, MBA | PAUL G. BARASH, MD

Lead Placement

	Electrode	
Lead Placement	*Positive*	*Negative*
Bipolar Leads		
I	LA	RA
II	LL	RA
III	LL	LA
Augmented Unipolar Leads		
aVR	RA	LA, LL
aVL	LA	RA, LL
aVF	LL	RA, LA
Precordial Leads		
V_1	4 ICS–RSB	
V_2	4 ICS–LSB	
V_3	Midway between V_2 and V_4	
V_4	5 ICS–MCL	
V_5	5 ICS–AAL	
V_6	5 ICS–MAL	

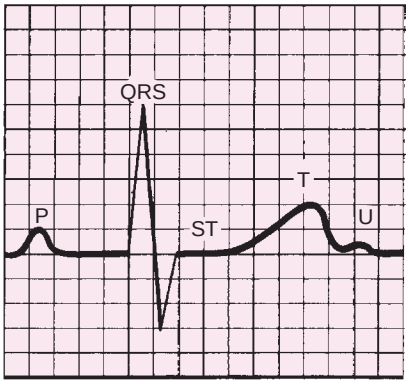
AAL, Interaxillary line; *ICS,* intercostal space; *LA,* left arm; *LL,* left leg; *LSB,* left sternal border; *MAL,* midaxillary line; *MCL,* midclavicular line; *RA,* right arm; *RSB,* right sternal border.

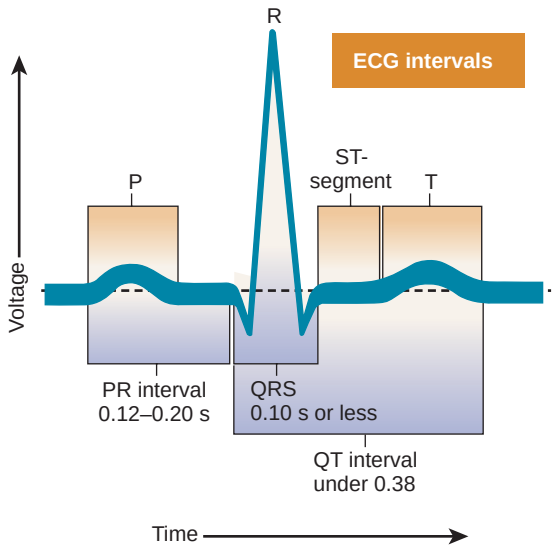




Normal Electrocardiogram: Cardiac Cycle

The normal electrocardiogram is composed of waves (P, QRS, T, and U) and intervals (PR, QRS, ST, and QT).

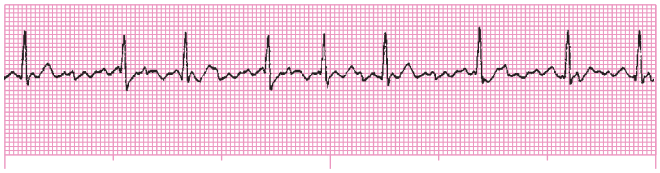




Atrial Fibrillation

Rate: Variable (~150–200 beats/min)
Rhythm: Irregular
PR interval: No P wave; PR interval not discernible
QT interval: QRS normal

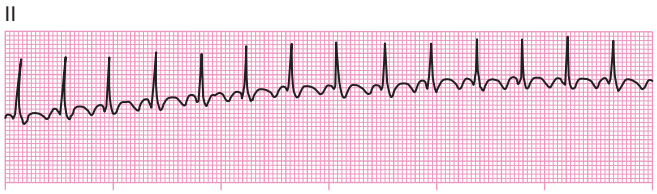
Note: This must be differentiated from atrial flutter: (1) absence of flutter waves and presence of fibrillatory line; (2) flutter usually associated with higher ventricular rates (>150 beats/min). Loss of atrial contraction reduces cardiac output (10–20%). Mural atrial thrombi may develop. It is considered controlled if the ventricular rate is <100 beats/min.



Atrial Flutter

Rate: Rapid, atrial usually regular (250–350 beats/min); ventricular usually regular (<100 beats/min)
Rhythm: Atrial and ventricular regular
PR interval: Flutter (F) waves saw-toothed; PR interval cannot be measured
QT interval: QRS usually normal; ST segment and T waves not identifiable

Note: Carotid massage slows the ventricular response, thus simplifying recognition of the F waves.

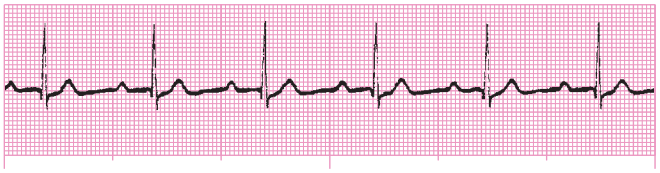


Atrioventricular Block

First-Degree

Rate: 60–100 beats/min
Rhythm: Regular
PR interval: Prolonged (>0.20 second) and constant
QT interval: Normal

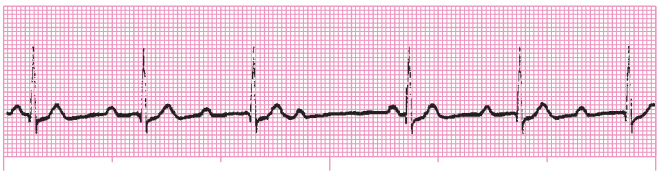
Note: It is usually clinically insignificant; it may be an early harbinger of drug toxicity.



Second-Degree: Mobitz Type I/Wenckebach Block

Rate: 60–100 beats/min
Rhythm: Atrial regular; ventricular irregular
PR interval: P-wave normal; PR interval progressively lengthens with each cycle until QRS complex is dropped (dropped beat); PR interval following dropped beat is shorter than normal.
QT interval: QRS complex normal but dropped periodically

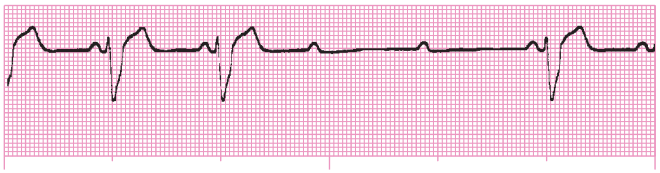
Note: It is commonly seen (1) in trained athletes and (2) with drug toxicity.



Second-Degree: Mobitz Type II Block

Rate: <100 beats/min
Rhythm: Atrial regular; ventricular regular or irregular
PR interval: P waves normal, but some not followed by QRS complex
QT interval: Normal but may have widened QRS complex if block is at level of bundle branch. ST segment and T wave may be abnormal, depending on location of block

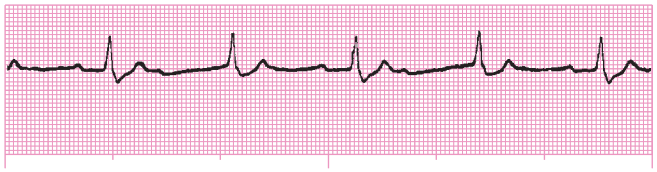
Note: In contrast to Mobitz type I block, the PR and RR intervals are constant and the dropped QRS occurs without warning. The wider the QRS complex (block lower in the conduction system), the greater is the amount of myocardial damage.



Third-Degree: Complete Heart Block

Rate: <45 beats/min
Rhythm: Atrial regular; ventricular regular; no relationship between P wave and QRS complex
PR interval: Variable because atria and ventricles beat independently
QT interval: QRS morphology variable, depending on the origin of the ventricular beat in the intrinsic pacemaker system (atrioventricular [AV] junctional vs ventricular pacemaker); ST segment and T wave normal

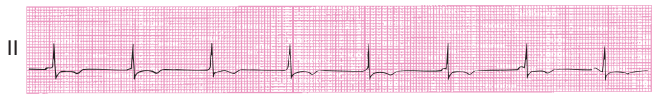
Note: AV block represents complete failure of conduction from atria to ventricles (no P wave is conducted to the ventricle). The atrial rate is faster than the ventricular rate. P waves have no relation to QRS complexes (eg, they are electrically disconnected). In contrast, with AV dissociation, the P wave is conducted through the AV node, and the atrial and ventricular rates are similar. Immediate treatment with atropine or isoproterenol is required if cardiac output is reduced. Consideration should be given to insertion of a pacemaker. This is seen as a complication of mitral valve replacement.



Atrioventricular Dissociation

Rate: Variable
Rhythm: Atrial regular; ventricular regular; ventricular rate faster than atrial rate; no relation between P wave and QRS complex
PR interval: Variable because atria and ventricles beat independently
QT interval: QRS morphology dependent on location of ventricular pacemaker; ST segment and T wave abnormal

Note: In AV dissociation, the atria and ventricles beat independently. The P wave is conducted through the AV node, and the atrial and ventricular rate are similar. In contrast, AV block represents complete failure of conduction from atria to ventricles (no P wave is conducted to the ventricle). The atrial rate is faster than the ventricular rate. P waves have no relation to QRS complexes (eg, they are electrically disconnected). Digitalis toxicity can manifest as AV dissociation.

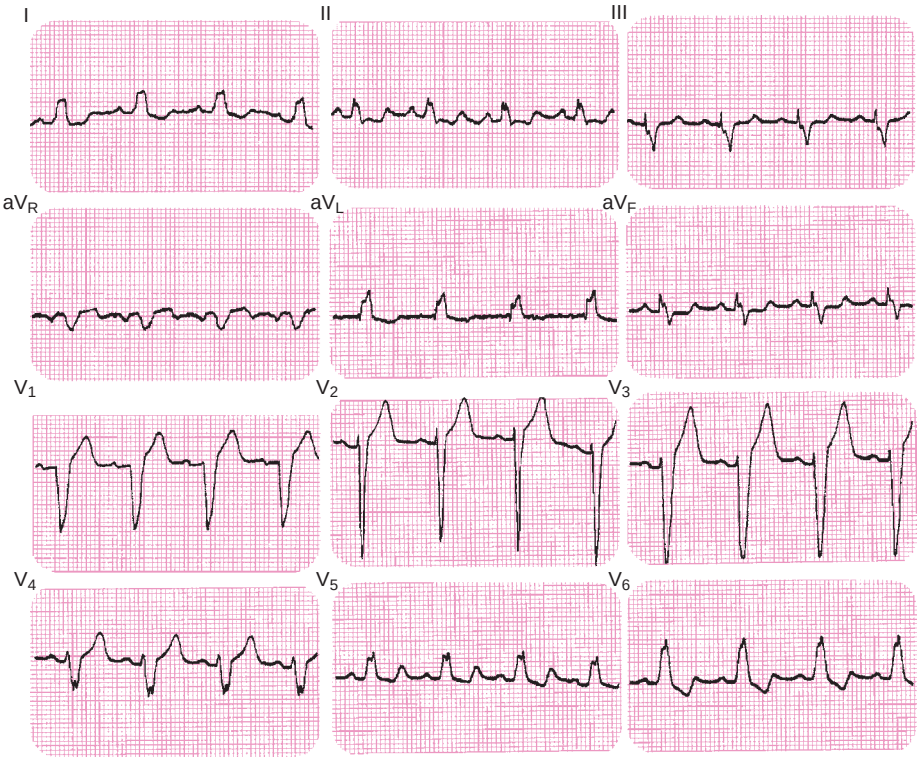


Bundle Branch Block

Left Bundle Branch Block

Rate: <100 beats/min
Rhythm: Regular
PR interval: Normal
QT interval: Complete left bundle branch block (LBBB; QRS >0.12 second); incomplete LBBB (QRS = 0.10–0.12 second); lead V_1 negative RS complex; I, aVL, V_6 wide R wave without Q or S component; ST-segment and T-wave defection opposite direction of the R wave

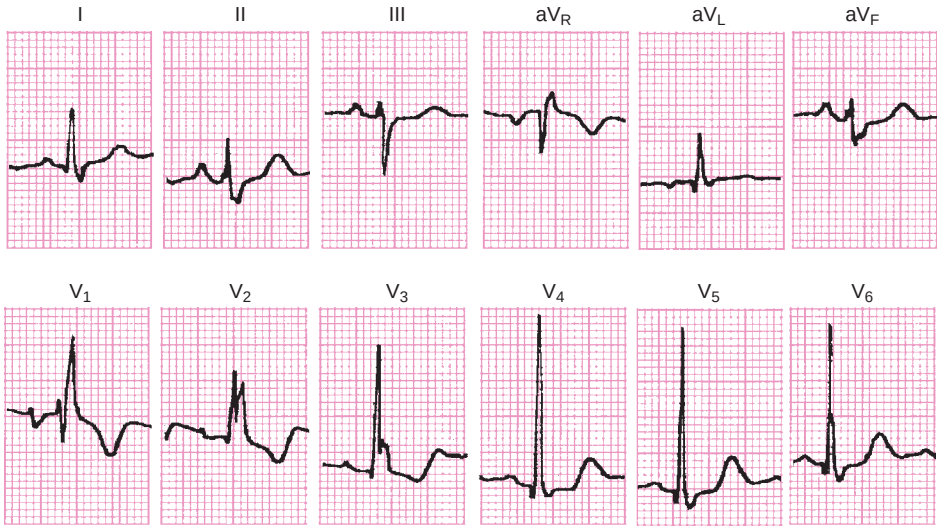
Note: LBBB does not occur in healthy patients and usually indicates serious heart disease with a poorer prognosis. In patients with LBBB, insertion of a pulmonary artery catheter may lead to complete heart block.



Right Bundle Branch Block

Rate: <100 beats/min
Rhythm: Regular
PR interval: Normal
QT interval: Complete right bundle branch block (RBBB; QRS >0.12 second); incomplete RBBB (QRS = 0.10–0.12 second); varying patterns of QRS complex; rSR (V_1); RS, wide R with M pattern; ST-segment and T-wave opposite direction of the R wave

Note: In the presence of RBBB, Q waves may be seen with a myocardial infarction (MI).

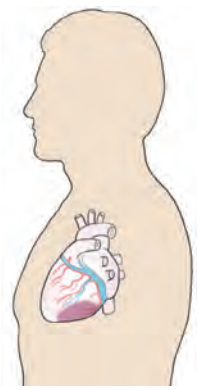


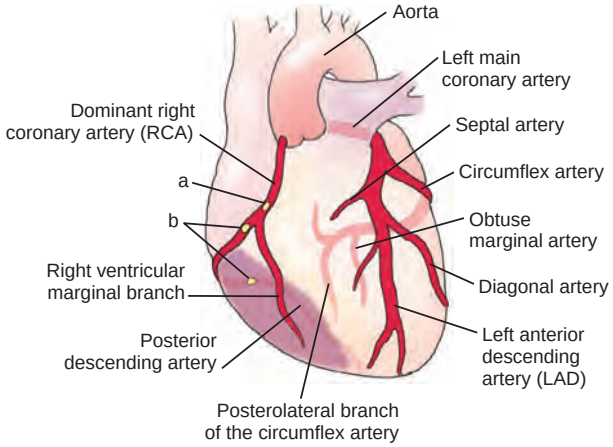
Coronary Artery Disease

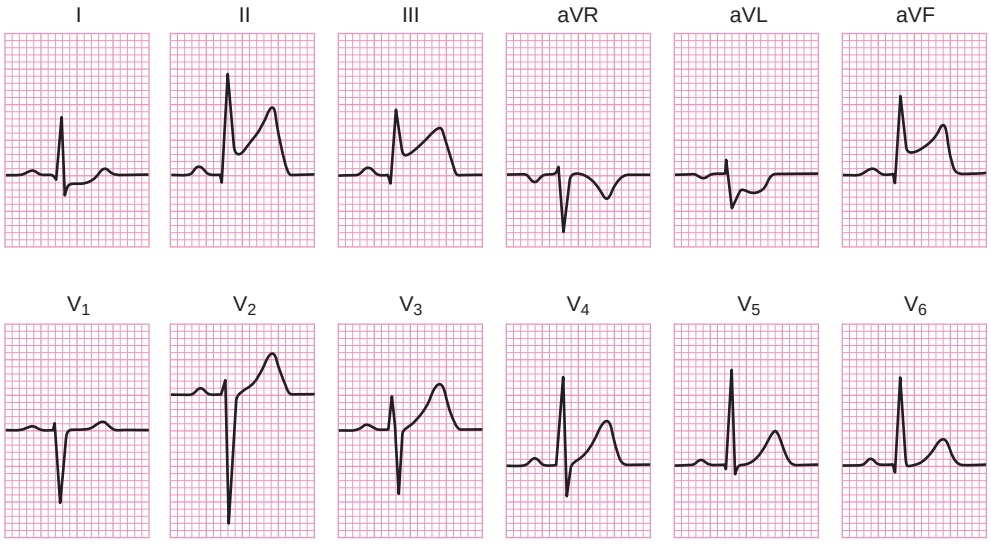
Transmural Myocardial Infarction

Q waves seen on the electrocardiogram, useful in confirming diagnosis, are associated with poorer prognosis and more significant hemodynamic impairment. Arrhythmias frequently complicate the course. Small Q waves may be a normal variant. For MI, Q waves last longer than 0.04 second, and depth exceeds one-third of the R wave (inferior wall MI). For inferior wall MI, differentiate it from right ventricular hypertrophy by axis deviation.

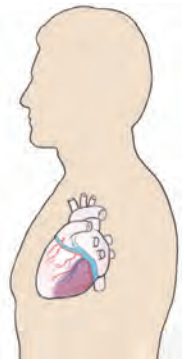
Anatomic Site	Leads	ECG Changes	Coronary Artery
Inferior	II, III, AVF	Q, ↑ST, ↑T	Right

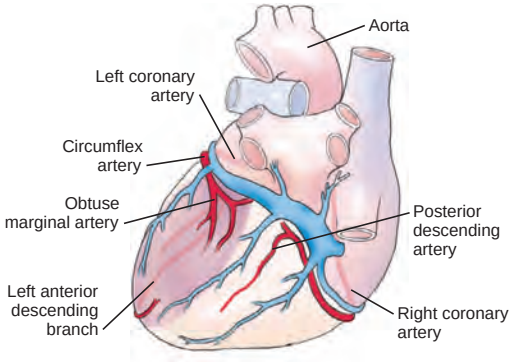


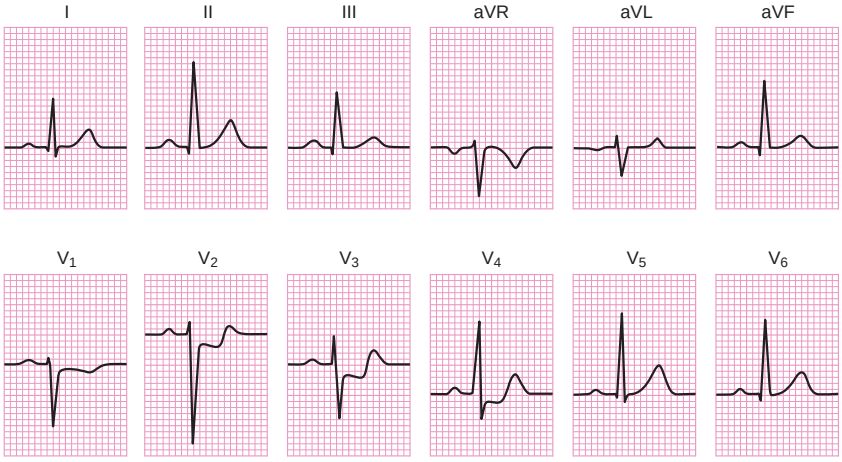




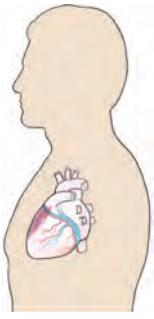
Anatomic Site	Leads	ECG Changes	Coronary Artery
Posterior	V_1–V_2	↑R, ↓ST, ↓T	Left circumflex

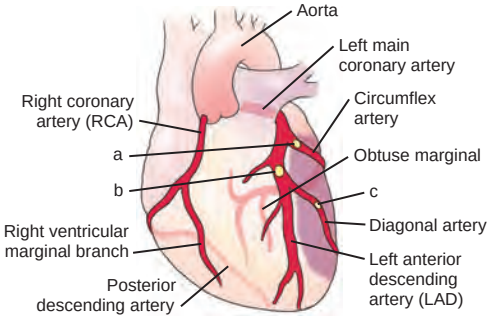


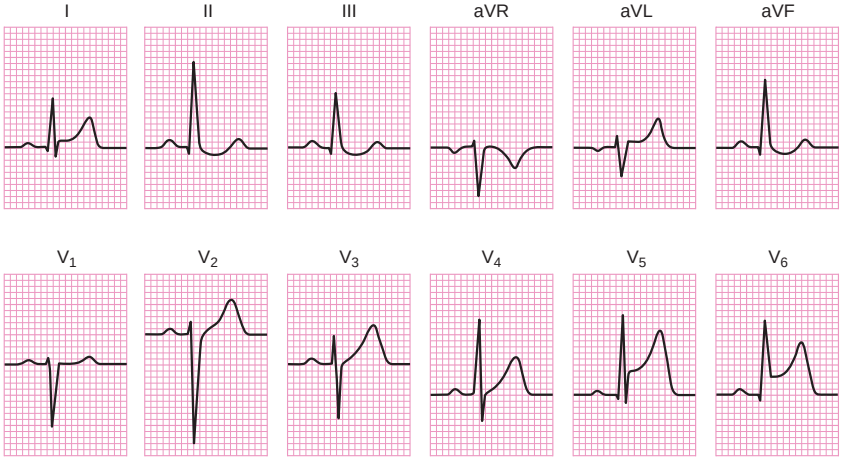




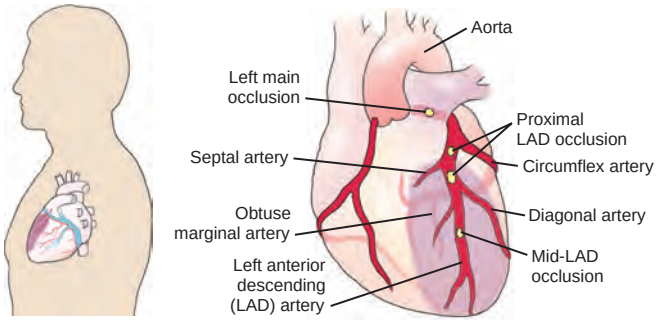
Anatomic Site	Leads	ECG Changes	Coronary Artery
Lateral	I, aVL, V_5, V_6	Q, ↑ST, ↑T	Left circumflex

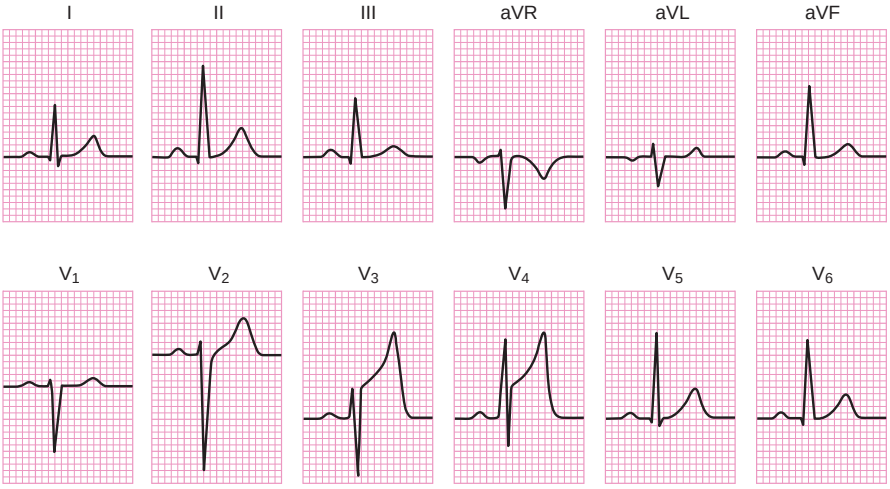




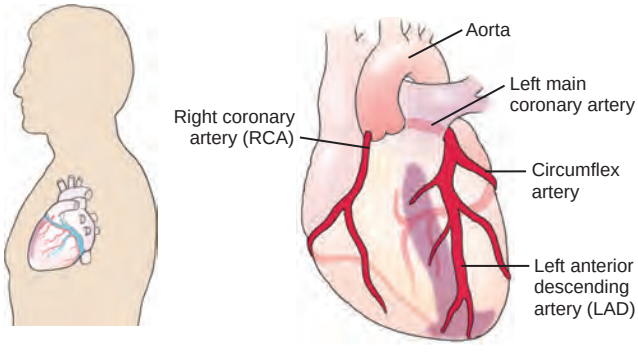


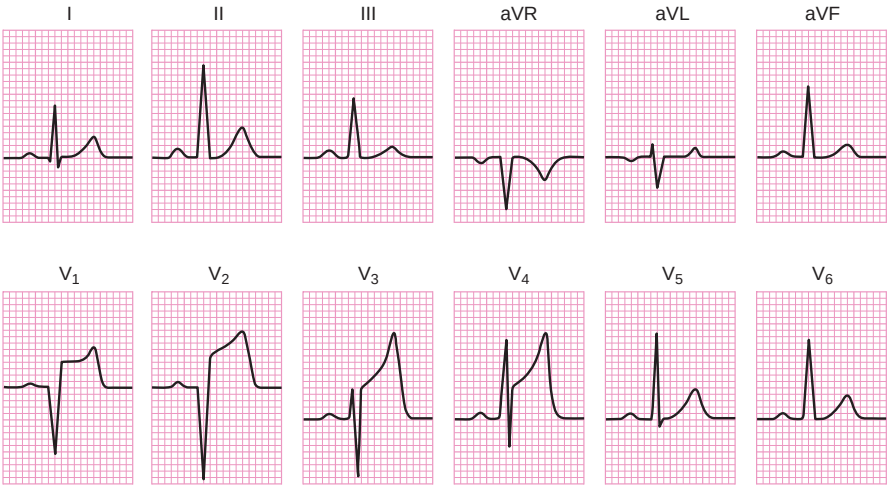
Anatomic Site	Leads	ECG Changes	Coronary Artery
Anterior	I, aVL, V_1–V_4	Q, ↑ST, ↑T	Left anterior descending





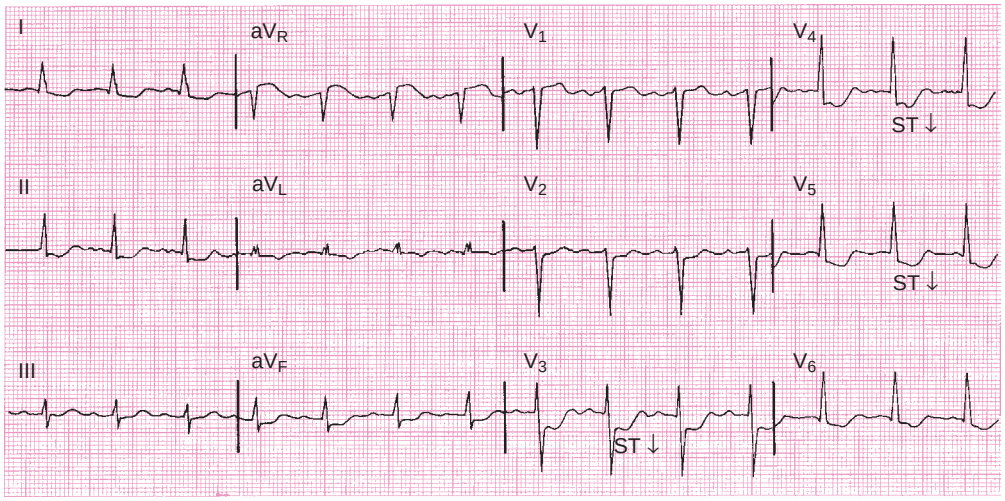
Anatomic Site	Leads	ECG Changes	Coronary Artery
Anteroseptal	V_1–V_4	Q, ↑ST, ↑T	Left anterior descending





Subendocardial Myocardial Infarction

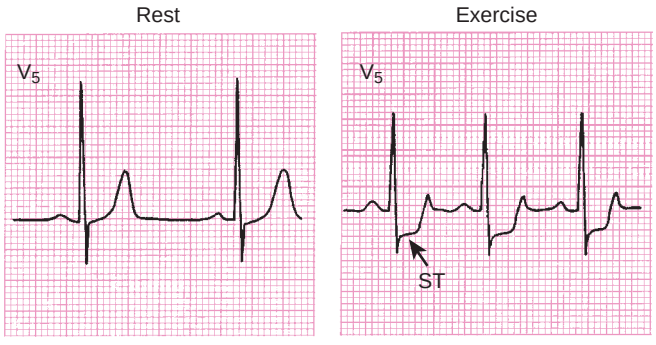
Persistent ST-segment depression or T-wave inversion occurs in the absence of a Q wave. This usually requires additional laboratory data (eg, isoenzymes) to confirm the diagnosis. The anatomic site of the coronary lesion is similar to that of transmural MI electrocardiographically.

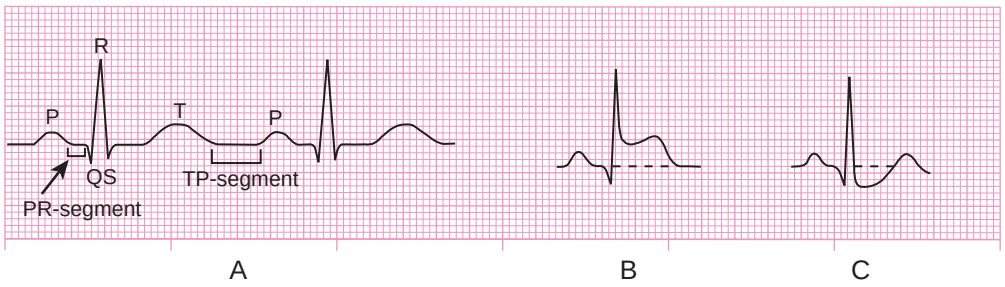


Myocardial Ischemia

Rate: Variable
Rhythm: Usually regular, but may show atrial and/or ventricular arrhythmias
PR interval: Normal
QT interval: ST segment depressed; J-point depression; T-wave inversion; conduction disturbances; coronary vasospasm (Prinzmetal) ST-segment elevation; (A) TP and PR intervals baseline for ST-segment deviation, (B) ST-segment elevation, (C) ST-segment depression

Note: Intraoperative ischemia usually is seen in the presence of "normal" vital signs (eg, ±20% of preinduction values).

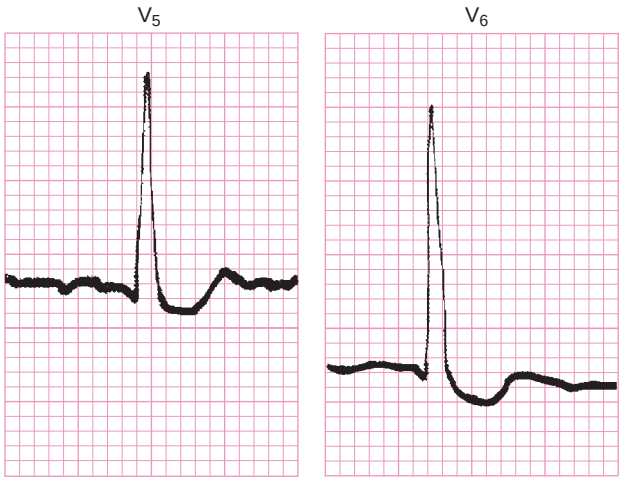




Digitalis Effect

Rate: <100 beats/min
Rhythm: Regular
PR interval: Normal or prolonged
QT interval: ST-segment sloping ("digitalis effect")

Note: Digitalis toxicity can be the cause of many common arrhythmias (eg, premature ventricular contractions, second-degree heart block). Verapamil, quinidine, and amiodarone cause an increase in serum digitalis concentration.

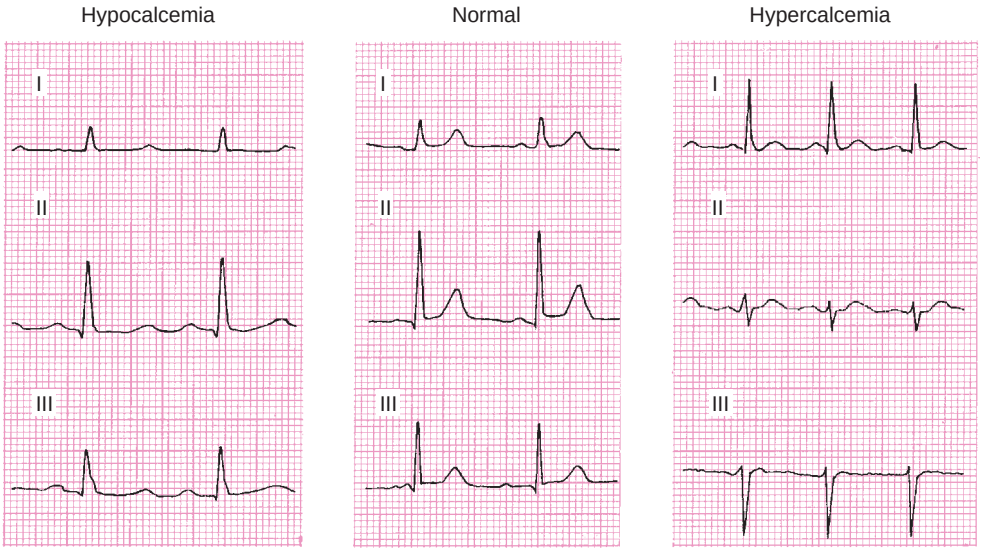


Electrolyte Disturbances

	↓Calcium	↑Calcium	↓Potassium	↑Potassium
Rate	<100 beats/min	<100 beats/min	<100 beats/min	<100 beats/min
Rhythm	Regular	Regular	Regular	Regular
PR interval	Normal	Normal/increased	Normal	Normal
QT interval	Increased	Decreased	Normal	Increased
Other			T wave flat U wave	T wave peaked

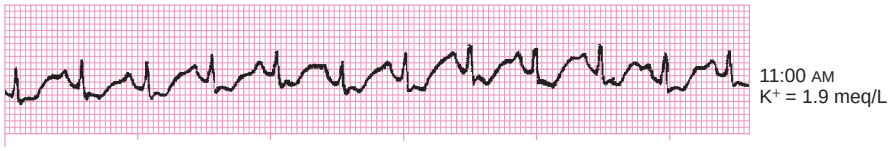
Note: Electrocardiographic (ECG) changes usually do not correlate with serum calcium. Hypocalcemia rarely causes arrhythmias in the absence of hypokalemia. In contrast, abnormalities in serum potassium concentration can be diagnosed by electrocardiogram. Similarly, in the clinical range, magnesium concentrations rarely are associated with unique ECG patterns. The presence of a "u" wave (>1.5 mm in height) also is seen in left main coronary artery disease, certain medications, and long QT syndrome.

Calcium

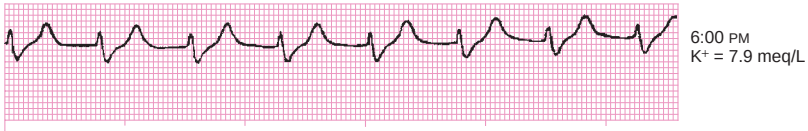


Potassium

Hypokalemia (K^+ = 1.9 mEq/L)



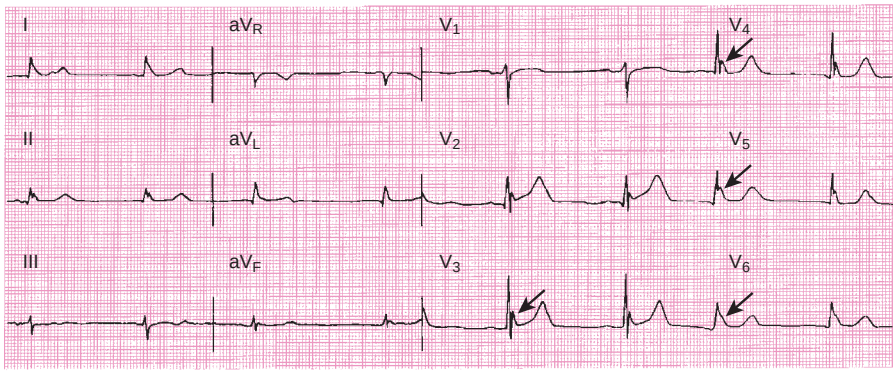
Hyperkalemia (K^+ = 7.9 mEq/L)



Hypothermia

Rate: <60 beats/min
Rhythm: Sinus
PR interval: Prolonged
QT interval: Prolonged

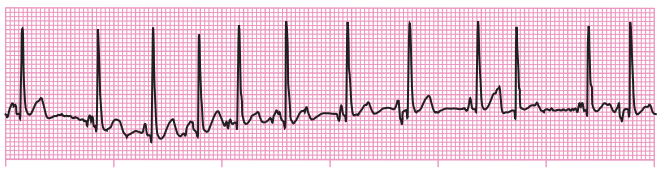
Note: This is seen at temperatures less than 33°C with ST-segment elevation (J point or Osborn wave). Tremor caused by shivering or Parkinson disease may interfere with ECG interpretation and may be confused with atrial flutter. This may represent a normal variant of early ventricular repolarization. (The *arrow* indicates a J point or Osborn waves.)



Multifocal Atrial Tachycardia

Rate: 100–200 beats/min
Rhythm: Irregular
PR interval: Consecutive P waves are of varying shape
QT interval: Normal

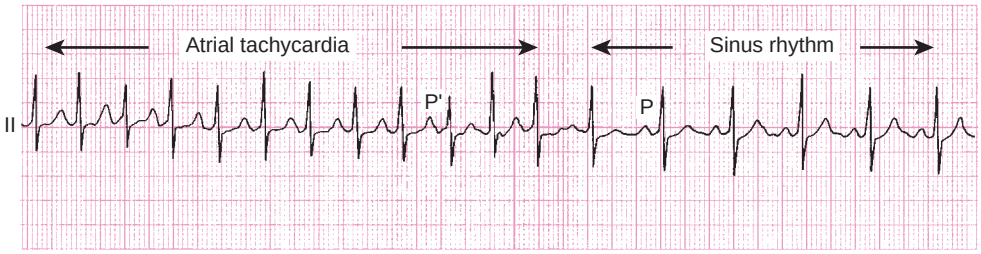
Note: This is seen in patients with severe lung disease. Carotid massage has no effect. At heart rates lower than 100 beats/min, it may appear as wandering atrial pacemaker. It may be mistaken for atrial fibrillation. Treatment is of the causative disease process.



Paroxysmal Atrial Tachycardia

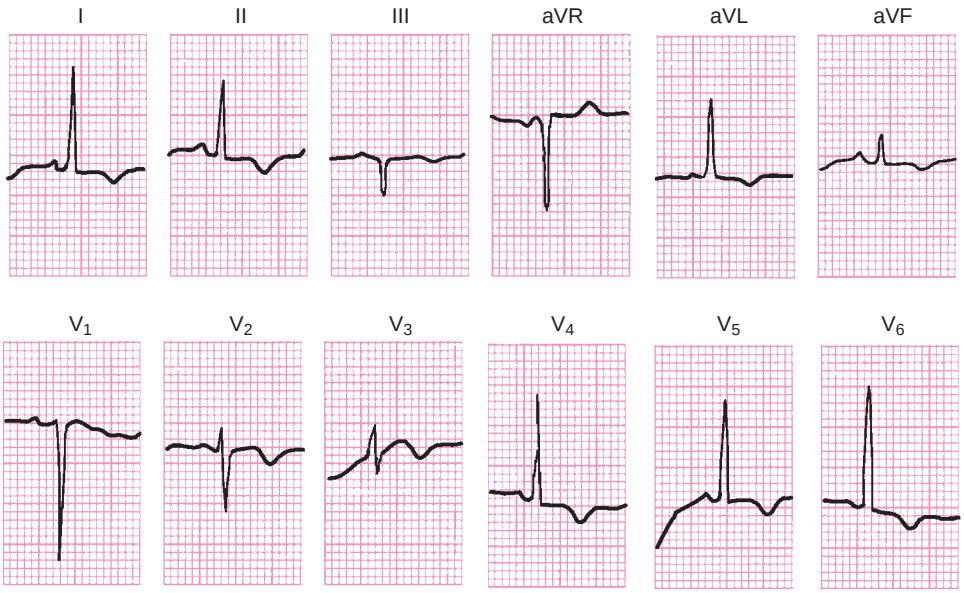
Rate: 150–250 beats/min
Rhythm: Regular
PR interval: Difficult to distinguish because of tachycardia obscuring P wave; P wave may precede, be included in, or follow QRS complex
QT interval: Normal, but ST segment and T wave may be difficult to distinguish

Note: Therapy depends on the degree of hemodynamic compromise. Carotid sinus massage may terminate the rhythm or decrease heart rate. In contrast to management of paroxysmal atrial tachycardia (PAT) in awake patients, synchronized cardioversion rather than pharmacologic treatment is preferred in hemodynamically unstable anesthetized patients.



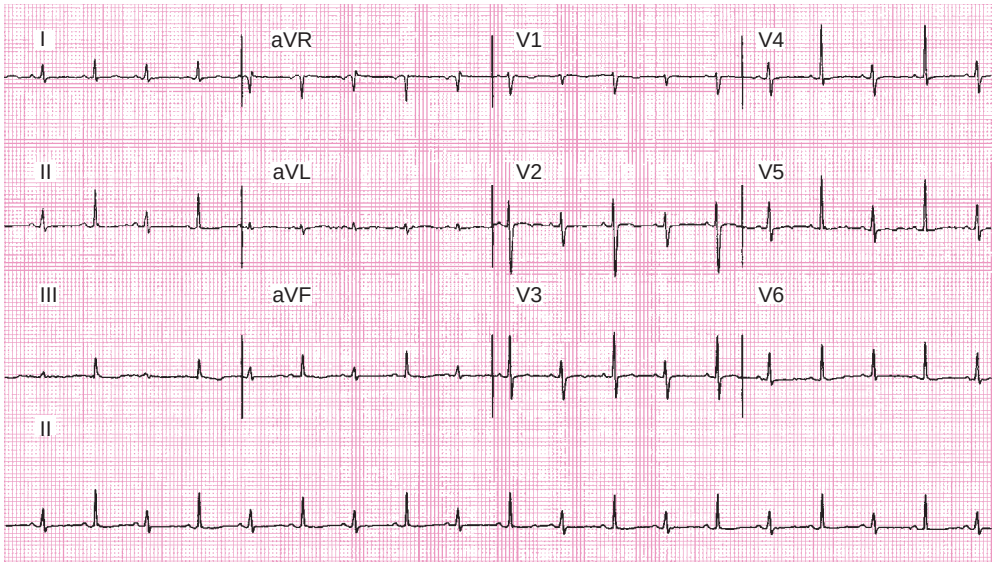
Pericarditis

Rate: Variable
Rhythm: Variable
PR interval: Normal
QT interval: Diffuse ST- and T-wave changes with no Q wave and seen in more leads than an MI



Pericardial Tamponade

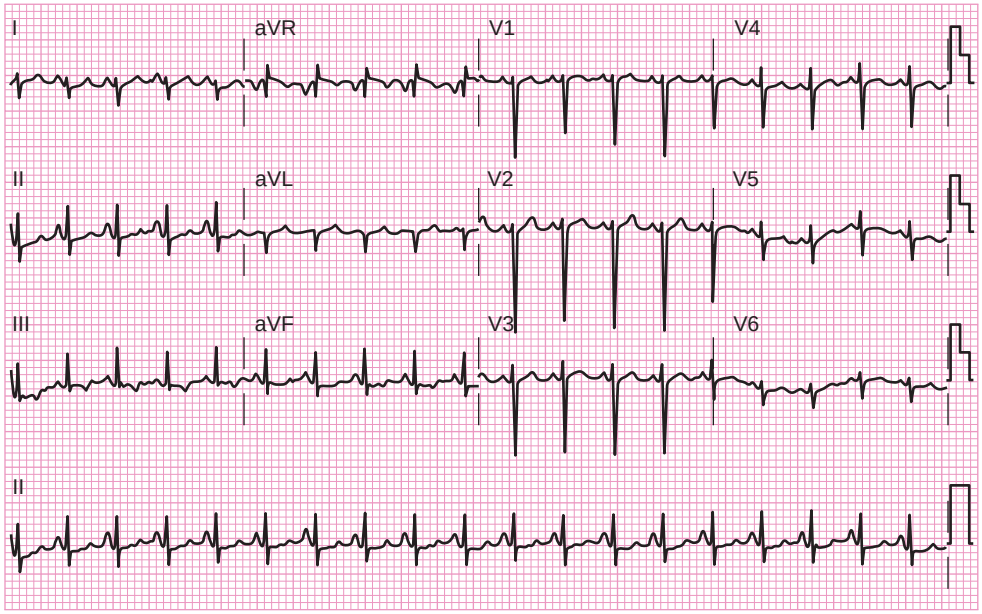
Rate: Variable
Rhythm: Variable
PR interval: Low-voltage P wave
QT interval: Seen as electrical alternans with low-voltage complexes and varying amplitude of P, QRS, and T waves with each heartbeat



Pneumothorax

Rate: Variable
Rhythm: Variable
PR interval: Normal
QT interval: Normal

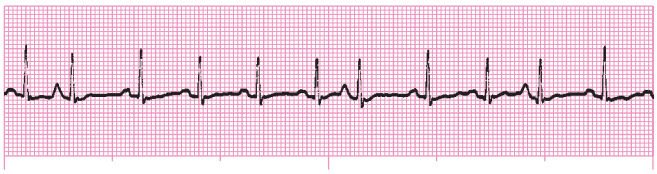
Note: Common ECG abnormalities include right-axis deviation, decreased QRS amplitude, and inverted T waves in leads V_1 to V_6. Differentiate from pulmonary embolus. It may manifest as electrical alternans; thus, pericardial effusion should be ruled out.



Premature Atrial Contraction

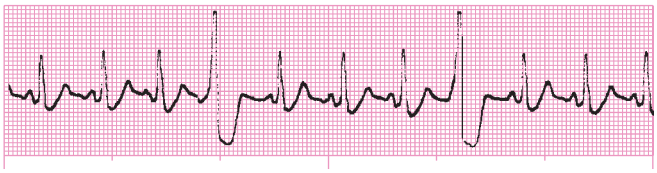
Rate: <100 beats/min
Rhythm: Irregular
PR interval: P waves may be lost in preceding T waves; PR interval variable
QT interval: QRS normal configuration; ST segment and T wave normal

Note: Nonconducted premature atrial contraction (PAC) appearance is similar to that of sinus arrest; T waves with PAC may be distorted by inclusion of a P wave in the T wave.



Premature Ventricular Contraction

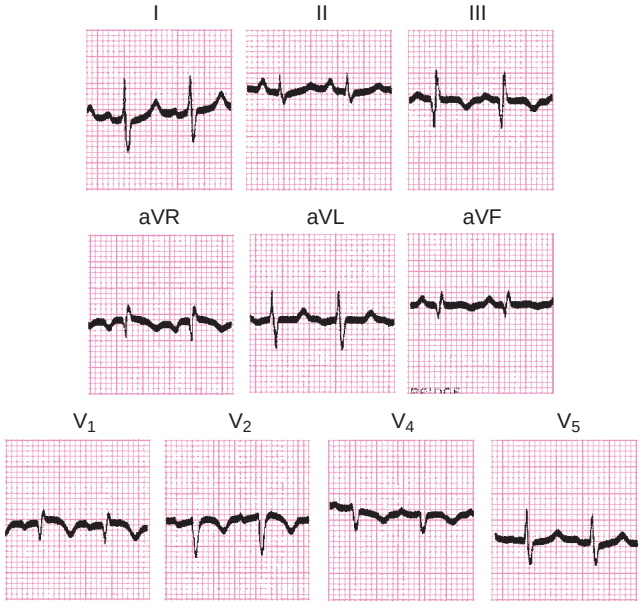
Rate: Usually <100 beats/min
Rhythm: Irregular
PR interval: P wave and PR interval absent; retrograde conduction of P wave can be seen
QT interval: Wide QRS (>0.12 second); ST segment cannot be evaluated (eg, ischemia); T wave opposite direction of QRS with compensatory pause; fourth and eighth beats premature ventricular contractions



Pulmonary Embolus

Rate: >100 beats/min
Rhythm: Sinus
PR interval: P-pulmonale waveform
QT interval: Q waves in leads III and AV_F

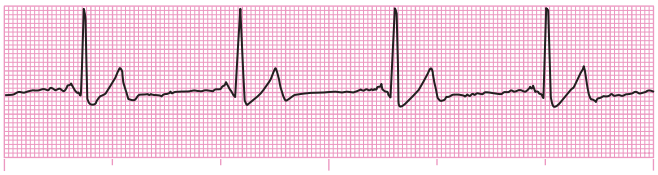
Note: Classic ECG signs of $S_1Q_3T_3$ with T-wave inversion are also seen in leads V_1 to V_4 and right ventricular strain (ST-segment depression in $V_{1–4}$). It may manifest with atrial fibrillation or flutter.



Sinus Bradycardia

Rate: <60 beats/min
Rhythm: Sinus
PR interval: Normal
QT interval: Normal

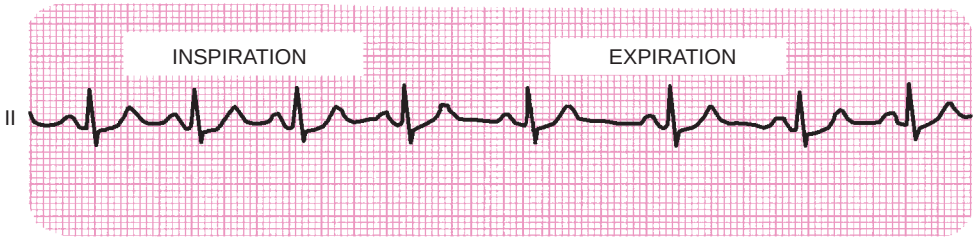
Note: This is seen in trained athletes as a normal variant.



Sinus Arrhythmia

Rate: 60–100 beats/min
Rhythm: Sinus
PR interval: Normal
QT interval: R-R interval variable

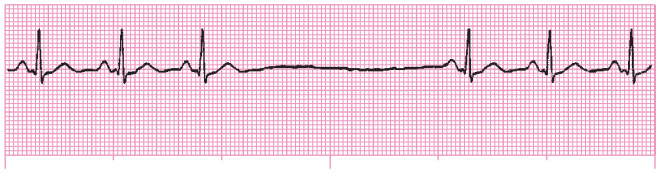
Note: Heart rate increases with inhalation and decreases with exhalation are ±10% to 20% (respiratory). Nonrespiratory sinus arrhythmia is seen in older adults with heart disease. It is also seen with increased intracranial pressure.



Sinus Arrest

Rate: <60 beats/min
Rhythm: Varies
PR interval: Variable
QT interval: Variable

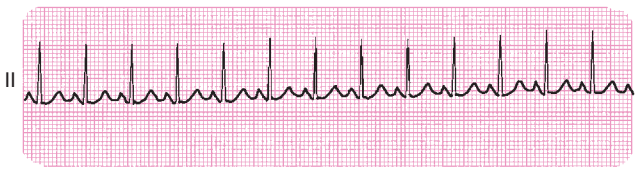
Note: Rhythm depends on the cardiac pacemaker's firing in the absence of sinoatrial stimulus (atrial pacemaker, 60–75 beats/min; junctional, 40–60 beats/min; ventricular, 30–45 beats/min). Junctional rhythm is most common. Occasional P waves may be seen (retrograde P wave).



Sinus Tachycardia

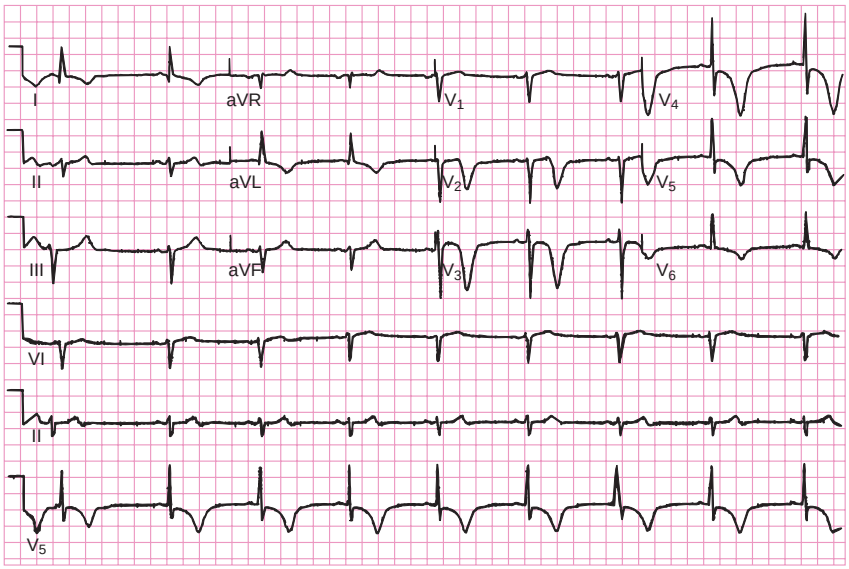
Rate: 100–160 beats/min
Rhythm: Regular
PR interval: Normal; P wave may be difficult to see
QT interval: Normal

Note: This should be differentiated from PAT. With PAT, carotid massage terminates the arrhythmia. Sinus tachycardia may respond to vagal maneuvers but reappears as soon as vagal stimulus is removed.



Subarachnoid Hemorrhage

Rate: <60 beats/min
Rhythm: Sinus
PR interval: Normal
QT interval: T-wave inversion deep and wide, prominent U waves; sinus arrhythmias; Q waves may be seen and may mimic acute coronary syndrome

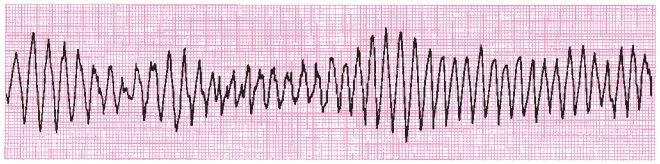


Torsades de Pointes

Rate: 150–250 beats/min
Rhythm: No atrial component seen; ventricular rhythm regular or irregular
PR interval: P wave buried in QRS complex
QT interval: QRS complexes usually wide and with phasic variation twisting around a central axis (a few complexes point upward, then a few point downward); ST segments and T waves difficult to discern

Note: This type of ventricular tachycardia is associated with a prolonged QT interval. It is seen with electrolyte disturbances (eg, hypokalemia, hypocalcemia, and hypomagnesemia) and bradycardia. Administering standard antiarrhythmic agents (eg, lidocaine, procainamide) may worsen torsades de pointes. Prevention includes treatment of the electrolyte disturbance. Treatment includes shortening of the QT interval, pharmacologically or by pacing; unstable polymorphic VT is treated with immediate defibrillation.

Torsades de Pointes: Sustained

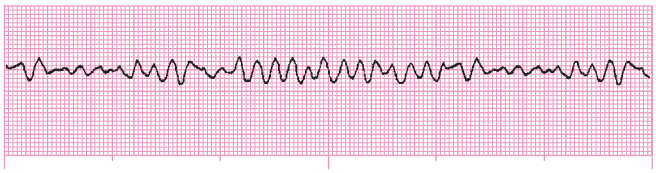


Ventricular Fibrillation

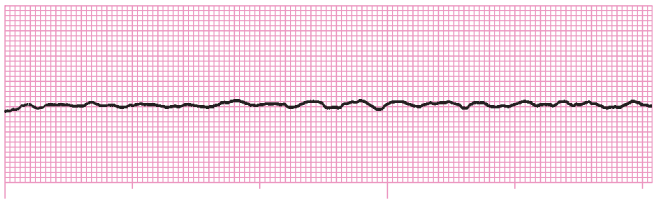
Rate: Absent
Rhythm: None
PR interval: Absent
QT interval: Absent

Note: "Pseudoventricular fibrillation" may be the result of a monitor malfunction (eg, ECG lead disconnect). Always check for the carotid pulse before instituting therapy.

Coarse Ventricular Fibrillation



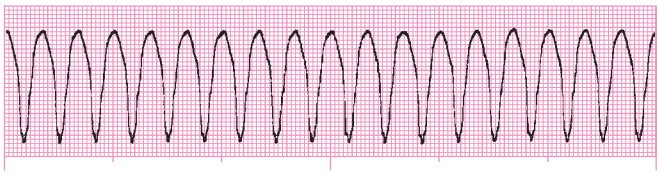
Fine Ventricular Fibrillation



Ventricular Tachycardia

Rate: 100–250 beats/min
Rhythm: No atrial component seen; ventricular rhythm irregular or regular
PR interval: Absent; retrograde P wave may be seen in QRS complex
QT interval: Wide, bizarre QRS complex; ST segment and T wave difficult to determine

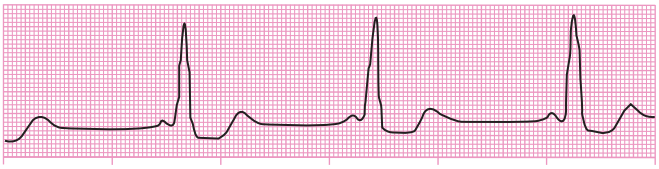
Note: In the presence of hemodynamic compromise, immediate direct current synchronized cardioversion is required. If the patient is stable, with short bursts of ventricular tachycardia, pharmacologic management is preferred. This should be differentiated from supraventricular tachycardia with aberrancy (SVT-A). A compensatory pause and AV dissociation suggest a premature ventricular contraction. P waves and SR′ (V_1) and slowing to vagal stimulus also suggest SVT-A.



Wolff-Parkinson-White Syndrome

Rate: <100 beats/min
Rhythm: Regular
PR interval: P wave normal; PR interval short (<0.12 second)
QT interval: Duration (>0.10 second) with slurred QRS complex; type A has delta wave, RBBB, with upright QRS complex V_1; type B has delta wave and downward QRS-V_1; ST segment and T wave usually normal

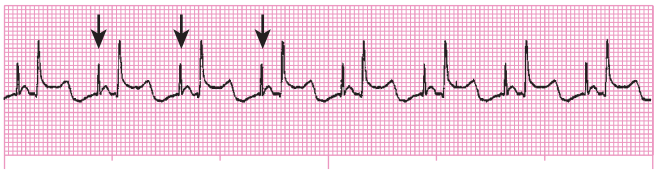
Note: Digoxin should be avoided in the presence of Wolff-Parkinson-White syndrome because it increases conduction through the accessory bypass tract (bundle of Kent) and decreases AV node conduction; consequently, ventricular fibrillation can occur.



Pacing

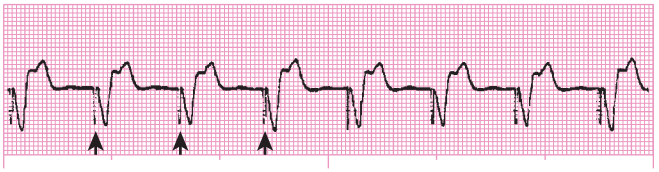
Atrial Pacing

Atrial pacing as demonstrated in this figure is used when the atrial impulse can proceed through the AV node. Examples are sinus bradycardia and junctional rhythms associated with clinically significant decreases in blood pressure. (The *arrows* are the pacemaker spike.)



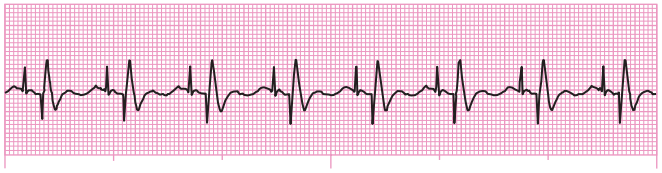
Ventricular Pacing

In this tracing, ventricular pacing is evident by absence of an atrial wave (P wave) and the pacemaker spike preceding the QRS complex. Ventricular pacing is used in the presence of bradycardia secondary to AV block or atrial fibrillation. (The *arrows* are the pacemaker spike.)



DDD Pacing

The DDD pacemaker (generator), one of the most commonly used, paces and senses both the atrium and the ventricle. Each atrial and ventricular complex is preceded by a pacemaker spike.



Acknowledgments

Illustrations in this appendix are reprinted from Aehlert B. *ECGs Made Easy.* 4th ed. St. Louis: Mosby; 2011; Goldberger AL. *Clinical Electrocardiography: A Simplified Approach.* 7th ed. Philadelphia: Mosby; 2006; Groh WJ, Zipes DP. Neurological disorders and cardiovascular disease. In: Bonow RO, Mann DL, Zipes DP, et al, eds. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 9th ed. Philadelphia: Saunders; 2012; Huszar RJ. *Basic Dysrhythmias: Interpretation and Management.* 2nd ed. St. Louis: Mosby Lifeline; 1994; and Soltani P, Malozzi CM, Saleh BA, et al. Electrocardiogram manifestation of spontaneous pneumothorax. *Am J Emerg Med.* 2009;27:750.e1–5.

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13

Monitoring of the Heart and Vascular System

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KEY POINTS

1. Patients with severe cardiovascular disease and those undergoing surgery associated with rapid hemodynamic changes should be adequately monitored at all times.
2. Standard monitoring for cardiac surgery patients includes invasive blood pressure, electrocardiography, central venous pressure, urine output, temperature, capnometry, pulse oximetry, and intermittent blood gas analysis.
3. Additional monitoring is based on specific patient, surgical, and environmental factors. In the absence of evidence that advanced monitoring improves outcome, potential benefits have to be weighed against potential risks on an individual basis.
4. The Society of Cardiovascular Anesthesiologists and the American Society of Echocardiography have published recommendations for intraoperative transesophageal echocardiography (TEE) (see Chapters 14 through 17). TEE is recommended for all patients undergoing cardiac surgery, unless contraindications to probe insertion apply.
5. Transthoracic echocardiography is a less invasive alternative to TEE in the perioperative setting.
6. Ultrasound-guided vascular access is now routinely practiced in many institutions.
7. The use of pulmonary artery catheters (PACs) has been steadily declining. Guidelines for PAC use have been published but not specifically for the cardiac surgery setting. Many practitioners still use PACs to guide treatment in patients with low cardiac output or pulmonary arterial hypertension.
8. The role of noninvasive neuromonitoring is expanding, including regional oxygen saturation (cerebral oximetry) and processed electroencephalography (such as bispectral index) (see Chapter 18).
9. The use of additional highly invasive monitoring techniques, such as left atrial or coronary sinus pressures and cerebrospinal fluid pressures, are restricted to very specific indications.
10. Minimally invasive and noninvasive techniques for hemodynamic assessment continue to be developed, with increasing functionality and accuracy. Their role in the care of cardiac surgery patients requires further evaluation.

Hemodynamic Monitoring

The availability of monitoring devices is increasing continually. These devices range from those that are completely noninvasive to those that are highly invasive, such as the pulmonary artery catheter (PAC). Limitations to less invasive monitoring technologies often apply, and interventions based on information gained from noninvasive monitoring carry intrinsic risks, such as when blood is transfused to a patient with low cerebral oximetry readings. To make the best use of any monitoring technology, the potential benefits to be gained from the information must outweigh the potential complications. This risk-benefit ratio is highly variable and must be evaluated for each clinical scenario individually.

In many patients with significant cardiovascular morbidity undergoing cardiac or major noncardiac surgery, the benefits obtained are often believed to outweigh the risks, explaining the widespread use of invasive monitoring. Although outcome changes are difficult to prove, the assumption that appropriate hemodynamic monitoring should reduce the incidence of major cardiovascular complications is reasonable. This is based on the presumption that the data obtained from these monitors are interpreted correctly and that therapeutic interventions known to improve outcomes are implemented in a timely fashion.

Standard monitoring for all patients undergoing surgery has been defined by the American Society of Anesthesiologists (ASA) practice guidelines.[1] In patients undergoing cardiac or major noncardiac surgery with expected large fluid shifts or hemodynamic instability, invasive blood pressure (BP) monitoring is nearly universally employed, which also enables frequent arterial blood sampling. Transesophageal echocardiography (TEE), a less invasive technology, provides extensive hemodynamic data and other diagnostic information and is described in detail in Chapters 14 through 17. The Society of Cardiovascular Anesthesiologists and the American Society of Echocardiography have published recommendations for intraoperative TEE use.[2] Unless contraindications to probe insertion apply, TEE is now recommended for all patients undergoing cardiac surgery. The role of noninvasive brain monitoring is expanding, including regional oxygen saturation (cerebral oximetry) and processed electroencephalography (such as bispectral index). In the absence of guidelines specifying their role, institutional practices often include some form of neuromonitoring in patients undergoing cardiac surgery. Box 13.1 summarizes monitoring typically used in cardiac and major noncardiac surgeries.

The next tier of monitoring is typically more invasive, including PACs with thermodilution cardiac output (CO) and other CO monitors, spinal fluid pressure for thoracic aorta surgery (see Chapter 23), and rarely, left atrial pressure (LAP) monitoring. The interpretation of these complex data requires an astute clinician who is aware of the patient's overall condition and the limitations of the monitors. Additionally, with the expansion of less invasive surgical techniques,

BOX 13.1 STANDARD MONITORING FOR CARDIAC SURGICAL PATIENTS

- (Invasive) blood pressure
- Electrocardiogram
- Pulse oximetry
- Capnometry
- Temperature
- Central venous pressure
- Transesophageal echocardiography
- Urine output
- Intermittent arterial blood sampling for blood gas and laboratory analyses
- Neuromonitoring (cerebral oximetry, processed electroencephalography)

BOX 13.2 EXTENDED MONITORING FOR PATIENTS BASED ON CASE-SPECIFIC FACTORS

- Retrograde cardioplegia pressure
- Pulmonary artery catheter
- Cardiac output measurements
- Left atrial pressure
- Cerebrospinal fluid (intrathecal) pressure

the anesthesiologist is getting more involved in guiding cardiopulmonary bypass (CPB) cannulation and adequacy of cardioprotection techniques. This includes retrograde cardioplegia cannula positioning in the coronary sinus (CS) and pressure monitoring. Advanced monitoring is summarized in Box 13.2.

Arterial Pressure Monitoring

Anesthesia for cardiac and major noncardiac surgeries is frequently complicated by rapid and sudden changes in BP. Sudden losses of large amounts of blood, direct compression of the heart, impaired venous return attributable to retraction and cannulation of the vena cavae and aorta, arrhythmias, and manipulations that may impair right ventricular outflow and pulmonary venous return all contribute to hemodynamic instability. Therefore a safe and reliable method of measuring acute changes in BP is indispensable. Numerous methods of noninvasive BP measurement are clinically available and are discussed later in this chapter. Despite significant technologic advancements, none of these noninvasive devices so far have proven to be suitable for cardiac surgery. Thus direct intraarterial monitoring remains the gold standard, providing a continuous, beat-to-beat indication of the arterial pressure and waveform and allowing frequent sampling of arterial blood for laboratory analyses.

General Principles

The arterial pressure waveform ideally is measured in the ascending aorta. The pressure measured in the more peripheral arteries is different from the central aortic pressure, because the arterial waveform becomes progressively more distorted as the signal is transmitted down the arterial system. The high-frequency components, such as the dicrotic notch, disappear, the systolic peak increases, the diastolic trough decreases, and a transmission delay occurs. These changes are caused by decreased arterial compliance in the periphery and reflection and resonance of pressure waves in the arterial tree.[3] This effect is most pronounced in the dorsalis pedis artery, in which the systolic blood pressure (SBP) may be 10 to 20 mm Hg higher and the diastolic blood pressure (DBP) 10 to 20 mm Hg lower than in the central aorta

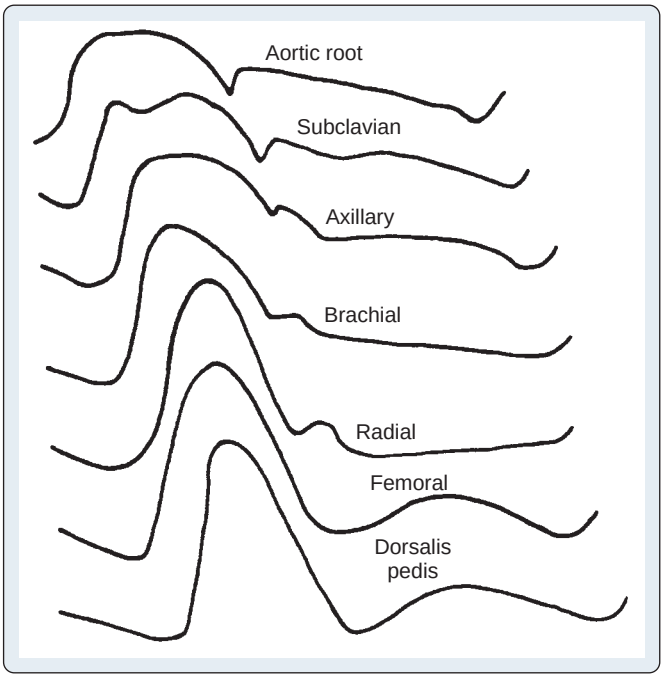


Fig. 13.1 The waveform of the arterial pressure changes significantly according to the site of the intraarterial catheter. These changes are shown as a progression from central monitoring *(top)* through peripheral monitoring *(bottom)*. These changes are thought to be caused by forward wave propagation and wave reflection. In the periphery, systolic pressure is higher, diastolic pressure is lower, and mean pressure is minimally lower. *(Modified from Bedford RF. Invasive blood pressure monitoring. In: Blitt CD, ed.* Monitoring in Anesthesia and Critical Care. *New York: Churchill Livingstone; 1985:505.)*

(Fig. 13.1).[4] Despite this distortion, the mean arterial pressure (MAP) measured in the peripheral arteries should be similar to the central aortic pressure under normal circumstances. After separation from CPB, however, MAP measured in a peripheral artery can be significantly lower than central aortic pressure for periods of time.[5,6]

The magnitude of BP is directly related to CO and systemic vascular resistance (SVR). This is conceptually similar to Ohm's law of electricity (voltage = current × resistance), in which BP is analogous to voltage, CO to current flow, and SVR to resistance. An increase in BP may reflect an increase in CO or SVR, or both.

MAP is probably the most useful parameter when assessing overall end-organ perfusion. MAP is measured directly by integrating the arterial waveform tracing over time or using the formula: MAP = (SBP + [2 × DBP]) ÷ 3. Perfusion of the heart differs from most other organs, with coronary perfusion of the left ventricle mostly occurring during diastole. Coronary blood flow to the normal right ventricle (RV) is maintained during systole and diastole. However, in patients with right ventricular hypertrophy or pulmonary arterial hypertension, perfusion of the RV becomes significantly decreased during right ventricular systole and more dependent on the diastolic phase of the cardiac cycle and diastolic perfusion pressure.[7,8]

Additional information can be gained from an arterial waveform tracing that supplements timely BP measurements.[9] For example, the slope of the arterial upstroke correlates with the derivative of pressure measured over time (dP/dt) and gives an indirect estimate of myocardial contractility. This information is not always reliable, because an increase in SVR alone will also result in an increase in the slope of the upstroke. The arterial pulse contour can be used to estimate stroke volume (SV) and CO. Large SBP variations during the respiratory cycle in the mechanically ventilated patient suggest hypovolemia.[10–12] A reduced pulse pressure and small area under the arterial pressure curve can indicate low CO; however, technical errors in pressure

transducing and associated cardiac pathologic conditions complicate these interpretations.

Components of a Pressure Measurement System

Pressure waves in the arterial (or venous) tree represent the transmission of forces generated in the cardiac chambers. Measurement of these forces requires their transmission to a device that converts mechanical energy into electronic signals. The components of a system for intravascular pressure measurement include an intravascular catheter, fluid-filled tubing and connections, an electromechanical transducer, an electronic analyzer, and electronic storage and display systems. For arterial pressure measurements, short, narrow catheters are recommended (20 gauge or smaller), because they have favorable dynamic response characteristics and are less thrombogenic than larger catheters.[13] An artifact associated with intraarterial catheters has been designated *end-pressure artifact*.[14] When flowing blood comes to a sudden halt at the tip of the catheter, it is estimated that an added pressure of 2 to 10 mm Hg results. Conversely, clot formation on the catheter tip will dampen the system and narrow the pulse pressure. The coupling system usually consists of pressure tubing, stopcocks, and a continuous flushing device. This is the major source of distortion of arterial pressure tracings. The arterial catheter should be kept patent with a continuous infusion of normal saline solution (1 to 3 mL/hr). Heparin is no longer routinely recommended as an additive to flush solutions, attributable to the risk of heparin-induced thrombocytopenia in susceptible patients. The function of pressure transducers is to convert mechanical forces into electrical current or voltage, which is accomplished by incorporating a variable resistor into a Wheatstone bridge–type electrical circuit. The resistor changes electrical resistance according to the mechanical forces transmitted via a fluid column. To avoid direct contact, the resistor is separated from the fluid column and blood by a diaphragm into which the resistive elements have been etched. The manufacturers have adopted an output standard of 5 μV per volt excitation per 1 mm Hg so that, theoretically, any transducer can be used with any monitor.[15] Modern disposable transducers are already calibrated and pass manufacturing standards, thus eliminating many of the difficulties that used to require frequent recalibration because of drifting of the zero point. Nevertheless, drifting of the zero point still occurs and may be attributed to the transducer-to-cable-to-monitor input connection. Unrecognized drifting of the zero point is a serious problem, possibly resulting in unwarranted and potentially harmful interventions. The major practical problem remaining with transducer systems, however, is improper levelling of the transducer height relative to the patient. For accurate pressure readings, and especially for accurately determining pressure values in the low pressure system, exact leveling of the transducer height with the heart must be achieved. Careful leveling with the midaxillary line is the most common method. Alternatively, fluid-filled pressure tubing passed from the surgical field is connected to a transducer, with the height of the transducer adjusted until the pressure reads zero. It is important to recall that electronically zeroing the transducer system is a distinct task from accurate leveling of the transducer unit. This problem is of less clinical relevance for arterial BP measurements yet still results in errors that could adversely affect care.

Characteristics of a Pressure Measurement System

The dynamic response of a pressure measurement system is characterized by its natural frequency and its damping.[16] These concepts are best understood by snapping the end of a transducer-tubing assembly with a finger. The waveform on the monitor demonstrates rapid oscillations above and below the baseline (the natural frequency), which quickly decays to a straight line attributable to friction in the system (damping). The peaks and troughs of an arterial pressure waveform will be amplified if the transducer-tubing-catheter assembly has a natural frequency that lies close to the frequencies of the underlying sine waves of an arterial pressure waveform (typically less than 20 Hz).

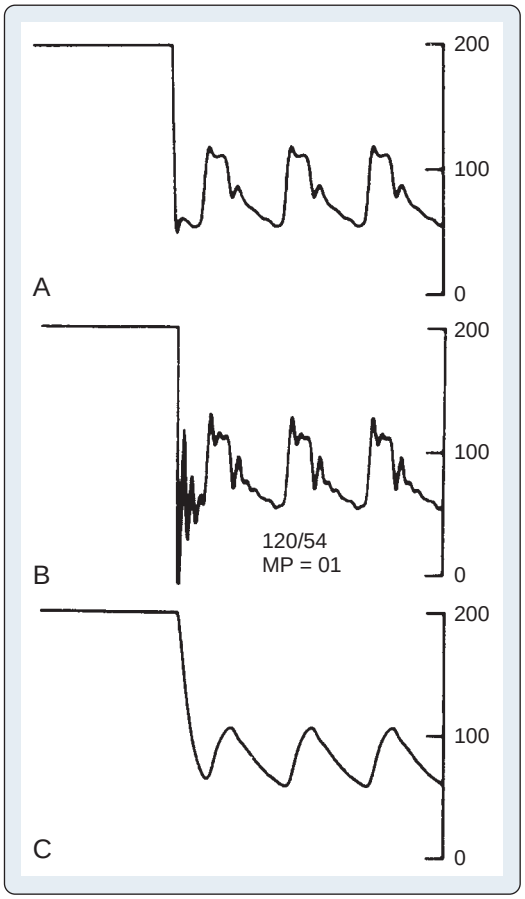


Fig. 13.2 The fast-flush test demonstrates the harmonic characteristics of a pressure monitoring system (ie, transducer, fluid-filled tubing, and intraarterial catheter). In an optimally damped system *(A)*, the pressure waveform returns to baseline after only one oscillation. In an underdamped system *(B)*, the pressure waveform oscillates above and below the baseline several times. In an overdamped system *(C)*, the pressure waveform returns to the baseline slowly with no oscillations. *(A–C, Adapted from Gibbs NC, Gardner RM. Dynamics of invasive pressure monitoring systems: clinical and laboratory evaluation.* Heart Lung. *1988;17:43–51.)*

This is commonly known as *ringing* or *resonance* of the system (Fig. 13.2). For an arterial pressure monitoring system to remain accurate at a higher heart rate (HR), its natural frequency should be higher. It is recommended that the natural frequency of the pressure transducing system is at least eight times higher than the frequency of the measured sine wave. Thus for an HR up to 180 beats per minute, the resulting minimum natural frequency requirement would be 24 Hz (ie, [180 × 8] ÷ 60 seconds).[17] The dynamic response of the bare transducers without the tubing is usually considerably higher, in the 200 to 500 Hz range. However, adding transducer tubing and three-way stopcocks significantly lowers the natural frequency. In general, longer transducer tubing decreases the natural frequency of the system and tends to amplify the height of the SBP (peak) and the depth of the DBP (trough) values.[16,18] Boutros and Albert[19] demonstrated that by changing the length of low-compliance (rigid) tubing from 6 inches to 5 feet, the natural frequency decreased from 34 to 7 Hz. As a result of the reduced natural frequency of the pressure transducing system, the SBP measured with the longer tubing exceeded reference pressures by 17.3%. Conversely, reducing the length of the tubing or a larger size cannula will increase the natural frequency.

Damping is the tendency of factors such as friction, compliant (soft) tubing, and air bubbles to absorb energy and decrease the amplitude of peaks and troughs in the waveform. The optimal degree of damping

is that which counterbalances the distorting effects of transducer-tubing systems with lower natural frequencies, which is very difficult to achieve. The damping of a clinical pressure measurement system can be assessed by observing the response to a rapid high-pressure flush of the transducer-tubing-catheter system (see Fig. 13.2). In a system with a low damping coefficient, a fast-flush test results in several oscillations above and below the baseline before the pressure becomes constant. In an adequately damped system, the baseline is reached after one oscillation, whereas in an overdamped system, the baseline is reached after a delay and without oscillations.[20–23] Overdamping causes a falsely lower SBP reading and a higher DBP reading, with the mean arterial BP mostly unaffected, unless a significant distortion occurs (eg, from clot formation). Underdamping of a system results in the opposite effects on BP readings. These may be a major source of error, causing an underreading of the SBP and overreading of DBP, although the MAP is relatively unaffected.

The formulas for calculating the natural frequency and damping coefficient are as follows:

$$\text{Natural frequency: } f_n = \frac{d}{8}\sqrt{\frac{3}{\pi L \rho V_d}}$$

$$\text{Damping coefficient: } \zeta = \frac{16\eta}{d^3}\sqrt{\frac{3LV_d}{\pi\rho}}$$

where d = tubing diameter;
L = tubing length;
ρ = density of the fluid;
V_d = transducer fluid volume displacement; and
n = viscosity of the fluid

Arterial Cannulation Sites

Factors that influence the site of arterial cannulation include the location of surgery, the possible compromise of arterial flow attributable to patient positioning or surgical manipulations, CPB cannulation and perfusion techniques, and any history of ischemia or prior surgery on the limb to be cannulated. Surgeons may use the axillary artery as the site of cannulation for CPB in patients who require anterograde selective cerebral perfusion or with a severely diseased ascending aorta.[24–26] Depending upon the surgical technique, possible complications associated with axillary artery cannulation include distal limb ischemia (direct axillary artery cannulation with the CPB arterial cannula), or limb overcirculation with systemic hypoperfusion (as may occur with axillary side graft anastomosis with graft perfusion).[27] Most clinicians monitor the arterial pressure in the contralateral upper extremity, but some have also advocated additional monitoring of the radial artery on the ipsilateral side to detect overcirculation or hypoperfusion of the arm and to intervene accordingly. Monitoring arterial BP at two or more sites may be warranted in complex cases with complex perfusion techniques and/or long CPB times. For example, a radial arterial pressure may be supplemented by more central aortic pressures obtained from the femoral or axillary arteries or the aorta itself in the surgical field. The advantage of a central arterial tracing is the increased accuracy compared with radial arterial pressure in patients after separation from CPB.[28,29] Although reasons for the difference between central and peripheral measurements of BP after separation from CPB are not entirely clear, they were transiently present in 17% to 40% of patients in several studies.[28,30,31] Kanazawa and associates[32] suggested that a decrease in the arterial elasticity is responsible for instances in which lower radial artery pressures (compared with aortic pressures) are observed after CPB. Temporary central aortic pressure monitoring can be achieved by using a needle (attached to pressure tubing) that is placed in the aorta or by pressure tubing connected to the aortic CPB cannula or the anterograde cardioplegia cannula. Central aortic monitoring is usually only necessary for several minutes until the problem resolves; in rare cases, a femoral arterial cannula is placed from the surgical field. Sites generally chosen for arterial cannulation are discussed in the following paragraphs.

Radial and Ulnar Arteries

The radial artery is the most commonly used artery for continuous BP monitoring because it is easy to cannulate, readily accessible during surgery, and the collateral circulation is usually adequate and easy to check. The ulnar artery provides most of the blood flow to the hand in approximately 90% of patients.[33] The radial and ulnar arteries are connected by a palmar arch, which provides collateral flow to the hand in the event of radial artery occlusion. The palm showed that if ulnar collateral flow is adequate, then circulatory perfusion pressure to the fingers is adequate after radial arterial catheterization.[34] Some clinicians perform the Allen test before radial artery cannulation to assess the adequacy of collateral circulation to the hand; however, the predictive value of the Allen test has been challenged. Barbeau and colleagues[35] compared the modified Allen test with pulse oximetry and plethysmography in 1010 consecutive patients undergoing percutaneous radial artery cannulation for cardiac catheterization. Pulse oximetry and plethysmography were more sensitive than the Allen test for detecting inadequate collateral blood supply, and only 1.5% of patients were not suitable for radial artery cannulation.

The Allen test is performed by compressing the radial and ulnar arteries and by exercising the hand until it is pale. The ulnar artery is then released (with the hand open loosely), and the time until the hand regains its normal color is noted.[36] With a normal collateral circulation, the color returns to the hand in approximately 5 seconds. If, however, the hand takes longer than 15 seconds to return to its normal color, then cannulation of the radial artery on that side is controversial. The hand may remain pale if the fingers are hyperextended or widely spread apart, even in the presence of a normal collateral circulation.[37] Variations on the Allen test include using a Doppler probe or pulse oximeter to document collateral flow.[38–40] If the Allen test demonstrates that the hand depends on the radial artery for adequate filling, then another cannulation site should be chosen. Rarely, if other cannulation sites are not available, then the ulnar artery may be selected.[41]

Brachial and Axillary Arteries

The brachial artery lies medial to the bicipital tendon in the antecubital fossa in close proximity to the median nerve. Brachial artery pressure tracings resemble those in the femoral artery with less systolic augmentation than radial artery tracings.[42] Brachial arterial pressures were found to reflect central aortic pressures more accurately than radial arterial pressures before and after CPB.[43] A few series of patients with perioperative brachial arterial monitoring have documented the relative safety of this technique.[28,44] Armstrong and associates[45] published data on 1326 patients with peripheral vascular disease undergoing angiography with percutaneous brachial artery access and found an overall complication rate of 1.28% with a higher risk of thrombosis in female patients. Since there is little or no collateral flow to the hand if brachial artery occlusion occurs, then most clinicians choose other sites, if possible.

The axillary artery is normally cannulated by the Seldinger technique near the junction of the deltoid and pectoral muscles. Because the tip of the 15- to 20-cm catheter may lie within the aortic arch, the use of the left axillary artery is recommended to minimize the risk of cerebral embolization during flushing. Lateral decubitus positioning or adduction of the arm occasionally results in kinking of axillary catheters with damping of the pressure waveform.

Femoral Artery

The femoral artery may be cannulated for monitoring purposes and typically provides a more reliable central arterial pressure after discontinuation of CPB. Scheer and colleagues[46] have reviewed the literature on peripheral artery cannulation for hemodynamic monitoring, including 3899 femoral artery cannulations. Temporary occlusion was found in 10 patients (1.45%), whereas serious ischemic complications requiring extremity amputation were reported in 3 patients (0.18%).

Other complications that were summarized from the published data were pseudoaneurysm formation (0.3%), sepsis (0.44%), local infection (0.78%), bleeding (1.58%), and hematoma (6.1%). Older literature stated that the femoral area was intrinsically dirty and that catheter sepsis and mortality were significantly increased, compared with other monitoring sites. This assertion could not be confirmed in the more recent literature; however, recent infection prevention guidelines discourage femoral cannulation.[47,48]

In patients undergoing thoracic aortic surgery, distal aortic perfusion (using partial CPB, left-sided heart bypass, or a heparinized shunt) may be performed during aortic cross-clamping to preserve spinal cord and visceral organ blood flow. In these situations, measuring the distal aortic pressure at the femoral artery or a branch vessel is useful (ie, dorsalis pedis or posterior tibial artery) to optimize the distal perfusion pressure. In repairs of aortic coarctation, simultaneous femoral and radial arterial monitoring may help determine the adequacy of the surgical repair by documenting the pressure gradient after the repair. Consulting the surgeon before cannulating the femoral vessels is necessary, because these vessels may be used for extracorporeal perfusion or placement of an intraaortic balloon pump during the surgical procedure.

Dorsalis Pedis and Posterior Tibial Arteries

The two primary arteries to the foot are the dorsalis pedis artery and the posterior tibial artery, which form an arterial arch on the foot that is similar to the one formed by the radial and ulnar arteries in the hand. The dorsalis pedis artery or the posterior tibial artery is a reasonable alternative to radial arterial catheterization.[49] The SBP is usually 10 to 20 mm Hg higher in the dorsalis pedis artery than in the radial or brachial arteries, whereas the DBP is 15 to 20 mm Hg lower (see Fig. 13.1).[50] These vessels should not be used in patients with severe peripheral vascular disease from diabetes mellitus or other causes.

Indications

The indications for invasive arterial monitoring are provided in Box 13.3.

BOX 13.3 INDICATIONS FOR INTRAARTERIAL MONITORING

- Major surgical procedures involving large fluid shifts or blood loss
- Surgery requiring cardiopulmonary bypass
- Surgery of the aorta
- Patients with pulmonary disease requiring frequent arterial blood gases
- Patients with recent myocardial infarctions, unstable angina, or severe coronary artery disease
- Patients with decreased left ventricular function (congestive heart failure) or significant valvular heart disease
- Patients in hypovolemic, cardiogenic, or septic shock, or with multiple organ failure
- Procedures involving the use of prolonged deliberate hypotension or deliberate hypothermia
- Massive trauma cases
- Patients with right-sided heart failure, chronic obstructive pulmonary disease, pulmonary hypertension, or pulmonary embolism
- Patients requiring inotropes or intraaortic balloon counterpulsation
- Patients with electrolyte or metabolic disturbances requiring frequent blood samples
- Inability to measure arterial pressure noninvasively (eg, extreme morbid obesity)

Contraindications

The contraindications to arterial cannulation include local infection, coagulopathy, vaso-occlusive disorders, and surgical considerations. Coagulopathy is a relative contraindication because it may result in hematoma formation during arterial cannulation. Applying direct arterial pressure with failed attempts or when the catheter is removed when using more central cannulation sites is more difficult. Therefore in anticoagulated patients, it is recommended that more peripheral arterial cannulation sites be considered when this form of monitoring is required. Radial and brachial arterial cannulations are contraindicated in patients with a history of Raynaud syndrome or Buerger disease (thromboangiitis obliterans). This consideration is especially important in the perioperative setting with Raynaud syndrome, because hypothermia of the hand is the primary trigger for vasospastic attacks.[51] It is recommended that large arteries, such as the femoral or axillary, be used for intraarterial monitoring if indicated in patients with either of these diseases.

Insertion Techniques

Direct Cannulation

Proper technique is helpful in obtaining a high degree of success in arterial catheterization. The wrist is often placed in a dorsiflex position on an armboard over a pack of gauze and immobilized in a supinated position. Overextension of the wrist should be avoided, since this flattens and decreases the cross-sectional area of the radial artery[52] and may cause median nerve damage by stretching the nerve over the wrist. When the artery is entered, the angle between the needle and skin is reduced to 10 degrees, the needle is advanced another 1 to 2 mm to ensure that the tip of the catheter also lies within the lumen of the vessel, and the outer catheter is then threaded off the needle. If blood ceases flowing while the needle is being advanced, then the needle has penetrated the back wall of the vessel.

Alternatively, the artery can be transfixed by the passage of the catheter-over-needle assembly "through-and-through" the artery. The needle is then completely withdrawn. As the catheter is slowly withdrawn, pulsatile blood flow emerges from the catheter when its tip is within the lumen of the artery. At this point the catheter can either be advanced in the lumen of the artery or a guide wire advanced into the lumen first, followed by advancing the catheter over the wire (modified Seldinger technique). Compared with a direct cannulation method, using the Seldinger technique increases the success rate of arterial catheter placement.[53] Rarely, a surgical cutdown may be required. An incision is made in the skin overlying the artery, and the surrounding tissues are dissected away from the arterial wall. Proximal and distal ligatures are passed around the artery to control blood loss but are not tied down. Under direct vision, the artery is cannulated with a catheter-over-needle assembly.

Ultrasound and Doppler-Assisted Techniques

Before the more widespread availability of high-resolution two-dimensional (2D) ultrasound devices, the acoustic signal of Doppler flow probes was frequently used to localize arterial vessels for cannulation.[54,55] In today's practice, Doppler-assisted techniques have been supplanted by 2D ultrasonic methods.[56] Most studies comparing a 2D ultrasound-guided (UG) technique to the traditional method of palpating the artery have shown a higher success rate at first attempt with UG techniques and fewer attempts overall. An UG technique is probably most useful in patients with severe peripheral vasculopathy, as well as in infants and small children. Levin and associates[57] randomized patients in a prospective study to UG radial artery cannulation versus the classic palpation technique. The use of ultrasound resulted in a higher success rate on the first attempt, and fewer subsequent attempts were required to place the arterial catheter. The overall time for catheter placement was not significantly different between the two groups (trend for shorter overall time in UG group). In a similar study, Shiver and colleagues[58] randomized patients in the emergency department to

UG versus the traditional palpation technique of placing the arterial catheter. Patients in the UG group required a significantly shorter time (107 vs 314 seconds; $P = .0004$), fewer placement attempts (1.2 vs 2.2; $P = .001$), and fewer sites required for successful arterial catheter placement.

The use of ultrasound in guiding arterial catheter placement is easy to learn when proper training in this technique is provided. There is, however, a significant learning curve, and studies reporting on the success rate of UG arterial cannulation compared with a traditional palpation technique have to be interpreted accordingly. Ganesh and associates,[59] for example, did not find a significant difference in the time and number of attempts required in a pediatric patient population randomized to palpation versus UG radial artery catheter placement. None of the designated operators, however, had significant experience with this technique, with 19 out of 20 pediatric subspecialty trainees and/or fully trained consultant anesthesiologists reporting experience with fewer than five cases. Fig. 13.3 shows a proper full-sterile set up for UG arterial cannulation. Fig. 13.4 demonstrates the "triangulation" technique typically applied with UG venous and/or arterial cannulation. The ultrasound imaging plane and the needle plane can be viewed as the two sides of a triangle that should meet and intersect at the depth of the structure (eg, radial artery) for which cannulation is attempted. The experienced operator will choose the distance (needle insertion site vs imaging plane) and insertion angle, depending on the depth of the target vessel. After perforating the skin, the ultrasound plane and the needle insertion angle both have to be adjusted further to follow the needle tip when viewed in the transverse (short-axis) approach. Failure to align the ultrasound plane accurately with the needle tip results in viewing the needle shaft instead. Figs. 13.5 and 13.6 show typical ultrasound images obtained during short-axis (transverse) cannulation. Note the anatomic variation with a larger radial artery (*A1*) next to the smaller artery (*A2*) positioned laterally. After puncturing the vessel, the catheter can be advanced into the lumen. A significantly higher success rate can usually be achieved using the through-and-through and modified Seldinger techniques.

If a longitudinal ("in-plane") approach is chosen (ie, the vessel is viewed in its long axis), the needle tip can be followed more easily as it is advanced; however, structures adjacent to the ultrasound plane (lateral to the vessel) cannot be viewed simultaneously. Exactly aligning the needle and vessel axis together in a 2D echo plane, particularly with a tortuous atherosclerotic artery, is technically more difficult. Although many practitioners prefer the transverse out-of-plane approach, studies comparing the two techniques show inconsistent findings.[60,61] Fig. 13.7 shows the arterial catheter entering the radial artery using the longitudinal (in-plane) approach. Aseptic technique, including sterile sheaths, should always be followed when using the UG technique of intraarterial catheter placement to prevent catheter-related

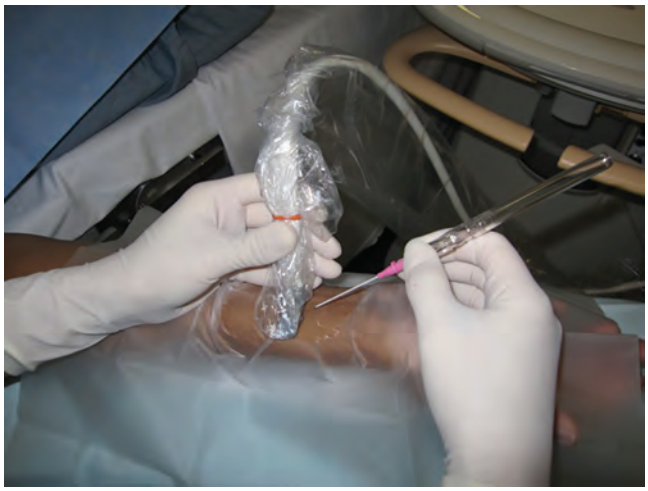


Fig. 13.3 Demonstration of aseptic technique for ultrasonic guidance of radial artery cannulation.

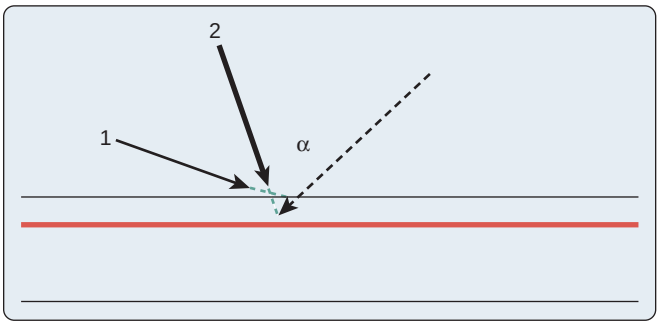


Fig. 13.4 Demonstration of the "triangulation" technique typically applied with ultrasound-guided (UG) venous and/or arterial cannulation in the transverse imaging approach. The echo imaging plane and the needle plane can be viewed as the two sides of a triangle that should meet and intersect at the depth of the structure (eg, radial artery *[red line]*) for which cannulation is attempted. The experienced operator will change the angle *(α)* between the two planes (ultrasound and needle) and the distance (needle insertion site vs imaging plane), depending on the depth of the structure. To follow the needle tip in the transverse approach (vessel viewed in short axis), the echo plane or needle insertion angle has to be further adjusted from needle entry through the skin to the perforation of the vessel. A greater angle is used (echo plane angled toward the skin *[1]*) to visualize the needle tip after it penetrates the skin, and then a more perpendicular angle relative to the skin is applied to see the needle tip entering the vessel lumen *(2)*.

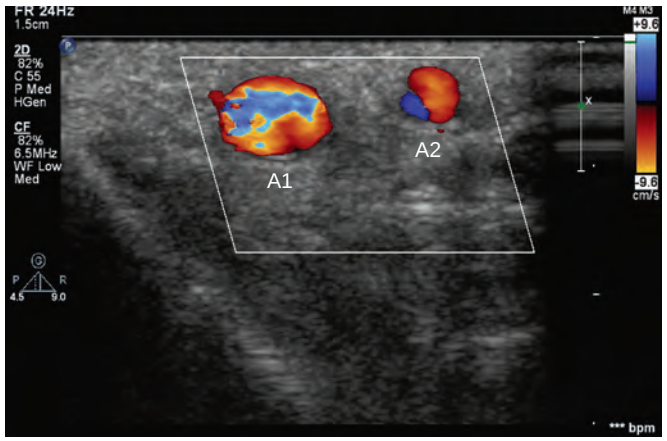


Fig. 13.5 A typical ultrasound image with color Doppler during short-axis (transverse) cannulation. Note the anatomic variation with a larger radial artery (*A1*) next to a smaller artery (*A2*) positioned laterally.

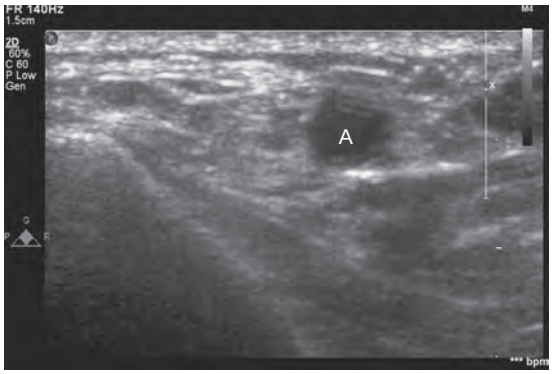


Fig. 13.6 Typical ultrasound image during short-axis (transverse) cannulation.

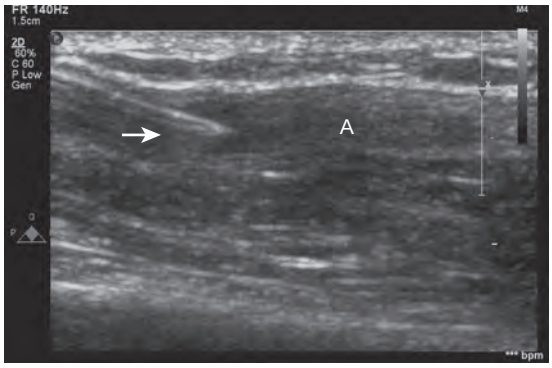


Fig. 13.7 Catheter entering the radial artery using the longitudinal (in-plane) approach.

BOX 13.4 ULTRASOUND-GUIDED ARTERIAL CANNULATION

Benefits

- Higher success rate on first attempt
- Fewer overall attempts
- Increased patient comfort (fewer attempts)
- Fewer complications (eg, anticoagulated patients)
- Demonstration of vessel patency, anatomic variants
- Low pulsatile or nonpulsatile flow (eg, nonpulsatile assist devices, extracorporeal membrane oxygenation, shock)
- Nonpalpable or weakly palpable pulses (eg, peripheral edema, hematoma)
- Emergency access (eg, catheter placement during resuscitation)

Concerns

- Risk of catheter-related infections if poor aseptic technique is applied
- Additional training required
- Costs involved with equipment required

infections. A high-frequency linear array ultrasonic transducer (8 to 12 MHz) is optimal for UG arterial catheter placement, since higher frequencies are needed for high-resolution imaging of the near field. Box 13.4 summarizes the potential benefits and concerns related to UG arterial catheter placement.

Complications

Infection from indwelling catheters is a common complication to all forms of invasive monitoring. In a recent prospective study evaluating 834 arterial catheters with a total of 3273 catheter days in a critical care unit setting, 13% were found to be colonized. Bacteremia was confirmed in 11 cases, resulting in a bloodstream infection rate of 1.3%, or 3.4 per 1000 catheter days.[62] Similarly, a metaanalysis showed an incidence of arterial catheter–related bloodstream infections of 2.9 per 1000 catheter days.[63] Another recent large metaanalysis included 49 studies with a total of 30,841 arterial catheters. Arterial catheter–related bloodstream infections were found in 222 cases, with a calculated incidence of catheter-related infections of 3.4 in 1000 catheters or 0.96 per 1000 catheter days. The prevalence was higher in studies that cultured all catheters, compared with those studies that cultured only when the arterial catheter was thought to be the source of infection. The risk of infection was also higher for the femoral site of insertion, compared with radial artery access.[64] Other studies have found similar infection rates, confirming that colonization and catheter-related bloodstream infection rates are comparable with central venous catheters.[65,66] These findings clearly stress the importance of using strict aseptic technique when inserting peripheral arterial catheters. In contrast to central venous catheterization, however, some of the published data on vascular catheter infections did not find that full sterile barriers during arterial catheter placement reduced the risk of infection.[67,68]

Guidelines for the prevention of intravascular catheter-related infections have been published by the Healthcare Infection Control Practices Advisory Committee (HICPAC) and the Centers for Disease Control and Prevention (CDC).[69] To summarize these guidelines, there is a category IA level of evidence for maintaining sterility for all components of the pressure monitoring system, using an antiseptic wipe before drawing blood from an arterial catheter other than a stopcock and avoiding the use of dextrose-containing flush solutions. Category IB level of evidence was found for avoiding the femoral and axillary insertion sites. The advisory committee recommends a minimum of a cap, mask, sterile gloves, and a small sterile fenestrated drape to be used during peripheral arterial catheter insertion (Category IB), whereas during axillary or femoral artery catheter insertion, maximal sterile barriers precautions should be used (Category II).

Hemorrhage from disconnecting the catheter-tubing assembly carries the potential risk of major blood loss or exsanguination. Temporary *arterial spasm* can be observed after radial artery cannulation and typically resolves without intervention. Arterial *thrombosis* is more frequently observed with prolonged duration of cannulation,[70] large catheters,[71] and a small radial artery size (ie, a greater proportion of the artery is occupied by the catheter).[72] However, despite the widespread use of radial artery cannulation, hand complications are rarely reported.[73–75] Because thrombosis may appear several days after the catheter has been removed, examinations should be continued through the postoperative period. Any evidence of hand ischemia should be investigated and treated promptly to prevent morbidity.[76] Traditional treatment for arterial occlusion or thrombosis with adequate collateral flow has been conservative. However, fibrinolytic agents (eg, streptokinase), stellate ganglion blockade, and surgical intervention are modalities that should be considered.[77]

Embolization of air or particulate matter that is flushed forcefully into an arterial catheter can move proximally and distally within the artery. Cerebral embolization is most likely from axillary cannulation sites but is also possible with brachial and radial artery catheters.[78,79] Emboli from the right arm are more likely to reach the cerebral circulation than those from the left arm because of the usual anatomy and direction of blood flow in the aortic arch. Other factors that influence the likelihood of cerebral embolization include the volume of flush solution, the rapidity of the injection, and the proximity of the intraluminal end of the catheter to the central circulation.[80,81]

Hematoma formation is common especially in patients who are anticoagulated and is usually well controlled with direct pressure application. *Nerve damage* is possible if the nerve and artery lie in a fibrous sheath (eg, the brachial plexus) or in a limited tissue compartment (eg, the forearm).[82] Direct nerve injuries may also occur from needle trauma during attempts at arterial cannulation. The median nerve is in close proximity to the brachial artery, and the axillary artery lies within the brachial plexus sheath. Pseudoaneurysm formation is a late vascular complication[83] and rarely progresses into an arteriovenous fistula.[84,85]

Despite the great advantages of intraarterial monitoring, limitations of invasive BP monitoring must be recognized. The monitoring system may be incorrectly zeroed, baseline drifting may occur, or the transducers may not be appropriately leveled with the heart as the reference point. Dampening of the pressure waveform is observed with kinking or partially thrombosed catheters. In vasoconstricted patients, those in hypovolemic shock, and during the post-CPB period, the brachial and radial artery pressures may be significantly lower than the true central aortic pressure. Another possible cause of inaccurate measurements is unsuspected arterial stenosis proximal to the monitored artery, as occurs with thoracic outlet syndrome and subclavian stenosis. Unsuspected Raynaud syndrome also can yield unreliable BP readings from peripheral arteries.

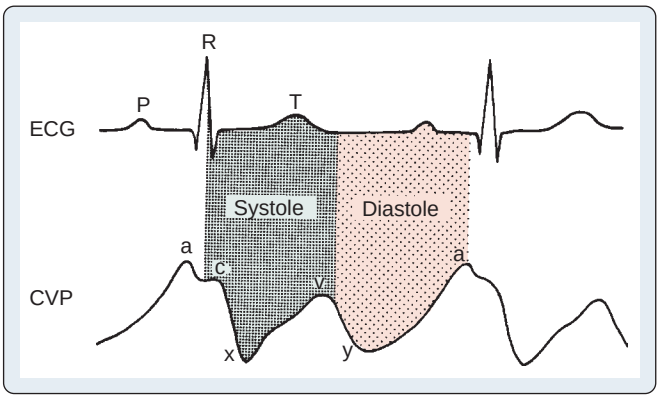


Fig. 13.8 Relationship of the central venous pressure (*CVP*) tracing to the electrocardiogram (*ECG*) in normal sinus rhythm. The normal CVP waveform consists of three upward deflections (*a*, *c*, and *v* waves) and two downward deflections (*x* and *y* descents). The *a* wave is produced by right atrial contraction and occurs just after the *P* wave on the ECG. The *c* wave occurs because of the isovolumic ventricular contraction forcing the tricuspid valve to bulge upward into the right atrium (RA). The pressure within the RA then decreases as the tricuspid valve is pulled away from the atrium during right ventricular ejection, forming the *x* descent. The RA continues to fill during late ventricular systole, forming the *v* wave. The *y* descent occurs when the tricuspid valve opens and blood from the RA empties rapidly into the right ventricle during early diastole. *(Adapted from Mark JB. Central venous pressure monitoring: clinical insights beyond the numbers.* J Cardiothorac Vasc Anesth. *1991;5:163–173.)*

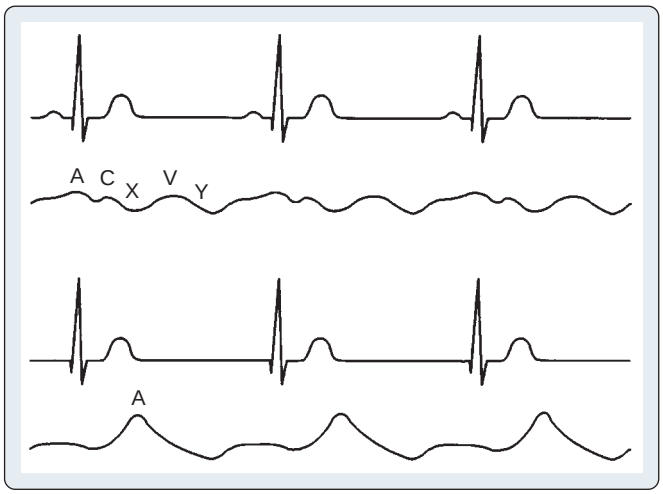


Fig. 13.9 Relationship of the central venous pressure tracing to the electrocardiogram during junctional (atrioventricular nodal) rhythm. The contraction of the atrium against the closed tricuspid valve results in the cannon *A* waves. Note that the P wave is hidden within the QRS complex of the electrocardiogram.

Central Venous Pressure Monitoring

Central venous pressure (CVP) catheters are used to measure the filling pressure of the RV, give an estimate of the intravascular volume status, and assess right ventricular function. For accurate pressure measurement, the distal end of the catheter must lie within one of the large intrathoracic veins or the right atrium (RA). As in any pressure monitoring system, having a reproducible landmark, such as the midaxillary line with a closed chest or the left atrium (LA) during surgery, as a zero reference is necessary. Frequent changes in patient positioning without proper leveling of the transducers relative to the heart produce proportionately larger errors compared with arterial pressure monitoring.

The normal CVP waveform consists of three upward deflections (A, C, and V waves) and two downward deflections (X and Y descents) (Fig. 13.8). The A wave is produced by right atrial contraction and occurs just after the P wave on the electrocardiogram (ECG). The C wave occurs because of the isovolumic ventricular contraction, forcing the tricuspid valve (TV) to bulge upward into the RA. The pressure within the RA then decreases as the TV is pulled away from the atrium during right ventricular ejection, forming the X descent. Right atrial filling continues during late ventricular systole, forming the V wave. The Y descent occurs when the TV opens and blood from the RA empties rapidly into the RV during early diastole.[86]

The CVP waveform may be useful in the diagnosis of pathologic cardiac conditions. For example, the onset of an irregular rhythm and loss of the A wave suggest atrial flutter or fibrillation. Cannon A waves occur as the RA contracts against a closed TV, as occurs in junctional (atrioventricular [AV] nodal) rhythm, complete heart block, and ventricular arrhythmias (Fig. 13.9). This occurrence is clinically relevant because nodal rhythms are frequently seen during anesthesia and may produce hypotension attributable to a decrease in SV. Cannon A waves may also be present when resistance to RA emptying is increased, as in tricuspid stenosis, right ventricular hypertrophy, pulmonary stenosis, or pulmonary hypertension. Early systolic or holosystolic "cannon V waves" (or C-V waves) occur if the degree of tricuspid regurgitation is significant. Large V waves may also appear later in systole if the ventricle becomes noncompliant as a result of ischemia or right ventricular failure. Tachycardia produces a blending of the waveforms, especially the A and C waves. It must be recognized, though, that many peaks and troughs in the CVP waveform are artifactually created from the transducer-tubing monitoring system. A comprehensive review of CVP waveform analysis in various pathophysiologic states has been published.[87]

Pericardial constriction produces characteristic waveforms in the CVP tracing (Fig. 13.10). The venous return is decreased because of the inability of the heart chambers to dilate as a result of the constriction. This causes prominent A and V waves and steep X and Y descents (creating an M configuration) resembling that observed with diseases that cause decreased right ventricular compliance. Egress of blood from the RA to the RV is initially rapid during early diastolic filling of the RV (creating a steep Y descent) but is short-lived and abruptly halted by the restrictive, noncompliant RV. The right atrial pressure then increases rapidly and reaches a plateau until the end of the A wave, at the end of diastole. This portion of the waveform is analogous to the ventricular diastolic dip-and-plateau sign.[87] With pericardial tamponade, the X descent is steep but the Y descent is not present, because early diastolic run-off is impaired by the pericardial fluid collection.

The CVP is a useful monitor if the factors affecting it are recognized and its limitations are understood. Thromboses of the vena cavae and alterations of intrathoracic pressure, such as those induced by positive end-expiratory pressure (PEEP), also affect measurement of the CVP.[88] The correlation with left-sided heart filling pressures and assessment of left ventricular preload is poor.[89–92] Clinically, following serial measurements (trends) rather than individual numbers is often more relevant. The response of the CVP to a volume infusion, however, is a useful test.

Techniques and Insertion Sites

Percutaneous central venous cannulation may be accomplished by catheter-through-needle, catheter-over-needle, or catheter-over-wire (Seldinger) techniques. The considerations for selecting the site of cannulation include the experience of the operator, ease of access, anatomic anomalies, and the ability of the patient to tolerate the position required for catheter insertion.

Internal Jugular Vein

Cannulation of the internal jugular vein (IJV) was first described by English and colleagues[93] in 1969. Advantages of this technique include the high success rate as a result of the relatively predictable relationship of the anatomic structures; a short, straight course to the RA that

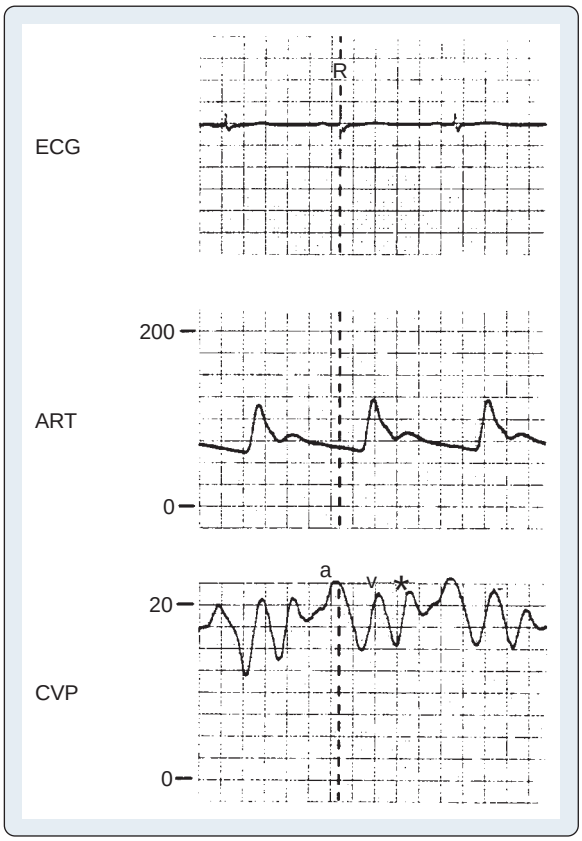


Fig. 13.10 Central venous pressure (*CVP*) waveform during pericardial constriction. The characteristic M configuration with prominent *a* and *v* waves, accompanied by steep x and y descents, is evident. An additional wave *(asterisk)* is present because of an impairment of ventricular filling by the rigid pericardial shell. *ART,* Arterial pressure; *ECG,* electrocardiogram. *(Adapted from Mark JB. Central venous pressure monitoring: clinical insights beyond the numbers.* J Cardiothorac Vasc Anesth. *1991;5:163–173.)*

almost always ensures RA or superior vena cava (SVC) localization of the catheter tip; and easy access from the head of the surgical table. The IJV is located under the medial border of the lateral head of the sternocleidomastoid (SCM) muscle (Fig. 13.11). The carotid artery is usually deep and medial to the IJV; however, this spatial relationship can vary and puncture of the carotid artery is best avoided by using an UG technique. The right IJV is preferred, because this vein takes the straightest course into the SVC, the right cupola of the lung may be lower than the left, and the thoracic duct is on the left side.[94] Unless a persistent left SVC is present, the right IJV has a larger diameter, compared with the left IJV.

The *middle approach* to the right IJV is shown in Fig. 13.12. The Trendelenburg position is chosen to distend the IJV. The head is then turned toward the contralateral side, and the fingers of the left hand are used to palpate the two heads of the SCM muscle and the carotid pulse. The needle is inserted slightly lateral to the carotid pulse at a 45-degree angle to the skin and directed toward the ipsilateral nipple until venous blood return is obtained. Alternatively, the use of a small-gauge *finder* needle can be used to avoid carotid puncture with a large-bore needle. When venous return is present, the whole assembly is lowered to prevent the needle from going through the posterior wall of the central vein and advanced an additional 1 to 2 mm until the tip of the catheter is within the lumen of the vein. Aspiration of blood must be confirmed before the catheter is then threaded into the vein. It is recommended by the ASA practice guidelines,[95] and often mandated by institutional protocols, that the correct intravenous catheter position be confirmed before placing a large-bore introducer sheath. Various techniques have been suggested. The small-bore catheter can be attached to a transducer by sterile tubing to observe the pressure waveform.[96–98] Another option is to attach the cannula to sterile tubing and allow blood to flow retrograde into the tubing.[99] The tubing is then held upright as a venous manometer, and the height of the blood column is observed. If the catheter is in a vein, then it will stop rising at a level consistent with the CVP and demonstrate respiratory variation. Despite its reported use in the past, color comparison and observation of nonpulsatile flow are notoriously inaccurate methods of determining that the catheter is not in the carotid artery. A guidewire is then passed through the 18-gauge catheter, and the catheter is exchanged for the wire. With the more widespread use of echocardiography, the

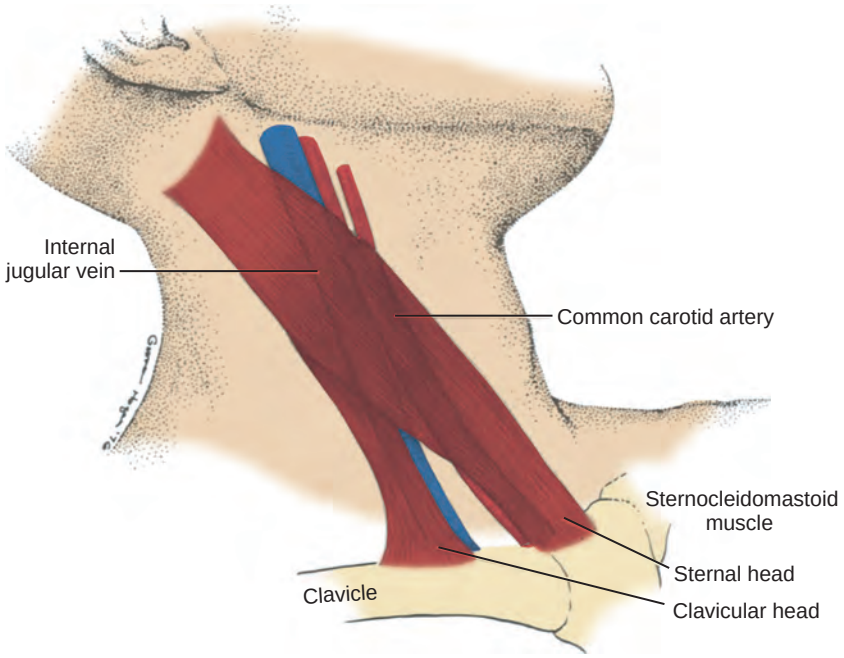


Fig. 13.11 The internal jugular vein is usually located deep to the medial border of the lateral head of the sternocleidomastoid muscle, just lateral to the carotid pulse. *a,* Artery; *v,* vein.

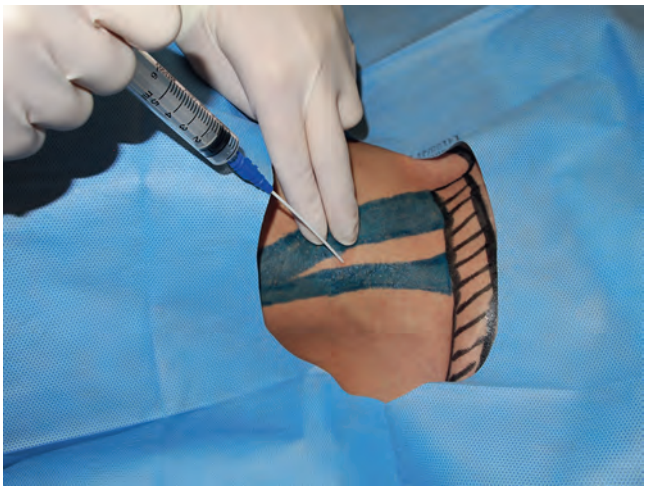


Fig. 13.12 Preferred middle approach to the right internal jugular vein. The needle enters the skin at the apex of the triangle formed by the sternal and clavicular heads of the sternocleidomastoid muscle. The needle is held at a 30- to 45-degree angle to the skin and directed toward the ipsilateral nipple.

correct intravenous position can also be confirmed by following the Seldinger wire along its course in the IJV more distally by handheld transcutaneous probes or demonstrated within the RA if the TEE probe was inserted before IJV cannulation. The use of more than one technique to confirm the venous location of the guidewire may provide additional reassurance of correct placement before cannulation of the vein with a larger catheter or introducer. Once it is certain that the guidewire is in the venous circulation, the CVP catheter is passed over it and the wire is removed. Although the described technique is most commonly performed for IJV cannulation, many other approaches to the right IJV have been described.[100–102] Additionally, with ultrasound guidance, strict adherence to external landmarks has become less important.

Ultrasound-Guided Internal Jugular Vein Cannulation

Clinical Evidence for Ultrasound-Guided Internal Jugular Vein Cannulation

Ultrasound has been increasingly used for central venous access, in particular to guide IJV cannulation and to define the anatomic variations of the IJV.[103] Using ultrasound to guide central venous cannulation increases the success rate and helps prevent complications and thus may ultimately help improve patient outcomes. Troianos and associates[104] compared UG IJV cannulation to a traditional landmark technique. Fewer attempts to successful cannulation were required, and the rate of complications such as carotid artery puncture was decreased in the UG group. More recent prospective studies confirmed these findings. In a prospective observational study, Serafimidis and colleagues[105] compared UG IJV cannulation to a landmark technique (347 patients vs 204 patients, respectively). UG cannulation had a higher success rate, required fewer attempts, took less time, and had fewer complications. Further evidence comes from several published metaanalyses comparing the UG versus traditional IJV landmark techniques.[106,107] Overall, most studies have demonstrated that 2D UG IJV cannulation has a higher success rate on the first attempt and fewer complications.[108–112] Those findings also were confirmed in pediatric patients.[113–118] Only one study reported that UG IJV cannulation in children was less successful, had a higher incidence of arterial puncture, but had no time difference compared with the landmark method.[119] However, US operators in this study had no experience in UG cannulation, only highlighting that the learning curve associated with this technique is significant.

Box 13.5 lists some of the recognized benefits and concerns of UG central venous cannulation. Circumstances in which ultrasound guidance of IJV cannulation can be particularly advantageous include patients with difficult neck anatomy (eg, short neck, obesity), prior neck surgery, anticoagulated patients, and infants.

BOX 13.5 ULTRASOUND-GUIDED CENTRAL VENOUS CANNULATION

Benefits
- Higher success rate on first attempt
- Fewer overall attempts
- Facilitates access with difficult neck anatomy (obesity, prior surgery)
- Fewer complications (eg, carotid artery puncture, anticoagulated patients)
- Demonstration of vessel patency, anatomic variants
- Relatively inexpensive technology

Concerns
- Training personnel to maintain aseptic technique when using sterile probe sheaths
- Additional training required
- Lack of observation of surface anatomy
- Potential loss of landmark-guided skills when needed for emergency central venous catheterization.

Technical Aspects

Ultrasound provides instantaneous and patient-specific information regarding the structural relationship between the IJV, the carotid artery, and adjacent anatomic structures (see Fig. 13.11). The spatial relationships can vary significantly, and the IJV may be absent or completely or partially overlapping the carotid artery.[120] Troianos and associates[121] found that in 54% of patients, greater than 75% of the IJV overlay the carotid artery. Patients who were older than 60 years were more likely to have this type of anatomy. Fig. 13.13 shows the anatomic relationship between the IJV and the carotid artery in two patients. In pediatric patients, Alderson and colleagues[122] found that the carotid artery coursed directly posterior to the IJV in 10% of patients. Sulek and associates[123] observed that the overlap of the IJV and the carotid artery was greater when the head is rotated 80 degrees, compared with head rotation of only 0 to 40 degrees. The data from 2 and 4 cm above the clavicle did not differ, and the percentage overlap was larger on the left side of the neck, compared with the right. Excessive rotation of the head of the patient toward the contralateral side may distort the normal anatomy in a manner that increases the risk of inadvertent carotid artery puncture. Ultrasound has also been used to demonstrate that the Valsalva maneuver increases IJV cross-sectional area by approximately 25% and that the Trendelenburg position increases it by approximately 37%.[124] Parry[125] showed that maximal right IJV diameter can be achieved by placing the patient in 15 degrees Trendelenburg position, slightly elevating the head with a small pillow, keeping the head close to midline and releasing the pressure administered to palpate the carotid artery before IJV cannulation. Box 13.6 summarizes some of the positional considerations in UG IJV cannulation.

For central venous catheterization, full aseptic technique is mandatory. After patient positioning and sterile preparation of the neck, a full-body sterile drape is applied and the probe is covered in a sterile sheath. Fig. 13.14 demonstrates proper sterile technique and positioning of the ultrasound probe. A triangulation technique as previously described for the radial artery is typically used. Although the long-axis (in-plane) approach allows better visualization of the true needle tip throughout the insertion and vessel penetration, the simultaneous display of the IJV and its relationship to the carotid artery is lost. Additionally, the size of the ultrasound probe in patients with short neck anatomy often does not provide adequate room for an in-plane approach to the IJV. Most practitioners therefore choose the short-axis (out-of-plane) approach to UG IJV cannulation. The most important

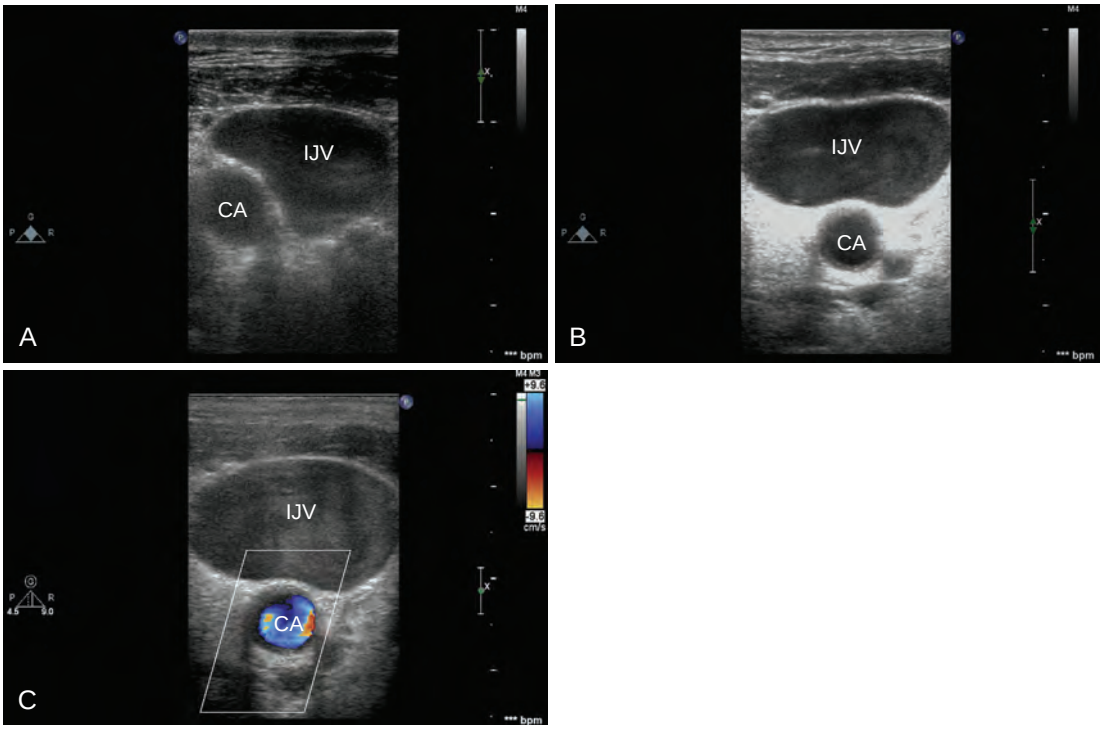


Fig. 13.13 Anatomic relationship between the internal jugular vein (*IJV*) and the carotid artery (*CA*) in two patients. (A) The IJV partially overlies the CA. (B) The CA is situated deep to the IJV. (C) Color Doppler demonstrates the flow in the CA.

BOX 13.6 POSITIONAL CONSIDERATIONS IN ULTRASOUND-GUIDED RIGHT INTERNAL JUGULAR VENOUS CANNULATION

- Slight Trendelenburg position
- Head turned slightly away from the cannulation side (turning too far may flatten the internal jugular venous [IJV] and rotate the IJV above the carotid artery)
- Overextension of the head should be avoided, mild head elevation can be advantageous (overextension flattens IJV)
- Minimal neck pressure by manual palpation and/or ultrasonic probe so as to avoid compression of the IJV
- Ultrasound probe should scan the course of the IJV to find the best cannulation site (largest IJV diameter and least overlap with the carotid artery)

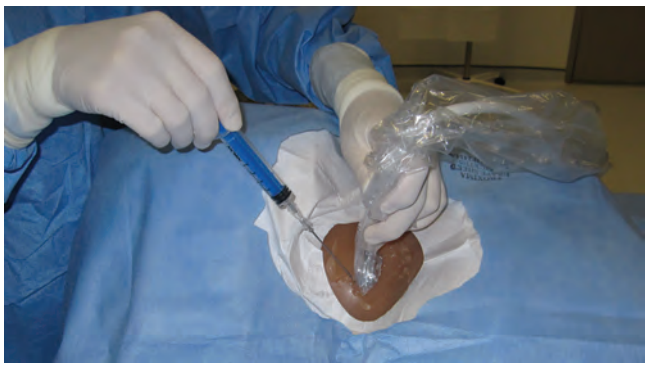


Fig. 13.14 The aseptic technique and positioning of the ultrasound probe for internal jugular vein cannulation is demonstrated.

aspect of imaging a needle out-of-plane is avoiding the mistake of visualizing the needle shaft rather than the needle tip. Otherwise, the needle tip could be in a structure not being imaged, such as the carotid artery or pleura. With training and experience, the practitioner learns to sweep the ultrasonic plane inferiorly along the course of the needle shaft until the needle tip is identified. Adjusting the ultrasonic plane and the angle of the needle insertion enables visualization of the needle tip as it enters the IJV. An extremely favorable sign of needle tip visualization during needle advancement is indentation of the anterior wall of the IJV as the needle tip encounters the vessel wall (Fig. 13.15). An alternative technique combining the advantages of a long- and short-axis approach, visualizing the needle during insertion while maintaining a view of both the carotid artery and the IJV has been described and termed medial oblique approach.[126]

It is important to realize that UG IJV cannulation has reduced, but not eliminated, inadvertent carotid arterial cannulation, and that

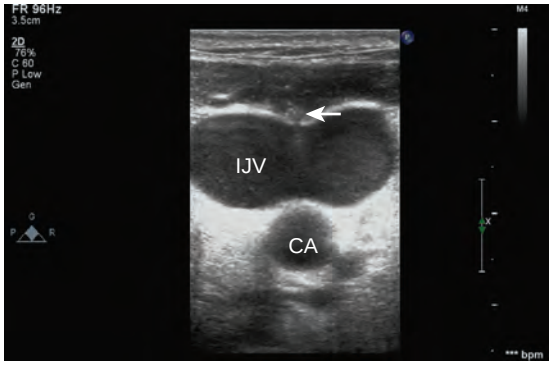


Fig. 13.15 The thin-walled internal jugular vein (*IJV*) is compressed by the advancing needle *(arrow)* during IJV cannulation. *CA,* Carotid artery.

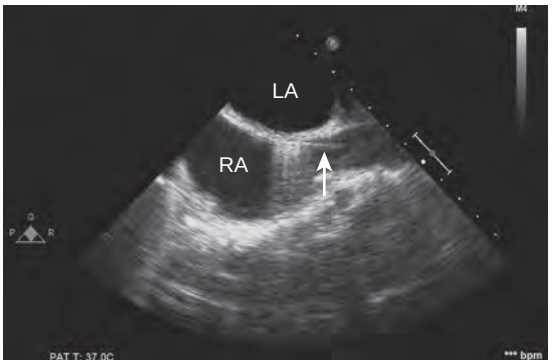


Fig. 13.16 The midesophageal bicaval transesophageal echocardiography view allows confirmation of the guidewire position in the right atrium *(arrow)*. *LA*, Left atrium; *RA*, right atrium.

the insertion of large catheters into the carotid artery with ultrasound guidance has been reported.[127–131] Venous cannulation always should be confirmed before advancing the dilators or inserting the large-bore catheter and introducer sheath. As previously noted, manometry, pressure transduction, blood gas analysis, or guidewire visualization using fluoroscopy or TEE imaging of the guidewire in the SVC or RA (Fig. 13.16) are all reasonable methods of ensuring venous cannulation before inserting a large-bore sheath.

Current Recommendations

Several specialty societies and national medical agencies have released guidelines and recommendations that strongly support the use of UG IJV cannulation. The Agency for Healthcare Research and Quality (AHRQ) in the United States lists UG central catheter placement as 1 of 11 patient safety practices with the greatest strength of evidence supporting its use to improve patient outcomes.[129] The National Institute of Clinical Excellence in the United Kingdom[130] also recommends UG IJV cannulation for children and adults. More recently, the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists have released a guideline document outlining the technique and the existing level of evidence that supports the use of an UG approach.[131] The taskforce recommended the use of UG IJV cannulation to improve success rate and reduce the incidence of complications in adult and pediatric patients. Although the writing committee did not recommend the routine use of UG for alternative central venous access (ie, subclavian and femoral vein) and arterial access, the committee did so merely based on the existing level of evidence from the published literature, not on the technical feasibility, safety concerns, or efficacy of using an UG technique. Additionally, the ASA has published practice guidelines for central venous cannulation.[95] The use of UG is recommended for vessel localization and needle guidance and can be used to verify correct intravascular position before the insertion of a large-bore catheter. Lastly, the HICPAC/CDC infection guidelines list a Category 1B level of evidence (strongly recommended) for using UG to place central venous catheters (if this technology is available) to reduce the number of cannulation attempts and mechanical complications. These guidelines further state that UG should only be used by those who are fully trained in this technique.[69] Based on the overwhelming evidence demonstrating efficacy and safety benefits, UG central venous access has become a standard at many institutions. Despite its increasingly widespread use, there is ongoing controversy whether UG for central venous cannulation has become a standard of care, which is a legal and not a medical determination.[132,133] The equipment needs[134] and the associated capital and training costs have been raised as reasons for the lack of universal adoption of this technique, despite the fact that UG central catheter can be cost-effective even when initial hardware purchase and training are taken into consideration.[135]

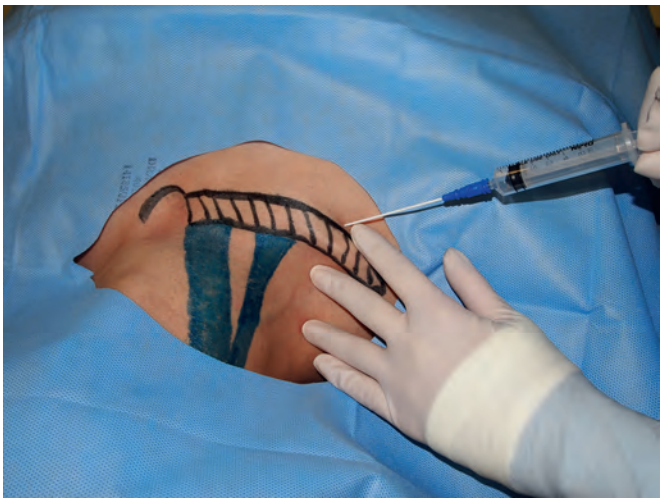


Fig. 13.17 The infraclavicular approach to the right subclavian vein. The patient is positioned with a rolled towel between the scapulae to increase the distance between the clavicle and the first rib. The needle enters the skin 1 cm inferior to the midpoint of the clavicle and is directed underneath the clavicle toward the sternal notch. If the needle is directed too far posteriorly, then the pleura may be punctured, resulting in a pneumothorax.

External Jugular Vein

Although the external jugular vein (EJV) is another means of reaching the central circulation, the success rate with this approach is lower because of the tortuous path followed by the vein. A valve is usually present at the point where the EJV perforates the fascia to join with the subclavian vein. Placing the patient in the Trendelenburg position and using a guidewire with the curved tip (ie, J-wire) can help increase the cannulation success rate.[136] The curved tip is necessary to negotiate the tortuous course between the EJV and the SVC. Manipulation of the shoulder and rotation of the guidewire between the operator's fingers may be useful maneuvers when difficulty is encountered in passing the wire into the SVC. The primary advantage of this technique is that advancing a needle into the deeper structures of the neck is not needed.

Subclavian Vein

The subclavian vein is readily accessible from supraclavicular or infraclavicular approaches and has long been used for central venous access.[137] The risk of causing a pneumothorax is higher compared with an IJV or EJV approach. Other complications associated with subclavian vein cannulation are subclavian arterial puncture, misplacement of the catheter tip, aortic injury, cardiac tamponade, mediastinal hematoma, and hemothorax.[138,139] The subclavian vein may be the cannulation site of choice, however, when CVP monitoring is indicated in patients undergoing carotid artery surgery. It is also useful for parenteral nutrition or for prolonged CVP access because the site is easier to maintain and well tolerated by patients.

The *infraclavicular approach* is performed with the patient supine or in the Trendelenburg position; additional maneuvers may include placing a folded sheet between the scapulae and pulling the shoulder inferiorly[140] (Fig. 13.17). The head is turned to the contralateral side. A thin-walled needle or intravenous catheter is inserted approximately 1 cm below the midpoint of the clavicle and advanced toward the suprasternal notch under the posterior surface of the clavicle. When a free flow of venous blood is obtained, the guidewire is passed into the subclavian vessel and is exchanged for a CVP catheter.

The *supraclavicular approach* is performed with the patient in the Trendelenburg position with the head turned away from the side of the insertion. This approach is usually not performed on the left side because of the risk of injuring the thoracic duct. The needle is inserted

at the lateral border of the SCM at the point of insertion into the clavicle, and directed to bisect the angle between the SCM and the clavicle and approximately 15 to 20 degrees posteriorly.

For both infraclavicular and supraclavicular subclavian vein access, the use of UG can greatly improve the identification of the vein, as well as help avoid arterial and pleural puncture.[141–143] However, these routes require more experience and training compared with UG IJV cannulation.

Antecubital Veins

Another route for CVP monitoring is through the basilic or cephalic veins. The advantages of this approach are the low likelihood of complications and the ease of access intraoperatively if the arm is exposed. The major disadvantage is that placement of the catheter in a central vein is often difficult to ensure. Chest radiographs are usually necessary to confirm that the tip of the catheter has been appropriately placed. Exact positioning of the catheter tip is crucial because movement of the arm will result in significant catheter migration and could cause cardiac perforation and tamponade.[144–146] Unsuccessful attempts result most frequently from the failure to pass the catheter past the shoulder or cannulation of the ipsilateral IJV. Turning the head to the ipsilateral side may help prevent IJV placement of the catheter.[147] Correct positioning is also required when used for the aspiration of air emboli in neurosurgical patients. Transducing the pressure waveform,[148] electrocardiography,[149] and the use of echocardiography[150] all have been described for correct positioning at the SVC-RA junction. Although peripherally placed central venous catheters avoid the placement of needles into deep venous structures, significant risks are still associated with their use.[151–154] Peripherally inserted central catheters are rarely used for monitoring purposes.

Femoral Vein

Cannulation of the femoral vein is technically simple, and the success rate is high. Cannulation of the vessel should be performed approximately 1 to 2 cm below the inguinal ligament. The vein typically lies medial to the artery. The older literature reported a high rate of catheter sepsis and thrombophlebitis with this approach. More recently published studies comparing the femoral access to the IJV and subclavian vein access were included in a large metaanalysis. No significant difference in the rate of catheter-related bloodstream infections was observed among the three sites.[155] This is probably due to using a stricter aseptic technique, disposable catheter kits, improved catheter technology, and the use of chlorhexidine in more recent trials instead of iodine-based antiseptic skin preparation in older studies. Despite these recent findings, the HICPAC/CDC infection guidelines list a Category 1A level of evidence (strongly recommended) to avoid using the femoral vein for central venous access in adult patients.[69] In patients with SVC obstruction, the femoral vein is necessary for intravenous access and to obtain a true CVP measurement. It is prudent for practitioners to document reasons supporting the use of the femoral site for monitoring purposes because of these guidelines.

Indications

In addition to hemodynamic monitoring, central venous access is typically warranted to establish a secure venous access route for the administration of vasoactive or irritating drugs, the rapid infusion of intravenous fluids, and total parenteral nutrition. Perioperative indications for the insertion of a central venous catheter are listed in Box 13.7. The limitations of CVP monitoring for assessing intravascular volume status are significant. The accuracy and reliability of CVP monitoring depend on many factors including the functional status of the right and left ventricles, the presence of pulmonary disease, and ventilatory factors, such as PEEP. The CVP may reflect left-sided heart-filling pressures but only in patients with good left ventricular function.

Despite obvious limitations, the CVP should be monitored continually in all patients during CPB. Although the catheter tip is ideally located at the SVC-RA junction, transducing the pressure from the most proximal catheter port or the introducer side-port is warranted during CPB (especially with bicaval cannulation). The venous pressure should be measured cephalad to the SVC CPB cannula, reflecting intracranial venous pressure. Insufficient drainage of the SVC attributable to cannula malposition, kinking, and surgical manipulation is detected by a significant increase in CVP and must be corrected promptly to restore optimal cerebral perfusion pressure (CPP = MAP − ICP or CVP) and to avoid cerebral edema. Problems with SVC drainage may be falsely inferred because of artifactually elevated CVP readings from inaccurate leveling of transducer height, compression of the catheter lumen from cannulation or surgical manipulation, and rapid fluid administration close to the transduced catheter port.

BOX 13.7 INDICATIONS FOR CENTRAL VENOUS CATHETER PLACEMENT

- Major operative procedures involving large fluid shifts or blood loss in patients with good heart function
- Intravascular volume assessment when urine output is not reliable or unavailable (eg, renal failure)
- Major trauma
- Surgical procedures with a high risk of air embolism, such as sitting-position craniotomies during which the central venous pressure catheter may be used to aspirate intracardiac air
- Frequent venous blood sampling
- Venous access for vasoactive or irritating drugs
- Chronic drug administration
- Inadequate peripheral intravenous access
- Rapid infusion of intravenous fluids (only when using large-bore cannulae)
- Total parenteral nutrition

Contraindications

The SVC syndrome is a contraindication to placing a CVP catheter in the jugular veins, subclavian veins, or upper extremities. Venous pressures in the head and upper extremities are elevated by the SVC obstruction and do not reflect right atrial pressure. Medications that are administered into the obstructed venous circulation reach the central circulation by collateral vessels in a delayed fashion. Rapid fluid administration into the obstructed venous circulation may exacerbate the elevated venous pressures and cause more pronounced edema. The mild SVC syndrome seen with some ascending aortic aneurysms, however, does not represent a contraindication to central venous cannulation of the upper body. Patients with certain types of congenital heart disease, such as single ventricle after Fontan palliation, now often survive into adulthood and may undergo cardiac surgery. Although not an absolute contraindication, many practitioners avoid placing large-bore catheters into the IJV to avoid the risk of thrombosis. Coagulopathies increase the risk for hemorrhagic complications of CVP placement, and needles should be inserted where pressure can easily be applied in case of a hematoma. Newly inserted pacemaker and/or automatic implantable cardioverter defibrillator (AICD) wires may be dislodged during the insertion of central venous catheters. If the patient is pacemaker dependent, then severe arrhythmias could result.

Complications

The complications of central venous cannulation can be divided into three categories: vascular access, catheter insertion, and catheter presence. These complications are summarized in Box 13.8, and specific information regarding several of the complications is detailed in this section.

BOX 13.8 COMPLICATIONS OF CENTRAL VENOUS CATHETERIZATION

Complications of Central Venous Access and Cannulation

- Arterial puncture with hematoma
- Arteriovenous fistula
- Hemothorax
- Chylothorax
- Pneumothorax
- Nerve injury
- Brachial plexus injury
- Stellate ganglion injury (Horner syndrome)
- Air embolus
- Catheter or wire shearing
- Guide wire loss and embolization
- Right atrial or right ventricular perforation

Complications of Catheter Presence

- Thrombosis, thromboembolism
- Infection, sepsis, endocarditis
- Arrhythmias
- Hydrothorax

Inadvertent arterial puncture during central venous cannulation is not uncommon.[156,157] The primary reasons this phenomenon occurs are that all veins commonly used for cannulation lie in close proximity to arteries (except the EJV and cephalic) and that the venous anatomy is quite variable. Localized hematoma formation is the usual consequence, which may be minimized if a small-gauge needle is initially used to localize the vein or UG is employed. If the arterial puncture is large or if the patient has a coagulopathy, then a massive hematoma may form. In the neck, this may lead to airway obstruction requiring urgent tracheal intubation. If the artery is cannulated with a large-bore catheter, then leaving the catheter or introducer sheath in place and requesting surgical consultation for further management are recommended.[95,158] Reports about successful percutaneous repair of inadvertent arterial injuries after central venous cannulation have been published.[159,160]

Arteriovenous fistula formation from the carotid artery to the IJV also has been reported after central venous cannulation.[161,162] Hemothorax may occur if the subclavian artery is lacerated during cannulation attempts. Symptoms of hypovolemia may predominate because of the large capacity of the pleural cavity.[163] Especially in smaller patients, the long and relatively stiff dilator of large introducer sheaths could possibly perforate at the SVC-innominate junction or the RA and cause massive hematoma, hemothorax, or pericardial tamponade.

Injury to the thoracic duct resulting in chylothorax has been reported after left IJV and left subclavian vein cannulation,[164–166] and is one the reasons for selecting right-sided IJV and subclavian approaches for central venous cannulation.

If the pleural cavity is entered and lung tissue is punctured during a cannulation attempt, then a pneumothorax may result. Tension pneumothorax is possible if air continues to accumulate as a result of a "ball-valve" effect. Pneumothorax is most common with subclavian punctures.

The brachial plexus, stellate ganglion, and phrenic nerve all lie in close proximity to the IJV and subclavian vein. These structures may be injured during cannulation attempts.[167,168] Transient deficits may result from the deposition of local anesthetic in the brachial plexus, stellate ganglion, or cervical plexus. Pseudoaneurysm has been reported after central venous cannulation.[169] Hematoma and true aneurysm formation resulted in vagal nerve palsy after inadvertent arterial puncture.[170]

Venous air embolism is a potentially fatal complication that can occur when there is negative pressure in the venous system. Paradoxical embolization is a risk if there is a patent foramen ovale or another intracardiac defect, such as an atrial or ventricular septal defect. During central venous cannulation, air embolism usually can be prevented with positional maneuvers, such as the Trendelenburg position, which increase the venous pressure in the vessel. Once the CVP catheter has been placed, it is important to ensure that the catheter is firmly attached to its connecting tubing. Air embolism may even occur after the catheter has been removed, if the subcutaneous tract persists.[171] The risk of air embolization is higher in spontaneously breathing patients.

The diagnosis of venous air embolism is likely when there is a sudden onset of tachycardia associated with pulmonary hypertension and systemic hypotension. A new murmur may be heard as a result of turbulent flow in the right ventricular outflow tract. Echocardiography (transesophageal or transthoracic) and precordial Doppler probe monitoring are highly sensitive methods of detecting air embolism. Venous air embolism may be effectively treated by aspirating the air by a catheter positioned at the SVC-RA junction. In the acute situation, and particularly if cardiovascular collapse occurs, the patient should be placed in a left lateral head down position to move the air embolus out of the right ventricular outflow tract. This maneuver may temporarily maintain left ventricular filling, CO, and systemic BP.

Catheter or guidewire fragments may be sheared off by the inserting needle and embolize to the right heart and pulmonary circulation when catheter-through-needle or Seldinger-type cannulation kits are used. Losing a guidewire within the patient is also possible by not withdrawing a sufficient length of the wire before inserting the catheter.[172] The catheter fragment or wire position within the circulation will determine whether surgery or percutaneous transvenous techniques are necessary for removal. To avoid catheter fragment embolization, the catheter must never be withdrawn through the inserting needle. Reinsertion of needles into standard (catheter-over-needle) intravenous cannulae cannot be recommended, particularly if the cannula is kinked. Additionally, guidewires should not be withdrawn through inserting needles when resistance is encountered. The needle and catheter or needle and guidewire should then be withdrawn simultaneously.

If right atrial or right ventricular perforation occurs during central venous cannulation, then pericardial effusion or tamponade may result. The likelihood of this complication is increased when inflexible guidewires, long dilators, or catheters are used. If pericardial tamponade is imminent, then immediate pericardiocentesis is indicated. If the catheter tip is placed extravascularly in the pleural cavity or erodes into this position, then the fluid that is infused into the catheter will accumulate in the pleural cavity (hydrothorax). A pleurocentesis or thoracostomy (chest) tube may be necessary, and surgical consultation may be required.

Transient atrial and ventricular arrhythmias commonly occur as the guidewire is passed into the RA or RV during central venous cannulation using the Seldinger technique. These arrhythmias most likely result from the relatively inflexible guidewire, causing extrasystoles as it contacts the endocardium. Ventricular fibrillation during guidewire insertion has been reported.[173] There are also reports of complete heart block from impingement of the wire in the region of the right bundle branch during insertion.[174] These cases can be managed successfully by quickly withdrawing the wire and, if persistent, by using a temporary transvenous or external pacemaker.

Strict aseptic technique and maximal sterile barrier precautions are required to minimize central line–associated bloodstream infections (CLABSIs), which are monitored as a quality indicator.[175] Subcutaneous tunneling of central venous catheters inserted into the internal jugular and femoral veins,[176,177] antiseptic barrier-protected hubs for central venous catheters,[178] and antiseptic/antibiotic-impregnated short-term central venous catheters[179,180] have been shown to reduce catheter-related infections.[181] Chlorhexidine-based skin preparations are now recommended for skin antisepsis,[69,95] and are associated with a reduced risk of CLABSI, despite studies suggesting that povidone-iodine solution was equally effective.[182–185] The routine replacement of central venous catheters to prevent catheter-related infections is not recommended.[69,186,187] When strict adherence to an aseptic technique during insertion cannot be guaranteed (ie, catheters inserted during an emergency), the catheter should be replaced as soon as possible.[69]

Pulmonary Arterial Pressure Monitoring

Clinical Efficacy and Related Trends in Pulmonary Artery Catheter Usage

At the time of the introduction of the flow-directed PAC in 1970,[188] the amount of diagnostic information that could be obtained at the bedside dramatically increased. Some of the earlier studies showed that clinicians were often unaware of hemodynamic problems or incorrectly predicted preload and CO without PAC monitoring.[189,190] Although PAC-derived data can help in the differential diagnosis of hemodynamic instability and guide treatment,[191] the clinical significance has been questioned. In 1996, Connors and colleagues[192] published the results of a large prospective cohort study with data collected from five U.S. teaching hospitals between 1989 and 1994. They enrolled 5735 critically ill adult patients in intensive care unit (ICU) settings and found that PAC monitoring was associated with increased mortality in this patient population. Further prospective randomized studies either confirmed these findings or showed no benefit associated with PAC monitoring. The results from this study were surprising to most clinicians and heavily debated. However, the level of evidence steadily increased, and eventually the PAC use started to decline significantly.

Between 1993 and 2004, PAC use in the United States alone decreased by 65% for all medical admissions.[193] The most significant decrease in PAC use was documented in patients with acute myocardial infarction, whereas those patients diagnosed with septicemia showed the least decline in use. These findings were almost identical to the surgical patient population, in which PAC use decreased by 63% in the same observed period. In another retrospective analysis, PAC use in patients hospitalized with acute coronary syndromes decreased from 5.4% in 2000 to 3.0% in 2007.[194] Similarly, a large multicenter longitudinal study at academic hospitals in Canada found that PAC use decreased by 50% between 2002 and 2006.[195] Leibowitz and Oropello[196] published data on PAC use in patients admitted to a surgical ICU (approximately 600 perioperative patients admitted per year) over an 8-year period. The number of PACs inserted decreased significantly from 23% of all admissions having a PAC inserted in 2000 to less than 2% in 2006. The patient risk profile (Acute Physiologic Assessment and Chronic Health Evaluation II [APACHE II] score) did not change, although hospital and ICU mortality in that patient population was slightly reduced in the observed period (Fig. 13.18). Similar findings were reported from other ICU settings.[197]

Concurrent with the decline of PAC use, echocardiography and less invasive CO monitors became increasingly available, often replacing the PAC as effective and less invasive or noninvasive bedside diagnostic tools. Currently, the incidence of right heart (PAC) catheterization is highly variable among hospitals and within hospitals according to service. A recent survey among the members of the Society of Cardiovascular Anesthesiologists found that a majority of practitioners (68.2%) still frequently (>75%) use a PAC for cases with CPB.[198] However, the use of a PAC differed significantly between private (79.2%), academic (64.5%), and governmental (34%) practice settings. With decreasing exposure to PACs, clinicians may become less likely to make the best use of PAC-derived hemodynamic data.[199]

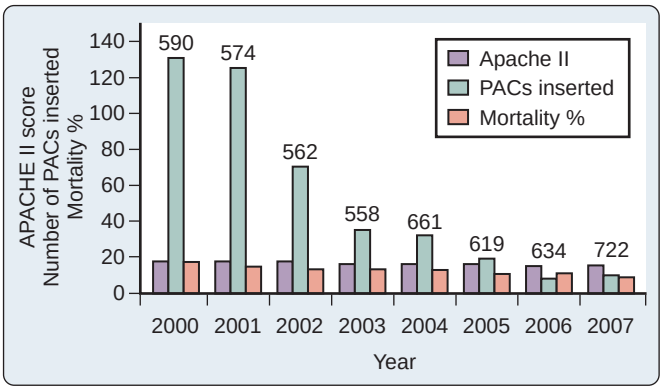


Fig. 13.18 Annual decrease in pulmonary artery catheter (*PAC*) use with stable risk scoring and mildly decreased mortality in one intensive care unit over an 8-year period. *APACHE II,* Acute Physiologic Assessment and Chronic Health Evaluation II. *(From Afessa B, Spencer S, Khan W, et al. Association of pulmonary artery catheter use with in-hospital mortality.* Crit Care Med. *2001;29:1145–1148. Used with permission.)*

Several large studies have addressed the controversies regarding the indications, risks, and benefits associated with PAC monitoring in various clinical settings after the publication of Connor's findings that PAC use may be harmful. However, as more studies have been published, evidence that PACs have little or no positive impact on patient outcomes is increasing.[200–204]

Noncardiac Surgery Setting

In 2001, Polanczyk and associates[205] published the results of an observational study on 4059 patients undergoing major elective noncardiac surgical procedures, examining the relationship between PACs and postoperative cardiac complications. Right-sided heart catheterization was associated with an increased incidence of major postoperative cardiac events. Similarly, a prospective randomized study by Rhodes and colleagues[206] found no significant difference in mortality in critically ill patients treated with or without the use of a PAC. Adjusting for the severity of illness, Murdoch and associates[207] found that the use of the PAC in ICU patients was safe, but no beneficial effect was demonstrated. Sandham and colleagues[208] reported a prospective, randomized, controlled outcome study of 1994 high-risk patients (ASA III or IV) scheduled for major noncardiac surgery, followed by ICU stay, that were managed with or without the use of a PAC. No benefit to therapy directed by PAC compared with standard care (without the use of PAC) was found, with a higher risk of adverse events in the PAC group. Yu and associates[209] performed a prospective cohort study of the relationship between PAC use and outcome in 1010 patients with severe sepsis. PAC monitoring did not improve outcomes in this patient population. Outcomes of patients with shock and acute respiratory distress syndrome (ARDS) also were not affected by PAC placement in a multicenter, randomized, controlled trial.[210] Sakr and colleagues[211] looked at outcomes related to PAC use in 3147 adult patients admitted to an ICU; this was a subanalysis of a large multicenter prospective observational study designed to evaluate the epidemiologic factors of sepsis in European countries. After propensity-score matching, no significant difference in outcome with or without PAC placement was found. Interestingly, significant differences in PAC use were reported between the various participating countries. The PAC-Man study was a randomized, controlled trial that enrolled 1041 patients from 65 ICUs throughout the United Kingdom.[212] Patients were randomly assigned to management with or without PAC placement. Treatment in both arms of the study was at the discretion of the treating clinician. Neither benefit nor harm related to PAC use was found. Two randomized, controlled studies did not show improved patient outcomes with PAC use in patients with ARDS.[210,213] Randomized trials including patients with acute myocardial infarction seemed to also confirm these data.[214,215] Cohen and associates[216] retrospectively studied 26,437 patients with acute coronary syndromes. A PAC was inserted in 2.8% of patients. In the United States, patients were 3.8 times more likely to have a PAC placed than non-US patients. After adjustment for confounding factors, PAC use was associated with a 2.6-fold increase in hospital mortality. The subset of patients who developed cardiogenic shock had similar outcomes both with and without PAC use.

The ESCAPE trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness)[217] included patients with symptoms of severe heart failure (HF). This multicenter, randomized, controlled trial enrolled 433 patients at 26 sites but had no specific treatment algorithm. However, the use of inotropes was discouraged and investigators were asked to follow national guidelines for the treatment of HF, which promote the use of diuretics and

vasodilators. The target in both groups was improvement of clinical symptoms of HF. In the PAC group, there was an additional target of a pulmonary capillary wedge pressure (PCWP) of 15 mm Hg and a CVP of 8 mm Hg. Overall, mortality did not differ between groups; however, more adverse events were recorded in the PAC group. Exercise and quality-of-life measures improved in both groups, and the investigators reported a statistically insignificant trend toward greater improvement with PAC use.

In a more recent prospective, observational multicenter HF trial in Japan (Acute Decompensated Heart Failure Syndromes [ATTEND] Registry), retrospective analysis with propensity-score matching showed decreased in-hospital mortality with PAC use in patients with low SBP or inotropic therapy.[218]

A metaanalysis by Barone and associates[219] asserted that only four prospective studies were adequately randomized and that the use of the PAC did not improve outcome in vascular surgery patients. In 2006, the Centers for Medicare and Medicaid Services and the AHRQ requested that the Tufts Medical Center Evidence-based Practice Center conduct a technology assessment report on PAC use in critical care settings. The primary goal of the review was to assess the utility of PAC monitoring regarding its relative effect and safety and how it affects outcomes in the Medicare population (ie, people at least 65 years old) hospitalized in critical care settings.[220] An elaborate and extensive (1966 to 2006) literature review and metaanalysis of various outcomes was performed, and the results published in 2008. Only prospective randomized trials meeting established quality criteria were included in the analyses. Outcomes assessed were mortality, length of ICU and hospital stays, and the incidence of medical morbidities (eg, time on mechanical ventilation, renal failure), as well as a summary of reports on complications associated with PAC use. Overall, the authors did not find evidence supporting the routine PAC use in the ICU setting. The report acknowledges, though, that the PAC provides an unparalleled way to assess hemodynamic data in critically ill patients and suggests its judicious use on an individual basis.

Cardiac Surgery Setting

Schwann and colleagues[221] assessed the outcome of 2685 patients undergoing coronary artery bypass grafting (CABG) in whom the decision to place a PAC was based on patient characteristics and risk factors. Using a highly selective strategy, no PAC was used in the majority of cases (91%), and the outcomes were comparable. In another retrospective trial, Ramsey and associates[222] found that PACs in elective CABG surgery were associated with increased in-hospital mortality, longer lengths of stay, and higher total costs. This effect was more pronounced in those hospital settings with low overall PAC use. Schwann and associates[223] retrospectively analysed patients who were enrolled in the Epidemiology II Multicenter Study of Perioperative Ischemia (McSPI) multicenter study (5065 patients, 70 centers). Using propensity-score matching, patients with and without PAC use were compared. All-cause mortality and a higher risk of severe end-organ complications were noted in patients with PAC use.

Resano and colleagues[224] looked at PAC use compared with CVP monitoring in patients undergoing off-pump coronary artery bypass (OPCAB) surgery and found no difference in outcome. In a prospective observational study, Djaiani and associates[225] looked at 200 consecutive patients undergoing CABG surgery during which PACs were placed, but the surgeon and anesthesiologist were blinded to numerical data other than CVP. Patients were managed as per routine, and data could be unblinded if required clinically. Twenty-three percent of patients required unblinding of data; within this subgroup, preliminary diagnosis was confirmed in 14%, and treatment was modified in 9%. The patients in the unblinded group went on to experience further morbidity. The investigators concluded that placement of a PAC can be safely delayed until the clinical need arises either intraoperatively or in the ICU. Overall, studies looking specifically at patients undergoing myocardial revascularization do not find clear evidence that the routine use of PACs is associated with improved outcomes.

The studies previously cited assessed clinical outcomes associated with PAC use in various clinical settings. Several investigators have attempted to address the hypothesis that patients in the ICU have diseases too far advanced to make invasive hemodynamic monitoring useful and that early goal-directed therapy (GDT) in the surgical unit may prevent major end-organ damage by means of earlier intervention.[226] Older studies that had reported improved outcome used invasive hemodynamic monitoring to optimize oxygen delivery in the perioperative period.[227–230] In their metaanalysis, Heyland and colleagues[231] similarly argued that "maximizing oxygen delivery" in the perioperative setting (ie, before the onset of irreversible organ damage) is more effective, in comparison with the chronic ICU setting. Based on the intention-to-treat analysis of patients with preoperative PAC placement, they reported improved survival. Chittock and associates[232] demonstrated that severity of illness may play an important role in defining subgroups of patients who may benefit from PAC monitoring. Of 7310 critically ill adult patients admitted to the ICU, those with APACHE II scores greater than 31 showed decreased mortality with PAC monitoring, whereas patients with lower APACHE II scores had increased mortality. Another metaanalysis by Ivanov and colleagues[233] showed a significant reduction in morbidity when PAC-guided strategies were applied. In a prospective randomized trial, Pölönen and associates[234] applied goal-directed PAC-guided therapy aimed at maintaining a mixed venous saturation >70% and blood lactate <2 mmol/L in patients after cardiac surgery. Using this strategy, they found that increasing oxygen delivery in the immediate postoperative period shortened hospital stay and decreased morbidity. In a retrospective database analysis of trauma patients admitted to an ICU (National Trauma Data Bank, 53.312 patients enrolled), severely injured and older patients had decreased mortality associated with PAC use.[235]

There may be various explanations as to why the great majority of findings do not favor PAC use. Placing a PAC is a highly invasive procedure. Vascular structures are accessed with large-bore introducer sheaths with all the possible complications listed. Most importantly, even in the best of all circumstances with uncomplicated PAC placement and correct data collection and interpretation, it has to be recognized that a PAC is only a monitoring tool. As such, a change in patient outcome cannot be expected unless the treatment that is initiated based on the PAC measurements is effective for improving patient outcome. In some of the most critically ill patients, such as those with sepsis, ARDS, or massive trauma, mortality remains high despite efforts to find new treatment strategies. Furthermore, diagnoses often can be made on clinical grounds only, and treatment strategies once thought to improve patient outcome actually may be harmful.

Despite the large number of outcome studies regarding PACs, flaws in study design and insufficient statistical power are still an issue. The most common design flaws are a lack of therapeutic protocols or treatment algorithms and inadequate randomization, which introduce observer bias.[236] Physician knowledge is another confounding variable, as demonstrated in a multicenter study that indicated competency in interpreting PAC-derived data was lacking in many individuals and depended on such factors as the level of training and the frequency of use.[237] In one study, 47% of physicians could not correctly determine the PCWP to within 5 mm Hg.[238]

In summary, there are no convincing data showing improved outcomes in patients undergoing cardiac surgery with PAC placement compared with CVP monitoring alone.[239] The perioperative literature on the subject suggests that PAC use in patients undergoing low-risk cardiac surgery may be harmful.[240] Clinical evidence gained from the majority of well-designed prospective studies indicates that patients undergoing low-risk cardiac surgery can be managed safely without PAC placement. Many clinicians, however, still consider high-risk cardiac surgery and, in particular, patients with right-sided HF or pulmonary hypertension to be indications for PAC placement (see Chapter 26). An understanding of the potential benefits and pitfalls of pulmonary artery (PA) catheterization will therefore remain essential for cardiac anesthesiologists for the foreseeable future.

Technical Aspects of Pulmonary Artery Catheter Use

Considerations for the insertion site of a PAC are the same as for CVP catheters. The HICPAC/CDC infection guidelines list specific recommendations regarding PAC use, strongly recommending use of a sterile sleeve to protect the PAC during insertion (Category IB).[69] Because of technical reasons related to the specifics of cardiac surgery, the right IJV approach remains the preferred access route for many practitioners. This is because of the direct path between this vessel and the RA during IJV approach and the frequent kinking of the introducers during sternal retraction when subclavian access is chosen.[241] However, with modern retractors and smaller incisions, catheter kinking occurs much less frequently, even with the introducer in the subclavian position. For infection prevention purposes, the HICPAC/CDC advisory actually recommends the subclavian route for PAC insertion.

Passage of the PAC from the vessel introducer to the PA can be accomplished by monitoring the pressure waveform from the distal port of the catheter or under fluoroscopic or echocardiographic (TEE) guidance. Waveform monitoring is the most common technique for perioperative right-sided heart catheterization in the surgical unit. First, the catheter must be advanced through the vessel introducer (15 to 20 cm) before inflating the balloon. The inflation of the balloon facilitates further advancement of the catheter through the RA and RV into the PA. Normal intracardiac pressures are shown in Table 13.1. The pressure waveforms seen during advancement of the PAC are illustrated in Fig. 13.19. In patients with prior TV ring annuloplasty, significant TR, and tricuspid stenosis, advancing the catheter past the TV may be cumbersome or even impossible. Catheter manipulation and positional changes may be useful. Trendelenburg positioning places the RV more superior to the RA and thus may aid in advancing the PAC past the TV. TEE guidance can prove invaluable in these cases. The experienced echocardiographer can assist in guiding the catheter tip toward the TV orifice by directing catheter and positional manipulations. The right atrial waveform is seen until the catheter tip crosses the TV and enters the RV. In the RV, there is a sudden increase in SBP but little change in DBP, compared with the right atrial tracing. Arrhythmias, particularly premature ventricular complexes, usually occur at this point, but they almost always resolve without treatment once the catheter tip has crossed the pulmonary valve. The catheter is advanced through the RV toward the PA. The reverse Trendelenburg and right lateral tilt minimize arrhythmias and facilitate catheter passage through the right ventricular outflow tract and pulmonary valve into the PA.[242] As the catheter crosses the pulmonary valve, a dicrotic notch appears in the pressure waveform, and the diastolic pressure suddenly increases. The PCWP (also termed *pulmonary capillary occlusion pressure*) tracing is obtained by advancing the catheter approximately 3 to 5 cm farther until a change in the waveform associated with a drop in the measured mean pressure occurs. Deflation of the balloon results in the reappearance of the PA waveform and an increase in the mean pressure value. Using the right IJV approach, the RA is entered at 25 to 35 cm, the RV at 35 to 45 cm, the PA at 45 to 55 cm, and the PCWP at 50 to 60 cm in most patients.

If the catheter does not enter the PA by 60 cm (from the right IJV approach), the balloon should be deflated and the catheter should be withdrawn into the RA or the inflow portion of the RV. Further attempts can then be made to advance the catheter into proper position using the techniques previously described. Excessive coiling of the catheter in the RA or RV should be avoided to prevent catheter knotting. The balloon should be inflated only for short periods to measure the PCWP. The PA waveform should be monitored continually to be certain that the catheter does not advance into a constant wedge position, which may lead to PA rupture or pulmonary infarction. Not infrequently, the PAC must be withdrawn a short distance because the catheter softens and advanced more peripherally into the PA over time, or on CPB attributable to the decreased size of the heart.

The PCWP waveform is analogous to the CVP waveform described previously. The A, C, and V waves seen when the PAC balloon is inflated (pulmonary capillary wedge position) are similarly timed in the cardiac cycle. Large V waves can be seen on the PCWP waveform during mitral regurgitation, left ventricular diastolic noncompliance, and episodes of myocardial ischemia.[243] They also are seen on the PA waveform (PAC not wedged) as large ("giant") V waves that occur slightly later than the typical upstroke on the PA tracing.[244] The V waves cause the PA waveform to become wider and to lose the dicrotic notch (Fig. 13.20). The cause of large V waves during myocardial ischemia is probably a decrease in diastolic ventricular compliance, or mitral regurgitation induced by ischemic papillary muscle dysfunction and annular dilatation from ventricular distension. In this instance, the V waves may occur earlier during the onset of the C wave (as seen with the onset of ventricular contraction) and are termed *C-V waves*.

Specific information that can be gathered with the PAC and the quantitative measurements of cardiovascular and pulmonary function that can be derived from this information are listed in Tables 13.2 and 13.3. One of the primary reasons that clinicians measure PCWP and PA diastolic (PAD) pressure is that these parameters are estimates of LAP, which can serve as an estimate of left ventricular preload.[245] The relationship between left ventricular end-diastolic pressure (LVEDP) and left ventricular end-diastolic volume (LVEDV) is described by the left ventricular compliance curve. This nonlinear curve is affected by many factors, such as ventricular hypertrophy and myocardial ischemia.[246–248] The relationship of these parameters is diagrammed in Fig. 13.21. In the echo era, left ventricular preload in the surgical unit is better evaluated using TEE measures, such as end-diastolic area or volume. However, elevation of either PCWP or LAP is still a useful criterion in estimating acute exacerbation of HF.

The PCWP and PAD pressure will not accurately reflect LVEDP in the presence of incorrect position of the PAC catheter tip, pulmonary vascular disease, high levels of PEEP, or mitral valvular disease. The patency of vascular channels between the distal port of the PAC and the LA is necessary to ensure a close relationship between the PCWP and

TABLE 13.1 Normal Intracardiac Pressures

Location	*Mean (mm Hg)*	*Range (mm Hg)*
Right atrium	5	1–10
Right ventricle	25/5	15–30/0–8
Pulmonary arterial systolic and diastolic pressures	23/9	15–30/5–15
Mean pulmonary arterial	15	10–20
Pulmonary capillary wedge pressure	10	5–15
Left atrial pressure	8	4–12
Left ventricular end-diastolic pressure	8	4–12
Left ventricular systolic pressure	130	90–140

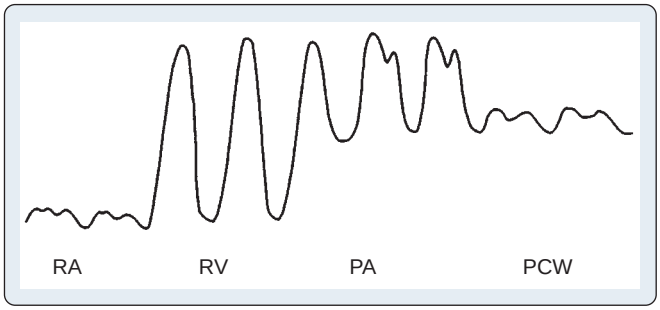


Fig. 13.19 The waveforms encountered during the flotation of a pulmonary artery catheter from the venous circulation to the pulmonary capillary wedge *(PCW)* position. Notice the sudden increase in systolic pressure as the catheter enters the right ventricle *(RV)*, the sudden increase in diastolic pressure as the catheter enters the pulmonary artery *(PA)*, and the decrease in mean pressure as the catheter reaches the PCW position. *RA*, Right atrium.

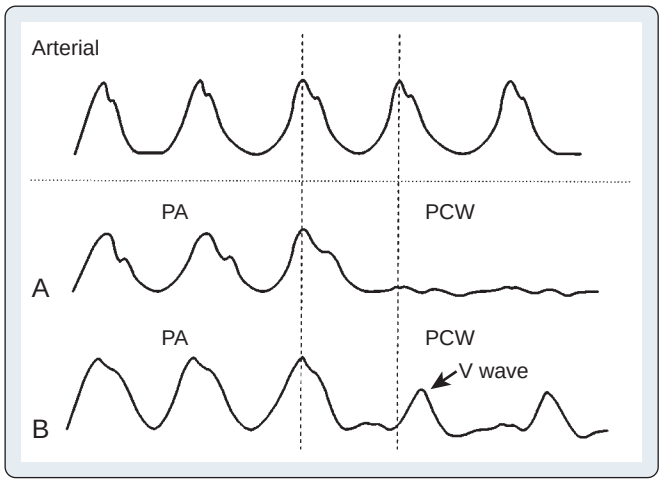


Fig. 13.20 The relationship of the systemic arterial waveform, the pulmonary arterial (*PA*) waveform, and the pulmonary capillary wedge (*PCW*) waveform in the normal situation (A) and in the presence of V waves (B). Note the widening of the PA waveform and the loss of the dicrotic notch in the presence of V waves. The peak of the *V wave (arrow)* occurs after the peak of the systemic arterial waveform.

TABLE 13.2 Derived Hemodynamic Parameters

Formula	*Normal Values*
Cardiac index (CI) CI = CO/BSA	2.6–4.2 L/min/m^2
Stroke volume (SV) SV = CO*1000/HR	50–110 mL (per beat)
Stroke index (SI) SI = SV/BSA	30–65 mL/beat/m^2
Left ventricular stroke work index (LVSWI) LVSWI = 1.36* (MAP–PCWP)* SI/100	45–60 gram-meters/m^2
Right ventricular stroke work index (RVSWI) RVSWI = 1.36* (MPAP–CVP)* SI/100	5–10 gram-meters/m^2
Systemic vascular resistance (SVR) SVR = (MAP–CVP)* 80/CO	900–1400 dynes·sec·cm^{-5}
Systemic vascular resistance index (SVRI) SVRI = (MAP–CVP)* 80/CI	1500–2400 dynes·sec·cm^{-5}/m^2
Pulmonary vascular resistance (PVR) PVR = (MPAP–PCWP)* 80/CO	150–250 dynes·sec·cm^{-5}
Pulmonary vascular resistance index (PVRI) PVRI = (MPAP–PCWP)* 80/CI	250–400 dynes·sec·cm^{-5}/m^2

BSA, Body surface area; *CO*, cardiac output; *CVP*, central venous pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *PAP*, pulmonary arterial pressure; *PCWP*, pulmonary capillary wedge pressure.

LAP. This condition is met only in the dependent portions of the lung (West zone III), in which the pulmonary venous pressure exceeds the alveolar pressure.[249] Otherwise, the PCWP will reflect alveolar pressure and not LAP. High levels of PEEP decrease the size of West zone III, and adversely affect the correlation between the PCWP and LAP, especially in the hypovolemic patient.[250–252] In patients on high levels of PEEP it is not clear what percentage of the increased intrathoracic pressure is actually transmitted to the catheter tip, and how much this affects the estimation of left ventricular preload. However, temporary removal of high levels of PEEP (eg, >10 mm Hg) is discouraged, because rapid reduction in the functional residual capacity and associated lung atelectasis might have acute adverse respiratory consequences. Conversely, low levels of PEEP applied to prevent atelectasis may actually maintain vascular patency and the correlation with left-sided filling pressures since hypoxia is associated with pulmonary vasoconstriction. In patients with ARDS the relationship between the PCWP and LAP

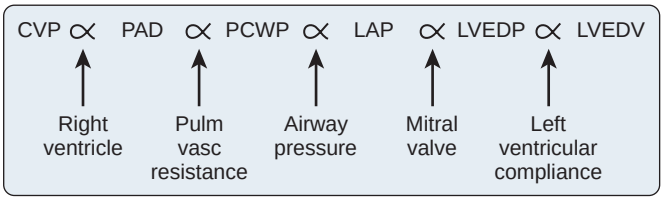


Fig. 13.21 The left ventricular end-diastolic volume (*LVEDV*) is related to left ventricular end-diastolic pressure (*LVEDP*) by the left ventricular compliance. The LVEDP is related to the left atrial pressure (*LAP*) by the diastolic pressure gradient across the mitral valve. The pulmonary capillary wedge pressure (*PCWP*) is related to the LAP by the pulmonary capillary resistance. The pulmonary artery diastolic (*PAD*) pressure is an estimate of the PCWP. The central venous pressure (*CVP*) will reflect the PAD pressure if right ventricular function is normal.

TABLE 13.3 Oxygen Delivery Parameters

Formula	*Normal Values*
Arterial oxygen content (CaO_2) $CaO_2 = (1.39^* Hb^* SaO_2) + (0.0031^* PaO_2)$	18–20 mL/dL
Mixed venous oxygen content (CvO_2) $CvO_2 = 1.39^* Hb^* SvO_2 + 0.0031^* PvO_2$	13–16 mL/dL
Arteriovenous oxygen content difference ($avDO_2$) $avDO_2 = CaO_2 - CvO_2$	4–5.5 mL/dL
Pulmonary capillary oxygen content (CcO_2) $CcO_2 = 1.39^* Hb^* ScO_2 + 0.0031^* PcO_2$	19–21 mL/dL
Pulmonary shunt fraction (Qs/Qt) $Qs/Qt = 100^* (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$	2–8 %
Oxygen delivery (DO_2) $DO_2 = 10^* CO^* CaO_2$	800–1100 mL/min
Oxygen consumption (VO_2) $VO_2 = 10 * CO * (CaO_2 - CvO_2)$	150-300 mL/min

CcO_2, Capillary oxygen content; *Hb*, hemoglobin; *PaO_2*, arterial partial pressure of oxygen; *PcO_2*, pulmonary capillary oxygen tension; *PvO_2*, venous oxygen tension; *SaO_2*, arterial oxygen saturation; *ScO_2*, pulmonary capillary oxygen saturation; *SvO_2*, venous oxygen saturation.

From McGrath RB. Invasive bedside hemodynamic monitoring. *Prog Cardiovasc Dis.* 1986; 29:129–144.

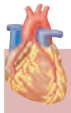
was preserved even when high levels of PEEP up to 20 cm water were applied.[253]

In general, the PCWP should be determined at end-expiration in both spontaneously breathing patients and those on mechanical ventilation. Significant valvular disease greatly increases the difficulty in correctly interpreting the PCWP. The presence of large V waves in the PCWP tracing of patients with mitral regurgitation leads to an overestimation of the LVEDP.[254] In patients with mitral stenosis, PCWP will be elevated despite decreased left ventricular preload (LVEDV). Significant aortic regurgitation will lead to premature mitral valve closure; as a result, LVEDV will be underestimated. Additionally, immediately after CPB, the PCWP may be inaccurate in assessing LAP and LVEDP.[255] Box 13.9 provides a summary of conditions that may alter the relationship between the PCWP and the LVEDP.

Special purpose PACs for continuous CO, continuous mixed venous oxygen saturation (SvO_2), pacing, and thermodilution right ventricular ejection fraction (RVEF) have been investigated clinically and are described later in this chapter; however, commercial availability is becoming more limited.

Indications

In a global sense, the indications for using a PAC are assessing hemodynamic parameters such as loading conditions of the heart (preload, afterload), CO, and indices useful in assessing oxygen delivery and demand (ie, SvO_2). In 2003, the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization published updated practice guidelines for PA catheterization.[256] These guidelines



BOX 13.9 CONDITIONS RESULTING IN DISCREPANCIES BETWEEN PULMONARY CAPILLARY WEDGE PRESSURE AND LEFT VENTRICULAR END DIASTOLIC PRESSURE

PCWP > LVEDP
- Positive pressure ventilation
- High levels PEEP
- Increased intrathoracic pressure
- Non–West lung zone III PAC placement
- Chronic obstructive pulmonary disease
- Increased pulmonary vascular resistance
- Left atrial myxoma
- Mitral valve disease (eg, stenosis, regurgitation)

PCWP < LVEDP
- Noncompliant left ventricle (eg, ischemia, hypertrophy)
- Aortic regurgitation (premature closure of the mitral valve)

LVEDP, Left ventricular end diastolic pressure; *PAC*, pulmonary artery catheter; *PCWP*, pulmonary capillary wedge pressure; *PEEP*, positive end-expiratory pressure.
Adapted from Tuman KJ, Carroll GC, Ivankovich AD. Pitfalls in interpretation of pulmonary artery catheter data. *J Cardiothorac Vasc Anesth*. Update. 1991;2:1–24.

emphasized that the patient, surgery, and practice setting had to be considered when deciding on the use of a PAC. Generally, the routine use of PACs is indicated in high-risk patients (eg, ASA IV or V) and high-risk procedures, during which large fluid changes or hemodynamic disturbances are expected. The practice setting is important, because evidence suggests that inadequate training or experience may increase the risk for perioperative complications associated with the use of a PAC. The recommendation is that the routine use of a PAC should be confined to centers with adequate training and experience in the perioperative management of patients with PACs (Box 13.10). The authors of this chapter have composed a list of possible procedural indications (Box 13.11).

Historically, the use of the PAC contributed to the understanding and care of patients with cardiac disease. The risks associated with perioperative PAC monitoring, however, seem to outweigh the benefits in low-to-moderate risk patients, whereas some high-risk patients undergoing major surgery may benefit from right-sided heart catheterization.

Contraindications

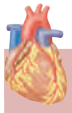
Contraindications to PA catheterization are summarized in Box 13.12.

Absolute Contraindications

Contraindications to the use of a PAC include severe tricuspid or pulmonic valvular stenosis. It is unlikely that a PAC would be able to cross the stenotic valve, and it might worsen the obstruction to flow if it did. Friable right atrial or right ventricular masses (ie, tumor, thrombus) are also absolute contraindications. The catheter may dislodge a portion of the mass, causing pulmonary or paradoxical embolization.

Relative Contraindications

The use of a PAC may be contraindicated in patients with severe arrhythmias. Transient atrial and ventricular arrhythmias are common during PAC placement. The risk of inducing an arrhythmia in a patient prone to malignant arrhythmias must be weighed against the potential benefits of the information gained from PAC monitoring. Appropriate preparations must be undertaken for the administration of antiarrhythmic drugs and cardiopulmonary resuscitation, as well as electrical cardioversion, defibrillation, or pacing, if required. In patients with preexisting left bundle branch block (LBBB), a complete heart block

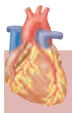


BOX 13.10 AMERICAN SOCIETY OF ANESTHESIOLOGISTS' PRACTICE GUIDELINES FOR PULMONARY ARTERY CATHETER USE

Opinions
- PA catheterization provides new information that may change therapy, with poor clinical evidence of its effect on clinical outcome or mortality.
- There is no evidence from large, controlled studies that preoperative PA catheterization improves outcome regarding hemodynamic optimization.
- Perioperative PAC monitoring of hemodynamic parameters leading to goal-directed therapy has produced inconsistent data in multiple studies and clinical scenarios.
- Having immediate access to PAC data allows important preemptive measures for selected subgroups of patients who encounter hemodynamic disturbances that require immediate and precise decisions about fluid management and drug treatment.
- Experience and understanding are the major determinants of PAC effectiveness.
- PA catheterization is inappropriate as routine practice in surgical patients and should be limited to cases in which the anticipated benefits of catheterization outweigh the potential risks.
- PA catheterization can be harmful.

Recommendations
- The appropriateness of PA catheterization depends on a combination of patient-, surgery-, and practice setting–related factors.
- Perioperative PA catheterization should be considered in patients with significant organ dysfunction or major comorbidity that pose an increased risk for hemodynamic disturbances or instability (eg, ASA IV or V patients).
- Perioperative PA catheterization in surgical settings should be considered based on the hemodynamic risk of the individual case rather than generalized surgical setting–related recommendations. High-risk surgical procedures are those during which large fluid changes or hemodynamic disturbances can be anticipated and procedures that are associated with a high risk of morbidity and mortality.
- Because of the risk of complications from PA catheterization, the procedure should not be performed by clinicians or nursing staff or in practice settings in which competency in safe insertion, accurate interpretation of results, and appropriate catheter maintenance cannot be guaranteed.
- Routine PA catheterization is not recommended when the patient, procedure, or practice setting poses a low or moderate risk for hemodynamic changes.

ASA, American Society of Anesthesiologists; *PA*, pulmonary artery; *PAC*, pulmonary artery catheter.
From American Society of Anesthesiologists. Practice guidelines for pulmonary artery catheterization. Available at: http://www.asahq.org/~/media/sites/asahq/files/public/resources/standards-guidelines/practice-guidelines-for-pulmonary-artery-catheterization.pdf



BOX 13.11 POSSIBLE CLINICAL INDICATIONS FOR PULMONARY ARTERY CATHETER MONITORING

Major procedures involving large fluid shifts or blood loss in patients with:
- Right-sided heart failure, pulmonary hypertension
- Severe left-sided heart failure not responsive to therapy
- Cardiogenic or septic shock or with multiple-organ failure
- Orthotopic heart transplantation
- Left ventricular–assist device implantation

BOX 13.12 CONTRAINDICATIONS FOR PULMONARY ARTERY CATHETERIZATION

Absolute Contraindications
- Severe tricuspid or pulmonary stenosis
- Right atrial or right ventricular mass
- Tetralogy of Fallot

Relative Contraindications
- Severe arrhythmias
- Left bundle branch block (consider pacing PAC)
- Newly inserted pacemaker wires, AICD, or CRT
- Severe coagulopathy

AICD, Automatic implantable cardioverter defibrillator; *CRT*, cardiac resynchronization therapy; *PAC*, pulmonary artery catheter.

may result and cause significant hemodynamic instability. The benefits of placing a PAC in these patients should clearly outweigh the risks, and using a pacing or paceport PAC should be considered, allowing for immediate pacing should a complete heart block occur. Alternatively, external pacing leads should be placed before the procedure.

Coagulopathy may be a relative contraindication to the use of a PAC and may be related to the potential complications of obtaining central venous access in the patient with a coagulopathy. The risk of inducing endobronchial hemorrhage with inadvertent migration of the PAC or prolonged balloon inflation may be increased.

Newly inserted pacemaker wires may be a contraindication, because of the risk of displacing them during PAC insertion or withdrawal. In approximately 4 to 6 weeks, the pacemaker wires become firmly embedded in the endocardium, and wire displacement becomes less likely. The risk is even higher with multiple electrodes in place such as with an AICD or for cardiac resynchronization therapy.

Complications

The complications associated with PAC placement include almost all of those detailed in the section on CVP placement. Additional complications that are unique to the PAC are detailed in the following paragraphs. The American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization concluded that serious complications attributable to PAC catheterization occur in 0.1% to 0.5% of patients monitored with a PAC.[256] Higher estimates are found in the literature and probably represent different patient populations, hospital settings, level of experience with PAC management, and other factors.[257]

Arrhythmias

The most common complications associated with PAC insertion are transient arrhythmias, especially premature ventricular contractions.[258] However, fatal arrhythmias have rarely been reported.[259,260] A positional maneuver entailing 5-degree head-up and right lateral tilt was associated with a statistically significant decrease in malignant arrhythmias (compared with the Trendelenburg position) during PAC insertion.[242]

Complete Heart Block

Complete heart block may develop during PA catheterization in patients with preexisting LBBB.[261–264] This potentially fatal complication is most likely due to electrical irritability from the PAC tip causing transient right bundle branch block (RBBB) as it passes through the right ventricular outflow tract. The incidence of developing RBBB was 3% in a prospective series of patients undergoing PA catheterization.[265] However, none of the patients with preexisting LBBB developed complete heart block in that series. In another study of 47 patients with LBBB, complete heart block occurred in 2 patients with recent-onset LBBB.[266] Having an external pacemaker immediately available or using a pacing PAC when placing a PAC in patients with LBBB is imperative.

Endobronchial Hemorrhage

Numerous cases of iatrogenic rupture of the PA have been recorded.[267–269] The incidence of PAC-induced endobronchial hemorrhage in one large series was 0.064% to 0.20%.[258] The ASA PAC guidelines report an incidence of 0.03% to 1.5% from the reviewed literature.[256] Regardless of the exact incidence, this rare complication is associated with a high mortality rate. Hannan and colleagues[270] reported a 46% mortality rate in a review of 28 cases of PAC-induced endobronchial hemorrhage, but the mortality rate was 75% in anticoagulated patients. From these reports, several risk factors have emerged: advanced age, female sex, pulmonary hypertension, mitral stenosis, coagulopathy, distal placement of the catheter, and balloon hyperinflation. Balloon inflation in distal PAs is probably accountable for most episodes of PA rupture because of the high pressures generated by the balloon.[271] Hypothermic CPB also may increase risk attributable to distal migration of the catheter tip with movement of the heart and hardening of the PAC.[272,273] Pulling back the PAC approximately 3 to 5 cm when CPB is instituted is common practice.

Consideration of the cause of the hemorrhage when forming a therapeutic plan is important. If the hemorrhage is minimal and a coagulopathy coexists, then correction of the coagulopathy may be the only necessary therapy. Protection of the uninvolved lung is of prime importance. Tilting the patient toward the affected side and placing a double-lumen endotracheal tube, as well as other lung-separation maneuvers, should protect the contralateral lung.[274] Strategies proposed to stop the hemorrhage include the application of PEEP, the placement of bronchial blockers, and pulmonary resection.[275] The clinician is obviously at a disadvantage unless the site of hemorrhage is known. A chest radiograph will usually indicate the general location of the lesion. Although the cause of endobronchial hemorrhage may be unclear, the bleeding site must be unequivocally located before surgical treatment is attempted. A small amount of radiographic contrast dye may help pinpoint the lesion if active hemorrhage is present. In severe hemorrhage and with recurrent bleeding, transcatheter coil embolization has been used and may emerge as the preferred treatment method.[276,277]

Pulmonary Infarction

Pulmonary infarction is a rare complication of PAC monitoring. An early study suggested that a 7.2% incidence of pulmonary infarction was reported with PAC use.[278] However, continuously monitoring the PA waveform and keeping the balloon deflated when not determining the PCWP (to prevent inadvertent wedging of the catheter) were not standard practice at that time. Distal migration of PACs may also occur intraoperatively as a result of the action of the RV, uncoiling of the catheter, and softening of the catheter over time. Inadvertent catheter wedging occurs during CPB because of the diminished right ventricular chamber size and retraction of the heart to perform the operation. Embolization of thrombus formed on a PAC also could result in pulmonary infarction.

Catheter Knotting and Entrapment

Knotting of a PAC usually occurs as a result of coiling of the catheter within the RV. Insertion of an appropriately sized guidewire under fluoroscopic guidance may aid in unknotting the catheter.[279] Alternatively, the knot may be tightened and withdrawn percutaneously along with the introducer if no intracardiac structures are entangled.[280] If cardiac structures, such as the papillary muscles, are entangled in the knotted catheter, then surgical intervention may be required.[281,282] Sutures placed in the heart may inadvertently entrap the PAC. Reports of such cases and the details of the percutaneous removal have been described.[283]

Valvular Damage

Withdrawal of the catheter with the balloon inflated may result in injury to the tricuspid[284] or pulmonary valves.[285] Placement of the PAC

with the balloon deflated may increase the risk of passing the catheter between the chordae tendineae.[286] Septic endocarditis has also resulted from an indwelling PAC.[287,288]

Thrombocytopenia

Mild thrombocytopenia has been reported historically with PAC use.[289] Although heparin-coated PACs may reduce this risk, these catheters can trigger heparin-induced thrombocytopenia.[290]

Thrombus Formation

The PAC is a foreign body that may serve as a nidus for thrombus formation,[291] but this is rarely seen with modern heparin-bonded PACs[292] and short-term use. Antifibrinolytic therapy may increase the risk of thrombus formation.[293,294]

Incorrect Placement

Aside from monitoring the pressure waveform from the distal lumen, TEE can be used to direct the PAC through the TV and into the correct position in the proximal PA. Without TEE guidance, incorrect placement of the PAC is not uncommon. Most frequently, the PAC is advanced too far and may result in spontaneous wedging of the catheter during CPB. Placement of the PAC in the liver has been described; the wedged hepatic venous pressures may mimic the PA pressure waveform.[295] Cannulation of the left IJV in patients with an unknown persistent left SVC would result in advancing the PAC through the CS.[296] In patients with a persistent foramen ovale or atrial or ventricular septal defect, the catheter may pass into the left side of the heart. In a case report of a patient with an ascending aortic aneurysm, compression of the SVC by the aneurysm led to traumatic placement of the PAC directly into the pulmonary vein.[297] Venous cannula obstruction has occurred in patients during CPB.[298–300] The temporal association with the abrupt loss of venous return and the negative pressure recorded on the distal lumen tracing are important indicators that this may be occurring. This stresses the importance of monitoring the pressure waveforms during CPB. TEE has proved invaluable for confirming the proper placement of PACs.

Balloon Rupture

Balloon rupture is not uncommon when the PAC has been left in place for several days or when the balloon is inflated with more than 1.5 mL of air. Small volumes of air injected into the PA are of little consequence, and balloon rupture is apparent if the injected air cannot be withdrawn from the balloon and blood is aspirated instead.

Ventricular Perforation

Right ventricular perforation is a rare complication with a balloon-tipped catheter, but it has been reported in the literature.[301]

Artifacts and Erroneous Measurements

Measuring the PCWP to determine the volume status of patients is particularly prone to errors, which can lead to spurious numbers and incorrect treatment of the patient. Incorrect leveling of the transducer height with the LA and interference from mechanical ventilation (Fig. 13.22) are both very common sources of erroneous measurements. "Catheter whip" is an artifact that is associated with long catheters and thus can be observed with PACs. Because the catheter tip moves within the bloodstream of great vessels, the fluid contained within the catheter is accelerated, resulting in superimposed pressure waves of 10 mm Hg in either direction. With echocardiography being almost uniformly available in cardiac surgical units, multiple monitoring tools and parameters are available to the practitioner confirming individual pressure readings.

Special Purpose Pulmonary Artery Catheters

With decreasing use of PACs, the availability of special purpose catheters is also decreasing.

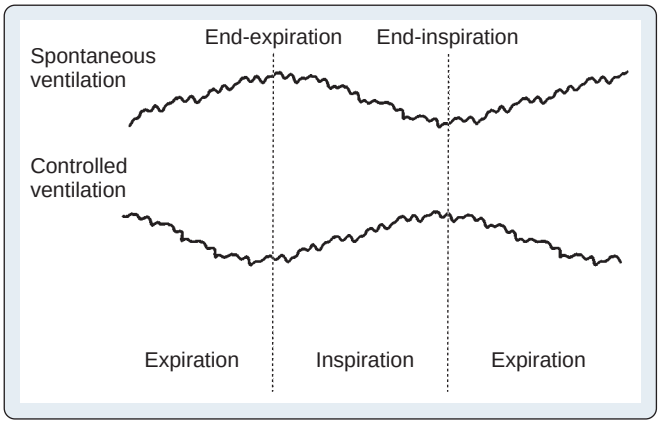


Fig. 13.22 Respiratory variation of the pulmonary capillary wedge pressure waveform during spontaneous and mechanical ventilation. Inspiration is marked by negative mediastinal pressure in the spontaneously breathing patient and by positive mediastinal pressure in the mechanically ventilated patient.

BOX 13.13 INDICATIONS FOR PERIOPERATIVE PLACEMENT OF PACING PULMONARY ARTERY CATHETERS

- Sinus node dysfunction or symptomatic bradycardia
- Hemodynamically relevant second-degree (Mobitz II) atrioventricular block
- Complete (third-degree) atrioventricular block
- Need for atrioventricular sequential pacing
- Left bundle branch block

Pacing Pulmonary Artery Catheters

Electrode-coated PACs and pacing wire catheters are available commercially. The possible indications for placement of a pacing PAC are shown in Box 13.13.

Electrode Catheters

This multipurpose PAC (Edwards Lifesciences Corp., Irvine, CA) contains three atrial and two ventricular electrodes for atrial, ventricular, or AV sequential pacing. The intraoperative success rates for atrial, ventricular, and AV sequential capture have been reported as 80%, 93%, and 73%, respectively.[302]

Pacing Wire Catheters

The Paceport and A-V Paceport PA catheters (Edwards Lifesciences Corp., Irvine, CA) have lumens for the introduction of a ventricular wire or both atrial and ventricular wires for temporary transvenous pacing. The success rate for ventricular and AV capture with Paceport PACs is higher, compared with electrode pacing PACs.[303,304] The use and indications for the placement of pacing PAC in a series of cardiac surgery patients has been published.[305–307]

Mixed Venous Oxygen Saturation Catheters

Monitoring the SvO_2 is a means of providing a global estimation of the adequacy of oxygen delivery relative to the needs of the various tissues (oxygen supply-demand ratio). The formula for SvO_2 calculation can be derived by modifying the Fick formula and assuming that the effect of dissolved oxygen in the blood is negligible:

$$SvO_2 = SaO_2 - \frac{\dot{V}O_2}{CO \cdot 1.34 \cdot Hb}$$

A decrease in the SvO_2 can indicate one of the following situations: decreased CO, increased oxygen consumption, decreased arterial oxygen saturation, or decreased hemoglobin (Hb) concentration. To measure SvO_2 in the laboratory, blood is aspirated from the distal port of the PAC slowly, so as not to contaminate the sample with oxygenated alveolar blood.

The addition of fiberoptic bundles to PACs has enabled the continuous monitoring of SvO_2 using reflectance spectrophotometry. The catheter is connected to a device that includes a light-emitting diode and a sensor to detect the light returning from the PA. SvO_2 is calculated from the differential absorption of various wavelengths of light by the saturated and desaturated Hb.[308] The values obtained with various fiberoptic catheter systems showed good agreement with in vitro (co-oximetry) SvO_2 measurements.[309–312]

The usefulness of the catheter may primarily be its ability to continuously monitor the balance between oxygen delivery and consumption.[313–316] However, severe deterioration in the condition of critically ill patients is often not predicted by changes in SvO_2.[317–319] London and colleagues[320] published a prospective, multicenter, observational study in which continuous monitoring of SvO_2 was compared with standard PAC monitoring in 3265 cardiac surgical patients. They failed to show any improved outcome associated with the use of continuous SvO_2 catheters and only a small reduction in resource use. Several recent studies found an association not only between low but also between supranormal central venous oxygen saturations and poor outcome measures, including in patients undergoing cardiac surgery.[321–324]

Cardiac Output Monitoring

The CO is the amount of blood delivered to the tissues by the heart each minute. This measurement reflects the status of the entire circulatory system, not just the heart, because it is governed by autoregulation from the tissues. The CO is equal to the product of the SV and the HR. Preload, afterload, HR, and contractility are the major determinants of the CO. This section describes the methods of CO monitoring including thermodilution CO derived from the PAC. Interestingly, a metaanalysis performed as part of the OPTIMISE trial published in 2014,[325] found that CO-guided hemodynamic therapy in noncardiac surgery was associated with fewer complications than control treatment.

Fick Method

The Fick formula is derived from the concept that oxygen consumed by the tissues per unit time is equal to the amount of oxygen extracted per unit time from the circulation. The oxygen extracted from the circulation is the product of the arteriovenous oxygen content difference and the CO:

$$VO_2 = (CaO_2 - CvO_2) \times CO$$

Rearranging the equation, CO is calculated using the following formula:

$$CO = \frac{VO_2}{(CaO_2 - CvO_2)}$$

in which CO is the cardiac output, VO_2 is the oxygen consumption, CaO_2 is the arterial oxygen content, and CvO_2 is the mixed venous oxygen content.

In the direct Fick method, oxygen consumption is measured by indirect calorimetry using algorithms based on inspired and expired oxygen concentrations and volumes. Oxygen consumption can be calculated when the rate of fresh gas flow, respiratory rate, and change of oxygen concentration are known. Arterial oxygen content is measured from an arterial blood sample, and mixed venous oxygen content can be obtained from the PAC. Because of technical difficulties, oxygen consumption in pediatric patients is commonly estimated using the formulas of LaFarge and Miettinen[326] with the use of gender, HR, and age as variables. Oxygen consumption and arteriovenous oxygen content differences must be measured at steady state because the Fick principle is valid only when tissue oxygen uptake equals lung oxygen uptake.

The accuracy and reproducibility of the direct Fick CO technique have been determined in a variety of animal and human experiments. Both measures usually have been found to be high.[327] The major limitations of the direct Fick technique are related to errors in sampling and analysis, difficulty in obtaining oxygen uptake continuously in the surgical unit, the presence of bulky equipment surrounding the endotracheal tube, or the inability to maintain steady-state hemodynamic and respiratory conditions.[328,329]

Some of these problems have been overcome with the introduction of metabolic modules for the measurement of oxygen consumption that are incorporated into the patient monitoring system and that do not depend on collecting gases in bulky sample chambers.[330] No flow or volume transducers are incorporated into these systems. Rather, continuous measurement of expiratory carbon dioxide (CO_2) concentrations in a constant flow allows for the calculation of the amount of CO_2 eliminated by the patient. This method is referred to as the "modified carbon dioxide Fick method." Inspiratory and expiratory oxygen and CO_2 concentrations are measured to obtain the respiratory quotient, which is then used to derive oxygen consumption.

In the indirect Fick method of calculating CO, expired gases such as CO_2 (intermittent partial rebreathing of CO_2) or acetylene replace oxygen consumption in the Fick equation.[331] Substituting CO_2 production for oxygen consumption, capnographic measurement of CO_2 concentrations may be used to provide a noninvasive Fick estimate of CO. The rebreathing technique is used to estimate mixed venous partial pressure of CO_2. In the clinical setting, patients are sedated and mechanically ventilated, and capnometry equipment is attached to a processor that calculates CO.[332] Studies comparing the CO_2 rebreathing method with standard measures of CO have yielded conflicting results.[333–337] Binder and Parkin[338] studied postoperative cardiac surgical patients. They compared the CO_2 method with the thermodilution method and showed a good correlation. In contrast, van Heerden and colleagues,[339] using a different device, found that CO measurements in cardiac surgery patients were overestimated using the CO_2 rebreathing technique.

Indicator Dilution

The indicator dilution method is based on the observation that, for a known amount of indicator introduced at one point in the circulation, the same amount of indicator should be detectable at a downstream point. The amount of indicator detected at the downstream point is equal to the product of CO and the change in indicator concentration over time. CO is calculated using the Stewart-Hamilton equation:

$$CO = I \times 60 \div \int C\,dt$$

in which CO is cardiac output, I is amount of indicator injected, and $\int C\,dt$ is the integral of indicator concentration over time (60 converts seconds to minutes).

Cold saline (ie, thermodilution) or lithium ions are used as indicators, whereas dye (eg, indocyanine green [ICG]) or radioisotopes are rarely used in current practice.[340] Blood flow is directly proportional to the amount of the indicator delivered and inversely proportional to the amount of indicator that is present at a sampling site distal to the injection site.

Thermodilution

Intermittent Thermodilution Cardiac Output

The thermodilution method, using the PAC, is the most commonly used method at present for invasively measuring CO in the clinical setting. With this technique, multiple CO measurements can be obtained at frequent intervals using an inert indicator and without blood withdrawal. A bolus of cold fluid is injected into the RA, and the resulting temperature change is detected by the thermistor in the PA.[341]

When a thermal indicator is used, the modified Stewart-Hamilton equation is used to calculate CO:

$$CO = \frac{V(T_B - T_I) \times K_1 \times K_2}{\int_0^\infty \Delta T_B(t)dt}$$

in which CO is the cardiac output (L/min), V is the volume of injectate (mL), T_B is the initial blood temperature (degrees Celsius), T_I is the initial injectate temperature (degrees Celsius), K_1 is the density factor, K_2 is the computation constant, and $\int_0^\infty \Delta T_B(t)dt$ is the integral of blood temperature change over time.

A computer that integrates the area under the temperature versus time curve is used to perform the calculation. CO is inversely proportional to the area under the curve.

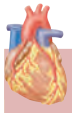
Accuracy

Accuracy describes the ability of a monitoring device to produce results close to the actual true value. With thermodilution CO, several factors may affect the accuracy of the system, including the temperature of the injectate, the speed and amount of injected volume, and technical errors such as fluid administration during CO measurement.

Most of the validation studies on thermodilution CO date back to when the PAC was introduced. Bilfinger and associates,[342] for example, found that the average difference between the thermodilution measurements and the reference values was 7% to 8% with room-temperature injectate and 11% to 13% with ice-cold saline injectate. Under strictly controlled in vitro conditions, the accuracy of the thermodilution CO technique varied from +/−7% to +/−13%. In early studies comparing thermodilution measurements with the direct Fick method, correlation coefficients of 0.96 were obtained.[343,344] Pelletier[345] compared total electromagnetic flow, including coronary blood flow, with thermodilution CO in dogs. He observed that, on average, thermodilution overestimated total aortic flow by +/−3%, compared with electromagnetic flow, whether iced or room-temperature injectate was used. When CO measurements were compared using the thermodilution and ICG methods, the results varied among various studies, with some investigators finding excellent correlations over a wide range of outputs, whereas others observed that thermodilution systematically overestimated dye dilution CO.[346–348]

The temperature-versus-time curve is the crux of this technique, and any circumstances that affect it have consequences for the accuracy of the CO measurement. Specifically, anything that results in less "cold" reaching the thermistor, more "cold" reaching the thermistor, or an unstable temperature baseline will adversely affect the accuracy of the technique. Less "cold" reaching the thermistor would result in overestimation of the CO, which could be caused by a smaller amount of indicator, an indicator that is too warm, a thrombus on the thermistor, or partial wedging of the catheter. Conversely, underestimation of the CO will occur if excessive volume of injectate or injectate that is too cold is used to perform the measurement. In patients with large intracardiac shunts, PAC-derived thermodilution CO is not recommended for accurate CO measurement. Box 13.14 lists common errors in PAC thermodilution CO measurements.

Wetzel and Latson[349] observed variations of up to 80% in measured CO when the rate of administration of intravenous crystalloid infusions caused fluctuations in baseline blood temperature. The rapid temperature decrease seen after weaning from hypothermic CPB has been shown to result in the underestimation of CO by 0.6 to 2.0 L/min.[350] In that study, the temperature decrease after CPB was 0.14 degrees C/min. Latson and colleagues[351] also found that the normal changes in the PA that occur with each respiratory cycle appear to be exaggerated in the early phase after hypothermic CPB. This may cause peak-to-peak errors in estimation of intermittent CO of up to 50% if initiated at different times during the ventilatory cycle. This effect was significantly decreased with thermal equilibration, approximately 30 minutes after CPB. Currently, this problem is less prevalent, because hypothermic CPB is used less.



BOX 13.14 COMMON ERRORS IN PULMONARY ARTERY CATHETER THERMODILUTION CARDIAC OUTPUT MEASUREMENTS

Underestimation of True Cardiac Output
- Injectate volume greater than programmed volume (typically 10 mL)
- Large amounts of fluid administered simultaneous to cardiac output measurement (Rapid infusions should be stopped.)
- Injectate colder than measured temperature injectate (Injectate temperature probe next to heat-emitting hardware instead of injectate fluid.)

Overestimation of True Cardiac Output
- Injectate volume less than programmed volume
- Injectate warmer than measured temperature injectate

Other Considerations
- Surgical manipulation of the heart
- Fluid administration from aortic CPB cannula
- Arrhythmias

CPB, Cardiopulmonary bypass.

TR generally has been considered as a source of error in thermodilution CO determinations. The scientific data, however, are contradictory. Some experimental reports indicate that TR does not impair the accuracy of thermodilution CO when compared with the Fick method[352] and electromagnetic flow probes.[353,354] In contrast, Heerdt and associates[355] reported that thermodilution CO had wide variability in the direction and magnitude of error compared with Doppler and electromagnetic CO in a single patient with acute TR. The severity of TR also seems to be important in determining its effect on CO measurements by thermodilution, with underestimation of CO occurring in the presence of more severe TR.[356]

Slowing of the HR has been described as a side effect of rapid injection of cold injectate into the heart.[357] In a prospective study, Harris and colleagues[358] observed that with the use of iced injectate, a decrease in HR of more than 10% occurred in 22% of the determinations. Nishikawa and Dohi[359] reported that a slowing HR was more likely in patients with a low cardiac index (CI), low mean PA pressure, and high SVR.

Precision

Precision describes the ability of a monitoring system to produce the same results with repeated measurements when all other variables remain unchanged. In vivo precision can be assessed by obtaining a large number of thermodilution CO measurements and calculating their average (mean) and standard deviation. Hoel[360] postulated that a true CO could be measured by calculating the average of an infinite number of thermal injections. Using probability calculus, he found that with two injections there was only a 50% probability of being within 5% of the true CO. With three injections, there was an 89% probability of being within 10% of the true CO. In an attempt to better delineate the reproducibility of the technique, Stetz and associates[361] reviewed 14 publications on the use of thermodilution in clinical practice. They concluded that with the use of commercial thermodilution devices, a minimal difference of 12% to 15% (average, 13%) between determinations was required for statistical significance, provided that each determination was obtained by averaging three measurements.

A few studies also have evaluated the effects of the timing of the injection in the respiratory cycle on the reproducibility of thermodilution CO. In mechanically ventilated dogs, Snyder and Powner[362] observed that CO variations were present in each respiratory cycle and were usually greater than 10%. Stevens and colleagues[363] studied the

effects of the respiratory cycle on thermodilution CO in critically ill patients. They confirmed that injections at specific times in the respiratory cycle resulted in less variability, but possibly decreased accuracy. Nevertheless, they concluded that in clinical practice, the improvement in reproducibility was more important than the decrease in accuracy.

The effects of injectate volume and temperature on the variability of thermodilution CO have also been studied in critically ill patients.[364] Six combinations of injectate volume (3, 5, and 10 mL) and temperature (iced and room temperature) were studied in 18 adult, intubated patients. The best reproducibility was obtained with 10-mL injections at 0°C or room temperature.

In summary, the precision of the thermodilution CO technique is not very good but can be improved by ensuring that, for each determination, the rate and duration of the injection are kept as constant as possible.[365] Whenever possible, 10-mL volumes of injectate should be used, and the timing of the injection in the respiratory cycle should be the same. However, if injection is always at the same point in the respiratory cycle, some loss in accuracy is to be expected.

Continuous Thermodilution Cardiac Output

Pulmonary arterial catheters with the ability to measure CO continuously were introduced into clinical practice in the 1990s. The method that has gained the most clinical use functions by mildly heating the blood—originally using a "pseudorandom stochastic" fashion. In vitro as well as in vivo studies have shown that good correlations exist between this method and other measures of CO.[366–371] Unfortunately, the correlation with CO measurements using the intermittent thermodilution method is inconsistent,[372,373] particularly with rapidly changing hemodynamics, for example, in the initial phase after separating from CPB.[374] In contrast, an excellent correlation exists between intermittent and continuous CO measurements obtained in more physiologically stable periods. Perhaps the reason for this observation lies in the unstable thermal baseline after hypothermic CPB that was described in the previous section. Based on the existing literature failing to show improved outcomes, the routine use of continuous CO PACs in cardiac surgery cannot be supported.

Dye Dilution

Before the introduction of the thermodilution method, the indicator dilution method using ICG dye had been the most popular technique of CO measurement. The dye was injected into a central vein and continuously sampled from arterial blood and passed through a densitometer to measure the change in indicator concentration over time. A computer calculated the area under the dye concentration curve by the integration of the dye concentrations over time and computed CO. After determining the CO, the sampled blood was returned to the patient. Recirculation of the indicator distorted the primary time-concentration curve, and the buildup of indicator in the blood resulted in high background concentrations, which limited the total number of measurements that could be obtained.

The introduction of lithium chloride as the indicator has led to a renaissance of the indicator dilution technique for the measurement of CO.[375–378] A lithium chloride solution is injected through a central venous catheter, and a lithium-selective electrode (that is connected to a standard intraarterial cannula) measures plasma lithium concentrations. Only intraarterial and central venous catheters are required. The Lithium Dilution CO system (LiDCO, Lake Villa, IL), only requires a peripheral venous catheter for injection of small doses of lithium and an arterial catheter equipped with a blood withdrawal system and lithium sensor. Agreement with PAC thermodilution is acceptable in most clinical settings.[379] This system also includes a continuous CO calculation capability based on the arterial pulse wave that must be calibrated to the lithium dilution value (see the following text).

Alternative Techniques for Assessing Cardiac Output

The development of less invasive technologies that allow measuring CO and assessing volume status independently from PA catheterization is flourishing. Numerous technologies based on methods such as transpulmonary thermodilution, indicator dilution (lithium), ultrasound, calibrated and uncalibrated arterial waveform analysis (invasive and noninvasive), and electrical bioimpedance and bioreactance are commercially available. These devices also provide hemodynamic parameters previously not easily accessible; for example, providing the practitioner with information regarding fluid responsiveness.

BOX 13.15 PARAMETERS DERIVED FROM TRANSPULMONARY THERMODILUTION

Discontinuous Parameters

- Thermodilution cardiac index (CI) and stroke volume (SV) index
- Global end-diastolic volume index (GEDVI)
- Cardiac function index (CFI)
- Global ejection fraction (GEF)
- Extravascular lung water index (EVLWI),
- Pulmonary vascular permeability index (PVPI)
- Oxygen delivery index (DO_2I)

Continuous Parameters

- Pulse contour CI and SV index
- Stroke volume variation (SVV)
- Pulse pressure variation (PPV)
- Cardiac power index (CPI)
- Left ventricular contractility (dPmax)

Transpulmonary Thermodilution

Transpulmonary thermodilution allows estimating CO, intrathoracic and global end-diastolic blood volume, extravascular lung water (EVLW), as well as additional parameters describing myocardial performance and pulmonary vascular permeability (Box 13.15). The underlying principle is used in commercially available bedside monitoring devices such as the PiCCO2 (PULSION Medical Systems SE, Munich, Germany) and the EV1000 and VolumeView (Edwards Lifesciences, Corp., Irvine, CA). The placement of a central venous catheter and a modified arterial catheter equipped with both temperature and pressure sensors are required. The tip of the arterial catheter is positioned in a central artery through access from the femoral (PiCCO2, VolumeView), brachial, axillary, or radial arteries (only PiCCO2). Hemodynamic parameters are measured and derived that may be useful in the differential diagnosis and decision making of critically ill patients. SV, CO and CI, static volume assessment, such as global end-diastolic volume index (GEDVI) and EVLW index, as well as dynamic indices, such as stroke volume variation (SVV) and pulse pressure variation (PPV) are displayed as absolute values and trends, facilitating GDT. Transpulmonary thermodilution–derived CO correlates well with PAC measurements.[380–382] For continuous CO measurements, an in vivo calibration has to be performed. Calibration is achieved by injecting a defined volume of a cold solution (VolumeView, PiCCO2) or room temperature solution (PiCCO2) into the central venous catheter. Earlier methods also incorporated calibration techniques, not simply based on temperature changes, such as cold ICG, but also referred to as double-indicator dilution technique. After transpulmonary passage, temperature (or dye concentration) changes are detected via the thermistor sensor, which is incorporated at the tip of the arterial catheter. The recorded thermodilution curve is used to compute CO based on the Stewart-Hamilton equation equivalent to PAC-derived CO measurements. Since transpulmonary fluid passage and peripheral arterial detection computes CO over a longer period, compared with PAC-derived CO, these methods are less susceptible to respiratory variations. With the COLD system (PULSION Medical Systems SE, Munich, Germany), the double-indicator dilution technique was used. As the cold fluid equilibrated rapidly with the extravascular space, intrathoracic thermal volume (ITTV) volumes in the RA, RV, pulmonary blood volume (PBV), EVLW, LA, and LV could be

derived from the product of CO and the mean transit time (MTT) of the cold indicator:

$$ITTV = CO * MTT_{(cold)}$$

The volumetric parameter intrathoracic blood volume (ITBV) (volumes in the RA, RV, PBV, LA, and LV) is calculated as the product of CO and the MTT of the dye indicator, which rapidly bonds to proteins and remains in the vascular system:

$$ITBV = CO * MTT_{(dye)}$$

The EVLW is calculated as the difference between ITTV and ITBV:

$$EVLW = ITTV - ITBV$$

For clinical purposes, the former cumbersome method of transpulmonary double-indicator (cold fluid and dye) dilution technique has been replaced by a single-indicator thermodilution (cold fluid only) method.[383] The largest mixing chamber (pulmonary thermal volume [PTV]) predominantly determines the slope of the downstream indicator dilution curve and can be measured as the product of the downslope time (DST) of the thermodilution curve and CO. PTV is then calculated as:

$$PTV = CO \times DST_{(cold)}$$

By using this equation, global end-diastolic volume can be calculated:

$$GEDV = ITTV - PTV$$

Since ITBV can be calculated from GEDV (ITBV = 1.25 × GEDV), calculating EVLW is possible using the single indicator technique[384] by using the following equation:

$$EVLW = ITTV - ITBV = ITTV - (1{,}25 \times GEDV)$$

The EV1000/VolumeView uses the same general assumptions; however, this device implements a slightly different algorithm, which also allows for adjustments in patients with lung resections.[385]

The clinical relevance and utility of incorporating some of these parameters into treatment algorithms and the potential impact on patient outcomes has been investigated. Several studies found that volumetric parameters, such as GEDVI and ITBVI, offer advantages in estimating cardiac preload compared with pressure-based measures.[386–389] In patients undergoing CABG surgery, prediction of the hemodynamic response to volume administration was improved, compared with pressure-based parameters, such as CVP and PCWP.[390] However, a recent metaanalysis also suggested that SV response can even be better predicted with dynamic parameters such as SVV and PPV.[391] Many clinicians find the information gained from measuring EVLW with transpulmonary thermodilution to be useful in managing critically ill patients. EVLW correlates with pulmonary edema and has been shown to have good prognostic value. In a retrospective analysis of 373 critically ill patients, the mortality rate was 65% in patients with an EVLW >15 mL/kg and only 33% in patients with an EVLW <10 mL/kg.[392]

Cardiac Output Measurements Using Ultrasound Technology

Measurements of SV and CO can be accomplished using various echocardiographic techniques. Adequate image quality is important in all echocardiographic estimates of CO, regardless of whether 2D, three-dimensional (3D), or Doppler-based techniques are used. (For a comprehensive review of echocardiography including echo-derived hemodynamic parameters see Chapters 14 through 16).

Two- and Three-Dimensional Echocardiography

Two-dimensional echocardiography allows for the calculation of CO using the following formula:

$$CO = (EDV - ESV) \times HR$$

in which CO is cardiac output, EDV is the end-diastolic volume, ESV is the end-systolic volume, and HR is the heart rate. Two-dimensional echo-derived left ventricular volume and CO determinations are based on geometric assumptions of chamber size and shape (ie, modified Simpson rule). Reliable estimation of CO depends on adequate imaging that allows for exact tracing of the endocardial border.[393–395] Single-beat 3D volume assessment is available and advances in processor speed and echocardiographic technology have already helped overcome some of the earlier problems of this technology. Good correlation and accuracy was demonstrated when 3D echocardiographic estimates of volumetric measures were compared with established methods.[396–398] In their recent update, the European Society of Cardiology recommended 3D estimation of ventricular volumes whenever feasible.[399]

Recently, a miniaturized monoplane TEE probe has become available. The probe can remain in place for up to 72 hours for continuous hemodynamic TEE monitoring. The views that are obtained are limited; however, the benefit of this technology is the continuous availability of cardiac imaging in high-risk patients. There are limited reports of the use of continuous TEE in patients who have undergone complicated cardiac surgery for algorithm-guided extracorporeal membranous oxygenation (ECMO) weaning,[400] and managing patients with ventricular-assist devices postoperatively.[401] Future studies will be required to demonstrate outcome benefits compared with conventional intermittent TEE or TTE imaging in the ICU.[402]

Doppler Ultrasound

Ultrasound can be used for the measurement of CO based on the Doppler principle. Information on blood flow is obtained by applying Doppler frequency shift analysis to echoes reflected by the moving red blood cells. Blood flow velocity, direction, and acceleration can be instantaneously determined. From this information, SV and CO are calculated using the following formula:

$$SV = VTI \times CSA$$

in which SV is stroke volume, VTI is the Doppler velocity-time integral (ie, area under the pulsed-wave Doppler spectral display curve), and CSA is the cross-sectional area at the site of flow measurement. The SV is then multiplied by HR to calculate the CO. Theoretically, CO may be measured at all anatomic sites in which a CSA is determined and a Doppler beam positioned. Technical limitations include the accuracy of the valve or outflow tract area calculations, and the degree of alignment between the ultrasound beam and the direction of blood flow.

Doppler-derived technology has also been incorporated into esophageal probes (CardioQ-System, Deltex Medical, Chichester, West Sussex, UK) allowing for beat-to-beat SV and CO measurements. The descending aortic blood flow velocities are interrogated, and SV and CO determination is based on the Doppler equation and nomograms incorporating the patient's age, weight, and height. Limitations are the use of nomogram estimates and Doppler alignment, as well as restricting measurements to blood flow in the descending aorta. Validation studies have shown good correlation with PAC-derived CO as long as technical errors can be avoided.[403] In addition to SV, this technology also determines systolic flow time, which is corrected for HR (flow time corrected [FTc]). As an indicator of cardiac afterload, FTc is inversely associated with SVR; however, the clinical value of FTc to optimize volume status is limited. The peak systolic velocity of the Doppler-derived blood flow is related to myocardial contractility and has been used to assess left ventricular performance and response to inotropic therapy. Most studies incorporating this technology into GDT have been performed in the noncardiac surgical setting.[404–406]

In cardiac surgery, esophageal Doppler-guided hemodynamic management was associated with reduced ICU and hospital lengths of stay[407] and reduced the incidence of gut mucosal hypoperfusion.[408]

Cardiac Output Derived From Arterial Pulse Wave Analysis

Waveform analysis is another method currently being used in several CO devices. The arterial pulse wave is obtained either invasively from transducing an indwelling arterial catheter or noninvasively using the volume-clamp method. It has long been known that pulsatility in the arterial tree is proportional to SV: the greater the SV, the greater the amplitude of the resulting pressure wave. This proportionality allows computing CO if a calibration constant, based on various factors including the resistance and compliance of the vessels, is known.[409] Variations of this originally described model are still the basis of modern pulse contour analysis devises.

$$PC-SV = cal \times \int_{systole} \left(\frac{P(t)}{SVR} + C(p) \times \frac{dP}{dt} \right) dt$$

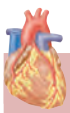
In this equation, PC – SV is pulse contour stroke volume, cal is the calibration factor, P(t) is the arterial BP, C(p) is the arterial compliance, and dp/dt is the shape of the arterial pressure curve. Pulsatility is easily assessed using parameters, such as the area under the pressure wave, area under the systolic portion of the wave, or standard deviation of the wave.

Calibrated Pulse Contour Cardiac Output

Deriving the calibration factor is more complex. A common approach has been to first measure the SV by another method (eg, lithium dilution, transpulmonary thermodilution), measure the pulsatility, and then determine the individual calibration factor. This calibration factor can subsequently be used to calculate SV continuously from the pulsatility of the wave. Several commercially available devices including the EV1000 and PiCCO2, as well as the LiDCOplus are using this approach.[410] The LiDCOplus System uses lithium chloride as an indicator for initial calibration and the calculation of the calibration factor. The dose of lithium needed for calibration is minimal and has no known therapeutic side effects.[411] In a modified version, the LiDCOplus System, the indicator can be injected into a peripheral vein and no central venous access is required. After the initial calibration, an autocalibration algorithm (PulseCO algorithm) is used for continuous assessment of beat-to-beat SV, CO, and variables such as SVV are displayed (Box 13.16).[412] The PiCCO2 system and the EV1000 Clinical Platform use transpulmonary thermodilution CO measurements to calibrate the continuous pulse contour CO algorithm. Recalibration of the device is required at least every 4 to 8 hours.[413]

Studies comparing lithium or thermodilution calibrated pulse wave analysis-derived CO to PAC-derived CO show acceptable correlations in many clinical settings,[379,410,414] including in patients following cardiac surgery.[415,416] However, other studies found significant limitations of this technology in cardiac surgery patients. For example, the accuracy of the PulseCO algorithm may be compromised in patients with aortic valve regurgitation, after aortic reconstruction, and in patients with an intraaortic balloon pump. A dampened arterial pulse signal or pronounced peripheral arterial vasoconstriction may result in inaccurate CO readings.[417] If the system is not recalibrated frequently when significant changes in vascular tone occur (eg, during weaning from CPB), then SV calculation may also yield inaccurate results.[418,419] In OPCAB surgery, agreement between the PiCCO2 pulse-contour analysis and PAC was acceptable; however, recalibration of the pulse-contour analysis improved the agreement further.[420]

In summary, calibrated pulse contour CO monitoring devices are a less invasive alternative to measuring CO. In case of rapid hemodynamic changes and alterations in vascular tone (eg, weaning from CPB or OPCAB surgery), these devices should be recalibrated frequently.



BOX 13.16 PARAMETERS DERIVED FROM PULSE CONTOUR ANALYSIS

Continuous Parameters (Not for All Monitoring Devices)

- Pulse contour/Pulse wave cardiac index and stroke volume index
- Stroke volume variation (SVV)
- Pulse pressure variation (PPV)
- Systemic vascular resistance (SVR)
- Cardiac power index (CPI)
- Left ventricular contractility (dPmax)

Uncalibrated and Autocalibrated Pulse Contour and Pulse Wave Technology

A trend to less invasive monitoring technologies can also be seen in the development of continuous CO devices that do not require invasive (ie, transpulmonary thermodilution) calibration. Two of these devices, the ProAQT (PULSION Medical Systems SE, Munich, Germany) and the LiDCOrapid System (LiDCO Ltd, Lake Villa, IL) estimate CO and dynamic parameters such as SVV and PPV from arterial pulse contour and pulse wave analysis without external calibration, using patient demographics such as age, height, weight, and gender. The ProAQT System uses a dedicated pressure transducer that is connected to any standard arterial catheter. In a third system, the FloTrac sensor is connected to a proprietary monitor (eg, EV1000 or Vigileo) that uses arterial pulse pressure instead of MAP to determine SV to minimize the absolute influence of vascular resistance on measurements.

Arterial pressure–based CO (APCO) can be described as shown:

$$APCO = HR \times \sigma_{AP} \times \chi$$

in which HR represents the heart rate; the product of σ_{AP}; and χ represents the SV. The arterial waveform is characterized using σ_{AP} (standard deviation of arterial pressure) and a calibration factor Chi (χ), which is estimated from patient demographics. The applied algorithm uses advanced statistical models to account for changes in vascular tone and its effect on the patient's pulse pressure.[421] The mathematical model adjusts the calculation of χ, using factors such as the mean, variance, skewness, and kurtosis of sampled arterial pressure data.

Clinical trials comparing uncalibrated and autocalibrated pulse contour and pulse wave technology to established calibrated systems including PAC thermodilution and transpulmonary thermodilution technology show inconsistent results. In a recent study in patients after liver surgery, the LiDCOrapid CO device failed to achieve criteria for accurate CO measurement, using transpulmonary thermodilution as a reference.[422] In patients undergoing CABG surgery, CO measured with the LiDCOrapid device before and after CPB resulted in unreliable CO readings (poor precision), compared with PAC-derived CO; only after external calibration did the percentage error decrease to 28%.[423] These findings were confirmed in other studies in patients undergoing cardiac surgery; primarily showing that uncalibrated CO methods such as the FloTrac suffer from a large bias and wide limits of agreement compared with thermodilution CO.[415,424–426]

However, these technologies are advancing rapidly, and recent software upgrades improved the accuracy and precision compared with thermodilution CO.[427–429] In a metaanalysis including 65 studies, the authors came to the conclusion that the accuracy and precision of the latest software version of the FloTrac-Vigileo system can be regarded as sufficient (percentage error <30%) for routine clinical use in "hypodynamic or normodynamic conditions" in the absence of large changes in vascular tone.

In conclusion, the results from these different validation studies indicate that this is a technology in evolution. At present, the application of uncalibrated arterial waveform analysis–based CO systems—especially for cardiac surgery patients—will remain controversial.

Cardiac Output Derived From Noninvasive Devices

Completely noninvasive devices for continuous BP monitoring and SV estimation have been developed. Although technologically interesting,

their use in cardiac surgery is limited since invasive arterial access is typically required for reasons other than BP and CO measurement.

Cardiac Output Derived From Volume-Clamp Monitoring Devices

In the early 1980s, Truijen and associates[430] developed a method for continuous noninvasive BP monitoring using the *volume-clamp* technology. The principle of this technology is based on the idea that blood volume in the arterial vascular bed varies during the cardiac cycle. The blood volume in the respective finger can be held constant using a rapid response finger pressure cuff (*volume clamping*). The cuff pressure and volume required correlates with BP and SV changes and allows reconstructing a continuous beat-to-beat BP curve and CO measurement.[431] The first generation devices such as the Finometer PRO (Finapres Medical Systems, Amsterdam, Netherlands) showed the actual BP of the finger artery. More recent devices show a reconstructed brachial artery BP (ClearSight system, Edwards Lifesciences, Irvin, CA; BMEYE Nexfin monitor, St. Louis, MO). Validation studies comparing volume clamp–based devices to invasive BP monitoring have yielded some promising results,[432] including cardiac surgery patients.[433–435] However, compared with invasive BP monitoring and thermodilution CO, the volume clamp–based devices still lack the accuracy for clinical use in patients with rapid hemodynamic changes and vasoactive drug administration.[436,437]

Cardiac Output Derived From Bioimpedance and Bioreactance Technology

Bioimpedance CO is based on the principle that cyclical increases in blood volume in the great vessels in the chest, as well as the alignment of red blood cells in the thoracic aorta resulting from increased velocity during the ejection phase, cause concomitant changes in electrical impedance. To measure thoracic electrical bioimpedance, an alternating current of low amplitude is introduced and simultaneously sensed by electrodes placed around the neck and laterally on the thorax or abdomen. Changes in thoracic bioimpedance are induced by ventilation and pulsatile blood flow, and processing of the measured signal results in a characteristic impedance (Z) waveform. Only the cardiac-induced pulsatile component of the total change in electrical impedance is analyzed time-dependent impedance change (dZ/dt) and the respiratory component is filtered out.

Volumetric and static variables including SV, CO, SVR, and thoracic fluid content can be determined with this technique. The limitations to this technology are still significant,[438] particularly in patients undergoing cardiac surgery.

Bioreactance is a further development of the bioimpedance principle estimating CO from the frequency of relative phase shifts of the electrical currents traversing the chest. Higher cardiac SV is associated with larger phase shifts. The benefits over the bioimpedance technique is that bioreactance CO is less affected by the precision of electrode placement, body movement, or respiratory excursions. Several validation studies comparing bioreactance CO with established methods have yielded conflicting results.[439–441] At this point, the data for a final evaluation of this technology are insufficient in cardiac surgery patients.

A summary of alternative methods of CO measurement is presented in Table 13.4

Right Ventricular Ejection Fraction and End-Diastolic Volume

Using rapid-response thermistors that are incorporated into PACs, determining the RVEF from the exponential decay of the thermodilution curve is possible. End-diastolic temperature points in the thermodilution curve are identified using the R-wave signal from an ECG input.[442,443] From these data, SV, right ventricular end-diastolic volume, and right ventricular end-systolic volume may be calculated. Assumptions that are essential to the accuracy of the technique include a regular RR interval, "instantaneous" mixing of the injectate or thermal heat signal with the right ventricular blood, and the absence of TR. The use of this type of monitoring could be justified in patients with severe right ventricular dysfunction attributable to myocardial infarction, right-sided coronary artery disease (CAD), pulmonary hypertension, right-sided HF, or intrinsic pulmonary disease. The accuracy of this technique has been questioned, however,[444,445] and RVEF catheters are rarely used, especially with TEE becoming more prevalent in the surgical unit setting.

Left Atrial Pressure Monitoring

In this invasive technique, a catheter is placed by the surgeon into the right superior pulmonary vein and advanced into the LA. A Teflon-pledgetted purse-string suture is placed around the catheter to provide a surface for clotting upon removal of the catheter. The catheter is brought out through the skin in the subxiphoid region and is sutured in place. Maintaining positive airway pressure or distending the LA in some other way during insertion of the catheter is important to prevent air entry into the pulmonary vein and the left side of the heart. An alternative method of placing an LAP via IJV access and advancement in the surgical field across the atrial septum has been described.[446]

Although important information can be gained from LAP monitoring, significant risks are associated with this monitoring technique. The possibility of air embolism to the coronary or cerebral circulations is always present. This problem exists on insertion and during its continued use postoperatively in the ICU. There is also the risk of clot formation on the catheter and subsequent embolization when the catheter is flushed or removed; therefore a continuous flushing system is necessary to avoid thrombus formation on the catheter tip in the postoperative period. Postoperatively, bleeding is also a risk when the LAP catheter is removed. It therefore should be removed while the chest tubes are still in place to diagnose and treat this problem. Other reported complications include catheter retention and prosthetic valve entrapment.[447] In the echo era, LAP monitoring is rarely performed.

Coronary Sinus Catheterization

In some centers, an endovascular CS catheter is placed to enable the administration of retrograde cardioplegia during minimally invasive cardiac surgical procedures. It is usually the responsibility of the cardiac anesthesiologist to place the CS catheter via the right IJV while being guided by TEE and fluoroscopy. The CS pressure and waveform can be measured during insertion and cardioplegia infusion. This procedure raises a number of issues including how deep to place the catheter and what pressures and flows to use with the administration of the cardioplegia. Retrograde cardioplegia flow rate is usually set at 150 to 200 mL/min with CS pressure over 30 mm Hg.

The insertion of the CS catheter (Fig. 13.23) can be difficult even with TEE and fluoroscopic monitoring. A modified bicaval view at approximately 110 degrees allows visualization of the catheter from the SVC to the CS (Fig. 13.24). After the catheter enters the CS, its final position is usually guided by fluoroscopy. The balloon is then inflated while looking for a change in the pressure tracing from a typical venous pressure tracing to a pulsatile tracing attributable to the transmission of the pressure back from the left ventricle (ventricularizaton) (Fig. 13.25). The ultimate sign of proper positioning is the establishment of asystole upon cardioplegia infusion. Further details of the insertion procedure can be found in articles by Lebon and colleagues[448] and Clements and associates.[449] Lebon and colleagues were able to position 95 of 96 CS catheters with a mean time of 6.3 minutes. Fluoroscopic confirmation took another 9.1 minutes for a total time of approximately 16 minutes. Ventricularization was observed in 86% of cases, and the CS pressure was greater than 30 mm Hg in 87.5% of patients.

Safety is another major concern with this technique. CS rupture and dissections have been reported by a number of authors.[450] If this catheter is used as part of port-access CPB, then it is one of only a few catheters that have to be monitored for malpositioning and possible complications (see Chapters 31 and 32).

TABLE 13.4 Summary of Alternative Means of Determining Cardiac Output

Technology	*Examples of Devices Available*	*Accuracy vs PAC*	*Potential Sources of Inaccuracy*	*Potential for Cardiac Surgery, Advantages*
TEE Doppler	Standard TEE	++++	Doppler beam misalignment Inaccurate 2D cross-sectional area measurement	+++ Minimally invasive Potentially very accurate Access to right and left side for shunt determination
Transesophageal Doppler	CardioQ-ODM (Deltex Medical) TECO (Medicina)	++	Distribution of blood flow, lower vs upper body Readjustment necessary before making decisions based on the Doppler values Possible small deviations of the absolute value of the parameters in individual cases Electric cauterization interferes with signal quality Not feasible in anatomical variations (ie, congenital anomalies)	++ Minimally invasive May be used postoperatively GDT algorithms available Outcome studies available in cardiac surgery
TEE 2D	Standard TEE	+++	Exceptions to Simpson's rule (ventricular aneurysm) Measurement of LV area	++ Minimally invasive
hTEE		+++	Technical limitations: Bad acoustic window Inability to evaluate all three demanded cross-sectional views Owing to the monoplane probe, not possible to interrogate all valves, only semiquantitative evaluation	+++ Minimally invasive Smaller probe, compared with standard TEE Direct visualization of RV, preload, RV, and LV function and effusion, continuous, can guide hemodynamic optimization by visualization
Indicator Dilution (Lithium)	LiDCO (LiDCO Group)	++++	Technical error, muscle relaxants, ingestion of lithium medication	++ Minimally invasive
Transpulmonary Thermodilution	PiCCO (PULSION Medical Systems) VolumeView (Edwards Lifesciences)	++++	Technical errors, thermal changes in chest, arrhythmia	+++ Less invasive, goal-directed algorithm available Outcome study in cardiac surgery showed benefit Beat-to-beat SV, SVV, and PPV Global end-diastolic volume Extravascular lung water
Arterial Pulse Wave	LiDCOrapid (LiDCO Group) ProACT (PULSION Medical Systems) FloTrac (Edwards Lifesciences)	++ ++	Arterial wave artifact Intraaortic balloon Aortic regurgitation Rapid changes in vascular tone	++ Minimally invasive Continuous Dynamic parameters provided No requirement for external calibration
Volume-clamp Method	Nexfin (BMEYE) ClearSight (Edwards Lifesciences) CNAP (CNSystems Medizintechnik) Finometer (FMS)	++	Imprecise in unstable hemodynamic conditions	+ Noninvasive Continuous Dynamic parameters provided
Bioimpedance Velocimetry	BioZ (Sonosite) LIFEGARD ICG (CAS Medical Systems) HIC-4000 (Microtronics Corporation; Bio-Impedance Technology) ICON (Osypka Medical, Cardiotronic) PhysioFlow (Manatec Biomedical) ECOM (ConMed Corporation) AESCULON (Osypka Medical GmbH)	++	Positioning of sensors may be problematic during cardiac surgery Ventilation pattern Lung water Opening and closing of chest	+ Noninvasive Continuous Technology improving
Bioreactrance	NICOM (Cheetah Medical)	+++	Inaccuracy attributable to variations in the thoracic blood volume as a result of respiration or arrhythmias	++ Noninvasive Continuous
Rebreathing Fick	NICO (Philips Respironics) Innocor (Innovision A/S)	+	Need for intubation and mechanical ventilation with fixed ventilator settings and minimal gas exchange abnormalities Increased pulmonary shunt fraction and hemodynamic instability	+ Noninvasive Semicontinuous or intermittent

Assessments at the time of writing are based on the available literature and experience.
++++ Very high; +++ high; ++ medium; + low; *2D,* Two dimensional; *GDT*, goal-directed therapy; *LV*, left ventricular; *PAC*, pulmonary artery catheter; *PPV*, pulse pressure variation; *RV*, right ventricular; *SV*, stroke volume; *SVV*, stroke volume variation; *TED*, transesophageal Doppler; *TEE*, transesophageal echocardiography.
CardioQ-ODM (Deltex Medical SC, Inc, Greenville, SC); LiDCO (LiDCO Group, Lake Villa, IL); PiCCO (PULSION Medical Systems, Irving, TX); FloTrac (Edwards Lifesciences Corp, Irvine, CA); ICON (Cardiotronic Inc., La Jolla, CA); BioZ (Sonosite, Bothell, WA); ECOM (ConMed Corporation, Utica, NY).

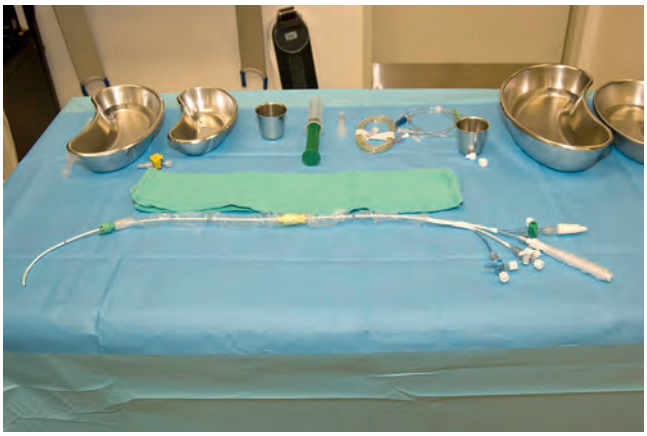


Fig. 13.23 Coronary sinus catheter (Endoplege; Sinus Catheter, Edwards Lifesciences, Irvine, CA). *(From Lebon JS, Couture P, Rochon AG, et al. The endovascular coronary sinus catheter in minimally invasive mitral and tricuspid valve surgery: a case series.* J Cardiothorac Vasc Anesth. *2010;24(5):746–751.)*

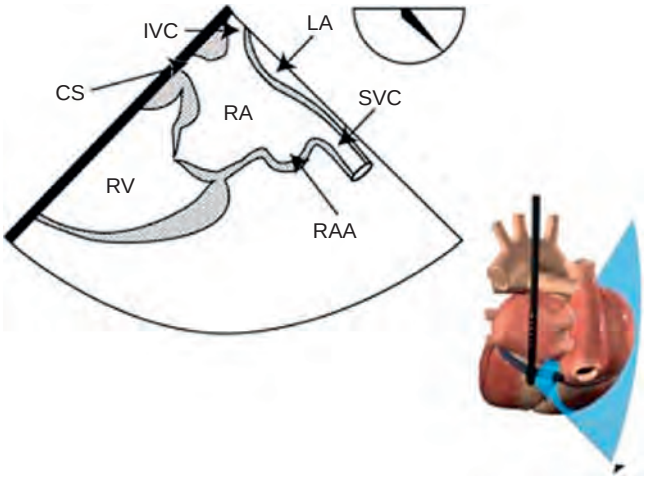


Fig. 13.24 A schematic representation of the modified bicaval view 110 degrees. *CS,* Coronary sinus; *IVC,* inferior vena cava; *LA,* left atrium; *RA,* right atrium; *RAA,* right aortic arch; *RV,* right ventricle; SVC, superior vena cava. *(Reproduced with permission from* Denault AY. *Transesophageal Echocardiography Multimedia Manual: A Perioperative Transdisciplinary Approach.* 2nd ed. London, UK: Informa Healthcare; 2010.)

Analysis and Interpretation of Hemodynamic Data

The information provided by hemodynamic monitoring permits the calculation of various derived parameters that assist in evaluating patients clinically. The formulas, normal values, and units for the calculation of various hemodynamic parameters are presented in Tables 13.2 and 13.3. These parameters include the SVR, pulmonary vascular resistance (PVR), SV, left ventricular stroke work, and right ventricular stroke work. As an example of information that may be obtained, graphs of PCWP versus SV can be constructed for individual patients; these Starling curves provide insight into the contractile state of the heart. Although these parameters are easily derived using the standard formulas, many modern monitors perform these calculations. To compare data among patients of different body weights and types, the various hemodynamic parameters may be normalized by indexing them to body surface area.

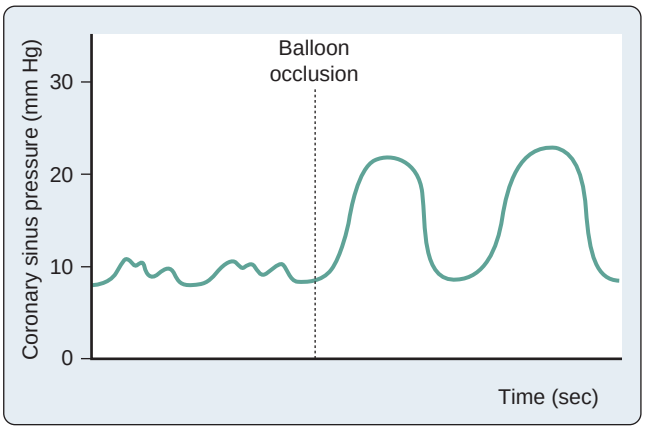


Fig. 13.25 Ventricularization after balloon inflation of the coronary sinus catheter. *(From Lebon JS, Couture P, Rochon AG, et al. The endovascular coronary sinus catheter in minimally invasive mitral and tricuspid valve surgery: a case series.* J Cardiothorac Vasc Anesth. *2010; 24(5):746–751.)*

Systemic and Pulmonary Vascular Resistances

Systemic vascular resistance represents an estimation of the afterload of the left ventricle. Afterload is roughly defined as the force that impedes or opposes ventricular contraction. Higher SVR results in increased left ventricular systolic wall stress. This has clinical significance because left ventricular wall stress is one of the major determinants of myocardial oxygen consumption (see Chapters 6 and 7). Clinically, calculations of SVR are used to assess the response to inotropic, vasodilator, and vasoconstrictive agents. The SVR is calculated, and then therapy is instituted accordingly. A repeat calculation of the SVR enables the clinician to titrate the therapy to the appropriate end point. Despite this common use in the surgical unit and ICU settings, good evidence suggests that SVR is not an accurate indicator of true afterload.[451] Nevertheless, SVR remains the most useful clinical technique for measuring afterload at the present time.

PVR remains the traditional measure of afterload of the RV. This is also a flawed assumption because the recruitable nature of the pulmonary vasculature violates the assumptions of the PVR formula in patients without significant pulmonary arterial hypertension.[452] As the PA pressure (PAP) increases, the healthy pulmonary vasculature bed distends (increasing the size of West zone III of the lung).[453] The net gain in the cross-sectional area of the pulmonary vasculature results in a decrease in the measured PVR. However, in patients with a chronically increased PAP, the pulmonary vasculature bed undergoes structural changes, stiffens, and may not be able to accommodate an increase in CO without a significant increase in right ventricular pressure and wall stress. Both PVR and PAP provide clinically useful information regarding the pulmonary vasculature, particularly when managing patients with pulmonary arterial hypertension and right ventricular failure, and both are readily available in patients with PACs.

Frank-Starling Relationships

Myocardial function depends on the contractile state and the preload of the ventricle (sarcomere length at end-diastole). The relationship between the ventricular preload and myocardial work (ventricular stroke work) is the Frank-Starling relationship. The slope of the curve indicates the contractile state of the myocardium (Fig. 13.26). Pressure measurements (ie, PCWP, LAP, LVEDP) are poor estimates of true ventricular preload. The relationship between end-diastolic pressure and volume is usually nonlinear (as described by the diastolic ventricular compliance curve) and is dynamic. The Frank-Starling relationship is extremely sensitive to changes in afterload. Patients with left or

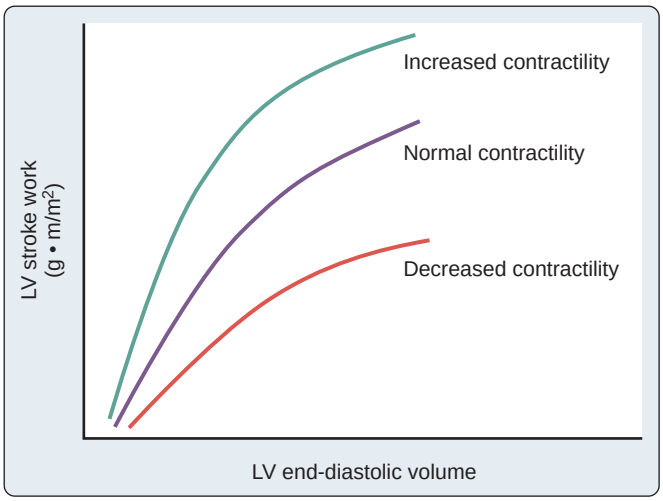


Fig. 13.26 The graph of left ventricular (*LV*) stroke work, stroke volume, or cardiac output, versus LV preload (ie, end-diastolic volume) is known as the Frank-Starling relationship. Shifting of the curve upward and to the left represents increased contractility. Shifting of the curve downward and to the right represents decreased contractility. Alterations in afterload significantly affect the curve.

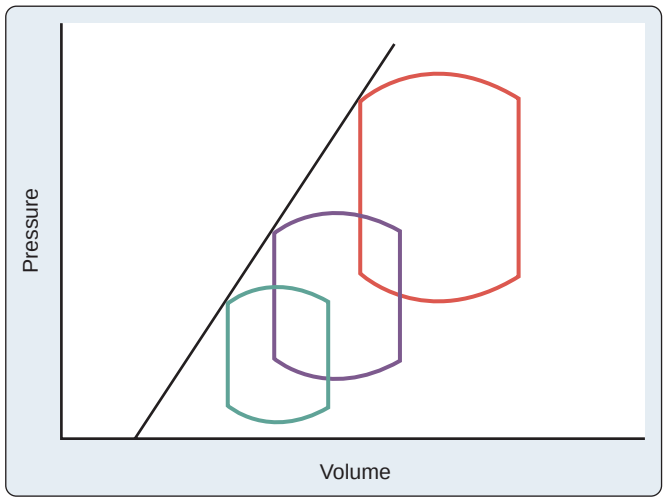


Fig. 13.27 The end-systolic pressure-volume relationship, also known as end-systolic elastance, is the line connecting the end-systolic points of multiple pressure-volume loops that are obtained at various preloads. An increased slope (ie, steeper line) represents increased contractility, and a decreased slope represents decreased contractility. This measurement is relatively insensitive to variations in afterload.

right ventricular dysfunction may have severe decrements in SV with increased SVR or PVR, respectively.

End-Systolic Elastance and Pressure-Volume Loops

An important limitation of isovolumic and ejection phase indices of contractility (eg, the Frank-Starling relationship) is their significant sensitivity to ventricular loading conditions. To overcome this shortcoming, the use of load-independent indices has been explored. One such index is the left ventricular end-systolic pressure-volume relationship (ESPVR), also known as *end-systolic elastance*.[454] To measure this, multiple end-systolic pressures and volumes need to be measured during rapid and, preferably, pronounced alterations in left ventricular preload (eg, inferior vena cava occlusion). On a pressure-volume diagram, points defined by the end-systolic pressures and volumes of the several contractions will be positioned on a single line. The slope of this line is relatively independent of loading conditions and proportional to contractility; the steeper the slope, the greater the contractility (Fig. 13.27) (see Chapter 6).

The intraoperative determination of contractility by this technique has been hampered by difficulties in obtaining accurate ventricular volumes and pressures. Continuous left ventricular pressure-volume loops may be displayed during cardiac surgery using left ventricular conductance and micromanometry catheters that are introduced through the pulmonary veins.[455] ESPVR is not a practical or routine means of assessing left ventricular contractility in the clinical setting.

Pulse Oximetry

Pulse oximetry is one of the most important anesthesia monitoring technologies and has been accepted as a worldwide intraoperative monitoring standard. This is reflected in current practice parameters and recommendations for perioperative anesthetic monitoring published by the ASA.[1] However, the results of outcome studies of pulse oximetry have been inconsistent, and the numbers of patients who would have to be studied in prospective well-controlled trials to show a change in outcome are prohibitively large.[456–458] In a metaanalysis of controlled trials (Cochrane Central Register of Controlled Trials, searched time period 1956 to 2009) with a total of 22,992 patients included in the analysis, using pulse oximetry in the perioperative setting reduced the incidence of hypoxemia in the surgical unit and in the recovery room.[459] Postoperative cognitive function, however, was not influenced by pulse oximetry monitoring. Postoperative complications (eg, cardiovascular, respiratory, neurologic, infectious) did not differ between patients monitored with or without pulse oximetry.

The advantages and limitations of the technique merit discussion to prevent misinterpretation of the data provided by pulse oximetry devices. The absorbance spectra of oxyhemoglobin and reduced Hb differ significantly. Oxyhemoglobin absorbs mostly infrared light (850 nm to 1000 nm) and transmits mostly red light (600 nm to 750nm), whereas deoxygenated Hb absorbs more red light and infrared light passes through. The pulse oximeter uses this principle to determine the relative concentration of oxyhemoglobin in the blood.

Several things in addition to arterial blood also absorb red and infrared light in the tissues. These include capillary blood, venous blood, melanin in the epidermal skin layer, cytochrome c oxidase within the mitochondrial respiratory chain and, to a lesser extent, in soft tissue, fat, and bone. The pulse oximeter uses this pulsatile component of the light absorbance to calculate the arterial oxygen concentration. Many factors interfere with the accuracy of pulse oximetry. Some of these factors include diminished tissue perfusion (eg, limb ischemia, hypothermia, vasoconstricting drugs), ambient light, intravenous dyes, carboxyhemoglobin, and methemoglobin.[460]

As the signal strength of the pulse decreases in relation to the continuous absorption of the tissues, the ratio of absorbance of red-to-infrared light approaches unity. This would normally correlate with a saturation of 85%. Regarding a poor plethysmography tracing with a saturation of 85% as possibly representing artifact and confirming the result with an independent technique are both important. It must also be recognized that standard blood gas analyzers calculate or derive the arterial saturation based on the measured partial pressure of oxygen (PaO_2) in the blood, which may cause significant errors in accurately determining low blood saturations.[461] Standard pulse oximetry devices are usually not calibrated to very low arterial blood saturation as can be observed with many of the mixing congenital heart lesions.[462–464] The gold standard for accurately determining blood saturations is analysis of an arterial blood sample in a device (co-oximeter) that measures oxyhemoglobin, deoxygenated Hb, methemoglobin, and carboxyhemoglobin using absorption of several light wavelengths.

Another problem in cardiac procedures is that the plethysmography tracing often decreases in amplitude over the course of the procedure until the signal-to-noise ratio is too low for accurate oximetry. This is most likely due to hypothermia of the digits but also may be related to positioning, hypovolemia, high catecholamine levels, and extremes

of age. It has been demonstrated that a digital perfusion pressure of 13 mm Hg and temperature of 24° C are the minimum requirements for accurate pulse oximetry readings before and after CPB.[465]

Reich and associates[466] showed that the incidence of pulse oximetry failure in the cardiac surgery setting is very high. The overall incidence of cases that had at least one continuous gap of 10 minutes or more in pulse oximetry data was 31%. The independent preoperative predictors of pulse oximetry data failure included ASA physical status III, IV, or V, and cardiac surgery. Intraoperative hypothermia, hypotension and hypertension, and duration of procedure also were independent risk factors.

The primary disadvantage of pulse oximetry, however, is that the PaO_2 must fall below 100 mm Hg before the device will begin to detect any change, and below 60 mm Hg before rapid changes will occur. Thus the device is not sensitive to changes in PaO_2 over wide ranges that are of clinical significance.

Oxygen Transport Calculations

The ultimate purpose of circulation is the delivery of oxygen to the tissues. Oxygen is bound to Hb and is also dissolved in the plasma (to a much smaller extent). If the Hb concentration, arterial and mixed venous blood gases, and CO are available, then oxygen transport calculations may be performed. Optimization of these parameters are then allowed to improve delivery and uptake of the proper amount of oxygen to the tissues. These calculations are shown in Table 13.2.

Monitoring Coronary Perfusion

Coronary perfusion pressure (CPP) to the LV primarily occurs during diastole and thus is defined as the diastolic arterial BP (DAP) minus the LVEDP:

$$CPP = DAP - LVEDP$$

Elevation of the LVEDP will decrease the gradient of blood flow to the vulnerable subendocardial tissue during diastole as will a decrease in the DBP.[467] If CAD is present, then significant stenosis will decrease the coronary artery DBP well below the aortic DBP, and elevation of LVEDP can seriously jeopardize the subendocardium.[468] An increase in the LVEDP is detrimental in two ways: decreased coronary blood flow and increased myocardial oxygen demand, which partially explains the ischemia that may be observed with over-distention of the left ventricle. Tachycardia is also detrimental because it decreases coronary filling time and increases oxygen demand. Subendocardial ischemia is commonly produced by a combination of tachycardia and elevated LVEDP (see Chapters 6 and 20).

Cerebral Oximetry

Near-infrared spectroscopy (NIRS) and its clinical application in cerebral oximetry devices are reviewed in greater detail in Chapter 18. Briefly, cerebral tissue saturations reflect a mostly venous-weighted signal that is measured continuously. Thus it correlates strongly with jugular bulb saturation, with higher readings attributable to the 25% to 30% admixture of arterial blood in cerebral tissue.[469] In practical terms, measured values reflect the delicate balance between cerebral oxygen delivery and demand, somewhat analogous to mixed venous oxygen saturation for whole body perfusion. Variables affecting cerebral saturations therefore include CO, (CPP = MAP – ICP or CVP), oxygen-carrying capacity, hypocarbia and hypercarbia, anesthetic depth, cerebral temperature, and technical considerations (eg, SVC cannula malposition).

Its use in cardiac surgery has been steadily increasing, attributable to the noninvasive nature of the technology and the magnitude of clinically relevant data that can be derived. Trend monitoring from a baseline value obtained during hemodynamically stable conditions, as well as absolute lower thresholds, have been recommended in clinical practice for decision making. Although, several studies have shown an association between low cerebral saturations and adverse events, few studies show that interventions based on cerebral oximetry monitoring improve outcome. In one of these studies, Murkin and colleagues[470] monitored NIRS and targeted therapy to optimize cerebral tissue oxygen saturation in patients undergoing CABG. They found that a composite measure of postoperative organ dysfunction was substantially improved in the treatment group when GDT aimed to maintain the cerebral tissue oxygen saturation values within 25% of the preinduction baseline. One of the strengths of cerebral oximetry monitoring is the early detection of catastrophic events, particularly during periods of nonpulsatile flow, such as during CPB or with certain left ventricular–assist devices or ECMO.[471–473]

Summary

The choice of appropriate monitoring is a difficult task. Despite many years of clinical experience, no convincing outcome data demonstrate the superiority of more invasive versus less invasive monitoring techniques. Therefore the clinician must make a rational decision based on the following conditions:

- Patient's underlying medical diseases
- Degree of hemodynamic compromise, myocardial ischemia risk, and fluid shift likely to result from the proposed surgery
- Effects of the anesthetic drugs and techniques on the patient's cardiovascular system
- Skills of the practitioner and his or her understanding of the risks, benefits, and alternatives to the different types of hemodynamic monitoring
- Integration of data from hemodynamic monitoring and TEE in the perioperative period

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14

Basic Intraoperative Transesophageal Echocardiography

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KEY POINTS

1. An ultrasound beam is a continuous or intermittent train of sound waves emitted by a transducer or wave generator that is composed of density or pressure. Ultrasound waves are characterized by their wavelength, frequency, and velocity.
2. Doppler frequency shift analysis can be used to obtain blood-flow velocity, direction, and acceleration of red blood cells, in which the magnitude and direction of the frequency shift are related to the velocity and direction of the moving target. These velocity flow measurements may be used to determine gradients and blood-flow volumes.
3. *Axial resolution* is the minimum separation between two interfaces located in a direction parallel to the ultrasound beam, enabling them to be imaged as two different interfaces. *Lateral resolution* is the minimum separation of two interfaces aligned along a direction perpendicular to the beam. *Elevational resolution* refers to the ability to determine differences in the thickness of the imaging plane.
4. Absolute contraindications to transesophageal echocardiography in intubated patients include esophageal stricture, diverticula, tumor, recent suture lines, and known esophageal interruption. Relative contraindications include symptomatic hiatal hernia, esophagitis, coagulopathy, esophageal varices, and unexplained upper gastrointestinal bleeding.
5. Horizontal imaging planes are obtained by moving the transesophageal echocardiography probe up and down (upper esophageal: 20–25 cm; midesophageal: 30–40 cm; transgastric: 40–45 cm; deep transgastric: 45–50 cm). Multiplane probes may further facilitate the interrogation of complex anatomic structures by allowing up to 180 degrees of axial rotation of the imaging plane without manual probe manipulation.
6. Diastolic dysfunction has three primary stages: impaired relaxation, pseudonormalization, and restrictive cardiomyopathy. The evaluation of diastolic function may be performed using Doppler analysis of mitral valve inflow and pulmonary vein flow, color M-mode propagation velocities, and tissue Doppler analysis of the mitral valve annulus.
7. Aortic stenosis may be evaluated by planimetry, transaortic gradients, or the continuity equation. The use of planimetry is usually limited by the presence of aortic valvular calcifications. Peak, as well as mean, gradients may be measured using continuous-wave Doppler over the aortic valve in either the deep transgastric or transgastric long-axis view. The continuity equation uses measurement of flow through the left ventricular outflow tract and the aortic valve to determine aortic valve area.
8. Quantification of aortic regurgitation is usually based on the analysis of color-flow Doppler patterns in the left ventricular outflow tract during diastole. The most reliable measurements are the vena contracta width and the ratio of proximal jet width to the width of the left ventricular outflow tract. Analysis of pressure half-time measurement of aortic regurgitant flows provides additional quantification of severity.
9. Mitral stenosis may be evaluated by planimetry of the valve in the transgastric basal short-axis view. Transmitral Doppler spectral analysis may be used to calculate mean transmitral gradient and mitral valve area using the pressure half-time measurement of the E wave.
10. Mitral regurgitation may be quantified by the analysis of color-flow Doppler spectra in the left atrium during ventricular systole. The severity of regurgitation may be further quantified using an analysis of pulmonary venous blood-flow velocities and measurements of regurgitant orifice areas using proximal isovelocity surface area.

Few areas in cardiac anesthesia have developed as rapidly as the field of intraoperative echocardiography. In the early 1980s, when transesophageal echocardiography (TEE) was first used in the surgical unit, its primary application was the assessment of global and regional left ventricular (LV) function. Since that time, there have been numerous technical advances: biplane and multiplane probes; multifrequency probes; enhanced scanning resolution; color-flow Doppler (CFD), pulsed-wave Doppler (PWD), and continuous-wave Doppler (CWD); automatic edge detection; Doppler tissue imaging (DTI); three-dimensional (3D) reconstruction; and digital image processing. With these advances, the number of clinical applications of TEE has significantly increased. The common applications of TEE include (1) assessment of valvular anatomy and function, (2) evaluation of the thoracic aorta, (3) detection of intracardiac defects, (4) detection of intracardiac masses, (5) evaluation of pericardial effusions, (6) detection of intracardiac air and clots, and (7) assessment of biventricular systolic and diastolic function. In many of these evaluations, TEE is able to provide unique and critical information that was not previously available in the surgical unit (Box 14.1).

Basic Concepts

Properties of Ultrasound

In echocardiography, the heart and great vessels are insonated with ultrasound, which is sound above the human audible range. The

BOX 14.1 COMMON APPLICATIONS OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

- Assessment of valvular anatomy and function
- Evaluation of the thoracic aorta
- Detection of intracardiac defects
- Evaluation of pericardial effusions
- Detection of intracardiac air, clots, or masses
- Assessment of biventricular systolic and diastolic function
- Evaluation of myocardial ischemia

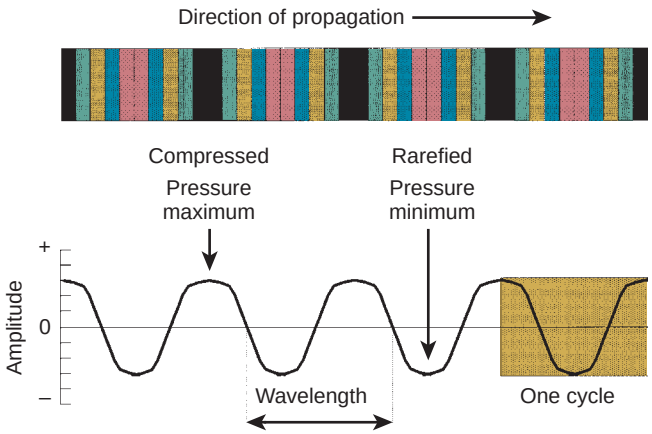


Fig. 14.1 A sound wave is a series of compressions and rarefactions. The combination of one compression and one rarefaction represents one cycle. The distance between the onset (peak compression) of one cycle and the onset of the next is the wavelength. *(From Thys DM, Hillel Z. How it works: basic concepts in echocardiography. In: Bruijn NP, Clements F, eds.* Intraoperative Use of Echocardiography. *Philadelphia: JB Lippincott; 1991:255–318.)*

ultrasound is sent into the thoracic cavity and is partially reflected by the cardiac structures. From these reflections, distance, velocity, and density of objects within the chest are derived.

An ultrasound beam is a continuous or intermittent train of sound waves emitted by a transducer or wave generator. It comprises density or pressure waves and can exist in any medium with the exception of a vacuum (Fig. 14.1). Ultrasound waves are characterized by their wavelength, frequency, and velocity.[1] *Wavelength* is the distance between the two nearest points of equal pressure or density in an ultrasound beam, and *velocity* is the speed at which the waves propagate through a medium. As the waves travel past any fixed point in an ultrasound beam, the pressure cycles regularly and continuously between a high and low value. The number of cycles per second (measured in hertz [Hz]) is called the *frequency* of the wave. Ultrasound is sound with frequencies above 20,000 Hz, which is the upper limit of the human audible range. The relationship among the frequency (f), wavelength (λ), and velocity (v) of a sound wave is defined by the following formula:

$$v = f \times \lambda \qquad \text{[Eq. 14.1]}$$

The velocity of sound varies with the properties of the medium through which it travels. In low-density gases, molecules must traverse long distances before encountering the adjacent molecules; therefore ultrasound velocity is relatively slow. In contrast, in solid, where molecules are constrained, ultrasound velocity is relatively high. For soft tissues, this velocity approximates 1540 m/sec but varies from 1475 to 1620 m/sec. In comparison, the velocity of ultrasound in air is 330 m/sec and 3360 m/sec in bone. Because the frequency of an ultrasound beam is determined by the properties of the emitting transducer and the velocity through soft tissue is approximately constant, wavelengths are inversely proportional to the ultrasound frequency.

Ultrasound waves transport energy through a given medium; the rate of energy transport is expressed as "power," which is usually expressed in joules per second or watts.[1] Since medical ultrasound is usually concentrated in a small area, the strength of the beam is usually expressed as power per unit area or "intensity." In most circumstances, intensity is usually expressed with respect to a standard intensity. For example, the intensity of the original ultrasound signal may be compared with the reflected signal. Since ultrasound amplitudes may vary by a factor of 10^5 or greater, amplitudes are usually expressed using a logarithmic scale. The usual unit for intensity comparisons is the decibel, which is defined as:

$$\text{Decibel (dB)} = 10 \cdot \log(I_1/I_0) \qquad \text{[Eq. 14.2]}$$

where I_1 is the intensity of the wave to be compared, and I_0 is the intensity of the reference waves.

Positive values imply a wave of greater intensity than the reference wave, and negative values indicate a lower intensity. Increasing the wave's intensity by a factor of 10 adds 10 dB to the decibel measurement, and doubling the intensity adds 3 dB.

Ultrasound Beam

Piezoelectric crystals convert between ultrasound and electrical signals. Most piezoelectric crystals that are used in clinical applications are the manufactured ceramic ferroelectrics, the most common of which are barium titanate, lead metaniobate, and lead zirconate titanate. When presented with a high-frequency electrical signal, these crystals produce ultrasound energy; conversely, when they are presented with an ultrasonic vibration, they produce an alternating current electrical signal. Commonly, a short ultrasound signal is emitted from the piezoelectric crystal, which is directed toward the areas to be imaged. This pulse duration is typically 1 to 2 sec. After ultrasound wave formation, the crystal "listens" for the returning echoes for a given period and then pauses before repeating this cycle. This cycle length is known as the pulse repetition frequency (PRF). This cycle length must be long enough to provide enough time for a signal to travel to and return from a given object of interest. Typically, the PRF varies from 1 to 10 kHz, which results in 0.1 to 1 msec between pulses. When reflected ultrasound waves return to these piezoelectric crystals, they are converted into electrical signals, which may be appropriately processed and displayed. Electronic circuits measure the time delay between the emitted and received echoes. Since the speed of ultrasound through tissue is constant, this time delay may be converted into the precise distance between the transducer and tissue. The amplitude or strength of the returning ultrasound signal provides information about the characteristics of the insonated tissue.

The 3D shape of the ultrasound beam is dependent on both the physical aspects of the ultrasound signal and the design of the transducer. An unfocused ultrasound beam may be thought of as an inverted funnel, in which the initial straight columnar area is known as the *near field* (also known as Fresnel zone), followed by the conical divergent area known as the *far field* (also known as Fraunhofer zone). The length of the near field is directly proportional to the square of the transducer diameter and is inversely proportional to the wavelength, specifically,

$$F_n = D^2/4\lambda \qquad \text{[Eq. 14.3]}$$

where F_n is the near field length, D is the diameter of the transducer, and λ is the ultrasound wavelength. Increasing the frequency of the ultrasound increases the length of the near field. In this near field, most energy is confined to a beam width no greater than the transducer diameter. Long Fresnel zones are preferred with medical ultrasonography, which may be achieved with large diameter transducers and high-frequency ultrasound. The angle of the far field convergence (θ) is directly proportional to the wavelength and inversely proportional to the diameter of the transducer and is expressed by the equation:

$$\sin\theta = 1.22\lambda/D \qquad \text{[Eq. 14.4]}$$

Further shaping of the beam geometry may be adjusted using acoustical lenses or the shaping of the piezoelectric crystal. Ideally, imaging should be performed within the near field or the focused aspect of the ultrasound beam because the ultrasound beam is most parallel with the greatest intensity and the tissue interfaces are most perpendicular to these ultrasound beams.

Attenuation, Reflection, and Scatter

Waves interact with the medium in which they travel and with one another. Interaction among waves is called *interference*. The manner in which waves interact with a medium is determined by its density and homogeneity. When a wave is propagated through an inhomogeneous medium (and all living tissue is essentially inhomogeneous), it is partly reflected, partially absorbed, and partly scattered.

Ultrasound waves are reflected when the width of the reflecting object is larger than one fourth of the ultrasound wavelength. Because the velocity of sound in soft tissue is approximately constant, shorter wavelengths are obtained by increasing the frequency of the ultrasound beam (see Eq. 14.1). Large objects may be visualized using low frequencies (ie, long wavelengths), whereas smaller objects require higher frequencies (ie, short wavelengths) for visualization. In addition, the object's ultrasonic impedance (Z) must be significantly different from the ultrasonic impedance in front of the object. The ultrasound impedance of a given medium is equal to the medium density multiplied by the ultrasound propagation velocity. Air has a low density and propagation velocity; therefore it has a low ultrasound impedance. Bone has a high density and propagation velocity; therefore it has a high ultrasound impedance. For normal incidence, the fraction of the reflected pulse compared with the incidence pulse is:

$$I_r = (Z_2 - Z_1)^2 / (Z_2 + Z_1)^2 \qquad \text{[Eq. 14.5]}$$

where I_r is intensity reflection coefficient, and Z_1 and Z_2 represent the acoustical impedance of the two media.

The greater the differences in ultrasound impedance between two objects at a given interface, the greater the ultrasound reflection. Because the ultrasound impedances of air or bone are significantly different from blood, ultrasound is strongly reflected from these interfaces, limiting the availability of ultrasound to deeper structures. This limitation of ultrasound energy to deeper structures results in ultrasound shadowing, which is discussed later in this chapter. Echocardiographic studies across lung or other gas-containing tissues or across bone are not feasible. Reflected echoes, also called *specular echoes*, are usually significantly stronger than scattered echoes. A grossly inhomogeneous medium, such as a stone in a water bucket or a cardiac valve in a blood-filled heart chamber, produces strong specular reflections at the water-stone or blood-valve interface because of the significant differences in ultrasound impedances. Furthermore, if the interface between the two objects is not perpendicular, then the reflected signal may be deflected at an angle and may not return to the transducer for imaging.

In contrast, if the objects are small, compared with the wavelength, then the ultrasound wave will be scattered. Media that are inhomogeneous at the microscopic level, such as muscle, produce more scatter than specular reflection because the differences in adjacent ultrasound impedances are low and the objects are small. These small objects will produce echoes that reflect throughout a large range of angles with only a small percentage of the original signal reaching the ultrasound transducer. Scattered ultrasound waves will combine in constructive and destructive fashions with other scattered waves, producing an interference pattern known as *speckle*. Compared with specular echoes, the returning ultrasound signal amplitude will be lower and will display as a darker signal. Although smaller objects can be visualized with higher frequencies, these higher frequencies result in greater signal attenuation, limiting the depth of ultrasound penetration.

Attenuation refers to the loss of ultrasound power as it traverses tissue. Tissue attenuation is dependent on ultrasound reflection, scattering, and absorption. The greater the ultrasound reflection and scattering, the less ultrasound energy is available for penetration and resolution of deeper structures; this effect is especially important during scanning with higher frequencies. In normal circumstances, however, absorption is the most significant factor in ultrasound attenuation.[2] Absorption occurs as a result of the oscillation of tissue caused by the transit of the ultrasound wave. These tissue oscillations result in friction with the conversion of ultrasound energy into heat. More specifically, the transit of an ultrasound wave through a medium causes molecular displacement. This molecular displacement requires the conversion of kinetic energy into potential energy as the molecules are compressed. At the time of maximal compression, the kinetic energy is maximized and the potential energy minimized. The movement of molecules from their compressed location to their original location requires conversion of this potential energy back into kinetic energy. In most cases, this energy conversion (either kinetic into potential energy or vice versa) is not 100% efficient and results in energy loss as heat.[1]

TABLE 14.1 Attenuation Coefficients

Material	*Coefficient (dB/cm/MHz)*
Water	0.002
Fat	0.66
Soft tissue	0.9
Muscle	2
Air	12
Bone	20
Lung	40

The absorption is dependent on both the material through which the ultrasound is passing and the ultrasound frequency. The degree of attenuation through a given thickness of material, x, may be described by:

$$\text{Attenuation (dB)} = a \cdot \text{freq} \cdot x \qquad \text{[Eq. 14.6]}$$

where a is the attenuation coefficient in dB per cm at 1 MHz, and freq represents the ultrasound frequency in megahertz (MHz).

Examples of attenuation coefficient values are given in Table 14.1. Although water, blood, and muscle have low ultrasound attenuation, air and bone have very high tissue ultrasound attenuation, limiting the ability of ultrasound to traverse these structures. Table 14.2 gives the distance in various tissues at which the intensity or amplitude of an ultrasound wave of 2 MHz is halved (the half-power distance).

Imaging Techniques

M Mode

The most basic form of ultrasound imaging is M-mode echocardiography. In this mode, the density and position of all tissues in the path of a narrow ultrasound beam (ie, along a single line) are displayed as a scroll on a video screen. The scrolling produces an updated, continuously changing time plot of the studied tissue section several seconds in duration. Because this is a timed *motion display* (normal cardiac tissue is always in motion), it is called *M mode*. Because only a very limited part of the heart is being observed at any one time and because the image requires considerable interpretation, M mode is not currently used as a primary imaging technique. M mode is, however, useful for the precise timing of events within the cardiac cycle and is often used in combination with CFD for the timing of abnormal flows (see "Color-Flow Doppler" section). Quantitative measurements of size, distance, and velocity are also easily performed in the M mode without the need for sophisticated analysis stations. Because M-mode images are updated 1000 times per second, they provide greater temporal resolution than two-dimensional (2D) echocardiography, thus more subtle changes in motion or dimension can be appreciated.

B Mode

The different reflectivities of various cardiac structures result in variations of the reflected ultrasound wave. The detected signals are

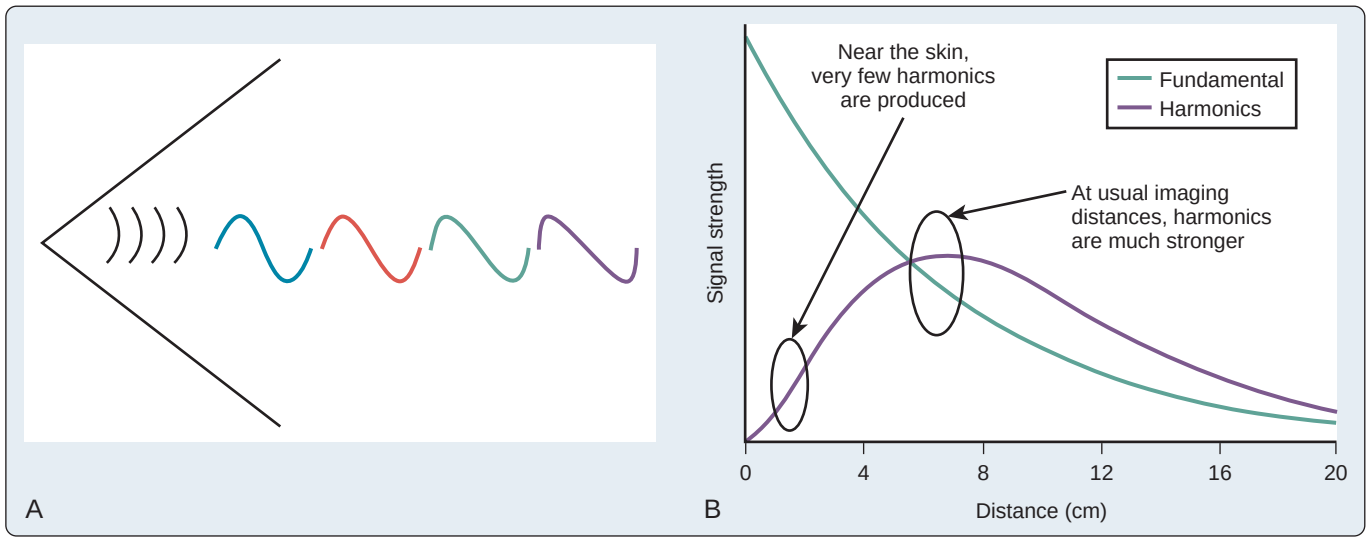


Fig. 14.2 Harmonic imaging. (A) Because the velocity of ultrasound transit is directly proportional to density, the peak amplitudes will travel slightly faster than the trough. With time, this differential velocity transit of the peak with the trough wave results in distortion of the propagated sin wave, resulting in a more peaked wave. (B) Relationship between imaging distance and strength of fundamental and harmonic frequencies is illustrated. As ultrasound pulse propagates, strength of fundamental frequency declines, whereas strength of harmonic frequency increases. At usual imaging distances for cardiac structures, strength of harmonic frequency is maximized. Note: Harmonic frequency strength is exaggerated in this schematic. Harmonic frequency signal strength is significantly lower than fundamental frequency signal strength. *(B, Used with permission. From Thomas JD, Rubin DN. Tissue harmonic imaging: why does it work?* J Am Soc Echocardiogr *1998;11:803–808.)*

TABLE 14.2 Half-Power Distances at 2 MHz

Material	*Half-Power Distance (cm)*
Water	380
Blood	15
Soft tissue (except muscle)	1–5
Muscle	0.6–1.0
Bone	0.2–0.7
Air	0.08
Lung	0.05

translated from the amplitude of the reflected signal to luminance and displayed as a brightness-mode or B-mode image. By rapid, repetitive scanning along many different radii within an area in the shape of a fan (sector), echocardiography generates a 2D image of a section of the heart. This image, which resembles an anatomic section, can be more easily interpreted than an M-mode display. Information on structures and motion in the plane of a 2D scan is updated 20 to 40 times per second. This repetitive update produces a live (real-time) image of the heart. Scanning 2D echocardiographic devices usually image the heart using an electronically steered ultrasound beam (phased-array transducer).

Harmonic Imaging

Harmonic frequency is ultrasound transmission of integer multiples of the original frequency. For example, if the fundamental frequency is 4 MHz, then the second harmonic frequency is 8 MHz, the third fundamental frequency is 12 MHz, and so on. Harmonic imaging refers to a technique of B-mode imaging in which an ultrasound signal is transmitted at a given frequency but will *listen* at one of its harmonic frequencies.[3,4] As ultrasound is transmitted through a tissue, the tissue undergoes slight compressions and expansions that correspond to the ultrasound wave, temporarily changing the local tissue density. Because the velocity of ultrasound transit is directly proportional to density, the peak amplitudes will travel slightly faster than the trough. This differential velocity transit of the peak with the trough wave results in distortion of the propagated sin wave, resulting in a more peaked wave. This peaked wave will contain frequencies of the fundamental frequency, as well as the harmonic frequencies (Fig. 14.2). Although very little distortion occurs in the near field, the amount of energy contained within these harmonics increase with ultrasound distance traversed as the ultrasound wave becomes more peaked. Eventually, the effects of attenuation will be more pronounced on these harmonic waves with a subsequent decrease in the harmonic amplitude. Because the effects of attenuation are greatest with high-frequency ultrasound, the second harmonic is usually used.

The use of tissue harmonic imaging is associated with improved B-mode imaging. Near-field scatter is common with fundamental imaging. Because the ultrasound wave has not yet been distorted, very little harmonic energy is generated in the near field, minimizing near-field scatter when harmonic imaging is used. Because higher frequencies are used, greater resolution may be obtained. Finally, with tissue harmonic imaging, side-lobe artifacts are substantially reduced and lateral resolution is increased.

Doppler Techniques

Most modern echocardiographic scanners combine Doppler capabilities with their 2D imaging capabilities. After the desired view of the heart has been obtained with 2D echocardiography, the Doppler beam, represented by a cursor, is superimposed on the 2D image. The operator positions the cursor as parallel as possible to the assumed direction of blood flow and then empirically adjusts the direction of the beam to optimize the audio and visual representations of the reflected Doppler signal. At the present time, Doppler technology can be used in at least four different ways to measure blood velocities: pulsed, high-repetition frequency, continuous-wave, and color-flow. Although each of these methods has specific applications, they are seldom concurrently available.

Doppler Effect

Information on blood-flow dynamics can be obtained by applying Doppler frequency shift analysis to echoes reflected by the moving red blood cells.[5,6] Blood-flow velocity, direction, and acceleration can be instantaneously determined. This information is different from that obtained in 2D imaging and hence complements it.

The Doppler principle as applied in echocardiography states that the frequency of ultrasound reflected by a moving target (red blood cells) will be different from the frequency of the reflected ultrasound. The magnitude and direction of the frequency shift are related to the velocity and direction of the moving target. The velocity of the target is calculated with the Doppler equation:

$$v = (cf_d)/(2f_0 \cos\theta) \qquad \text{[Eq. 14.7]}$$

where v represents the target velocity (blood-flow velocity), c is the speed of sound in tissue, f_d signifies the frequency shift, f_0 represents the frequency of the emitted ultrasound, and θ is the angle between the ultrasound beam and the direction of the target blood-flow velocity. Rearranging the terms,

$$f_d = v(2f_0 \cos\theta)/c \qquad \text{[Eq. 14.8]}$$

As is evident in Equation 14.8, the greater the velocity of the object of interest, the greater the Doppler frequency shift. In addition, the magnitude of the frequency shift is directly proportional to the initial emitted frequency (Fig. 14.3). Low-emitted frequencies produce low Doppler frequency shifts, whereas high-emitted frequencies produce high Doppler frequency shifts. This phenomenon becomes important with aliasing as discussed in the following text. Furthermore, the only ambiguity in Equation 14.7 is that the direction of the ultrasonic signal could refer to either the transmitted or the received beam. However, by convention, Doppler displays are made with reference to the received beam; thus if the blood flow and the reflected beam travel in the same direction, then the angle of incidence is zero degrees and the cosine is +1. As a result, the frequency of the reflected signal will be higher than the frequency of the emitted signal.

Equipment currently used in clinical practice displays Doppler blood-flow velocities as waveforms. The waveforms consist of a spectral analysis of velocities on the ordinate and time on the abscissa. By convention, blood flow toward the transducer is represented above the baseline. If the blood flows away from the transducer, then the angle of incidence will be 180 degrees, the cosine will equal −1, and the waveform will be displayed below the baseline. When the blood flow is perpendicular to the ultrasonic beam, the angle of incidence will be 90 or 270 degrees, the cosine of either angle will be zero, and no blood flow will be detected. Because the cosine of the angle of incidence is a variable in the Doppler equation, blood-flow velocity is measured most accurately when the ultrasound beam is parallel or antiparallel to the direction of blood flow. In clinical practice, a deviation from parallel of up to 20 degrees can be tolerated, resulting in an error of only 6% or less.

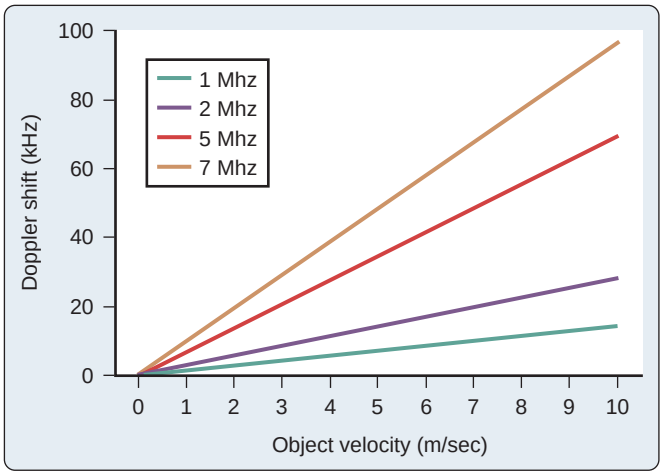


Fig. 14.3 Graph of Doppler shift frequency versus velocity for various emitted ultrasound frequencies. A lower emitted ultrasound frequency will produce a lower Doppler frequency shift for a given velocity. This lower Doppler frequency shift will allow for a higher velocity measurement before aliasing occurs.

Pulsed-Wave Doppler

In PWD, blood-flow parameters can be determined at precise locations by emitting repetitive short bursts of ultrasound at a specific frequency (PRF) and analyzing the frequency shift of the reflected echoes at an identical sampling frequency (f_s). A time delay between the emission of the ultrasound signal burst and the sampling of the reflected signal determines the depth at which the velocities are sampled; the delay is proportional to the distance between the transducer and the location of the velocity measurements. To sample at a given depth (D), sufficient time must be allowed for the signal to travel a distance of 2 × D (from the transducer to the sample volume and back). The time delay, T_d, between the emission of the signal and the reception of the reflected signal is related to D and to the speed of sound in tissues (c), by the following formula:

$$D = cT_d/2 \qquad \text{[Eq. 14.9]}$$

The operator varies the depth of sampling by varying the time delay between the emission of the ultrasonic signal and the sampling of the reflected wave. In practice, the sampling location or sample volume is represented by a small marker, which can be positioned at any point along the Doppler beam by moving it up or down the Doppler cursor. On some devices, varying the width and height of the sample volume is also possible.

The trade-off for the ability to measure flow at precise locations is that *ambiguous information* is obtained when flow velocity is very high. Information theory suggests that an unknown periodic signal must be sampled at least twice per cycle to determine even rudimentary information such as the fundamental frequency; therefore the rate of PRF of PWD must be at least twice the Doppler frequency shift produced by flow.[7] If not, the frequency shift is *undersampled*. In other words, this frequency shift is sampled so infrequently that the frequency reported by the instrument is erroneously low.[1]

A simple reference to Western movies will clearly illustrate this point. When a stagecoach gets underway, its wheel spokes are observed as rotating in the correct direction. As soon as a certain speed is attained, rotation in the reverse direction is noted because the camera frame rate is too slow to observe the motion of the wheel spokes correctly. In PWD, the ambiguity exists because the measured Doppler frequency shift (f_D) and the sampling frequency (f_s) are in the same frequency (kilohertz [kHz]) range. Ambiguity will be avoided only if the f_D is less than one half the sampling frequency:

$$f_D < f_s/2 \qquad \text{[Eq. 14.10]}$$

The expression $f_s/2$ is also known as the *Nyquist limit*. Doppler shifts above the Nyquist limit will create artifacts described as *aliasing* or *wraparound*, and blood-flow velocities will appear in a direction opposite to the conventional one (Fig. 14.4). Blood flowing with high velocity toward the transducer will result in a display of velocities above and below the baseline. The maximum velocity that can be detected without aliasing is dictated by:

$$V_m = c^2/8Rf_0 \qquad \text{[Eq. 14.11]}$$

where V_m represents the maximal velocity that can be unambiguously measured, c signifies the speed of sound in tissue, R is the range or distance from the transducer at which the measurement is to be made, and f_0 represents the frequency of emitted ultrasound.

Based on Equation 14.11, this aliasing artifact can be avoided by either minimizing the R or f_0. Decreasing the depth of the sample volume in essence increases f_s. This higher sampling frequency allows for the more accurate determination of higher Doppler frequency shifts (ie, higher velocities). Furthermore, since f_o is directly related to

f_d (see Eq. 14.7), a low-emitted ultrasound frequency will produce a lower Doppler frequency shift for a given velocity (see Fig. 14.3). This lower Doppler frequency shift will allow for a high-velocity measurement before aliasing occurs.

High-Pulse Repetition Frequency Doppler

On some instruments, PWD can be modified to a high-PRF mode. In conventional PWD, only a single burst of ultrasound is considered to be in the body at any given time; however, in high-PRF Doppler, two to five sample volumes are simultaneously presented. Information coming back to the transducer may be coming back from depths of two, three, or four times the initial sample volume depth. The returning signals can be a mix of signals that have previously been emitted and have traveled to distant gates and other signals that were just sent and returned from the first range gate.

The high-PRF mode allows increasing the sampling frequency because the scanner does not wait for the return of the information from distant gates; nonetheless, it receives information back within the specified time-gate period. Because high-sampling frequencies are used, higher velocities can be measured with this method than with PWD ; however, the exact gate from which the ultrasound signals are reflected is unknown (range ambiguity) (Box 14.2).

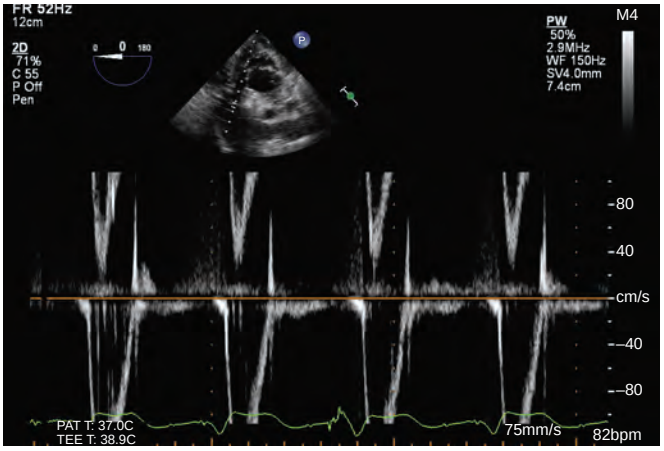


Fig. 14.4 Example of aliasing (deep transgastric view). Pulsed-wave Doppler through the aortic valve is demonstrated. Because the blood-flow velocity through the aortic valve is very high, it appears to wrap around the velocity scale when pulsed-wave Doppler is used.

Continuous-Wave Doppler

The CWD technique uses continuous, rather than discrete, pulses of ultrasound waves. Ultrasound waves are continuously being both transmitted and received by separate transducers. As a result, the region where flow dynamics are measured cannot be precisely localized. Because of the large range of depths being simultaneously insonated, a large range of frequencies is returned to the transducer. This large frequency range corresponds to a large range of blood-flow velocities. This large-velocity range is known as *spectral broadening*. Spectral broadening during CWD interrogation contrasts with the homogeneous envelope obtained with PWD (Fig. 14.5). Blood-flow velocity is, however, measured with great accuracy even at high flows, since sampling frequency is very high. CWD is particularly useful for the evaluation of patients with valvular lesions or congenital heart disease, in whom anticipated high pressure–high velocity signals are anticipated. CWD is also the preferred technique when attempting to derive hemodynamic information from Doppler signals.

Color-Flow Doppler

Advances in electronics and computer technology have allowed the development of CFD ultrasound scanners capable of displaying real-time blood flow within the heart as colors while also showing 2D images in black and white. In addition to showing the location, direction, and velocity of cardiac blood flow, the images produced by these devices allow the estimation of flow acceleration and differentiation of laminar from turbulent blood flow. CFD echocardiography is based on the principle of multigated PWD in which blood-flow velocities are sampled at many locations along many lines covering the entire imaging sector.[8] At the same time, the sector is also scanned to generate a 2D image.

A location in the heart where the scanner has detected flow toward the transducer (the top of the image sector) is assigned the color red. Flow away from the direction of the top is assigned the color blue.

BOX 14.2 PULSED-WAVE VERSUS CONTINUOUS-WAVE DOPPLER ANALYSIS

- Pulsed-wave Doppler
  - Spatial specificity
  - Ambiguity in the measurement of high velocities
- Continuous-wave Doppler
  - Ability to measure high velocities accurately
  - Spatial ambiguity

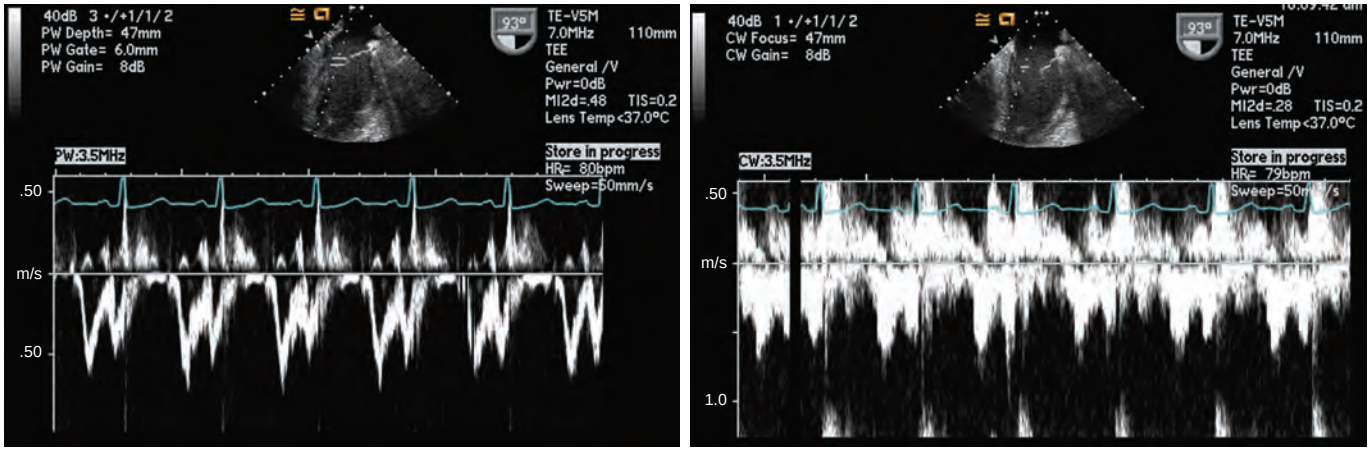


Fig. 14.5 Pulsed-wave Doppler (PWD) versus continuous wave Doppler (CWD). Both images are Doppler spectra through the mitral valve. *Left,* PWD is used. Because a specific region of interest is defined by the Doppler gate, a clean envelope of transmitral flow is displayed. *Right,* CWD is used. Because spatial specificity is lost, spectral broadening of velocities are displayed.

This color assignment is arbitrary and determined by the equipment's manufacturer and the user's color mapping. In the most common color-flow coding scheme, the faster the velocity (up to a limit), the more intense the color. Flow velocities that change by more than a preset value within a brief time interval (flow variance) may have an additional hue added to either the red or the blue. Both rapidly accelerating laminar flow (change in flow speed) and turbulent flow (change in flow direction) satisfy the criteria for rapid changes in velocity. In summary, the brightness of the red or blue colors at any location and time is usually proportional to the corresponding flow velocity, whereas the hue is proportional to the temporal rate of change of the velocity.

Contrast Echocardiography

Normally, red blood cells scatter ultrasound waves weakly, resulting in their black appearance on ultrasonic examination. Contrast echocardiography is performed by injecting nontoxic solutions containing gaseous microbubbles. These microbubbles present additional gas-liquid interfaces, which substantially increase the strength of the returning signal. This augmentation in signal strength may be used to better define endocardial borders, optimize Doppler envelope signals, and estimate myocardial perfusion.

Gramiak and colleagues[9] originally reported the use of contrast echocardiography in 1968. They described visualization of aortic valve (AV) incompetence during left-sided heart catheterization (Box 14.3). Subsequently, contrast echocardiography has been used to image intracardiac shunts,[10] valvular incompetence,[11] and pericardial effusions.[12] In addition, LV injections of hand-agitated microbubble solutions have been used to identify semiquantitative LV endocardial edges,[13] cardiac output (CO),[14] and valvular regurgitation.[15]

Contrast agents are microbubbles, consisting of a shell surrounding a gas. Initial contrast agents were agitated free air in either a saline or a blood-saline solution. These microbubbles were large and unstable; consequently, they were unable to cross the pulmonary circulation and were effective only for right-sided heart contrast. Because of their thin shell, the gas quickly leaked into the blood with resultant dissolution of the microbubble. Agents with a longer persistence were subsequently developed.

More modern contrast agents have both improved the shell surrounding the microbubble, as well as modification of the gas. The shell must inhibit the diffusion of gas into the blood and must enhance the pressure that a microbubble can tolerate before dissolving.[16] Gases with low shell diffusivity and blood saturation concentration result in a microbubble of increased survival because the gas would rapidly equilibrate with blood and the gas would tend to stay within the shell. Improvements in the shell both increase the tolerance of the microbubble to ultrasound energies and decrease the diffusion of the gas into the blood; both changes further increase the persistence of the microbubbles. At the same time, there must be an element of fragility; the microbubbles must be disrupted by ultrasound signals that produce appropriate imaging effects. The use of high–molecular-weight and less-soluble gases further increases the persistence of the contrast agents. Currently, the perfluorocarbons are the most common gases used in contrast agents. The microbubbles need to be small enough to traverse the pulmonary circulation with a predominant size particle that approaches the size of an erythrocyte. The number of larger particles needs to be minimized to reduce the risk of obstruction of pulmonary capillary flow. Because the reflected energy of contrast agents is high, attenuation of the ultrasound signal is common. This signal attenuation interferes with the visualization of distal structures.

An ultrasound signal produces compression and rarefaction (expansion) of the medium through which it travels. When this compression and rarefaction impact a microbubble, the bubble is compressed and expanded, respectively.[17] These changes result in changes in the bubble volume, causing bubble vibrations with subsequent effects on the returning ultrasound signal. These bubble pulsations may result in changes in the bubble radius by a factor of 20 or more.[18]

The acoustic properties of these microbubbles depend on the amplitude of the ultrasound signal. The amplitude of an ultrasound signal is usually defined by its mechanical index (MI), which is the peak negative pressure divided by the square root of the ultrasound frequency. Normally, when bubbles are insonated by ultrasound at their intrinsic resonant frequency, they vibrate; during the peak of the signal, they are compressed, and at the nadir of the signal, they expand. An ideal bubble would oscillation at the insonated ultrasound frequency.[19] At low ultrasound amplitudes (MI < 0.1), the microbubbles oscillate at the frequency of the insonated signal with the degree of compression being equal to the degree of expansion. This is called *linear oscillation*. With fundamental imaging, no special contrast echocardiographic signals are produced.[20] With increasing signal amplitudes (MI 0.1–0.7), the degree of expansion exceeds the degree of compression, which results in nonlinear oscillations. These nonlinear oscillations result in the creation of ultrasound waves at harmonic frequencies of the delivered ultrasound waves. Although some bubble destruction will occur at all amplitudes, further increases in ultrasound amplitude (MI 0.8–1.9) result in more compression and expansion with subsequent extensive bubble destruction. This bubble destruction, called *scintillation*, results in a brief but high output signal appearing as swirling. Because of the extensive bubble destruction, intermittent imaging must be performed to allow contrast replenishment. The role of most contrast imaging modalities is to create and display these nonlinear components while suppressing the linear echoes from tissue and tissue motion.[21]

Further improvements in image acquisition can be achieved using harmonic imaging.[18] As explained previously, nonlinear oscillations result in the creation of harmonics. It was theorized that if the receiver was tuned to receive the first harmonic of the transmitted ultrasound signal, then the signal-to-noise ratio can be improved by predominately imaging signals from the microbubbles producing these harmonics. Because tissue also produces harmonics, tissue gray-scale imaging was also enhanced. Further improvements may include subharmonic and ultraharmonic imaging, which may provide more specific contrast enhancement. Harmonic imaging with TEE improves endocardial visualization and allows partial assessment of myocardial perfusion.[22] Harmonic-powered Doppler is more sensitive for detecting basilar perfusion in the far field compared with harmonic gray-scale imaging.[23]

The first-generation agents were Albunex and Levovist. Currently, Optison (Mallinckrodt, St. Louis, MO) and Definity (DuPont Pharmaceuticals, Waltham, MA) are available for use in the United States; Levovist and SonoVue (Bracco Diagnostics, Princeton, NJ) are approved in Europe. Albunex is no longer available. Albunex used albumin encapsulation to stabilize a 4-μm air bubble that could opacify the left ventricle but did not result in good microvascular perfusion. Levovist uses an air microbubble within a fatty acid shell.

Optison is a refinement to Albunex, with the substitution of perfluoropropane within an albumin shell. Definity uses perfluoropropane within a liposome shell. SonoVue consists of hexafluoride with a

BOX 14.3 DIAGNOSTIC APPLICATIONS FOR CONTRAST ECHOCARDIOGRAPHY

- Assessment of congenital heart disease
- Enhancement of endocardial borders for qualitative assessment of wall motion abnormalities
  - Measurement of left ventricular function
  - Quantification of valvular regurgitation
  - Enhancement of color-flow Doppler signals
- Assessment of myocardial perfusion
  - Measurements of perfusion area after coronary artery bypass graft surgery
  - Assessment of quality of coronary bypass grafts and cardioplegia distribution
  - Correct assessment of the results of surgery for ventricular septal defect

phospholipid shell. New agents under development may use polymer shells whose flexibility and size can be more precisely controlled. These agents may be targeted to specific organs or vectors.

The safety of contrast echocardiography must be considered. The contrast agents, themselves, must have a high therapeutic index. Multiple large bubbles may obstruct pulmonary microcirculation. The disruption of microbubbles by high-amplitude ultrasound may rupture of capillaries and injure surrounding tissue.[24] Rare allergic and life-threatening anaphylactic or anaphylactoid reactions occur at a rate of approximately 1 per 10,000.[21] Premature ventricular contractions have been described during high-intensity triggered imaging.[25] Other investigators were not able to demonstrate an increase in premature ventricular complex occurrence during or after imaging with triggered ultrasound at an MI of 1.[26] Contraindications to the use of perflutren-containing agents included pulmonary hypertension, serious ventricular arrhythmias, severe pulmonary disease, cardiac shunting, or hypersensitivity to perflutren, blood, blood products, or albumin. If current recommendations are followed, then contrast echocardiography rarely results in significant side effects.[16]

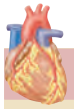
Echocardiographic Scanners

The transformation of reflected ultrasound echoes into 2D moving images is a complex process involving numerous electronic and digital manipulations. For example, a 2D echocardiographic image at 60 Hz is generated by scanning the heart every 16.7 msec or 60 times each second. The image is generated by combining these scan lines. A process called *interlacing* combines successive scans into a frame of 1/30 of a second. Because the eye cannot resolve an image lasting 1/30 of a second, microprocessors further process the frame electronically in real time to create the image of a heart moving through time. The intrinsic persistence of the display screen enhances image quality, and the end result is a fairly smooth image.

Resolution

Resolution is the ability to describe two point targets as distinct. An ultrasound image may be described by its axial, lateral, and elevational resolution (Box 14.4). *Axial resolution* is the minimum separation between two interfaces located along the same scan line in the acoustic beam, enabling them to be imaged as two different interfaces. The most precise image resolution is along this axial direction. The higher the frequency of the ultrasound signal, the greater the axial resolution, because ultrasound waves of shorter wavelengths may be used. Shorter bursts of ultrasound waves (ie, short pulse length) provide greater axial resolution. Pulse length should be no more than two or three cycles or they may slow B-mode frame rate. The range of frequencies contained within a given ultrasound transmission is referred to as the *frequency bandwidth*. Generally, the shorter the pulse of the ultrasound produced, the greater the frequency bandwidth; more low- and high-frequency information is in the same pulse. Because of the relationship between short pulse lengths and high bandwidths, high bandwidths are associated with better axial resolution. High-transducer bandwidths also allows for better resolution of deeper structures because they simultaneously have low-frequency information as well. Depth does not affect axial resolution.

Lateral resolution is the minimum separation of two targets aligned along an arc perpendicular to the ultrasound beam. The most important determinant of lateral resolution is both ultrasound beam width (or ultrasound beam focusing) and acoustic line spacing. For focusing, the narrower the beam, the better the lateral resolution. For line spacing, the closer the acoustic lines, the better the resolution. If a small object appears within the near field, it can then be accurately resolved laterally; however, if it appears within the far field, then the resolution of this small object will appear to blur because of the increase in the width of the ultrasound beam and the increased separation between ultrasound lines. Elevational resolution, or out of plane, refers to the ability to determine differences in the thickness of the imaging plane. The thickness of the ultrasound beam is a major determinant of elevational resolution. Elevational resolution is an important factor in live biplane imaging and 3D imaging. In these modes, all three resolution factors are important.



BOX 14.4 OPTIMIZATION OF RESOLUTION

- Axial
  - High ultrasound frequency
  - Short duration of ultrasound pulse
  - High-frequency bandwidth
- Lateral
  - Narrow beam width
- Elevational
  - Thickness of the ultrasound beam

Preprocessing

Ultrasound echoes are received and converted to electronic signals by the transducer. On most modern echocardiographic scanners, the analog electronic signals undergo several modifications before being digitized and eventually displayed as an image. Preprocessing describes the modifications performed on the analog and digital signal before storage.

Dynamic Range Manipulation

The intensity of echocardiographic signals spans a wide range from very weak to very strong. A high dynamic range (DR) allows the visualization of very strong and very weak signals on the same image. Very strong signals (eg, metallic valve struts) falling above the saturation level of the electronic circuitry create *white* oversaturated signals that compromise resolution. Very weak signals below the sensitivity of the instrument will not be detected and therefore not seen. The DR of the instrument is defined by the limits at which extremely strong or weak signals are eliminated; DR, within hardware limits, is under operator control (Fig. 14.6). In this manner, signals of low intensity that contain little useful information and are mostly noise can be selectively accepted or rejected.

A wide DR is needed to improve overall resolution, whereas a narrow range facilitates the discrimination between true image signals and noise. In clinical echocardiography, strong signals that arise from dense tissues (eg, cardiac valves) and weaker signals arising from soft tissues (eg, myocardium) are of interest. To give the weaker signals a greater representation in the DR, an amplifier converts the linear signal intensity scale into a logarithmic scale. Although this conversion increases the number of weaker signals detected, it also, unfortunately, amplifies noise.

Transmit Power and Overall Gain

Acoustic transmit power is proportional to the amplitude of the acoustic wave. Ultrasound systems work within acoustic safety limits to prevent heating tissue. Transmit power can be measured by the MI. Signals that are farther away can be strengthened by increasing the MI. In contrast, the overall receive gain control of an ultrasound scanner does not affect transmit power. It increases and decreases the receive intensity of the acoustic signals in a proportional manner by amplifying signals after they are received by the transducer, thus acting as a volume control.

Time-Gain Compensation

Because any wave traveling through tissues is attenuated proportionally to the traveled distance, it is necessary to compensate for the weaker echos returning from more distant objects than those from equally dense objects closer to the transducer. Depth compensation, or time-gain compensation (TGC), compensates for this difference

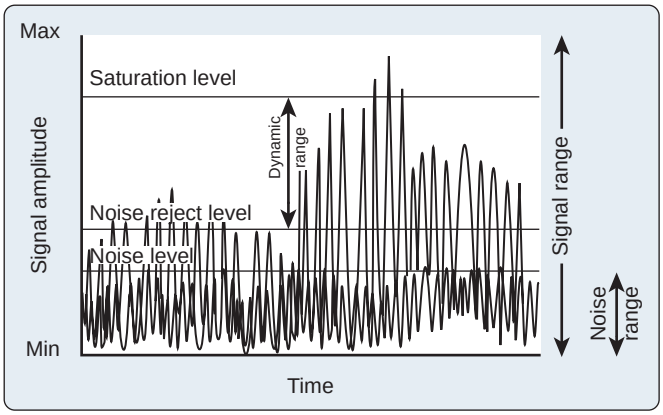


Fig. 14.6 Dynamic range of a representative echocardiographic display system. All ultrasound signals begin at zero signal level and can increase in amplitude until they reach the signal saturation level. Many of the low-intensity signals fall within the range of the background noise and are therefore obscured. All systems have a built-in system reject, which eliminates both the system noise and the low-intensity echoes that lie just above the noise level. The dynamic range of the system is between the noise reject level and the saturation level. Signals within the dynamic range appear on the image display. *(From Thys DM, Hillel Z. How it works: basic concepts in echocardiography. In: Bruijn NP, Clements F, eds.* Intraoperative Use of Echocardiography. *Philadelphia: JB Lippincott; 1991:255–318.)*

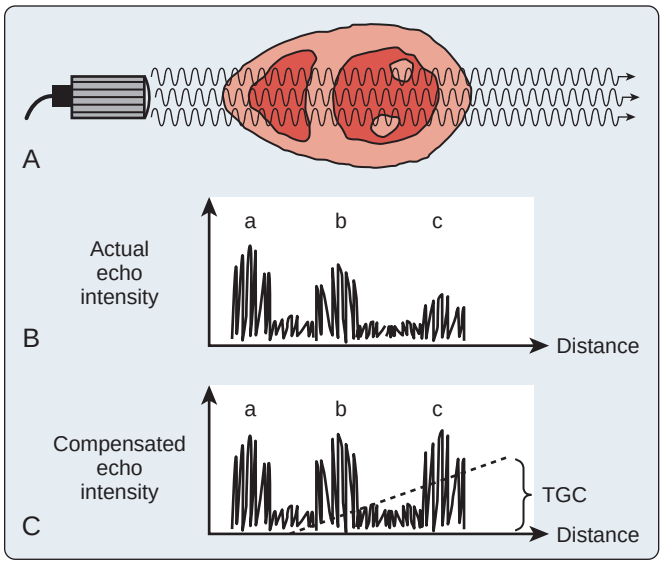


Fig. 14.7 (A) As an ultrasound beam is aimed across the heart, specular echoes are reflected at the right ventricular wall *(a)*, the septum *(b)*, and the left ventricular wall *(c)*. (B) The normal loss of echocardiographic strength is due to the decreasing intensity of the beam as it propagates through the heart. (C) Time-gain compensation *(TGC)* allows the intensity of the far-field signals to be increased selectively. *(From Thys DM, Hillel Z. How it works: basic concepts in echocardiography. In: Bruijn NP, Clements F, eds.* Intraoperative Use of Echocardiography. *Philadelphia: JB Lippincott; 1991:255–318.)*

in echo amplitudes (Fig. 14.7). Because echoes traveling from farther depths are received later, time is used to discern depth. TGC can be manually or automatically controlled.

Lateral gain control is an innovation that allows the application of gain control to selected angular blocks from one side to the other of the ultrasound image. This feature enhances the image strength of structures that are nearly parallel to the ultrasound beam (eg, the septum and lateral wall on a short-axis [SAX] view at the level of the papillary muscles). Thus lateral gain control is used to bring out imaging of the SAX view of the myocardium (Fig. 14.8).

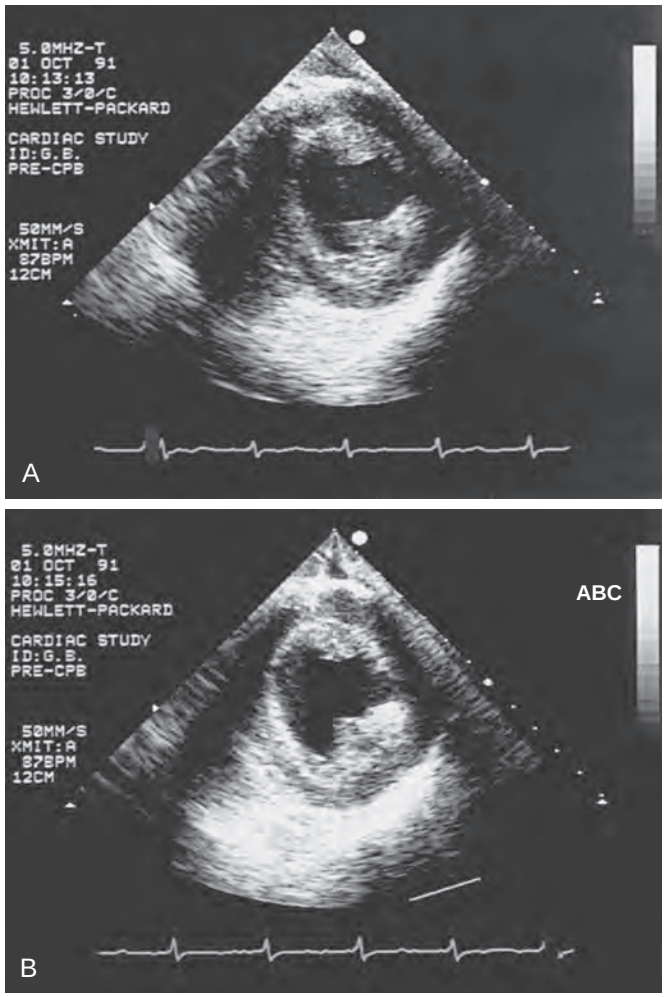


Fig. 14.8 (A) Standard two-dimensional short-axis view of the left ventricle at the level of the papillary muscles. Note that the image drops out in the septal and lateral walls (vertical portions of the wall). (B) Identical view after the application of lateral gain adjustments. The septal and lateral walls appear brighter, and less dropout is seen.

Leading-Edge Enhancement

Leading-edge enhancement, or differentiation, is another type of preprocessing used to sharpen the image. The reflected echocardiographic signal undergoes half-wave rectification and is smoothed into a signal envelope (Fig. 14.9A and B). An amplifier then differentiates the leading edge of the smoothed signal envelope to its first mathematical derivative (Fig. 14.9C), and a narrower and brighter image spot is formed (Fig. 14.9D and E). Because a 2D echocardiographic image comprises multiple radially juxtaposed scan lines, excessive edge enhancement narrows bright spots in the direction of travel of the echocardiographic beam (ie, axially but not laterally). For this reason, leading-edge enhancement is primarily performed on M-mode scans, whereas instruments with 2D-mode capability use little or no edge enhancement in the 2D mode. Therefore M-mode images often have a higher resolution than 2D images and are better suited for quantitative measurements.

Postprocessing

Digital Scan Conversion

After completing analog preprocessing, ultrasound devices digitize the image data with an analog-to-digital converter (Fig. 14.10). Further processing is performed while data are stored in the digital memory (input processing) or as they are received from the memory (output processing). The acoustic beam is swept in a polar fashion similar to

waving a flashlight. A display screen works in a rectangular format. An early step in digital processing uses a scan converter to transform the information obtained as radial sector scan lines into a rectangular (Cartesian) format for television screen display.

As an example, the digital storage of images is sketched. Computer memory stores the information of two adjacent columns in the image, for example, 128. There is also one row of memory for each of, for example, the 512 horizontal television image lines (raster lines). Therefore a typical television display of an echocardiographic image consists of 128 columns by 512 rows for a total of 65,536 picture elements or pixels. Although the monitor displays only 64 shades of gray for each pixel, for example, a 10-bit memory unit assigned to each pixel has the capacity to store 1024 degrees of brightness. Each pixel can be assigned 10 binary bits of memory for a total of 2^{10} (1024) possible storage combinations. The memory that is actually used depends on the specific system and manufacturing specifications.

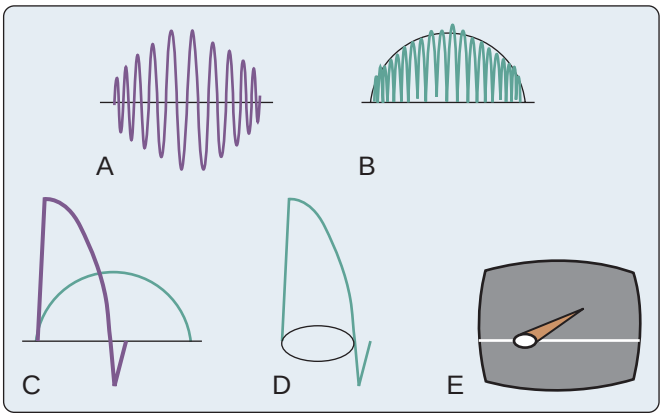


Fig. 14.9 Leading-edge enhancement techniques. (A) Radiofrequency (RF) type of echocardiographic display. (B) This video represents the average height of the upper half of the RF signal. (C) Differentiation is obtained by taking the first derivative of the video display. (D, E), Intensity modulation represents the conversion of signal amplitude to intensity, changing the signal from a spike to a dot. *(From Thys DM, Hillel Z. How it works: basic concepts in echocardiography. In: Bruijn NP, Clements F, eds.* Intraoperative Use of Echocardiography. *Philadelphia: JB Lippincott; 1991:255–318.)*

Temporal Processing

As digital data are entered into memory, they can undergo temporal averaging; that is, images can be averaged over time to change the aesthetics of the image. In the variable persistence mode, information from previous images is combined with current image data. A weighted average of the old and new data is then entered into memory as the new current data. A mechanism is built in to allow variable representation of the old data into the new image. A different input-processing option calculates the arithmetic mean of the new data and up to nine frames of existing data. The drawback is that averaging reduces temporal resolution and the ability to see quickly moving structures.

Gray-Scale Modification

The video image is generated from data retrieved from memory via the scan converter. During retrieval, data can be subjected to histogram modification or gray-ramp processing. This process redistributes the gray-level assignment of each pixel according to new values, which can bring out darker pixels and suppress brighter pixels. Manufacturers spend great efforts in creating their own ramps, which gives a signature appearance to the image. All levels of gray receive some representation, even though the original image may have been formed from only a limited range of grays.

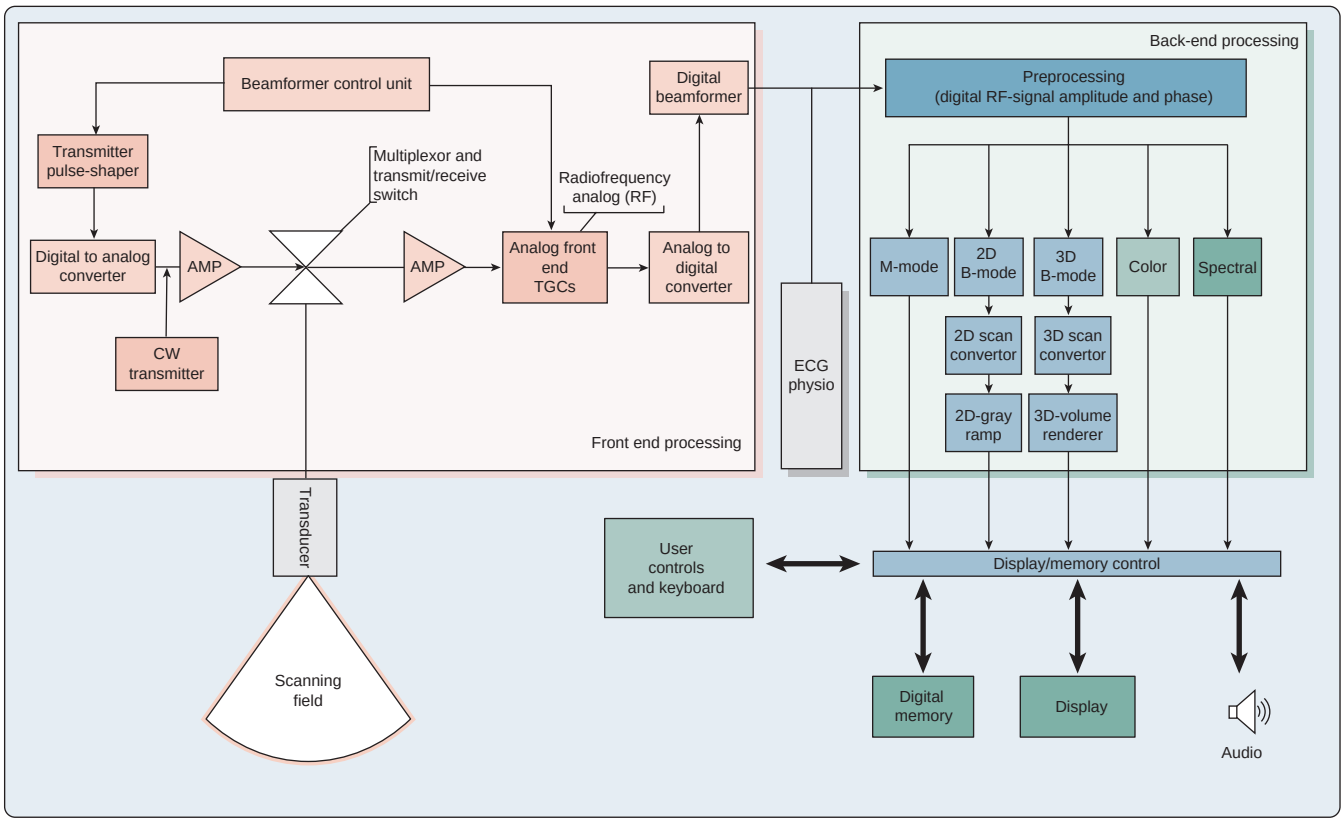


Fig. 14.10 Schematic drawing of modern ultrasound machine. *AMP*, Electronic amplifier; *CW*, continuous wave; *ECG*, electrocardiogram; *RF*, radio frequency; *TGC*, time-gain compensation; *2D*, two-dimensional; *3D*, three-dimensional.

Equipment

Because fat, bone, and air-containing lung interfere with sound-wave penetration, clear transthoracic echocardiographic views are particularly difficult to obtain in patients with obesity, emphysema, or abnormal chest wall anatomy. To avoid these problems, TEE transducers were developed. Sound waves emitted from an esophageal transducer only have to pass through the esophageal wall and the pericardium to reach the heart, improving image quality and increasing the number of echocardiographic windows. Other advantages of TEE include the stability of the transducer position and the possibility of obtaining continuous recordings of cardiac activity for extended periods.

The first TEE examination was performed in 1975. The probe used allowed only M-mode imaging and had limited control of direction. Two-dimensional TEE was first performed with a mechanical system,[27] which consisted of a vertical and a horizontal mechanical scanner connected to 3.5-MHz ultrasonic transducer contained in a 12′20′6-mm oil bag. The transducers were rotated by a single-phase commutator motor via flexible shafts. Subsequently, phased-array transducers were mounted into gastroscope housings.[28,29] With their greater flexibility and control, these probes allowed 2D scanning of the heart through many planes, and the probes became the prototypes of the currently used models.

All TEE probes share several common features. All of the currently available probes use a multifrequency transducer that is mounted on the tip of a gastroscope housing. The majority of the echocardiographic examination is performed using ultrasound between 3.5 and 7 MHz. The tip can be directed by the adjustment of knobs placed at the proximal handle. There are two knobs in most adult probes; one allows anterior and posterior movement, and the other permits side-to-side motion. Multiplane probes also include a control to rotate mechanically the echocardiographic array from 0 to 180 degrees. Thus in combination with the ability to advance and withdraw the probe and to rotate it, many echocardiographic windows are possible. Another feature common to most probes is the inclusion of a temperature sensor to warn of possible heat injury from the transducer to the esophagus.

Currently, most adult echocardiographic probes are multiplane (variable orientation of the scanning plane), whereas pediatric probes are either multiplane or biplane (transverse and longitudinal orientation, parallel to the shaft). The adult probes usually have a shaft length of 100 cm and are between 9 and 12 mm in diameter. The tips of the probes vary slightly in shape and size but are generally 1 to 2 mm wider than the shaft. The size of these probes requires the patient to weigh at least 20 kg. Depending on the manufacturer, the adult probes contain between 32 and 64 elements per scanning orientation. In general, the image quality is directly related to the number of elements used. The pediatric probes are mounted on a narrower, shorter shaft with smaller transducers. These probes may be used in patients weighing as little as 1 kg. Because of size limitations, these probes may not possess a lateral control knob. The use of the pediatric probe on all patients to decrease the risk of esophageal injury has been questioned. The answer is that the smaller probes provide less diagnostic information. The numbers of elements are reduced, the aperture is smaller, there is less control of the tip, and the smaller transducer tip does not usually make good contact in the adult esophagus. These factors combine to significantly reduce image quality.

An important feature that is often available is the ability to alter the scanning frequency. A lower frequency, such as 3.5 MHz, has greater penetration and is more suited for the transgastric (TG) view. It also increases the Doppler velocity limits. Conversely, the higher frequencies yield better resolution for detailed imaging. One of the limitations of TEE is that structures very close to the probe are seen only in a very narrow sector. Newer probes may also allow a broader near-field view. Finally, newer probes possess the ability to scan simultaneously in more than one plane. Nonmechanical matrix array probes use a diced crystal stack that can scan both laterally and elevationally. This 2D array can create a 3D ultrasound image and can also create simultaneous intersecting 2D images. This type of probe needs a beamformer capable of creating 3D reconstruction.

Image Storage

All modern echocardiographic scanners allow the operator to store or freeze a single echocardiographic image on the display screen. This feature allows the scrutiny of any unusual transient anatomic or physiologic observations. Once frozen, an image can also be subjected to some simple quantitative measurements. With the continuous motion of the cardiac structures, however, capturing the exact frame that is to be analyzed is often difficult. For this reason, techniques to acquire several consecutive frames have been developed.

Cine Memory

When activated, this mode captures a sequence of several echocardiographic images in digital memory. Because of the digital storage technique, the quality of the stored images is high. The images can be displayed again in several different ways. In one method, the frames are displayed one by one as the operator manually controls the transition from one frame to the next using a trackball. Any amount of time can be spent on a single frame. The images can also be replayed continuously in repeated endless-loop fashion at the same speed as the original recording speed or at a different speed.

Videotape

Many echocardiographic scanners are equipped with ½-inch video home system (VHS), *super* VHS (sVHS), or ¾-inch videocassette recorders (VCRs). Their advantages include low cost and their ability to record multiple cardiac cycles, facilitating the creation of a 3D image in the reviewer's mind.[30] Because VCRs store images in analog format, the quality of videotaped images is currently inferior to the real-time display, the digital cine memory replay, or digital storage. In the United States, videotape is used to record images using the National Television Standards Committee (NTSC) format. When videotape is used, resolution is limited by this NTSC format, which is not lost with digital storage.[30] Other disadvantages include the inability to randomly access parts of the current examination or previous examinations, difficulty sharing examinations with colleagues, and the degradation of videotape quality over time.[30]

Digital Storage

Digital image storage is rapidly becoming an alternative to videotape storage. Although the digital storage of echocardiographic images has increased the complexity of study storage, the American Society of Echocardiography (ASE) and others have suggested that digital storage has advantages over other modalities (Box 14.5).[31,32] These advantages include the following:

1. Reading is more efficient. With the use of VCR videotapes, the echocardiographer needs to review the entire 10 to 30 minutes of the study, which includes both important and redundant information. Using digital storage, the echocardiographer can direct his or her attention to specific clips, data may be accessed randomly, and the noncontributory segments of the study need not be viewed.
2. Because the studies are stored on a central server, the echocardiographer may read studies at any location that contains a workstation. When the storage system is properly configured, studies may be read on campus via institutional intranet connections or may be read off site.
3. Because of study centralization indexing and archiving in digital storage systems, previous studies may be rapidly accessed for comparison with a current study. The need to rummage through racks of old videotapes and search for a specific study is eliminated. This centralization of studies decreases the inefficient use of clinical staff time retrieving and loading physical media such

BOX 14.5 ADVANTAGES OF DIGITAL ECHOCARDIOGRAPHIC STORAGE[31,32]

1. More efficient reading
2. Ability to read studies in a variety of locations
3. Easy comparison with previous studies
4. Easier quantification
5. Ability to include images with reports to referring physicians
6. High image quality
7. No image degradation over time
8. Uses less storage space than VCRs do
9. Integration of the images and reports within the hospital's electronic medical record
10. More robust research
11. Easy implementation of a clinical performance improvement program
12. Improved overall accuracy and reproducibility
13. Greater facilitation of medical education
14. Decreases in medicolegal risk

as VCR videotapes or digital media. Because these older studies are more easily available, unnecessary duplication of procedures is decreased and the delivery of optimal patient care increases.

4. Since the Digital Imaging and Communications in Medicine (DICOM) file header contains information about the acquisition of the study, spatial, temporal, and velocity calibrations are included with each image, and quantification may be rapidly accomplished within the analysis program without special tools.
5. More convenient communication with the referring physician may be facilitated because the study images may be included easily with the report.
6. The standard resolution of VHS images is equivalent to 480 × 320 pixels, whereas the standard resolution of sVHS is equivalent to 560 × 480 pixels. Digital images provide a resolution of 800 × 600 pixels or higher, which are exactly as they are recorded by the ultrasound machine. No degradation occurs during the transfer of images from the ultrasound machine to the digital storage systems, as will occur with videotape transfer.
7. Over time, videotape degrades. A magnetic realignment of the VCR tape occurs with resultant degradation of image quality. Digital echocardiographic storage provides a more stable image quality.
8. The physical storage of VCRs requires significant space, which is usually a premium in either a hospital or an office environment.
9. The echocardiographic reports may be incorporated within the hospital's electronic medical record.
10. Because the highest quality images are available, more robust research may be performed. Communication with core laboratories is simplified.
11. A clinical quality-assurance program may be easily implemented, within which echocardiograms can be re-reviewed randomly on a regular basis. If consultation is necessary, then sharing studies with colleagues both from within and outside of the institution can be easily accomplished over digital networks.
12. Because physicians may be directed to the important aspects of the echocardiographic examination, of echocardiographic examinations provide improved accuracy and reproducibility.
13. Because moving images can be easily incorporated into presentations, facilitation of medical education is greater.
14. Since studies may be easily and reliably retrieved, medicolegal risk is reduced.

Because of these advantages, the ASE has unequivocally recommended that all examinations should be digitally captured and stored.[31] The increased efficiency of digital reading of echocardiographic studies has been demonstrated by Mathewson and associates,[33] who timed study acquisition and analysis during approximately 750 pediatric echocardiograms. As a group, the digitally captured images contained more hemodynamic measurements and thus required more time for acquisition. The average times for study acquisition were 26.0 ± 8.9 minutes for videotape and 28.4 ± 11.5 minutes for the single-beat digital method. In contrast, interpretation of these studies was more rapid using digital methods, with an average interpretation time of 6.5 ± 3.7 minutes for the videotape compared with 4.6 ± 3.9 minutes for the digital method.

Image Terminology

Image Creation

A single static echocardiographic image is rendered by a number of dots or pixels on a screen. The image resolution is defined by the number of columns and rows of pixels displayed, which is typically 800 and 600, respectively, for medical ultrasound. Each pixel of the image is described by its red, green, and blue components and is represented by three bytes of data; each of these bytes contain a number from 0 to 255, which represents the level of the pixels' primary colors. If 256 levels are possible for each of these three primary colors, then a total of 16.8 million colors (256^3) may be represented. A video clip consists of a series of sequentially displayed static images. Most echocardiographic video clips have approximately 30 frames per second. If no methods of compression are used, then the storage requirements for digital storage of echocardiographic clips become huge. A single image would require 921,600 bytes of data (640 columns × 480 rows × 3 bytes per pixel). If a 30 frame-per-second temporal resolution is used, then an uncompressed 10-minute examination would require 16,588,800,000 bytes or 15.4 gigabytes (GB) of storage.

Clinical Compression

Because of these space requirements, clinical examinations must be subject to compression. The two major categories of compression are clinical and digital. During the performance of echocardiographic examinations, many cardiac cycles may be obtained during image acquisition. During standard analog storage of examinations using VCR technologies, the videotape is allowed to run continuously, capturing the entire examination. With clinical compression, short clips are stored to represent each relevant echocardiographic view. Typically, either several seconds or several cardiac cycles are recorded, which may be played back in a loop when displayed for interpretation.

Does clinical compression effect the interpretation of echocardiographic examinations? Haluska and colleagues[34] reported high concordance between videotaped and digital echocardiographic interpretations of adult echocardiographic examinations. Most observed discordances were minor, with lesser values being reported with the digital method. For example, degrees of mitral regurgitation (MR) were reported to be milder by the digital method compared with video presentation. Most major discordances were cases of assessment of AV and mitral valve (MV) thickening and the degree of MR; the authors hypothesized that the major discordances were caused by undersampling and not image quality. The routine acquisition of longer video clips may not necessarily increase the accuracy of digital echocardiographic readings. Shah and associates[35] evaluated 102 patients with regurgitant valvular disease, recording findings on videotape, as well as digitally using one, two, and three cardiac cycles. They observed substantial agreement when the videotape and one-cycle digital presentations were compared. There were no increases in agreement when two or three cardiac cycles were presented digitally.

Digital Compression

There are two basic types of digital image compression: lossless and lossy. Lossless compression reduces the file size by replacing identical values in a given image data set with the single value and the number of repetitions. This type of digital compression allows for exact reconstruction of the data set and does not result in a loss of data. Because no data are lost, there is no degradation of image quality. The creation of a lossless data set requires substantial processing power and may affect

the speed of file manipulations. Lossless compression may allow for a threefold reduction in file size. In contrast, lossy compression reduces the image size by permanently eliminating nonessential image information. Although the goal of lossy compression is image compression without the loss of image quality, excessive lossy compression may result in degradation of image quality. Lossy compression may provide a 20-fold reduction in image size.

In a comparison of quantitative measurements of sVHS and digital Moving Pictures Expert Group 1 (MPEG-1)–derived images, Garcia and colleagues[36] demonstrated excellent agreement among linear, area, and Doppler measurements. The MPEG-1 measurements were reproducible and provided a higher quality, compared with the sVHS images. Other studies have confirmed the diagnostic quality of images subjected to MPEG-1 compression.[37,38] Harris and associates[39] compared the image quality of sVHS recording with MPEG-2 compressions, analyzing 80 matched examination interpretations among four echocardiographers. They reported an overall concordance rate of 94%. Most of the reported discrepancies (4% total) were minor. They concluded that MPEG-2 compression offers excellent concordance with sVHS image review. Similar high-quality compression may be seen with newer compression schemes such as MPEG-4.[40]

Digital Imaging and Communications in Medicine Standard

With the increased use of medical imaging, standardized formats for image storage were developed to allow for the uniform acquisition, storage, and distribution of examinations. In 1983, the American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) formed a joint committee to create a standard format for storing and transmitting medical images, which was published in 1985.* This original protocol was limited to single-frame grayscale images and required highly specific nonstandard hardware for information transfer and storage. Images were stored in a proprietary format; consequently, image viewing was difficult. Subsequently, this format has been developed further and renamed DICOM.[41] Its current version may be found on the NEMA website; version PS3 is being used.*

Each DICOM file has both header and image data. The header data may contain a variety of patient demographic information, acquisition parameters, and image dimensions. Informational object definitions specify the source of the data, supply the rules that determine which data elements are required and which are optional, and define the valid methods of data manipulation. In the case of echocardiography, 2D, color, and Doppler echocardiographic techniques are all supported. Calibration information for linear, temporal, and velocity data are available. Information may be exchanged using a variety of methods.

Image Acquisition, Transmission, Analysis, and Storage

Image Acquisition

Most modern ultrasonography machines have the ability to store electronic studies in a DICOM-compatible format for transmission to the Picture Archiving and Communication System (PACS), as well as modality worklist capability. This modality worklist capability enables a piece of imaging equipment to obtain details of patients and scheduled examinations electronically from the DICOM worklist server. Because of the need for image transmission, each ultrasound machine must be properly configured before its introduction into clinical service. The machine must be assigned an appropriate Application Entry (AE) Title and Internet protocol (IP) address, which will uniquely identify the machine to the network. The IP address of the gateway, through which the machine is expected to communicate, must be entered, as well as the IP addresses of both the PACS and DICOM worklist servers.

Before performing an examination, the patient must be properly identified. If a modality worklist capability is present on the ultrasound machine, then the patient information will already have been prepopulated on the ultrasound machine. The minimum examination should consist of all 28 ASE/SCA (Society of Cardiovascular Anesthesiologists) recommended standard multiplane TEE views with the appropriate Doppler and color-Doppler spectra.[42,43] Most of these views are saved as video clips, and the Doppler images are saved as static images. When available, appropriate 3D images should be obtained as well. Calibration information for off-line analysis (eg, length, time, velocity) is automatically stored for 2D and Doppler spectrum. Because of the size of the data set, this calibration information and the ability to perform off-line data manipulation of 3D data set are not usually available. Because electrocardiographic monitoring should be used, clips of a fixed number of cardiac cycles may be specified and automatically saved. Because electrocautery artifacts may interfere with cycle determination, a fixed time (eg, 1 to 2 seconds) may be alternatively specified. Although dependent on the number and duration of video clips and images stored, the usual echocardiographic examination is between 50 and 100 MB. After the conclusion of the study, all examination information may be sent via the local area network (LAN) to the PACS server.

Study Transmission

Normally, echocardiographic studies are initially stored on the internal hard drive of the ultrasound machine. These studies will normally be retained until deleted by the end user. Because studies stored on these machines are not accessible via a global PACS, they must be transferred centrally. Although studies may be copied onto removable media, such as digital videodisks (DVDs), compact disks (CDs), universal serial bus (USB) devices, or magnetooptical devices and manually transferred to a server ("sneaker-netted"), transmission via a LAN is most efficient.

LAN transmission speed will limit the speed of information exchange. Although older LANs may provide 10 megabits per second (Mbps) connectivity, a minimum of 100 Mbps is usually necessary between the ultrasound machines and the PACS server. A connection speed of 100 Mbps to 1 GB per second (Gbps) may be necessary to connect the PACS station to the review stations (Table 14.3). In addition to transmission speed, network architecture (eg, interconnectivity of gateways, bridges, switches, servers) has an important role in the performance of a network. Most ultrasound devices will support a network switch with autonegotiate features, allowing for the rapid transmission of information. Some older devices may only support lower speeds of communications and/or less efficient duplex modes and may not function properly with a switch set for autonegotiate functionality. Several network connections may need to be left at a fixed setting to allow communication with these older devices.

Image Storage: Picture Archiving and Communication System Server

After the creation of a study entry by the DICOM worklist server, an acquisition number is assigned by the worklist server. As discussed earlier, this information is sent to the ultrasound machine but may

TABLE 14.3 Transmission Time Requirement for a 50-MB Study

Speed of Connectivity	*Study Download Time*
28.8 kbps modem	3.9 hours
112 Kbps ISDN	1 hour
768 Kbps DSL or cable modem	8.6 minutes
1.54 Mbps T1 (trunk) line	4.4 minutes
10 Mbps Ethernet	40 seconds
100 Mbps Ethernet	4 seconds
1 Gbps Ethernet	0.4 seconds

DSL, Digital subscriber line; *Gbps,* gigabytes per second; *ISDN,* integrated services digital network; *Kbps,* kilobytes per second; *Mbps,* megabits per second.

Adapted from Thomas JD, Adams DB, Devries S, et al; Digital Echocardiography Committee of the American Society of Echocardiography. Guidelines and recommendations for digital echocardiography. *J Am Soc Echocardiogr.* 2005;18: 287–297.

*http://www.nema.org/Standards/Pages/Digital-Imaging-and-Communications-in-Medicine.aspx. Accessed April 19, 2015.

also be sent to the PACS server. The important demographic information is stored, as well as the details of the expected echocardiographic examination. When completed, the study is sent from the ultrasound machine to the PACS server. Typically, the study will be stored on the PACS server for a short period (days) before being sent to long-term storage. In many cases, these data will also be mirrored to an off-site disaster recovery server and storage as well. The more recent studies (typically 6 months to a few years old) are usually stored on redundant arrays of independent disks (RAIDs) for rapid retrieval of data, whereas the older studies (older than a few years) may be stored on less expensive and slower media such as DVDs, digital linear tape, or advanced intelligent tape. With the decreasing price of RAID storage, a greater number of studies may be stored on this fast-access medium.

Study Distribution and Analysis

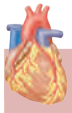
Dedicated Workstations

The need for study analysis is heavily dependent on physician work flow. In the typical cardiac anesthesia practice, the vast majority of studies are performed, interpreted, and reported by the physician at the time of the examination. In contrast, most outpatient echocardiographic studies are performed by a technician and sent to digital storage. They are then later recalled by the cardiologist for review, analysis, interpretation, and report generation. Nonetheless, most digital storage solutions will provide dedicated workstations for image review, analysis, and report generation capabilities, and anesthesia providers have the option to use these resources. Typically, these workstations will have fast connections with the PACS server, allowing for rapid transmission of a particular study to a workstation for analysis. Usually, multiple studies can be displayed for comparison. Image configurations may be adjusted by the user, and farther off-line image adjustments (eg, brightness, contrast) can usually be made. Clip playback speeds can be easily controlled, including the ability to start or stop and step through a study. Because calibration information has been incorporated with the study, off-line calculations may be performed. Images or clips can be selected for exportation as standard image or video files for incorporation into teaching materials. Reporting software may be offered as an option for these image analysis workstations. Measurements and qualitative descriptions may be entered for both generation of a study report and population of a structured query language (SQL) database, which may be used for performance improvement or research.

Off-Site Distribution

Echocardiographic images may be distributed off site as well. Mirroring the recently obtained studies on a separate server to handle all off-site distribution of studies (Web server) is usually the most efficient. The distribution of studies is limited by two basic constraints: security and communication. Most off-site distribution of medical images uses an Internet browser application to both retrieve studies from the PACS and display these studies for the user. An open-access system through the public Internet may present challenges vis-à-vis the Health Insurance Portability and Accountability Act (HIPAA) privacy regulation. Security of this medical information must be ensured by either a log-in system, allowing for auditing of access to patient information, or a virtual personal network (VPN), which is a method of providing remote access to an institutional LAN.

As discussed earlier, individual studies may be 50 to 100 MB in size. If high-speed network connectivity is available (such as 1 Gbp), then a 50-MB study may be transmitted to a workstation in less than 1 second (see Table 14.3). This high-speed connectivity is, however, not usually available to a user outside of the institutional LAN. If studies are to be accessed outside of an institution, the Internet must be used to download and view these studies; transmission speed may limit the speed of study display. An old-technology dial-up modem may require almost 4 hours to download a 50-MB study, whereas a 1.54-Mbps T1 line may require approximately 5 minutes. Because of these transmission speed issues, studies must be compressed before off-site study transmission. Using one of the lossy compression routines is most common. Although there is generally some image degradation, image quality may still be reasonable for some diagnostic work. Because these compression routines are used and the actual DICOM image file is not sent, calibration information is lost; consequently, off-line image measurements and calculation may be problematic.



BOX 14.6 COMPLICATIONS FROM INTRAOPERATIVE TRANSESOPHAGEAL ECHOCARDIOGRAPHY

- Injury from direct trauma to the airway and esophagus
  - Esophageal bleeding, burning, tearing
  - Dysphagia
  - Laryngeal discomfort
  - Bacteremia
  - Vocal cord paralysis
- Indirect effects
  - Hemodynamic and pulmonary effects of airway manipulation
  - Distraction from patient care

Complications

Complications resulting from intraoperative TEE can be separated into two groups: injury from direct trauma to the airway and esophagus and indirect effects of TEE (Box 14.6). In the first group, potential complications include esophageal bleeding, burning, tearing, dysphagia, and laryngeal discomfort. Many of these complications could result from pressure exerted by the tip of the probe on the esophagus and the airway. Although maximum flexion of the probe will not result in pressure above 17 mm Hg in most patients, occasionally, even in the absence of esophageal disease, pressures greater than 60 mm Hg will result.[44] To look more closely at the effects on the esophagus, animal autopsy studies have been performed. In dogs as small as 5 kg on cardiopulmonary bypass (CPB) with full heparinization, no evidence of macroscopic or microscopic injury to the esophageal mucosa was noted after 6 hours of maximally flexed probe positioning.[45]

Further confirmation of the low incidence of esophageal injury from TEE is apparent in the few case reports of complications. In a study of 10,000 TEE examinations, there was one case of hypopharyngeal perforation (0.01%), two cases of cervical esophageal perforation (0.02%), and no cases of gastric perforation (0%).[46] Kallmeyer and colleagues[47] reported overall incidences of TEE-associated morbidity and mortality of 0.2% and 0%, respectively. The most common TEE-associated complication was severe odynophagia, which occurred in 0.1% of the study population, dental injury (0.03%), endotracheal tube malpositioning (0.03%), upper gastrointestinal hemorrhage (0.03%), and esophageal perforation (0.01%). Piercy and associates[48] reported a gastrointestinal complication rate of approximate 0.1%, with a great frequency of injuries among patients older than 70 years and among women. Lennon and colleagues[49] reported a 1.2% incidence of upper gastrointestinal complications consistent with TEE injury among 516 patients undergoing cardiac surgery with TEE. In this study, 0.38% of the patients exhibited signs of complications early, whereas the remainder exhibited signs later. If resistance is met while advancing the probe, then the procedure should be aborted to avoid potentially lethal complications.

Another possible complication of esophageal trauma is bacteremia. Studies have shown that the incidences of positive blood cultures in patients undergoing upper gastrointestinal endoscopy and those undergoing TEE are 4% to 13%[50,51] and 0% to 17%,[52–54] respectively. Although bacteremia may occur, it does not always cause endocarditis. Antibiotic prophylaxis in accordance with the American Heart Association (AHA) guidelines is not routinely recommended but is optional in patients with prosthetic or abnormal valves or in patients who are otherwise at high risk for endocarditis.[55]

In one of the earliest studies using TEE, transient vocal cord paralysis was reported in two patients undergoing neurosurgery in the sitting position with the head maximally flexed and the presence of an armored endotracheal tube.[56] This complication was believed to be attributable to the pressure the TEE probe exerted against the larynx. Since this initial report, no further problems of this kind have been reported with the use of newer equipment.

The second group of complications that result from TEE includes hemodynamic and pulmonary effects of airway manipulation and, particularly for new TEE operators, distraction from patient care. Fortunately, in the anesthetized patient, hemodynamic consequences to esophageal placement of the probe are rare, and no studies specifically address this issue. More important for the anesthesiologist are the problems of distraction from patient care. Although these reports have not appeared in the literature, the authors have heard of several endotracheal tube disconnections that went unnoticed to the point of desaturation during TEE examination. Additionally, instances during which severe hemodynamic abnormalities have been missed because of a fascination with the images or the controls of the echocardiograph machine have been reported. Clearly, new echocardiographic operators should enlist the assistance of an associate to watch the patient during the echocardiographic examination. This second anesthesiologist will become unnecessary after sufficient experience is gained. Ensuring that all respiratory and hemodynamic alarms are activated during the echocardiographic examination is also important. One report that appeared in the literature recounted an incident during which an esophageal stethoscope was inadvertently pushed into the patient's stomach during TEE; it was noticed to be missing only when the patient developed a small bowel obstruction.[57]

Safety Guidelines and Contraindications

To ensure the continued safety of TEE, the following recommendations are made. The probe should be inspected before each insertion for cleanliness and structural integrity. If possible, the electrical isolation should also be checked. The probe should be inserted gently; if resistance is met, then the procedure should be aborted. Minimal transducer energy should be used, and the image should be frozen when not in use. Finally, when not imaging, the probe should be left in the neutral, unlocked position to avoid prolonged pressure on the esophageal mucosa.

Absolute contraindications to TEE in intubated patients include esophageal stricture, diverticula, tumor, recent suture lines, and known esophageal interruption. Relative contraindications include symptomatic hiatal hernia, esophagitis, coagulopathy, esophageal varices, and unexplained upper gastrointestinal bleeding. Notably, despite these relative contraindications, TEE has been used in patients undergoing hepatic transplantation without reported sequelae.[58,59]

Credentialing

The observance of guidelines for training, credentialing, certifying, and recertifying medical professionals has become increasingly common in the current era. Although there have been warnings[60] and objections[61] to anesthesiologists making diagnoses and aiding in surgical decision making, there is no inherent reason that an anesthesiologist cannot provide this valuable service to the patient.

In 1990, a task force from the American College of Physicians, the American College of Cardiology (ACC), and the AHA created initial general guidelines for echocardiography.[62] The ASE also provided recommendations for general training in echocardiography and has introduced a self-assessment test for measuring proficiency. These organizations have recommended the establishment of three levels of performance with a minimum number of cases for each level: level 1, an introduction and understanding of the indications (120 2D and 60 Doppler cases); level 2, independent performance and interpretation (240 2D and 180 Doppler cases); and level 3, laboratory direction and training (590 2D and 530 Doppler cases).[61,63] However, these guidelines are limited because they are not based on objective data or achievement. Furthermore, because different individuals learn at different rates, meeting these guidelines does not ensure competence nor does failure to meet these guidelines preclude competence.

Proficiency in echocardiography can be more efficiently achieved in a limited setting (ie, the perioperative period) with fewer clinical applications (eg, interpreting wall motion, global function, MR severity) than in a setting that introduces every aspect of echocardiography. The American Society of Anesthesiologists (ASA) and the SCA have worked together to create a document on practice parameters for perioperative TEE.[64,65] The SCA then created a Task Force on Certification for Perioperative TEE to develop a process that acknowledges basic competence and offers the opportunity to demonstrate advanced competence as outlined by the SCA/ASA practice parameters. In 1998, the National Board of Echocardiography was formed. Currently, perioperative transesophageal echocardiography examination (PTEeXAM) has two levels of board certification: basic and advanced. The basic level is limited to "… non-diagnostic monitoring within the customary practice of anesthesiology."[†] In contrast, the advanced track allows the diplomate to "… utilize the full diagnostic potential of perioperative TEE including direction of the surgical decision-making process."[‡] Both certifications require (1) holding a valid license to practice medicine; (2) board certification in an approved medical specialty, such as anesthesiology; and (3) training and/or experience in the perioperative care of surgical patients with cardiovascular disease. The basic track requires the study of 150 echocardiographic examinations (50 of these examinations require the presence of a supervising physician) and the passing of either the basic or advanced PTEeXAM; the advanced track requires the study of 300 echocardiographic examinations (150 of these examinations require the presence of a supervising physician) and the passing of the advanced PTEeXAM.

Training and Quality Assurance

TEE training should begin with a dedicated training period. This training is most easily accomplished during a cardiac anesthesia fellowship but can be completed by postgraduate physicians as well. The subject can be approached through a combination of tutorials, scientific review courses, self-instruction with teaching videos, interactive learning programs, and participation in echocardiographic reading sessions.[66,67] Frequently, a symbiotic relationship with the cardiology division can be established within which anesthesiologists can teach the fundamentals of airway management, surgical unit physiologic considerations, and the use of local anesthetics while learning the principles of echocardiography from the cardiologists.

In 2006, the ASE and SCA suggested guidelines to ensure quality improvement in perioperative TEE.[68] At the very least, each echocardiogram should be recorded in a standardized fashion and accompanied by a written report for inclusion in the patient's chart after a discussion with the anesthesia and surgical teams. Although images may also be copied and included in the chart, the ASE has unequivocally recommended that all examinations should be digitally captured and stored.[31] Careful records of any complications should be maintained. To ensure that the proper images are being obtained and that the interpretations are correct, the studies should be periodically reviewed. Components of this review should include the documentation of the indications and consent, the appropriate use of the system technology and controls, the adequacy and presentation of the imaging planes, and an assessment of whether the written report is supported by the documented images.[68] This review is another opportunity in which the relationship between cardiology and anesthesiology can be productive.

[†]http://www.echoboards.org/content/basic-pte. Accessed March 25, 2015.
[‡]http://www.echoboards.org/content/advanced-pteexam. Accessed March 25, 2015

Practice Parameters

In 2010, the ASA and the SCA Task Force on Transesophageal Echocardiography updated the 1996 practice guidelines for the use of perioperative TEE.[64,65] The major change in these guidelines recommend that perioperative TEE should be used in all adult patients, without contraindications for TEE, undergoing cardiac or thoracic aortic procedures. A complete TEE examination should be performed in all patients with the following intent: (1) to confirm and refine the preoperative diagnosis, (2) to detect new or unsuspected pathologic conditions, (3) to adjust the anesthetic and surgical plan accordingly, and (4) to assess the results of the surgical intervention.

For patients in the catheterization laboratory, the use of TEE may be beneficial. Especially in the setting of catheter-based valve replacement and repair and transcatheter intracardiac procedures, both consultants and ASA members agree that TEE should be used. In the setting of noncardiac surgery, TEE may be beneficial in patients with known or suspected cardiovascular pathologic conditions, which could potentially lead to severe hemodynamic, pulmonary, or neurologic compromise. In life-threatening situations of circulatory instability, TEE remains indicated. A similar viewpoint is taken by the consultants and ASA members in regards to critically ill patients. TEE should be used to obtain diagnostic information that is expected to alter management, especially in the intensive care unit, when the quality of transthoracic images is poor or when other diagnostic modalities are not obtainable in a timely manner.

A study published by Minhaj and colleagues[69] found that in 30% of patients, the routine use of TEE during cardiac surgery revealed a previously undiagnosed cardiac pathologic condition, leading to a change in surgical management in 25% of patients studied. Eltzchig and associates[70] were able to confirm these findings in a significantly larger cohort showing that the perioperative use of TEE may improve outcome. This group reported that 7% of 12,566 consecutive TEE examinations directly influenced surgical decision making. Combined procedures (coronary artery bypass graft [CABG], valve procedures) were most commonly influenced by perioperative TEE. In 0.05% of the examinations, the surgical procedure was actually cancelled as a direct result of the intraoperative TEE examination.

Practice guidelines are systematically developed recommendations that assist the practitioner and patient in making decisions about health care. These recommendations may be adopted, modified, or rejected according to clinical needs and constraints. Practice guidelines are not intended as standards or absolute requirements, and their use cannot guarantee any specific outcome. Practice guidelines are subject to revisions from time to time as medical knowledge, technology, and technique evolve. Guidelines are supported by analysis of the current literature and by synthesis of expert opinion, open-forum commentary, and clinical feasibility data.

Technique of Probe Passage

Anesthesiologists may need to insert TEE probes in awake or anesthetized patients. Awake insertions are identical in technique to awake upper gastrointestinal endoscopy and should be performed when the patient has an empty stomach. Using a bite block is also important. Probe insertion usually requires topical oral and pharyngeal anesthesia and moderate sedation. The probe is well lubricated, and the function of the directional controls is tested before insertion. The vast majority of patients are able to assist the probe's passage through the pharynx with a swallowing action. The presence of a TEE probe, however, would complicate airway management during anesthetic induction. Thus most anesthesiologists introduce TEE probes in anesthetized patients after tracheal intubation. To improve image quality, evacuating the stomach via suction before probe insertion is also useful.

The passage of a TEE probe through the oral and pharyngeal cavities in anesthetized patients may be challenging at times. The usual technique is to place the well-lubricated probe in the posterior portion of the oropharynx with the transducer element pointing inferiorly and anteriorly. The remainder of the probe may be stabilized by looping the controls and the proximal portion of the probe over the operator's neck and shoulder. The operator's left hand then elevates the mandible by inserting the thumb behind the teeth, grasping the submandibular region with the fingers, and then gently lifting. The probe is then advanced against a slight but even resistance, until a loss of resistance is detected as the tip of the probe passes the inferior constrictor muscle of the pharynx, which usually occurs 10 cm past the lips in neonates to 20 cm past the lips in adults. Further manipulation of the probe is performed under echocardiographic guidance.

Difficult TEE probe insertion may be caused by the probe tip abutting the pyriform sinuses, vallecula, posterior tongue, or an esophageal diverticulum. Overinflation of the endotracheal tube cuff could also obstruct passage of the probe. Maneuvers that might aid the passage of the probe include changing the neck position, realigning the TEE probe, and applying additional jaw thrust by elevating the angles of the mandible. The probe may also be passed with the assistance of laryngoscopy. The probe should never be forced past an obstruction. This could result in airway trauma or esophageal perforation.

Comprehensive Intraoperative Multiplane Transesophageal Echocardiographic Examination

Over the last 3 decades, perioperative TEE has become more recognized as a valuable hemodynamic monitor and diagnostic tool. In 1993, the ASE established the Council for Intraoperative Echocardiography to address issues related to the rapidly increasing utility of TEE in the perioperative period and its important impact on anesthesia and surgical decision making. In 1997, the board members of the Council, along with the SCA, decided to create the *ASE/SCA Guidelines for Performing a Comprehensive Intraoperative Multiplane Examination*,[42] which included the collective endorsement of a standard recommended set of 20 anatomically directed cross-sectional views and the corresponding nomenclature. As implied in the original manuscript published in 1999,[42] these guidelines were established to:

1. Facilitate training in intraoperative TEE by providing a framework in which to develop the necessary knowledge and skills.
2. Enhance and improve the technical quality and completeness of individual studies.
3. Facilitate the communication of intraoperative echocardiographic data among centers to provide a basis for multicenter investigations.
4. Standardize the description of intraoperative echocardiographic data to encourage the industrial development of efficient and rapidly acquiring labeling, storage, and analysis systems.

In 2014, the ASE and SCA updated their recommendations for performing a comprehensive TEE examination that includes 28 recommended views.[43] This document was created with the appreciation of the expanding role of TEE not only intraoperatively, but also in the intensive care unit, interventional laboratory, and outpatient setting. The increasing use of TEE was also recognized for its potential as a diagnostic tool to monitor cardiac performance and as an imaging guide for interventional procedures. Consequently, cardiac surgeons, anesthesiologists, cardiac interventionalists, and clinical cardiologists have all increased their appreciation for TEE as a tool for diagnosing cardiac pathologic conditions, monitoring cardiac performance, and guiding interventional procedures.

The guidelines for the intraoperative TEE examination were not intended to be all-encompassing but rather to serve as a framework for a systematic and complete examination of cardiac and great vessel anatomy of the normal patient and to serve as a baseline for later comparison.[42,43] Although the updated recommendations for performing a comprehensive TEE examination present a suggested protocol of image acquisition, the authors of the document realized that the order

and number of views may differ for various indications. Thus a more thorough intraoperative TEE examination, including the delineation of intracardiac and extracardiac anatomy, a description of congenital heart defects, and qualitative and quantitative Doppler analysis, is recommended and warranted in appropriate patients. Ideally, a complete intraoperative TEE examination not only provides information relevant to the particular diagnosis in question, but it also identifies unanticipated findings that may have a significant impact on perioperative management (ie, patent foramen ovale [PFO], atrial thrombus, severe aortic atherosclerosis).

Multiplane Transesophageal Echocardiographic Probe Manipulation: Descriptive Terms and Technique

The process of obtaining a comprehensive intraoperative multiplane TEE examination begins with a fundamental understanding of the terminology and technique for probe manipulation (Fig. 14.11). Efficient probe manipulation minimizes esophageal injury and facilitates the process of acquiring and sweeping through 2D image planes. Horizontal imaging planes are obtained by moving the TEE probe up and down (proximal and distal) in the esophagus at various depths relative to the incisors (*upper esophageal [UE]*: 20–25 cm; *midesophageal [ME]*: 30–40 cm; *TG*: 40–45 cm; *deep TG*: 45–50 cm). Vertical planes are obtained by manually turning the probe to the patient's left or right. Further alignment of the imaging plane can be obtained by manually rotating one of the two control wheels on the probe handle, which flexes the probe tip to the left or right direction or in the anterior or posterior plane. Multiplane probes may further facilitate interrogation of complex anatomic structures, such as the MV, by allowing up to 180 degrees of axial rotation of the imaging plane without manual probe manipulation.

Comprehensive Intraoperative Transesophageal Echocardiographic Examination: Imaging Planes and Structural Analysis

Left and Right Ventricles

The left ventricle should be examined carefully for global and regional function using multiple transducer planes, depths, and rotational and angular orientations (Fig. 14.12). Although a 17-segment model for assessing regional ventricular function has been developed (Fig. 14.13), the original comprehensive intraoperative TEE examination proposed a regional assessment scheme that required a systematic approach to evaluate each of the 16 individual LV segments: 6 basal, 6 mid, and 4 apical (see Fig. 14.13).[42,43,71] Analysis of segmental function is based on a qualitative visual assessment that includes the following grading system of both LV wall thickness and motion (endocardial border excursion) during systole: 1 = normal (>30% thickening); 2 = mild hypokinesis (10% and 30% thickening); 3 = severe hypokinesis (<10% thickening); 4 = akinesis (no thickening); 5 = dyskinesis (paradoxic motion). The recently recommended ME five-chamber view enables visualization of the septal and lateral walls (slightly anterior) of the left ventricle at 0 to 20 degrees from its base to the apex, along with the left ventricular outflow tract (LVOT), right ventricle and both atria (Table 14.4; see Fig. 14.12 and Video 14.1). Slight TEE probe advancement eliminates the LVOT from the image window and permits the development of the *ME four-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.2), demonstrating a slightly more mid-to-inferior plane. TEE probe rotation to approximately 80 to 100 degrees develops the ME *two-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.3), which removes the right-sided chambers from the imaging window but enables visualization of the inferior and anterior LV walls at the basal, mid, and apical levels segments. The *ME long-axis (LAX)* view at 120 to 160 degrees (see Fig. 14.12, Table 14.4, and Video 14.4) allows evaluation of the remaining anteroseptal and inferolateral (posterior) LV segments. Because the left ventricle is usually oriented inferiorly to the true horizontal plane, slight retroflexion of the probe tip may be required to minimize LV foreshortening. The *TG midpapillary SAX* view *(TG mid-SAX)* at 0 to 20 degrees (see Fig. 14.12, Table 14.4, and Video 14.5) is the most commonly used view for monitoring LV function, because it allows a midpapillary assessment of the LV segments supplied by the corresponding coronary arteries (right coronary artery, left circumflex, and left anterior descending [LAD]). This view also enables qualitative and quantitative evaluation of pericardial effusions. Advancing or withdrawing the probe at the TG depth enables LV evaluation at the respective newly recommended *TG apical SAX* and basal levels (*TG basal SAX*) (see Fig. 14.12, Table 14.4, and Videos 14.6 and 14.7), respectively. Further evaluation of the left ventricle can be obtained at the midpapillary TG depth by rotating the probe forward to the *TG two-chamber* view (80 to 100 degrees) (see Fig. 14.12, Table 14.4, and Video 14.8) and *TG LAX* (90 to 120 degrees) (see Fig. 14.12, Table 14.4, and Video 14.9). Global LV function requires assessment of dilatation (>6 cm at end-diastole), hypertrophy (>1.2 cm at end-diastole), and contractility. A more extensive quantitative evaluation of ventricular performance can be acquired by planimetry measurements of end-diastolic and end-systolic areas from which ejection fraction (EF), ventricular volumes, CO, and mean circumferential shortening can be calculated, which are discussed in greater detail in the following text.

Right ventricular (RV) regional and global function can be assessed from the *ME five-chamber* and *four-chamber* views (see Fig. 14.12, Table 14.4, and Videos 14.1 and 14.2), which allows visualization of the septal and free walls. Although a formal segmental scheme has not been developed for the RV free wall, regional assessment of the septum can be performed. Turning the probe to the right and advancing slightly from the ME depth allows visualization of the tricuspid valve (TV), coronary sinus (CS), and RV apex. Rotating the probe between 60 and

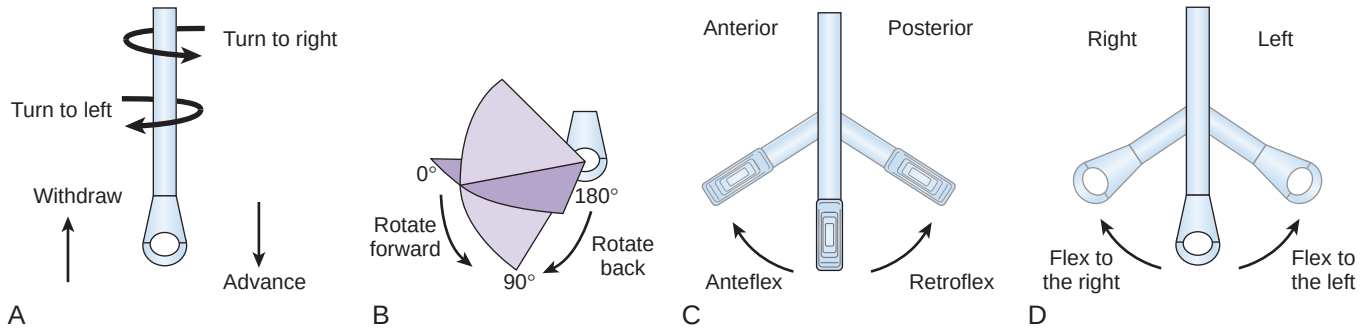


Fig. 14.11 Ways to adjust the probe. (A) Probe movement in the esophagus. (B) Scanning angles obtained by crystal rotation. (C) Movement of the tip forward and back. (D) Movement of the tip from side to side.

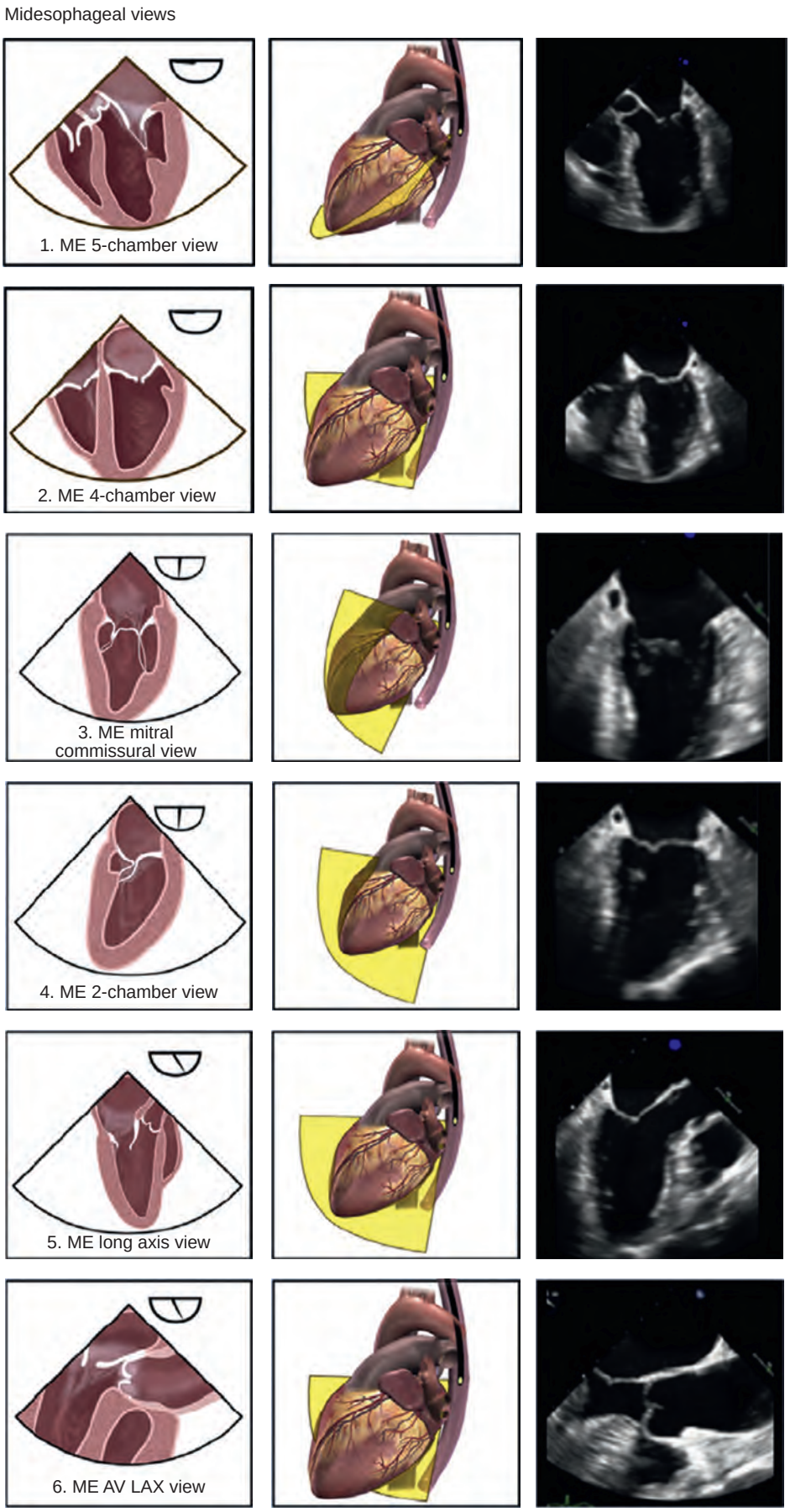


Fig. 14.12 Schematic drawings of the comprehensive examination. *AV,* Aortic valve; *LAX,* long axis; *ME,* midesophageal; *RV,* right ventricle; *SAX,* short axis; *TG,* transgastric; *UE,* upper esophageal. *(Adopted with permission. From Hahn RT, Abraham T, Adams MS, et al. Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists.* J Am Soc Echocardiogr. *2013;9:921–964.)*

Midesophageal views

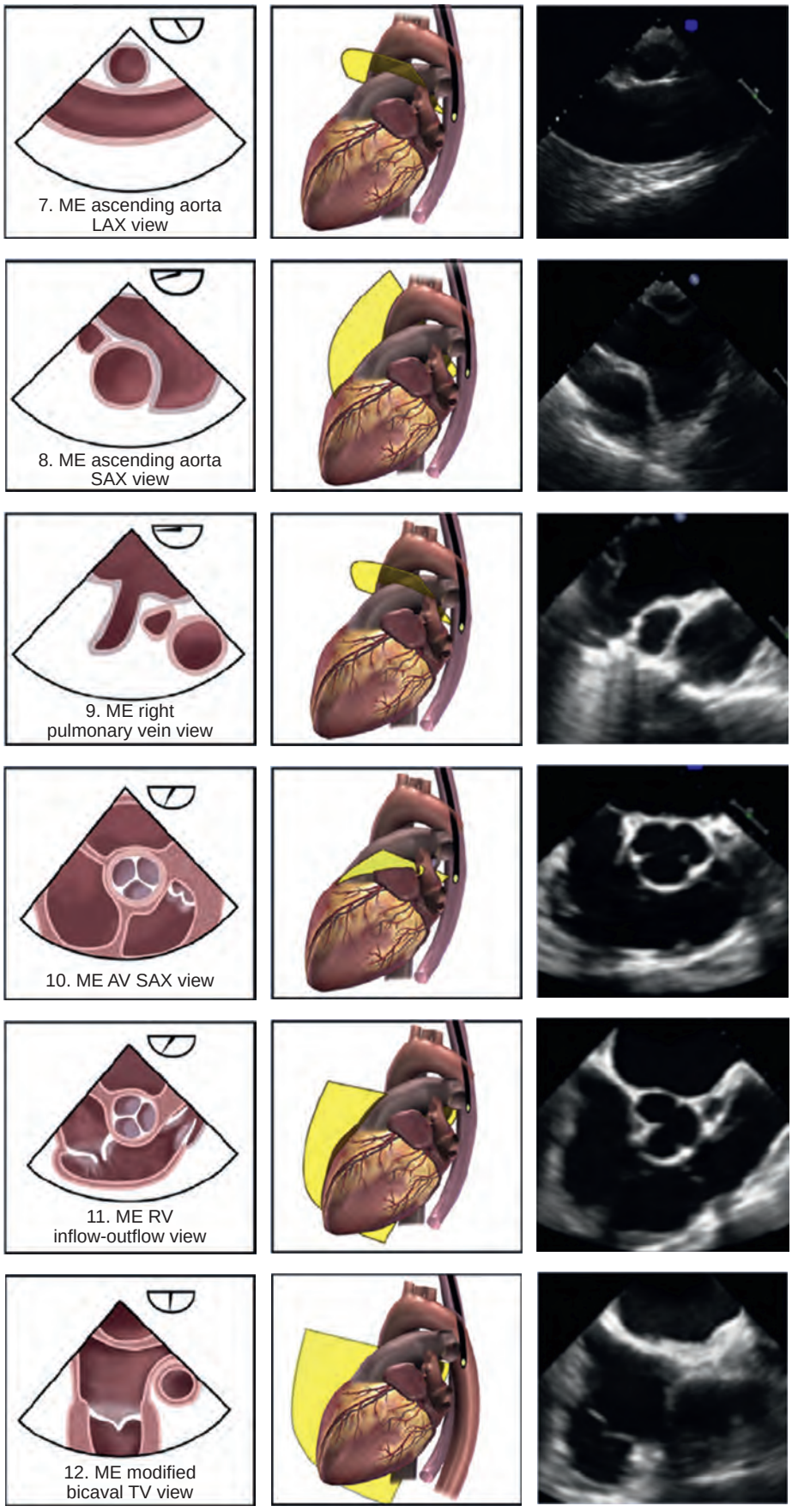


Fig. 14.12, cont'd

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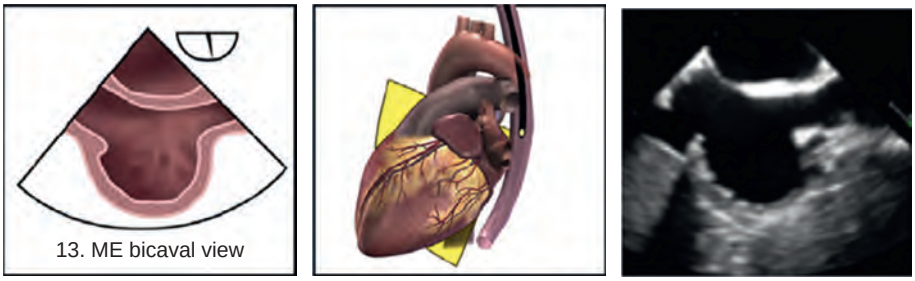
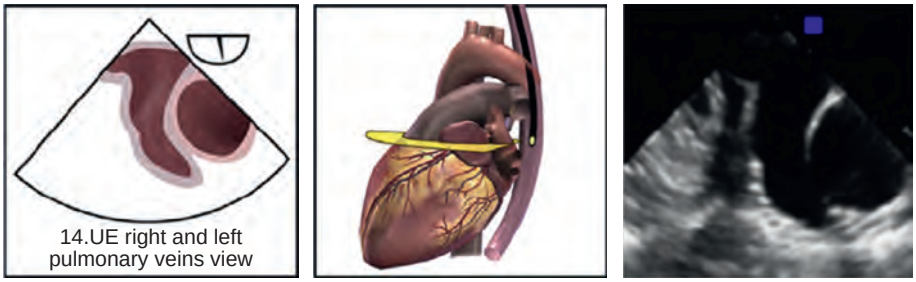
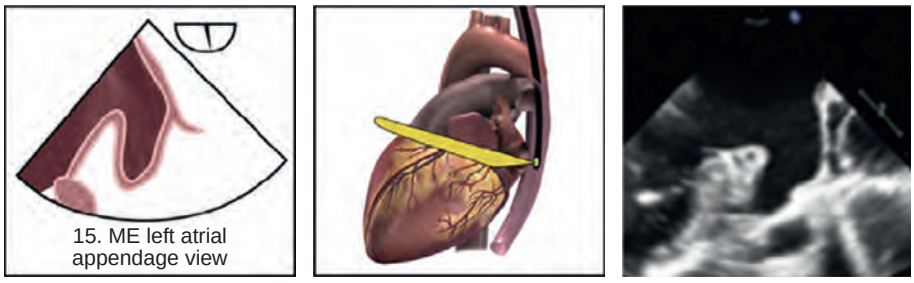
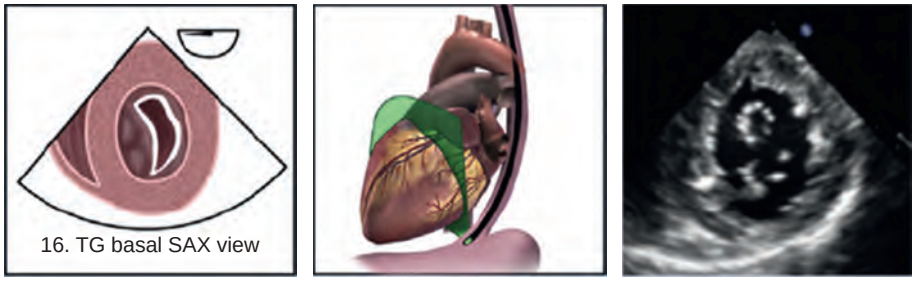
Midesophageal views

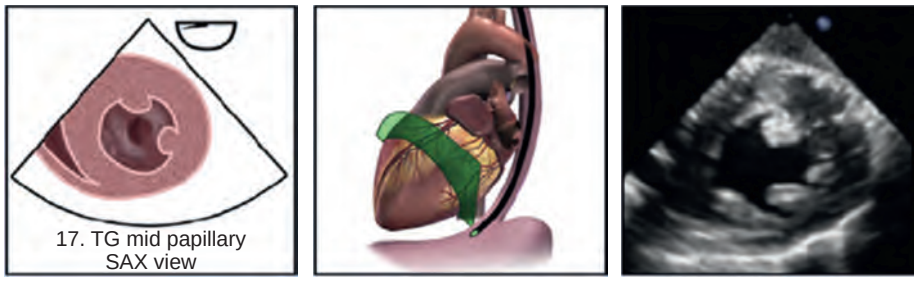






Transgastric views





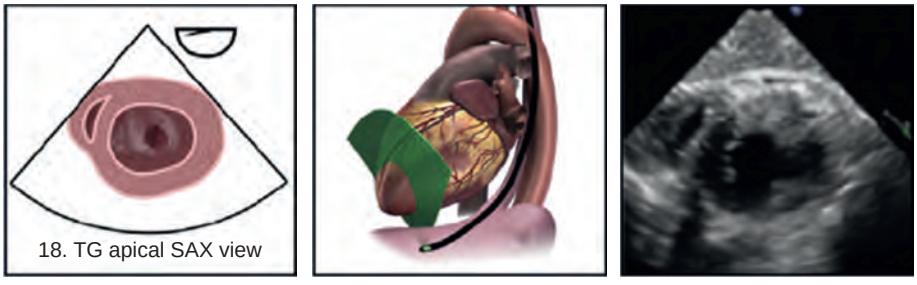


Fig. 14.12, cont'd

Transgastric views

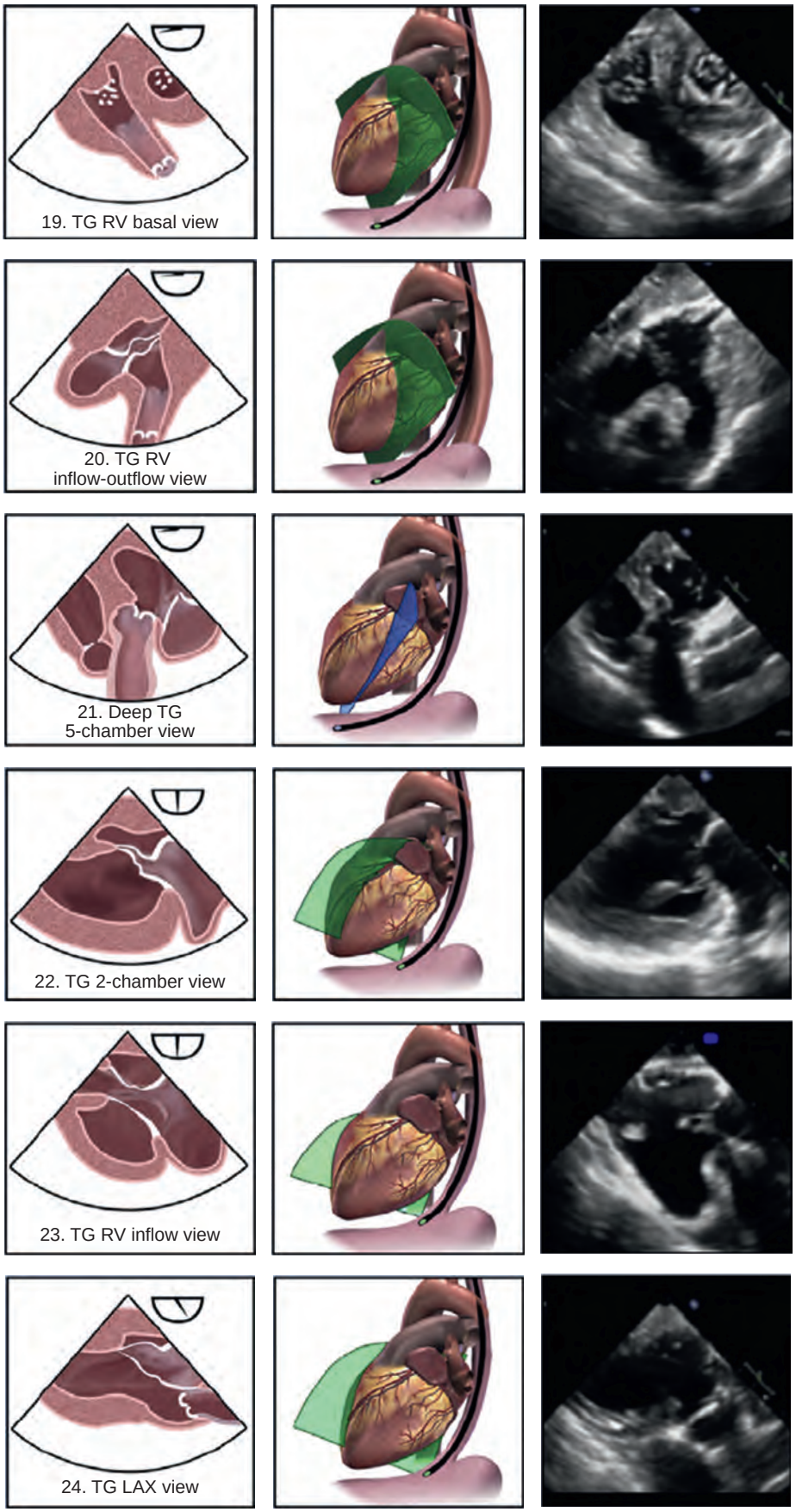


Fig. 14.12, cont'd

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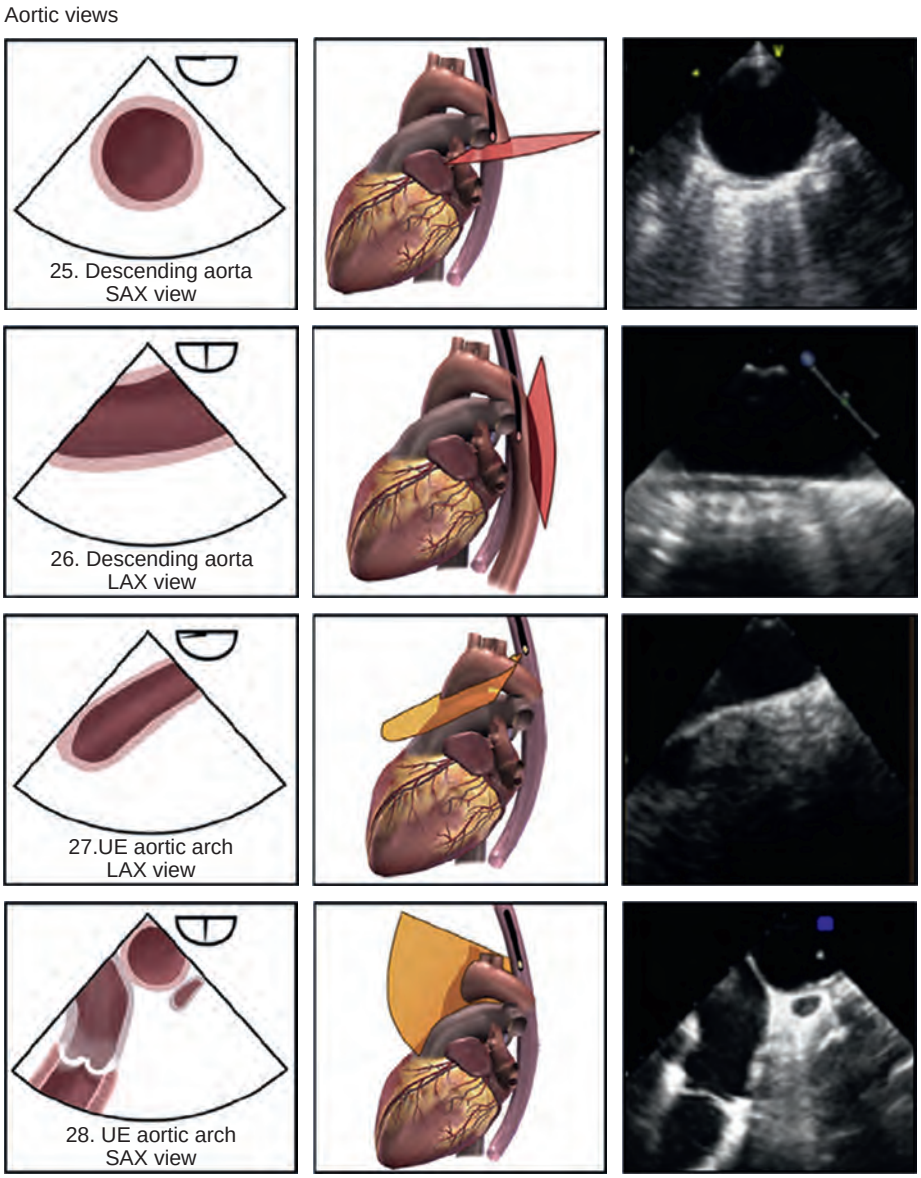
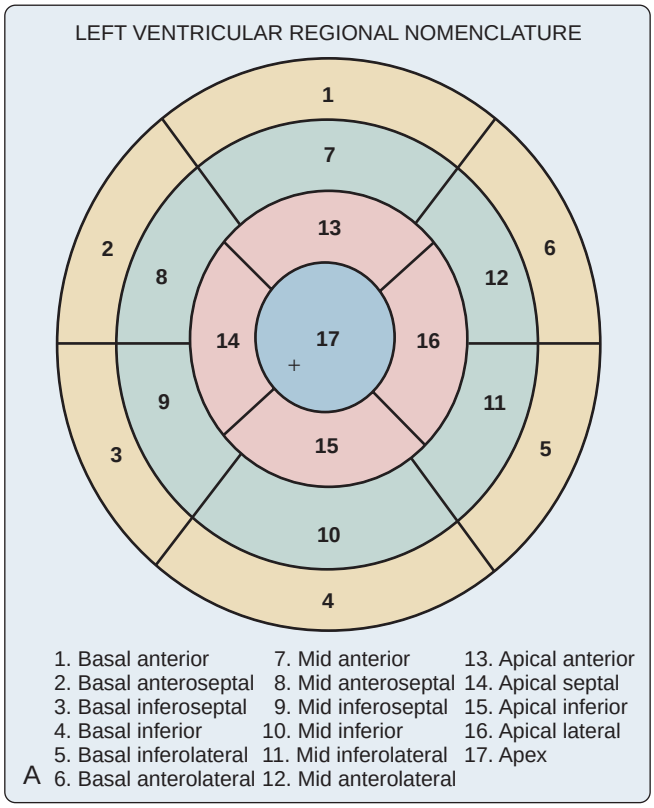


Fig. 14.12, cont'd

90 degrees reveals the *ME RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.10), in which the right atrium (RA), TV, inferior RV free wall, right ventricular outflow tract (RVOT), pulmonic valve (PV), and main pulmonary artery (PA) can be viewed wrapping around the centrally oriented AV. This view often allows optimal Doppler beam alignment to evaluate the TV and can also be helpful for directing PA catheter floating and positioning. The same right-sided structures can also be visualized from a different perspective by advancing the probe to the TG depth to obtain the newly recommended *TG RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.11). The *TG midpapillary SAX* view (see Fig. 14.12, Table 14.4, and Video 14.5) displays the crescent-shaped, thinner-walled right ventricle to the left of the left ventricle. Slightly withdrawing the probe reveals the right ventricle at a more basal level along with the PV in the newly recommended TG RV basal view (see Fig. 14.12, Table 14.4, and Video 14.12). The *TG RV inflow* view (see Fig. 14.12, Table 14.4, and Video 14.13) is developed by turning the probe to the right to center the right ventricle at this depth and rotating the multiplane angle forward to 100 to 120 degrees, thereby revealing the inferior RV free wall. Slight anteflexion, advancement, and rotation of the probe back toward 0 degrees can often reveal the RVOT and PV. Despite the asymmetric shape of the right ventricle, global function can still be assessed from the *ME five-chamber* and *four-chamber*, *TG midpapillary* and *RV basal SAX*, *ME RV inflow-outflow*, and *TG RV inflow* views using a quantitative evaluation scheme similar to that previously delineated for the left ventricle. Qualitative echocardiographic findings consistent with a diagnosis of global RV dysfunction include dilatation and hypertrophy, flattened or leftward shift of the atrial and ventricular septum, tricuspid regurgitation (TR), and a dilated CS. The more detailed discussion of RV evaluation appears later in this chapter.

Mitral Valve

The echocardiographic evaluation of the MV requires a thorough assessment of its leaflets (anterior and posterior), annulus, and the subvalvular apparatus (chordae tendineae, papillary muscles, and adjacent LV walls) to locate lesions and to define the cause and severity of the pathophysiologic condition. The mitral leaflets can be further divided into posterior leaflet scallops: lateral (P1), middle (P2), and medial (P3) that correspond with respective anterior leaflet sections: lateral third (A1), middle third (A2), and medial third (A3). The leaflets are



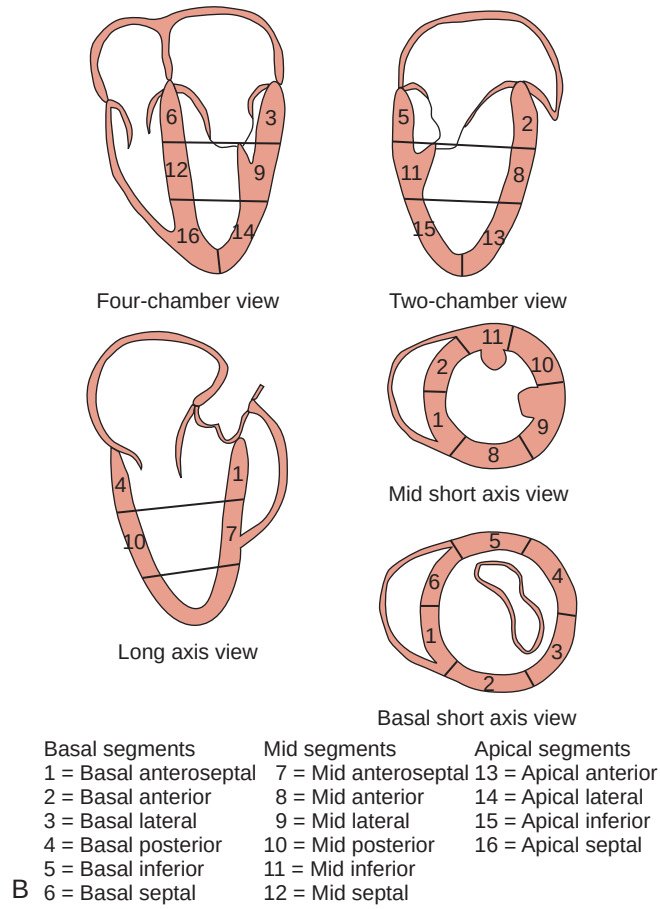


Fig. 14.13 Left ventricular segmental nomenclature. (A) 17 segments. (B) 16 segments.

united at the anterolateral and posteromedial commissures. The *ME four-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.2) displays the larger appearing anterior leaflet (A2,3) to the left of the posterior leaflet (P2,1), whereas the *ME five-chamber* view reveals more of A1 and P1. Anteflexing the probe provides imaging of the anterolateral aspect of the MV, whereas gradual advancement of the probe and retroflexion shift the image plane to the posteromedial aspect of MV. Maintaining the probe at the ME depth and rotating the multiplane angle forward to 60 to 70 degrees develops the *ME mitral commissural* view (see Fig. 14.12, Table 14.4, and Video 14.14), in which A2 is flanked by P1 on the right and P3 on the left, giving A2 the appearance of a "trap-door" as it moves in and out of the imaging plane throughout the cardiac cycle. Farther forward rotation of the probe to 80 to 100 degrees develops the *ME two-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.3), revealing P3 to the left and A1 on the right. Final forward probe rotation to 120 to 160 degrees reveals the *ME LAX* view (see Fig. 14.12, Table 14.4, and Video 14.4), which images P2 on the left and A2 on the right. The *TG basal SAX* view (see Fig. 14.12, Table 14.4, and Video 14.7) enables visualization of both MV leaflets ("fish-mouth view") if the probe is anteflexed and withdrawn slightly from the midpapillary level of the left ventricle. In this view, the posteromedial commissure is in the upper left, the anterolateral commissure is in the lower right, the posterior leaflet is to the right, and the anterior leaflet is to the left of the displayed image. Rotation of the probe to 80 to 100 degrees develops the *TG two-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.8) that is especially useful for evaluating the chordae tendinea and corresponding papillary muscles. Further functional evaluation of the MV requires a quantitative Doppler evaluation (PWD, CWD, and CFD) of transmitral and pulmonary venous flow for assessing MR, stenotic lesions, and LV diastolic function.

Aortic Valve, Aortic Root, and Left Ventricular Outflow

The three cusps of the semilunar AV are best visualized simultaneously in the *ME AV SAX* view (see Fig. 14.12, Table 14.4, and Video 14.15), which is obtained by rotating the probe forward to 30 to 60 degrees. The noncoronary cusp is superior, lying adjacent to the atrial septum; the right cusp is inferior; and the left cusp lies to the right, pointing in the direction of the left atrial appendage (LAA). This view permits planimetry of the AV orifice, evaluation of congenital anomalies of the AV (eg, bicuspid AV), and qualitative assessment of aortic insufficiency (AI) when CFD is used. Withdrawing the probe slightly through the sinuses of Valsalva allows for imaging the right coronary artery inferiorly, and the left main coronary branching into the LAD coronary artery and left circumflex. The *ME AV LAX* view (see Fig. 14.12, Table 14.4, and Video 14.16) can be obtained at the same depth while rotating the probe to 120 to 160 degrees, allowing for visualization of the LVOT, AV annulus, and leaflets (right and either noncoronary or left), sinuses of Valsalva, sinotubular junction, and proximal ascending aorta. This view is particularly useful for evaluating AI with CFD, systolic anterior motion of the MV, and proximal aortic pathologic conditions (eg, dissections, aneurysms). The same structures can be viewed from a different perspective in the *ME five-chamber* view at 0 to 20 degrees. Rotating the probe back to 90 to 120 degrees and advancing into the stomach to TG level develops the *TG LAX* view (see Fig. 14.12, Table 14.4, and Video 14.9). In this view, the LVOT and AV are oriented to the right and inferiorly in the displayed image, thereby providing an optimal window for parallel Doppler beam alignment for the assessment of flows and pressure gradients (aortic stenosis [AS], hypertrophic obstructive cardiomyopathy). Rotating the probe back farther to 0 to 20 degrees, advancing deep into the stomach, and anteflexing the tip so that it lies adjacent to the LV apex, allows for the development of the *deep TG LAX* view, now referred to as the *deep TG five-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.17), which also provides optimal Doppler beam alignment for measuring transaortic valve and LVOT flow velocities and may provide an additional window for assessing flows through muscular ventricular septal defects and LV apical pathologic conditions (thrombus, aneurysms).

Text continued on p. 454

TABLE 14.4 Comprehensive Intraoperative Multiplane Transesophageal Echocardiographic Examination

View	**Midesophageal Five-Chamber**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left ventricular outflow tract Left ventricle and atrium Right ventricle and atrium Mitral and tricuspid valves Interatrial and interventricle septa
Clinical utility	Ventricle function: global and regional Intracardiac chamber masses: thrombus, tumor, air; foreign bodies Mitral and tricuspid valve evaluation: pathologic and pathophysiologic conditions Congenital or acquired interatrial and ventral septal defects Hypertrophic obstructive cardiomyopathy evaluation Ventricular diastolic evaluation via transmitral and pulmonary vein Doppler-flow profile analysis Pericardial evaluation: pericarditis; pericardial effusion
View	**Midesophageal Four-Chamber**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left ventricle and atrium Right ventricle and atrium Mitral and tricuspid valves Interatrial and interventricle septa Left pulmonary veins Right pulmonary veins Coronary sinus
Clinical utility	Ventricle function: global and regional Intracardiac chamber masses: thrombus, tumor, air; foreign bodies Mitral and tricuspid valve evaluation: pathologic and pathophysiologic conditions Congenital or acquired interatrial and ventral septal defects Hypertrophic obstructive cardiomyopathy evaluation Ventricular diastolic evaluation via transmitral and pulmonary veins Doppler-flow profile analysis Pericardial evaluation: pericarditis; pericardial effusion Coronary sinus evaluation: coronary sinus catheter placement; dilation secondary to persistent left superior vena cava
View	**Midesophageal Mitral Commissural**
Multiplane angle range	60–70 degrees
Anatomy imaged	Left ventricle and atrium Mitral valve
Clinical utility	Left ventricle function: global and regional Left ventricle and atrial masses: thrombus, tumor, air; foreign bodies Mitral valve evaluation: pathologic and pathophysiologic conditions Ventricular diastolic evaluation via transmitral Doppler-flow profile analysis
View	**Midesophageal Two-Chamber**
Multiplane angle range	80–100 degrees
Anatomy imaged	Left ventricle, atrium, atrial appendage Mitral valve Left pulmonary veins Coronary sinus
Clinical utility	Left ventricle function: global and regional Left ventricle and atrial masses: thrombus, tumor, air; foreign bodies Mitral valve evaluation: pathologic and pathophysiologic conditions Ventricular diastolic evaluation via transmitral and pulmonary vein Doppler-flow profile analysis Coronary sinus evaluation: coronary sinus catheter placement; dilation secondary to persistent left superior vena cava
View	**Midesophageal Long Axis**
Multiplane angle range	120–160 degrees
Anatomy imaged	Left ventricle and atrium Left ventricular outflow tract Aortic valve Mitral valve Ascending aorta
Clinical utility	Left ventricle function: global and regional Left ventricle and atrial masses: thrombus, tumor, air; foreign bodies Mitral valve evaluation: pathologic and pathophysiologic conditions Ventricular diastolic evaluation via transmitral Doppler-flow profile analysis Aortic valve evaluation: pathologic and pathophysiologic conditions Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Hypertrophic obstructive cardiomyopathy evaluation
View	**Midesophageal Aortic Valve Long Axis**
Multiplane angle range	120–160 degrees
Anatomy imaged	Aortic valve Proximal ascending aorta Left ventricular outflow tract Mitral valve Right pulmonary artery
Clinical utility	Aortic valve: pathologic and pathophysiologic conditions Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Mitral valve evaluation: pathologic and pathophysiologic conditions

TABLE 14.4 Comprehensive Intraoperative Multiplane Transesophageal Echocardiographic Examination—cont'd

View	**Midesophageal Ascending Aorta Long Axis**
Multiplane angle range	100–150 degrees
Anatomy imaged	Ascending aorta Right pulmonary artery
Clinical utility	Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Anterograde cardioplegia delivery evaluation Pulmonary embolus, thrombus
View	**Midesophageal Ascending Aortic Short Axis**
Multiplane angle range	0–60 degrees
Anatomy imaged	Ascending aorta Superior vena cava (short axis) Main pulmonary artery Right pulmonary artery Left pulmonary artery Pulmonic valve
Clinical utility	Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Pulmonic valve: pathologic and pathophysiologic conditions Pulmonary embolus, thrombus evaluation Superior vena cava pathologic conditions: thrombus, sinus venosus atrial septal defect Pulmonary artery catheter placement
View	**Midesophageal Right Pulmonary Vein**
Multiplane angle range	0–30 degrees
Anatomy imaged	Mid-ascending aorta Superior vena cava Right pulmonary vein
Clinical utility	Ascending aorta dissection, aneurysm, plaque Superior vena cava thrombus Right pulmonary vein Doppler-flow velocity
View	**Midesophageal Aortic Valve Short Axis**
Multiplane angle range	30–60 degrees
Anatomy imaged	Aortic valve Interatrial septum Coronary ostia and arteries Right ventricular outflow tract Pulmonary valve
Clinical utility	Aortic valve: pathologic and pathophysiologic conditions Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Left and right atrial masses: thrombus, embolus, air, tumor, foreign bodies Congenital or acquired interatrial septal defects evaluation
View	**Midesophageal Right Ventricular Inflow-Outflow ("Wraparound")**
Multiplane angle range	60–90 degrees
Anatomy imaged	Right ventricle and atrium Left atrium Tricuspid valve Aortic valve Right ventricular outflow tract Pulmonic valve and main pulmonary artery
Clinical utility	Right ventricle and atrial masses and left atrial: thrombus, embolus, tumor, foreign bodies Pulmonic valve and subpulmonic valve: pathologic and pathophysiologic conditions Pulmonary artery catheter placement Tricuspid valve: pathologic and pathophysiologic conditions Aortic valve: pathologic and pathophysiologic conditions
View	**Midesophageal Modified Bicaval Tricupid Valve**
Multiplane angle range	50–70 degrees
Anatomy imaged	Right and left atria Superior vena cava (long axis) Inferior vena cava orifice Interatrial septum Right pulmonary veins Coronary sinus and thebesian valve Eustachian valve Tricuspid valve
Clinical utility	Right and left atrial masses: thrombus, embolus, air, tumor, foreign bodies Superior vena cava pathologic conditions: thrombus, sinus venosus atrial septal defect Inferior vena cava pathologic conditions: thrombus, tumor Femoral venous line placement Coronary sinus catheter line placement Right pulmonary vein evaluation: anomalous return, Doppler evaluation for left ventricular diastolic function Congenital or acquired interatrial septal defects evaluation Pericardial effusion evaluation Tricuspid valve evaluation for stenosis, regurgitation, and calculated estimation of pulmonary artery pressures from regurgitant Doppler-flow velocity profile

Continued

TABLE 14.4 Comprehensive Intraoperative Multiplane Transesophageal Echocardiographic Examination—cont'd

View	**Midesophageal Bicaval**
Multiplane angle range	80–110 degrees
Anatomy imaged	Right and left atria Superior vena cava (long axis) Inferior vena cava orifice: advance probe and turn to right to visualize inferior vena cava in the long axis, liver, hepatic and portal veins Interatrial septum Right pulmonary veins: turn probe to right Coronary sinus and thebesian valve Eustachian valve
Clinical utility	Right and left atrial masses: thrombus, embolus, air, tumor, foreign bodies Superior vena cava pathologic conditions: thrombus, sinus venosus atrial septal defect Inferior vena cava pathologic conditions: thrombus, tumor Femoral venous line placement Coronary sinus catheter line placement Right pulmonary vein evaluation: anomalous return, Doppler evaluation for left ventricular diastolic function Congenital or acquired interatrial septal defects evaluation Pericardial effusion evaluation
View	**Upper Esophageal Right and Left Pulmonary Veins**
Multiplane angle range	90–100 degrees
Anatomy imaged	Pulmonary veins Pulmonary artery Ascending aorta
Clinical utility	Pulmonary vein pathologic condition Ascending aortic aneurysm, dissection Pulmonary embolism, thrombus
View	**Midesophageal Left Atrial Appendage**
Multiplane angle range	90–110 degrees
Anatomy imaged	Left pulmonary veins Left atrial appendage
Clinical utility	Left pulmonary vein Doppler-flow velocity Left atrial appendage thrombus
View	**Midesophageal Ascending Aortic Short Axis**
Multiplane angle range	0–60 degrees
Anatomy imaged	Ascending aorta Superior vena cava (short axis) Main pulmonary artery Right pulmonary artery Left pulmonary artery Pulmonic valve
Clinical utility	Ascending aorta pathologic conditions: atherosclerosis, aneurysms, dissections
View	**Transgastric Basal Short Axis**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left and right ventricles Mitral valve Tricuspid valve
Clinical utility	Mitral valve evaluation ("fish-mouth view"): pathologic, pathophysiologic conditions Tricuspid valve evaluation: pathologic, pathophysiologic conditions Basal left ventricular regional function Basal right ventricular regional function
View	**Transgastric Midpapillary**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left and right ventricles Papillary muscles
Clinical utility	Mid left and right ventricular regional and global functions Intracardiac volume status
View	**Transgastric Apical Short Axis**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left and right ventricles
Clinical utility	Apical left and right ventricular regional functions Ventricular aneurysm
View	**Transgastric Right Ventricular Basal**
Multiplane angle range	0–20 degrees
Anatomy imaged	Left and right ventricle Right ventricular outflow tract Tricuspid valve (short axis) Pulmonic valve
Clinical utility	Left and right ventricular regional and global functions Intracardiac volume status Tricuspid valve pathologic condition Pulmonic valve regurgitation and stenosis evaluation

TABLE 14.4 Comprehensive Intraoperative Multiplane Transesophageal Echocardiographic Examination—cont'd

View	**Transgastric Right Ventricular Inflow-Outflow**
Multiplane angle range	60–90 degrees
Anatomy imaged	Right ventricle and right atrium Left atrium Tricuspid valve Aortic valve Right ventricular outflow tract Pulmonic valve and main pulmonary artery
Clinical utility	Right ventricle and atrial masses and left atrial: thrombus, embolus, tumor, foreign bodies Pulmonic valve and subpulmonic valve: pathologic, pathophysiologic conditions Pulmonary artery catheter placement Tricuspid valve: pathologic, pathophysiologic conditions Aortic valve: pathologic, pathophysiologic conditions
View	**Transgastric Two-Chamber**
Multiplane angle range	80–100 degrees
Anatomy imaged	Left ventricle and left atrium Mitral valve: chordae and papillary muscles Coronary sinus
Clinical utility	Left ventricular regional and global functions (including apex) Left ventricular and atrial masses: thrombus, embolus, air, tumor, foreign bodies Mitral valve: pathologic, pathophysiologic conditions
View	**Transgastric Right Ventricular Inflow**
Multiplane angle range	100–120 degrees
Anatomy imaged	Right ventricle and right atrium Tricuspid valve: chordae and papillary muscles
Clinical utility	Right ventricular regional and global functions Right ventricular and atrial masses: thrombus, embolus, tumor, foreign bodies Tricuspid valve: pathologic, pathophysiologic conditions
View	**Transgastric Long Axis**
Multiplane angle range	90–120 degrees
Anatomy imaged	Left ventricle and outflow tract Aortic valve Mitral valve
Clinical utility	Left ventricular regional and global functions Mitral valve: pathologic, pathophysiologic conditions Aortic valve: pathologic, pathophysiologic conditions
View	**Deep Transgastric Long Axis**
Multiplane angle range	0–20 degrees (anteflexion)
Anatomy imaged	Left ventricle and outflow tract Interventricular septum Aortic valve and ascending aorta Left atrium Mitral valve Right ventricle Pulmonic valve
Clinical utility	Aortic and subaortic valve: pathologic, pathophysiologic conditions Mitral valve: pathologic, pathophysiologic conditions Left and right ventricular global functions Left and right ventricular masses: thrombus, embolus, tumor, foreign bodies Congenital or acquired interventricular septal defect evaluation
View	**Upper Esophageal Aortic Arch: Long Axis**
Multiplane angle range	0 degrees
Anatomy imaged	Aortic arch; left brachiocephalic vein; left subclavian and carotid arteries; right brachiocephalic artery
Clinical utility	Ascending aorta and arch pathologic conditions: atherosclerosis, aneurysms, dissections; aortic cannulation site evaluation for cardiopulmonary bypass
View	**Upper Esophageal Aortic Arch: Short Axis**
Multiplane angle range	90 degrees
Structures imaged	Aortic arch; left brachiocephalic vein; left subclavian and carotid arteries; right brachiocephalic artery Main pulmonary artery and pulmonic valve
Clinical utility	Ascending aorta and arch pathologic conditions: atherosclerosis, aneurysms, dissections Pulmonary embolus; pulmonary valve evaluation (insufficiency, stenosis, Ross procedure); pulmonary artery catheter placement
View	**Descending Aorta Short Axis**
Multiplane angle range	0 degrees
Anatomy imaged	Descending thoracic aorta Left pleural space
Clinical utility	Descending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Intraaortic balloon placement evaluation Left pleural effusion
View	**Descending Aorta Long Axis**
Multiplane angle range	90–110 degrees
Anatomy imaged	Descending thoracic aorta Left pleural space
Clinical utility	Descending aorta pathologic conditions: atherosclerosis, aneurysms, dissections Intraaortic balloon placement evaluation Left pleural effusion

Tricuspid Valve

The echocardiographic evaluation of the TV requires a thorough assessment of its three leaflets (anterior, posterior, and septal), annulus, chordae tendinea, papillary muscles, and the corresponding RV walls. In the *ME five-chamber* view, the septal TV leaflet is displayed on the right side and the anterior leaflet is usually on the left side of the annulus. Advancing the probe slightly reveals the *ME four-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.2), with the septal TV leaflet on the right side and the posterior TV leaflet usually on the left side of the annulus. Rotating the multiplane angle to 50 to 70 degrees develops the *ME RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.10), which displays the posterior TV leaflet on the left side of the image and the anterior TV leaflet on the right side of the image adjacent to the AV. Slightly turning the probe rightward from the *ME bicaval* view permits the development of the newly recommended *ME-modified bicaval TV* view (see Fig. 14.12, Table 14.4, and Video 14.18) with the anterior leaflet on the right and the posterior leaflet on the left. The ME-modified bicaval view often provides better alignment of a CWD beam with a TR jet for estimating pulmonary artery pressures (PAPs). The *TG RV inflow* view (see Fig. 14.12, Table 14.4, and Video 14.13) is obtained by advancing the probe into the stomach and rotating to 100 to 120 degrees. This view is ideal for visualizing the chordae tendinea and papillary muscles in the right ventricle. Rotating back to the *TG mid-SAX* at 0 to 20 degrees and slightly withdrawing the probe to obtain the *TG RV basal* view provides a cross-sectional, SAX view of the TV, displaying the anterior leaflet in the far field, the posterior leaflet to the left in the near field, and the septal leaflet on the right side of the image. A more extensive quantitative analysis of TV pathophysiologic condition requires the use of Doppler echocardiography (PWD, CWD, and CFD) by aligning the beam parallel to transtricuspid flow in the *ME four-chamber* view, *ME RV inflow-outflow* view, or *ME-modified bicaval* view.

Pulmonic Valve and Pulmonary Artery

The PV is a trileaflet, semilunar valve. The *ME AV SAX* view (see Fig. 14.12, Table 14.4, and Video 14.15) displays the transition between the RVOT and PV. Rotating the probe back toward 0 degrees and withdrawing slightly develops the *ME ascending aortic SAX* view (see Fig. 14.12, Table 14.4, and Video 14.19) displaying the transition between the PV and the main PA and its bifurcation. Although the right PA is usually easy to visualize by turning the probe to the right, the left PA is often obscured by the interposing, air-filled, left mainstem bronchus. This view can be used in the Doppler echocardiographic assessment of a PV pathophysiologic condition because of the parallel alignment of the beam relative to the flow and can also be used to locate pulmonary emboli. The *ME RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.10) can also be used to assess the PV and main PA, which lie on the right side of the image adjacent to the AV, although the newly recommended *TG RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.11) with the PV on the right side of the screen and the more reliable *upper esophageal (UE) aortic arch SAX* view (see Fig. 14.12, Table 14.4, and Video 14.20), which displays the PV oriented to the left of the cross-sectional view of the aortic arch and usually provides a more parallel Doppler beam orientation through for the evaluation of pulmonic regurgitation or stenosis. Withdrawing the probe slightly in the *deep TG five-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.17), in combination with slight anteflexion and turning to the right, can often allow visualization of the RVOT and PV to the left in the far field and provide an alternative imaging plane for Doppler echocardiographic evaluation in patients with subpulmonic and PV pathologic conditions.

Left Atrium, Left Atrial Appendage, Pulmonary Veins, and Atrial Septum

The left atrium is the closest cardiac structure to the TEE probe when positioned in the esophagus. Consequently, the left atrium is usually easily displayed in the superior aspect of the 2D image sector. The *ME five-chamber* and *four-chamber* views (see Fig. 14.12, Table 14.4, and Videos 14.1 and 14.2) display the left atrium almost in its entirety with the LAA oriented to its superior and lateral aspects when the probe is slightly withdrawn. The muscular ridges of the pectinate muscles within the LAA should not be confused with thrombi. A slightly farther withdrawal of the probe, turning it to the left, and rotating the array to approximately 90 degrees, develops the newly defined *UE left pulmonary vein view* (see Fig. 14.12, Table 14.4, and Video 14.21), which allows the left upper pulmonary vein (LUPV) to be imaged as it enters the left atrium from the anterior-to-posterior direction and separated from the lateral border of the LAA by the *warfarin ridge*. In contrast with the LUPV, which is usually optimally aligned for parallel Doppler beam alignment, the left lower pulmonary vein (LLPV) enters the left atrium just below the LUPV in a lateral-to-medial direction and is more perpendicularly aligned. Pulmonary venous Doppler-flow velocity profiles are useful for the qualitative and quantitative assessment of LV diastolic function. Turning the probe to the right at this depth reveals the newly defined *UE right pulmonary* view (see Fig. 14.12, Table 14.4, and Video 14.21), and a slight advancement and rotation of the array to 0 degrees permits visualization of the newly defined *ME right pulmonary vein* view (see Fig. 14.12, Table 14.4, and Video 14.22), which both reveal the right upper pulmonary vein (RUPV) entering the left atrium in an anterior-to-posterior direction and the right PA or superior vena cava (SVC), respectively. The right lower pulmonary vein (RLPV) can sometimes be visualized as it enters perpendicular to the LAX of the left atrium by slightly advancing the probe. The interatrial septum (IAS), consisting of thicker limbus regions flanking the thin fossa ovalis, can also be imaged in the *ME four-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.2). Benign lipomatous hypertrophy of the IAS must be distinguished from pathologic lesions such as atrial myxomas. The patency of the IAS and the presence of a PFO or congenital atrial septal defects (ASDs) should be assessed with Doppler echocardiography and intravenous injections of agitated saline. Advancing and rotating the probe to 80 to 100 degrees develops the *ME two-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.3), which allows for further imaging of the left atrium from left to right. The LAA and LUPV can be seen by turning the probe slightly to the left to develop the newly defined *ME LAA* view (see Fig. 14.12, Table 14.4, and Video 14.23). Rotating the probe to the right at this level and adjusting the multiplane angle to 80 to 110 degrees will develop the *ME bicaval* view (Fig. 14.12 and Table 14.4; see Video 14.24), which delineates the SVC entering the RA to the right of the image and the inferior vena cava (IVC) entering from the left. The IAS can be seen in the middle of the image separating the left and right atria. The RUPV and the RLPV can usually be seen if the probe is turned farther to the right just beyond the point at which the LAX of the SVC can no longer be visualized. This transition of images can also be used in conjunction with Doppler echocardiography to identify sinus venosus ASDs and anomalous pulmonary venous return.

Right Atrium and Coronary Sinus

The RA can be most easily visualized in the *ME five-chamber* and *ME four-chamber* views (see Fig. 14.12, Table 14.4, and Videos 14.1 and 14.2) by turning the probe to the patient's right side, as well as in the *ME RV inflow-outflow* view (see Fig. 14.12, Table 14.4, and Video 14.10). In these views, the entire RA can be visualized for size, overall function, and the presence of masses (thrombi, tumors). Rotating the multiplane angle to 80 to 110 degrees develops the *ME bicaval* view (see Fig. 14.12, Table 14.4, and Video 14.24), which displays the RA and its internal structures (Eustachian valve, Chiari network, crista terminalis). The SVC can be imaged entering the RA on the right, superior to the right atrial appendage, and the IVC enters the RA on the left of the display. Advancing and turning the probe to the right will allow for a qualitative evaluation of the intrahepatic segment of the IVC and hepatic veins. At the TG depth, both the *TG RV inflow-outflow* and *TG RV inflow* views may provide more optimal imaging windows for visualizing the RA and collateral structures. Pacemaker electrodes and central venous catheters for hemodynamic monitoring or CPB can be easily imaged in this view.

The CS lies posteriorly in the atrioventricular groove, emptying into the RA at the inferior extent of the atrial septum. The CS can be viewed in LAX entering the RA just superior to the tricuspid annulus by advancing and slightly retroflexing the probe from *ME four-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.2). The CS can be imaged cross sectionally in the SAX in the *ME two-chamber* view (see Fig. 14.12, Table 14.4, and Video 14.3) in the upper left of the display. Turning the probe to the left in this view often allows visualization of the CS in the LAX as it traverses the atrioventricular groove. The CS and thebesian valve can also be visualized in the *ME-modified bicaval* view (see Fig. 14.12, Table 14.4, and Video 14.18) on the upper left of the image as it enters the RA at an obtuse angle. Echocardiographic visualization of the CS can be useful for directing the placement of CS catheters used for CPB.

Thoracic Aorta

The proximal and midascending thoracic aorta can be visualized in the SAX in the *ME ascending aortic SAX* view (see Fig. 14.12, Table 14.4, and Video 14.19). Advancing and withdrawing the probe should enable visualization of the thoracic aorta from the sinotubular junction to a point 4- to 6-cm superior to the AV and allow an inspection for aneurysms and dissections. Rotating the multiplane angle to 100 to 150 degrees develops the *ME ascending aortic LAX* view (see Fig. 14.12, Table 14.4, and Video 14.25), which optimally displays the parallel anterior and posterior walls for measuring proximal and midascending aortic diameters. This display can also be obtained from the *ME AV LAX* view (see Table 14.4, Fig. 14.6, and Video 14.6) by slightly withdrawing and turning the probe to the left.

TEE imaging of the aortic arch is often obscured by the interposing, air-filled trachea. The most optimal views of the aortic arch are obtained by withdrawing the probe from the *ME ascending aortic SAX* view at 0 degrees (see Fig. 14.12, Table 14.4, and Video 14.19) and rotating to the left to obtain the *UE aortic arch LAX* view (see Fig. 14.12, Table 14.4, and Video 14.26), which displays the proximal arch followed by the mid-arch, the great vessels (brachiocephalic, left carotid artery, and left subclavian artery), and the distal arch before it joins the proximal descending thoracic aorta imaged in cross section. Alternatively, rotating the probe to 90 degrees develops the *UE aortic arch SAX* view (see Fig. 14.12, Table 14.4, and Video 14.20). Turning the probe to the left in this view delineates the transition of the distal arch with the proximal descending thoracic aorta. Turning the probe to the right and slightly withdrawing it will allow for the mid-arch and great vessels to be imaged on the right side of the screen, followed by the distal ascending aorta when the probe is subsequently advanced and rotated forward to the 120-degree *ME ascending aortic LAX* view (see Fig. 14.12, Table 14.4, and Video 14.25). Epiaortic aortic scanning may be particularly useful for assessing the extent of ascending aortic and arch pathologic conditions (ie, aneurysms, dissection, atherosclerosis) to determine cross-clamping and cannulation sites for CPB.

A SAX image of the descending thoracic aorta is obtained by turning the probe leftward from the *ME four-chamber* view to produce the *descending aortic SAX* view (see Fig. 14.12, Table 14.4, and Video 14.27). Rotating the multiplane angle of the probe from 0 to 90 to 110 degrees produces an LAX image, the *descending aortic LAX* view (see Fig. 14.12, Table 14.4, and Video 14.28). The descending thoracic aorta should be interrogated in its entirety, beginning at the distal aortic arch, by continually advancing the probe and turning slightly to the left until the celiac and superior mesenteric arteries are visualized branching tangentially from the anterior surface of abdominal aorta when the probe is in the stomach. A thorough examination of the descending thoracic aorta may be necessary to evaluate the distal extent of an aneurysm or dissection. In addition, the *descending aortic SAX* and *LAX* views can be useful for confirming appropriate intraaortic balloon positioning.

Anatomic Variants and Artifacts

Anatomic variants may be confused as pathologic conditions. Ultrasound-based artifacts are imaging defects related to the physics of ultrasound, leading to the generation or alteration of structures.

Anatomic Variants

Right Atrium

The RA is a common source of normal anatomic variations; many of these structures are embryologic remnants, which may be confused with thrombi or masses. The Eustachian valve is formed in utero and directs oxygenated blood from the IVC toward the PFO. If this structure fails to regress into adulthood, then it can be most commonly visualized in an ME bicaval view as a variable-length, thin structure emanating from the junction of the IVC and RA (see Fig. 14.14 and Video 14.29). Although the Eustachian valve may be misinterpreted as a thrombus, it may be a source of infective endocarditis or associated with increased incidence of a PFO.[72,73] A sinus venosus remnant also emanating from the IVC-RA junction is the Chiari network (see Fig. 14.15 and Video 14.30). In contrast with the Eustachian valve, the Chiari network is a highly mobile and fenestrated structure and is strongly associated with a PFO and atrial septal aneurysms.[72]

The crista terminalis is a fibromuscular ridge located at the SVC-RA junction, separating the smooth posterior from the anterior trabeculated RA segment including the RA appendage; this structure may be seen best in the ME bicaval view (see Fig. 14.16 and Video 14.31). This ridge of tissue may vary in size. When the crista terminalis is large, it may appear as a pedunculated mass and misinterpreted as a thrombus or tumor. Lipomatous hypertrophy of the IAS may be appreciated in the ME bicaval view (see Fig. 14.17 and Video 14.32). This lipomatous hypertrophy is a collection of adipose tissue in the IAS that spares the thin fossa ovalis (septum primum), creating a classical "dumb-bell" shape. The enlarged septum may be misdiagnosed as a cardiac tumor such as an atrial myxoma. Another cause of enlarged atrial septum is hematoma infiltrating the fibrous skeleton of the heart after valvular surgery.

The ME-modified bicaval view is often used to identify the CS on the left side of the screen and is particularly useful for CS catheter placement. Some patients may possess a small valve called the thebesian valve that allows blood returning from the coronary venous circulation to enter the RA (see Fig. 14.18 and Video 14.33). This valve may interfere with the placement of the CS retrograde cardioplegia catheters.

A persistent left superior vena cava (PLSVC) is a congenital anomaly of the thoracic venous system. Instead of drainage into the left innominate vein and subsequently into the right SVC, the left arm and neck drain into a PLSVC with continuation into the CS. This variation may

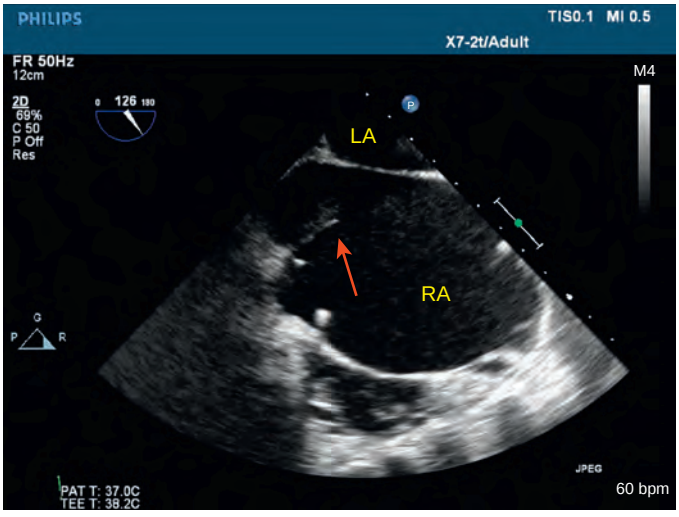


Fig. 14.14 Midesophageal bicaval view. The *red arrow* indicates a Eustachian valve in a patient with severe right atrial enlargement. *LA*, Left atrium; *RA*, right atrium. (Video clip available online.)

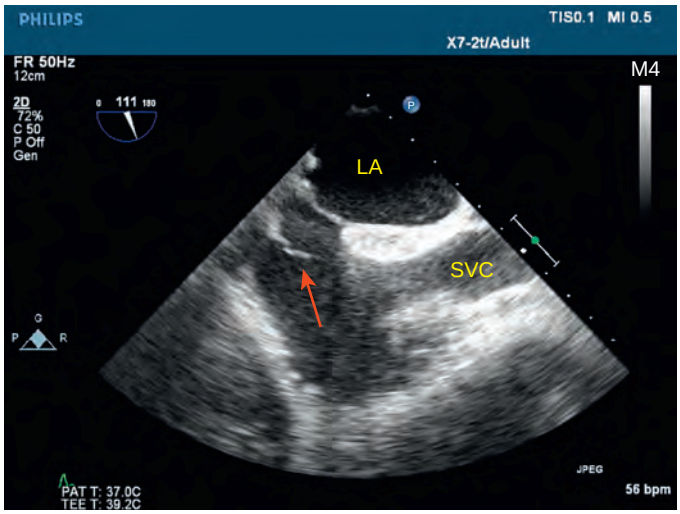


Fig. 14.15 Midesophageal bicaval view with a *red arrow* indicating a Chiari network, which is thin and undulating, compared with a relatively rigid Eustachian valve. *LA,* Left atrium; *SVC,* superior vena cava. (Video clip available online.)

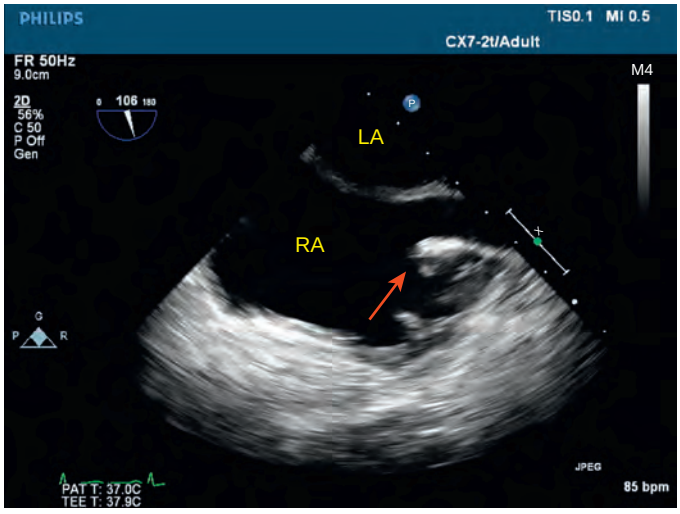


Fig. 14.16 Midesophageal bicaval view. The *red arrow* indicates a prominent crista terminalis separating the superior vena cava from the right atrial appendage. *LA,* Left atrium; *RA,* right atrium. (Video clip available online.)

be suspected echocardiographically as a dilated CS entering the RA (see Fig. 14.19 and Video 14.34). In this setting, the CS often measures greater than 1 centimeter in diameter. In an ME four-chamber view, the dilated CS may be observed to the right of the left atrium. Diagnosis of a PLSVC may be confirmed via contrast (agitated saline) injection into a left arm vein.[74]

Right Ventricle

The right ventricle, similar to the right atrium, has a smooth inflow and a trabeculated free wall and apex. When hypertrophied, the trabeculations may become large and confused with thrombus. In addition to the trabeculations, several muscular bands encircle the right ventricle. The moderator band is most prominent and is easily identified echocardiographically in multiple RV views (see Fig. 14.20 and Video 14.35). This muscular band, which contains the right bundle branch, connects the RV free wall to the interventricular septum (IVS) and may be identified in the four-chamber view as a muscular structure attached to either the RV free wall or septum.[75]

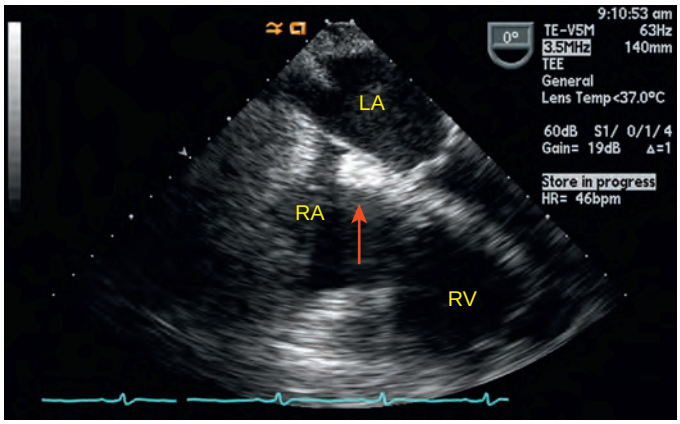


Fig. 14.17 Midesophageal 4-chamber view with slight probe rotation to the right. The *red arrow* indicates the lipomatous hypertrophy of the interatrial septum. Note the fossa ovalis remains thin without any lipomatous infiltration. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle. (Video clip available online.)

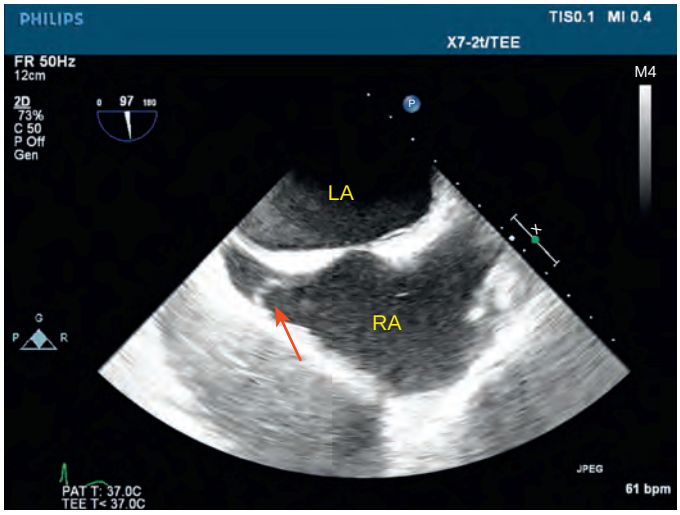


Fig. 14.18 Modified-midesophageal bicaval view with the coronary sinus in view on the left side of the image. The *red arrow* indicates a prominent thebesian valve at the coronary sinus ostium. *LA,* Left atrium; *RA,* right atrium. (Video clip available online.)

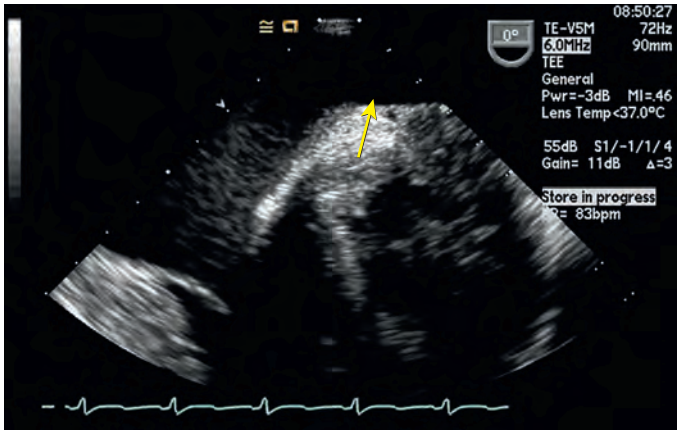


Fig. 14.19 Left inferior vena cava. A large coronary sinus is visualized emptying into the right atrium. (Video clip available online.)

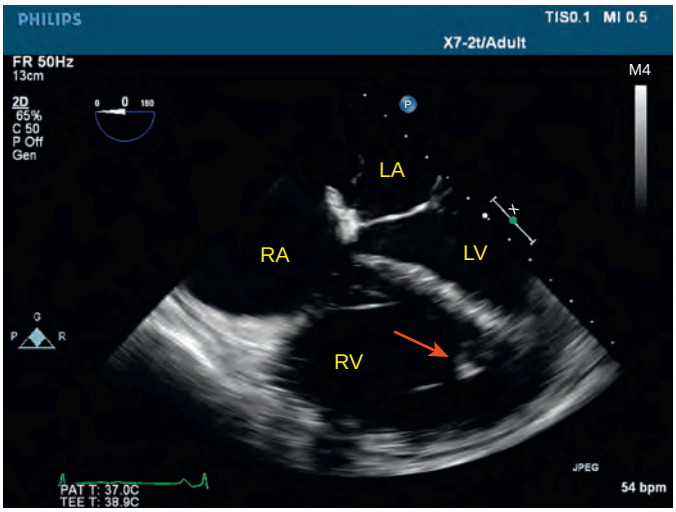


Fig. 14.20 Midesophageal four-chamber view in a patient with severe pulmonary hypertension, a dilated and dysfunctional right atrium (*RA*) and right ventricle (*RV*). The *red arrow* indicates a prominent moderator band. *LA*, Left atrium; *LV*, left ventricle. (Video clip available online.)

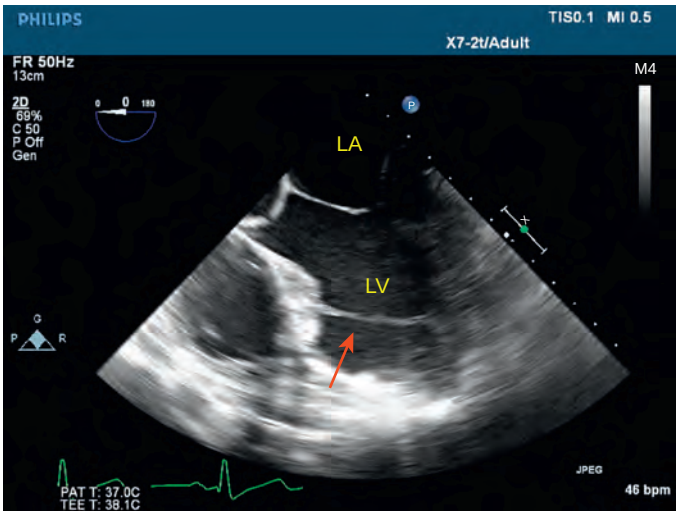


Fig. 14.22 Midesophageal five-chamber view. The *red arrow* demonstrates a false tendon in the left ventricle *(LV)*. *LA*, Left atrium. (Video clip available online.)

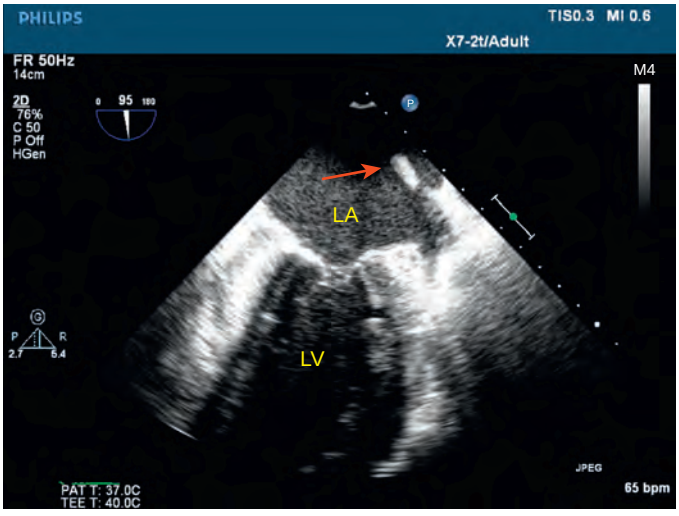


Fig. 14.21 Midesophageal two-chamber view. The *red arrow* indicates the ligament of Marshall, commonly known as the *Coumadin ridge*. This structure separates the left upper pulmonary vein above from the left atrial appendage below. *LA*, Left atrium; *LV*, left ventricle. (Video clip available online.)

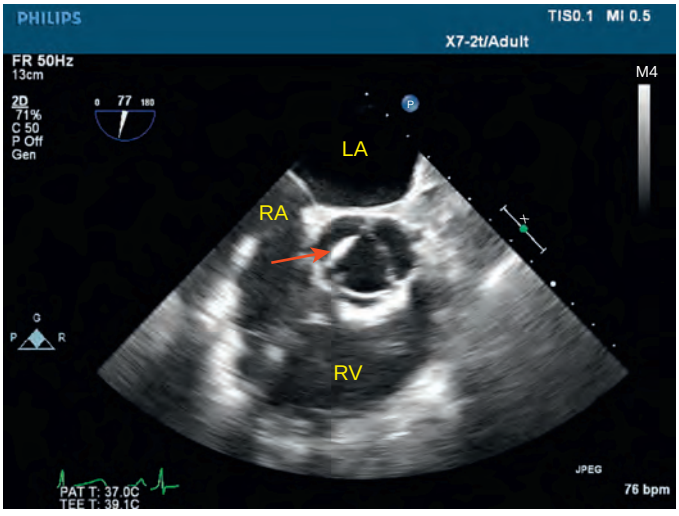


Fig. 14.23 Midesophageal aortic valve short-axis view. The *red arrow* indicates the thickened portion of the noncoronary cusp of the aortic valve that constitutes the nodule of Arantius. *LA*, Left atrium; *RA*, right atrium; *RV*, right ventricle. (Video clip available online.)

Left Atrium

The left superior pulmonary vein is separated from the LAA by a small ridge of tissue commonly visualized in the ME two-chamber view (see Fig. 14.21 and Video 14.36). This ridge, termed the *ligament of Marshall*, is commonly known as the *Coumadin ridge* because of its history of being misdiagnosed as an atrial clot with subsequent inappropriate use of anticoagulation therapy. Its appearance echocardiographically is variable but may extend into the left atrium and be confused with an atrial thrombus.

Left Ventricle

Although smoother than the RV endocardial surface, the left ventricle is also trabeculated. With hypertrophy, these trabeculations may be mistaken for intracavitary thrombus. Although less commonly identified and finer in size, the left ventricle may have intracavitary bands similar to the moderator band of the right ventricle. These bands, termed *false tendons*, typically have little clinical significance and are often identified near the apex of the left ventricle in an *ME four-chamber* view (see Fig. 14.22 and Video 14.37).

Aortic Valve

A few normal AV anatomic variants may lead to misdiagnoses of endocarditis, cardiac masses, or thrombus. Nodules of Arantius may be identified as thickened central areas on the AV leaflets (see Fig. 14.23 and Video 14.38). Although clinically insignificant, they may become hypertrophied and confused with cardiac masses. Lambl excrescences are thin projections of fibrous tissue that are covered by a layer of endothelial cells, extending most commonly from the AV and identified echocardiographically upon valve closure (see Fig. 14.24 and Video 14.39). In an ME AV LAX view, they are most often identified as thin mobile structures, extending into the aortic lumen from the AV leaflets. They are clinically insignificant; however, they may rarely develop larger *fronds* that may embolize and create clinically significant cerebral sequelae that requires anticoagulation or resection.[76] Papillary

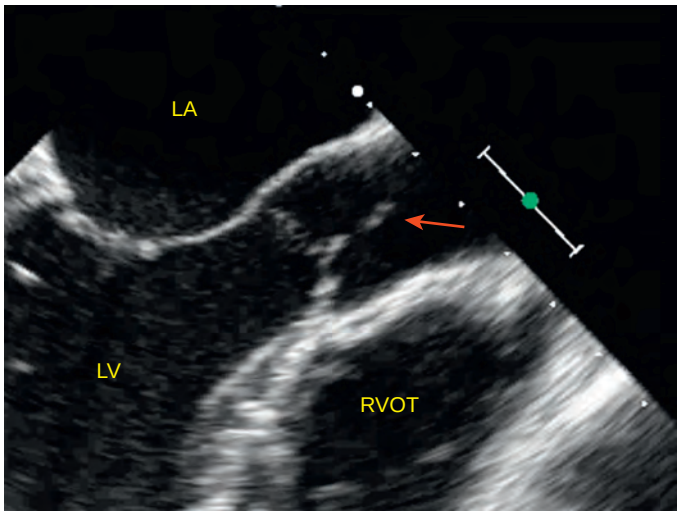


Fig. 14.24 Midesophageal long-axis view. The *red arrow* indicates a Lambl excrescence, the long filamentous mobile structure emanating from the aortic valve closure. *LA,* Left atrium; *LV,* left ventricle; *RVOT,* right ventricular outflow tract. (Video clip available online.)

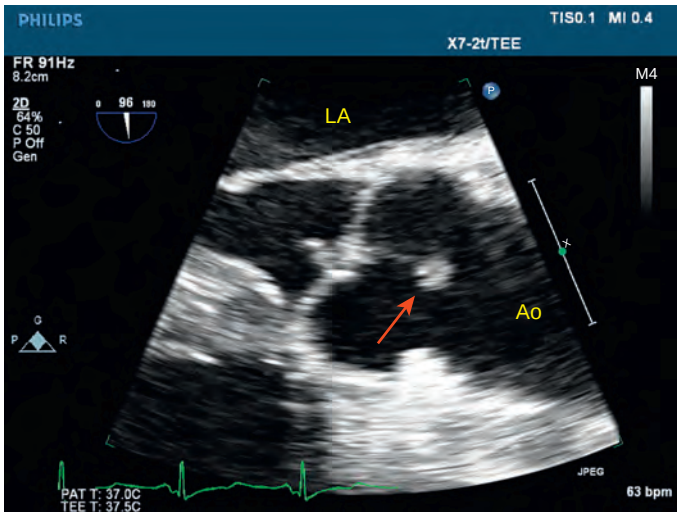


Fig. 14.25 Midesophageal aortic valve long-axis view. The *red arrow* indicates a papillary fibroelastoma, a pedunculated and mobile mass attached to the aortic valve. *LA,* Left atrium; *Ao,* ascending aorta. (Video clip available online.)

fibroelastomas, benign tumors, are thicker or larger than Lambl excrescences and carry a significantly higher rate of thromboembolism. These mobile pedunculated masses are also often identified along the line of valve closure; however, they are identified as a mass on a *stalk,* as opposed to the linear adherent structure of a Lambl excrescence (see Fig. 14.25 and Video 14.40). As a result of an increased embolism risk, they require surgical resection.[77] Finally, if the AV cups are imaged en face, the normally thin aortic cusp may appear as a mass on the valve attributable to this imaging artifact (see Fig. 14.26 and Video 14.41).[78]

Pericardium

The pericardium is a saclike structure that surrounds the cardiac structures, as well as the great vessels entering and leaving the heart. The pericardium has areas of reflections where it is folded on itself, creating sinuses. Generally, this is not apparent echocardiographically until a small amount of pericardial fluid collects, creating an echo-free space within the reflections. The transverse sinus is located posterior to the ascending aorta and anterior to the left atrium, most commonly

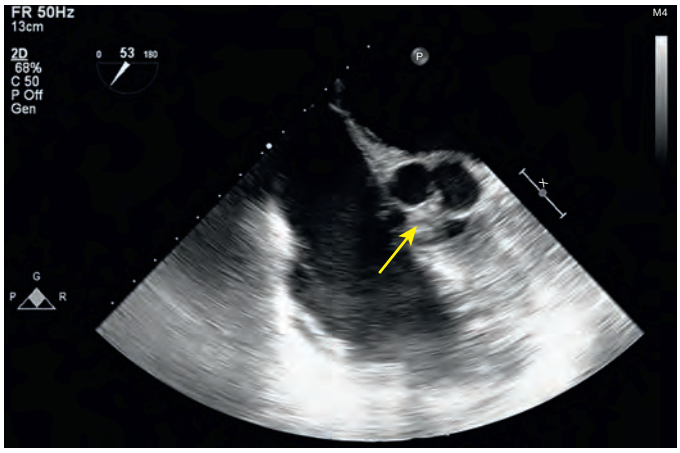


Fig. 14.26 Midesophageal aortic valve short-axis (off angle) view. The right coronary cusp of the aortic valve *(yellow arrow)* is imaged en face, so it appears as a mass. Other views through the aortic valve are normal.

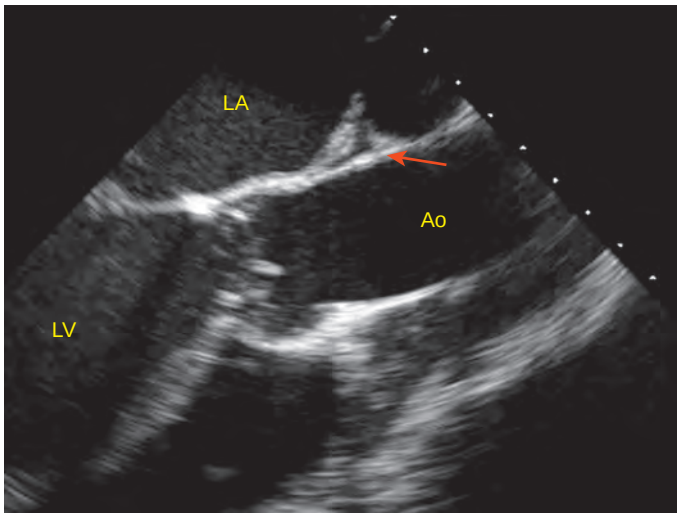


Fig. 14.27 Midesophageal long-axis view. The *red arrow* indicates the transverse sinus, a small echolucent area between the ascending aorta and the left atrium *(LA)* in a patient with a trivial pericardial effusion. *LV,* Left ventricle; *Ao,* ascending aorta. (Video clip available online.)

identified in the ME LAX view as an echolucent area and occasionally containing some fat pieces (see Fig. 14.27 and Video 14.42). The echolucent area may be confused with a cardiac abscess. Another pericardial reflection, the oblique sinus, may be observed when pericardial fluid collects, leading to an echocardiographic lucent area posterior to the left atrium and pulmonary veins.

Imaging Artifacts

Imaging artifacts may result in brightness errors or factual errors. Acoustic shadowing results in a loss of ultrasound energy with a resultant dark image distant to the object that is causing the shadowing. Acoustic impedance is a function of the density of tissue and the speed of ultrasound in that tissue; the greater the difference in the acoustic impedance, the greater the reflected signals. Acoustic shadowing occurs when a large difference in acoustic impedance at a given interface occurs. When ultrasound reaches structures with an acoustic impedance significantly different than water (eg, calcium prosthetic valves, air), a large amount of ultrasound is reflected back toward the ultrasound probe, leaving little to no ultrasound to penetrate deeper structures (see Fig. 14.28 and Video 14.43). The result is a highly echogenic structure with echolucent shadows distant to the structure. Alternate views must be used to image the shadowed structure. Attenuation

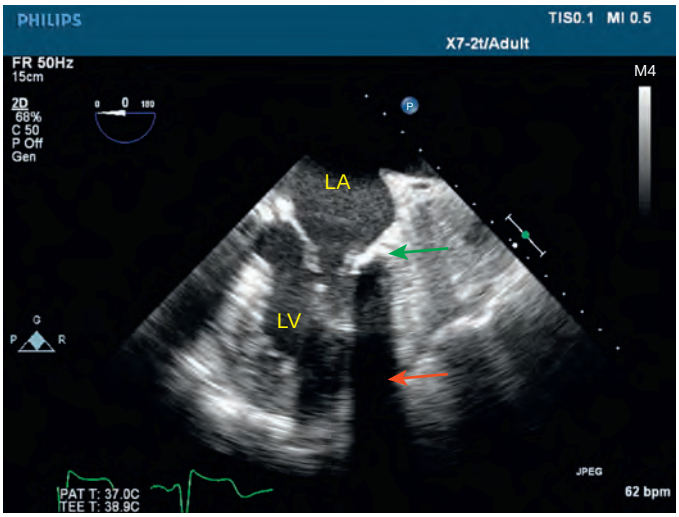


Fig. 14.28 Midesophageal five-chamber view with slight left probe rotation. The *green arrow* indicates a heavily calcified posterior leaflet of the mitral valve, whereas the *red arrow* indicates the area of distal acoustic shadowing, secondary to the more proximal highly reflective calcium. *LA,* Left atrium; *LV,* left ventricle. (Video clip available online.)

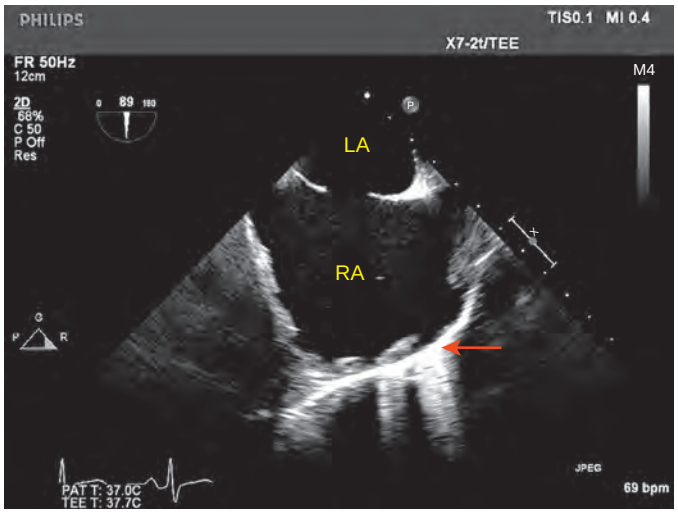


Fig. 14.29 Midesophageal bicaval view of a patient with a secundum atrial septal defect. The large right atrium allows more ultrasound energy to penetrate deeper, causing enhancement of the deeper pericardium *(red arrow). LA,* Left atrium; *RA,* right atrium. (Video clip available online.)

refers to the loss of ultrasound energy with resultant darker images. As ultrasound energy propagates, some of the energy will be lost from reflection, absorption, or refraction and not available for reflection back to the ultrasound probe. This attenuation results in objects that are more distant from the probe becoming progressively darker. The degree of attenuation may be controlled by adjusting the ultrasound frequency. Although lower frequencies result in a lower resolution, attenuation is also decreased, allowing for insonation of more distant structures.

To produce ultrasound signals, the piezoelectric crystals vibrate at a high frequency. Although the vibrations of the crystals are a necessary component of ultrasound wave generation, they may interfere with image formation close to the transducer, resulting in near-field clutter. This artifact is commonly seen during epiaortic ultrasonography when a phase-array probe is held on the anterior surface of the ascending aorta. The near-field clutter limits the anterior wall imaging. This clutter may be eliminated by using an echolucent spacer between the transducer and the object of interest; as a result, the objects are physically removed from the very near field of the transducer.

Alternatively, other imaging artifacts may result in bright images. If a superficial structure is either a weak reflector or has reduced attenuation, then ultrasound energy will not be reflected back to the transducer; therefore more ultrasound energy is available for more distant structures. This increased energy availability results in a bright display of deeper structures (Fig. 14.29; see Video 14.44). Gain or TGC may be used to optimize the image. Noise plays a role in ultrasound imaging. Excessive gain settings not only increase the brightness of the returning signals but also the brightness of any noise in the system. This amplification of returning noise leads to excessive areas of brightness where little to no signal is expected (Fig. 14.30; see Video 14.45). Electrocautery is another common source of noise in the surgical unit.

Ultrasonic imaging requires a direct line of propagation to and from the target. The depth of the target is determined by the time it takes for the ultrasound signal to return to the ultrasound transducer. A strong specular reflector, such as a prosthetic valve, may cause some ultrasound to reflect at an angle, rather than back toward the probe. If the ultrasound subsequently reflects off another object and then toward the ultrasound probe, then an artifact will be displayed. Termed *multipath*, the increased time to reflect back to the ultrasound probe will be interpreted by the machine as being along the same path as the first target, however deeper in position (Fig. 14.31). This imaging

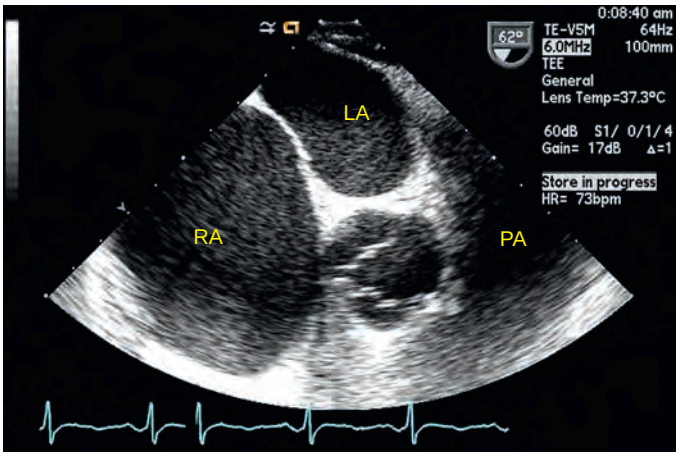


Fig. 14.30 Midesophageal right ventricular inflow-outflow view of patient with severe right atrial enlargement. Note the excessive gain, causing a "washed-out" appearance of myocardial tissue, as well as echogenicity of blood-filled chambers that should typically be echolucent. This artifact can cause the misdiagnosis of spontaneous echocardiographic contrast and the risk of thrombus formation. *LA,* Left atrium; *PA,* pulmonary artery; *RA,* right atrium. (Video clip available online.)

artifact therefore produces an artifactual area of echogenicity that is not truly present.

If a pencil is inserted into a cup of water and viewed at an oblique angle, then it will appear bent because of light refraction. Ultrasound refraction is similar to multipath; however, the ultrasound beam bends when passing through an object at an oblique angle. If this refracted ultrasound reflects off another object and returns to the probe, then the ultrasound machine will display the object as if it were along the originally delivered ultrasound pathway (Fig. 14.32).

When a structure is imaged, the ultrasound pulse is reflected once by the structure back to the ultrasound probe. Reverberation, ringing, and mirror artifact occur when the ultrasound is trapped, causing a to-and-fro reflection within the object. If the object is thin, such as bronchial rings or aortic calcifications, then the trap will be thin and the back-and-forth reflection will result in multiple reflections returning to the ultrasound probe. These multiple reflections, termed *ringing*, will appear as a bright flashlight artifact extending from the structure

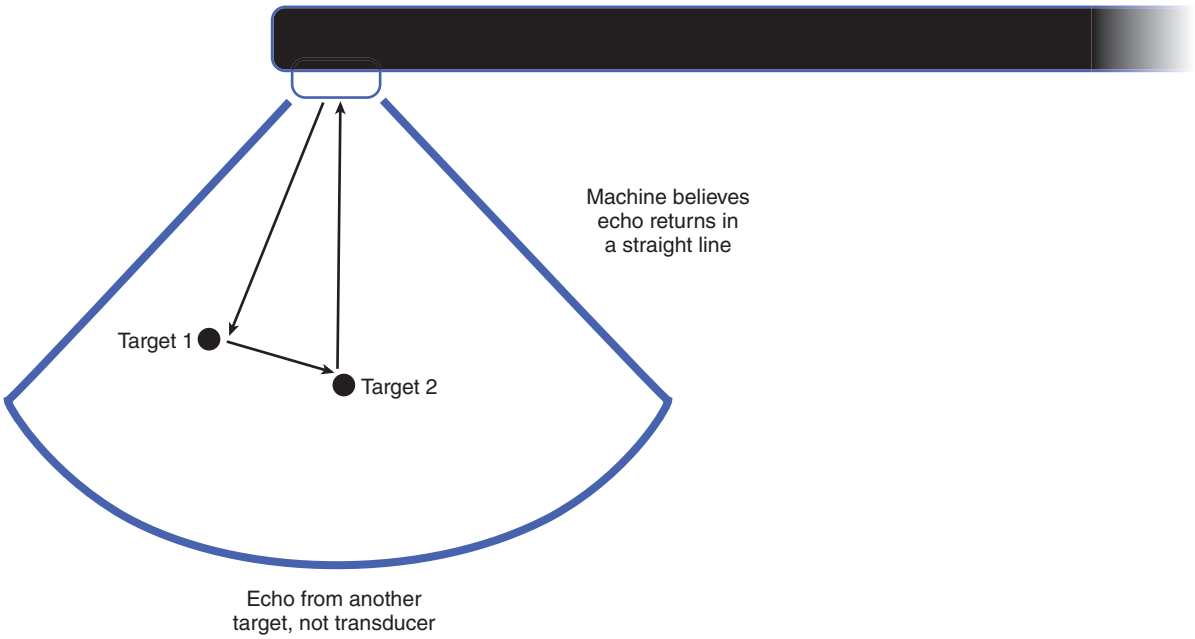


Fig. 14.31 Multipath artifacts involve ultrasound energy reflecting between two objects before returning to the ultrasound probe. The delay in the ultrasound returning to the machine causes the software to interpret and display the reflected energy deeper along the initial ultrasound path.

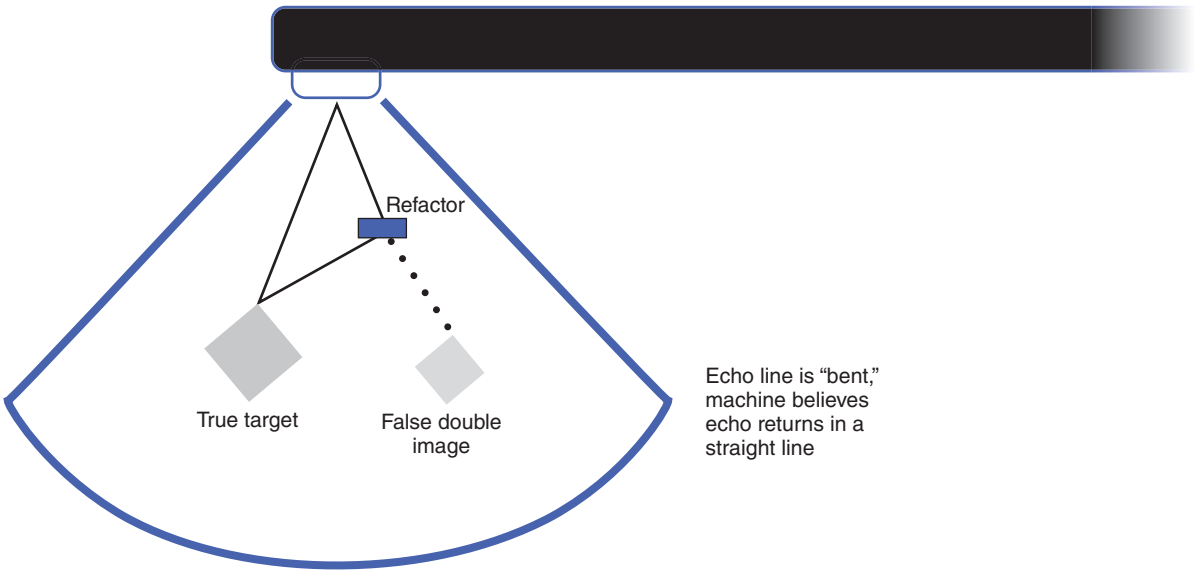


Fig. 14.32 Refraction artifacts involve ultrasound waves being bent as they are transmitted through the object at an oblique angle. In this example, some of the off-axis ultrasound energy is refracted toward the probe, leading to the generation of an artifact image along another angled pathway.

with impairment of imaging deeper to the structure (Fig. 14.33; see Video 14.46). If the trap is larger, such as the two sides of the aortic wall, then the ringing between the walls delays the ultrasound returning to the probe, yielding a second image of the aortic walls distal to the first returned signals. Termed *mirror artifact*, the displayed image will contain a duplicate structure distal to the properly displayed structure, such as a "double-barrel aorta" (Fig. 14.34). In addition to the anatomic structures, the surface of the ultrasound probe itself may act as a trap, creating both ringing and mirror artifacts.

The ultrasound machine software assumes that the transmitted and reflected ultrasound waves are propagated linearly and originate from the center of the probe. This assumption is not entirely true. The ultrasound signal is actually emitted as multiple radiation lobes at various angles from the probe's aperture with the energy summed in constructive and destructive patterns. The main beam contains the largest constructive pattern with decreasing intensity in the side lobes with increased angle of production; therefore most of the imaging occurs from the stronger central main lobe (Fig. 14.35). A strong reflector in the territory of the weaker side lobe may return to the probe; however, the software will inappropriately display the structure within the intended main lobe display area, which is termed *side-lobe artifact*. These side-lobe artifacts often occur within a generally echolucent area. For example, a side-lobe artifact of a central venous catheter may be displayed within the echolucent ascending aorta and misinterpreted as an aortic dissection. As the beam oscillates to display a single frame, multiple side-lobe artifacts may yield an imaging artifact with a curved

appearance (Fig. 14.36). Grating lobes are a type of side lobe when the ultrasound elements are spaced larger than one half of the wavelength, leading to larger angular lobes. This artifact is not usually encountered because ultrasound manufacturers ensure the spacing is appropriate for the typical wavelengths used.

An object may appear in an incorrect location because of range ambiguity. After initiating an ultrasound pulse, the machine spends time "listening" for the returning ultrasound signal. If a prior ultrasound signal returns from a deep structure while listening from a subsequent ultrasound pulse, then the signal may be interpreted as being in a significantly more shallow location (Fig. 14.37).

Clinical Applications

Left Ventricular Assessment

Assessment of Left Ventricular Size

Measurements of LV size may be performed using M-mode or 2D or 3D measurements[79] (Table 14.5). When performing measurements of internal linear diameters, measurements should be taken perpendicular to the LV LAX at or immediately below the level of the MV leaflet tips. M-mode measurements allow for a high temporal resolution that provides reproducible measurements; however, measurements may only be performed in a single axis and are commonly off axis. Two-dimensional measurements of ventricular diameter provide additional information concerning axis alignment, thereby increasing the accuracy of the measurements. This 2D measurement is only representative if the left ventricle is normally shaped.

Early in the development of echocardiography, Feigenbaum and colleagues[80] compared echocardiographic and angiographic volumes to show that M-mode echocardiographic measurements were related to actual ventricular size by cubing single M-mode echocardiographic dimensions and comparing them with their angiographic equivalents. Although reasonably good correlations were obtained, they never intended to use M-mode ventricular diameters for the actual, clinical measurements of ventricular volumes.

LV volume measurements may be with biplane disk summary or area-length measurements using 2D echocardiography or using 3D data sets. Because volume estimations of LV volume from linear measurements assume a fixed geometry LV shape, volume calculations from linear measurements (such as the Teichholz and Quinones methods) are no longer recommended for clinical use in the 2015 ASE guidelines.[79] Since the biplane disk summation method (modified Simpson method) corrects for shape distortions, it is currently the recommended method of 2D volume measurements. With biplane disk summation, the total LV volume is calculated from the summation of a stack of elliptical disks. The height of each disk is calculated as a fraction of the LV LAX, based on the longer of the two lengths from the two- and four-chamber views. The cross-sectional area (CSA) of the disk is based on the diameters obtained, and the volume of the disk is estimated. The volume is obtained by the summation of these values (Fig. 14.38). In contrast, the area-length method assumes a bullet-shaped ventricle; this assumption is not always accurate. Both of these 2D methods may be limited by apex foreshortening, which decreases the accuracy of the measurement.

Although these approximations result in an acceptable calculation of LV volumes in the elliptically shaped normal left ventricle, it is not accurate for the pathologic ventricle. Additionally, the placement of the 2D plane can be subject to positioning errors, which may lead to chamber foreshortening that can lead to measurement errors even in a normally configured left ventricle. Measurements using 3D data sets are not restricted by geometric assumptions nor are they effected by ventricular foreshortening (Fig. 14.39). Studies comparing LV volumes

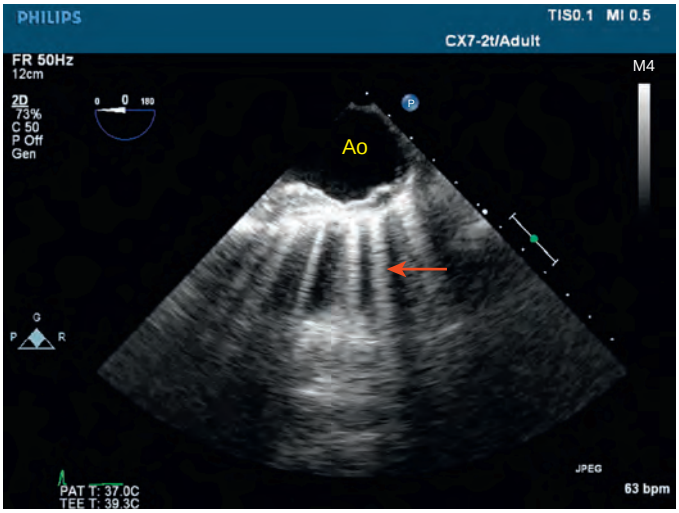


Fig. 14.33 Descending aortic short-axis view in a patient with grade IV atheromatous disease. Note the ringing artifact with bright "flashlight beams" extending from the aortic wall *(red arrow)*. *Ao,* Descending aorta. (Video clip available online.)

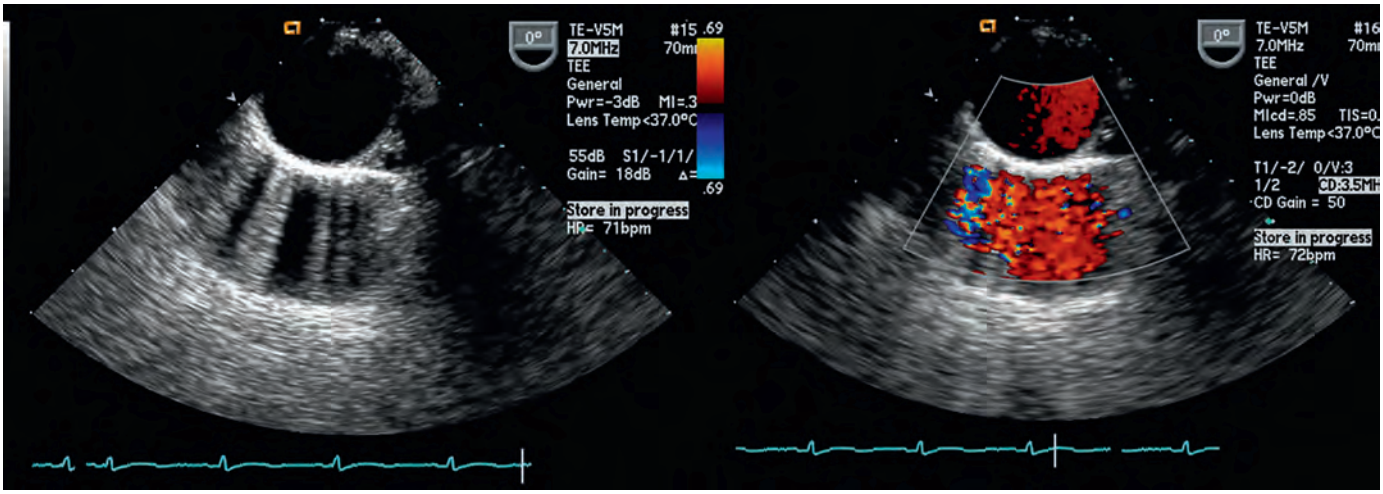


Fig. 14.34 Mirroring artifact; descending aortic short-axis view. The descending aorta is best imaged at the top of the figure. Because ultrasound waves are trapped within the aortic wall, a secondary image appears deeper to the original image. When color-flow Doppler is added to the image on the right, flow appears in both the top original image and in the mirror image.

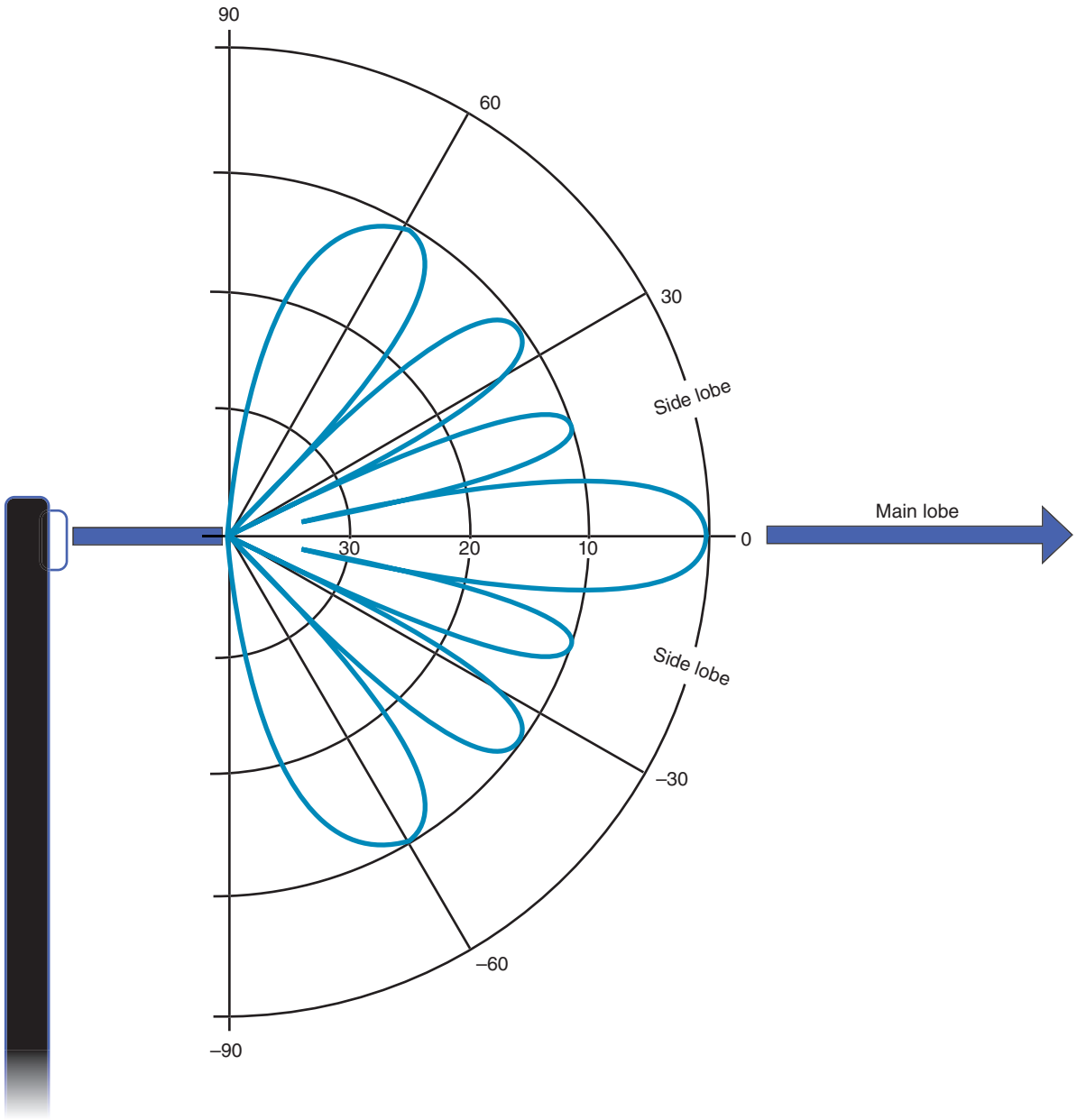


Fig. 14.35 Ultrasound energy is actually emitted as multiple radiation lobes at various angles from the probe's aperture with the energy summed in constructive and destructive patterns. The main beam is the largest constructive pattern, and the side lobes decrease in intensity with increased angle of production. Although weak in intensity, these side lobes may be the source of artifacts if they encounter strong reflectors.

and mass measured by 3D echocardiography, 2D echocardiography, and magnetic resonance imaging (MRI), which is the gold standard, showed significantly better correlation between 3D echocardiography and MRI than between 2D echocardiography and MRI.[81–83] Jenkins and associates[84] compared LV measurements obtained by 2D and 3D echocardiography with MRI-derived measurements in 110 patients.[84] Three-dimensional measurements were performed both online using tracing and offline using edge detection. Although all echocardiographic measurements underestimated LV volumes, they found that the EF estimates were similar. The correlation between MRI and online 3D echocardiography was better than 2D echocardiography; however, the off-line 3D echocardiography provided the best correlation with MRI-derived volumes.

Left Ventricular Preload by End-Diastolic Dimensions

Although preload is often estimated by measuring left-sided heart filling pressures (pulmonary capillary wedge pressure [PCWP], left atrial pressure [LAP], or left ventricular end-diastolic pressure [LVEDP]) in conventional hemodynamics, measuring LV end-diastolic dimensions or calculating LVEDPs can determine preload in echocardiography. In M-mode echocardiography, a single ventricular diameter is obtained, whereas one or multiple tomographic cuts are recorded in

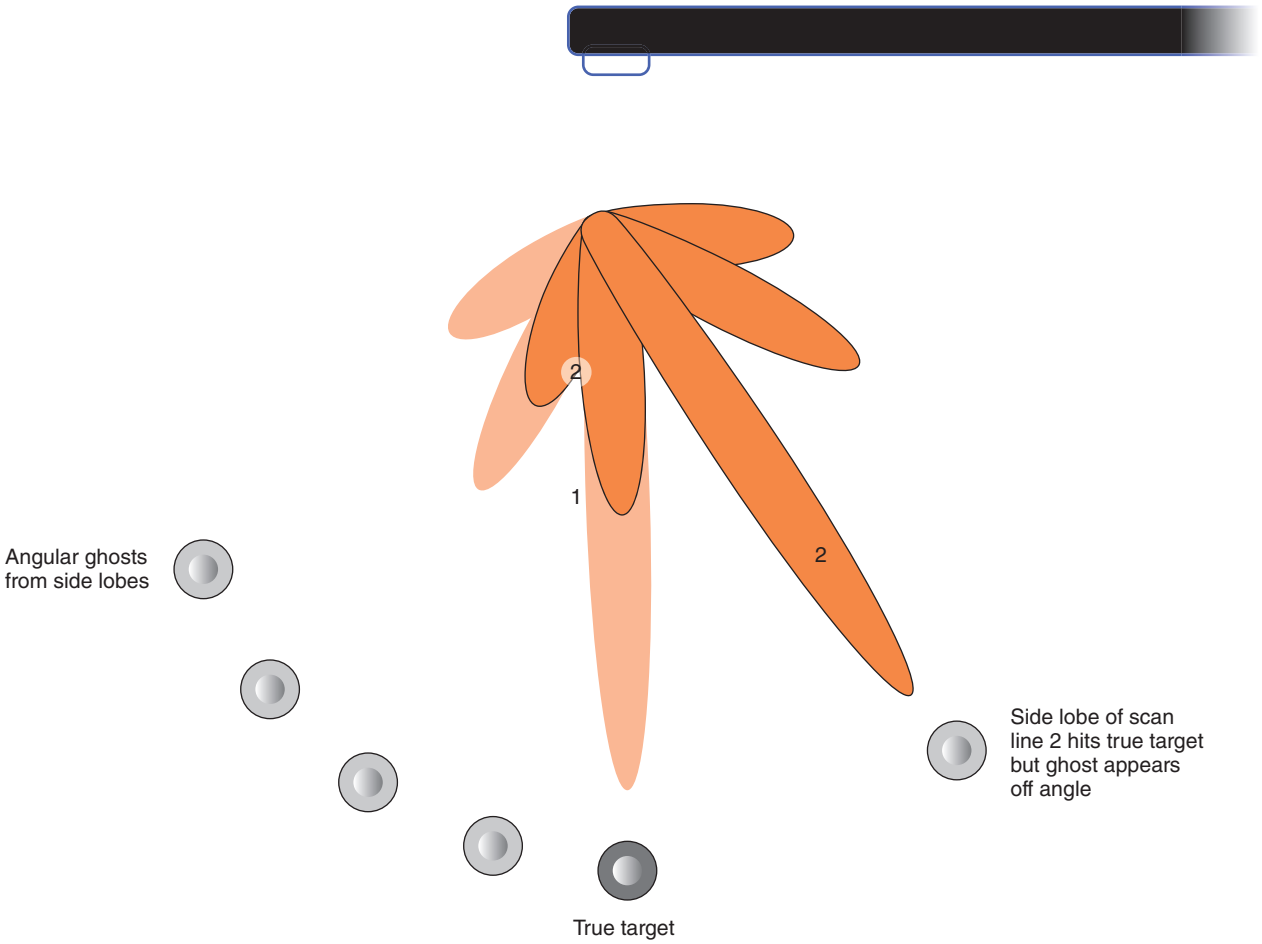


Fig. 14.36 Multiple side-lobe artifacts may yield an imaging artifact with a curved appearance attributable to the beam oscillating to generate a single frame and multiple artifacts displayed next to each other.

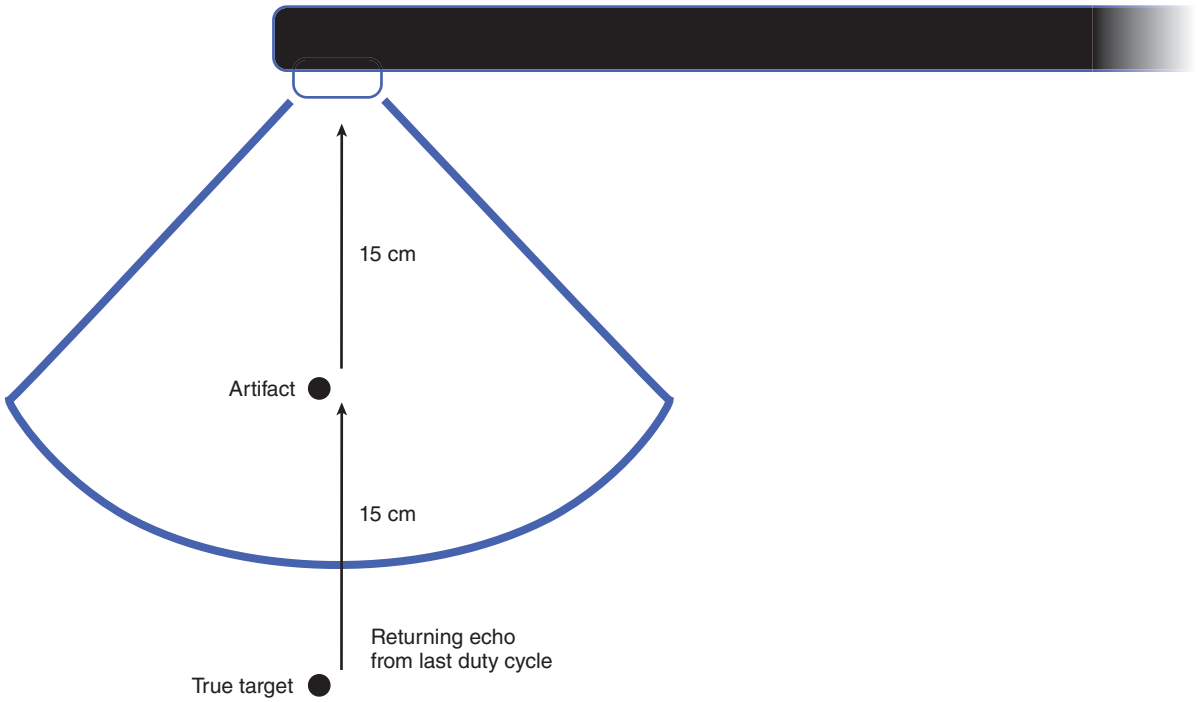


Fig. 14.37 Termed *ranged ambiguity*, a prior ultrasound signal returning from a deep structure, while listening from a subsequent ultrasound pulse, may cause the ultrasound machine to display the artifact in a significantly more shallow location.

TABLE 14.5 Normal Value for Two-Dimensional Left Ventricle Size and Function

	Male	*Female*
	Mean ± SD	*Mean ± SD*
LV Internal Diameters		
Diastolic (mm)	50.2 ± 4.1	45.0 ± 3.6
Systolic (mm)	32.4 ± 3.7	28.2 ± 3.3
LV Volumes (Biplane)		
LV EDV (mL)	106 ± 22	76 ± 15
LV ESV (mL)	41 ± 10	28 ± 7
LV Volumes Normalized by BSA		
LV EDV (mL/m^2)	54 ± 10	45 ± 8
LV ESV (mL/m^2)	21 ± 5	16 ± 4
LV EF (Biplane)	62 ± 5	64 ± 5

BSA, Body surface area; *EDV,* end-diastolic volume; *EF,* ejection fraction; *ESV,* end-systolic volume; *LV,* left ventricle; *SD,* standard deviation.

Adapted from Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.

2D echocardiography. It has been proposed that end-diastolic dimensions provide a better index of preload than the PCWP. When PCWP and end-diastolic volume (EDV), derived from SAX areas at the level of the papillary muscles, were compared as predictors of cardiac index (CI) in patients undergoing CABG surgery, a strong correlation was observed between end-diastolic area (EDA) or EDV and CI, whereas no significant correlation was found between PCWP and CI.[85]

In a study of 32 patients during cardiovascular surgery, Beaupre and colleagues[86] compared SAX area changes with simultaneous PCWP changes obtained from PA catheters. Estimates of stroke volume (SV) derived from SAX area changes were consistent with thermodilution data in 91% of patients. In contrast, EDA changes correlated with PCWP changes in only 23% of patients. Because LV compliance changes dramatically during cardiovascular surgery, PCWP is an inadequate guide to LV preload. Clements and associates[87] studied 14 patients during resection of abdominal aortic aneurysms. At multiple times during surgery, echocardiograms and first-pass radionuclide studies were recorded simultaneously. The correlation between echocardiographic and radionuclide estimates was excellent; however, virtually no correlation was observed between estimates from either of these techniques and PAPs. Thus TEE (but not the PAC) provides the anesthesiologist with a direct, quantitative method to assess LV preload and ejection. However, if severe regional wall motion abnormalities (RWMAs) are present, then information from a single cross section may not be adequate for estimating these parameters.

TEE is often limited to a single SAX view at the level of the papillary muscles. Some evidence suggests that SAX EDAs measured at this level correlate reasonably well with measurements obtained by on-heart echocardiography and with EDVs measured simultaneously using radionuclides. However, findings by Urbanowicz and colleagues[88] were in disagreement with these conclusions. Using a combined radionuclide and thermodilution technique, these investigators found that the correlation coefficient between the left ventricular end-diastolic area (LVEDA) by TEE and the LVEDV was only 0.74. In addition, they noted discordant changes in four of nine patients. Overall, it has been shown that despite variable loading conditions, changes in LV SAX area reflect changes in LV pressure or compliance factors. There are two main echocardiographic signs of decreased preload:

1. Decrease in EDA (<5.5 cm^2/m^2) invariably reflects hypovolemia. It is, however, difficult to set an upper limit of EDA below which hypovolemia can be confirmed. This is particularly true in patients with impaired contractility where a compensatory baseline increase in preload makes the echocardiographic diagnosis of hypovolemia difficult.
2. Obliteration of the end-systolic area (the "kissing ventricle sign") that accompanies the decrease in EDA in severe hypovolemia.

Left Ventricular Mass

LV geometry can be classified into four distinct patterns based on wall thickness, cavity size, and mass: normal, concentric hypertrophy, eccentric hypertrophy, and concentric remodeling (Fig. 14.40).[89–91] Concentric hypertrophy results from pressure overload states such as AS and hypertension and results in an increase in wall thickness and muscle mass of the left ventricle without LV dilation. Eccentric hypertrophy results from volume overload states such as aortic or MR and leads to an increase in muscle mass with LV dilation. Thus both pressure and volume overload states can result in increased left ventricular mass (LVM). The differentiation of patients with increased LVM into concentric versus eccentric hypertrophy requires calculation of relative wall thickness (Eq. 14.12 and Table 14.6). Concentric remodeling refers to a state of increased wall thickness without an increase in overall muscle mass and is generally a precursor to concentric hypertrophy. These entities are distinct from the asymmetric hypertrophy that is found in disorders such as hypertrophic obstructive cardiomyopathy in which only the septal portion of the left ventricle becomes hypertrophic.

LVM equals the product of LV wall volume and the density of the myocardium (1.04 g/mL). LV myocardial wall volume is assessed by subtracting intracavitary LV volume from the volume enclosed by the epicardium.[92] Relative wall thickness is a parameter based on wall thickness and cavity size at end-diastole. It is calculated via the following formula[93]:

$$\text{Relative wall thickness} = [2 \times (\text{ILWTd})]/(\text{LVIDd}) \qquad \text{[Eq. 14.12]}$$

where ILWTd is inferolateral wall thickness diameter at end-diastole (cm), and LVIDd represents LV internal diameter at end-diastole (cm).

A relative wall thickness greater than 0.42 is considered elevated. A patient with normal LVM but increased relative wall thickness would be categorized as concentric remodeling.

ASE guidelines[93] recommend the estimation of LVM based on the geometric assumption of the left ventricle as the shape of an American football (a prolate ellipsoid with a major : minor axis ratio of 2 : 1) and uses linear measurements of the LV SAX dimensions using either 2-D or M-mode measurements.[92] The ASE-recommended linear formula[93] uses ILWTd, anteroseptal wall thickness at end-diastole (ASWTd), and LVIDd (all measured in centimeters):

$$\text{LVM (g)} = 0.8 \times (1.04[(\text{LVIDd} + \text{ILWTd} + \text{ASWTd})^3 - (\text{LVIDd})^3]) + 0.6 \qquad \text{[Eq. 14.13]}$$

The calculations necessary for determining LVM are incorporated into many echocardiographic software systems. This formula requires precise identification of the endocardial surfaces, because even small errors are magnified when cubed in the formula. Although the ASE convention has been to measure the distance between the leading edges of the structures, refinements in image processing now allow improved image resolution for measurement of the actual visualized thicknesses and to measure chamber dimensions from endocardium to endocardium.[93] Trabeculations and spaces should be excluded from the endocardial border. M-mode measurements are limited by the beam orientation being frequently off-axis; 2D echocardiographic images are more precise and thus are the standard mode of calculation. The ASE recommends measuring ILWTd and ASWTd from the standard TG mid-SAX view (Fig. 14.41A).[93] LVIDd is best measured from either the ME two-chamber view (Fig. 14.41B) or the TG two-chamber view (Fig. 14.41C), depending on which image is of higher quality.[93] LVIDd is measured at the junction of the basal and middle thirds of the left ventricle (just above the tips of the papillary muscles) on a line perpendicular to the LAX of the ventricle. When unable to obtain these views in a way that adequately shows the true major and minor axes of the left ventricle, LVIDd can be measured from the TG mid-SAX view, measuring from endocardium to endocardium (see Fig. 14.41A).

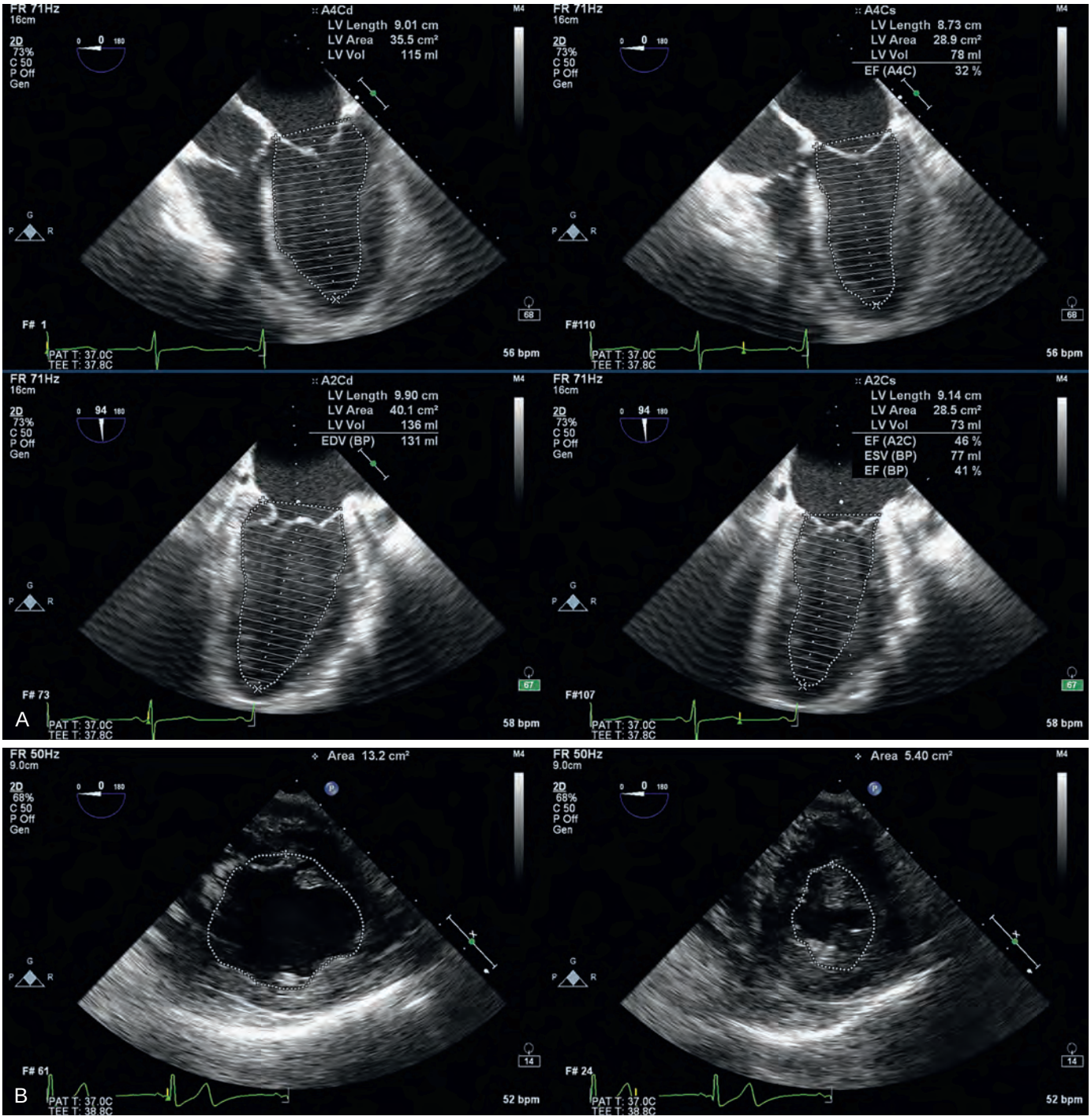


Fig. 14.38 (A) Measurement of left ventricular *(LV)* volume by modified Simpson method. *(Top row)* Midesophageal four-chamber view. *(Second row)* The orthogonal mid esophageal two-chamber view. The column on the left is diastole, and the column on the right is systole. With biplane disk summation, the total LV volume is calculated from the summation of a stack of elliptical disks. The height of each disk is calculated as a fraction of the LV long-axis view, based on the longer of the two lengths from the two- and four-chamber views. The cross-sectional area of the disk is based on the diameters obtained, and the volume of the disk is estimated. The volume is obtained by the summation of these values. (B) Measurement of fractional area change in the transgastric midpapillary view. The left ventricular area during diastole and systole are determined. The fractional area change is calculated by subtracting the systolic area from the diastolic area and then dividing that number by the diastolic area.

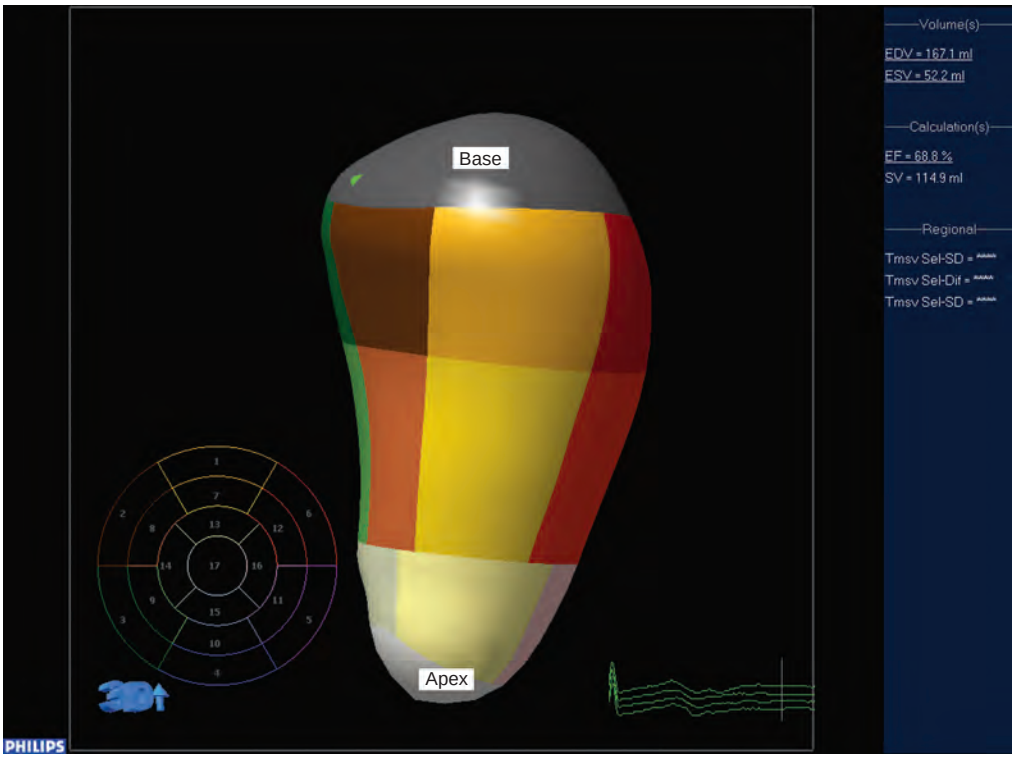


Fig. 14.39 Measurement of left ventricular volume by three-dimensional reconstruction.

Reference values as recommended by ASE are provided in Table 14.7. However, it must be noted that LVM values obtained using TEE are greater by an average of 6 g/m^2 because of minor differences found in inferolateral wall thickness on TEE.[94]

Left Ventricular Systolic Function

The echocardiographic assessment of global and regional LV function consists of 2D, 3D, or Doppler evaluation of cardiac structures. Using echocardiography, contractility has most frequently been estimated with ejection-phase indices. A wide array of ejection-phase indices have been described, but all require that end-diastolic and end-systolic dimensions be measured. In M-mode echocardiography, these dimensions will often be simple, linear, internal dimensions of the LV cavity. The ratio:

$$FS = (LVIDd - LVIDs)/LVIDD \qquad [Eq.\ 14.14]$$

where LVIDd, representing LV internal diastolic dimension, and LVIDs, representing LV internal systolic dimension, will yield fractional shortening (FS), a basic ejection-phase index of contractility. This one-dimensional method for measuring LV systolic function is not accurate with significant RWMAs.

With 2D echocardiography, multiple tomographic cuts can be obtained and used to calculate ventricular volumes using a variety of formulas such as modified Simpson formula (see Fig. 14.38A).[95] Using the ventricular volumes, EF can be calculated using the standard formula:

$$EF = (LVEDV - LVESV)/LVEDV \qquad [Eq.\ 14.15]$$

where LVEDV is LV end-diastolic volume, and LVESV is LV end-systolic volume.

EF less than 52 in men or less than 54 in women is suggestive of abnormal LV systolic function.[79]

During intraoperative TEE, it is most convenient to monitor a single, SAX view at the level of the midpapillary muscles. Once the end-diastolic and end-systolic endocardial areas have been delineated with the help of tracing software, contractility may be estimated using the fractional area of contraction (FAC) or the ejection fraction area (EFA) (see Fig. 14.38B):

$$FAC = (LVEDA - LVESA)/LVEDA \qquad [Eq.\ 14.16]$$

where LVEDA is LV end-diastolic area, and LVESA is LV end-systolic area.

Conventional TEE methods cannot discriminate the effects of load on contractility (ie, impaired contractility and falsely high EF in severe MR or intact contractility and falsely low EF in severe AS). Additionally, all conventional echocardiographic methods examine only a single LV diameter or tomographic plane at a time. Taking into consideration the frequent LV foreshortening that occurs in the ME tomographic planes or the presence of segmental abnormalities (particularly in patients with coronary artery disease [CAD]), realizing why true representation of global LV function is not always feasible with these methods is easy.

The 2015 ASE guidelines recommend the calculation of EF from EDV and end-systolic volume (ESV) estimates using either 2D (using the modified Simpson method) or 3D echocardiography (see Fig. 14.39).[79] If the endocardium cannot be well visualized, then contrast may be used. Three-dimensional and tissue Doppler measurements of LV function are discussed in Chapter 15.

Left Ventricular Diastolic Function

Evaluation of diastolic function requires the assessment of the LV pressure-volume relationship during diastole filling. This relationship can only be measured hemodynamically. Echocardiographic assessment of diastolic function attempts to evaluate diastolic filling by evaluating patterns and time of flow, such as from the left atrium into the left ventricle or from pulmonary veins into the left atrium. The primary determination of flow is the pressure differences in the two chambers.[96] The early diastolic pressure difference between the left atrium and the left ventricle primarily reflects the rate of LV relaxation. Thus if filling is delayed, then impaired relaxation is usually present. It is important to remember that other factors, such as chamber and myocardial compliance, LV loading conditions, ventricular interaction, and pericardial constraint, can also influence rates of LV filling.

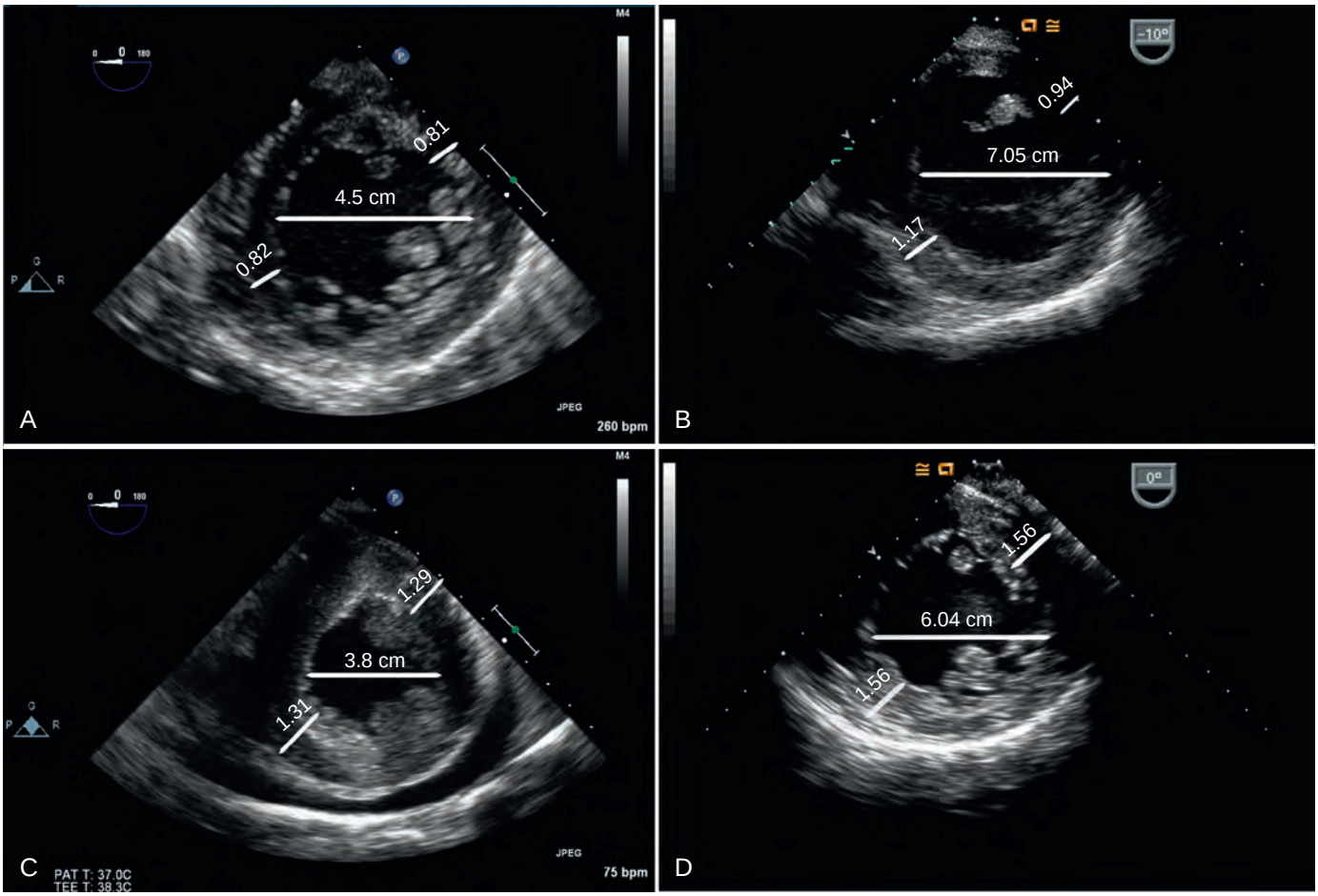


Fig. 14.40 Transesophageal echocardiographic images of the four patterns of left ventricular geometry. (A) Normal. (B) Eccentric hypertrophy. (C) Concentric remodeling. (D) Concentric hypertrophy. *(From Weiner M, Kahn RA, Evans AS. Transesophageal echocardiographic assessment of left ventricular mass.* Anesth Analg. *2015;121:323–328.)*

TABLE 14.6 Left Ventricular Geometry

		Left Ventricular Mass (Grams)	
		Normal: ≤224 (M), 162(F)	*Hypertrophy: >224 (M), 162(F)*
Relative wall thickness	Normal (≤0.42)	Normal geometry	Eccentric hypertrophy
	Increased (>0.42)	Concentric remodeling	Concentric hypertrophy

Reference values for left ventricular mass are shown in Table 14.7.
Adapted from Armstrong AC, Gidding S, Gjesdal O, et al. LV mass assessed by echocardiography and CMR, cardiovascular outcomes, and medical practice. *JACC Cardiovasc Imaging.* 2012;5:837–848.

The evaluation of diastolic function may be evaluated using LA size, Doppler analysis of MV inflow and pulmonary vein flow, color M-mode propagation velocities, and tissue Doppler analysis of the MV annulus.[97–100]

Indices for Evaluation

Left Atrial Size

LA size is most accurately measured in the ME two- and four-chamber views.[79] Although the Doppler velocity and time-interval measurements reflect filling pressures at the time of analysis, LA size measurements reflect cumulative effects over time.[99] LV enlargement may occur in the absence of diastolic dysfunction. If LA enlargement is present, then this measurement must be used in conjunction with other indices of LV diastolic function to interpret its significance.

Transmitral Doppler Analysis

Transmitral Doppler spectrum may be measured using PWD. Typically, the PWD gate is positioned at the tip of the MV leaflets in an ME four-chamber view.[99] Normally, transmitral spectrum consists of an early diastolic phase (E wave) and a late diastolic component associated with atrial contraction (A wave) (Fig. 14.42A). The velocity sweep speeds of 25 to 50 mm/sec should be initially used to evaluate respiratory variations in flow that may occur with pulmonary or pericardial disease, after which it may be increased to 100 mm/sec. The peak E- and A-wave velocities, A-wave duration, and E-wave deceleration time (DT) should be determined. The E-wave DT is measured from the peak of the E wave until the actual or extrapolated intersection with zero. In addition, the isovolemic relaxation time (IVRT) may be measured by placing a CWD cursor in the LVOT to simultaneously measure aortic ejection and ventricular inflow. Normal values are listed in Table 14.8. Generally, with increasing age, E-wave velocity and E/A ratio decrease and A-wave velocity and DT increase.

Mitral E-wave velocities are primarily determined by early diastolic LA-LV pressure gradient, which is primarily influenced by both LA preload and LV relaxation.[101] The A-wave velocity is affected by LV compliance and LA contractile function.[99] Finally, the E-wave DT is

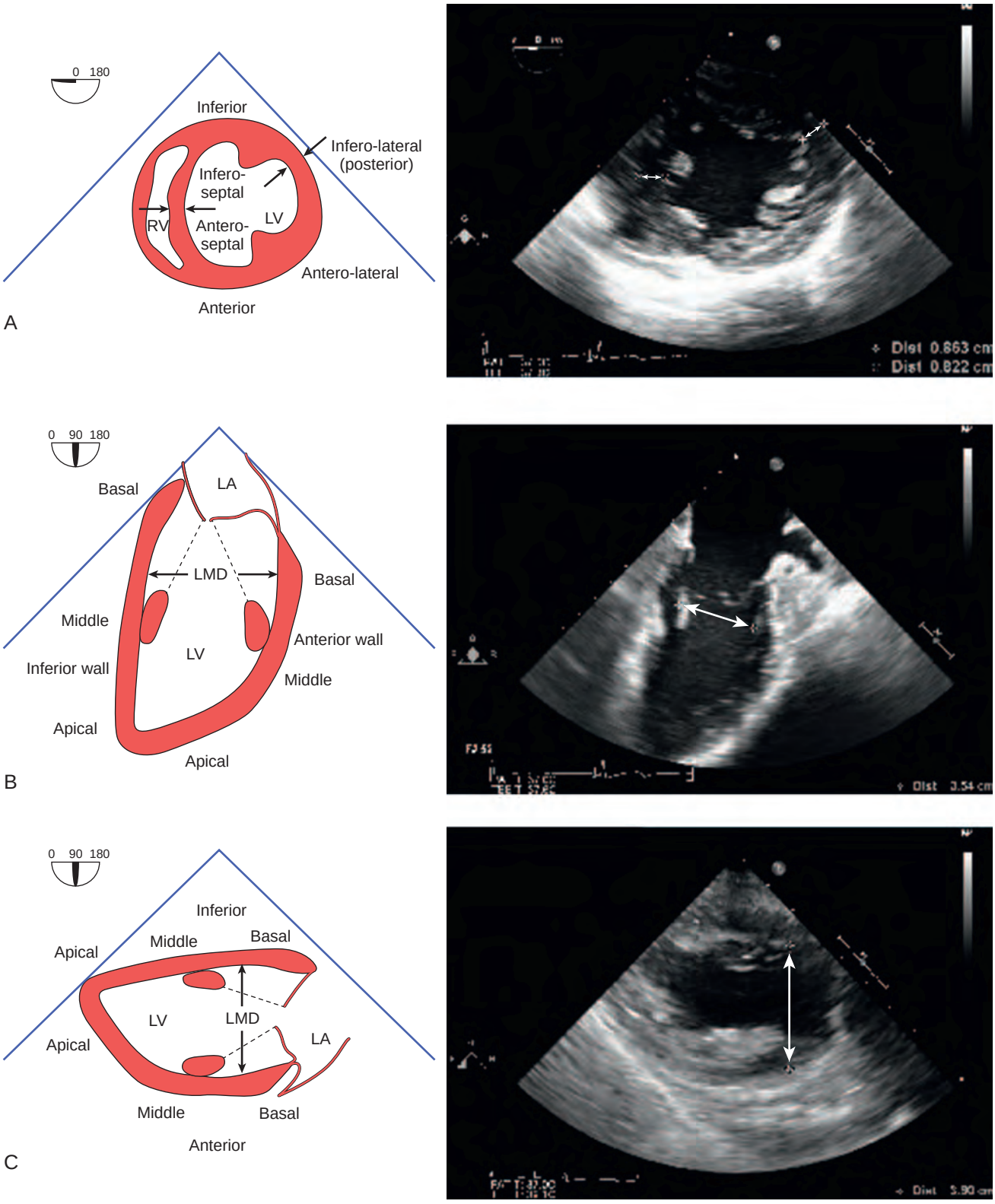


Fig. 14.41 Transesophageal echocardiographic images used in the calculation of left ventricular mass. (A) Transgastric midpapillary short-axis view showing the recommended measurements of the inferolateral wall thickness diameter at end-diastole (ILWTd) and anteroseptal wall thicknesses at end-diastole (ASWTd). (B) Midesophageal two-chamber view shows the measurement of the left ventricular internal diameter at end-diastole (LVIDd). (C) Transgastric 2-chamber view shows the measurement of the left ventricular internal diameter at end-diastole (LVIDd). Using the formula: Left ventricular mass (g) = $0.8 \times (1.04[(\text{LVIDd} + \text{ILWTd} + \text{ASWTd})^3 - (\text{LVIDd})^3]) + 0.6$. The left ventricular mass of this patient equals 84.6 grams. *LA,* Left atrium; *LV,* left ventricle; *LMD,* left ventricular diameter; *RV,* right ventricle. *(Permission pending from Weiner M, Kahn RA, Evans AS. Transesophageal echocardiographic assessment of left ventricular mass.* Anesth Analg. *2015;121:323–328.)*

TABLE 14.7 Echocardiographic Reference Ranges for Left Ventricular Mass[93]

	Men				Women			
	Normal Range	*Mildly Abnormal*	*Mildly Abnormal*	*Mildly Abnormal*	*Normal Range*	*Mildly Abnormal*	*Mildly Abnormal*	*Mildly Abnormal*
LVM (g)	88–224	225–258	259–292	≥293	67–162	163–186	187–210	≥211
LVM/BSA (g/m^2)	49–115	116–131	132–148	≥149	43–95	96–108	109–121	≥122
LVM/height (g/m)	52–126	127–144	145–162	≥163	41–99	100–115	116–128	≥129
LVM/height$^{2.7}$ (g/m$^{2.7}$)	20–48	49–55	56–63	≥64	18–44	45–51	52–58	≥59

BSA, Body surface area; *LVM,* left ventricular mass.

No echocardiographic ranges for LVM/height[89,91] are provided by the current guidelines from the American Society of Echocardiography.

From Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005;18:1440–1463.

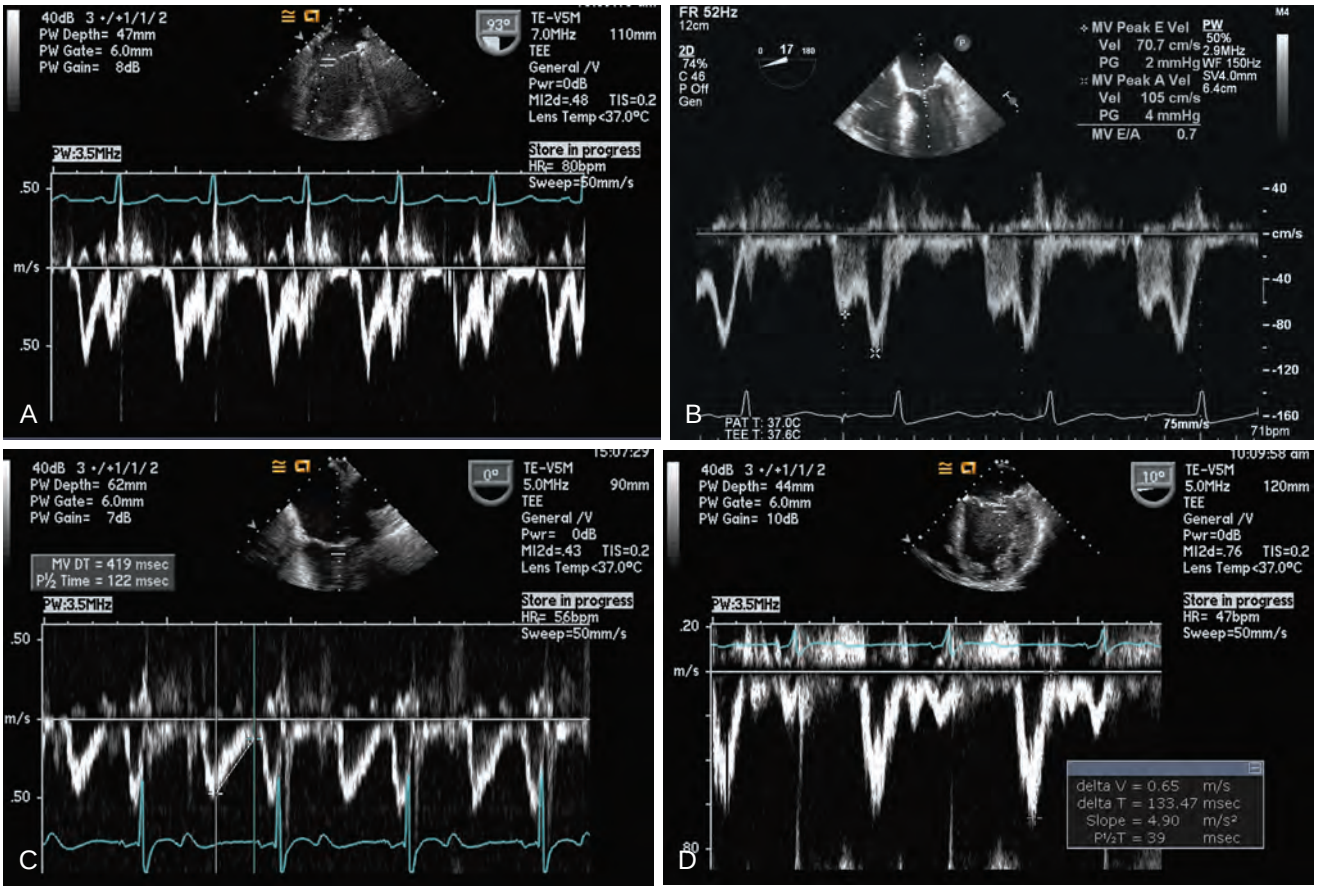


Fig. 14.42 Transmitral flow and diastolic dysfunction. (A) Normal transmitral spectrum consists of an early diastolic phase (E wave) and a late diastolic component associated with atrial contraction (A wave). The E-wave velocity is usually larger than the A-wave velocity. (B) Delayed relaxation. With delayed relaxation, the A wave becomes smaller than the E wave. (C) Pseudonormalization. With worsening diastolic dysfunction, left atrial pressure increases with a concomitant increase in the E-wave velocity. Although there is an increase in the E-wave deceleration time, differentiation of the pseudonormalization pattern from normal is dependent on additional indices of diastolic function. (D) With the restrictive pattern, the E wave becomes dominant with a very rapid deceleration time.

influenced by LV relaxation, LV diastolic pressures after MV opening, and LV compliance. With normal diastolic function, the E/A of MV inflow ratio is between 0.8 and 1.5, with an E-wave DT greater than 140 milliseconds. With impaired relaxation, the A-wave velocity increases, and the E/A ratio becomes less than 0.8 (Fig. 14.42B). The E-wave DT is usually longer than 200 milliseconds. Further worsening in diastolic function results in increases in LAP. This increased LAP increases the E-wave velocity. This increased E-wave velocity results in a *pseudonormalization* of the E/A ratio (Fig. 14.42C). Further progression to restrictive cardiomyopathy results in the rapid increase in ventricular pressure during early diastole with resultant shortened early diastolic filling. This is characterized by an E/A wave ratio greater than 1.5 and an E-wave DT less than 140 milliseconds (Fig. 14.42D).

Pulmonary Venous Flow Analysis

The pulmonary veins may be imaged from a number of views as described earlier. The location of the vein may be optimized by CFD. Ideally, a 2- to 3-mm PWD sample volume is placed more than 0.5 cm

TABLE 14.8 Normal Values for Doppler Diastolic Measurements[99,100]

	Age (in years)			
Measurement	*16–20*	*21–40*	*41–60*	*>60*
IVRT (msec)	50 ± 9 (32–68)	67 ± 8 (51–83)	74 ± 7 (60–88)	87 ± 7 (73–101)
E/A ratio	1.88 ± 0.45 (0.98–2.78)	1.53 ± 0.40 (0.73–2.33)	1.28 ± 0.25 (0.78–1.78)	0.96 ± 0.18 (0.6–1.32)
DT (msec)	142 ± 19 (104–180)	166 ± 14 (138–194)	181 ± 19 (143–219)	200 ± 29 (142–258)
A duration (msec)	113 ± 17 (79–147)	127 ± 13 (101–153)	133 ± 13 (107–159)	138 ± 19 (100–176)
PV S/D ratio	0.82 ± 0.18 (0.46–1.18)	0.98 ± 0.32 (0.34–1.62)	1.21 ± 0.2 (0.81–1.61)	1.39 ± 0.47 (0.45–2.33)
PV Ar (cm/sec)	16 ± 10 (1–36)	21 ± 8 (5–37)	23 ± 3 (17–29)	25 ± 9 (11–39)
PV Ar duration (msec)	66 ± 39 (1–144)	96 ± 33 (30–162)	112 ± 15 (82–142)	113 ± 30 (53–173)
Septal e′ (cm/sec)	14.9 ± 2.4 (10.1–19.7)	15.5 ± 2.7 (10.1–20.9)	12.2 ± 2.3 (7.6–16.8)	10.4 ± 2.1 (6.2–14.6)
Septal e′/a′ ratio	2.4[a]	1.6 ± 0.5 (0.6–2.6)	1.1 ± 0.3 (0.5–1.7)	0.85 ± 0.2 (0.45–1.25)
Lateral e′ (cm/sec)	20.6 ± 3.8 (13–28.2)	19.8 ± 2.9 (14–25.6)	16.1 ± 2.3 (11.5–20.7)	12.9 ± 3.5 (5.9–19.9)
Lateral e′/a′ ratio	3.1[a]	1.9 ± 0.6 (0.7–3.1)	1.5 ± 0.5 (0.5–2.5)	0.9 ± 0.4 (0.1–1.7)

Data expressed as mean ± standard deviation (SD; 95% confidence intervals).
[a]SD not available.
Ar, Atrial reversal; *DT*, deceleration time; *IVRT*, isovolemic relaxation time; *PV*, pulmonic valve; *S/D*, systolic/diastolic.
Adapted from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22;107–133; Klein AL, Burstow DJ, Tajik AJ, et al. Effects of age on left ventricular dimensions and filling dynamics in 117 normal persons. *Mayo Clin Proc*. 1994:69;212–224.

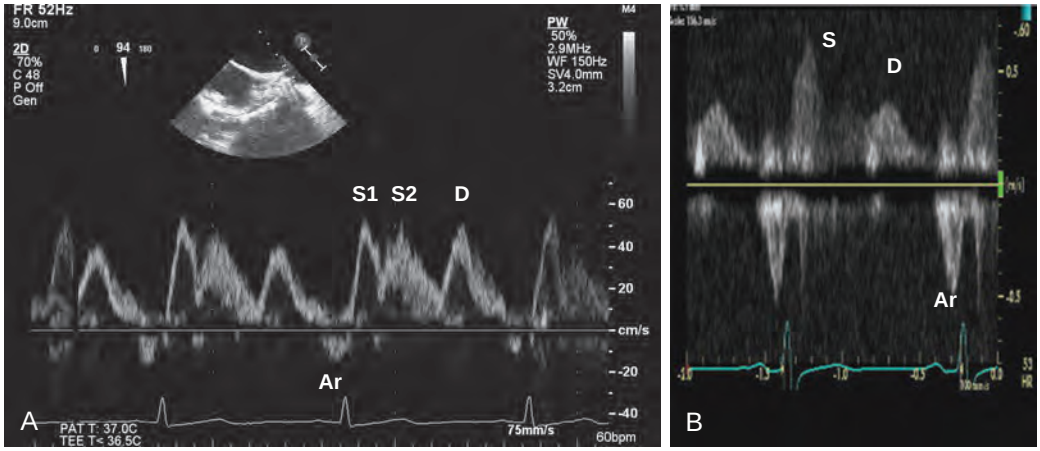


Fig. 14.43 Pulmonary venous tracing. (A) The normal pulmonary venous tracing is characterized by flow into the left atrium (toward the transducer) during both systole *(S)* and diastole *(D)* with a small flow reversal during atrial systole. The systolic component, which occurs immediately after the QRS complex, consists both of an *S1* and *S2* component. The S1 component represents the suction effect during atrial relaxation, whereas the S2 component represents flow as a result of right ventricular systole. Flow during diastole *(D)* is normally less than systolic flow. Atrial contraction produces an atrial reversal wave *(Ar)* immediately before ventricular systole. (B) With worsening left ventricular diastolic function, there is an increase in atrial Ar velocity and duration. The mitral inflow spectrum from a transthoracic ultrasound is demonstrated on the left, and the pulmonary venous spectrum is on the right. Pulmonary venous Ar velocity is significantly increased at 50 cm/sec and its prolonged duration is at >200 milliseconds in comparison with mitral A (late diastolic) velocity. *(B, Reproduced with permission from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography.* J Am Soc Echocardiogr. *2009;22:107–133.)*

into the pulmonary vein, ensuring that the direction of pulmonary blood flow is parallel to the Doppler beam. The normal pulmonary venous tracing consists of a large positive systolic wave (ie, flow toward the left atrium), a smaller diastolic wave, and a negative atrial wave (Fig. 14.43A). The systolic wave may have both S1 and S2 components. The S1 component is associated with a *suction* effect of LA relaxation, whereas the S2 component is related to the pushing of blood by the right ventricle across the pulmonary circulation.[102] The peak systolic and diastolic velocities should be measured, as well as the atrial reversal velocity and duration. If both S1 and S2 components of the pulmonary systolic flows are present, then the S2 velocity should be used for calculations because S1 is related to atrial relaxation. After measuring of the transmitral Doppler spectrum, the difference between the atrial reversal duration and the A-wave duration should be calculated. The atrial systole component of the pulmonary venous flow (ie, atrial reversal) velocity is usually less than 35 cm/sec, and its duration is usually less than the transmitral E-wave duration.

As summarized by Nagueh and associates,[99] "S1 velocity is primarily influenced by changes in LA pressure and LA contraction and relaxation, whereas S2 is related to SV and pulse-wave propagation in the PA tree. D velocity is influenced by changes in LV filling and compliance and changes in parallel with mitral E velocity. Pulmonary venous Ar [atrial reversal wave] velocity and duration are influenced by LV late diastolic pressures, atrial preload, and LA contractility. A decrease in LA compliance and an increase in LA pressure decrease the S velocity and increase the D velocity, resulting in an S/D ratio <1, a systolic filling fraction <40%, and a shortening of the DT of D velocity, usually <150 ms. With increased LVEDP, Ar velocity and duration increase, as well as the time difference between Ar duration and mitral A-wave duration." Increases in LAP results in a blunting of the systolic component

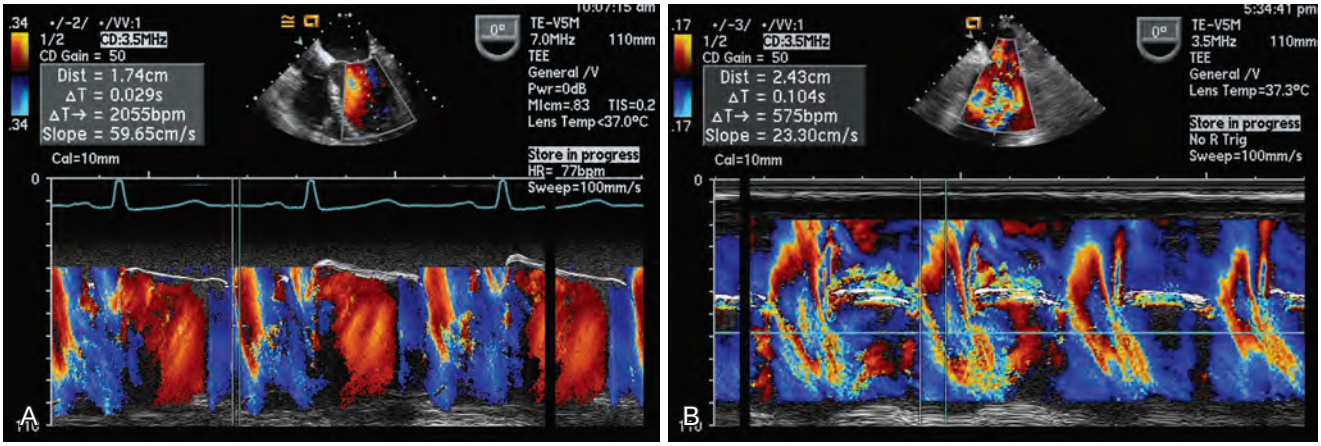


Fig. 14.44 Color M-mode propagation velocity. (A) Normal. The color M-mode slope of the left ventricular inflow is greater than 50 cm/sec. (B) With decreased diastolic function, the M-mode propagation slope is decreased.

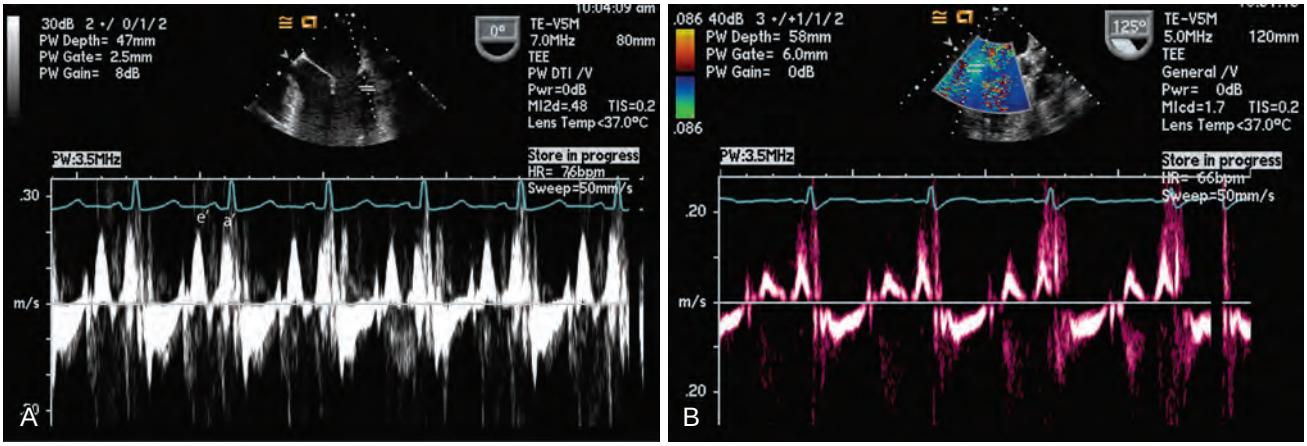


Fig. 14.45 Tissue Doppler measurements. (A) Normal tissue Doppler spectrum. e′ is both greater than a′ and more than 8 cm/sec. (B) With worsening left ventricular diastolic function, the e velocity decreases.

of pulmonary venous flow, compared with diastolic pulmonary venous flow. With greater increases in LVEDP, the atrial reversal wave velocity exceeds 35 cm/sec and the duration becomes greater than 30 milliseconds compared with the transmitral E-wave duration (Fig. 14.43B).

Color M-Mode Flow Propagation Velocity

Mitral-apical propagation velocity (V_p) may be measured using color M-mode imaging. A clear view of LV inflow is obtained. CFD mapping is superimposed on the LV inflow, and the color mapping is adjusted to a displayed and aliased signal in the center of the ventricular inflow.[103] The M-mode scan line is displayed extending through the MV leaflet opening to the LV apex. V_p is determined by measuring the slope of the aliasing velocity from the mitral inflow to approximately 4 cm into the LV cavity during early systole (Fig. 14.44A). A V_p greater than 50 cm/sec is considered normal.[99] This early filling wave is driven by the pressure gradient between the LV base and apex, which represents a suction force attributable to LV restoring forces and relaxation. A decrease in V_p serves as a semiquantitative marker of LV diastolic dysfunction (Fig. 14.44B). In most cases of diastolic dysfunction, other indices of diastolic function are present; if these indices are inconclusive, then V_p may provide useful information concerning the estimation of LVEDP.

Tissue Doppler

Spectral Doppler is usually used to determine blood-flow velocities. Because these velocities are relatively high and the amplitude of the Doppler signal is low, high amplitude–low velocity ultrasound signals are usually ignored. In contrast, during tissue Doppler examination, the primary interest is in the high amplitude–low velocity ultrasound signals created by the myocardium; low amplitude–high velocity signals are ignored. DTI of the MV annulus may be used to judge diastolic function.[104] Most modern ultrasound machines have presets optimized for tissue Doppler analysis that include the high amplitude–low velocity signals that are normally excluded. The sample volume should be positioned with 1 cm of the septal and lateral annular insertion points and should cover the longitudinal excursion of the mitral annulus in both systole and diastole.[99] Normally, this DTI wave consists of two diastolic components: one in early diastole (e′) and one in late diastole (a′) (Fig. 14.45). Measurements should be taken at both points and the results averaged. The septal e′ wave is generally lower than the lateral e′-wave velocity. The peak e′- and a′-wave velocities should be determined, and both the e′/a′ and E/e′ ratios should be calculated. These two signals are in the opposite direction of MV inflow. The major determinants of e′-wave velocity are LV relaxation, preload, systolic function, and LV minimal pressure. These indices may not be accurate with heavy annular calcification, mitral stenosis (MS), prosthetic MVs or annuli, or constrictive pericarditis. Because preload has minimal effect on e′-wave velocity, the E/e′ ratio is useful to correct for E-wave velocities in the presence of diastolic dysfunction. Normal values for these parameters are listed in Table 14.8. Septal E/e′ ratios less than 8 and septal e′-wave velocities greater than 8 cm/sec usually indicate

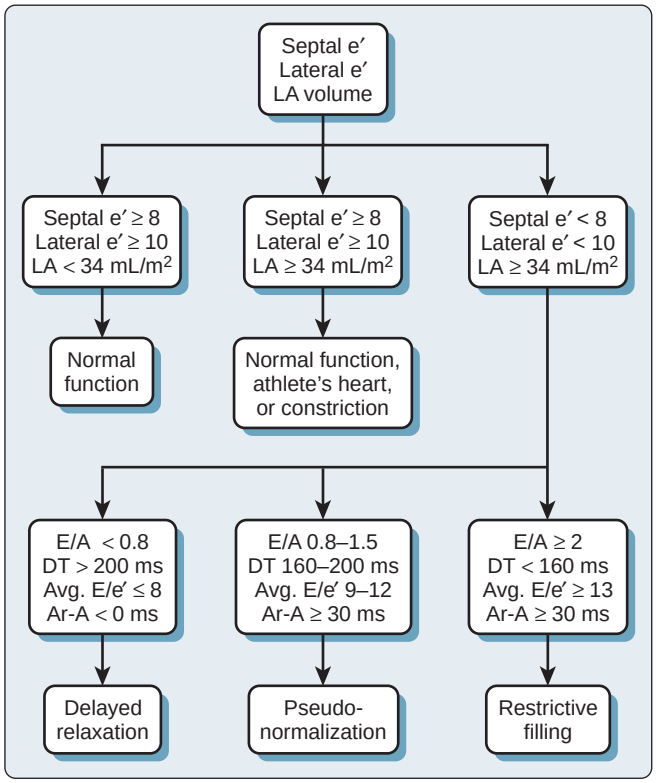


Fig. 14.46 Classification of diastolic dysfunction. *A*, Late diastolic transmitral velocity; *Ar-A*, difference between pulmonary venous atrial reversal duration and transmitral A-wave duration; *DT*, E-wave deceleration time; *E*, early diastolic transmitral velocity; *e′*, early diastolic tissue Doppler velocity; *LA*, left atrial.

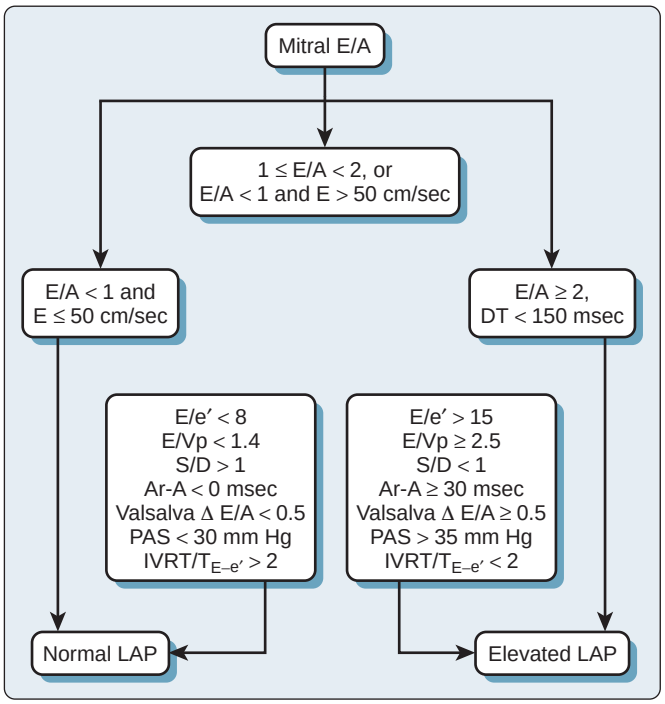


Fig. 14.47 Evaluation of left atrial pressure *(LAP)* with depressed ejection fraction. *A*, Late diastolic transmitral velocity; *Ar-A*, difference between pulmonary venous atrial reversal duration and transmitral A-wave duration; *Avg*, average; *DT*, E-wave deceleration time; *E*, early diastolic transmitral velocity; *e′*, early diastolic tissue Doppler velocity; *IVRT*, isovolemic relaxation time; *LA*, left atrial; *Lat*, lateral; *PAS*, pulmonary artery systolic pressure.

normal LV filling pressures, whereas septal E/e′ ratios greater than 16 and septal e′-wave velocities less than 8 cm/sec (lateral e′-wave velocity less than 8.5 cm) usually indicate increased LV filling pressures.[97,99]

Classification of Diastolic Dysfunction

There are three primary stages of diastolic dysfunction: impaired relaxation, pseudonormalization, and restrictive cardiomyopathy, which may be classified using the indices presented in Fig. 14.46.[99] In patients with mild diastolic dysfunction (impaired relaxation), the mitral E/A ratio is less than 0.8, DT is more than 200 milliseconds, IVRT is 100 milliseconds or longer, systolic is greater than diastolic pulmonary venous flow, annular e′-wave velocity is less than 8 cm/sec, and the E/e′ ratio is less than 8. In most of these cases, the LAP is not elevated. With the progression to moderate diastolic dysfunction, the increase in LV filling pressures is mild to moderate. With these increases in LAP, the early diastolic LA-LV pressure gradient increases, which results in a pseudonormalization of the E/A ratio (0.8 to 1.5). This ratio may decrease by more than 50% with Valsalva. Other supporting data for the diagnosis of moderate diastolic dysfunction include an increase of the E/e′ ratio from 9 to 12, e′ less than 8 cm/sec, a pulmonary venous atrial reversal wave velocity greater than 30 cm/sec, the diastolic pulmonary venous blood-flow velocity greater than the systolic velocity, and the difference between pulmonary venous atrial reversal duration and transmitral A-wave (Ar-A) duration of 30 milliseconds or longer. Finally, severe diastolic dysfunction (restrictive LV filling) may be diagnosed with an E/A ratio of 2 or more, DT less than 160 milliseconds, IVRT 60 milliseconds or less, pulmonary venous systolic filling fraction 40% or less of the diastolic fraction, mitral A-flow duration shorter than the atrial reversal wave duration, and an average E/e′ ratio greater than 13 (or septal E/e′ greater than 15 or more and lateral E/e′ greater than 12 or more).

Left Atrial Pressure

The indices used to estimate LAP are discussed in detail in the earlier section that describes the evaluation of diastolic dysfunction. The current recommendation suggests different algorithms for the evaluation of LAP based on the EF.[99] These recommendations are summarized in Figs. 14.47 and 14.48. Mitral inflow patterns may be used with reasonable accuracy to estimate LAP in patients with depressed EFs. If the E/A ratio is less than 1 and the E wave is 50 cm/sec or less, then the LAP is probably normal; if E/A pressure is greater than 2 and the DT is less than 150 milliseconds, then the LAP is probably elevated. In the intermediate E/A ratios or a high E-wave velocity, other indices must be considered as well. Signs consistent with normal LAP include E/e′ less than 8, E/V_p less than 1.4, pulmonary venous systolic pressure greater than diastolic velocity, Ar-A duration less than 0 milliseconds, and systolic PA pressure less than 30 mm Hg. However, if E/e′ is more than 15, E/V_p is greater than or equal to 2.5, pulmonary venous systolic is less than diastolic velocity, Ar-A is greater than 30 milliseconds, and systolic PA pressure is greater than 35 mm Hg, then increased LAP should be suspected.

With a normal EF, the E/e′ ratio is the primary measurement to be considered (see Fig. 14.48). If the septal, lateral, or average E/e′ is less than or equal to 8, then the LAP is normal.[105] If the septal E/e′ is greater than or equal to 15, the lateral E/e′ is 12 or more, or the average E/e′ is greater than or equal to 13, then the LAP is considered elevated. For intermediate values of E/e′ ratio, other factors associated with diastolic function must be considered. LA volume greater than 34 mL/m^2, Ar-A duration longer than 30 milliseconds, PA systolic pressure greater than 35 mm Hg, or the ratio of the IVRT/$T_{E-e'}$ less than 2 (which is defined as the time difference between the QRS to E-wave interval and the QRS to e′) are supportive of increased LAP. If more than one of these conditions is present, then a conclusion of higher LAP may be made with greater confidence. LA volume less than 34 mL/m^2, Ar-A duration less

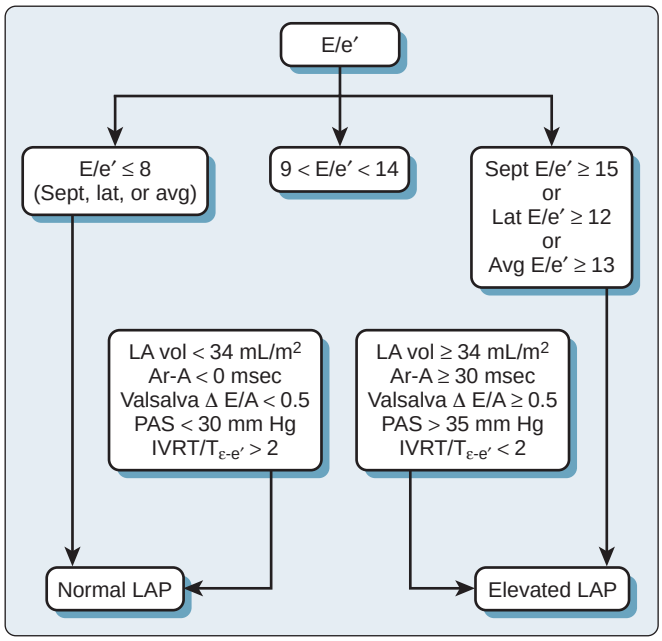


Fig. 14.48 Evaluation of left atrial pressure *(LAP)* in normal ejection fraction. *A*, Late diastolic transmitral velocity; *Ar-A*, difference between pulmonary venous atrial reversal duration and transmitral A-wave duration; *Avg*, average; *DT*, E-wave deceleration time; *E*, early diastolic transmitral velocity; *e′*, early diastolic tissue Doppler velocity; *IVRT*, isovolemic relaxation time; *LA*, left atrial; *Lat*, lateral; *PAS*, pulmonary artery systolic pressure; *Sept*, septal.

than 0 milliseconds, systolic PA pressure less than 30 mm Hg, or the ratio of the IVRT/TE $T_{E\text{-}e'}$ greater than 2 are supportive of normal LAP.

Right Ventricular Function

The right ventricle is a complex structure that pumps venous blood to the normally low pressure–low resistance pulmonary arterial circuit. Owing to the historical focus on the left side of the circulation, lack of geometric assumptions of RV shape, and the difficulty in imaging the right-sided heart, information regarding the right ventricle has been limited until relatively recently. When RV function and loading conditions are normal, the right ventricle is typically triangular when viewed in the ME four-chamber view, yet crescent-shaped when viewed in the TG mid-SAX view. The right ventricle consists of three portions: (1) the inflow portion near the TV, chordae tendineae, and papillary muscles; (2) the trabeculated apical myocardium; and (3) the RVOT near the ventricular septum and PV. These three portions of the right ventricle create a *wrap-around* appearance, which is apparent in an ME RV inflow-outflow view. Unlike the left ventricle, which has a pistonlike contraction, the right ventricle contracts in a peristaltic-like manner with contraction of the inflow, followed in sequence by the apical and outflow portion. Although the RV SV is the same as the left ventricle, the low resistance and high-compliance pulmonary circulation results in an RV stroke work that is normally 25% of the LV stroke work.[106] Because the RV afterload is low, the RV wall thickness is approximately one half that of the left ventricle, and the RV myocardial mass is one sixth of the LV mass. Finally, the left and right ventricles share the IVS because of their close anatomic relationship enclosed within the pericardial sac.[107,108] This ventricular interdependence plays a significant role in the RV pathophysiologic dysfunction because the septum contributes to nearly one third of the typical RV stroke work.[109]

RV dysfunction is often in response to increased pulmonary vascular afterload and pulmonary hypertension, which leads to increased RV wall tension and an imbalance of RV oxygen supply and demand. Myocardial ischemia is another source of RV dysfunction. When

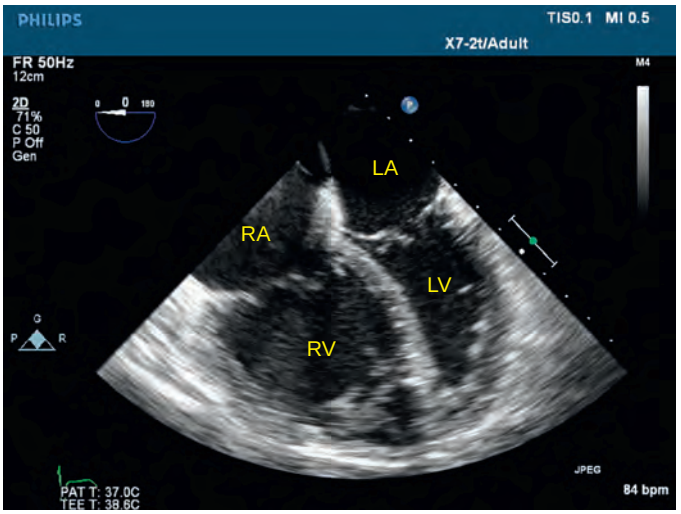


Fig. 14.49 Midesophageal four-chamber view with the probe turned to the patient's right side, bringing the right atrium *(RA)* and right ventricle *(RV)* into view. Note the RV appears larger in area than the LV, which indicates severe right ventricular enlargement. *LA*, Left atrium; *LV*, left ventricle. (Video clip available online.)

increased afterload and/or RV ischemia occur, these result in decreased systolic function with a rise in RV diastolic pressures and chamber dilatation. The chamber dilatation and septal shift toward the left ventricle from rising RV pressures worsens the RV CO. RV dilation leads to a dilated TV annulus, subsequent TR, RA enlargement, and further RV volume overload. Perioperatively, patients with co-existing RV dysfunction fare more poorly than patients without RV dysfunction.[110,111] Therefore appropriate perioperative echocardiographic evaluation of RV function is essential to a comprehensive TEE examination. The specific TEE views required to assess the right ventricle have been described earlier in this chapter.

Right Ventricular Anatomic Assessment

As previously described, the right ventricle is particularly sensitive to increases in afterload. The presentation of this response to chronic increases in afterload may be volume- or pressure-related changes such as RV dilation, hypertrophy, septal wall abnormalities, and RV failure. RV dilation is readily identified by echocardiography and may be assessed qualitatively or quantitatively. Qualitatively, the RV size is compared with the LV size in the ME four-chamber view in which its CSA normally occupies two-thirds of the *normal* LV CSA. Mild enlargement is an increase greater than two thirds; moderate enlargement is present when the chambers are equal in size, whereas severe enlargement is present when the RV area is larger than the LV area (Fig. 14.49; see Video 14.47). Quantitatively, the right ventricle is difficult to assess because of the complex RV shape and poor interobserver reproducibility of RV chamber size measurements. Current chamber quantification guidelines suggest upper reference values for a diameter of 4.1 cm at the base and 3.5 cm in the midlevel of the right ventricle on a transthoracic RV-focused apical four-chamber view.[79] Guidelines specific to TEE are unavailable.

RV hypertrophy in response to pulmonary hypertension is defined as an RV free-wall thickness greater than 5 mm at end-diastole. Chronic severe pulmonary hypertension often results in an RV free-wall thickness greater than 10 mm. ME four-chamber, RV inflow-outflow, or TG RV inflow views with M-mode echocardiography may be used to assess this wall thickness (Fig. 14.50).

RV pressure or volume overload may cause distortion or flattening of the IVS most easily identified in the TG mid-SAX view. The overload of the right ventricle, as well as the underfilled left ventricle from reduced RV CO, leads to a leftward deviation of the septum and a *D-shaped* LV chamber appearance. The timing of this septal flattening

allows the identification of RV pressure or volume overloading. RV pressure overload causes septal flattening at end-systole when the pressure is the highest in the right ventricle, whereas volume overload causes septal flattening at end-diastole when the RV volume is at its greatest[112] (Fig. 14.51; see Videos 14.48 and 14.49).

Right Ventricular Systolic Function

Similar to the difficultly with anatomic assessments, the asymmetric right ventricle creates challenges in the evaluation of RV systolic function. Several modalities, including 2D-, Doppler-, strain-, and 3D-based methods, exist to evaluate RV function. Most have been validated with reference values using transthoracic echocardiography (TTE), and this data have been extrapolated to TEE.[113]

Two Dimensional–Based Methods

Although the right ventricle contracts in a peristaltic-like manner from the base through the apex to the outflow portion, the largest contributor to its systolic function is the longitudinal basal contraction.

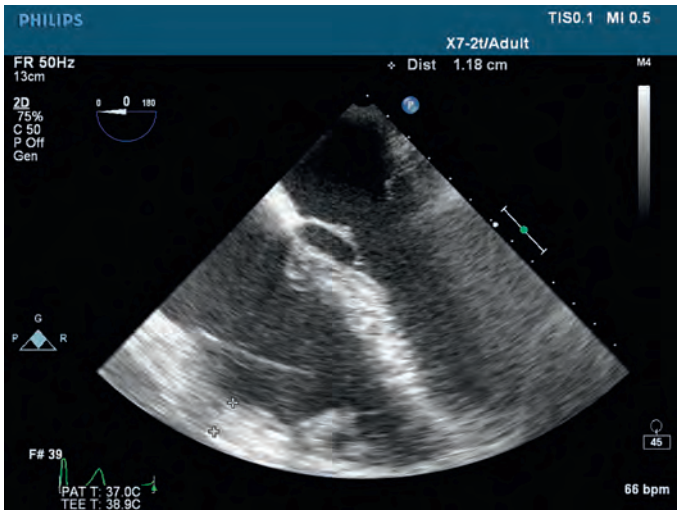


Fig. 14.50 Midesophageal four-chamber view of a patient with severe chronic thromboembolic pulmonary hypertension, demonstrating significant right ventricular hypertrophy (wall thickness measuring 11.8 mm).

Therefore one of the easily deployed and widely used measurement tools is tricuspid annular plane systolic excursion (TAPSE), which is a measurement of the longitudinal contraction of the lateral tricuspid annulus toward the apex during systole. Because the septal segment of the tricuspid annulus is fixed, the longitudinal contraction of the right ventricle causes a hingelike movement of the lateral annulus. This movement can be measured in the ME four-chamber view as the change in distance from annulus to apex in diastole and systole.[112] M-mode scan of this movement is often helpful in a transthoracic four-chamber view. However, the off-axis alignment of tricuspid motion in a transesophageal ME four-chamber view does not allow proper measurement; therefore a modified TG RV inflow-outflow aided by M-mode echocardiography allows for a more accurate measurement[95] (Figs. 14.52 and 14.53; see Video 14.50). Current chamber quantification guidelines suggest that a value less than 17 mm is suggestive of RV systolic dysfunction.[79]

Used in a similar manner as LV systolic evaluation, RV fractional area of change is another 2D-based method of systolic function evaluation. This measurement may be obtained in an ME four-chamber view, tracing the right ventricle from the lateral tricuspid annulus, down the RV free wall to the apex, and returning along the septum to the tricuspid annulus. The change in this area measurement between diastole and systole is calculated as a percent of change (Fig. 14.54). As with TTE, in which an RV-focused, four-chamber view is necessary, anteflexion or probe insertion is necessary to obtain an RV-focused ME four-chamber view to avoid RV foreshortening.[113] An RV fractional area of change less than 35% is indicative of RV dysfunction.[79]

Although the left ventricle allows typical geometric assumptions, yielding estimates of volume (ie, disk summation), the right ventricle's asymmetric nature precludes an accurate estimation of RV volumes. Attempts at RV volumes from 2D imaging typically results in an underestimation when compared with MRI techniques, whereas 3D echocardiography has the ability to overcome this shortcoming and is discussed in the following text.[113]

Doppler-Based Methods

The rate in rise of pressure (dP/dt) may be used to assess RV systolic function. Using a CWD signal of a TR jet and the simplified Bernoulli equation at 0.5 and 2 m/sec allow the determination of the change in pressure and the time required generating that pressure (Fig. 14.55). A dP/dt value less than 400 mm Hg divided by time in seconds likely reflects abnormal RV function; however, normative data are lacking.[113]

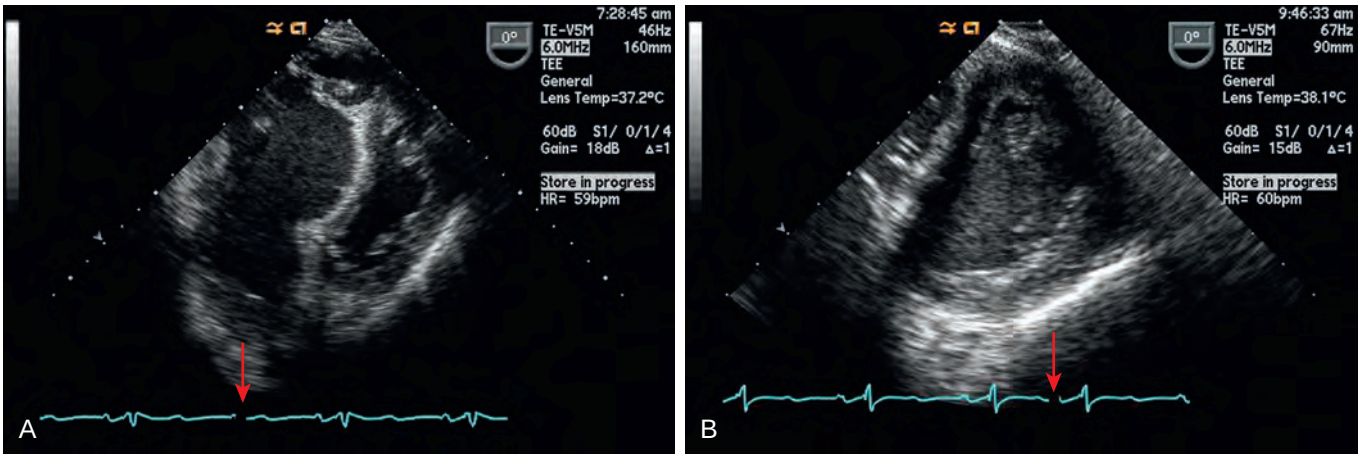


Fig. 14.51 Right ventricular overload (RV) is identified by the timing of septal flattening in the transgastric midpapillary short-axis view. (A) A D-shaped interventricular septum is identified at end-diastole, demonstrating RV volume overload. The *red arrow*, at the end of the P-wave on the electrocardiogram (ECG), marks end-diastole. (B) Septal bowing is noted at end-systole identifying RV pressure overload. The *red arrow*, at the end of the T-wave on the ECG, marks end-diastole. (Video clips available online.)

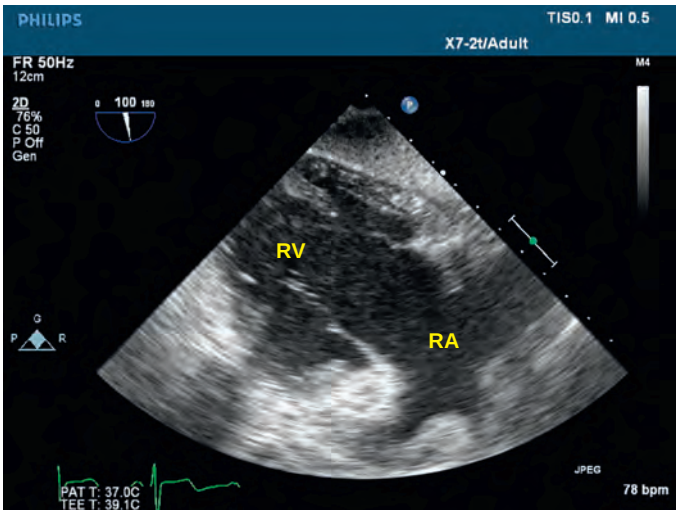


Fig. 14.52 Modified transgastric right ventricular inflow view obtained by deeper insertion and anteflexion of the transesophageal echocardiography probe from the conventional transgastric right ventricular inflow view, offers improved alignment with the tricuspid annulus for M-mode and tissue Doppler imaging interrogation. *RA*, Right atrium; *RV*, right ventricle. (Video clip available online.)

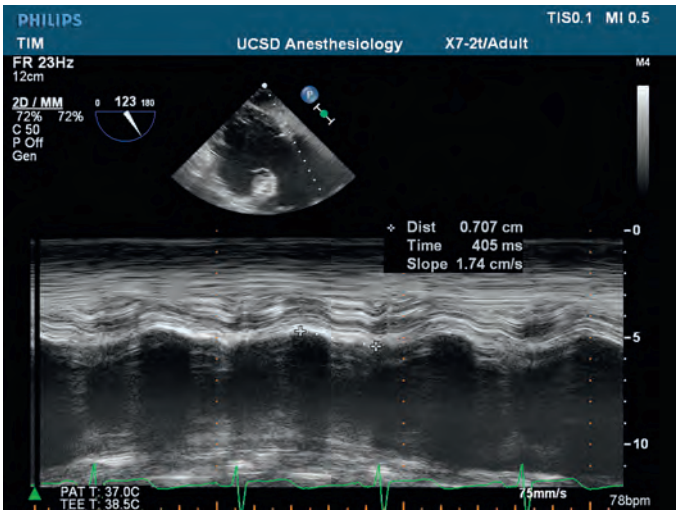


Fig. 14.53 M-mode interrogation of the tricuspid valve annulus is demonstrated in a modified transgastric right ventricular inflow view. The calipers note a reduced tricuspid annular plane systolic excursion (TAPSE) in a patient with pulmonary hypertension and decreased right ventricular function.

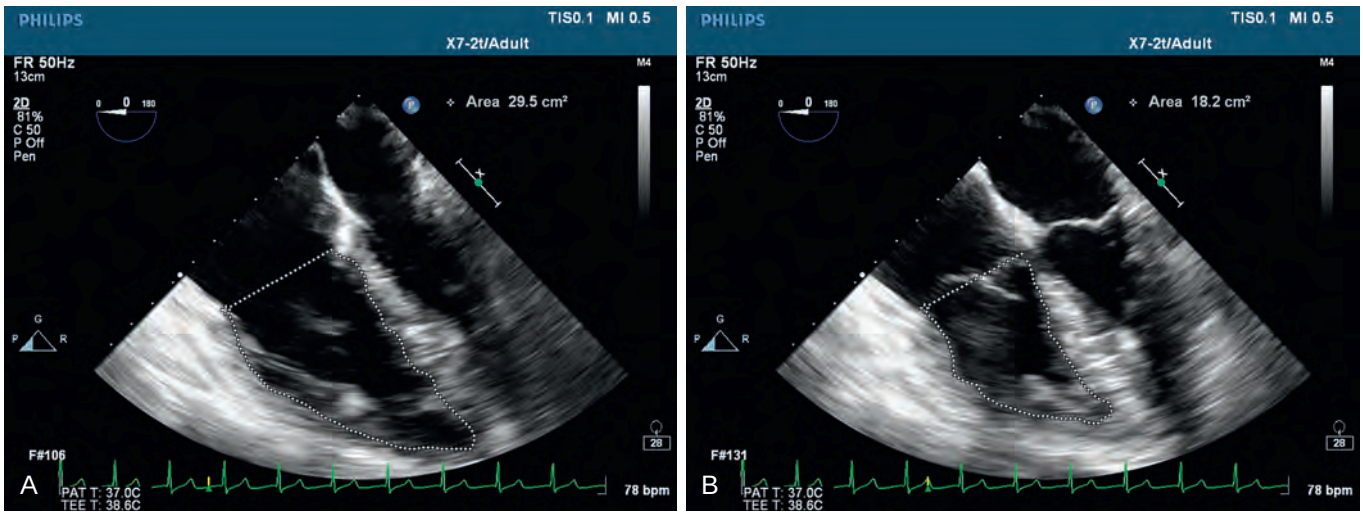


Fig. 14.54 Midesophageal four-chamber view in diastole (A) and systole (B) with the endocardial borders traced from lateral tricuspid valve annulus toward the apex and returning to the septal tricuspid valve annulus. This patient exhibits normal right ventricular systolic function with an FAC of 38.3%. FAC = (EDA – ESA)/EDA. *EDA*, End-diastolic area; *ESA*, end-systolic area. *FAC*, fractional area change.

Tissue Doppler imaging of the RV myocardial motion allows the assessment of both global and regional systolic function. A PWD tissue profile of the lateral basal RV segment near the tricuspid annulus allows measurement of peak systolic velocity (S′) and RV index of myocardial performance (RIMP).

As described earlier with respect to TAPSE, the longitudinal contraction of the lateral wall is a major contributor to RV systolic function. Measurement of the peak systolic velocity of the lateral tricuspid annulus is an easily obtained method of RV assessment (Fig. 14.56). Again, the angle of the Doppler beam is important, rendering the ME four-chamber view suboptimal, whereas a modified RV inflow view provides improved angle alignment.[95] This method correlates well with RV EF determined by MRI; however, assessment can be influenced by severe TR.[114,115] Similar to TAPSE, this method is an extrapolation from a regional measurement to global RV systolic function. Current guidelines suggest a value less than 9.5 cm/sec as indicative of dysfunction.[79]

Finally, the RIMP method of measurement is used to estimate global systolic and diastolic RV function. RIMP is defined as a ratio of the isovolumic time (isovolumetric relaxation time [IVRT] and isovolumetric contraction time [IVCT]) and the ejection time (ET):

$$\text{RIMP} = [(\text{IVRT} + \text{IVCT})/\text{ET}] \qquad \text{[Eq. 14.17]}$$

These time measurements may be measured by either the PWD method or tissue Doppler method. However, different normative values exist, based on the method used to determine RIMP. The PWD method uses two separate cardiac cycle measurements. ET is measured as the duration of flow in the RVOT from either a UE aortic arch SAX view or a TG RV inflow-outflow view. From a separate cardiac cycle, IVRT and IVCT can be measured as the tricuspid closure opening

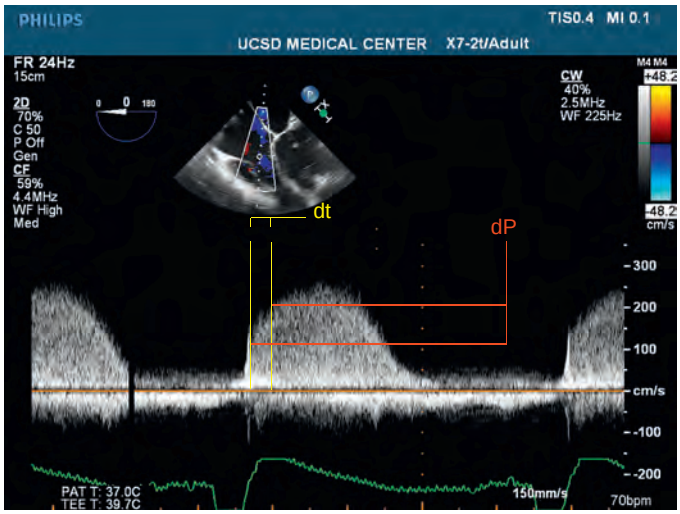


Fig. 14.55 Spectral Doppler analysis of the tricuspid regurgitation jet shows how to perform the calculation of derivative of pressure measured over time *(dP/dt).* Flow velocities of 1 and 2 m/sec are marked, and the time interval between them is measured, converting milliseconds to seconds. The change in pressure in this case is 16 – 4 = 12 mm Hg. dP/dt is calculated as 12 mm Hg/time (in seconds). Values less than 400 mm Hg/sec suggests right ventricular dysfunction.

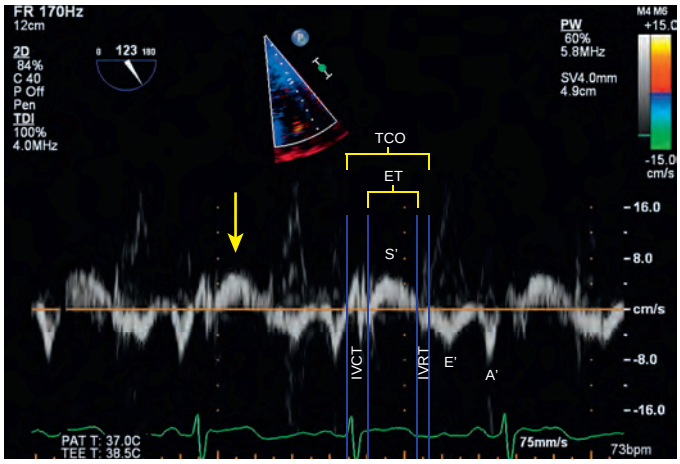


Fig. 14.56 Pulsed-wave tissue Doppler imaging of the lateral tricuspid valve annulus in a modified transgastric right ventricular inflow view. The *yellow arrow* marks the maximum (peak) tissue velocity *(S′).* A peak velocity less than 9.5 cm/sec indicates right ventricular dysfunction. This image also allows the determination of tissue Doppler method of right ventricular myocardial performance index (RIMP), calculated as (TCO–ET)/ET. *A′,* Atrial tricuspid velocity; *E′,* Early tricuspid diastolic velocity; *ET,* ejection time; *IVCT,* isovolumic contraction time; *IVRT,* isovolumic relaxation time; *S′,* peak tricuspid systolic velocity; *TCO,* tricuspid closure opening time.

time (TCO) minus the ET (TCO is the time between the end of a transtricuspid A wave to the beginning of an E wave that includes IVRT, IVCT, and ET). This measurement may be obtained from an ME four-chamber view or ME-modified bicaval view. RIMP may then be calculated using the following equation (Fig. 14.57):

$$\text{RIMP} = \text{TCO} - \text{ET}/\text{ET} \qquad \text{[Eq. 14.18]}$$

The tissue Doppler method, however, can determine RIMP with a single cardiac cycle, reducing heart rate variability from the PWD method. A tissue Doppler profile of the basal RV segment near the tricuspid annulus provides S′, E′, and A′ measurements. ET is the duration of S′, during which TCO is the duration of time between the

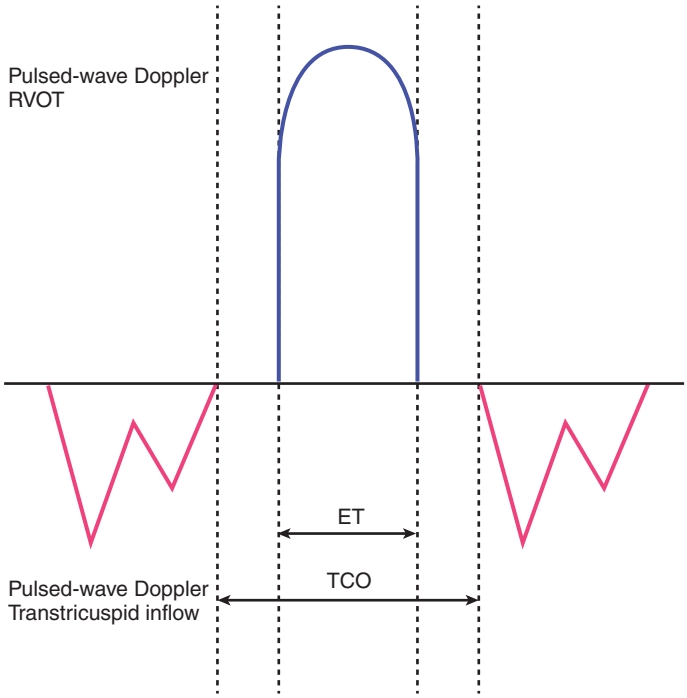


Fig. 14.57 Schematic diagram of time intervals from separate Doppler-derived interrogations of right ventricular outflow tract *(RVOT)* and transtricuspid flow. Above the baseline represents transesophageal echocardiography (TEE)-based Doppler of the RVOT (such as from the upper esophageal [UE] aortic arch short-axis view); below the baseline represents TEE-based Doppler measurement of transtricuspid inflow (such as from the midesophageal four-chamber view). Myocardial performance index is calculated as (TCO – ET). *ET,* Ejection time; *TCO,* tricuspid closure opening time.

end of A′ and the beginning of E′. The calculation of RIMP (TCO – ET/ET) remains the same (see Fig. 14.56). Elevated values of RIMP indicate greater global RV dysfunction with differing normal values between PWD and tissue Doppler methods. Current quantification guidelines note an upper limit of normal as RIMP is greater than 0.43 by PWD and greater than 0.54 by tissue Doppler.[79] Elevated RIMPs have been correlated to severely reduced RV EF by cardiac MRI and predicts hemodynamic instability and mortality after cardiac valvular surgery.[114,116]

Strain-Based Methods

As discussed in Chapter 15, strain represents the percentage of change in myocardial deformation, whereas strain rate represents the rate of the deformational change. When applied to the right ventricle, an ME four-chamber view can provide longitudinal strain measurement by evaluating the myocardial deformation of the base toward the apex (Fig. 14.58). RV global longitudinal strain (RV GLS), an average of strain measurements along the RV free wall, was found to be a sensitive marker of RV dysfunction, had the potential for detecting early RV dysfunction, and correlated well with mortality.[117–119] Both tissue Doppler-based and speckle tracking–based strain require off-line analysis and often use vendor-specific algorithms, which complicate the compilation of normative data. Current guidelines suggest that an RV GLS less than 20% in deformation is suggestive of abnormal RV function; however, further research is necessary to evaluate its perioperative role.[79]

Three-Dimensional Methods

Three-dimensional echocardiography (with off-line semiautomatic border detection) allows volumetric renderings of the right ventricle, as well as the determinations of right ventricular end-diastolic volume (RVEDV) and right ventricular end-systolic volume (RVESV),

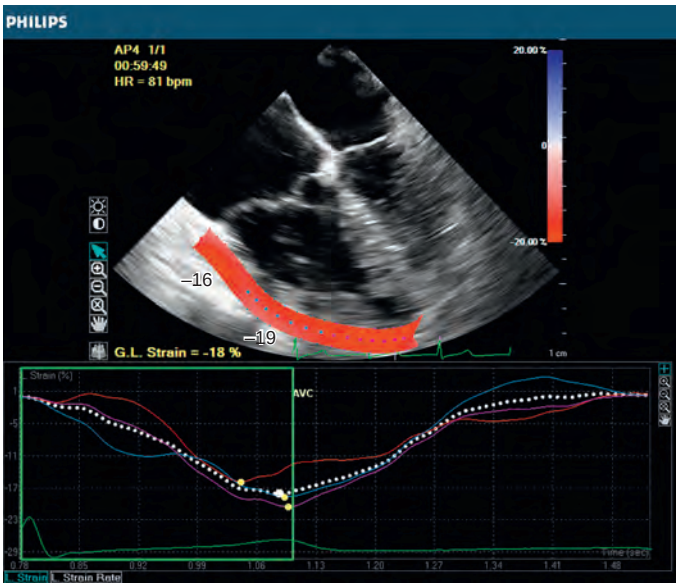


Fig. 14.58 Speckle-tracking–based strain evaluation of the right ventricle from a midesophageal four-chamber view in a patient with right ventricular (RV) enlargement and pulmonary hypertension. RV global longitudinal strain (RV GLS) is calculated as an average of strain measurements along the right ventricular free wall, including basal, midportion and apical RV segments.

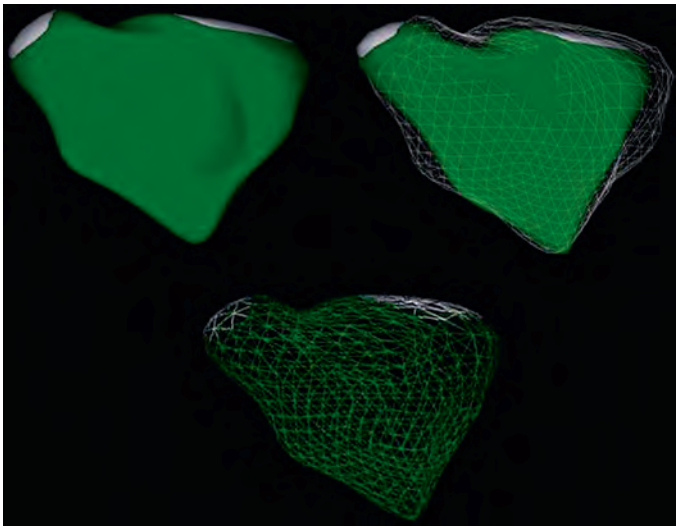


Fig. 14.59 Three-dimensional volumetric analysis using the off-line four-dimensional right ventricular-function software (TomTec Imaging Systems, Germany). *(Reproduced with permission from Jainandunsing JS, Matyal R, Shahul SS, et al. 3-dimensional right ventricular volume assessment.* J Cardiothorac Vasc Anesth. *2013;27:367–375.)*

SV, and EF, which are not dependent on geometric assumptions. One commercially available package, 4D RV-function (TomTec Imaging System, Munich, Germany), uses RV-focused 3D echocardiography data sets from either TTE or TEE origin and provides semiautomatic volume rendering with RV volumes and EF[120] (Fig. 14.59). This package may be used intraoperatively from TEE-derived data sets.[117,121] Three-dimensional echocardiography–based RV volumes correlated to cardiac MRI and radionuclide ventriculography, whereas intraoperative 3D echocardiography–based RV EF has been correlated to both TTE-based 3D echocardiography RV EF and 2D-based measurements of RV function, such as RV FAC and TAPSE.[121–123] Current guidelines suggest a 3D echocardiography RV EF less than 45% is indicative of RV dysfunction.[79]

Hemodynamic Assessment

Intravascular Pressures

Echocardiographic techniques may be used to estimate intracardiac and intravascular gradients. Newton's conservation of energy states that the energy within a closed system must remain the same. If blood passes through an area of stenosis, then the potential energy (as represented by high pressure) must be converted into kinetic energy as observed as high blood-flow velocities. In addition, if the system is pulsatile, then some energy will be expended for blood acceleration and deceleration. Finally, some energy will be lost as heat by the viscous forces generated by friction. These relationships have been described by Bernoulli as:

$$p_1 - p_2 = \tfrac{1}{2}\rho(v_2^2 - v_1^2) + \rho\int(dv/dt)ds + R(\mu) \qquad \text{[Eq. 14.19]}$$

where, p_1 is the pressure proximal to the obstruction; p_2 is the pressure proximal to the obstruction; $p_1 - p_2$ is the pressure difference over the obstruction; v_1 is the velocity proximal to the obstruction; v_2 is the velocity proximal to the obstruction; ρ is the density of blood, which is equal to approximately 1.06 gm/mL; $\int(dv/dt)ds$ is the integral of the blood-flow acceleration over a given distance; and $R(\mu)$ is the resistance (R) and a function of blood viscosity (μ).

The first term represents the kinetic energy expenditure that results in the acceleration of blood over the obstruction. The second term of the equation represents unsteady acceleration and deceleration of pumping blood. These are *inertial* terms. The final term represents kinetic energy loss attributable to viscous friction. The Bernoulli equation assumes reasonably that blood is incompressible. During clinical application, the energy expended attributable to the cyclic acceleration and deceleration, as well as the energy loss attributable to viscous forces, are both negligible and may be ignored, leaving just the first term. Because both velocities are squared and v_2 is significantly larger than v_1 ($v_2 \gg v_1$), v_1 may be ignored as well, the equation may be simplified to:

$$p_1 - p_2 = 0.5\,\rho(v_2^2) \qquad \text{[Eq. 14.20]}$$

For clinical echocardiography, the simplified Bernoulli equation may be modified further to convert SI units (pascals [Pa], kg/m^2) to mm Hg. Because 1 mm Hg is equal to 133.3 Pa:

$$p_1 - p_2 \times 133.3 = 0.5 \times 1060 \times v_2^2$$

Thus $p_1 - p_2 = 3.976v_2^2$

Therefore the clinically relevant simplified Bernoulli equation is:

$$p_1 - p_2 = 4v_2^2 \qquad \text{[Eq. 14.21]}$$

With this formula and canceling assumptions, the pressure gradient across a fixed orifice can be approximated. It may be applied to the measurement of intravascular pressures, as well as the gradient across a stenotic orifice.

Determination of Intravascular Pressures

The velocity of blood traveling through a regurgitant valve is a direct application of pressure gradient calculations and can be used to calculate intracardiac pressure. For example, TR velocity reflects systolic pressure differences between the right ventricle and the right atrium. RV systolic pressure can be obtained by adding estimated or measured RA pressure (RAP) to the systolic pressure gradient across TV during systole. This systolic gradient may be estimated as 4(TR velocity)^2. In the absence of RVOT obstruction, PA systolic pressure will be the same as RV end-systolic pressure (RVESP). For example,

If TR velocity = 3.8 m/sec and RAP = 10 mm Hg, then,

$$\text{RVESP} = (\text{TR velocity})^2 \times 4 + \text{RAP}$$

$$4(3.8)^2 = 58 \text{ mm Hg} + 10 \text{ mm Hg}$$

$$\text{RVESP} = \text{PA systolic} = 68 \text{ mm Hg}$$

Similarly, pulmonary regurgitation (PR) velocity represents the diastolic pressure difference between the PA and the right ventricle. Therefore PA end-diastolic pressure = right ventricular end-diastolic pressure (RVEDP) + 4(PR end-diastolic velocity)^2. Note that RVEDP is equal to RAP (estimated or measured). MR velocity represents the systolic pressure difference between the left ventricle and the left atrium. In patients *without LVOT obstruction or AS*, systolic blood pressure is essentially equal to LV systolic pressure; therefore LAP is equal to SBP – 4(MR)^2. Finally, aortic regurgitation (AR) velocity reflects the diastolic pressure gradient between the aorta and the left ventricle. In summary,

$$\text{PAP systolic} = \text{RVESP} = 4(\text{TR})^2 + \text{RAP}$$

$$\text{PAP diastolic} = 4(\text{PR})^2 + \text{RAP}$$

$$\text{LAP} = \text{SBP} - 4(\text{MR})^2$$

$$\text{LVEDP} = \text{DBP} - 4(\text{AR})^2$$

Stevenson[124] compared six different echocardiographic techniques to measure PAP. When compared with direct measurements, some of these techniques yielded highly accurate correlations (r = 0.97), but they were not always applicable in all patients.

Cardiac Output

Two-Dimensional Echocardiographic Measurement

SV is calculated as the difference between EDV and ESV. The ASE has recommended that the diastolic dimension coincide with the Q wave on the ECG. The end-systolic dimension is best measured at the time of the peak downward motion of the posterior endocardium. When TEE was used to obtain ventricular dimensions, correlations between echo and indicator dilution varied from r = 0.72 in patients undergoing cardiac surgery to r = 0.97 in critically ill patients.[125] In patients undergoing CABG, SV was derived from 2D SAX views using echocardiography.[126] Comparisons of echo-derived CI with simultaneous thermodilution-derived CI yielded a correlation coefficient of 0.80.

Doppler Measurements

In addition to measuring gradients, the measurements of blood-flow velocity may be used to estimate flow with a given structure. The derivative of a function is the slope of the curve at a given point, whereas an integral of a function is the area under the curve between two points along its X axis. Given an equation that would describe distance traversed, the time derivative or slope at any given point would represent its velocity; the time derivative of the velocity at any given point would be its acceleration (Fig. 14.60). Similarly, given a graph of acceleration versus time, the integral would yield a velocity measurement; the integral of a velocity-versus-time graph would yield a distance traversed (ignoring initial conditions). A CWD velocity profile is a display of velocity versus time. If this velocity profile is integrated between two time points, that is, calculates the area under the curve, then the distance traversed of a "region of blood" during this period may be estimated. Because flow velocity is not constant throughout a flow cycle, all of the flow velocities during the entire ejection period are integrated to measure "distance traversed" of this "region of blood." This integration of flow velocities in a given period is called the *velocity-time integral* (VTI) and has the units centimeters. When flows at a particular location along the LVOT or aorta are required (ie, spacial specificity is necessary), then PWD should be used, provided velocity does not exceed the phased-wave Nyquist limit. High PRF can be used. Multiple regions of interest points may be seen, indicating range ambiguity of the cursor. If the velocities are too high, then localizing the jet without assumptions is not possible.

VTI may be used to calculate flow. The cross-sectional area (CSA) for a circular orifice, such as the LVOT is:

$$\text{CSA} = \pi(\text{D}/2)^2 \qquad \text{[Eq. 14.22]}$$

where D represents the diameter obtained by 2D imaging. Flow across a given orifice or SV is equal to the product of the CSA of the orifice and distance traversed during a single cardiac cycle, as calculated by the VTI. SV and CO may thus be calculated as:

$$\text{SV} = \text{CSA} \times \text{VTI} \qquad \text{[Eq. 14.23]}$$

$$\text{CO} = \text{SV} \times \text{HR} \qquad \text{[Eq. 14.24]}$$

When using these equations, there are a number of assumptions, including (1) laminar blood flow in the area interrogated; (2) a flat or blunt flow velocity profile, such that the flow across the entire CSA interrogated is relatively uniform; and (3) Doppler angle of incidence between the Doppler beam and the main direction of blood flow is less than 20 degrees, so that the underestimation of the flow velocity is less than 6%.

An example of the use of PWD to measure SV is illustrated. In Fig. 14.61A, the ME LAX view is used to image the LVOT. The diameter of the LVOT is 2.2 cm, which corresponds to a radius of 1.1 cm. As described earlier,

$$\text{CSA} = \pi\, r^2 = 3.14\,(1.1)^2 = 3.80\ \text{cm}^2$$

In Fig. 14.61B, a PWD spectrum is measured through the LVOT as imaged in the deep TG view, and the VTI is calculated as 19 cm. The SV is:

$$\text{SV} = \text{CSA} * \text{VTI} = 3.8\ \text{cm}^2 * (19\ \text{cm}) = 72\ \text{cm}^3$$

A number of Doppler methods have been attempted to calculate SV. Probably the most popular and accepted method is the LVOT approach. Other methods using the mitral, tricuspid, and pulmonic orifices have been attempted with variable results. Their respective accuracy is dependent on the angle between the insonated Doppler signal and blood flow. It should be noted, however, that the major determinant of variability in estimating SV by the use of any technique is the accurate measurements of the CSA. As described in Equation 14.20, the measurement of the CSA is directly proportional to the

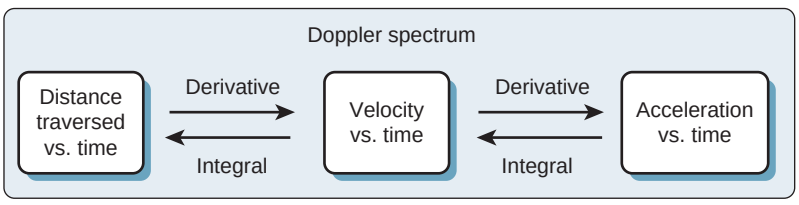


Fig. 14.60 Relationship among distance, velocity, and acceleration. The derivative of the function of position versus time results in its velocity; the derivative of the velocity at any given point would be its acceleration. Similarly, the integral of acceleration is velocity; the integral of velocity is the distance traversed. A Doppler spectrum is displayed a velocity versus time spectrum. If one integrates this spectrum between two time points, that is, calculates the area under the curve, the distance traversed during this period may be calculated.

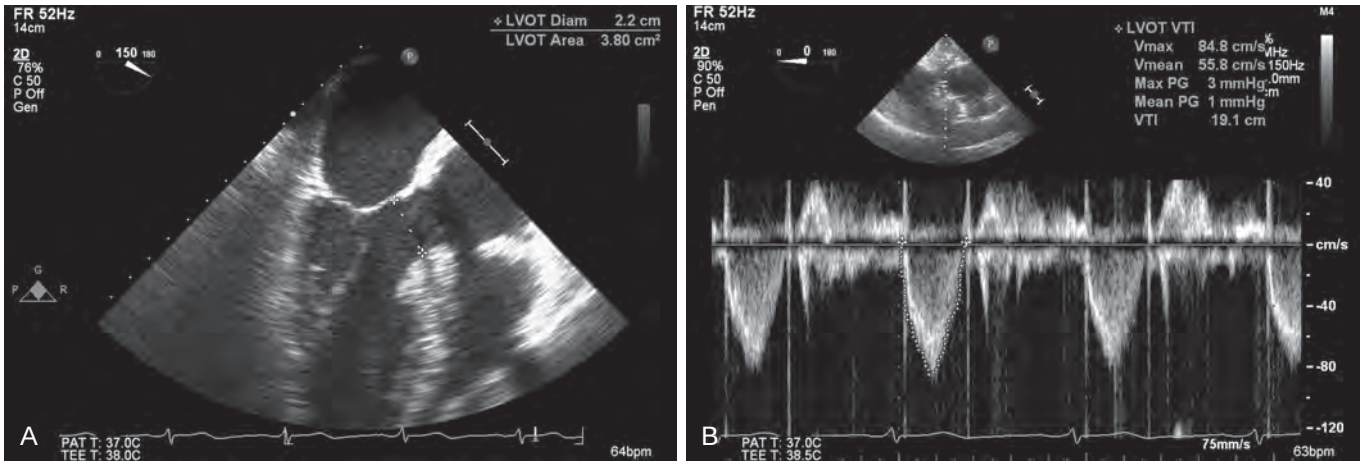


Fig. 14.61 Calculation of cardiac output. (A) Midesophageal long-axis view. The diameter of the left ventricular outflow tract is measured. (B) Velocity time integral through the left ventricular outflow tract. Since spatial specificity is necessary, a pulsed-wave Doppler spectrum is used.

square of the radius; therefore any error in diameter measurement would be squared in the final results.

A second source of variability in measuring flow involves the proper recording of reproducible Doppler signals. If the LVOT is chosen as the CSA, then the VTI should be obtained from the Doppler signal at this level. For this purpose, the systolic forward flow must be obtained from either a deep TG or TG LAX view. The sample volume of the PWD should be placed in the high portion of the LVOT *exactly* at the same level where the diameter was measured. Occasionally, the Doppler signal is difficult to obtain, and the morphologic structure of the spectrum may be similar to a triangle with a spike at the peak velocity rather than a round "bell-shape" flow signal. Under such circumstances, estimating the VTI is inappropriate, because underestimations or overestimations are likely to result. If attention is given to proper recording techniques, then the interobserver variability in measuring the aortic VTI in normal subjects should be less than 5%.

When the results of various studies are compared, it is important to know the method of calculating the VTI and the CSA, as well as where the Doppler sampling volume was located. Because PWD provides a spectral display of instantaneous velocities, mean velocities or velocity modes are used for the integration of flow velocity. The measurement of the mitral orifice diameter should probably be repeated at various angles. It has been well established that the size of the mitral orifice varies with varying flows. The importance of the sample volume location has been demonstrated in several studies.[127] The SV is underestimated when the sampling volume is placed at the mitral leaflet tips and overestimated when placed at the mitral annulus.

Using TEE, Roewer and colleagues[128] calculated SV in 27 surgical patients. A comparison of Doppler-determined CO values with those obtained by thermodilution yielded an excellent correlation (r = 0.95). LaMantia and associates,[129] who performed a similar study in 13 cardiac surgical patients, found only a modest correlation (r = 0.68). Other investigations have used pulmonary arterial Doppler-flow velocity integrals and estimations of the vessel area to perform off-line calculations of SV and CO.[130] Muhiudeen and colleagues[131] found that transmitral Doppler CO did not correlate with that obtained by thermodilution and pulmonary arterial Doppler CO correlated only weakly (r = 0.65) with that obtained by thermodilution. They concluded that transesophageal Doppler has significant limitations at the off-line monitor of CO. In contrast, Savino and associates[130] found good agreement and correlation (r = 0.93) between transesophageal pulmonary arterial Doppler and thermodilution CO. They were, however, unable to visualize the main PA in 24% of patients. In addition, the method was tedious and not suitable for online analysis with current equipment and software.

In 50 cardiac surgery patients, CO obtained by thermodilution was compared with deep TG PWD through the LVOT.[132] Of these patients, 7 patients were excluded from analysis because Doppler measurements could not be obtained. Good correlations were obtained with a bias of 0.015 L/min with 29% error. The authors estimated that these Doppler estimates of CO were 92% sensitive and 71% specific for detecting more than 10% change in CO.

The use of 3D echocardiography may increase the accuracy of CO measurements. Because geometric variability is more easily compensated in these measurements, ESV and EDV may be calculated and CO may be determined. Culp and associates[133] compared 3D echocardiographic determinations of CO with thermodilution during the period before bypass in 20 patients undergoing cardiac surgery. In their study, the mean bias was 0.27 L/min with a plus or minus 35% limit of agreement. They observed a good correlation between these two measurements; however, there were significant bias and wide limits of agreements among the measurements. Off-line analysis of 3D echocardiographic images may be used to estimate CO. In a study of 40 patients undergoing heart transplantation, 3D echocardiographic reconstruction of LVEDV and LVESV were estimated, allowing for the calculation of SV and CO.[127] These CO measurements were closely correlated with thermodilution-derived measures, with a mean bias of 0.06 L/min and a standard deviation of 0.4 L/min. It should be noted, however, that each measurement required approximately 3 minutes per case, and poor image quality precluded analysis in four patients. Three-dimensional TTE determination of SV was highly correlated to catheterization data.[134] These 3D data sets tended to underestimate the SV by 7.5 mL or 17%.

As described earlier, homogeneous laminar flow and a cylindrical outlet is assumed during Doppler measurements. This, unfortunately, may not be the case. Three-dimensional color-Doppler echocardiography may be used to more accurately define the CSA of either the LVOT or the MV, as well as more accurately describe the blood flow through these areas. In 3D color-Doppler determination of CO, multiple 2D echocardiographic slices with their associated Doppler data are obtained through a particular surface. Flow data may be computed using Gaussian control surface theory.[135] Gaussian theory states that for a curved surface, the flow passing through the surface is equal to the sum of all velocity components normal to the surface (Fig. 14.62).

In a group of 47 postcardiac transplantation patients, CO was determined by thermodilution, as well as 2D and 3D Doppler echocardiography through both the LVOT and the MV.[136] The 3D measurement provided a lower bias and narrower limits of agreement both in the LVOT measurements (−1.84 ± 16.8 vs −8.6 ± 36.2 mL) and in the MV inflow position (−0.2 ± 15.6 vs 10.0 ± 26 mL).

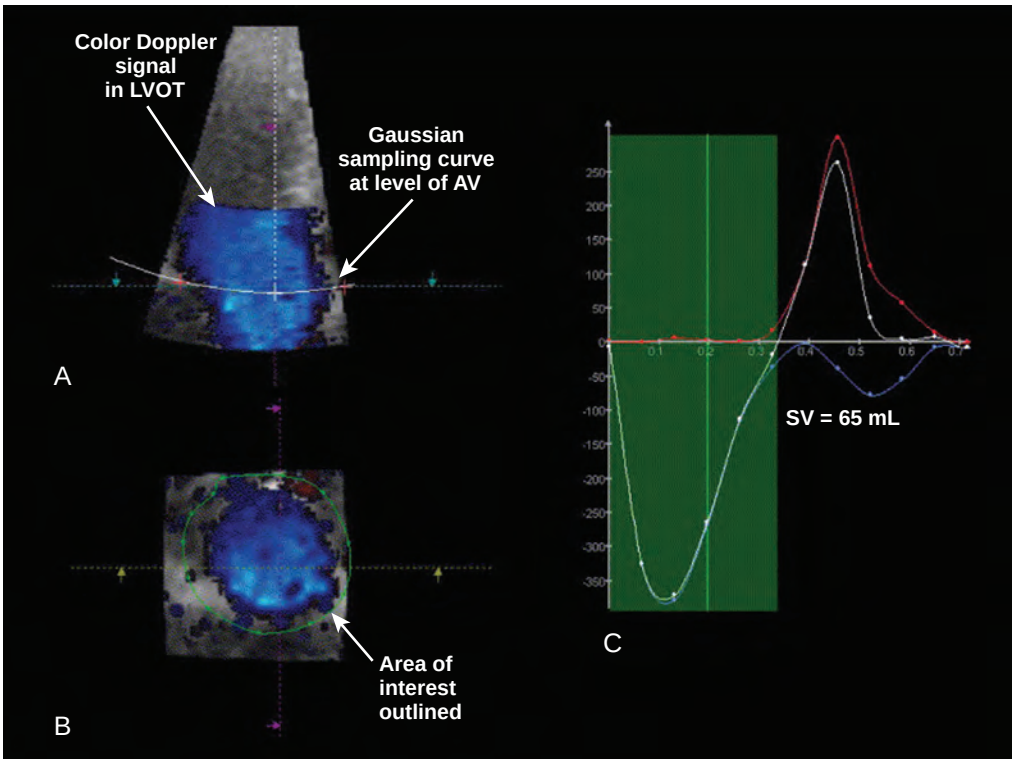


Fig. 14.62 Calculation of flow using Gaussian control surface theory. (A) One of two orthogonal cut planes of real-time three-dimensional Doppler echocardiographic volume with sampling curve placed at the level of the aortic valve *(AV)*. (B) Third plane as if viewed from left ventricular cavity, with the region of interest, Doppler signal within left ventricular outflow tract *(LVOT)*, outlined. (C) Flow rate–time curve generated by integration of Doppler signals within the region of interest, at level of sampling curve, over course of systole *(green)*. *SV,* Stroke volume. *(Reproduced with permission from Pemberton J, Ge S, Thiele K, et al. Real-time three-dimensional color Doppler echocardiography overcomes the inaccuracies of spectral Doppler for stroke volume calculation.* J Am Soc Echocardiogr. *2006;19:1403–1410).*

Contrast Applications

Diagnostic applications for contrast echocardiography include enhancement of endocardial borders from qualitative assessment of wall-motion abnormalities, measurement of LV function, assessment of congenital heart disease, quantification of valvular regurgitation, enhancement of CFD signals, and assessment of myocardial perfusion. During cardiac surgery, the special and unique applications of myocardial contrast echocardiography (MCE) include measurements of perfusion area after CABG surgery, assessment of the quality of coronary artery grafts and cardioplegia distribution, and correct assessment of the results of surgery for ventricular septal defect. Noncardiac intraoperative applications include assessment of perfusion in the kidney and in skeletal muscle. Work is ongoing to investigate the potential for analyzing cerebral blood flow with contrast-echocardiographic techniques.

Enhancement of Right-Sided Structures

Hand-agitated saline solutions are still useful to enhance right-sided structures. These saline solutions can be easily prepared by hand agitation of saline between two 10-mL Luer lock syringes connected by a three-way stopcock; small amounts of blood or air may be added to improve right-sided opacification. This technique is most commonly used to opacify the right atrium and right ventricle, assisting in the diagnosis of intraatrial and ventricular shunts and to enhance pulmonary arterial Doppler signals. The most common indication is the detection of a PFO. After obtaining a bicaval view, a Valsalva maneuver is induced, and hand-agitated saline is injected into a large vein. After the right atrium is opacified, the Valsalva is released, and the left atrium is examined for contrast (Fig. 14.63; see Video 14.51).

Left Ventricular Opacification

The commercially available contrast agents allow for left ventricular opacification (LVO) as well. Relatively low MI modes are usually used (less than 0.2) to allow for bubble detection without bubble destruction. The images are processed such that the linear scatters from tissue are completely eliminated, leaving only nonlinear scatters from the bubble contrast. The LVO allows enhancement of LV endocardial borders in patients whose normal studies are challenging.[137,138] Such challenging studies include patients who are obese, with pulmonary disease, are critically ill, or are on a ventilator.[21] The use of LVO substantially increases the accuracy of LV volume determination, compared with electron-beam computed tomography measurements. In addition, its use decreases interobserver variability associated with these measurements and increases the number of myocardial segments that may be accurately described during stress echocardiography.[139,140] Underestimation of LV volume measurements, which is common with standard echocardiography, may be virtually eliminated with the use of LVO.[141] Finally, LVO provides greater visualization of structural abnormalities such as apical hypertrophy, noncompaction, ventricular thrombus, endomyocardial fibrosis, LV apical ballooning (Takotsubo cardiomyopathy), LV aneurysms or pseudoaneurysms, and myocardial rupture.[21]

Aortic Dissections

Echocardiographic contrast may be used to diagnosis aortic dissections. Artifacts may be distinguished from true aortic dissection and artifact by the homogeneous distribution of contrast within the aortic lumen.[21] The intimal flap may be visualized, the entry and exit points may be identified, and the extension into major aortic branches may be

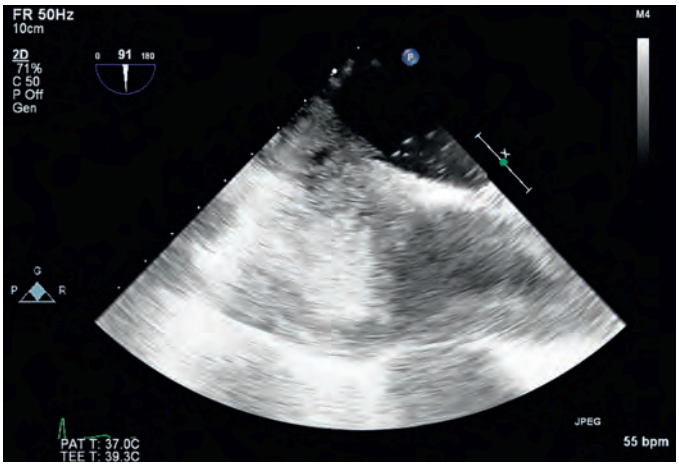


Fig. 14.63 Injection of hand-agitated saline. The right atrium is opacified by hand-agitated saline central venous injection. Several bubbles may be seen in the left atrium after traversing a patent foramen ovale in the atrial septum. (Video available online.)

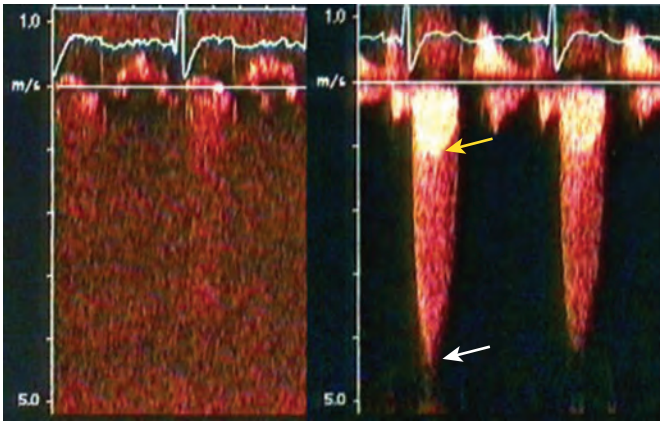


Fig. 14.64 Doppler enhancement of aortic stenosis. The image displays the Doppler spectrum through the left ventricular outflow tract in a patient with aortic stenosis. The image on the *left* is without contrast and the image on the *right* is after contrast enhancement. The contrast-enhanced image clearly demonstrates the high-velocity envelope consistent with aortic stenosis that could not be visualized without contrast. The *yellow arrow* indicates the velocity through the left ventricular outflow tract, and the *white arrow* denotes flow through the aortic valve. *(Reproduced with permission from Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography.* J Am Soc Echocardiogr. *2008;21:1179–1201.)*

more easily defined. The use of contrast further increases the successful differentiation between the true and false lumen.

Doppler Enhancement

The administration of contrast will enhance the echocardiographic Doppler spectrum, in which the signal is weak or suboptimal.[142] The enhancement is particularly useful in the evaluation of AS but may also be used with transmitral evaluation, pulmonary venous flow determination, or regurgitant tricuspid valvular flow (Fig. 14.64). Whereas the threshold for detecting contrast is substantially less for Doppler, compared with 2D imaging, contrast agents are usually used initially for the latter application.

Myocardial Perfusion

The second-generation agents allow for perfusion of the myocardial microcirculation. This perfusion allows for the assessment of perfusion patterns, coronary artery stenosis, and myocardium at risk during acute coronary syndromes.[20] Currently, only Imagify has US Food and Drug Administration (FDA) approval for myocardial perfusion imaging.

TABLE 14.9 Diagnosis of Fixed Myocardial Deficits, Ischemia, Stunning, and Hibernation Based on Perfusion and Wall Motion Findings

	Rest Perfusion	*Stress Perfusion*	*Rest Wall Motion*	*Stress Wall Motion*
Fixed deficit	Deficit	Deficit	Akinetic	Akinetic
Ischemia	Normal	Deficit	Normal	RWMA
Stunning	Normal		RWMA	
Hibernation	Hypoperfusion		Hypokinetic	

RMWA, Regional wall motion abnormality.

Lindner and colleagues[143] described a method for the quantification of myocardial blood flow using contrast echocardiography. If a contrast agent is administered at a steady rate, then the blood concentration and myocardial concentration of the contrast agent will equilibrate. If a single high-amplitude (ie, high MI) ultrasound pulse is delivered to a myocardial region of interest, then the microbubbles will be destroyed; they will be replenished as the contrast-filled blood perfuses the myocardium. The rate of contrast replenishment in the myocardium is directly related to myocardial blood flow. Repeated ultrasound pulses are delivered at short frequencies until a maximum MCE signal is obtained. A time-myocardial contrast intensity curve is constructed. Myocardial-contrast echocardiographic-derived indications of myocardial perfusion rate have relatively good between-study and between-reading reproducibility.[144]

If contrast echocardiography is used in conjunction with traditional echocardiography, then different flow patterns can be described as outlined in Table 14.9. A fixed myocardial deficit may be diagnosed with a perfusion deficit during rest and stress with akinetic segments during both of these periods. An ischemic segment may be defined as a segment with normal perfusion and wall motion with rest and a perfusion deficit during stress that is accompanied by a RWMA. Myocardial stunning may be diagnosed if normal perfusion is observed during rest in the presence of a hypokinetic rest wall motion, and hibernation may be diagnosed with rest hypoperfusion and with hypokinetic rest wall motion. The addition of MCE may increase the sensitivity, but not the specificity, of dipyridamole-exercise echocardiography. Moir and colleagues[145] combined MCE with dipyridamole-exercise echocardiography in 85 patients. They detected significant coronary artery stenosis in 43 patients involving 69 coronary areas. The addition of MCE-improved sensitivity for the detection of CAD (91% vs 74%; $P = 0.02$) and accurate recognition of disease extent (87% vs 65% of territories; $P = 0.003$).

Valvular Evaluation

Aortic Valve Evaluation

Two-dimensional TEE provides information on valve area, leaflet structure, and mobility. The valve has three fibrous cusps, right, left, and noncoronary, that are attached to the root of the aorta. Each cusp has a nodule, the nodule of Arantius, in the center of the free edge at the point of contact of the three cusps. The spaces between the attachments of the cusps are called the *commissures*, and the circumferential connection of these commissures is the *sinotubular junction*. The aortic wall bulge behind each cusp is known as the *sinus of Valsalva*. The sinotubular junction, the sinuses of Valsalva, the valve cusps, the junction of the AV with the ventricular septum, and the anterior MV leaflet comprise the AV complex. The aortic ring is at the level of the ventricular septum and is the lowest and narrowest point of this complex. The three leaflets of the AV are easily visualized, and vegetations or calcifications can be identified on basal transverse imaging or longitudinal imaging.

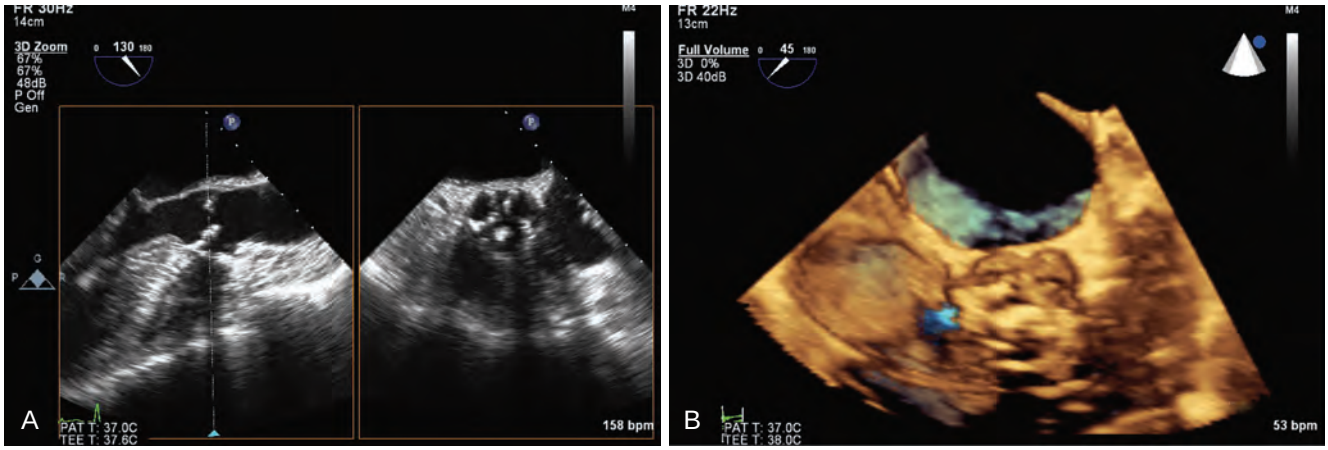


Fig. 14.65 Aortic stenosis. (A) Both midesophageal aortic valve (AV) short- and long-axis views are demonstrated. The AV is stenotic, thickened, and calcific with significant valvular restriction. (B) Three-dimensional reconstruction. The AV is viewed from the ascending aorta. (Video available online.)

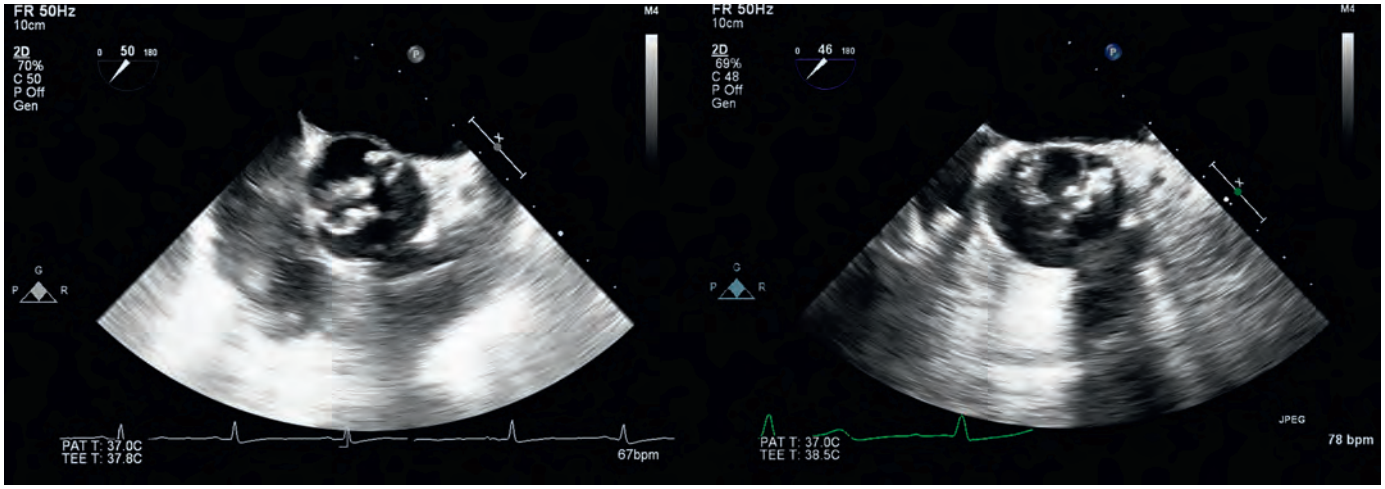


Fig. 14.66 Aortic stenosis. Bicuspid versus unicuspid aortic stenosis. Midesophageal aortic valve short-axis views. *(Left)* Bicuspid aortic valve. A fusion of the right and left coronary cusps is demonstrated, producing a bicuspid aortic valve. *(Right)* Unicuspid aortic valve is characterized by a single commissure opening and closing as a single unit. (Video available online.)

Aortic Stenosis

AS may be caused by congenital unicuspid, bicuspid, tricuspid, or quadricuspid valves; rheumatic fever; or degenerative calcification of the valve in older adults (Figs. 14.65 and 14.66; see Video 14.52).[146,147] Valvular AS is characterized by thickened, echogenic, calcified, immobile leaflets and is usually associated with concentric LV hypertrophy and a dilated aortic root. The valve leaflets may be domed during systole; this finding is sufficient for a diagnosis of AS.[148]

The quantification of AS is summarized in Table 14.10. Aortic valve area (AVA) may be measured by planimetry (Fig. 14.67).[149] A cross-sectional view of the AV orifice may be obtained by using the ME AV SAX view, which corresponds well to measurements of the AVA obtained by TTE and cardiac catheterization, assuming the degree of calcification is not severe. With severe calcification, echocardiographic shadowing is significant, which limits the accuracy of this measurement.

Alternatively, AS may be quantified using CWD echocardiography (Fig. 14.68).[150] The evaluation of severity, however, is contingent on the alignment of the ultrasonic beam with the direction of blood flow through the LVOT. This alignment may be obtained using either a deep TG or TG LAX view. Because severe stenosis limits AV opening, the imaging of the actual AV orifice may be challenging. Superimposition of a CFD spectrum over the calcific AV may guide accurate CWD curser placement (Fig. 14.69; see Video 14.53). Normal Doppler signals across the AV have a velocity of less than 1.5 m/sec and have peak signals during early systole. With worsening AS, the flow velocity increases and the peak signal is later in systole. Severe AS is characterized by a peak velocity of greater than 4 m/sec, which will usually correspond to a mean gradient greater than 40 mm Hg.[151] These high

TABLE 14.10 Summary of Aortic Stenosis

	Aortic Sclerosis	*Mild*	*Moderate*	*Severe*
Aortic jet velocity (m/sec)	≤2.5	2.6–2.9	3.0–4.0	>4.0
Mean gradient (mm Hg)		<20	20–40	>40
Aortic valve area (cm^2)		>1.5	1.0–1.5	<1.0
Indexed aortic valve area (cm^2/m^2)				≤0.6

Adapted from Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1–23.

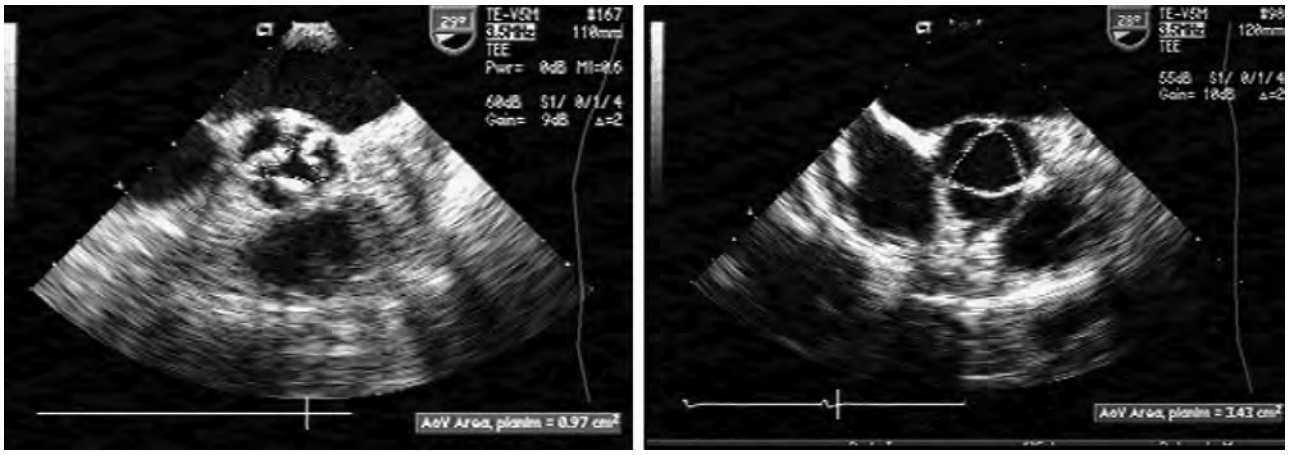


Fig. 14.67 Aortic valve stenosis by planimetry. The panel on the *left* illustrates a stenotic aortic valve, whereas the panel on the *right* illustrates a normal aortic valve. Because calcification is not significant, planimetry may be used to estimate aortic valve area.

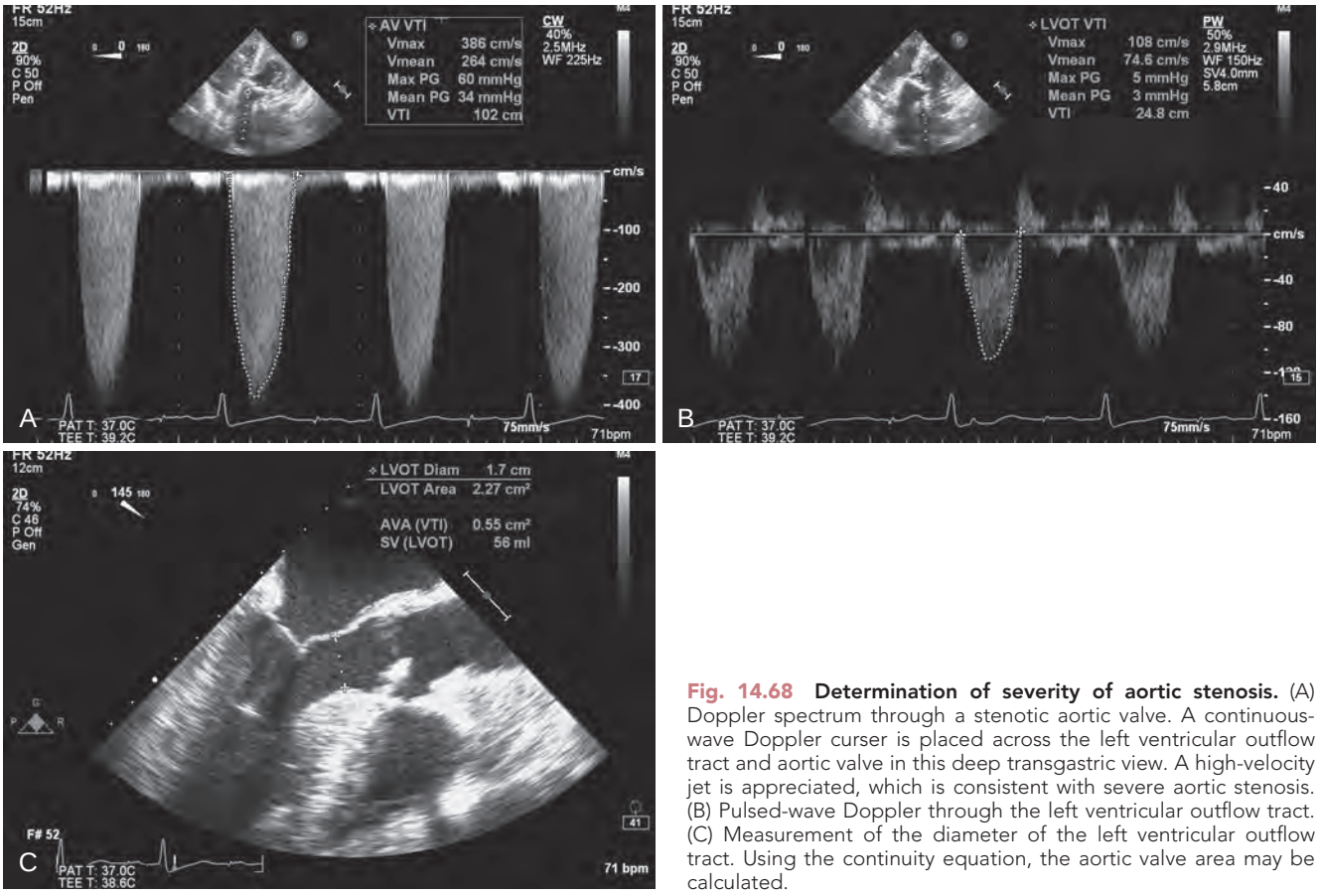


Fig. 14.68 Determination of severity of aortic stenosis. (A) Doppler spectrum through a stenotic aortic valve. A continuous-wave Doppler curser is placed across the left ventricular outflow tract and aortic valve in this deep transgastric view. A high-velocity jet is appreciated, which is consistent with severe aortic stenosis. (B) Pulsed-wave Doppler through the left ventricular outflow tract. (C) Measurement of the diameter of the left ventricular outflow tract. Using the continuity equation, the aortic valve area may be calculated.

velocities will limit the use of PWD and necessitate the use of either CWD or high PRF Doppler.

The higher velocity central jet is characterized by a high-pitched audio sound and a fine feathery appearance on the Doppler signal and is usually less dense than the thicker parajets that are distal to the valve. Peak and mean transvalvular gradients may be calculated using the peak and mean velocities of the signals, respectively. Peak gradients measured by Doppler ultrasonography tend to be higher than those measured in the cardiac catheterization laboratory because Doppler-determined peak gradients are instantaneous, whereas those reported by the cardiac catheterization laboratory are peak-to-peak systolic pressure differences. In addition, Doppler determinations of peak gradient may overestimate the gradient because of pressure recovery effects (Fig. 14.70). As blood flows past a stenotic AV, the potential energy of the high-pressure left ventricle is converted into kinetic energy; there is a decrease in pressure with an associated increase in velocity. Distal to the orifice, flow decelerates again with both conversion of this loss of kinetic energy into heat, as well as a reconversion of some kinetic energy into potential energy with a corresponding increase in pressure. This increase in pressure distal to the stenosis

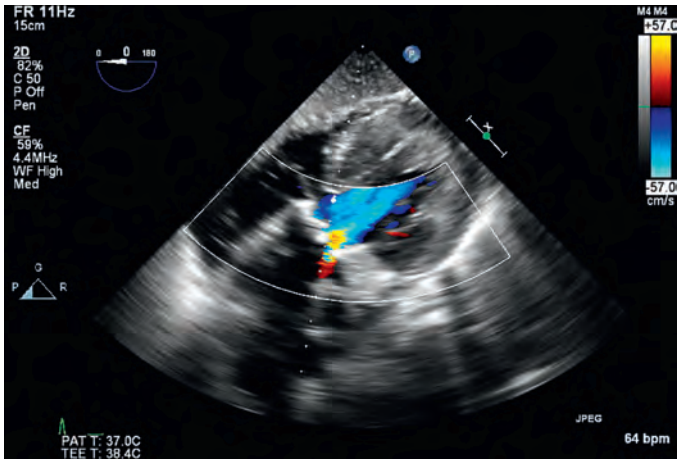


Fig. 14.69 Lining up the cursor: deep transgastric view. Superimposition of color-flow Doppler across the stenotic aortic valve allows for a more accurate identification of the limited aortic valve opening. With this information, the cursor may be more easily placed to obtain a continuous-wave Doppler spectrum.

is called the *pressure recovery effect*.[152] Although usually minor, these differences in the observed gradient become more significant with a small aorta and moderate-to-severe AS.[153]

Alternatively, AVA may be calculated using the continuity equation by comparing blood flow through the LVOT with blood through the AV (see Fig. 14.68). As previously discussed in greater detail, SV may be estimated by multiplying the CSA of a particular orifice by the VTI over one cardiac cycle through that orifice. The continuity equation describes the conservation of a physical quantity, that is, energy and mass. Blood flow in one portion of the heart must be equal to the blood flow in another portion of the heart. This application of the continuity equation is commonly used to calculate the AVA. In this case, it is assumed that the blood flow as measured at the level of the LVOT must be equal to the blood flow through the AV. Using either a deep TG or TG LAX view, the Doppler spectrum of the AV and LVOT is displayed. Whereas spatial specificity is necessary for the LVOT measurement, PWD is used. The high velocities that are detected over a stenotic AV usually preclude the use of PWD because of aliasing (ie, exceeding the Nyquist limit); therefore CWD is used. Although CWD allows the measurement of high velocities, spacial specificity is lost. This loss of spacial specificity is not important, since physiologically, these high-velocity flows must be over the stenotic AV if that is the smallest orifice. Once these Doppler spectra have been obtained, the VTI over one cardiac cycle through each of these structures is calculated. The diameter of the LVOT is measured in an ME LAX view. Remembering,

$$SV = CSA * VTI \qquad \text{[Eq. 14.25]}$$

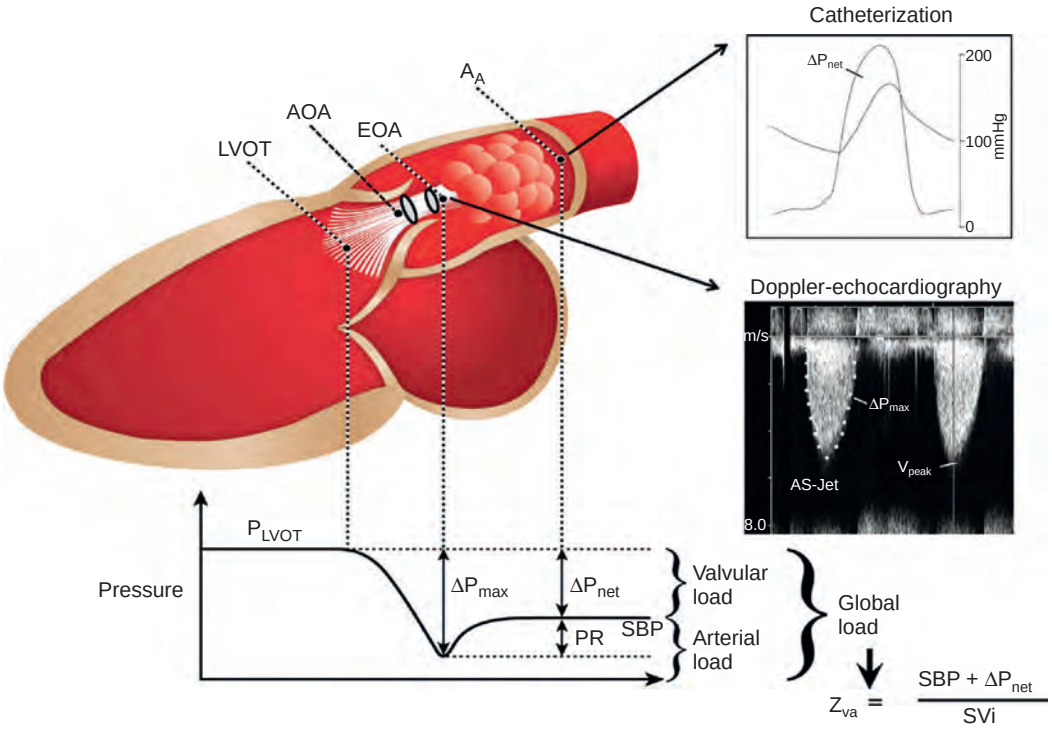


Fig. 14.70 Pressure recovery effect. When the blood flow contracts to pass through a stenotic orifice (anatomic orifice area *[AOA]*), a portion of the potential energy of the blood (namely, pressure) is converted into kinetic energy (namely, velocity), thus resulting in a pressure drop and acceleration of flow. Downstream of the vena contracta (effective orifice area *[EOA]*), a large part of the kinetic energy is irreversibly dissipated as heat because of flow turbulences. The remaining portion of the kinetic energy that is reconverted back to potential energy is called the *pressure recovery (PR)*. A_A, Cross-sectional area of the aorta at the level of the sinotubular junction; ΔP_{max}, maximum transvalvular pressure gradient recorded at the level of vena contracta (mean gradient measured by Doppler); ΔP_{net}, net transvalvular pressure gradient recorded after pressure recovery (mean gradient measured by catheterization); *LVOT*, left ventricular outflow tract; *PLVOT*, pressure in the LVOT; *SBP*, systolic blood pressure; *SVi*, stroke volume index; V_{peak}, peak aortic jet velocity; Z_{va}, valvuloarterial impedance. *(Reproduced with permission from Pibarot P, Dumesnil JG. Improving assessment of aortic stenosis.* J Am Coll Cardiol. *2012; 60:169–180.)*

where SV is stroke volume, CSA is cross-sectional area, and VTI represents velocity time integral. The continuity equation states that:

$$SV_{LVOT} = SV_{AV} \quad \text{[Eq. 14.26]}$$

where LVOT represents left ventricular outflow tract, and AV is aortic valve.

Substituting the SV equation into the continuity equation,

$$CSA_{LVOT} * VTI_{LVOT} = CSA_{AV} * VTI_{AV} \quad \text{[Eq. 14.27]}$$

Rearranging the terms,

$$CSA_{AV} = CSA_{LVOT} * VTI_{LVOT} / VTI_{AV} \quad \text{[Eq. 14.28]}$$

Because the LVOT is essentially cylindrical, the CSA_{LVOT} may be estimated by

$$CSA_{LVOT} = \pi (radius_{LVOT})^2 \quad \text{[Eq. 14.29]}$$

Because CSA_{LVOT}, VTI_{LVOT}, and VTI_{AV} are known, the CSA_{AV} or AVA may be calculated (see Fig. 14.68 for an example of the calculation of AVA).

Multiple sources of error may affect the calculation of the AVA using the continuity equation.[154] LVOT measurements may vary from 5% to 8%; therefore when the LVOT measurement is squared in the continuity equation, it may become a large source of error. Because the accuracy of the SV measurement through the LVOT assumes laminar flow, any of the sources of turbulence will affect results. In the presence of AI, the required high-systolic velocities may result in a skewed velocity profile. As discussed earlier, patients with a small aorta and moderate-to-severe AS may have significant pressure recovery effects that may overestimate the severity of the gradient and hence underestimate the AVA. Garcia and associates[155] proposed an index called the energy-loss coefficient (ELCo):

$$ELCo = (AVA \times A_a)/(A_a - AVA) \quad \text{[Eq. 14.30]}$$

where A_a is the cross section of the aorta measured 1 cm downstream from the sinotubular junction. This coefficient is closer to the AVA obtained at the time of catheterization and may be more representative of the energy loss caused by the stenosis and thus of the increased burden on the ventricle.[156]

AS severity should be described by maximum velocity, mean gradient, and AVA. Aortic velocity allows classification of stenosis as mild (2.6 to 2.9 m/sec), moderate (3 to 4 m/sec), or severe (greater than 4 m/sec).[154] Normal AVA is 3 to 4 cm^2. AVA consistent with mild AS is greater than 1.5 cm^2. An AVA of 1.0 to 1.5 cm^2 is consistent with moderate AS, and an area less than 1 cm^2 or 0.6 cm^2/m^2 is consistent with severe disease.[154,157]

Although multiplane TEE planimetric estimations of AVA may be flawed by heavy aortic valvular calcification, measurements using the continuity equation are accurate, compared with Gorlin-derived values.[158,159] In a study using TEE, Stoddard and colleagues[160] reported good correlation between AVA measurements using the continuity equation and planimetry; however, they reported a steep learning curve for the acquisition of a suitable TG LAX view that adequately aligns flow through the AV with the ultrasound beam.

Classical Low Flow–Low Gradient, Paradoxic Low Flow–Low Gradient, and Pseudosevere Aortic Stenosis

In addition to the normal flow, high-gradient AS observed in patients with normal EFs and normal COs, a subgroup of patients may have low flow–low gradient AS.[161] In particular, patients with a low SV, secondary to either severe systolic or diastolic dysfunction, may have severe AS as quantified by an AVA with low transaortic-valve gradients. In classical low flow–low gradient AS, the measured gradient underestimates the severity of the AS. If the resistance through the AV is constant, then the pressure gradient is directly related to the CO; a low CO is associated with a low-pressure gradient across the AV. Stated differently, a given severity of AS will result in a higher gradient across the AV with normal ventricular function, compared with a patient with decreased ventricular function. The presentation of patients with severe LV dysfunction and significant AV disease may be the classical low flow–low gradient AS, which is a low AVA with a mild-to-moderate gradient across the AV. These patients with low flow–low gradient severe AS may have AVA less than 1.0 cm^2 or 0.6 cm^2/m^2, a mean transvalvular gradient less than 40 mm Hg, and a low LV EF.[161]

One of the major diagnostic challenges in the evaluation of low flow–low gradient AS is its differentiation from pseudosevere AS. The evaluation of AV gradients must be considered in the context of LV function. Although the determination of AVA takes into account CO, AVA may, nonetheless, vary with flow rates.[162] Although this effect is not clinically significant with normal LV function, it becomes more pronounced with LV dysfunction, because a minimum blood flow is required to maximally open the AV. When LV systolic dysfunction is sufficiently severe, then there may be insufficient power to open the AV. The inability to open the AV attributable to myocardial dysfunction is known as pseudosevere AS. With increases in contractility, the AV may be opened to a near-normal area. In other words, severe AS is a valvular disease, whereas pseudosevere AS is a myocardial disease; patients with pseudosevere AS will not generally benefit from AV replacement.[161] Differentiation between severe AS with LV systolic dysfunction from mild-to-moderate AS with another cause of LV dysfunction may be made with dobutamine stress testing. With improved cardiac function, there is an increase in transvalvular gradient with no change in AVA in patients with classical low flow–low gradient AS. With pseudosevere AS, an improvement in cardiac function will not result in an increase in transvalvular gradient, but an improvement will result in an increase in AVA.

As opposed to patients with severe systolic dysfunction with classical low flow–low gradient AS, patients with small hypertrophied ventricles secondary to concentric remodeling may exhibit normal EF or paradoxic low flow–low gradient AS.[163,164] These patients have a preserved EF (greater than 50%) with an SV less than 35 mL/m^2 and significant diastolic dysfunction (ie, restrictive cardiomyopathy). Patients with this restrictive disease have decreased SV and flow; therefore the left ventricle may not be able to produce a large gradient across a stenotic AV, even with a normal EF. Typically, these patients have echocardiographic signs of diastolic dysfunction, including a high E/A ratio, decreased E-wave DT, decreased color M-mode propagation velocity, and a decreased tissue Doppler e′-wave velocity. Such patients may exhibit a normal EF and concentric hypertrophy or myocardial fibrosis, low-to-moderate AV gradient, and an AVA consistent with severe disease (see Chapter 21).

Aortic Regurgitation

AR may result from either diseases of the aortic leaflets or the aortic root.[165] Valvular lesions that may result in AR include leaflet vegetations and calcifications, perforation, or prolapse. AR may be caused by annular dilation secondary to a variety of causes, including annuloaortic ectasia, Marfan syndrome, aortic dissection, collagen vascular disease, and syphilis.

Cusp pathologic conditions (eg, redundancy, restriction, mobility, thickness, integrity), commissural variations (eg, fusion, splaying, alignment, attachment site), and root morphologic characteristics (eg, septal hypertrophy, root dimensions) should be ascertained.[165,166] Leaflet movement (excessive, restricted, or normal), origin of jet (central or peripheral), and direction of regurgitant jet (eccentric or central) should be determined to provide insight into the underlying pathologic conditions. Other signs that may be associated with AR include high-frequency diastolic fluttering of the MV (see Video 14.54), premature closing of the MV, or reverse doming of the MV.[167,168]

The mechanism of AR may be classified according to leaflet movement (Table 14.11).[165,169] Type I dysfunction is a result of dilation of the aortic annulus, sinuses of Valsalva, or sinotubular junction without any other causes of regurgitation (Figs. 14.71 and 14.72; see Video 14.55). This dilation results in the tethering of the AV cusps as a result of a mismatch between AV annular and the sinotubular junction

diameters.[170] This functional AR appears as an anatomically normal AV with a coaptation leaflet height (ie, maximum distance between point of cusp coaptation and the annular plane) greater than 8 to 10 mm and a sinotubular junction-annulus ratio greater than 1.6, resulting in a concentric jet of AR. Type II lesions result in eccentric jets. The cusp tissue quality and quantity is good. Cusp prolapse or flail is classified as Type IIa dysfunction (Fig. 14.73). The cusp prolapse may be further subdivided: cusp flail, partial cusp, and whole-cusp prolapse. Cusp flail is defined as the complete eversion of a cusp into the LVOT, which is usually seen best in the ME LAX view. Partial-cusp prolapse occurs when the distal part of a cusp prolapses into the LVOT. There is a clear bending of the cusp in the LAX view and the presence of a small circular or oval structure near the cusp free edge in the SAX view. Whole-cusp prolapse is the overriding of the free edge of the cusp of the plane of the AV with a billowing of the cusp into the LVOT. When the LVOT is viewed in the SAX view, the billowing of the cusp may be seen as a circular or elliptical figure (Fig. 14.74 and Video 14.56). Type IIb dysfunction is a free-edge fenestration. In these cases, there is an eccentric AR jet without definite evidence of a cusp prolapse. Finally Type III dysfunction is a result of a poor quality or quantity of leaflet tissue (Fig. 14.75 and Video 14.57). This may be a result of thickened, rigid, or destroyed valves attributable to endocarditis or calcification. If present, then the degree of calcification should be graded (Table 14.12).

Physiologic factors that may affect the estimated severity of AR include aortic diastolic pressure, LVEDP, heart rate, and LV compliance.[171] The severity of AR may be underestimated in the presence of eccentrically directed jets. In addition, several technical factors affect the perceived severity of regurgitation as well, including severe

TABLE 14.11 Classification of Aortic Regurgitation

Type	*Description*	*Echocardiographic Findings*
I	Enlarged aortic root with normal cusps	Aortic root dilation with retraction of aortic valve leaflets
IIa	Cusp prolapse	
	• Cusp flail	Complete eversion of a cusp into the LVOT in long-axis views
	• Partial cusp prolapse	Distal part of a cusp prolapsing into the LVOT (clear bending of the cusp body on long-axis views and the presence of a small circular structure near the cusp free edge on short-axis views)
	• Whole cusp prolapse	Free edge of a cusp overriding the plane of aortic annulus with billowing of the entire cusp body into the LVOT (presence of a large circular or oval structure immediately beneath the valve on short-axis views)
IIb	Cusp fenestration	Presence of an eccentric AR jet without definite evidence of cusp prolapse
III	Poor cusp tissue quality or quantity	Thickened and rigid valves with reduced motion Tissue destruction (endocarditis) Large calcification spots and extensive calcifications of all cusps interfering with cusp motion

AI, Aortic regurgitation; *LVOT*, left ventricle outflow tract.

Adapted from Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14(7):611–644; and le Polain de Waroux JB, Pouleur AC, Goffinet C, et al. Functional anatomy of aortic regurgitation: accuracy, prediction of surgical repairability, and outcome implications of transesophageal echocardiography. *Circulation.* 2007;116:264–269.

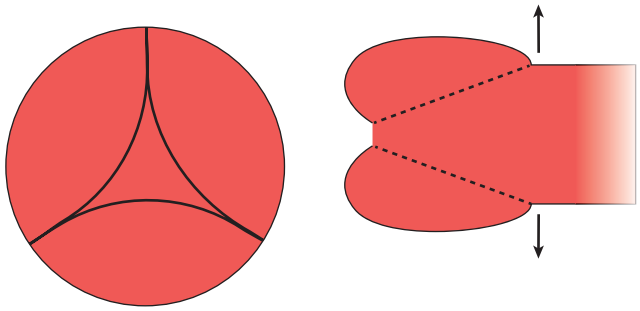


Fig. 14.71 Mechanism of aortic regurgitation type I. The *dotted lines* represent the attachment of the leaflet tips to the sinotubular junction. Normally the leaflet tips coapt fully in diastole (short-axis view) and that the diameter of the sinotubular junction is similar to that at the base of the annulus. This panel shows incomplete leaflet closure when the sinotubular junction dilates *(arrows)* relative to the aortic annulus, resulting in leaflet tethering and a persistent diastolic orifice. *(Reproduced with permission from Movsowitz HD, Levine RA, Hilgenberg AD, Isselbacher EM. Transesophageal echocardiographic description of the mechanisms of aortic regurgitation in acute type A aortic dissection: implications for aortic valve repair.* J Am Coll Cardiol. *2000;36:884–890.)*

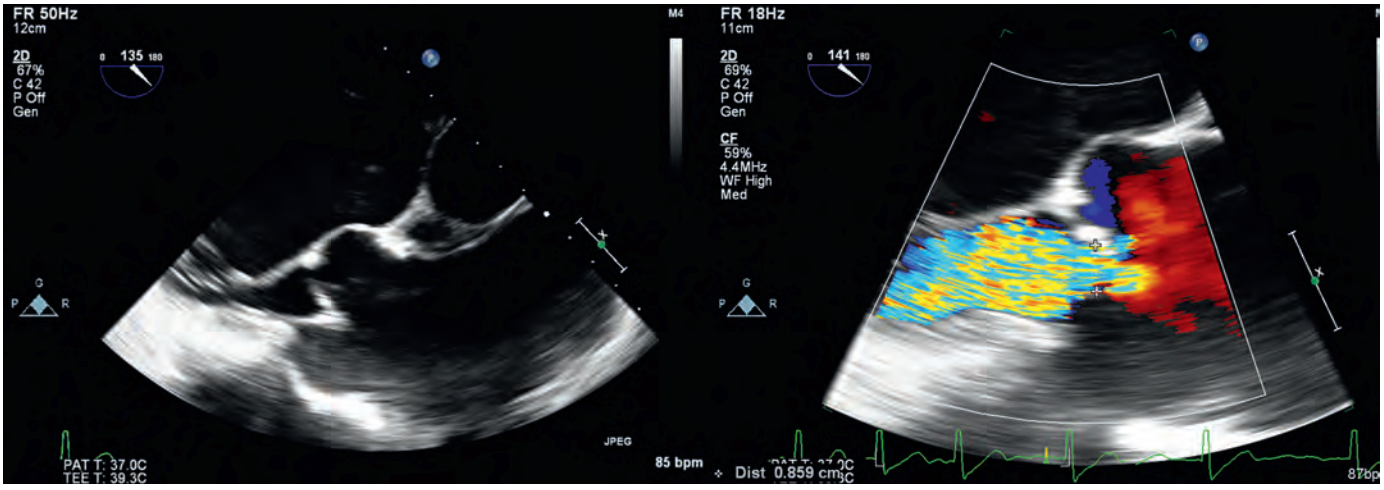


Fig. 14.72 Type I aortic regurgitation. Midesophageal aortic valve long-axis view demonstrates functional aortic regurgitation, secondary to an ascending aortic aneurysm. *(Left)* The sinus of Valsalva is very enlarged with respect to the aortic valve annulus. This enlargement results in the tethering of the aortic valve. The coaptation plane of the aortic leaflets are significantly distal to the plane of the aortic annulus. *(Right)* Addition of color-flow Doppler demonstrates severe aortic regurgitation. (Video available online.)

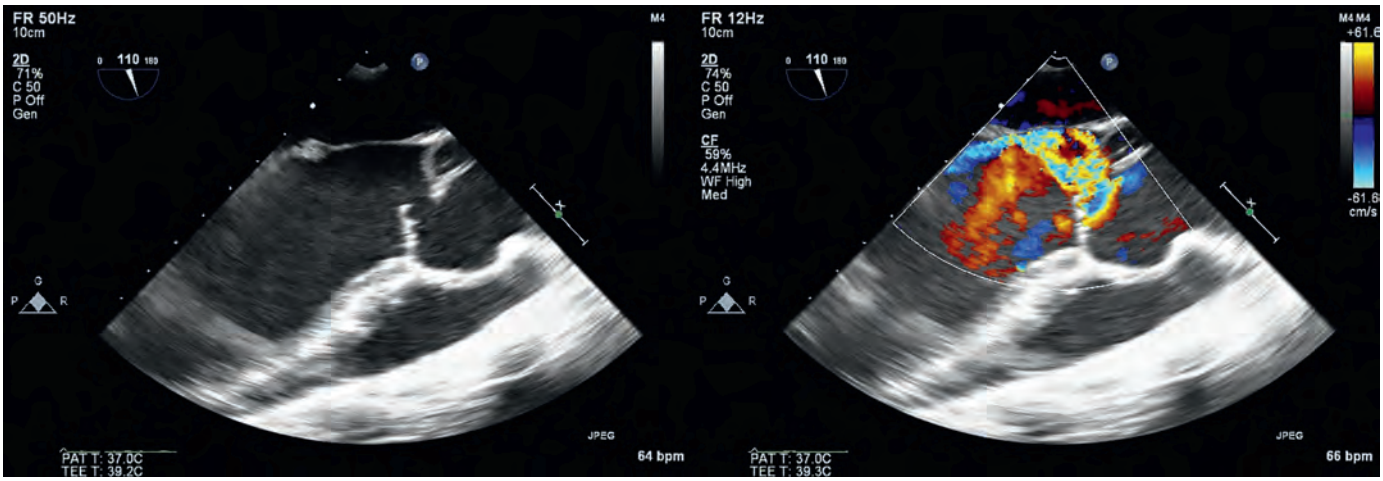


Fig. 14.73 Type II aortic regurgitation. Midesophageal aortic valve long-axis view demonstrates *(left)* the right coronary cusp *(most anterior)* prolapsing into the left ventricular outflow tract. *(Right)* Addition of color-flow Doppler reveals a large posteriorly directed regurgitant jet. An impressive proximal isovelocity surface area shell is seen on the aortic side of the aortic valve. (Video available online.)

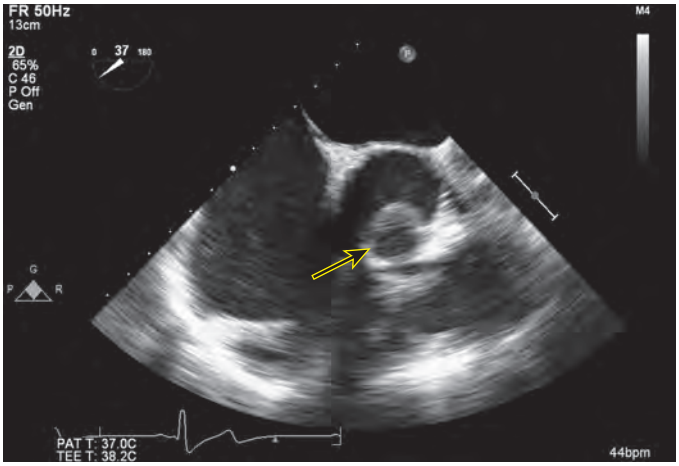


Fig. 14.74 Right coronary cusp in left ventricular outflow tract. After obtaining a midesophageal aortic valve short-axis view, the probe is advanced, allowing for the visualization of the left ventricular outflow tract. The right coronary cusp (see Fig. 14.73) may be visualized in the left ventricular outflow tract below the level of the aortic annulus as a circular structure *(yellow arrow)*. This image provides supportive evidence of a right coronary cusp prolapse. (Video available online.)

malalignment of ultrasonic planes with blood flow, the presence of a prosthetic MV interfering with ultrasound penetration, gain settings, and PRF.

The criteria for qualitative grading of AR are summarized in Table 14.13. CFD has traditionally been the major method of assessing the severity of valvular regurgitation. Nyquist limits should provide an aliasing velocity of approximately 50 to 60 cm/sec and a color gain that just eliminates the random color speckle from nonmoving regions.[172] Aortic regurgitant flow through the LVOT is characteristically a high-velocity, turbulent jet extending through the LVOT and left ventricle during diastole. In addition to providing the regurgitant jet area, the origin and width of the jet and the spatial orientation should be carefully defined. The severity of AR may be assessed by examining the width of the jet by CFD measurements. Unfortunately, the determination of the severity of AI by measurements of regurgitant jet areas alone has been questioned and is probably useful only for distinguishing mild from severe regurgitation.[173] Furthermore, the jet length and area measurements are very dependent on the LV diastolic pressure

TABLE 14.12 Grading of Aortic Valve Calcification

Grade	*Description*
1	No calcification
2	Isolated small calcification spots
3	Bigger calcification spots interfering with cusp motion
4	Extensive calcification of all cusps with restricted cusp motion

Adapted from Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2013;14(7):611–644.

gradient and ventricular compliance and therefore are not recommended to quantitate AR severity.[165] The severity of the regurgitant jet may be overestimated if the gain is too high or the Nyquist limits are too low. Furthermore, excessive degradation of frame rate may be encountered if the CFD field is too large.

The vena contracta is the narrowest portion of a regurgitant jet that usually occurs at or immediately upstream from the valve (Fig. 14.76). This jet width is directly proportional to the severity of the AR, and is usually characterized by high-velocity and laminar flow, and is slightly smaller than the regurgitant orifice.[172] A vena contracta diameter less than 0.3 cm is consistent with mild AR, and a diameter greater than 0.6 cm is consistent with severe AR. It should be noted, however, that jet shape might influence the estimation of the severity of regurgitation. An eccentric jet may be confined to a wall of the LVOT and thus appear very narrow, underestimating the severity of regurgitation. Similarly, central jets may expand fully in the LVOT and may overestimate the severity of regurgitation. The accuracy of the measurement may be improved by normalizing the jet width to the LVOT diameter by an examination of the ratio of the proximal jet width within the LVOT to the LVOT width (w_J/w_{LVOT}).[174,175] This ratio may be more accurately determined using color M-mode echocardiography (Fig. 14.77). Either an ME LAX or AV LAX view is obtained. CFD is superimposed on the image. The cursor is placed on the ventricular side of the AV to include both the LVOT and the regurgitant jet. M-mode imaging is initiated, and the LVOT diameter (w_{LVOT}) and AR jet width (w_J) is measured. A w_J/w_{LVOT} value of 0.25 discriminates mild from moderate regurgitation, and a valve of 0.65 discriminates moderate from severe regurgitation.[151,172]

CWD characteristics of the regurgitant flow may be used to estimate the degree of AR (Fig. 14.78). A very faint signal density is associated

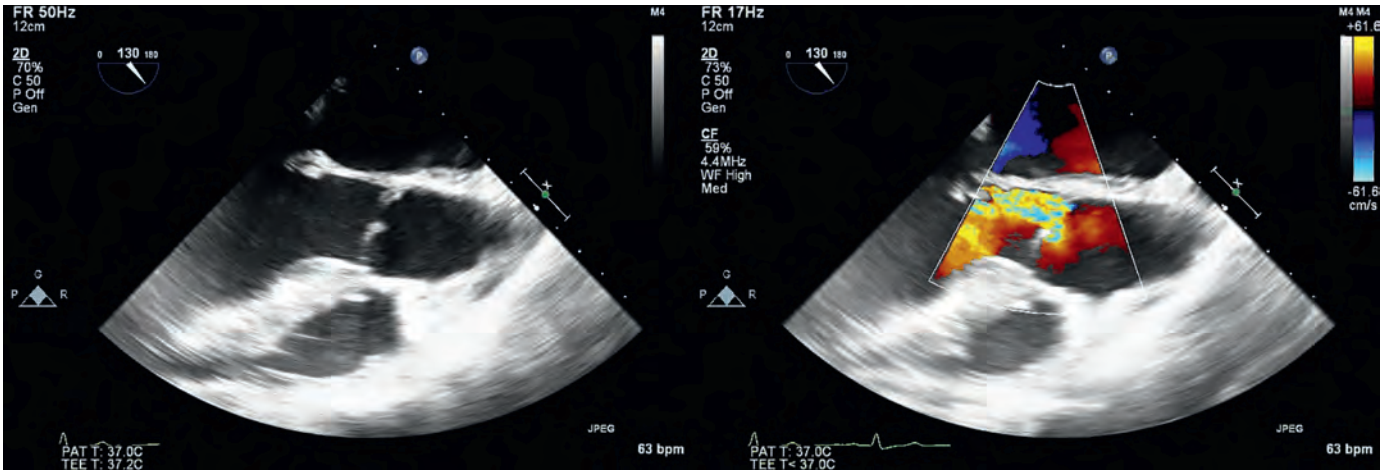


Fig. 14.75 Type III aortic regurgitation. *(Left)* Although the midesophageal aortic valve long-axis view reveals a normal anterior right coronary cusp, the more posterior cusps (left and noncoronary) are small and retracted. This retraction results in a large defect in the aortic valve. *(Right)* Addition of color-flow Doppler reveals a large regurgitant jet beginning at the posterior aspect of the aortic valve, which continues along the posterior wall of the left ventricular outflow tract. (Video available online.)

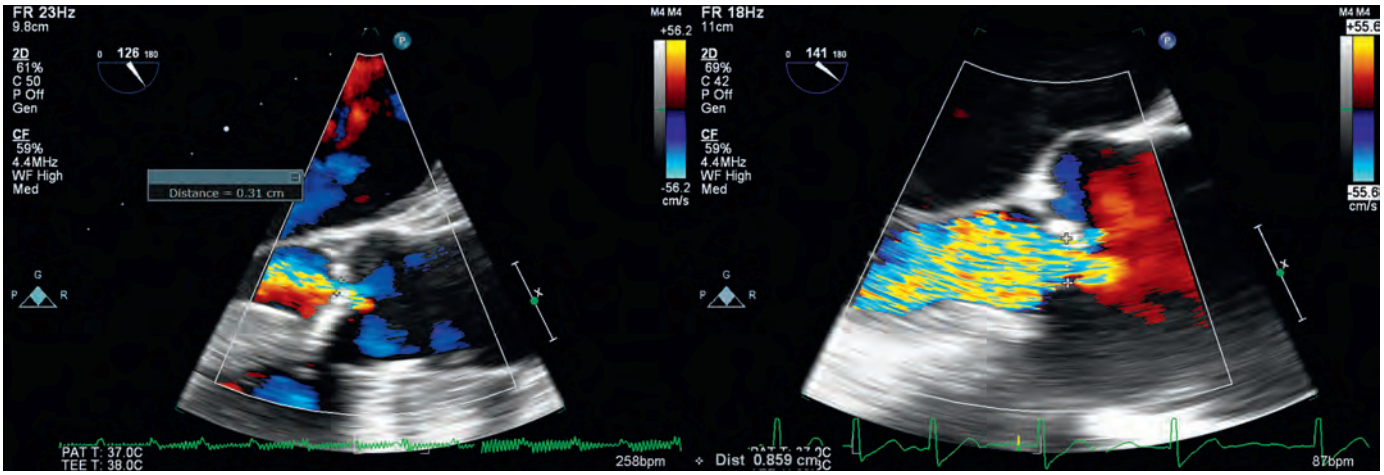


Fig. 14.76 Color-flow Doppler spectrum of a regurgitant aortic valve. Midesophageal aortic valve long-axis view visualizes an aortic regurgitant jet in the left ventricular outflow tract. *(Left)* The vena contracta is approximately 3 mm, which is consistent with mild regurgitation. *(Right)* The vena contracta is greater than 8 mm, which is consistent with severe aortic regurgitation.

TABLE 14.13 Quantification of Aortic Regurgitation

		Moderate		
	Mild	*Mild-to-Moderate*	*Moderate-to-Severe*	*Severe*
Left atrial size	Normal	Normal or dilated		Usually dilated
Aortic cusps	Normal or abnormal	Normal or abnormal		Abnormal and flail or wide coaption defect
Jet width in LVOT[a]	Small in central jets	Intermediate		Large in central jets; variable in eccentric jets
Continuous wave jet density	Incomplete or faint	Dense		Dense
Jet deceleration rate (pressure half time, ms)	Slow >500	Medium 200–500		Steep <200
Vena contracta width (cm)[a]	<0.3	0.3–0.6		≥0.6
Jet width/LVOT width (%)[a]	<25	25–45	46–64	≥65
Jet CSA/LVOT CSA (%)[a]	<5	5–20	21–59	≥60
Regurgitant orifice area (cm^2)	<0.1	0.10–0.19	0.20–0.29	≥0.3
Regurgitant volume (mL/beat)	<30	30–44	45–59	≥60
Regurgitant fraction (%)	<30	30–39	40–49	≥50

[a]At Nyquist limits of 50 to 60 cm/sec.

CSA, Cross sectional area; *LVOT,* left ventricular outflow tract.

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(22):2438–2488; Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14(7):611–644; and Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

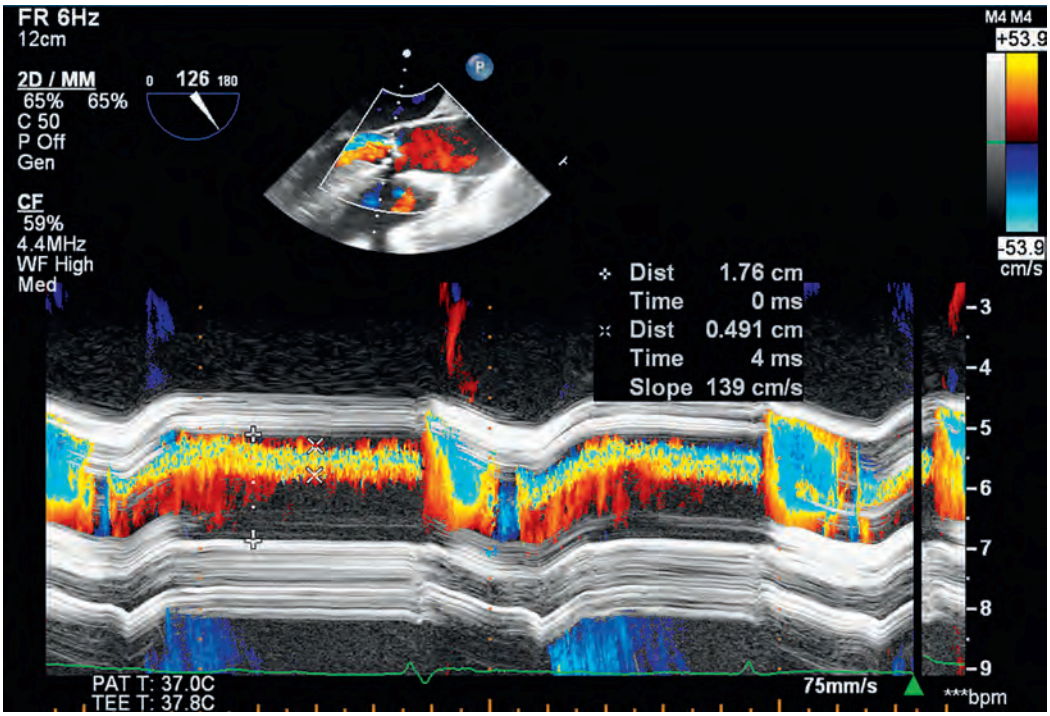


Fig. 14.77 Color M-mode image of the vena contracta. Color-flow Doppler is superimposed on the left ventricular outflow tract (LVOT), and the cursor is positioned at the downstream origin of the regurgitant aortic flow. This results in a high temporal resolution spectrum, allowing the accurate measurement of both the vena contracta and the width of the LVOT. In this case, the vena contracta is 0.49 cm and the LVOT 1.76 cm. These measurements yield a vena contracta to LVOT width ratio of 0.28, which is consistent with moderate aortic insufficiency.

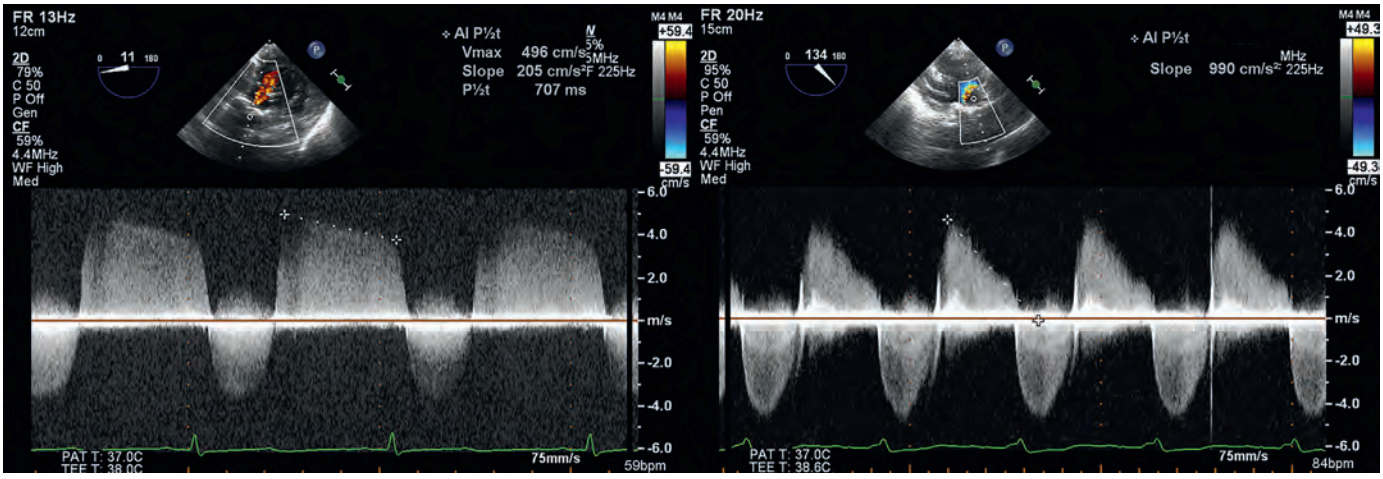


Fig. 14.78 Continuous-wave Doppler determination of aortic regurgitation severity. Continuous retrograde flow from the aorta into the left ventricle through a regurgitant aortic valve may be demonstrated with continuous-wave Doppler. *(Left)* In this example, the flow velocity mildly degrades during diastole, yielding a shallow slope. This low slope value is consistent with mild aortic insufficiency. *(Right)* Severe aortic insufficiency results in a greater slope of the regurgitant Doppler spectrum, which is consistent with severe aortic insufficiency.

with mild AR, whereas a dense signal may represent more retrograde flow. In addition, the pressure half-time or slope of the AR jet may be determined. A normally functioning AV will maintain a large gradient during diastole between the aorta and the left ventricle. With a small degree of AR, there will be a small volume of blood entering the left ventricle through the AV, resulting in a slow increase in LV pressure during diastole. Doppler measurements will show a regurgitant flow of high velocity, which is maintained during most of diastole (corresponding to a long pressure half-time). As aortic regurgitant flow becomes more severe, there is a more rapid equilibration between aortic and LV diastolic pressure, with the nadir of the gradient at end-diastole. As pressures equilibrate, the driving pressure across the AV decreases and Doppler-derived AR velocities decrease over the diastole. This pattern of AI flow is characterized by short pressure half-time.

Pressure half-time measurements have been validated as a measure of the severity of AR.[176] A pressure half-time of less than 200

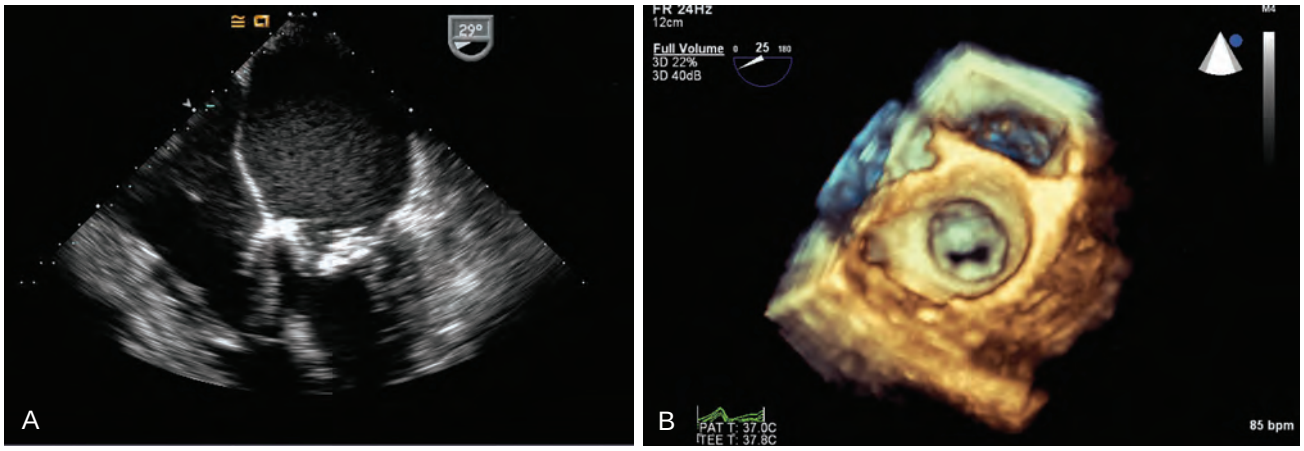


Fig. 14.79 Mitral stenosis. (A) Midesophageal four-chamber view demonstrates a severely stenotic mitral valve with severe calcification of the annulus and leaflets, which is associated with severe left atrial dilation. (B) A significant commissural fusion with severe leaflet restriction is reveals in a three-dimensional reconstruction in another patient with rheumatic heart disease. (Video available online.)

milliseconds is consistent with severe AR, whereas a pressure half-time greater than 500 milliseconds is consistent with mild AR.[172] The accuracy of this technique may be influenced by physiologic variables.[177] A higher systemic vascular resistance increases the rate of decline, whereas a reduced ventricular compliance will increase the rate of intraventricular pressure rise, which will also affect the diastolic slope without affecting valvular competence. In a given patient, however, pharmacologic manipulation of afterload or inotropy may result in changes in aortic regurgitant slopes and pressure half-times that are contradictory to other measures of regurgitation. The density of the pressure half-time spectrum does not provide useful information concerning the severity of AR.[165]

Proximal isovelocity surface area (PISA) measurements and flow convergence are secondary techniques for the evaluation of the severity of AI; their calculation is discussed in greater detail in the MR section of this chapter. A PISA measurement provides accurate quantification of the severity of AR.[178] Furthermore, aortic diastolic flow reversal may provide an indication of the severity of regurgitation. With increasing AR, both the duration and velocity of the flow velocity increase; holodiastolic reversal is consistent with at least moderate AR.[179] Finally, the SV calculation through the LVOT may be compared with either the MV or pulmonary valve, assuming there is no more than minimal regurgitation of these latter valves. The difference in SV will be equal to the regurgitant volume.

Mitral Valve Evaluation

The MV consists of two leaflets, chordae tendineae, two papillary muscles, and a valve annulus. The anterior leaflet is larger than the posterior and is semicircular; however, the posterior MV leaflet has a longer circumferential attachment to the MV annulus.[180] The posterior valve leaflet may be divided into three scallops: lateral (P1), middle (P2), and medial (P3). The leaflets are connected to each other at junctures of continuous leaflet tissue called the *anterolateral* and *posteromedial commissures*. Primary, secondary, and tertiary chordal structures arise from the papillary muscle, subdividing as they extend and attach to the free edge and several millimeters from the margin on the ventricular surface of both the anterior and posterior valve leaflets.[181] The annulus of the MV primarily supports the posterior MV leaflet, whereas the anterior MV leaflet is continuous with the membranous ventricular septum, AV, and aorta.

Mitral Stenosis

The most common cause of MS is rheumatic heart disease; other causes are congenital valvular stenosis, vegetations and calcifications of the leaflets, parachute MV, and annular calcification. In addition to

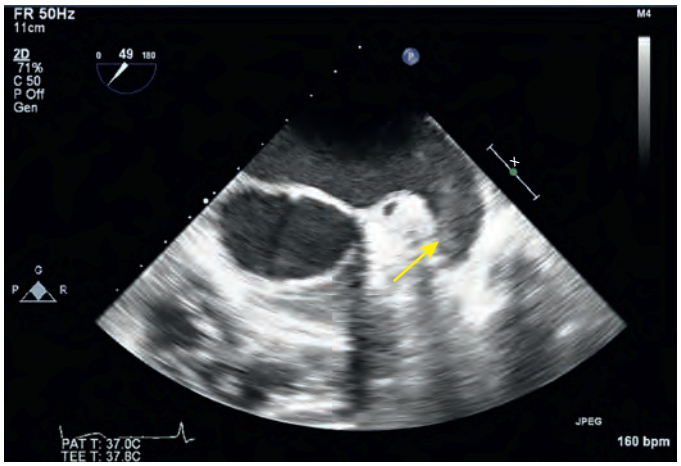


Fig. 14.80 Spontaneous echocardiographic contrast. Because of the low flow in the left atrium, there is low-velocity blood flow with subsequent rouleaux formation by red blood cells *(yellow arrow)*. (Video available online.)

structural valvular abnormalities, MS may be caused by nonvalvular causative factors such as intraatrial masses (myxomas or thrombus) or extrinsic constrictive lesions.[182,183] Generally, MS is characterized by restricted leaflet movement, a reduced orifice, and diastolic doming (Fig. 14.79 and Video 14.58).[184] The diastolic doming occurs when the MV is unable to accommodate all the blood flowing from the left atrium into the left ventricle; consequently, the body of the leaflets separates more than the edges. In rheumatic disease, calcification of the valvular and subvalvular apparatus, as well as thickening, deformation, and fusion of the valvular leaflets at the anterolateral and posteromedial commissures, produce a characteristic fish mouth–shaped orifice.[185] Other characteristics that may be associated with chronic obstruction to LA outflow include an enlarged left atrium, spontaneous echocardiographic contrast or smoke (which is related to low-velocity blood flow with subsequent rouleaux formation by red blood cells[186]) (Fig. 14.80 and Video 14.59), thrombus formation, and RV dilation.

The leaflets, annulus, chordae, and papillary muscles may be assessed in the ME four-chamber, commissural, two-chamber, and LAX views. If annular calcification is significant, then the TG views may be necessary to assess the subvalvular apparatus. Because of the propensity for thrombus formation, the entire left atrium and the LAA should be carefully interrogated for thrombus.

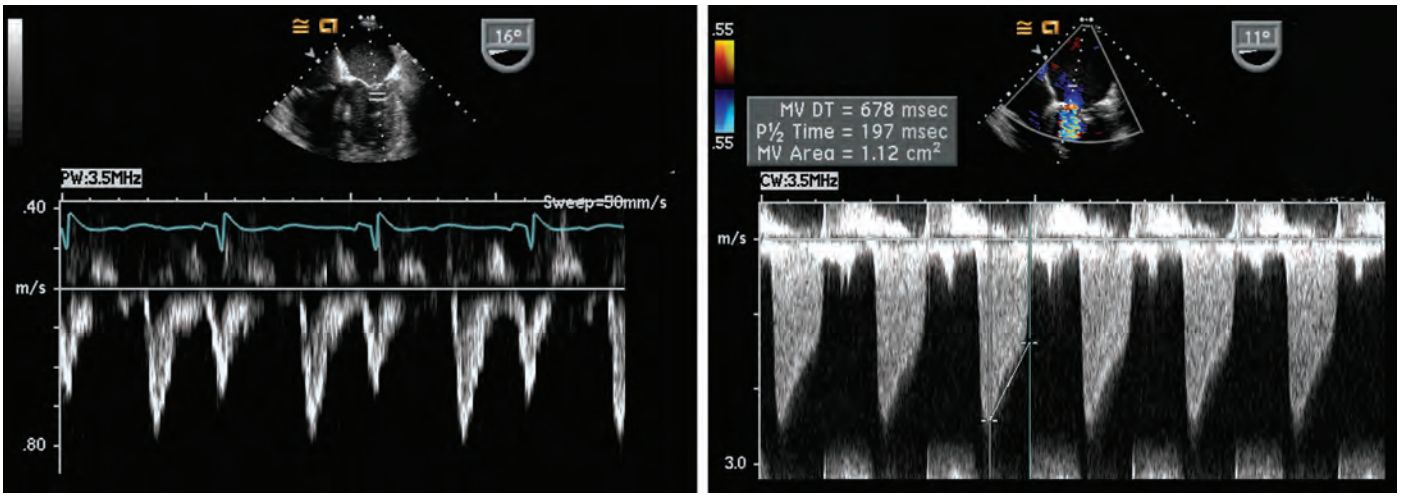


Fig. 14.81 Transmitral Doppler spectrum. The panel on the *left* is the normal transmitral Doppler flow measured using pulsed-wave Doppler. A clean envelope is visualized with E-wave velocity greater than the A-wave velocity. Both waves have velocities less than 1 m/sec with a normal deceleration time. The panel on the *right* visualizes the transmitral flow in the presence of mitral stenosis. Because of the high gradient, continuous-wave Doppler was used. High-velocity gradients may be appreciated, and a longer pressure half-time is consistent with significant mitral stenosis.

Because planimetry of the MV orifice is not influenced by assumptions of flow conditions, ventricular compliance, or associated valvular lesions, its use is the reference standard for the evaluation of mitral valve area (MVA) in MS.[154] This orifice opening is best visualized in the TG basal SAX view and is best measured in mid-diastole. Although technically difficult at times, care should be taken to image the orifice at the leaflet tips. Severe calcification of the MV may interfere with MVA determination, and, in patients with significant subvalvular stenosis, the underestimation of the degree of hemodynamic compromise may occur when determining MVA by planimetry.[148]

Doppler Assessment of Mitral Valvular Stenosis

A transmitral Doppler spectrum is measured along the axis of transmitral blood flow, which usually may be obtained in an ME four- or two-chamber view (Fig. 14.81). Transmitral valve flow is characterized by two peaked waves of flow away from the transducer. The first wave (E) represents early diastolic filling, whereas the second wave (A) represents atrial systole. Transvalvular gradient may be estimated using the modified Bernoulli equation: pressure gradient = 4 × velocity^2.[187] Because peak gradient is heavily influenced by LA compliance and ventricular diastolic function, the mean gradient is the relevant clinical measurement.[154] The values obtained through this method have high correlation with those obtained using a transeptal puncture during cardiac catheterization.[188] The high velocities that may occur with MS limit the use of PWD echocardiography; CWD echocardiography should be used.

Normally, with MV opening during early diastole, a torrential increase in transmitral flow occurs, which rapidly decreases to zero during diastasis when the LA and LV pressures equilibrate. With MS, a gradient between the left atrium and the left ventricle may be maintained for a longer period. This sustained pressure differential maintains flow between the atrium and the ventricle, decreasing the slope of this early transmitral flow. The rate of decline of the E-wave velocity may be described by its pressure half-time, which is the time interval from the peak E-wave velocity to the time when the E-wave velocity has declined to one half of its corresponding peak pressure value. The pressure half-time is inversely proportional to the MVA[189]:

$$\text{MVA} = 220/\text{pressure half-time} \qquad \text{[Eq. 14.31]}$$

The E-wave may have a bimodal characteristic, with an initial rapid decline in transmitral velocity in early diastole, compared with the latter aspect of diastole. In these cases, this latter gentler slope should be measured. The advantage of this technique is that it is independent of valvular geometry. This formula assumes that the MV is at least mildly stenotic. The presence of either MR or AR will decrease the accuracy of pressure half-time measurements for the determination of MS.[190] If there is associated AR, then care should be taken that the aortic regurgitant jet is not included in the transmitral flow measurement.[191] Inadvertent inclusion of this aortic regurgitant flow may result in a false elevation of transmitral velocity, as well as a false decrease in pressure half-time.[192] Alternatively, AR may result in a rapid increase in diastolic LV pressures, thus decreasing transmitral flow velocity. The continuity equation, using either the LVOT or the PA and PISA method, may be used as secondary methods for the evaluation of the severity of MS.

TABLE 14.14 Quantification of Mitral Stenosis

	Mild	*Moderate*	*Severe*
Valve area (cm^2)	>1.5	1.0–1.5	>1.5
Mean gradient (mm Hg)	<5	5–10	>10

Adapted from Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1–23.

The assessment of the severity of MS is summarized in Table 14.14. The mean transmitral gradient and the MVA, as determined by the pressure half-time, are the major measurements to be considered; however, planimetry may be used if discrepancy between these two measures occurs.[154] Determination of the severity of MS by PISA measurement or by the continuity equation should not be considered as primary indices for evaluation.

Mitral Regurgitation

MR may be classified as primary or secondary. Primary causes of regurgitation are structural or organic, whereas secondary causes are functional without evidence of structural abnormalities on the MV. The most common causes of primary MR are degenerative (Barlow disease, fibroelastic degeneration, Marfan syndrome, Ehlers-Danlos syndrome, annular calcification), rheumatic disease, toxic valvulopathies, and endocarditis.[165] MR may be caused by disorders of any component of the MV apparatus, specifically, the annulus, the leaflets

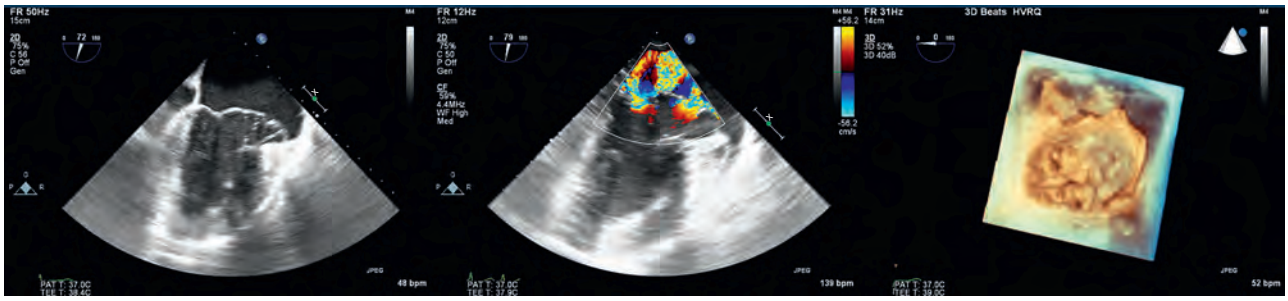


Fig. 14.82 Barlow disease. *(Left and center)* Midesophageal commissural view demonstrates Barlow disease, which is usually characterized by gross redundancy of multiple segments of the anterior or posterior leaflets and chordal apparatus. The leaflets are bulking and billowing with multiple areas of prolapse. The chordae are more often elongated rather than ruptured. Atrialization of the leaflets (ie, displacement of the leaflet attachment toward the atrium) occurs, especially at the origin of P1 at the right side of the image. There is significant annular dilation. *(Center)* Addition of color-flow Doppler reveals complex and multiple areas of regurgitation. *(Left)* Three-dimensional reconstruction of the mitral valve illustrates the redundancy of the leaflets and the prolapse of multiple sections of the leaflet. (Video available online.)

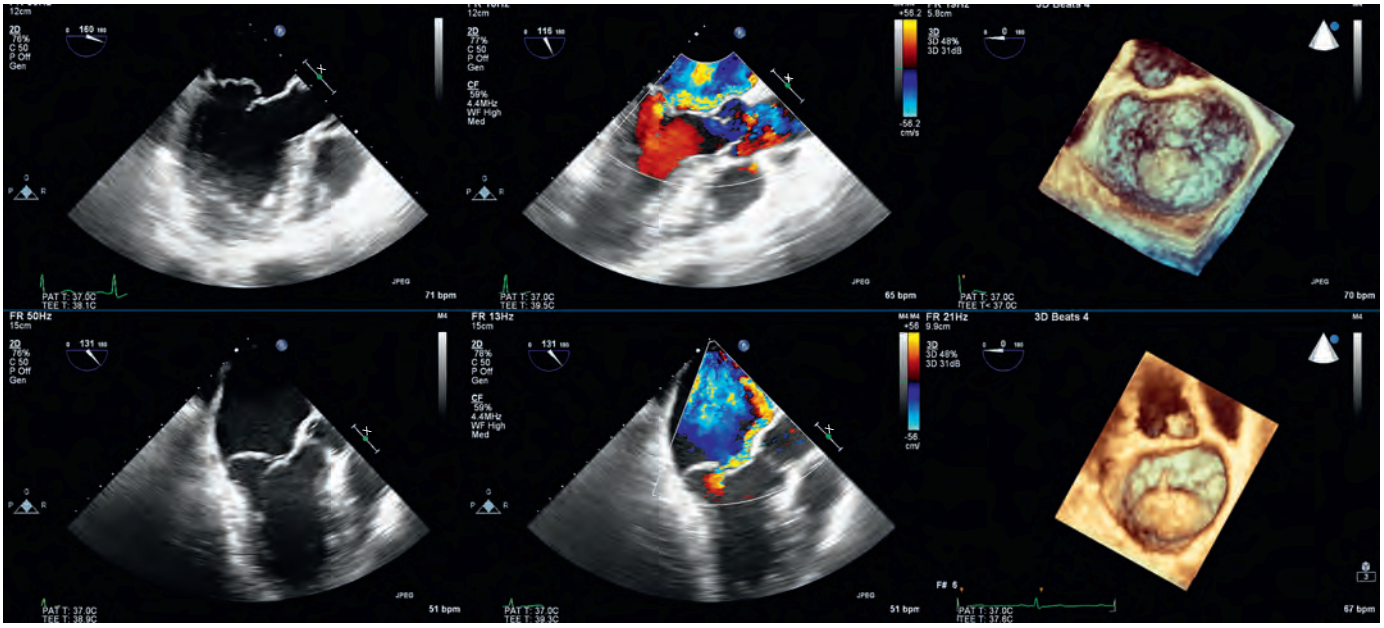


Fig. 14.83 Fibroelastic deficiency. Prolapse versus flail. *Left and center* images are the midesophageal long-axis view. The *top row* of images illustrates prolapse of the center scallop of the posterior leaflet (P2). The leaflet is seen above the level of the annular plane, but the leaflet tip is pointing toward the ventricular side. With the application of color-flow Doppler *(center image)*, a large anteriorly direct jet may be appreciated. *(Right image)* Three-dimensional reconstruction as seen from the atrium. The posterior leaflet is visualized in the lower aspect of the image. The prolapsed segment is clearly seen above the level of the other mitral valve segments. *(Lower row, left image)* In contrast to the prolapse, the P2 segment is flailed. A chordae is attached to P2, which rides above the anterior leaflet during systole. The tip of P2 is directed toward the atrium. Color-flow Doppler reveals a large eccentric jet similar to the case of leaflet prolapse. *(Right)* The three-dimensional reconstruction clearly reveals the ruptured chordae associated with P2. (Video available online.)

and chordae, or the papillary muscles. With chronic regurgitation, the annulus and atrium dilate and the annulus loses its normal elliptical shape, becoming more circular.[193] Annular dilation, in turn, leads to poor leaflet coaptation and worsening of valve incompetence. Although increased LA and LV dimensions may suggest severe MR, smaller dimensions do not exclude the diagnosis.[194]

The most common cause of chronic primary MR in developed countries is MV prolapse.[151] Younger individuals exhibit Barlow syndrome, whereas older populations have fibroelastic deficiency disease. A Barlow valve is usually characterized by gross redundancy of multiple segments of the anterior or posterior leaflets and chordal apparatus (Fig. 14.82 and Video 14.60). The leaflets are bulky and billowing with multiple areas of prolapse.[195] The chordae are more often elongated rather than ruptured. The leaflets are thickened with severe myxomatous degeneration. Atrialization of the leaflets (ie, displacement of the leaflet attachment toward the atrium) may occur. The annulus is usually severely dilated and may be calcified.

In contrast, fibroelastic deficiency usually affects only a single segment (Fig. 14.83 and Video 14.61). The nonaffected leaflets tend to be thin, with a thickening of the affected segment. Elongated chords may produce prolapse of one or both attached leaflets; if only one leaflet is affected, then leaflet malalignment may occur during systole.

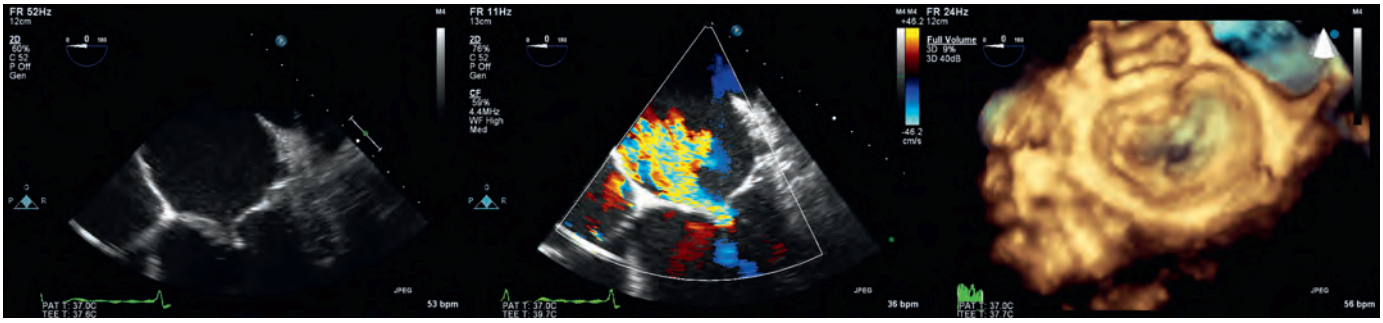


Fig. 14.84 Mitral regurgitation Type IIIa. *(Left and center)* Midesophageal four-chamber view reveals the thickened mitral valve leaflets that are seen coapting below the level of the annular plane. Although not apparent on the still images, leaflet movement both during systole and diastole is restricted, which is characteristic of type IIIa mechanism. In this particular case, the posterior leaflet is thicker with a more restricted movement. *(Center)* Color-flow Doppler demonstrates a large jet directed toward the restricted posterior leaflet. *(Right)* The three-dimensional reconstruction reveals the restriction of the mitral valve leaflets. (Video available online.)

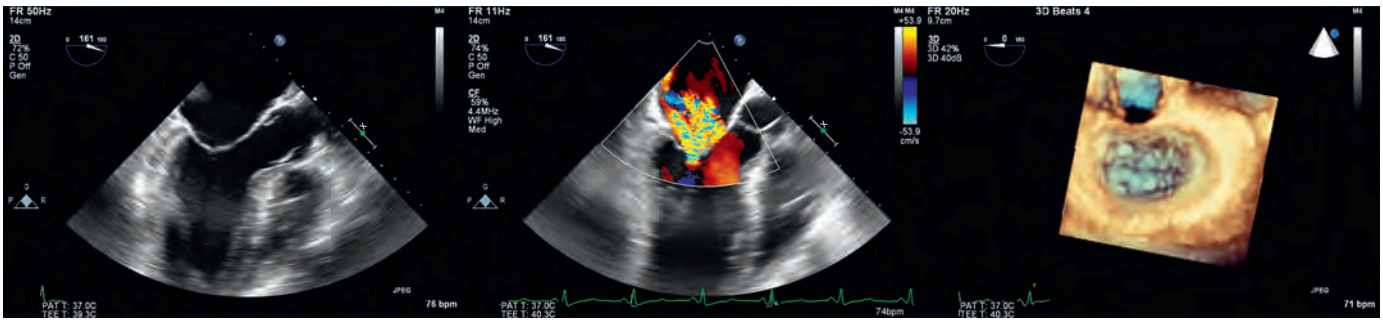


Fig. 14.85 Mitral regurgitation Type IIIb. *(Left and center)* Midesophageal long-axis view demonstrates the thin and anatomically normal anterior and posterior leaflets. Both leaflets are visualized coapting below the level of the mitral valve annulus. Although not apparent on the static images, they move well during diastole but are restricted during systole. *(Center)* Application of color-flow Doppler reveals a severe mitral regurgitant jet. Because the cause of the regurgitation is functional, a regurgitant orifice area greater than 0.2 cm^2 is considered severe. *(Right)* Three-dimensional reconstruction reveals the posterior and anterior leaflets; both leaflets are seen coapting below the level of the mitral valve annulus with resultant compromised coaptation. (Video available online.)

Excessively mobile structures near the leaflet tips during diastole may represent elongated chords or ruptured minor chords. These structures do not prolapse into the atrium during systole. In contrast, ruptured major chords are identified as thin structures with a fluttering appearance in the atrium during systole and are associated with evident prolapse of the affected leaflet; in this instance, the valve segment is termed as *flail*. A flail leaflet segment generally points in the direction of the left atrium, and this directionality of leaflet pointing is the principal criterion for distinguishing a flailed leaflet from severe valvular prolapse.[196,197] Flail leaflets are most commonly caused by ruptured chordae and less commonly caused by papillary muscle rupture.

Regurgitation may also be caused by papillary muscle infarction in association with infarction of the adjacent LV myocardium, attributable to a lack of the normal tethering function performed by these structures. When the adjacent segment is aneurysmal, the dyskinetic wall motion may prevent proper coaptation of the valve by restricting the normal movement of the mitral leaflets during systole.[198] Prior infarctions may be indicated by thinning of the myocardium, atresia of the papillary muscles, and dyskinetic wall segments. Atretic papillary muscles are identified by their diminutive size and increased echocardiographic density on SAX imaging. This shrinkage in papillary muscle size may result in retraction of chordae and subsequent MR. Papillary muscle rupture typically appears as a mass (papillary muscle head) that prolapses into the left atrium during systole and is connected to the leaflet only by its attached chords. In addition to these structural abnormalities, MR is suggested by LV volume overload, a dilated hypercontractile left ventricle, a high EF, and systolic expansion of the left atrium.[199]

In patients with recent endocarditis, vegetations may be attached to the leaflets or chords. With rheumatic valve disease, thickening and/or calcification of the leaflets, restriction of leaflets, and a variable degree of shortening and thickening of the subvalvular apparatus may be identified. Myxomatous degeneration produces ballooning and scalloping of the valve leaflets, as well as localized areas of thinning and thickening, which can be seen echocardiographically. This intrinsic disease progression associated with the leaflets may interfere with MV function with resultant regurgitation (Fig. 14.84; see Video 14.62).

With secondary or functional MR, the MV is structurally normal (Fig. 14.85; see Video 14.63).[151,165] LV dilation, secondary to another process such as myocardial infarction or idiopathic-dilated cardiomyopathies, result in papillary muscle displacement and annular dilation with resultant tethering of the MV leaflets with incomplete leaflet coaption. Since the valvular regurgitation is only one component of the disease process, its progress is worse than primary MR and its treatment is less clear.

Summarizing, the mechanism of MR is frequency described using the Carpentier classification, which is reviewed in Table 14.15 and Fig. 14.86.[200] The classification is based on leaflet movement. Type I is associated with normal leaflet movement (Fig. 14.87; see Videos 14.64

and 14.65). The cause of the MR may be secondary to annular dilation with poor leaflet coapation or may be caused by a leaflet cleft or perforation. Type II is associated with excessive leaflet movement or prolapse (see Fig. 14.83 and Video 14.61). Most commonly, this type of regurgitation is caused by chordal rupture. Type III is subdivided into Types IIIa and IIIb. Type IIIa is restricted leaflet motion during both systole and diastole (see Fig. 14.84 and Video 14.62). This type of MR is usually caused by processes of the leaflets, themselves, that interfere with normal leaflet function, such as rheumatic MV disease. Type IIIb, also known as functional MR, is restricted leaflet motion during systole (see Fig. 14.85 and Video 14.63). This is the most common mechanism for functional MR secondary to LV enlargement. The leaflets, themselves, are usually anatomically normal; however, substantial chordal tethering may interfere with complete valvular closure during diastole. This type of MR commonly occurs with LV dilation, which commonly results in restriction of P2 and P3.

TABLE 14.15 Carpentier Classification of Mitral Regurgitation[200]

	Leaflet Motion	*Etiology*
Type I	Normal	Annular dilation Leaflet perforation
Type II	Excessive (prolapsed)	Chordal elongation or rupture Papillary muscle elongation or rupture
Type IIIa	Restricted leaflet motion during systole and diastole	Leaflet and chordal thickening (eg, rheumatic heart disease)
Type IIIb	Restricted leaflet motion during systole	Left ventricular enlargement

Adapted from Carpentier A. Cardiac valve surgery–the "French correction." *J Thorac Cardiovasc Surg.* 1983;86:323–337.

Qualitative Grading Using Color-Flow Doppler

The diagnosis of MR is made primarily by the use of color-flow mapping. Because flow is best detected when it is parallel to the ultrasonic beam and because some MR jets may be thin and eccentric, multiple views of the left atrium should be interrogated for evidence of MR. It is important to remember that the regurgitant flow disturbances are 3D-velocity fields with complex geometry, which must be sampled from multiple imaging planes to provide an accurate estimate of the maximal spatial extent of the CFD signal. It is common to detect trivial degrees of MR that extend just superior and posterior to the MV leaflet. MR is detected more frequently by TEE, compared with TTE, and the degree of regurgitation is often graded as being more severe using TEE.[201,202]

Eccentric jet direction provides corroborative evidence of structural leaflet abnormalities, which may include leaflet prolapse, chordal elongation, chordal rupture, or papillary muscle rupture (Fig. 14.88). For example, a jet that is directed laterally along the posterior wall of the left atrium is associated with anterior leaflet prolapse. Similarly, a jet that is directed medially behind the anterior mitral leaflet is associated with prolapse of the posterior leaflet.

Atrioventricular valve regurgitation is graded semiquantitatively as mild, moderate, or severe and is summarized in Table 14.16. Regurgitation less than mild may be classified as either trivial or trace. Some authors have suggested subdividing moderate regurgitation into mild-moderate and moderate-severe grades.[165,172] The most common method of grading the severity of MR is CFD mapping of the left atrium. With the Nyquist limit set at 50 to 60 cm/sec, jet areas less than 4 cm^2 or 20% of the LA size are usually classified as mild, whereas jets greater than 10 cm^2 or 40% of the atrial volume are classified as severe.[172] The area of the Doppler jet may be influenced by technical factors such as gain setting, carrier frequency of the transducer, imaging of low-velocity flows, differentiation of regurgitant from

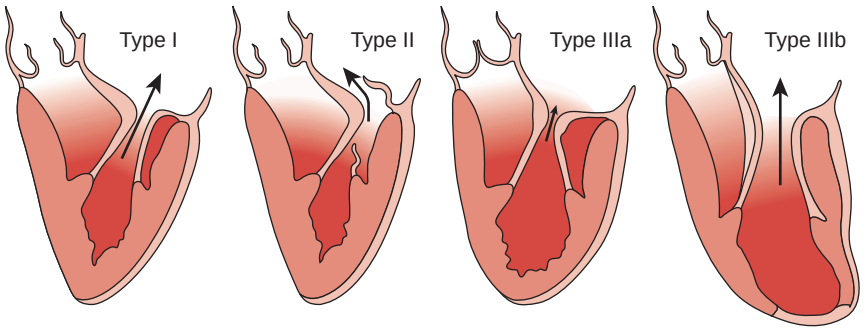


Fig. 14.86 Schematic representation of Carpentier classification of mitral regurgitation. *(Adapted from Adams D. Understanding degenerative disease (the pathophysiologic triad). Available at:* http://www.mitralvalverepair.org/content/view/58/.)

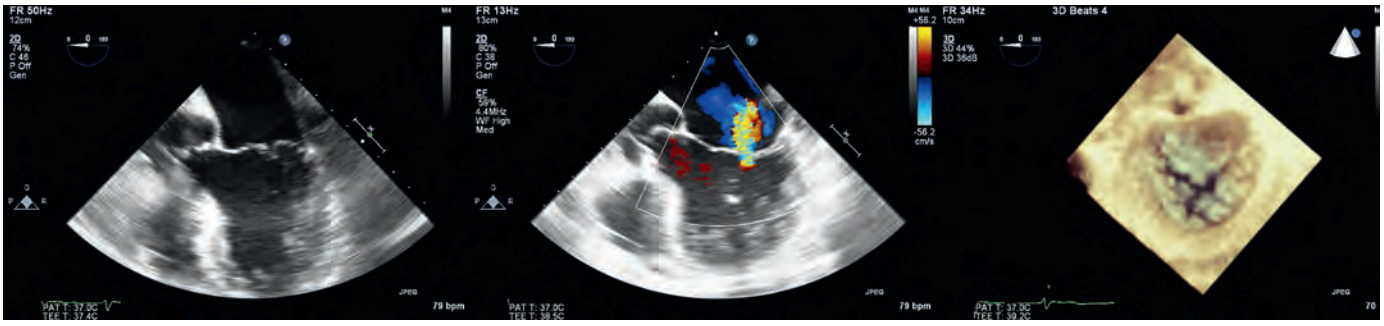


Fig. 14.87 **Mitral regurgitation Type I.** *(Left and center)* Midesophageal five-chamber view reveals the anterior and posterior leaflets coapt at the level of the mitral valve annulus, but the space between the two leaflets is significant. *(Center)* Application of color-flow Doppler reveals a central jet. *(Right)* In addition to the poor coaption of the anterior and posterior leaflet, this three-dimensional reconstruction visualizes a large cleft in the posterior leaflet, which contributes to the regurgitation. (Video available online.)

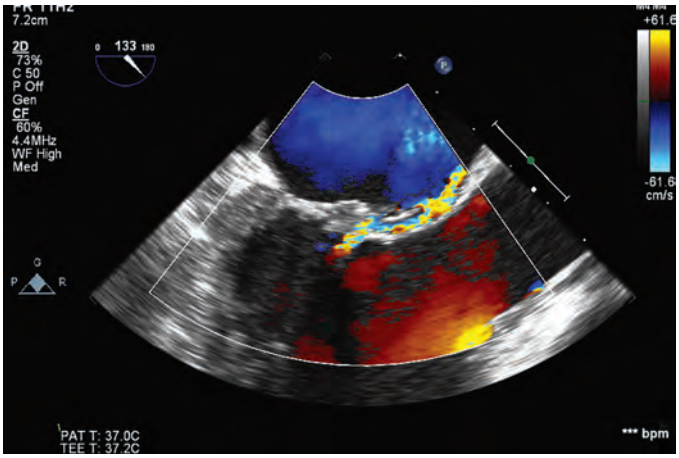


Fig. 14.88 Eccentric mitral valve regurgitant jet. An eccentric mitral regurgitant jet is being directed anteriorly. If the area of the jet, alone, is used to estimate the degree of regurgitation, then the severity of regurgitation will be underestimated.

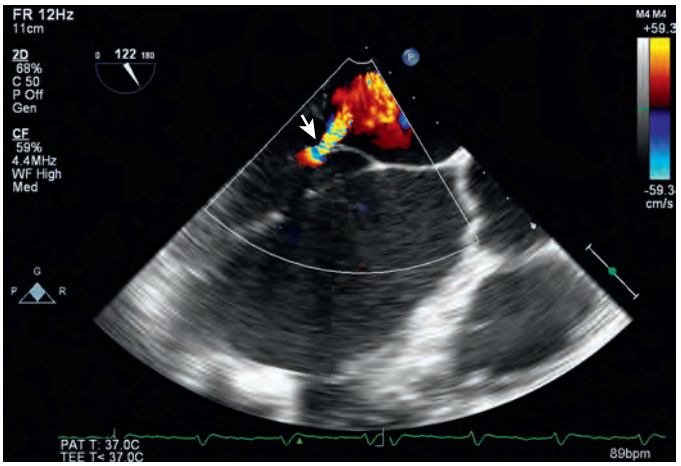


Fig.14.89 Mitral valve vena contracta is demonstration in the mid-esophageal long-axis view. The *arrow* points to the vena contracta of the mitral regurgitant jet.

TABLE 14.16 Summary of Mitral Regurgitation

		Moderate		
	Mild	*Mild-Moderate*	*Moderate-Severe*	*Severe*
Left atrial size	Normal	Normal or dilated		Usually dilated
Color-flow jet area[a]	Small central jet (<4 cm^2 or <20% left atrial area)			Large central jet (>10 cm^2 or >40% left atrium) or variable-sized wall impinging jet
Pulmonary venous flow	Systolic dominance	Systolic blunting		Systolic flow reversal
Continuous-wave jet contour	Parabolic	Usually parabolic		Early peaking triangular
Continuous-wave jet density	Incomplete or faint	Dense		Dense
Vena contracta width (cm)	<0.3	0.3–0.69		≥0.7
Regurgitant orifice area (cm^2)	<0.20	0.20–0.29	0.30–0.39	≥0.40

[a]At Nyquist limits of 50–60 cm/sec. This method is not recommended in the 2013 European Association of Cardiovascular Imaging Guidelines.

Adapted from Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14(7):611–644; and Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

displacement flow, complexities in jet geometry such as multiple jets and vortex flow, temporal variation of jet size during systole, and differences between machines in color-Doppler display.[203] In addition, jet direction should be considered when grading regurgitation, because eccentric jets that cling to the atrial wall (Coanda effect) have a smaller area than central (free) jets with similar regurgitant volumes and regurgitant fractions.[204–206] Because of these mitigating factors, the 2013 European guidelines do not recommend the use of regurgitant jet area to quantitate the severity of MR.[165] An alternative method of grading MR is based on the vena contracta width (Fig. 14.89).[207] Although the vena contracta is commonly circular, it may be elliptical in shape with secondary causes or functional regurgitation.[165] In these cases, multiple views of the vena contracta along different axes should be obtained and averaged. A vena contracta width of less than 0.3 cm is associated with mild MR, whereas a width greater than 0.7 cm is associated with severe MR.[172]

CWD integration may also be used in the assessment of the severity of MR (Fig. 14.90).[208] A peak velocity that occurs during early systole and is directed toward the left atrium can be appreciated with MR, and the intensity of this recording may be proportional to the severity of regurgitation.[209] A dense full signal is associated with severe MR, whereas an incomplete and faint signal is associated with less severe regurgitation.

Pulmonary Vein Flow Pattern

Pulmonary vein flow imaged by TEE provides useful information regarding regurgitant severity.[210] Normally, pulmonary venous flow consists of a phase of retrograde flow during atrial systole and two phases of antegrade flow during ventricular systole and diastole. Because systolic pulmonary venous flow is augmented by active atrial relaxation, systolic antegrade pulmonary venous flow is usually greater than diastolic antegrade pulmonary venous flow. With MR, LAP is increased during ventricular systole, which may either reduce antegrade systolic pulmonary venous flow or cause reversal of systolic flow in cases of severe regurgitation (Fig. 14.91). Systolic pulmonary venous flow reversal is a specific sign of severe MR.[165]

Interrogating both right and left pulmonary veins is important. With eccentric jets, flow reversal may be more prominent in the pulmonary veins toward which the jet is directed; however, central MR may also result in discordant pulmonary venous flow patterns.[211] Although discordant flow primarily occurred with eccentric mitral regurgitant jets with systolic reversal primarily in the RUPV, some patients with central regurgitation may also have discordant pulmonary venous flows.

Proximal Isovelocity Surface Area

In addition to these previously discussed indices of MR, regurgitant flow convergence and flow volume also may be used to assess the degree of MR (Fig. 14.92).[212] Quantification of MR by the PISA assumes that as blood flows toward a regurgitant lesion, flow converges radially. This convergence occurs along increasing isovelocity hemispheres converging on the regurgitant lesion. CWD may be used to identify these hemispheres of increasing velocity proximal to the lesion (identified by aliasing), and flow may be determined. Before performing the PISA calculations, a well-defined hemisphere must be imaged. This may be performed either by reducing the Nyquist limits or by shifting the CFD

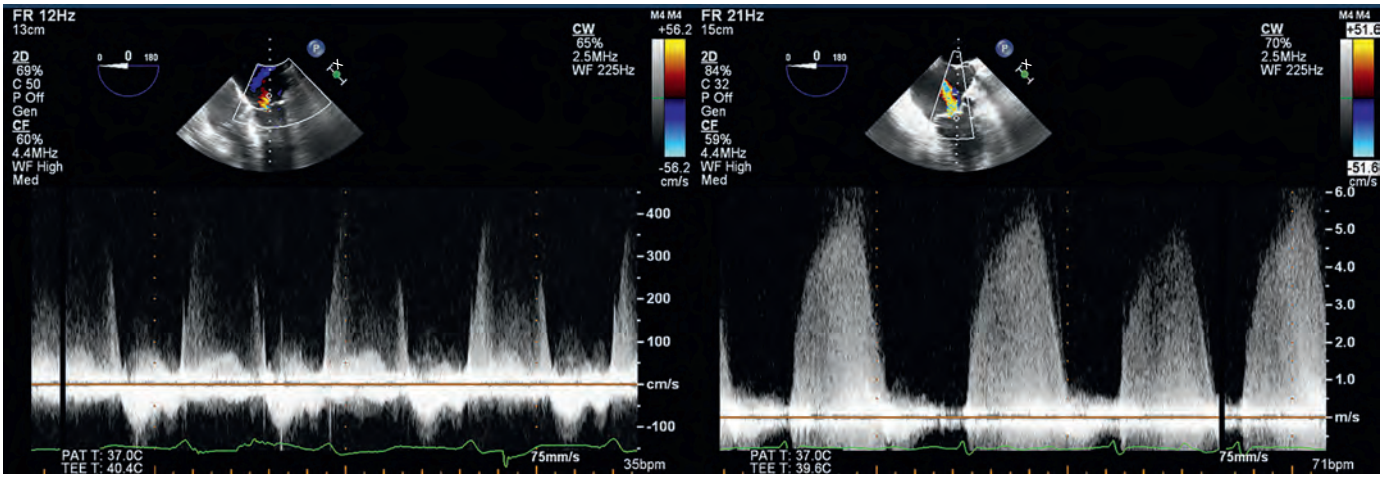


Fig. 14.90 Doppler spectrum with mitral regurgitation. *(Left)* Mild degree of mitral regurgitation results in a lighter incomplete Doppler spectrum when the regurgitant flow is visualized. *(Right)* With severe regurgitation, the Doppler spectrum becomes more solid and more intense in character.

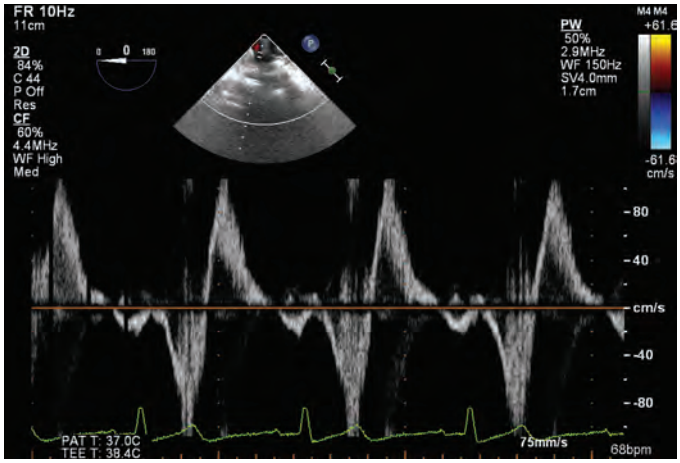


Fig. 14.91 Pulmonary venous flow with severe mitral regurgitation. The systolic component of the pulmonary venous tracing, which occurs immediately after the QRS wave, indicates flow away from the left atrium (away from the transducer). This pulmonary systolic venous reversal is consistent with severe mitral regurgitation.

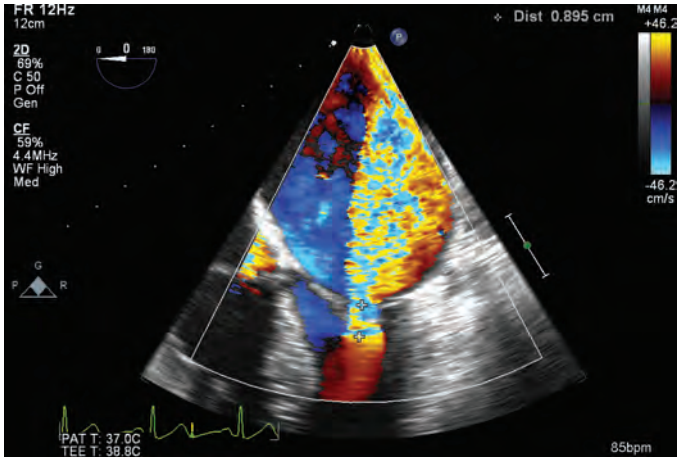


Fig. 14.92 Determination of mitral regurgitation by proximal isovelocity surface area (PISA). Assuming normal hemodynamics, the regurgitant orifice area (ROA) of the mitral regurgitant volume may be estimated. The Nyquist limit should be set for approximately 40 cm/sec, and the radius of the PISA shell in centimeters *(r)* is measured. The ROA in square millimeters (mm^2) is approximately equal to $r^2/2$. In this case, the PISA radius is approximately 0.9 cm, which would yield an ROA of approximate 0.4 mm^2.

mapping baseline toward the direction of flow. The flow through this well-defined hemisphere is:

$$\text{Flow} = (\text{surface area of the hemisphere}) \times (\text{velocity at the hemisphere}) \quad \text{[Eq. 14.32]}$$

$$\text{If surface area hemisphere} = 2\pi r^2 \quad \text{[Eq. 14.33]}$$

where r is the radius of the hemispheric spheres,

$$\text{then flow hemisphere is} = 2\pi r^2 v_n \quad \text{[Eq. 14.34]}$$

where v_n is the Nyquist limit.
Because flow through these isovelocity spheres equals flow through the regurgitant lesion,

$$2\pi r^2 v_n = \text{ROA } V_o \quad \text{[Eq. 14.35]}$$

where ROA is the area of the regurgitant orifice area (ROA), and V_o is the maximal regurgitant velocity. Solving for ROA, yields:

$$\text{ROA} = 2\pi r^2 v_n / V_o \quad \text{[Eq. 14.36]}$$

Because the regurgitant volume is equal to the area of the regurgitant lesion, multiplied by the velocity-time integral of the regurgitant velocity (VTI_{regurg}),

$$\text{Regurgitant volume} = \text{VTIregurg (ROA)} = \text{VTIregurg } (2\pi r^2 v_n / V_o) \quad \text{[Eq. 14.37]}$$

If the base of the hemisphere is not flat (ie, 180 degrees), then a correction for wall constraint should be performed by multiplying the ratio of the adjacent angle formed by the wall and 180 degrees.[172]

The PISA method of determining MR is time consuming; however, it has been validated as a method of identifying patients with severe MR.[213] Generally, it is most accurate for central jet compared with an eccentric one. Because the hemispheric radius is squared, care must be taken to ensure and measure a well-defined shell. If the Nyquist limits are set for 40 cm/sec and assuming that the patient has "normal" systolic blood pressures (the difference between the systolic LV pressure and LAP is approximately 100 mm Hg), then the calculation of ROA may be estimated to be[214]:

$$\text{ROA} = r^2/2 \quad \text{[Eq. 14.38]}$$

where r is the radius of the PISA shell in centimeters (see Fig. 14.92).

The quantification of the severity of chronic function MR (ie, Type IIIb) is more complex. Because the primary mechanism is severe LV

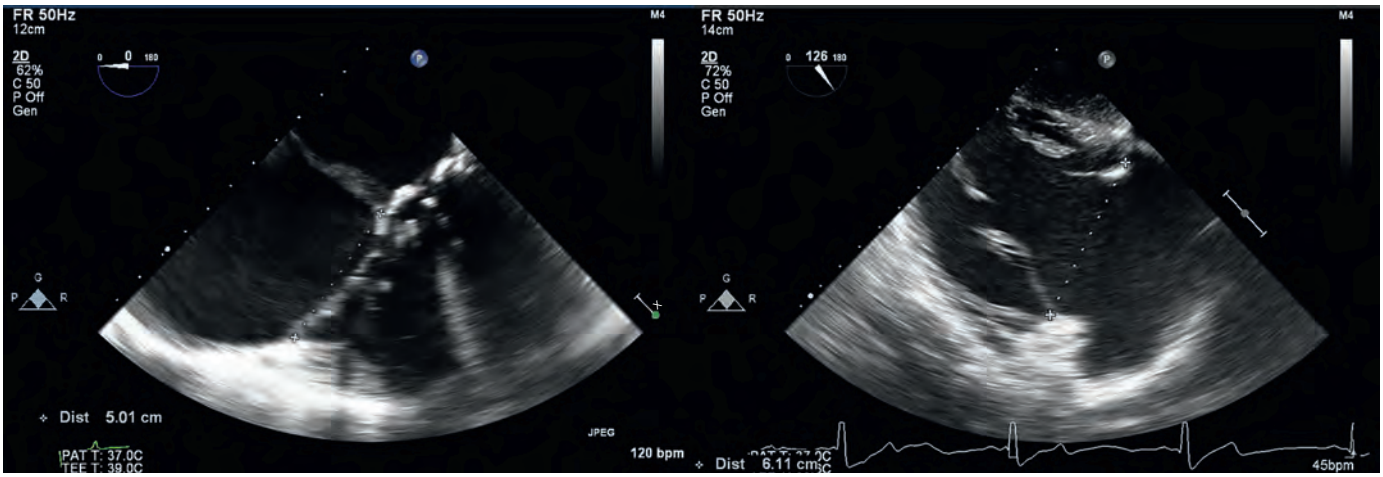


Fig. 14.93 Measurements of tricuspid annular diameters. The common views for the determination of tricuspid annular diameter are illustrated. (*Left*) Midesophageal four-chamber view. (*Right*) Transgastric right ventricular inflow.

dysfunction and ventricular dilation, secondary to either ischemic or nonischemic cardiomyopathy, adverse outcomes are associated with a smaller calculated effective regurgitant orifice, compared with MR of other causes.[151] Because of the crescent shape of the regurgitant orifice, 2D-based measurements underestimate the severity of the regurgitation. The 2014 AHA/ACC guidelines for the treatment of valvular disease suggest that an ROA greater than 0.2 cm^2, regurgitant volumes greater than 30 mL, and regurgitant percentages greater than 50% should be considered severe.

Tricuspid Valve

The TV consists of three leaflets, an annular ring, chordae tendineae, and multiple papillary muscles.[215] The anterior leaflet is usually the largest, followed by the posterior and septal leaflets. The septal leaflet of the TV is usually farther apical than the septal attachments of the MV. Chordae arise from a large single papillary muscle, double or multiple septal papillary muscles, and several small posterior papillary muscles, attached to the corresponding walls of the right ventricle.

Intrinsic structural abnormalities of the TV that can be well characterized by TEE include rheumatic tricuspid stenosis, carcinoid involvement of the TV, TV prolapse, flail TV, Ebstein anomaly, and tricuspid endocarditis. Rheumatic involvement of the TV, which is typically seen with concomitant MV involvement, is characterized by thickening of the leaflets (particularly at their coaptation surfaces), fusion of the commissures, and shortening of the chordal structures resulting in restricted leaflet motion.[216] Carcinoid syndrome results in a diffuse thickening of the TV and PV and endocardial thickening of right-sided heart structures, which may result in restricted TV motion (mixed stenosis and regurgitation).[217]

Supravalvular, valvular, or subvalvular restriction may cause tricuspid stenosis. The most common cause of tricuspid stenosis is rheumatic heart disease, whereas less common causes include carcinoid syndrome and endomyocardial fibrosis. Tricuspid stenosis is characterized by a domed thickened valve with restricted movement. TR may be secondary to annular or RV dilation, pathologic conditions of the leaflets, or subvalvular apparatus. CWD measurements of the inflow velocities across the TV can be used to estimate the mean diastolic TV gradient with the modified Bernoulli equation.[218] Optimal alignment of the Doppler cursor parallel to tricuspid inflow can be difficult to achieve from transesophageal imaging windows. Often alignment can be achieved, however, by positioning the probe deep within the stomach such that the RV apex is imaged at the top of the sector scan. Alternatively, probe positioning at more rostral levels can display the TV adjacent to a basal SAX view of the AV (multiplane crystal orientation 25 to 30 degrees), which may be suitable for CWD interrogation.

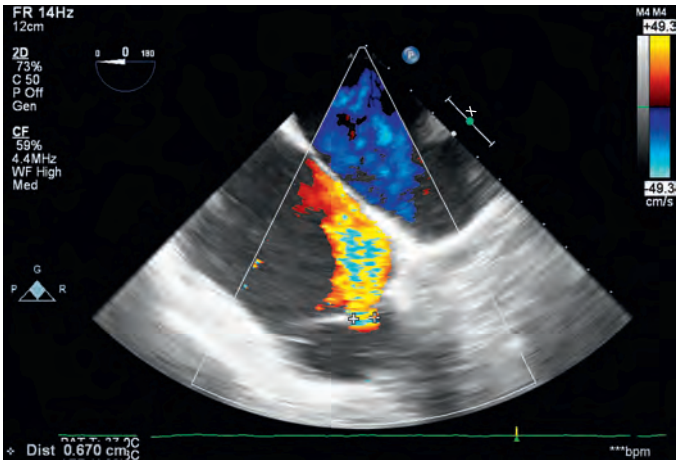


Fig. 14.94 Vena contracta of tricuspid regurgitant jet. Midesophageal four-chamber view visualizes a large tricuspid regurgitant jet. Measurement of the vena contracta of this jet is greater than 0.6 cm, which is consistent with severe tricuspid regurgitation. (Video available online.)

Although TR may have primary causative factors, most causes are secondary or functional as a result of either tricuspid annular dilation (>40 mm) or RV dilation (Figs. 14.93 and 14.94; see Video 14.66).[165] RV enlargement result in annular dilation and papillary muscle displacement with tethering of the TV leaflets. This tethering may result in poor leaflet coaption. This TR results in additional RV enlargement and further leaflet tethering with worsening TR.

Primary disorders of the tricuspid apparatus include rheumatic disease, prolapse, congenital disease, radiation, infective, carcinoid, blunt chest wall trauma, RV endomyocardial biopsy–related trauma, and intraannular RV pacemaker or implantable cardioverter-defibrillator leads.[151] The bulky and redundant tricuspid leaflet tissue observed in TV prolapse is associated with billowing of leaflet tissue superior to the tricuspid annular plane into the RA. In patients with an overtly flail TV, the disrupted leaflet tissue wildly prolapses into the RA, exhibiting high-frequency systolic vibrations. Destructive processes such as infective endocarditis, valve trauma induced by inadvertent endomyocardial biopsy of the tricuspid apparatus, and spontaneous rupture of chordae may all result in a partially flail TV apparatus.

Similar to MR, the mechanisms of TR may be classified using the Carpentier classification. Type I: leaflet perforation or pure annular

dilation; Type II: increased leaflet motion (eg, prolapse or flail); or Type III: restricted process, which may be either intrinsic or functional.[165] The normal tricuspid annular diameter in the ME four-chamber view is 28 ± 5 mm; a diameter greater than 35 mm is considered significant (see Fig. 14.93).[165] Evaluation of the severity of TR is frequently required in patients with severe MV disease, severe LV systolic dysfunction and secondary right-sided heart failure, or RV dysfunction attributable to long standing pulmonary hypertension.

The quantification of TR is summarized in Table 14.17. The apparent severity of TR is exquisitely sensitive to right-sided heart loading conditions. Thus during the intraoperative evaluation of TR, PA, and right atrial pressures should be kept near levels observed in the awake resting state. Some authors suggest that the severity of TR can be estimated by the apparent size (area in a given imaging plane, volume reconstructed in three dimensions) of the color-flow disturbance of TR relative to right atrial size.[219] A central jet area of less than 5 cm^2 is consistent with mild regurgitation, whereas a jet area greater than 10 cm^2 is consistent with severe regurgitation.[172] However, recent guidelines suggest that color-flow area of the regurgitant jet should not be used to quantitate the severity of TR.[165] A vena contracta width less than 0.3 mm is consistent with mild regurgitation, whereas a VC greater than 0.7 cm is consistent with severe regurgitation (see Fig. 14.94).[220] Although its application is limited, the severity of TR may also be quantified using flow convergence (PISA).[221] At a Nyquist limit of 28 cm/sec, a PISA radius less than 5 mm suggests mild TR, whereas a radius greater than 9 mm suggests severe TR; an ROA greater than 40 mm^2 or a regurgitant volume greater than 45 mL is also consistent with severe TR. To further assist in the evaluation of the hemodynamic significance of TR, the hepatic veins can be interrogated from deep gastric positioning of the transesophageal probe (Fig. 14.95). The presence of blunted systolic hepatic vein flow is associated with moderate TR, and retrograde systolic flow is associated with hemodynamically severe TR.

TABLE 14.17 Quantification of Tricuspid Regurgitation

	Mild	*Moderate*	*Severe*
Right atrial size	Normal	Normal or dilated	Usually dilated
Tricuspid valve leaflets	Usually normal	Normal or abnormal	Abnormal/flail or wide coaption defect
Jet area—central jets (cm^2)[a]	<5	5–10	>10
Continuous-wave jet density	Soft and parabolic	Dense, variable contour	Dense, triangular with early peaking
Vena contracta width (cm)[a]	Not defined	<0.7	>0.7
PISA radius (cm)[b]	≤0.5	0.6–0.9	>0.9
ROA mm^2	Not defined	Not defined	>40
Regurgitant volume	Not defined	Not defined	>45 mL
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal

[a]At Nyquist limits of 50 to 60 cm/sec.
[b]At Nyquist limits of 28 cm/sec.
PISA, Proximal isovelocity surface area; *ROA,* regurgitant orifice area.
Adapted from Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2013;14(7):611–644; and Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777–802.

Myocardial Ischemia Monitoring

Regional Wall Motion and Systolic Wall Thickness

Echocardiography has been used for decades in assessing RWMAs associated with myocardial ischemia.[222] The ability to reliably detect RWMAs is clinically relevant because of its diagnostic and therapeutic implications. Consequently, it is important to note that RWMAs detected by TEE must always be interpreted within the clinical context, because not every RWMA is diagnostic for myocardial ischemia. Myocarditis, ventricular pacing, and bundle branch blocks can easily lead to wall motion abnormalities that can potentially lead to mismanagement of the patient.

When describing RWMAs, common classifications should be used to describe the anatomic localization and degree of dysfunction to ensure that communication is possible between the echocardiographer and nonechocardiographer, as well as documentation of ongoing disease course. Both the 16- and 17-segment models of the left ventricle have been published by the ASE (see Fig. 14.13A).[79,223] This model subdivides the left ventricle into three zones (basal, mid, and apical). The basal (segments 1 to 6) and midventricular zones (segments 7–12) are further subdivided into six segments each, whereas the apical zone consists of only four (segments 13–16). Another model published by the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging has added a 17th segment to the model. The 17th segment represents the apical cap of the previously described 16-segment model.

By understanding coronary anatomy, the echocardiographer can make assumptions regarding localization of a potential coronary artery

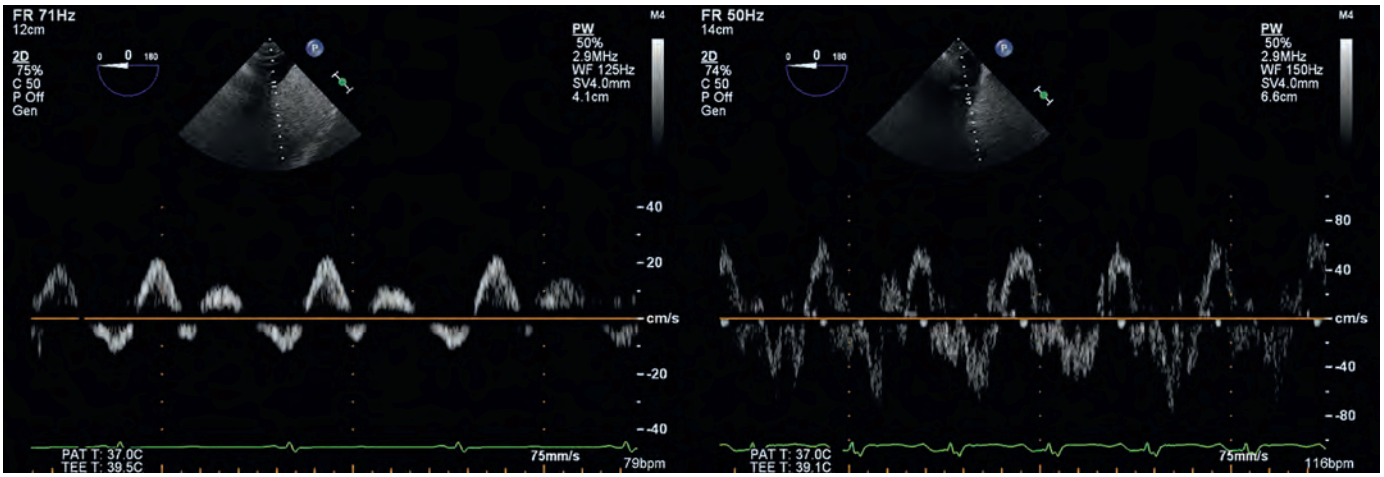


Fig. 14.95 Hepatic venous flow. *(Left)* The normal hepatic venous Doppler spectrum reveals flow toward the right atrium during both systole and diastole. *(Right)* With severe tricuspid regurgitation, flow is away from the right atrium during systole.

lesion based on the region of abnormal wall motion. Using the ASE model, the segments 1, 2, 7, 13, 14, and 17 are in the distribution territory of the LAD artery. Segments 5, 6, 11, 12, and 16 are associated with the circumflex artery and segments 3, 4, 9, 10, and 15 belong to the right coronary artery (see Fig. 14.13B). This segmental distribution can be variable among patients because of the variability of the coronary arteries. In addition to describing a system that defines the anatomic segments of the left ventricle, grading segment thickening and excursion is important.

Wall Motion

The simplest assessment of wall motion is performed by eyeballing the motion of the individual segments of the left ventricle as described earlier in the ASE model. This qualitative assessment is classified as being normal, hypokinetic, akinetic, dyskinetic, or aneurismal. Subsequently, a numeric score of 1 to 5 can then be assigned. A wall motion index can then be derived by dividing the total score by the number of segments observed. A score of 1 would represent a normal ventricle. The higher the score, the more abnormal the ventricle. This score can be used to predict outcome after cardiac surgery and risk stratifying patients for adverse cardiac events.[224–226]

In addition to movement, the normal myocardium thickens during systole. Wall thickening can be assessed qualitatively, or it can be quantitatively evaluated by calculating systolic wall thickening from the following equation:

$$\text{PSWT} = \text{SWT} - \text{DWT}/\text{SWT} \times 100 \qquad \text{[Eq. 14.39]}$$

where PSWT is the percentage of systolic wall thickening, SWT represents end-systolic wall thickening, and DWT is end-diastolic wall thickening.

The degree of thickening can also be used to assess overall function of the observed segment. A thickening greater than 30% is normal, 10% to 30% represents mild hypokinesia, 0% to 10% is severe hypokinesia, no thickening is akinesia; if the segment bulges during systole, then dyskinesia is present.

Diagnosis of Ischemia

The precise sequence of functional changes that occur in the myocardium after interruption of flow has been studied in models of acute ischemia, including percutaneous transluminal coronary angioplasty (PTCA).[227–229] Abnormalities in diastolic function usually precede abnormal changes in systolic function. Normal function is critical for LV filling and is dependent on ventricular relaxation, compliance, and atrial contraction. Diastolic ventricular function can be assessed by monitoring the rate of filling associated with changes in the chamber dimensions (see earlier discussion). Regional systolic function can be estimated by echocardiographic determination of wall thickening and wall motion during systole in both LAX and SAX views of the ventricle. The SAX view of the left ventricle at the papillary muscle level displays myocardium perfused by the three main coronary arteries and is therefore very useful. However, because the SAX view does not image the ventricular apex, which is a very common location of ischemia, the LAX and longitudinal ventricle views are also clinically important.[230]

Although wall thickening is probably a more specific marker of ischemia than wall motion, its measurement requires visualization of the epicardium, which is not always possible. Alternatively, by observing the movement of the endocardium toward the center of the cavity during systole, systolic wall motion can almost always be assessed. As the myocardial oxygen supply-demand balance worsens, graded systolic wall motion abnormalities progress from mild hypokinesia to severe hypokinesia, akinesia, and finally dyskinesia.[231] Normal contraction is defined as greater than 30% shortening of the radius from the center to the endocardial border. Mild hypokinesia refers to inward contraction that is slower and less vigorous than normal during systole, with radial shortening of 10% to 30%. Severe hypokinesia is defined as less than 10% radial shortening. The precise distinction between varying degrees of hypokinesia can be difficult. Akinesia refers to the absence of wall motion or no inward movement of the endocardium during systole. Dyskinesia refers to paradoxic wall motion or movement outward during ventricular systole (see Chapter 20). These measurements of regional wall motion are obviously based on the determination of the center of the ventricular cavity. Unfortunately, because of cardiac translation, this center may move during the cardiac cycle. Two reference systems have been used: fixed reference and floating reference. Because of its relative simplicity and the fact that in most situations the impact of translation is minimal, the fixed-reference system is generally used. In conditions of significant translation, such as after CPB, the more cumbersome floating-reference system may be more appropriate.[232]

Relation to Other Monitors

Clinical studies have indicated that RWMAs occur earlier and are a more sensitive indicator of myocardial ischemia than the abnormal changes detected with an ECG or PAC.[233–239] In one study, 30 patients undergoing PTCA were simultaneously monitored with 12-lead ECGs and echocardiography.[236] All the patients had isolated obstructive lesions in their LAD coronary arteries, stable angina, normal baseline ECGs, normal baseline myocardial function with no history of infarction, and no angiographic evidence of collateralization. In the study, all patients developed RWMAs approximately 10 seconds after coronary artery occlusion. Electrocardiographic changes occurred in 27 of 30 patients approximately 22 seconds after coronary occlusion.

Smith and colleagues[235] evaluated 50 patients at high risk for myocardial ischemia during peripheral vascular or cardiac surgery with TEE and a multilead ECG. In their study, 6 patients had repolarization changes diagnostic of ischemia and 24 had new evidence of RWMAs. ECG repolarization changes were always accompanied by a corresponding RWMA. In 50% of the patients who experienced ST-segment changes, the RWMAs had occurred minutes before. Three patients with evidence of new RWMAs developed perioperative myocardial infarctions; however, only one patient of the three had evidence of ST-segment changes.

The value of PCWP monitoring for ischemia has also been compared with changes in regional LV function assessed with TEE. In one study, PCWP, 12-lead ECG, and LV wall motion were evaluated in 98 patients before CABG at predetermined intervals.[237] Myocardial ischemia was diagnosed by TEE in 14 patients. In 10 of the 14 patients, ischemia was associated with repolarization changes on the ECG. An increase of at least 3 mm Hg in PCWP was tested as an indicator for ischemia and was sensitive only 33% of the time, with a positive predictive value of only 16%. Overall, most studies indicate that the sensitivity of wall motion analysis for the detection of myocardial ischemia is generally superior to that of the ECG or PCWP.

Limitations

Although TEE appears to have many advantages over traditional intraoperative monitors of myocardial ischemia, potential limitations remain as well. The most obvious limitation of TEE monitoring is the fact that ischemia cannot be detected during critical periods, such as induction, laryngoscopy, intubation, emergence, and extubation. In addition, the adequacy of RWMA analysis may be influenced by artifact.[240] The ultrasound system, itself, or the particular tangential section being imaged can produce artifacts.

The septum, in particular, must be given special consideration with respect to wall motion and wall thickness assessment.[240,241] The septum comprises two parts: the lower muscular portion and the basal membranous portion. The basal septum does not exhibit the same degree of contraction as the lower muscular part. At the most superior basal portion, the septum is attached to the aortic outflow track. Its movement at this level is normally paradoxic during ventricular systole. The septum is also a unique region of the left ventricle because it is a region of the right ventricle as well and is therefore influenced by forces from both ventricles. In addition, sternotomy, pericardiotomy, and CPB have been found to alter the translational and rotational motion of the heart within the chest, which may cause changes in ventricular septal motion.[241]

For these reasons, use of a floating reference system in the intraoperative period is recommended. Consequently, the exact imaging plane for wall motion assessment is critical. The SAX view of the left ventricle at the level of the midpapillary muscles is used to ensure constant internal landmarks as reference (anterior and posterior papillary muscles) and to ensure monitoring of the muscular septal region. It must be recognized that, although myocardial blood flow from the coronary arteries is best represented at the SAX midpapillary muscle level, there may be other myocardial regions that are underperfused and not adequately represented in one echocardiographic imaging plane.[242] One solution to this problem is to frequently reposition the probe to view other cross sections of the heart.

Another potential problem of RWMA assessment is the evaluation of the discoordinated contraction that occurs as a result of a bundle-branch block or ventricular pacing. In these situations, the system used to assess RWMAs must compensate for global motion of the heart (usually accomplished with a floating frame of reference) and evaluate not only regional endocardial wall motion but also myocardial thickening.

Not all RWMAs are indicative of myocardial ischemia or infarction. Clearly, under normal conditions, all hearts do not contract in a homogeneous and consistent manner.[243] It is reasonable to assume, however, that most of the time an acute change in the regional contraction pattern of the heart during surgery is likely attributable to myocardial ischemia. An important exception to this rule may apply in models of acute coronary artery occlusion. In these models, it has been established that myocardial function becomes abnormal in the center of an ischemic zone, but it is also true that the myocardial regions adjacent to the ischemic zones become dysfunctional as well. Several studies have reported that the total area of dysfunctional myocardium commonly exceeds the area of ischemic or infarcted myocardium.[244,245] The impairment of function in nonischemic tissue has been thought to be caused by a *tethering effect* (Fig. 14.96). Tethering, or the attachment of noncontracting tissue that is normally perfused, probably accounts for the consistent overestimation of infarction size by echocardiography when compared with postmortem studies.[246]

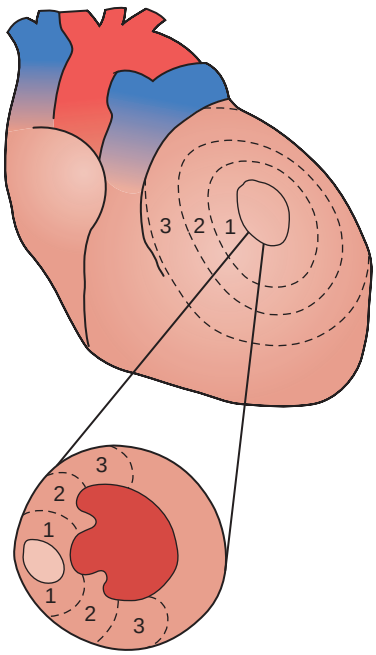


Fig. 14.96 Tethering effect. Myocardial function becomes abnormal in the center of an ischemic zone, as well as in regions adjacent to the ischemic zone. Attachment of noncontracting tissue *(central zone)* mechanically impairs contraction in normally perfused adjacent tissue (zones 1 through 3).

Another limitation of RWMA analysis during surgery is that it does not differentiate stunned or hibernating myocardium from acute ischemia, nor does it differentiate the cause of ischemia between increased oxygen demand and decreased oxygen supply.[247] Finally, it should be noted that areas of previous ischemia or scarring may become unmasked by changes in afterload and appear as new RWMAs.[248] This is particularly important in vascular surgery, during which major abrupt changes in afterload occur.

Outcome Significance

Data regarding the significance of intraoperative detection of RWMAs suggest that transient abnormalities unaccompanied by hemodynamic or ECG evidence of ischemia may not represent significant myocardial ischemia and are usually not associated with postoperative morbidity.[249] Hypokinetic myocardial segments appear to be associated with minimal perfusion defects compared with the significant perfusion defects that accompany akinetic or dyskinetic segments. Therefore hypokinesia may be a less predictive marker for postoperative morbidity.[235,250,251]

Intraoperative detection of new or worsened and persistent RWMAs during peripheral vascular surgery has been reported to be associated with postoperative cardiac morbidity by several investigators. The occurrence of new RWMAs during vascular surgery appears to be common; however, most of the time they are transient and clinically insignificant.[249–251] New RWMAs that are recognized to persist until the conclusion of surgery, in contrast, imply acute perioperative myocardial infarction. Intraoperative RWMAs therefore may be spurious, reversible with or without treatment, or irreversible. The former may be associated with clinically insignificant short periods of ischemia, whereas the latter are associated with significant ischemia or infarction.[235,250,251]

Intraoperative TEE has helped predict the results of CABG surgery. After CABG to previously dysfunctional segments, immediate improvement of regional myocardial function (which is sustained) has been demonstrated.[252,253] In addition, prebypass compensatory hypercontracting segments have been reported to revert toward normal immediately after successful CABG.[254] Persistent RWMAs after CABG appear to be related to adverse clinical outcomes, and lack of evidence of RWMAs after CABG has been shown to be associated with a postoperative course without cardiac morbidity.[247]

Stress Echocardiography

Dynamic imaging with stress echocardiography was first introduced in the late 1970s and may better distinguish viable from nonviable myocardium. Stress echocardiography uses mechanical, pharmacologic, or other stresses to the heart to achieve predetermined peak stress levels. Stress echocardiography has emerged as a safe and sensitive method for the detection of CAD and a cost-efficient alternative to scintigraphy. Reversible RWMAs attributable to transient myocardial ischemia are the hallmark of atherosclerotic CAD. Among the means for initiating the stress response are exercise, atrial pacing, intravenous dipyridamole, adenosine, and dobutamine. Exercise and dobutamine cause myocardial ischemia through significant increases in heart rate, systolic blood pressure, and contractility. Dipyridamole-induced ischemia, in contrast, is primarily due to blood flow maldistribution, with a reduction in subendocardial flow in the regions of myocardium supplied by a stenotic coronary artery. Because dipyridamole predominantly affects the supply part of the supply-demand ratio, flow maldistribution may not be severe enough to always induce endocardial ischemia. It is not surprising that sensitivity is greater for detecting ischemic heart disease with exercise followed by dobutamine, whereas specificity is greater with dipyridamole echocardiography. The application of stress echocardiography for the assessment of perioperative cardiac risk in patients undergoing major vascular surgery has been investigated and shown to be a safe and cost-efficient method for identifying patients at high and low risk of perioperative cardiac events. A metaanalysis by Mantha and associates[255] determined that its positive predictive

value compares favorably with dipyridamole-thallium, Holter ECG, and radionuclide ventriculography for perioperative risk stratification (see Chapters 1, 2, and 43).

A transient imbalance between oxygen supply and demand leads to ischemia. Signs of diastolic dysfunction, followed by RWMAs, occur before ECG changes and the clinical symptom of pain. Consequently, echocardiography is a useful tool because both diastolic dysfunction and RWMAs can readily be diagnosed. Since metabolic balance of the myocardium is a dynamic phenomenon, stress testing is frequently used to increase oxygen consumption. Although historically, bicycle or treadmill testing has been used to provoke RWMAs, these modes of stress can only be performed in patients able to exercise and require very rapid acquisition of sonographic images. Consequently, pharmacologic-induced stress is often preferred. Dobutamine is the preferred agent, since the effects observed on RWMAs are more pronounced when compared with adenosine or dipyridamole.

The test is performed by infusion of dobutamine, increasing the dose every 3 minutes based on a preset protocol (5, 10, 20, 30, 40 μg/kg/min). The goal is to increase the heart rate and metabolic demand, thus provoking RWMAs that can be visualized echocardiographically. The test is stopped if the target heart rate is achieved ([220 – age] × 0.85), ST depression greater than 2 mm, significant tachyarrhythmia, symptomatic severe hypotension, blood pressure greater than 240 mm Hg systolic or 140 mm Hg diastolic. Serious side effects are rare (1:1000 patients).[256] The accuracy of dobutamine stress echocardiography is consistently reported to be good with sensitivity and specificity averaging 82% and 81%, respectively.[257] These results are comparable to perfusion imaging and superior to exercise ECG. As with other forms of stress testing, the higher the degree of vascular disease (one- vs three-vessel disease) the more accurate the test.[258]

Ischemia-Related Diagnoses

Echocardiography is widely used in patients with ischemic heart disease for characterization of cardiac anatomy, as well as for analysis of intracardiac flow velocities by Doppler echocardiographic modalities. TEE has been shown to greatly enhance the diagnostic potential for detecting life-threatening sequelae of myocardial infarction, such as a ruptured ventricular septum or ruptured papillary muscles.[259,260] It has also been recognized that TEE may enable the identification of subtle, but potentially significant, problems that complicate the management of ischemic heart disease, such as anomalous coronary artery origins[261] and atrial infarction. In addition, it is important to note that the assessment of right- and left-sided heart function can be accomplished with intraoperative echocardiography. The assessment of right- and left-sided heart damage during intraoperative ischemia monitoring is essential because the presence of RV dysfunction may be a limiting factor and thus influence perioperative treatment.

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15

Transesophageal Echocardiography: Advanced Echocardiography Concepts

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KEY POINTS

1. Intraoperative transesophageal echocardiography (TEE) plays a valuable role in interventional cardiac procedures, when used to guide transseptal puncture, evaluation of left atrial thrombus, closure of paravalvular leaks, transcatheter valve deployment, and during removal of transvenous lead extractions. Real-time three-dimensional (3D) TEE can be displayed to both the interventionalist and the echocardiographer for guidance and intraprocedural monitoring.
2. Precise evaluation of left ventricular function and synchrony may be characterized by measurements of tissue velocity and deformation in one or two dimensions. Myocardial strain is the systolic deformation of a myocardial fiber normalized to its original length, while strain rate expresses the speed of deformation. Doppler tissue imaging uses the Doppler signal while speckle-tracking imaging uses the two-dimensional speckled pattern of myocardium to calculate strain, strain rate, velocity, and displacement.
3. Intracardiac tumors are rare; when a cardiac mass is identified, it is frequently a thrombus or vegetation.
4. Hypertrophic cardiomyopathy is the most commonly inherited cardiomyopathy and often manifests with asymmetric thickening of the septum and dynamic outflow tract obstruction (>30 mm Hg gradient considered significant). Myocarditis can manifest clinically as a fulminant (hyperacute) course that demonstrates thickened, edematous myocardium with severely reduced left ventricular or biventricular ejection fraction. The patient is often critically ill with a good chance for recovery if supported through the initial process.
5. Dimensions of the aortic annulus should be measured in systole from leading edge to leading edge, whereas measurements of the aortic root and ascending aorta should be taken at end-diastole. Measuring from leading edge to leading edge produces dimensions similar to inner edge computed tomography and magnetic resonance imaging measurements.
6. The diagnosis of cardiac tamponade is pathophysiologic and requires both the presence of a pericardial effusion and an increase in pericardial pressure that limits ventricular filling. Echocardiographic findings that confirm the diagnosis of cardiac tamponade are early systolic right atrial collapse and diastolic right ventricular collapse when the pericardial pressure exceeds chamber pressure.
7. The use of both transthoracic echocardiography and TEE across the perioperative spectrum, such as in presurgical testing clinics, postanesthesia care units, and the critical care arena, can be accomplished by the development of a clinical perioperative echocardiography consult service. Quality assurance, ongoing education, and the implementation of appropriate use criteria are critical pieces in forming such a service.
8. Real-time, 3D TEE offers improved insight for diagnosing valve defects and predicting the success of surgical mitral valve repair.
9. A thorough echocardiography evaluation of valve positioning and description, evaluation of leaflet mobility, spectral Doppler flow profile, and color-flow Doppler assessment should be performed with all prosthetic valves. Abnormal leaflet mobility, color flow, or Doppler profile should alert the echocardiographer to prosthetic valve dysfunction.

The Development of a Perioperative Echocardiography Service

The practice of cardiac anesthesia has evolved over the past several years to require advanced skills in echocardiography. Many cardiac anesthesiologists perform consultative services in varies modalities such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and advanced three-dimensional (3D) imaging. The use of echocardiography across the perioperative spectrum, including presurgical testing clinics, postanesthesia care units, and critical care units, has led many specialists to provide echocardiography evaluation both inside and outside of the operating suite. Rescue echocardiography, both TTE and TEE, has been shown to change medical and surgical decision making, and many programs are expanding their resources to include cardiac ultrasound assessment by rapid response teams and during noncardiac surgical procedures.[1] Anesthesiology departments have begun to implement on-site TTE examinations into their preoperative clinics, where physicians who see patients can consult with a colleague who has expertise in TTE and obtain immediate results. The need for clinical echocardiography services beyond the clinical duties of cardiac cases has led some centers to develop perioperative echocardiography clinical services.[2] This section touches briefly on the development of a perioperative echocardiography clinical service.

Training Physicians in Perioperative Echocardiography

The ability for anesthesiologists to obtain both basic and advanced certification in perioperative TEE, as well as increasing trainee exposure to perioperative ultrasound, has led to various levels of training and expertise in echocardiography within institutions. Perhaps the most difficult task in developing a clinical service is the education and training of a critical mass of experts in perioperative echocardiography. Defining the team, establishing training and certification requirements, and credentialing physicians to lead the service is time consuming, costly, and yet crucial to success. Although the team may consist of mostly cardiac anesthesiologists with advanced training, echocardiography is expanding in the perioperative arena as its own subspecialty, and an echocardiography consult service may have a mixture of both advanced and basic perioperative echocardiography providers. Institutional support to train physicians and provide competency assessment and quality assurance programs must be solidified before the clinical service is developed.

Training in both TTE and TEE is becoming more and more prevalent. Although certification in perioperative TTE does not yet exist for anesthesiologists as it does for TEE, many critical care and cardiac anesthesiologists are learning the skill and implementing it in their clinical practice (see Chapter 17).

Echocardiography Equipment

Before a commitment to provide a clinical service can be made, echocardiography equipment and space must be solidified (see Chapter 14). With the creation of portable echocardiography or laptop machines, fast echocardiography assessment of an unstable or critically ill patient is more rapidly available. Handheld ultrasound devices, although simple to use and store, do not currently provide Doppler assessment that is needed in rescue echocardiography for hemodynamic evaluation or valve assessment. Access to portable machines that can be moved rapidly, similar to those in the emergency department, improves utilization.

Image Storage and Reporting

The importance of image acquisition and proper storage of reporting cannot be stressed enough. Perioperative patients that require either TTE or TEE examinations are often unstable or undergoing surgical evaluation, and different physician providers from various specialties need access to the reports and images for clinical decision making. The ability to store and transfer images must be implemented early on. Digital transfer of images into a hospital echocardiography database is important, as well as standard reporting of examinations performed. As the performance of ultrasound crosses specialty lines, so should the information. Reporting should follow recommendations from the American Society of Echocardiography and the Intersocietal Accreditation Commission.[3,4] Institutional expenditures and clinical revenue generated by the development of a perioperative echocardiography consult service were recently described in a paper by Shillcutt and colleagues.[2]

Clinical Areas of Implementation

Perioperative echocardiography can be implemented in several different anesthesia care areas from decision making to discharge. Perioperative echocardiography consult services include preoperative assessments of patients undergoing moderate- to high-risk noncardiac surgical procedures or patients with significant cardiac disease, rescue echocardiography (evaluation of unstable surgical patients in the operating rooms, recovery areas, or critical care units), and assessment of patients with unknown cardiac status who are undergoing urgent intervention. One report on the use of echocardiography in noncardiac surgical interventions at a single academic medical center found that the general surgery service, followed by vascular surgery, and the critical care service used the perioperative echocardiography consult service more often compared with other areas.[2] The most common indications for the use of both TTE and TEE in noncardiac operations were hypotension (49% of cases), a history of coronary artery disease (16% of cases), and a history of heart failure (12% of cases).[2]

Multiple studies suggest that perioperative echocardiography influences medical and surgical decision making.[5–8] Future studies need to determine the effect of perioperative echocardiography on operating room efficiency and improved patient outcomes.

Three-Dimensional Transesophageal Echocardiography

Three-Dimensional Reconstruction

Echocardiography has become a vital tool in the practice of contemporary cardiac anesthesiology. As with any technology, a considerable evolution has occurred since echocardiography was first introduced into the operating room in the early 1980s. Among the most important advances has been the progression from one-dimensional (eg, M-mode) imaging to two-dimensional (2D) imaging, as well as spectral Doppler and real-time color-flow mapping superimposed over a 2D image. The heart, however, remains a 3D organ. Although multiplane 2D images can be acquired easily with modern TEE probes by simply rotating the image plane electronically from 0 to 180 degrees, the final process occurs when the echocardiographer stitches the different 2D planes together to create a mental 3D image. Transmitting this mental image to other members of the surgical team can be challenging. By directly displaying a 3D image onto the monitor, cardiac anatomic and functional features can be assessed more rapidly and communication between the echocardiographer and the cardiac surgeon facilitated before, during, and immediately after surgery.[9]

Historic Overview

Concepts of 3D echocardiography (3DE) originated in the 1970s.[10] Because of the limitations of hardware and software capabilities in that era, the acquisition times required to create a 3D image prohibited widespread clinical acceptance, limiting its use for research purposes only. Technologic advances in the 1990s enabled 3D reconstruction from multiple 2D images obtained from different imaging planes. By capturing an image every 2 to 3 degrees as the probe rotated 180 degrees around a specific region of interest (ROI), high-powered computers were able to produce a 3D image, which could be refined further with postprocessing software. These multigated image planes were acquired under electrocardiographic (ECG) and respiratory gating to overcome motion artifact. The limitations of this technology were the time required to process and optimize the 3D image and the inability to obtain instantaneous, real-time imaging of the heart.

In 2007, a real-time 3D TEE probe with a matrix array of piezoelectric crystals within the transducer head was released on the market. This 3D imaging matrix array, compared to conventional 2D imaging transducers, not only has columns in a single one-dimensional plane but also rows of elements. That is, instead of having a single column of 128 elements, the matrix array comprises more than 50 rows and 50 columns of elements (Fig. 15.1). Although this matrix technology was available for TTE (precordial) scanning, a breakthrough in engineering design was required before the technology could be transitioned into the limited space of the head of a TEE probe.

Limitations of Three-Dimensional Imaging

Notably, 3DE is subject to the same laws of acoustic physics as 2DE. Artifacts such as ringing, reverberations, shadowing, and attenuation occur in 3D, as well as 2D, and M-mode. In addition, it is important to realize that the product of frame rate, sector or volume size, and imaging resolution equal a constant. That is, by increasing the requirements of one of these variables, a decrease in either one or both of the others will occur. For example, increasing sector size would result in a loss in either frame rate or image resolution, or both. Modern

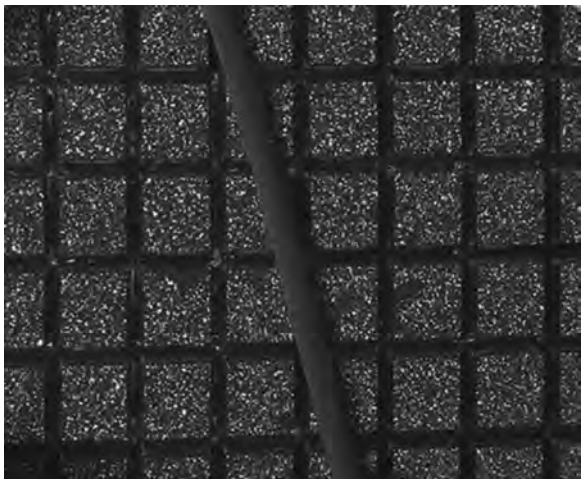

Fig. 15.1 Matrix array transducer consisting of 50 rows and 50 columns of piezoelectric elements. A human hair demonstrates the size of each individual element.

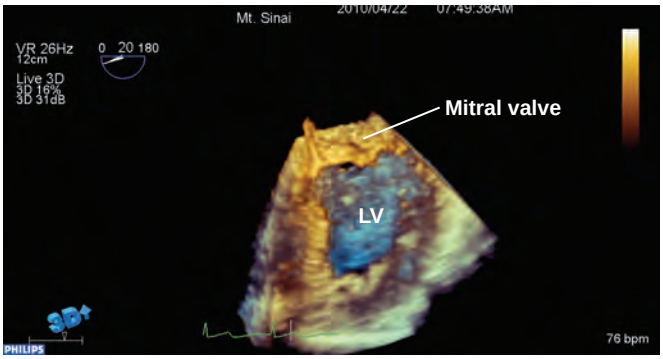

Fig. 15.2 Live three-dimensional image of mitral valve and left ventricle *(LV)*. Because of the matrix structure of the ultrasound transducer, this image represents a true live image. Change in transesophageal echocardiographic probe positioning by the echocardiographer results in instantaneous changes in the volumetric data set.

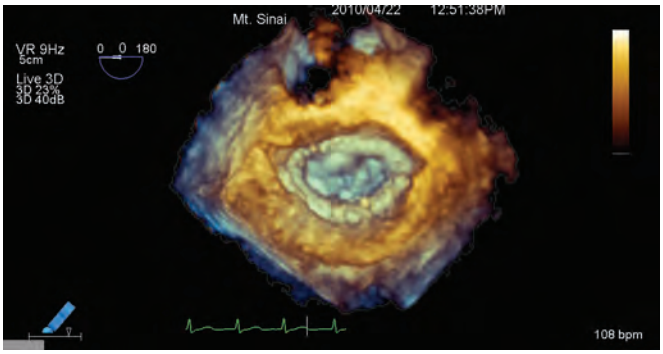

Fig. 15.3 Three-dimensional (3D) zoom mode acquisition of a mitral valve repair from the left atrial perspective. Annuloplasty ring is easily visualized. In analogy to the live 3D mode, the 3D zoom mode acquires instantaneous images.

ultrasound devices are equipped with incredible computing power, enabling them to display large 2D sectors while still maintaining excellent image resolution and high frame rates. Unfortunately, this does not apply to real-time instantaneous 3D imaging. The large number of data that must be acquired and processed requires the echocardiographer to reduce sector size to maintain adequate resolution and frame rate. The rate-limiting factor in 3D imaging is no longer processing power but rather the speed of ultrasound in tissue.

Display of Three-Dimensional Images

The classic 20 views of 2D TEE are not required in 3DE because entire volumetric data sets are acquired that can be spatially oriented and cropped at the discretion of the echocardiographer. Recently, the American Society of Echocardiography published guidelines detailing the acquisition and display of cardiac anatomy by 3D TEE. These views, given by experts, explain the surgical views for display intraoperatively.[11] In the operating room, every attempt should be made to place the views of the valve in the surgical orientation for communication of findings with the surgeon.

The limiting factor in 3DE is no longer processer performance but the speed of sound traveling through tissue (1540 m/s). Although the matrix configuration of the elements allows live and instantaneous scanning, the size of this sector is limited to guarantee adequate image resolution and frame rate. If larger sectors are to be scanned, the constraint of transmit time of ultrasound is sidestepped by stitching 4 to 8 gated beats together, which enables wider volumes to be generated while maintaining frame rate and resolution. Several modes of 3DE are described in the following subsections.

Narrow Sector (Live Three-Dimensional)–Real Time

In this mode, a 3D volume pyramid is obtained. The image shown in this mode is real time. The 3D image changes as the transducer is moved just as in live 2D imaging. Manipulations of the TEE probe (eg, rotation, change in position) lead to instantaneous changes in the image seen on the monitor (Fig. 15.2).

Wide Sector Focused (Three-Dimensional Zoom)–Real Time

If only a specific ROI requires imaging, the zoom mode can be used in a similar fashion as in 2DE. A typical example for this mode would be the mitral valve (MV) apparatus. The 3D zoom mode displays a small magnified pyramidal volume that may vary from 20 × 20 degrees up to 90 × 90 degrees, depending on the density setting. This small data set can be spatially oriented at the discretion of the echocardiographer. A key advantage to this mode is the fact that the real-time 3D images are devoid of rotational artifacts, as are commonly encountered with ECG-gated 3D acquisitions (Fig. 15.3).

Large Sector (Full Volume)–Gated

Because of insufficient time for sound to travel back and forth in large volumes while maintaining a frame rate greater than 20 Hz and reasonable resolution in live scanning modes, one maneuver to overcome this limitation entails stitching four to eight gates together to create a full-volume mode. These gated slabs or subvolumes represent a pyramidal 3D data set as would be acquired in the live 3D mode. This technique can generate more than 90-degree scanning volumes at frame rates greater than 30 Hz. Increasing the number of gates from four to eight creates smaller 3D slabs; this can be used to maintain frame rates, resolution, or both, as the volumes (pyramids) become larger (Fig. 15.4).

Unfortunately, as with any conventional gating technique, patients with arrhythmias are prone to motion artifacts when the individual data sets are combined; however, as long as the RR intervals fall within a reasonable range, a full-volume data set still can be reconstructed (eg, atrial fibrillation, electrocautery artifact). The acquired real-time 3D data set subsequently can be cropped, analyzed, and quantified using integrated software in the 3D operating system (QLAB; Philips Healthcare, Andover, Mass; Fig. 15.5).

Three-Dimensional Color Doppler–Gated

Because numerous data must be acquired with 3D color Doppler mode, a gating method similar to that of the full-volume mode must be used. However, because of the large number of data required, 8 to 11 beats must be combined to create an image. Jet direction, extent, and

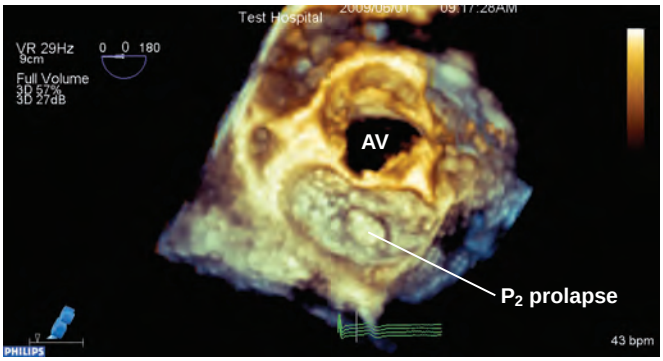

Fig. 15.4 Full-volume mode acquisition of the mitral valve from the left atrial perspective. Although the sector size is similar to that in Fig. 12-8, the improvement in temporal resolution is a consequence of the four-beat acquisition (9 vs 29 Hz). This mode does not permit instantaneous live imaging. *AV,* Aortic valve.

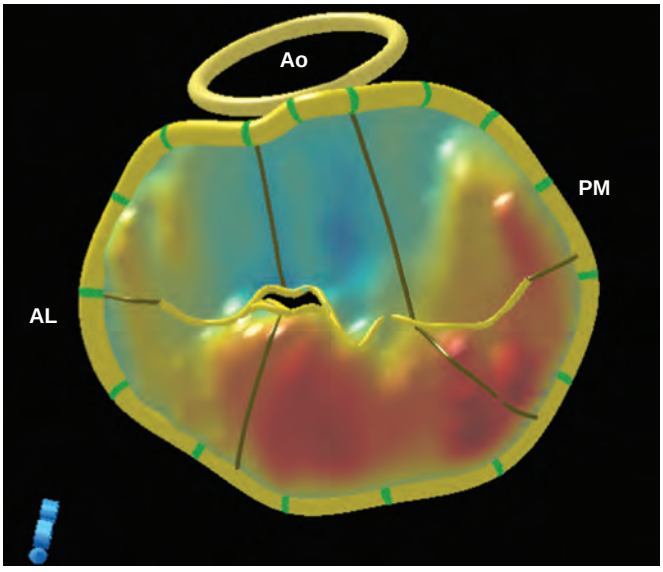

Fig. 15.5 Mitral valve quantification acquired with the full-volume mode. Red coloring of the leaflet indicates areas that exceed the annular plane (type II dysfunction). *AL,* Anterolateral; *Ao,* aorta; *PM,* posteromedial.

geometric features can be recognized easily with the use of this technique. Reports emerging in the late 1990s showed that the strength of this methodology lies in its ability to quantitate regurgitant lesions; 3D quantification of mitral regurgitation (MR) correlates better than 2D imaging, when using angiography as the gold standard.[12] In an experimental setting, 3D quantification was more accurate (2.6% underestimation) than 2D or M-mode methods, which had the tendency to underestimate regurgitant volumes (44.2% and 32.1%, respectively; Fig. 15.6).[13]

Clinical Applications

Right Ventricle

The right ventricle is a complex, crescent-shaped structure that does not lend itself easily to geometric assumptions as its left ventricle counterpart and has been the Achilles heel of 2D imaging. Because of the numerous reports that have linked right ventricular (RV) function to prognostic outcome in cardiopulmonary diseases, it is of great interest to quantify its function echocardiographically.[14]

A preliminary report showed that 3DE marginally underestimated RV volumes when compared with cardiac magnetic resonance imaging (MRI), and that correlation to cardiac MRI-measured volumes was

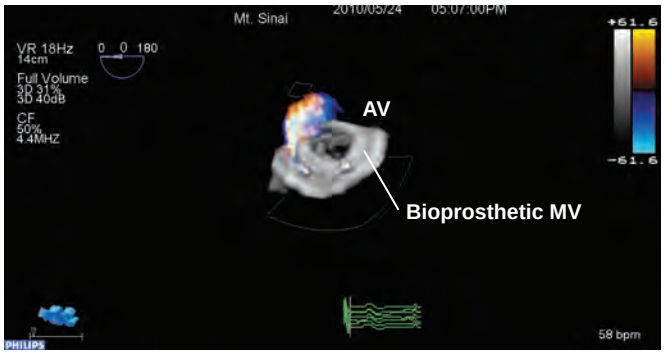

Fig. 15.6 Color three-dimensional acquisition of a mitral valve *(MV)* bioprosthesis. The aortic valve *(AV)* is labeled for orientation. Three paravalvular leaks can be identified.

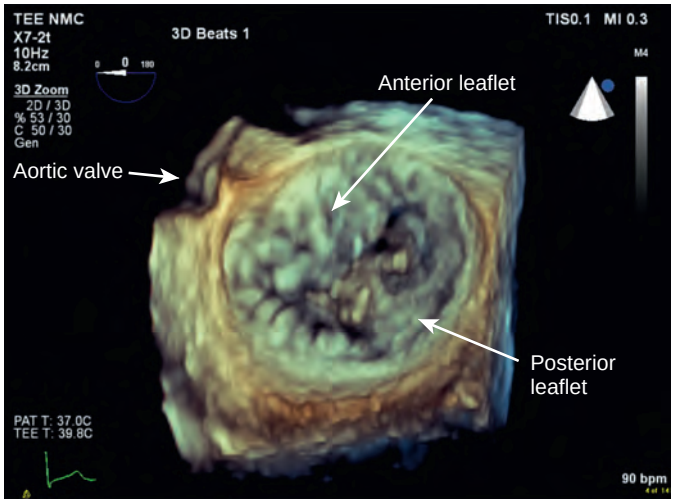

Fig. 15.7 Three-dimensional transesophageal echocardiographic image of the mitral valve displayed in the surgeon's view.

as good as that obtained by cardiac computed tomography (CT).[15] Further research in this field will undoubtedly lead to increased understanding of perioperative RV function.

Mitral Valve Apparatus

To ensure a high success rate of MV reconstruction, the cardiac anesthesiologist must have detailed understanding and insight into the mechanisms responsible for regurgitant lesions and must be able to identify these echocardiographically. The MV apparatus can best be viewed by utilizing the 3D zoom mode. The data block should be spatially oriented to view the MV from the left atrial (LA) perspective, with the aortic valve (AV) positioned at the top of the monitor (12 o'clock). This orientation, commonly referred to as the *surgeon's view,* puts the MV in an anatomically correct position (Fig. 15.7). This mode is especially useful in patients with atrial fibrillation, an arrhythmia frequently encountered in patients with MV disease, because it represents a live and instantaneous imaging mode not influenced by gating artifacts. Occasionally, in patients with Barlow disease, the valve is so grotesquely enlarged that temporal resolution suffers from the large sector required to image the entire valve. In these cases, a full-volume mode allows the imager not only to visualize the entire valve but also to maintain acceptable image and temporal resolution.

Although a comprehensive 2DE examination can help the physician identify the mechanism of MR in most cases, 3DE can not only help identify the mechanism but also provide information with regard to annular and leaflet geometry, which cannot be obtained by 2D imaging. Measurements that can be obtained easily include (1) the major anatomically oriented 3D axes of the annulus, anteroposterior

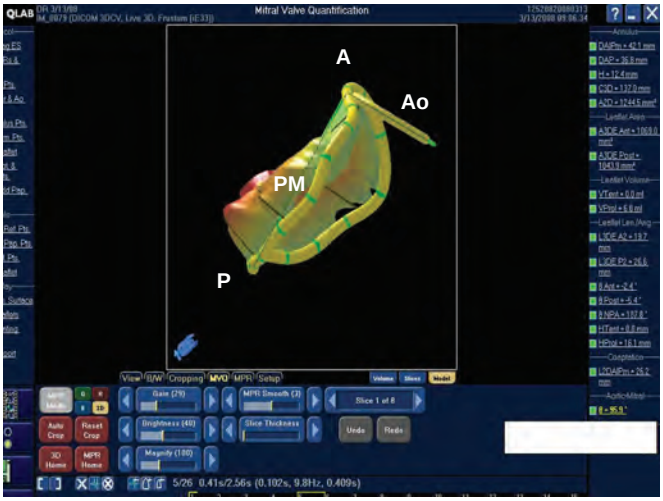

Fig. 15.8 Mitral valve quantification showing the aortomitral angle of 95.9 degrees. Patient at increased risk for development of systolic anterior motion after mitral valve repair surgery. *A*, Anterior; *Ao*, aorta; *P*, posterior; *PM*, posteromedial.

and anterolateral-posteromedial diameters, as well as annular height; (2) 3D curvilinear leaflet lengths and areas of all segments (A_1, A_2, A_3, P_1, P_2, P_3); (3) total and functional anterior and posterior leaflet surface areas; and (4) the angle between the AV annulus and the MV annulus (aortomitral angle). A narrow angle should alert the imager to the possibility of systolic anterior motion during the period after repair (Fig. 15.8).

Aortic and Tricuspid Valves

Unlike with the MV, acquiring high-quality images of the AV and the tricuspid valve (TV) represents a more difficult undertaking. The explanation lies, on the one hand, in the thinner leaflet tissue that generally comprises both the AV and the TV and, on the other hand, on the orientation of the tissue as a reflector. Because these factors result in weaker acoustic signal strength, the 3D volume renderer is more apt to tag these as transparent and render the voxels as blood—that is, invisible. Caution must be taken by the echocardiographer not to misdiagnose these imaging artifacts as perforations. Both the AV and the TV should be displayed in the surgical view, as shown in Figs. 15.9 and 15.10, respectively. A description of these views can be found in this text's companion textbook, Reich and Fischer's *Perioperative Transesophageal Echocardiography: A Companion to Kaplan's Cardiac Anesthesia*.[16]

Congenital and Interventional Procedures

Congenital heart disease is complex and characterized by multiple variants. Three-dimensional echocardiography can facilitate improved understanding of the anatomic features of congenital heart disease. The ability to spatially orient the data block to allow for views of atrial or ventricular septal defects (VSDs) and their relation to adjacent structures represents a milestone in improving understanding of these complex disease processes. The size and location of intracardiac shunts are crucial parameters when evaluating whether to pursue an interventional procedure. The understanding of congenital valvular pathology (eg, cleft MV, Ebstein's anomaly) can be greatly enhanced by 3DE. Thus, real-time 3DE offers improved insight for diagnosing valve defects and predicting the success of a surgical valve repair (Fig. 15.11).

Perioperative Echocardiographic Evaluation of Valves

Echocardiography has many roles and applications that provide healthcare professionals with invaluable information about patients with new murmurs, arrhythmias, thromboembolic events, and/or heart failure.

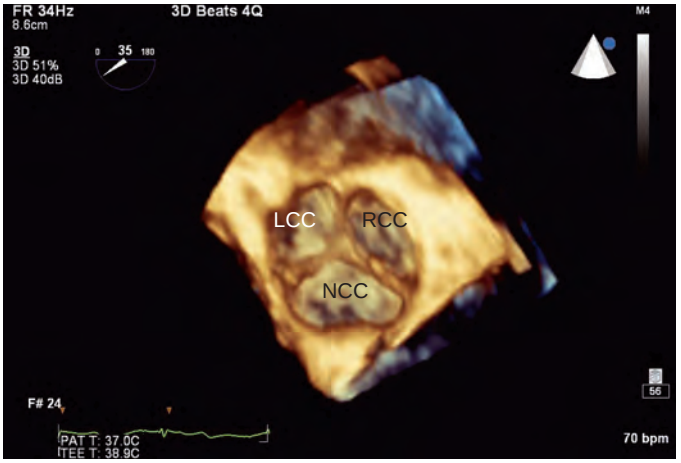

Fig. 15.9 Three-dimensional transesophageal echocardiographic image of the aortic valve displayed in the surgeon's view. *LCC*, Left coronary cusp; *NCC*, noncoronary cusp; *RCC*, right coronary cusp.

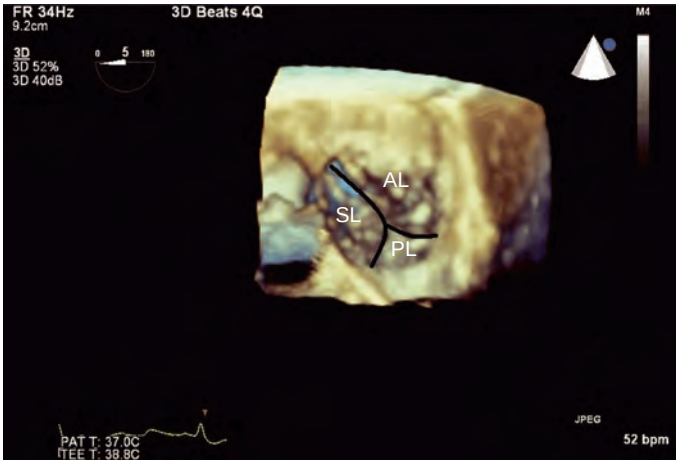

Fig. 15.10 Three-dimensional transesophageal echocardiographic image of the tricuspid valve displayed in the surgeon's view. *AL*, Anterior leaflet; *PL*, posterior leaflet; *SL*, septal leaflet.

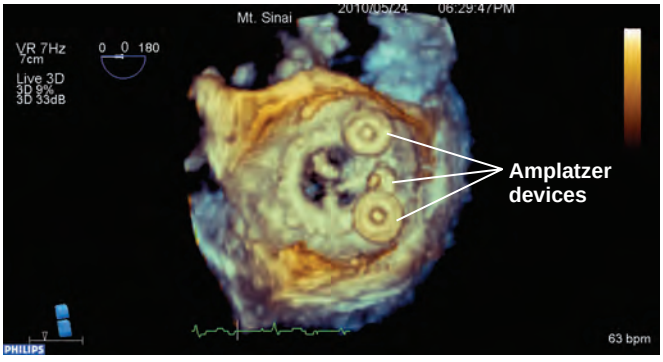

Fig. 15.11 Patient with multiple paravalvular leaks. Percutaneous intervention successfully deploying three Amplatzer devices.

For patients with suspected valvular dysfunction, echocardiography is the method of choice for the detection, diagnosis, and subsequent follow-up evaluations.[17–20] An understanding of valvular dysfunction and resultant hemodynamic and cardiopulmonary effects is crucial to patient care.

The same principles and techniques used in the assessment of native valves apply to the echocardiographic assessment of prosthetic

valves; the latter are much more demanding because of specific differences among types of valve prostheses, including flow patterns, expected Doppler velocities, and regurgitant flows.[21,22] In addition, artifacts produced by prosthetic materials may obstruct imaging, thereby requiring the echocardiographer to view the prosthesis from multiple angles. Knowledge of the normal functions of each prosthetic valve is necessary.

Whereas the evaluation of native and prosthetic valves is primarily focused on the valve itself, the examiner must still perform a comprehensive examination of the surrounding cardiac tissues to assess for coexisting disease or secondary abnormalities and dysfunction.[23] Clinical decisions are based on symptoms, severity of valve dysfunction, and the ability of the heart to compensate.[24–27]

Valve dysfunction involves three pathophysiologic conditions: regurgitation, stenosis, and endocarditis/masses/embolic events. In most cases, however, valve dysfunction occurs as a result of endocarditic masses; however, some patients may have only mild regurgitation.

General Points Regarding Valve Assessment

General echocardiographic principles guide the assessment of the heart valves, in that a comprehensive examination is performed that uses all modes of imaging from multiple echocardiographic windows and multiple angles (see Chapter 14). In so doing, a 3D construct of the valve apparatus is formed. With advancements in technology, live imaging, reconstructed 3D imaging, or both are a routine part of the echocardiographic examination.

An understanding of valvular anatomy, function, and dysfunction helps explain cardiac hemodynamics, secondary cardiac changes, and patient presentations. In addition to assessing the degree of dysfunction, evidence of decompensation can guide therapeutic decision making, including the type and timing of invasive care. Whereas acute valvular dysfunction is not well tolerated, chronic dysfunction allows the heart to compensate and better tolerate pressure and/or volume loading conditions. Compensatory mechanisms initially include hypertrophy and increases in contractility in the presence of pressure and/or volume overload. Further progression causes increasing degrees of hypertrophy, dilation, and dysfunction until clinical decompensation occurs. Obstructive lesions result in relatively greater hypertrophy than dilation, whereas the opposite is true for regurgitant lesions.

Valvular dysfunction has numerous causal factors, some of which are common across all four valves, and others which are specific.[17–22] Causal factors can be grouped by valve, acuity, valvular disorder, or nonvalvular disorder (Tables 15.1 and 15.2). Valvular disorders may be described by leaflet mobility, as is the case for MR and aortic regurgitation (AR). Echocardiography is the mainstay of diagnostic imaging to assess and quantify valvular function and dysfunction as well as the degree of cardiac compensation, allowing healthcare professionals to

TABLE 15.1 Causes of Acute and Chronic Valvular Stenosis[a]

	Acute Stenosis	*Chronic Stenosis*
Aortic	Thrombus/mass Acute prosthetic valve dysfunction Dehiscence/distortion Iatrogenic result of repair	Valvular stenosis Trileaflet calcific disease Bicuspid Unicuspid Subvalvular obstruction Subvalvular membrane Congenital LVOT narrowing Dynamic LVOT obstruction Supravalvular obstruction Iatrogenic Williams syndrome Tumor/masses Prosthetic valve dysfunction
Mitral	Thrombus/mass Acute prosthetic valve dysfunction Dehiscence/distortion Iatrogenic result of repair	Valvular stenosis Rheumatic valvitis Calcific stenosis Congenital anomalies Parachute valve Lupus Carcinoid Endomyocardial fibrosis Nonvalvular stenosis Cor triatriatum Pulmonary vein stenosis (ablation) Tumor/masses Prosthetic valve dysfunction
Tricuspid	Thrombus/mass Acute prosthetic valve dysfunction Dehiscence/distortion Iatrogenic result of repair	Valvular stenosis Rheumatic valvitis Congenital anomalies: atresia Carcinoid Endomyocardial fibrosis Hypereosinophilic syndrome Nonvalvular stenosis Tumor/masses Prosthetic valve dysfunction
Pulmonary	Thrombus/mass Acute prosthetic valve dysfunction Dehiscence/distortion Iatrogenic result of repair Iatrogenic result of homograft (supravalvular stenosis)	Valvular stenosis Fibrous thickening/fusion Bicuspid valve Calcification (rare) Dysplasia/hypoplasia Carcinoid Subvalvular obstruction Congenital RVOT narrowing Dynamic LVOT obstruction Supravalvular obstruction atresia Tumor/masses Prosthetic valve dysfunction

[a]Where possible, causes are grouped.
LVOT, Left ventricular outflow tract; *RVOT,* right ventricular outflow tract.

TABLE 15.2 Causes of Acute and Chronic Valvular Regurgitation[a]

Valve	*Acute Regurgitation*	*Chronic Regurgitation*
Aortic	Endocarditis Aortic dissection (type A) Ruptured fenestration Chest trauma/flail-rupture Prosthetic valve dysfunction	Type I: Aortic root dilation Type II: Leaflet prolapse or fenestration Type III: Leaflet abnormality/retraction Rheumatoid, XRT, medicines Bicuspid/tricuspid/quadricuspid
Mitral	Chordal rupture papillary Muscle rupture papillary Muscle dysfunction/ischemia Endocarditis Acute rheumatic fever Acute cardiomyopathy Prosthetic valve dysfunction	Type I: Normal leaflet mobility Dilated annulus, endocarditis, leaflet perforation Type II: Excessive leaflet mobility Myxomatous disease Fibroelastic deficiency Ruptured papillary muscle Endocarditis Type III: Restricted leaflet Rheumatic, XRT, ischemia/infarct Dilated cardiomyopathy
Tricuspid	Chordal rupture papillary Muscle rupture papillary Muscle dysfunction/ischemia Endocarditis Acute rheumatic fever Acute cardiomyopathy Prosthetic valve dysfunction	Functional: Normal valve leaflet Pulmonary hypertension Tricuspid annular dilation RAE, RVE Tethering Valvular abnormality Ebstein's anomaly Rheumatic valvitis Myxomatous disease XRT, drug (Phentermine) Carcinoid Lupus marantic endocarditis Connective tissue disease
Pulmonary	Endocarditis Acute pulmonary hypertension Chest trauma/flail-rupture Prosthetic valve dysfunction	Functional: Normal valve leaflet Pulmonary hypertension Valvular abnormality Rheumatic valvitis Congenital absence Carcinoid syndrome Tetralogy of Fallot Iatrogenesis (wires/pacemaker/plasty) Pulmonary artery dilation

[a]Where possible, causes are grouped.
RAE, Right atrial enlargement; *RVE,* right ventricular enlargement; *XRT,* radiation therapy.

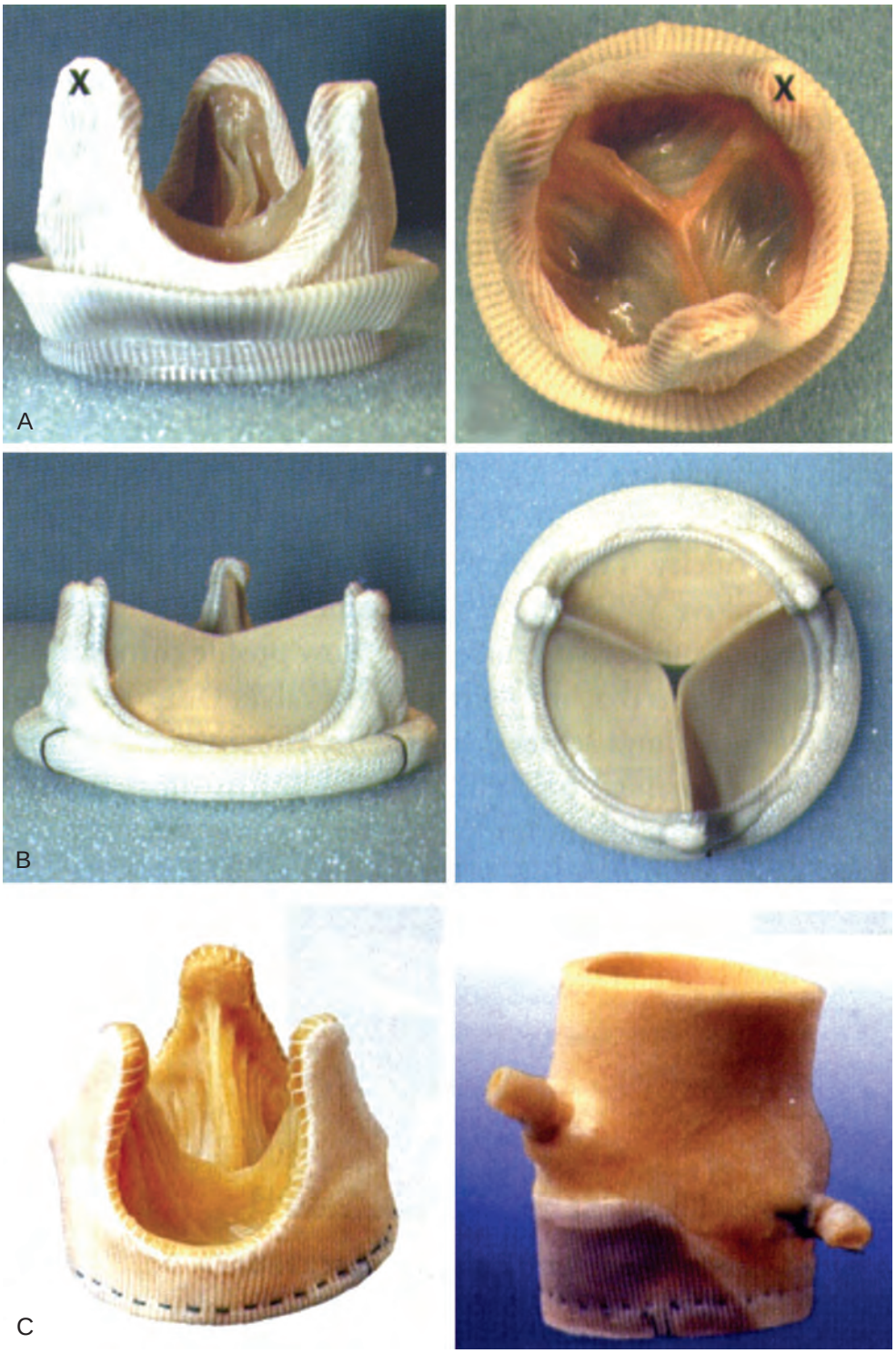

Fig. 15.12 Bioprosthetic valves. Three examples of bioprosthetic/tissue valves that have been implanted into the aortic and/or mitral valve positions. (A) Hancock porcine bioprosthesis with cloth-covered stent. This valve does not have a central opening. (B) Carpentier Edwards pericardial valve. Note central opening. (C) Stentless valves with flexible and lower profile cloth-covered rim sewn into the native tissues. *Left,* Toronto/St Jude Medical valve. *Right,* Medtronic Freestyle valve.

better manage, treat appropriately, and, ideally, prevent, reverse, or reduce long-term dysfunction.

General Considerations With Prosthetic Valves

Types of Prosthetic Valves

Prosthetic valves are usually broadly grouped as biologic or mechanical.[21,22] Bioprosthetic valves (Fig. 15.12) are composed of three biologic cusps with an anatomic structure similar to the native valve annulus. All bioprosthetic valves are similar in that the trileaflet valve opens to create a circular orifice with a flow pattern that is similar to the native valve. For imaging purposes it is useful to know whether the valve is stented or stentless.

Stented bioprostheses are composed of three tissue cusps/leaflets that are sewn into a fabric-covered metal support. This support/stent may cause shadowing or reverberations during ultrasound imaging. The manufacturer's valve size refers to the external diameter of the sewing ring, not the actual diameter of the valve orifice.

Stentless bioprostheses include all replacements without a prosthetic stent. Examples include St Jude Medical and Medtronic valves

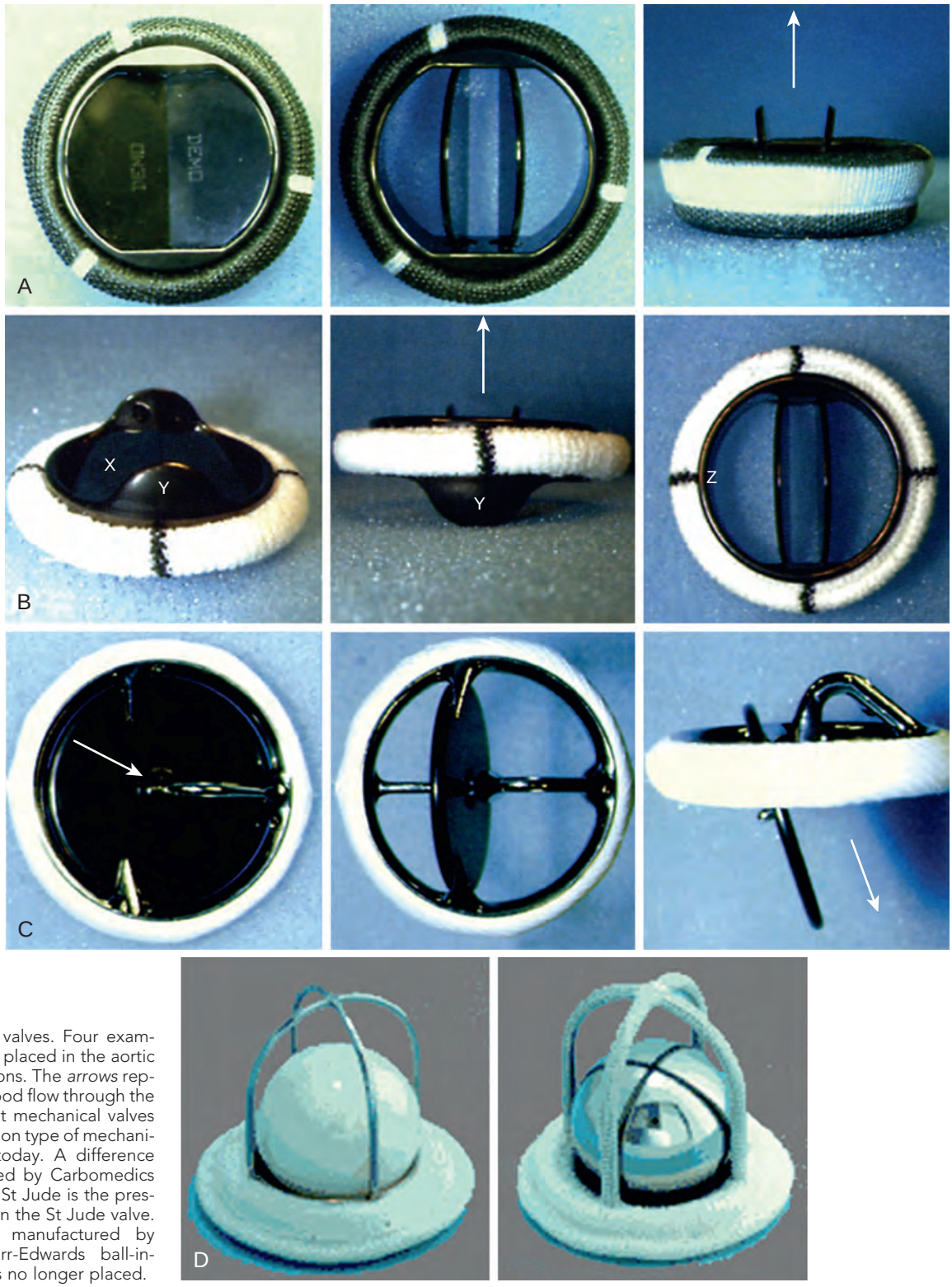

Fig. 15.13 Mechanical valves. Four examples of mechanical valves placed in the aortic and/or mitral valve positions. The *arrows* represent the direction of blood flow through the valve. (A) and (B) Bileaflet mechanical valves represent the most common type of mechanical heart valve placed today. A difference between (A) manufactured by Carbomedics and (B) manufactured by St Jude is the presence of a pivot guard *y* on the St Jude valve. (C) Single-leaflet valve manufactured by Medtronic-Hall. (D) Starr-Edwards ball-in-cage valve, a valve that is no longer placed.

(see Fig. 15.12). Stentless valves are considered xenografts consisting of either a preparation of porcine aorta or sculpted bovine pericardium without any added strut support. Xenografts differ in method of preservation of valve cusps, anticalcification regimens, and composition, as well as designs of stents and sewing rings. There also are cadaveric human AVs or pulmonary valves (PVs) that are cryopreserved shortly after being harvested. Typically the valve is harvested along with some of the respective ventricular outflow tract and great vessel, preserved as a block, and trimmed at surgery before implantation. Homografts are used only in the aortic and pulmonary positions as well as in valved conduits.

A wide variety of mechanical valves (Fig. 15.13) are currently available. Although variations exist, they all share similarities. The most commonly implanted is a bileaflet valve in which two semicircular disks rotate around struts that are attached to the valve housing. These open to form two large lateral orifices and a smaller central orifice.

BOX 15.1 CAUSES OF PROSTHETIC VALVE REGURGITATION

- Paravalve
  - Calcification
  - Abscess
  - Dehiscence
- Leaflet pathology: excess mobility
  - Abscess
  - Tears
  - Degeneration
  - Endocarditis
    - Bioprosthetic valves: leaflet perforation/destruction
    - Mechanical valves: interference with valve opening/closing
- Leaflet pathology: restriction/distortion
  - Suture
  - Thrombus
  - Pannus
  - Preserved leaflet valve apparatus interfering with closure of mechanical leaflets
  - Stuck leaflet

BOX 15.2 CAUSES OF PROSTHETIC VALVE STENOSIS/OBSTRUCTION

- Prosthetic valve stenosis
  - Stuck leaflet
  - Thrombus
  - Pannus
- Nonvalvular obstruction
  - Dehiscence
  - Obstructing retained native tissue
  - Suture causing restriction of leaflet
  - Subvalvular obstruction (aortic and pulmonary valves)
  - Systolic anterior motion (aortic and pulmonary valves)
  - Supraannular narrowing (aortic and pulmonary valves)
- Doppler issues/artifacts/errors: normal prosthetic valve function
  - Sampling of other flow (ie, sample mitral regurgitation during assessment of the aortic valve)
  - Subvalvular obstruction
  - High cardiac output
  - Significant aortic valve insufficiency
- Patient-prosthesis mismatch
- Compliance issues (net changes) affecting pressure half time

TABLE 15.3 Expected Ranges of Areas and Pressure Gradients for Prosthetic Valves in the Aortic and Mitral Positions

Diameter (mm)	*Peak Gradient (mm Hg)*	*Mean Gradient (mm Hg)*	*Effective Orifice Area (cm^2)*
Stented Bioprosthetic Aortic Valve			
19	32–44	24–26	0.8–1.2
21	25–28	17–21	1.1–1.5
23	21–29	12–16	1.3–1.7
25	16–24	9–13	1.9
27	19–22	6–12	2.2
29	18–22	10–12	2.8
Stentless Aortic Valve			
19		12–13	1.2–1.3
21	17–40	7.5–18	1.2–1.6
23	18–29	7–18	1.6–2.2
25	14–28	5–17	1.6–2.3
27	26	4.7–18	1.9–2.7
29	24	4	2.4
Bileaflet Mechanical Aortic Valve			
16	40–50	25–30	0.6
17	30–40	20–25	0.9–1.0
19	30–40	15–20	0.9–1.2
21	25–30	13–20	1.2–1.4
23	19–25	11–20	1.4–1.8
25	17–23	9–12	1.9–2.2
27	14–20	8–11	2.3–2.5
29	10–20	6–9	2.8–3.1
31	10–15	5–10	3.1
Bileaflet Mechanical Mitral Valve			
25	10	4	1.8–2.7
27	8–11	3–4	1.8–2.9
29	8–10	5	1.8–2.3
31	8–12	4–5	2.0–2.8
33	8–9	4–5	3.0
Stented Bioprosthetic Mitral Valve			
25	10–15	5.9–6.3	2.0–2.4
27	9.5–16	5.4–6.2	2.0–2.6
29	5–13	3.6–4.6	2.4–2.6
31	4–13.5	2.0–5.0	2.3–2.4
33	12.8	3.8	3.4

The data highlight the variability of reported data reflecting a host of operator variables and assumptions of physical principles. The data also provide practitioners with a reference to determine which prosthetic valve size is most appropriate for the individual patient to avoid patient-prosthesis mismatch. Similar data are applied when right-sided valves are being replaced as similar valves are employed; however, clinical echocardiographic data are not similarly available.

Several other types of mechanical valves were implanted in the past and will be encountered in patients. The ball-in-cage valve houses a spherical occluder contained within a metallic cage. This occluder fills the cage orifice in the closed position but rides above the orifice during antegrade flow. Single tilting disk valves contain a single circular disk controlled by a metal strut that opens at an angle to the annulus plane.

Since prosthetic valves share commonalities regarding function and normal flows, there also are similar causes of dysfunction (Boxes 15.1 and 15.2).

Doppler Echocardiography for Prosthetic Valves

Compared with a normal native valve, prosthetic valves have a smaller effective orifice area (EOA). Antegrade velocities and pressure gradients across a normally functioning prosthetic valve are higher than a normal native valve in the same space. Knowledge of normal hemodynamics for native and prosthetic valves is important for determining normalcy of each valve. Manufacturers publish data on the flow characteristics of each specific prosthetic valve and its various sizes (Table 15.3). After valve placement, cardiologists can use these data to determine what constitutes normal function for each type and size of prosthetic valve.

Whereas Doppler-derived peak and mean pressure gradients across native and bioprosthetic valves are consistent for flow moving through a single orifice, the Doppler-derived pressure gradients across dual orifices (eg, mechanical valves) present a more complex clinical scenario (Figs. 15.14 and 15.15). In the latter, flow and pressure gradient through and across each orifice are dependent on orifice size and geometry. Although it has not been thoroughly studied, since pressure and flow are directly related, it is possible to obtain accurate data regardless of whether or not the Doppler beam is parallel to a larger or smaller orifice. The bileaflet prosthetic valve has been studied in flow models (Figs. 15.14 through 15.16). Two semicircular disks hinge open to form two larger semicircular lateral orifices and a smaller slit-like central orifice. In the narrow central flow stream, higher blood velocities occur as a result of local acceleration forces. Whether or not continuous-wave Doppler–obtained transvalvular velocities are different across the central and peripheral orifices is unknown. Theoretically, similar to the dual orifice valve, the pressure gradient across a narrower

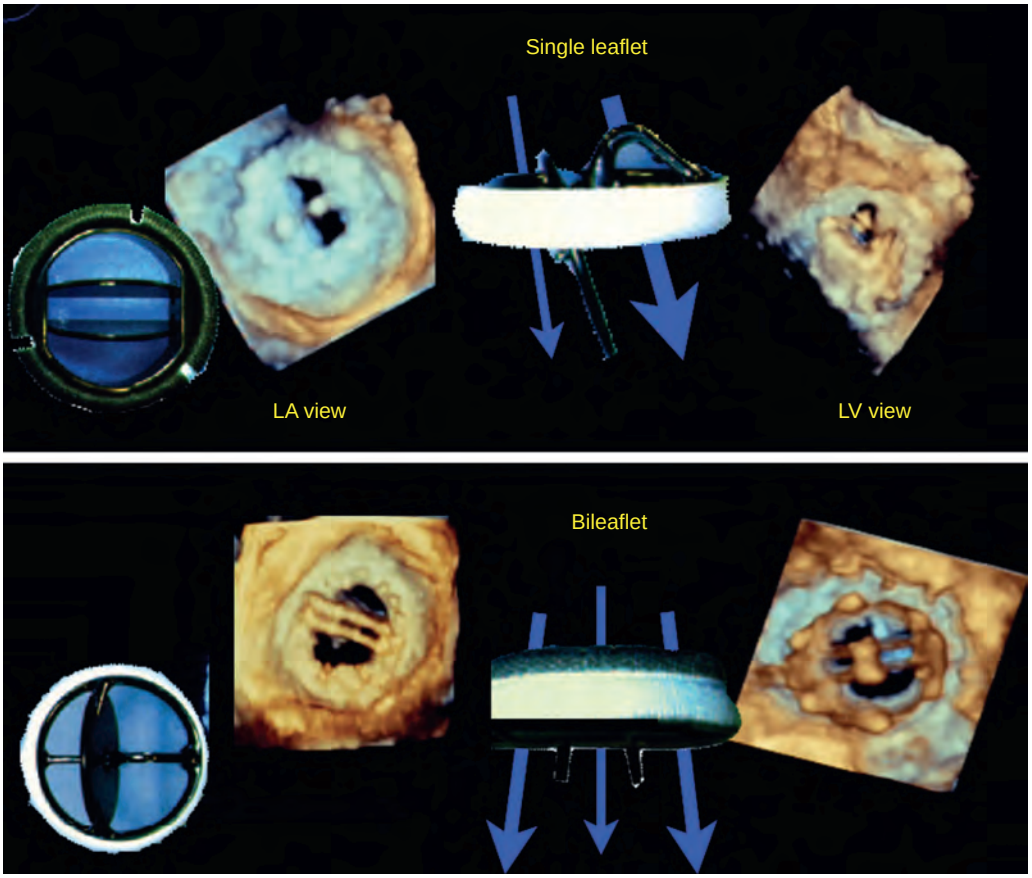

Fig. 15.14 Flows across mechanical prosthetic valves. This figure highlights the differences in both appearance and flow across a single-leaflet and a bileaflet mechanical prosthetic valve. Three-dimensional echocardiographic imaging shows valves, in mitral position, from the perspectives of the left atrium *(LA)* and left ventricle *(LV)* and highlights the paths through which blood flows while traversing the valve.

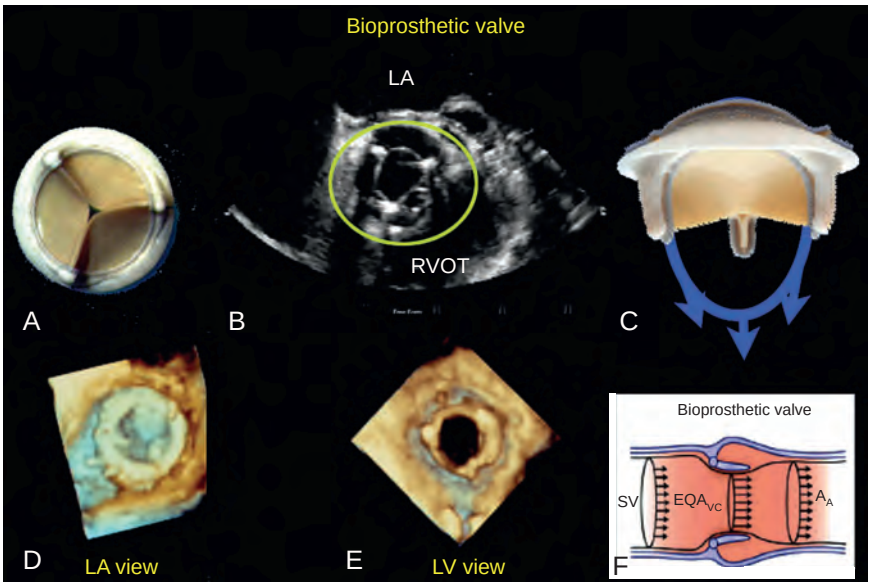

Fig. 15.15 Flows across bioprosthetic valves. The figure highlights the appearance and flow across a bioprosthetic valve. The valve is shown in the mitral and aortic positions. (A) and (B) Valve in short-axis view looking from downstream. (C) View highlighting the main single forward flow pattern. (D) and (E) Three-dimensional echocardiographic views of the mitral position from the left atrial *(LA)* perspective during systole and the left ventricular *(LV)* perspective during diastole. (F) Another view highlighting the main single forward flow pattern. A_A, Ascending aorta; EQA_{VC}, estimated qualitative area vena contracta; *RVOT*, right ventricular outflow tract; *SV*, stroke volume.

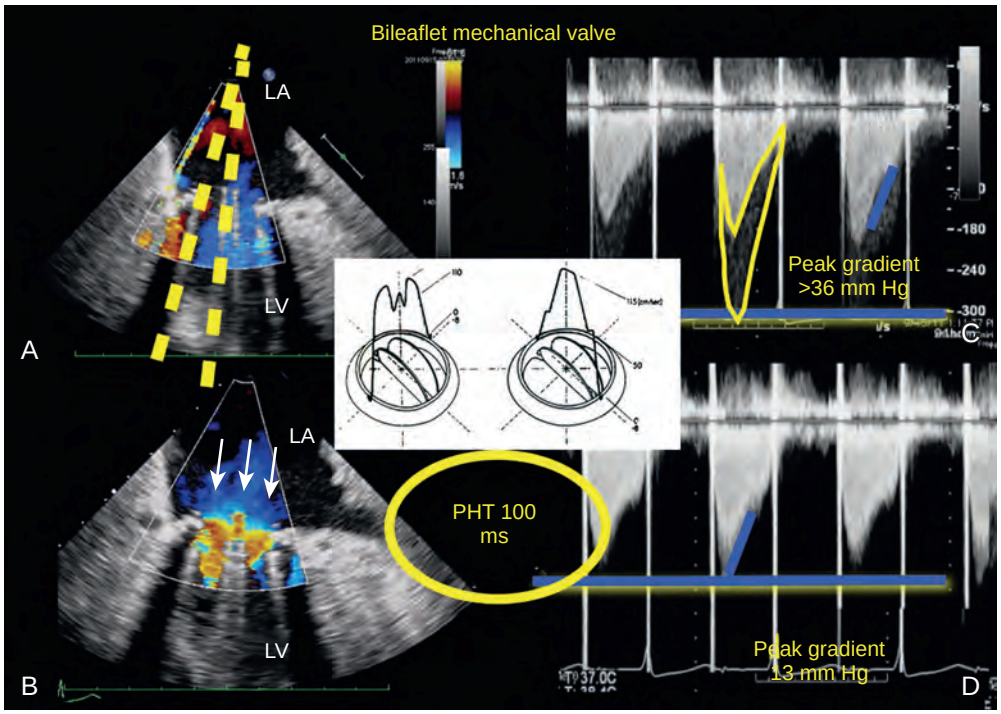

Fig. 15.16 Normal flows across a bileaflet mechanical valve. (A) and (B) Imaging of a bileaflet mechanical valve perpendicular to the leaflets. Three forward jets of blood flow through the two lateral and one central orifice. Flow through these orifices is on a slight stagger, as seen in the schematic in the middle. (C) The flow through the middle orifice passes with a higher velocity and may record a higher gradient than what is truly representative of the valve. The Doppler profile shows two components: a lower and more dense profile, which suggests the large majority of flow, that represents flow through the lateral orifices, and a faster less dense profile (fewer blood cells) that comes from the central orifice. The Doppler profile records a high peak gradient (>36 mm Hg) from the central orifice that does not accurately reflect the mitral valve area measured by the pressure half time *(PHT)* technique (220/100 ms = 2.2 cm^2). (D) The more dense profile from a lateral orifice is more consistent with a larger valve area recorded using the PHT. *LA*, Left atrium; *LV*, left ventricle.

orifice will be identical to the peripheral ones since blood flow through the orifices is directly related to the orifice size.[21,22,28]

Given the wide range of pressure gradients across any specific prosthetic valve, determining the valve EOA, or a dimension-less index, adds useful information. Measuring valve area is, at minimum, complementary to more basic Doppler velocity and pressure gradient data. Indexing the valve areas to individual body surface area (BSA) allows an assessment of the valve relative to the patient's size. A relatively small valve area (relative to the BSA) is called *patient-prosthesis mismatch (PPM)*.[29] PPM is more commonly described and discussed in the context of AV surgery. PPM is associated with short- and long-term adverse outcomes.[29]

Color-Flow Doppler

Normal native valvular flows have relatively low velocity. More than 70% of patients with normal valvular flow display trace or mild mitral, tricuspid, and PV regurgitation without obvious defect.[20] By contrast, only about 15% of patients display trace or mild aortic insufficiency (AI) in the absence of disease.[20]

All *mechanical valves* display normal regurgitant jets, sometimes referred to as *washing jets* (Fig. 15.17).[20–22,28] These flows are thought to prevent the formation of thrombi at sites of blood flow stasis. These jets are typically small (vena contracta < 3 mm) and low velocity, have a uniform color pattern (minimal aliasing at most), and do not extend far from the valve plane. The patterns of regurgitation detected by color-flow Doppler (CFD) are distinct (signature patterns) for each mechanical valve type, corresponding to their fluid dynamics. While casting an identifiable signature pattern of "regurgitant plumes," the associated regurgitant fraction is less than 10% to 15%.[21]

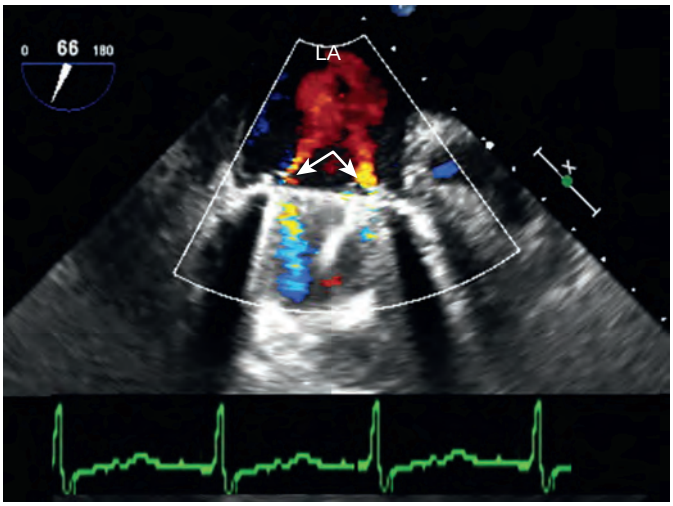

Fig. 15.17 Flow profile of a bileaflet mechanical valve. Image of a bileaflet mechanical valve parallel to the leaflet demonstrates the signature regurgitant washing jets for the bileaflet mechanical valve *(white arrows)*. When imaging in parallel to the mechanical leaflets, two inward directing jets can be seen. *LA*, Left atrium.

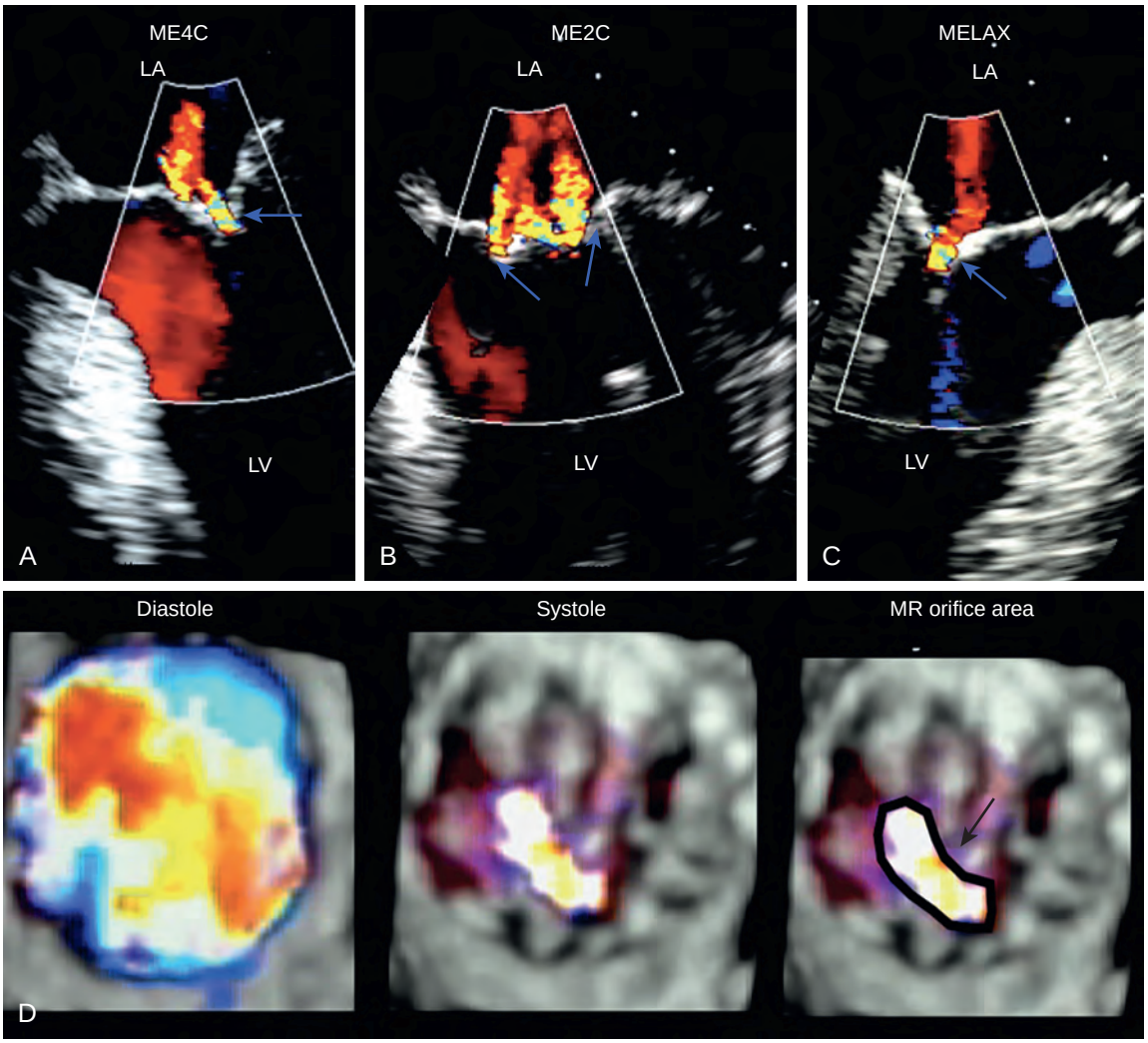

Fig. 15.18 Three-dimensional (3D) image of the regurgitant orifice. (A–C) Two-dimensional appearances of the same mitral regurgitant jet from three different midesophageal *(ME)* echocardiographic windows: four-chamber *(4C)*, two-chamber *(2C)*, and long-axis *(LAX)*, respectively. Vena contracta measurements from the ME4C and MELAX views are more accurate correlates of mitral regurgitation *(MR)* severity as they measure perpendicular to the MR jet, while the ME2C window views parallel to the MR jet. (D) This is confirmed using 3D imaging of the regurgitant jet during diastole *(left)* and systole *(middle)* from the left ventricular *(LV)* perspective. The shape of the regurgitant orifice, during systole on the *right*, is elliptical. The implications are that the effective regurgitant orifice is not circular and the flow convergence (proximal isovelocity surface area [PISA]) is not hemispherical as the principle behind the equation assumes it to be, creating errors in the PISA method. Three-dimensional imaging, when feasible, allows a direct measure of the regurgitant orifice area shown in black *(right)*.

A ball-in-cage valve in the open position shows antegrade blood flow around all sides of the ball occluder and across the cage orifice.[21,22] In the closed position, CFD demonstrates a small regurgitant jet circumferentially around the ball as it seats in the cage orifice. Antegrade blood flow across a single tilting disk prosthetic valve is characterized by a CFD across a major and a minor orifice. CFD indicates nonlaminar and asymmetric flow as blood accelerates along the tilted surface of the open disk. In the closed position, a single tilting disk normally demonstrates a regurgitation jet directed away from the sewing ring starting at the edge of the major orifice. Surgical preference on implantation determines the open disk position and hence the direction of the regurgitant jet normally seen on disk closure. The bileaflet valve has a complex blood flow profile on CFD imaging (see Fig. 15.16). In the open position, CFD shows antegrade flow through two larger lateral orifices and a small central orifice. When a bileaflet mechanical valve is imaged in the closed position, multiple washing jets of regurgitation are normally seen in the plane parallel to the leaflet-opening plane. All the regurgitant jets are located inside the sewing ring, with two jets originating from where the leaflets meet the housing and a third, central jet originating where the leaflets meet each other.

Bioprosthetic valves also display characteristic flow patterns. Stented and stentless valves display antegrade flow patterns closer to that of a normal native valve through a single orifice. Normal retrograde or regurgitant jets are centrally directed and do not extend far from the closed valve, are limited in jet area, and are homogenous in color.

Although generally accurate, recent data using 3D imaging suggested that geometric assumptions about the shape of the proximal isovelocity surface area (PISA) may be erroneous; that is, it is not necessarily hemispherical and the defect may not be circular (Fig. 15.18).[30] Three-dimensional imaging with CFD highlights important details of both stenotic and regurgitant jets and helps to explain why simpler 2D assessments may not provide the same accuracy (Figs. 15.19 through 15.21). Specifically, geometric assumptions required for several of the equations and principles are not always accurate. Visualizing the flow

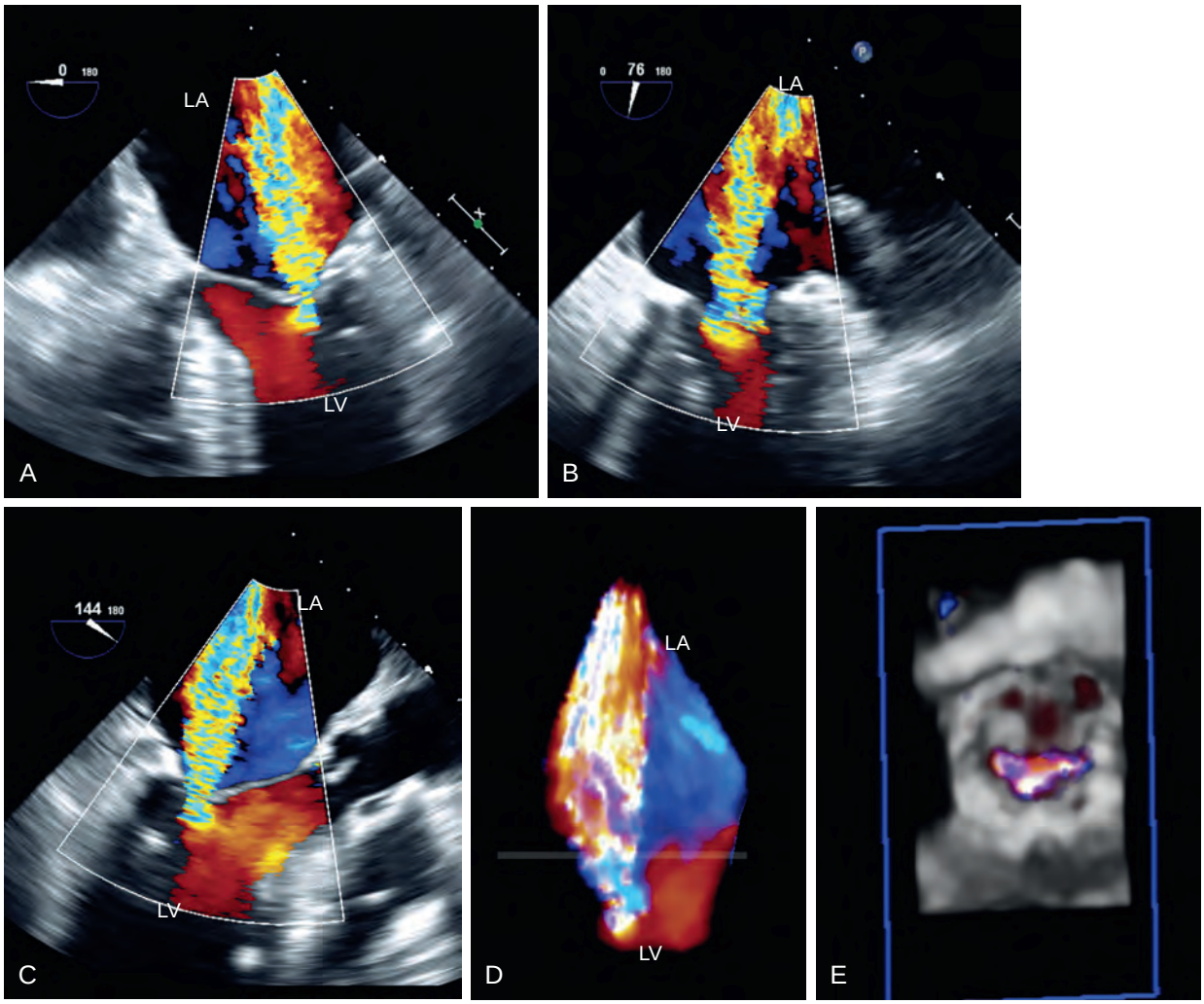

Fig. 15.19 Assessment of mitral regurgitant (MR) jet. (A–C) Two-dimensional (2D) color Doppler views of a centrally directed MR jet. (D) and (E) Three-dimensional (3D) color Doppler assessment of the same regurgitant flow. (D) The MR jet on three levels (below, above, and at the level of the mitral valve) demonstrates the expansion of the regurgitant jet immediately after it passes through that regurgitant orifice (ie, entrainment). (E) Similar to Fig. 15.16, this shows an elliptical regurgitant orifice that is not similarly highlighted in the 2D color Doppler evaluations (A–C). Assumptions made regarding the shape of the MR jet, centrally or eccentrically directed, may not be accurate as evidenced by 3D imaging. Using 3D color Doppler imaging, planimetry of the regurgitant orifice area can be measured. *LA*, Left atrium; *LV*, left ventricle.

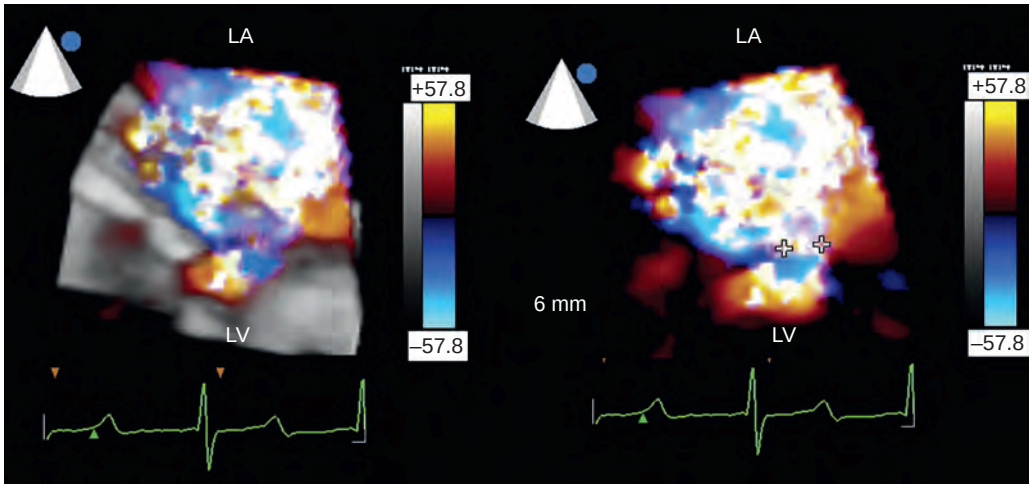

Fig. 15.20 Three-dimensional (3D) color Doppler imaging of a regurgitant mitral jet. The two images demonstrate the use of 3D color Doppler imaging to image flow from multiple levels to see the full shape of, in this case, regurgitant flow. Shown is the evaluation of a paravalvular regurgitant jet of a prosthetic mitral valve. The regurgitant jet is seen below, at, and above the valve to allow a more accurate measure of the vena contracta. As seen in Fig. 15.18, expansion of the regurgitant jet is seen on the atrial side. This expansion helps to understand why the regurgitant jet area may not reflect the regurgitant orifice accurately. In the case, the 3D view of the regurgitant flow aided in determining the size and number of occluder devices. *LA*, Left atrium; *LV*, left ventricle.

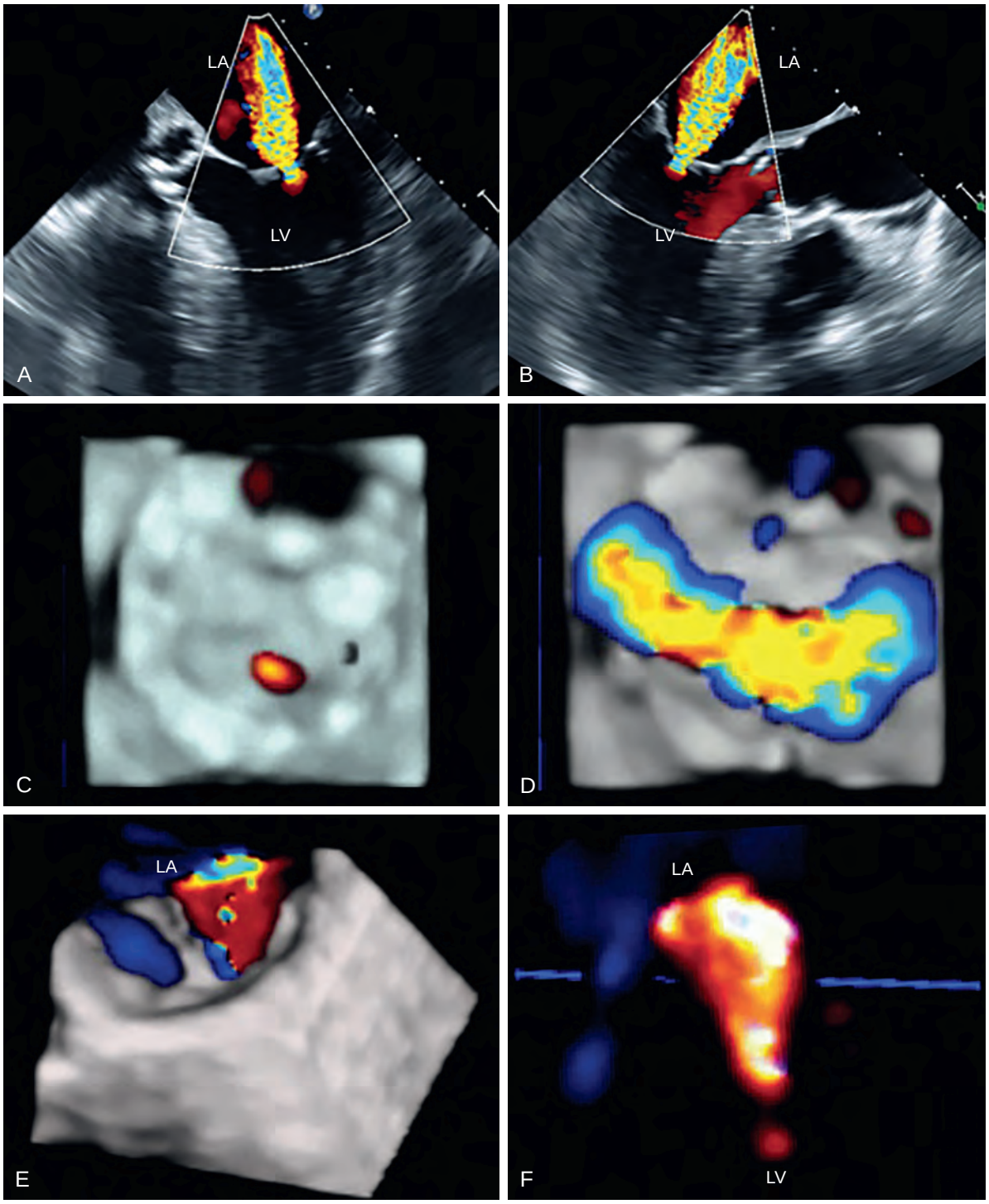

Fig. 15.21 Entrainment of the regurgitant jet. (A) and (B) Centrally regurgitant jet from the mid-esophageal windows. (C) The regurgitant orifice from the left ventricular perspective during systole. (D) Flow during diastole. (E) and (F) Three-dimensional shape of the regurgitant jet on multiple levels as it passes through the regurgitant valve orifice. The jet appears to expand as a result of entrainment. This explains why the vena contracta is a better reflection of the regurgitant orifice than the subsequent jet area, the latter overestimating the regurgitant orifice area due to entrainment. *LA*, Left atrium; *LV*, left ventricle.

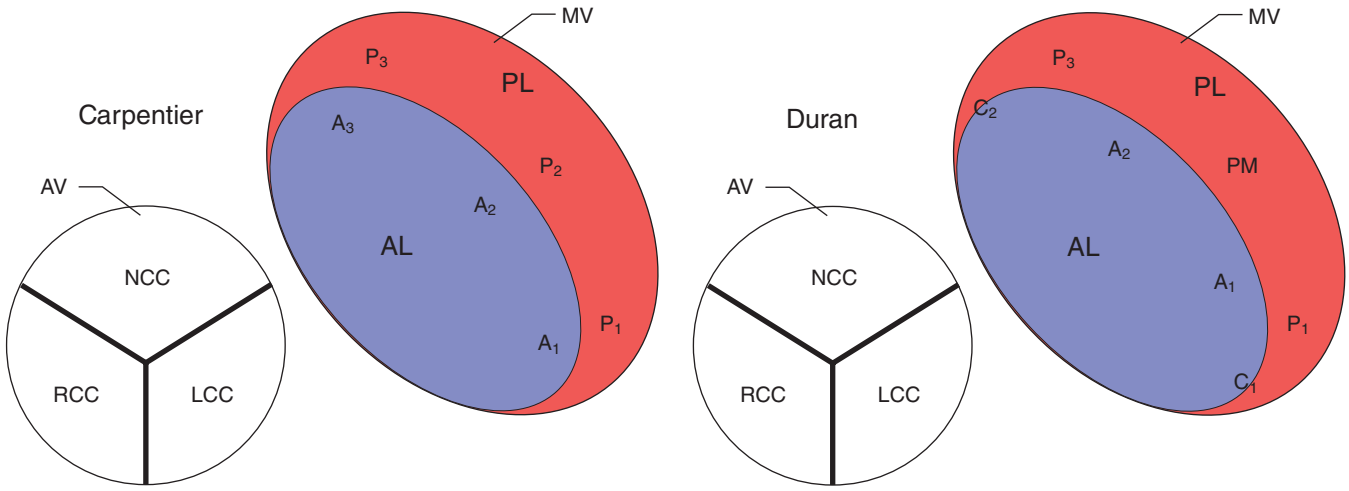

Fig. 15.22 Schematic showing the Carpentier and Duran nomenclatures of the mitral leaflet scallops. Whereas both recognize the posterior leaflet as having three scallops (P_1, P_2, P_3), the Duran labeling distinguishes the anterior leaflet as an anterior lateral section (A_1) and a posteromedial section (A_2) and two commissural areas on the periphery (C_1 and C_2). In contrast, the Carpentier nomenclature identifies three scallops on the anterior leaflet (A_1, A_2, A_3) corresponding to those on the posterior leaflet. *AL,* Anterior leaflet; *AV,* aortic valve; *LA,* left atrium; *LAA,* left atrial appendage; *LCC,* left coronary cusp (of the aortic valve); *LV,* left ventricle; *MV,* mitral valve; *NCC,* noncoronary cusp; *RCC,* right coronary cusp; *PL,* posterior leaflet.

profile on three levels—prevalve, valve, and postvalve—displays the characteristics of flow and the orifice through which blood flows (see Figs. 15.19 through 15.21). The equations apply well to mild and severe defects, but they are less accurate for moderate dysfunction. Although the flow convergence method provides more detail regarding this range of dysfunction, it is now known that inaccuracies exist. The recent advancements in 3D imaging allow a more accurate area measurement using planimetry (see Fig. 15.21), when feasible.

The following sections apply these echocardiographic principles toward assessing valvular function. Similar principles apply across the different valves. As a general fact, validation of analyses is greater for left-sided heart valves than for those on the right side.

Mitral Valve

Normal Anatomic and Functional Features of the Native Valve

The anatomic and functional features of MV have been reviewed extensively (see Chapter 14), and understanding of MV function and failure has contributed to the success of MV repair.[31,32] The normal MV is a thin bileaflet (each <2 mm thick) valve, of which the anterior and posterior leaflets insert into their respective annuli. Each of the leaflets is divided into segments or scallops, which have been defined by Carpentier and Duran (Fig. 15.22).[33–38] Both investigators describe the posterior leaflet as having three scallops or segments; anterolateral and superior (P_1), middle (P_2), and posteromedial and inferior (P_3). Duran divides the anterior leaflet into two larger segments (anterior [A_1] and posterior [A_2]) and two smaller commissural segments (C_1 and C_2). By contrast, Carpentier describes the anterior leaflet with relation to the posterior leaflet; A_1, A_2, and A_3 lying in the same respective planes. Although the posterior annulus covers two-thirds of the annular circumference, the posterior leaflet covers one-third of the coapting area, while the anterior leaflet is responsible for two-thirds of this space (see Fig. 15.22). Functionally, it appears that the posterior leaflet provides a coapting surface for the larger anterior leaflet. During coaptation the leaflets overlap by at least 6 mm and the base of the coaptation point lies within 6 mm of the annular plane but not above it. The importance of the leaflet heights or lengths and coaptation point is seen in their effect on blood flow direction into and out of the left ventricle.[39–42] During ventricular diastole the anterior leaflet is concave to the left atrium, directing blood flow toward the ventricular apex along the posterolateral wall (Fig. 15.23). Subsequently, before and during ventricular contraction, blood flow is directed toward the left ventricular outflow tract (LVOT) along the anteroseptal wall. During this latter time period the anterior leaflet is convex toward the left atrium enlarging the LVOT just before and during systolic ejection. This pattern of blood flow sets up a vortex with energy that drives flow up and toward the AV with minimal interference and maximum efficiency (see Fig. 15.23). Other anatomies or configurations or flow directions are less efficient.

The chordae connect the mitral leaflets to the two papillary muscles (anterolateral and posteromedial) and ventricular walls, and create important interactions between the mitral apparatus and the ventricular myocardium (Fig. 15.24). The anterolateral papillary muscles connect to the more anterior and lateral portions of each leaflet and the posteromedial papillary muscle connects to the more posterior and medial portions. The primary purpose is to prevent leaflet prolapse or flail by creating tension during papillary muscle contraction (ie, ventricular systole). There are multiple types of chordae. While the primary chordae prevent prolapse, other secondary, tertiary, and quaternary chords connect areas of the mitral leaflets to the ventricular walls. These chordae help maintain both function and shape of the ventricle.

The normal mitral annulus is a 3D saddle-shaped dynamic structure (Fig. 15.25).[39,43] Its shape and position change throughout the cardiac cycle to optimize forward flow into the ventricle, prevent regurgitant flow, and accommodate ventricular systolic outflow. During diastole the mitral annulus is more planar and forward toward the ventricular cavity opening up wide and directing flow toward the posterolateral ventricular wall creating a vortex and vortical forces, resulting in flow toward the apex and then anteroseptal toward the LVOT prior to systolic ejection. In conjunction with the end of diastole and onset of systole, the mitral annulus contracts posterolaterally toward the membranous portion and superiorly toward the atrium, both actions increasing size of the LVOT, increasing its reservoir capacity prior to ejection, and minimizing interactions between systolic outflow and the mitral leaflets.

Prosthetic or Repaired Mitral Valve

It is important to know the details of the surgical procedure including what kind of valve was placed or how the valve was repaired. Previous

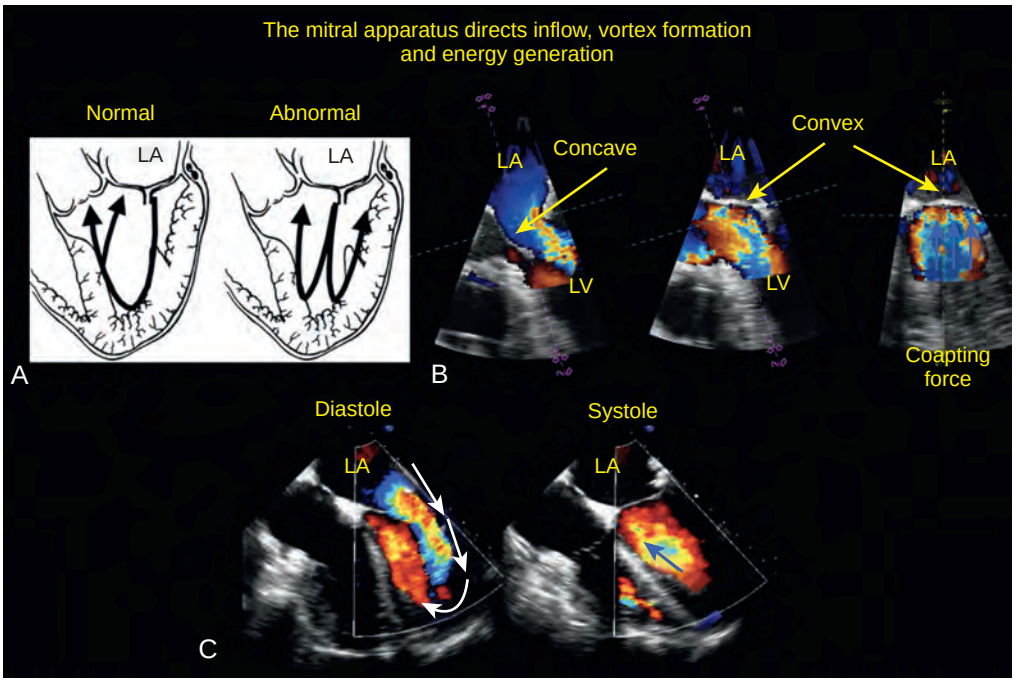

Fig. 15.23 Flow directions of transmitral and intracavitary flows. (A) Schematic showing normal and abnormal patterns. The normal pattern consists of transmitral flow directed toward the left ventricular apex along the posterolateral wall, which is followed by flow directed toward the left ventricular outflow tract along the anterior and anteroseptal walls. This normal pattern is associated with the development of normal flow vortexes, which creates energy, all contributing toward more efficient flow, which minimizes the chance of systolic outflow interacting with slack mitral leaflet portions, thereby increasing the risk of systolic anterior motion (SAM). By contrast, the abnormal flow patterns create less energy and are less efficient. Furthermore, its flow directions have potential implications when the different flows potentially interact with slack mitral leaflets and increase the chance of SAM. (B) and (C) Movement of the anterior leaflet and how it directs blood flow into the left ventricle. Normal changes in the mitral leaflets create normal flow patterns resulting in normal flow configurations. *LA,* Left atrium; *LV,* left ventricle.

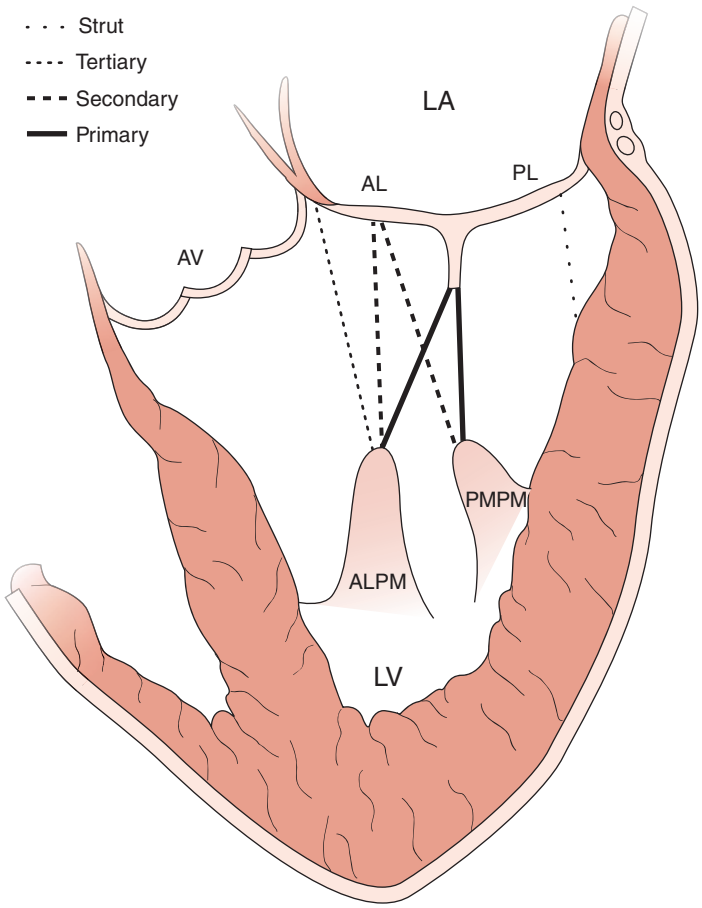

Fig. 15.24 Chordal anatomy. Schematic shows the four main categories of chordae tendineae that allow the mitral valve to function normally, which includes its affect on left ventricular shape and function. The primary chords are responsible for normal coaptation. The secondary chords associated with the tethering phenomenon seen during left ventricular remodeling have been a target of repair (cutting) for type IIIb mitral regurgitation. The tertiary chords attach from the papillary muscle to the base of the anterior leaflet, while the strut chords connect that base of the posterior leaflet to the posterolateral left ventricular wall. *AL,* Anterior leaflet; *ALPM,* anterolateral papillary muscle; *AV,* aortic valve; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *PL,* posterior leaflet; *PMPM,* posteromedial papillary muscle.

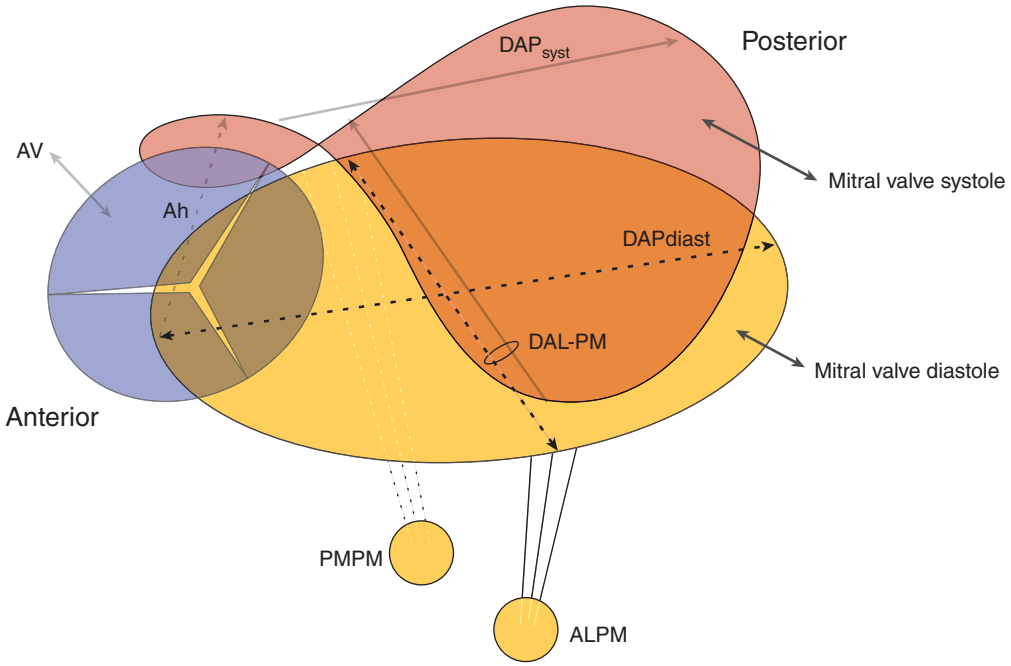

Fig. 15.25 Annular changes. Schematic shows three measures of the mitral annulus and how they change during the cardiac cycle. The *black dashed arrows* represent the annular dimensions at end-diastole. During ventricular systole the anteroposterior distance (DAPsyst) decreases and moves laterally (ie, away from the left ventricular outflow tract [LVOT]). The intercommissural line (DAL-PM) decreases and moves posterior. The annular height increases and moves the anterior portion of the annulus away from the LVOT. Altogether, the mitral annular area declines during ventricular systole, and moves away from the LVOT to allow for unhindered systolic outflow. *Ah,* Annular height; *ALPM,* anterolateral papillary muscle; *AV,* aortic valve; *DAP,* anterior posterior diameter; *diast,* diastole; *PMPM,* posteromedial papillary muscle; *syst,* systole.

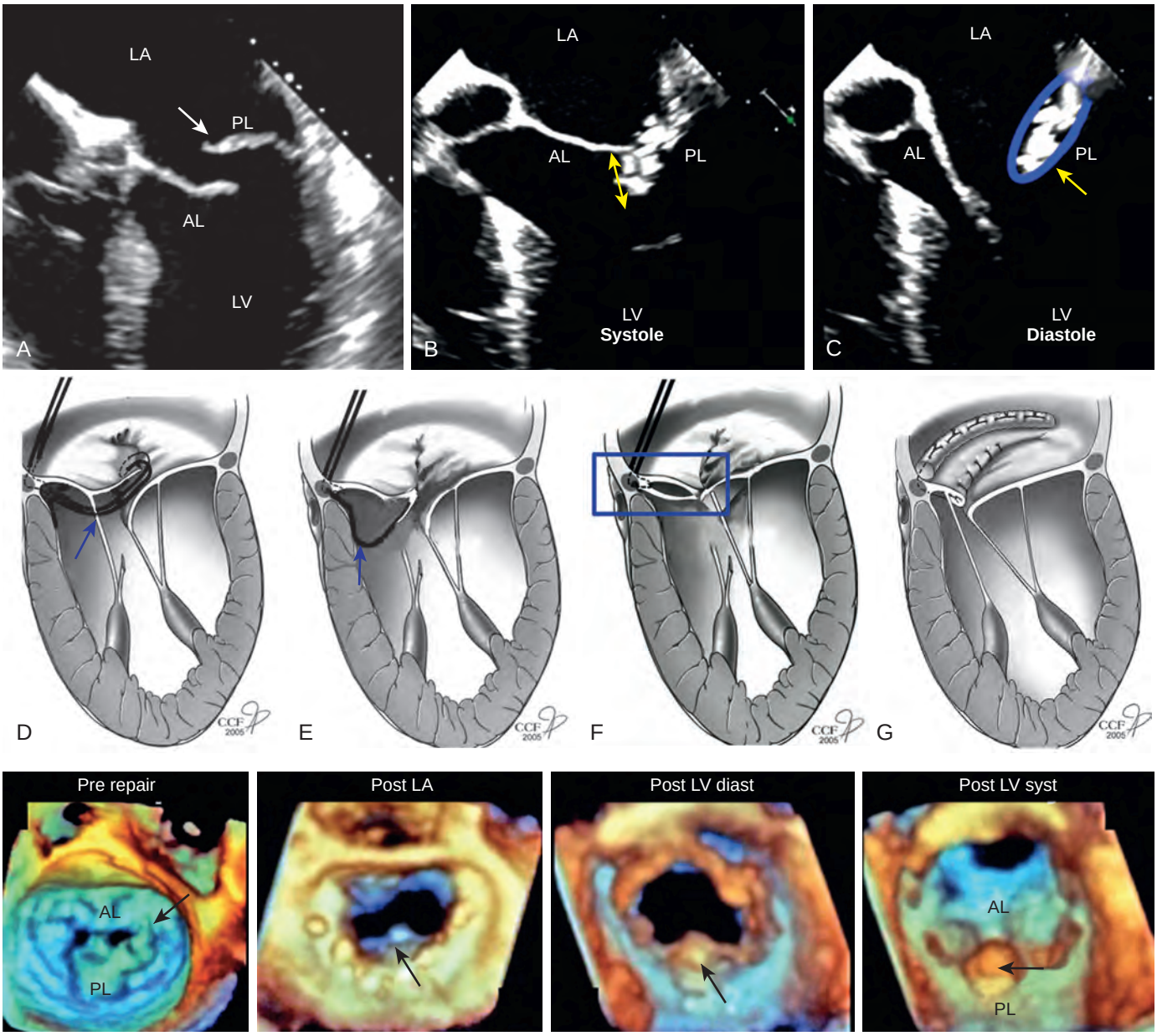

Fig. 15.26 Before and after valve repair. The folding leaflet plasty is a repair technique that reduces posterior leaflet *(PL)* height without resecting the leaflet. Suture is placed on the edge of the prolapsing scallop, passed below (left ventricle [*LV*] side) the leaflet and then through the respective annular segment. The leaflet is pulled down and folded over itself to produce a significant coapting surface for the anterior leaflet. (A) Patient with a flail PL. (B) and (C) Same patient postrepair image obtained during LV systole *(syst)* and diastole *(diast)*, respectively. (B) shows the coaptation zone *(yellow arrow)* created by the folding plasty, which can be seen in (C) *(blue surround* that is pointed to by the *yellow arrow)*. (D) and (E) Path of repair suture *(blue arrow)*, until (F) leaflet is folded *(blue box)*. (G) Annuloplasty ring supporting the repair. The lower series of images are three-dimensional views of the repair. The *black arrow* in the first image on the left shows the flail PL and torn chord *(thin black arrow)*, while the next three show the repair with the folded PL highlighted by the *black arrows*. *AL*, Anterior leaflet; *LA*, left atrium.

knowledge of normal echocardiographic findings for specific valves and/or successfully repaired valves helps delineate what is normal and what is not. Details include whether or not a bioprosthetic or mechanical valve was placed, and what kind and how many leaflets. For valve repairs, information regarding annulus type (flat vs saddle shaped, full vs partial), and leaflet resection, repair, or augmentation helps echocardiographers understand what they see during imaging.[21,31,32,44]

The repaired valve relies mostly on a normally mobile anterior leaflet that is adequate in size to cover the coapting surface (Figs. 15.26 and 15.27).[31,32] The primary role of the posterior leaflet is to provide a coapting surface for the anterior leaflet. Typically, the anterior leaflet in a patient with MV disease is minimally resected but otherwise repaired, whereas the posterior leaflet is often resected. Variations include repair or folding of the posterior leaflet to provide a larger coapting surface and a larger valve area (see Figs. 15.26 and 15.27). The Alfieri repair is an alternative repair procedure that reduces or prevents prolapse.[45–47] It is classically performed centrally, resulting in a figure-of-eight opening; however, it may also be performed peripherally along the commissures to form a dual figure-of-eight orifice in diastole (Fig. 15.28). For all echocardiographic assessments, recording

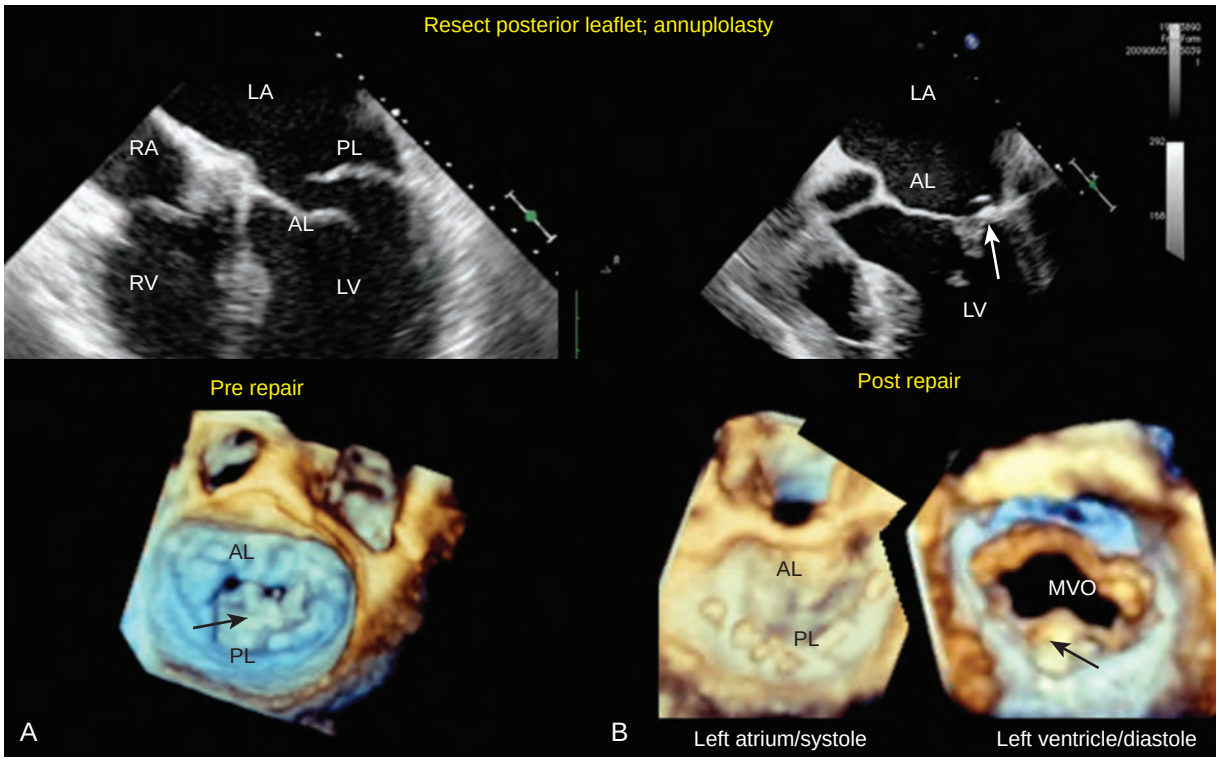

Fig. 15.27 Before and after mitral valve repair. (A) In the prerepair period, the posterior leaflet *(PL)* is seen as flail. The three-dimensional image similarly shows the flail scallop *(arrow),* which in this case, is the middle scallop of the posterior leaflet (P_2) with two torn chordae. (B) The repaired valve is mostly dependent on the anterior leaflet *(AL)* to cover the coating surface, while the PL covers a smaller portion of the coapting area but also provides a coapting surface for the larger and more mobile anterior leaflet *(arrow). LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

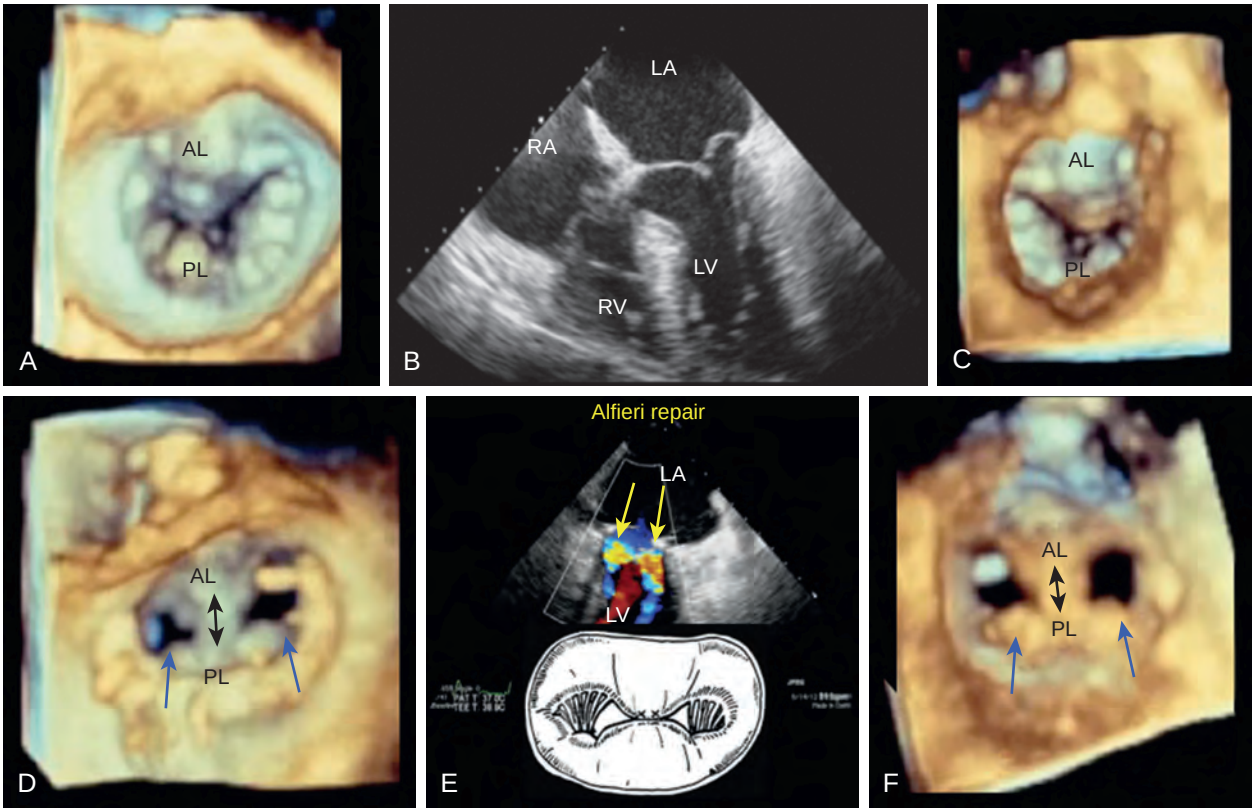

Fig. 15.28 Alfieri repair. (A) and (B) The case of a bileaflet prolapse or myxomatous disease is used to demonstrate the Alfieri repair, in which a running suture (*small black arrow* in [D] and [F] and middle schematic [E]) is classically placed centrally but may also be placed peripherally. The centrally placed suture creates a figure-of-eight orifice as compared to (A–C) the single orifice. (D–F) After Alfieri repair. Three-dimensional views from (D) the left atrial and (F) ventricular perspectives show a figure-of-eight orifice. (E) Two-dimensional image shows the color Doppler display of two separate jets.

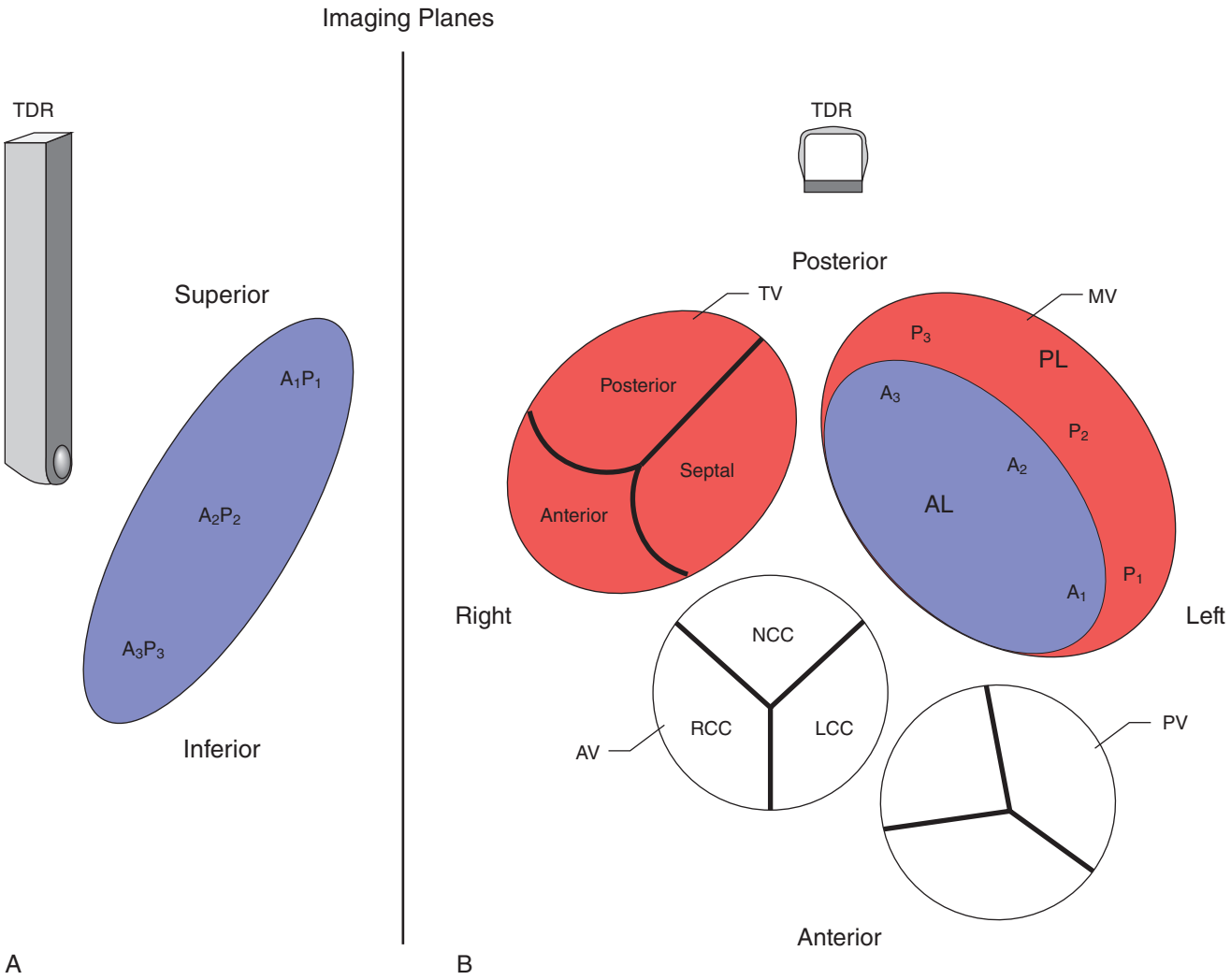

Fig. 15.29 Imaging planes. Schematics showing the vertical (A) and horizontal (B) position of the mitral valve, the latter in relation to other surrounding structures and as would be seen by the transducer positions. *A_1, A_2, A_3,* Anterior leaflet scallops; *AL,* anterior leaflet; *AV,* aortic valve; *LA,* left atrium; *LAA,* left atrial appendage; *LCC,* left coronary cusp (of the aortic valve); *LV,* left ventricle; *NCC,* noncoronary cusp; *P_1, P_2, P_3,* posterior leaflet scallops; *PL,* posterior leaflet; *PV,* pulmonary valve; *RCC,* right coronary cusp; *TDR,* transducer; *TV,* tricuspid valve.

of the patient's hemodynamic status improves the perspective at the time of evaluation.

The Echocardiographic Examination

The 2D and Doppler examinations are accomplished from a number of echocardiographic windows, with emphasis on mid-esophageal (ME) windows (0–150 degrees), to analyze the native valve before and after repair and/or the prosthetic MV (Figs. 15.28 through 15.31).[21,22,31–33] Although transgastric (TG) views may complement imaging of the valve, it may be more useful to visualize the LVOT as well as the subvalvular apparatus (see Figs. 15.31 through 15.33).

Evaluation is made of leaflet mobility (normal, excessive, restrictive), thickness, and any associated mobile structures, the latter of which may represent suture materials; fractured calcium deposits; and retained chordae or leaflet or endocarditis. Imaging of the subvalvular apparatus identifies thickening or suspected calcification, mobility or flail of the chordae and/or papillary muscles. The valve should appear stable and secured in the surrounding tissues. Echocardiographic lucency of the surrounding tissues may suggest infection or abscess, dehiscence, or rupture (Fig. 15.34).

For mechanical prosthetic valves, imaging perpendicular to the leaflets allows seeing the opening and closing of the leaflet edges while parallel imaging facilitates viewing of signature regurgitant jets. Viewing from multiple windows improves the completeness of the examination and the diagnostic abilities (Figs. 15.14, 15.17, 15.35–15.38). Additional concerns regarding bioprosthetic valves are positioning of the struts or, more specifically, if they lay near or in the LVOT, potentially causing obstruction to systolic outflow (Fig. 15.39).

The Doppler examination assesses, both qualitatively and quantitatively, the presence, direction, and width of normal and abnormal blood flows of the native, prosthetic, and repaired valves. Imaging from multiple windows improves the assessment and ability to differentiate between normal and abnormal forward and regurgitant jets. The ME windows offer the best proximity of the valve to the transducer and of alignment between blood flow and the ultrasound beam. Although qualitative CFD assessments may suggest high velocities based on the presence of aliasing (turbulence), this may or may not indicate abnormal flow. Further quantitative analysis should be performed to clarify the flow.

Different prosthetic valves have signature flow profiles.[21,28] Bioprosthetic valves allow a large central forward flow and, for some

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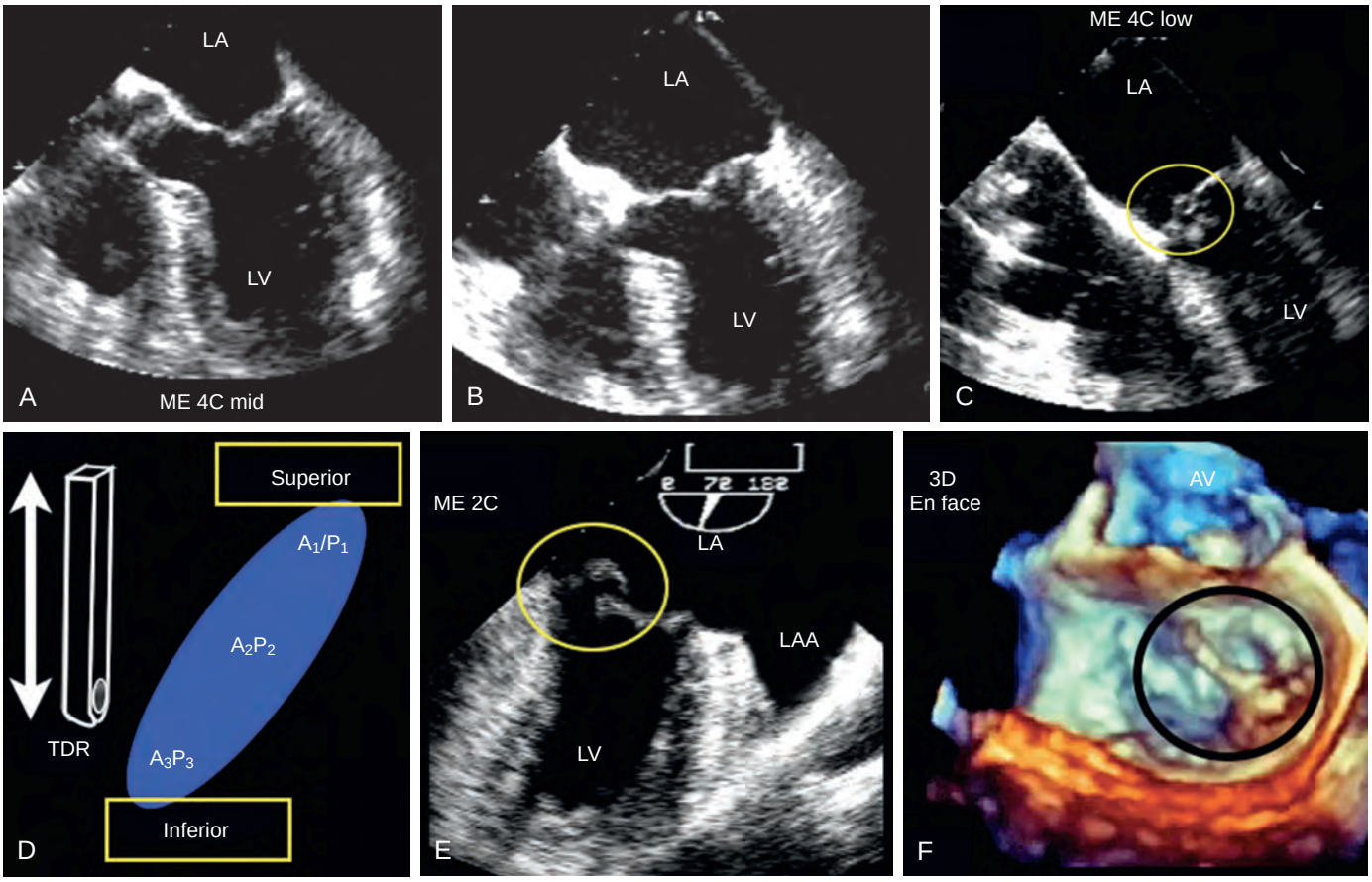

Fig. 15.30 P_3 flail: vertical imaging planes (associated with Video 15.2). Multiple views of a flail of the posterior (P_3) portion of posterior leaflet with a torn chord. (A–C) Images obtained by advancing the transesophageal echocardiography probe from the midesophageal *(ME)* four-chamber *(4C)* level to a lower esophageal level, showing the P_3 defect *(yellow circle)*. (D) Schematic showing how the mitral valve also exists in a vertical plane. (E) Lesion *(yellow circle)* in ME two-chamber *(2C)* view. (F) Lesion *(black circle)* in three-dimensional *(3D)* en face view, showing the defect and the torn chord. *A_1, A_2, A_3,* Anterior leaflet scallops; *AL,* anterior leaflet; *AV,* aortic valve; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *P_1, P_2, P_3,* posterior leaflet scallops; *PL,* posterior leaflet; *TDR,* transducer.

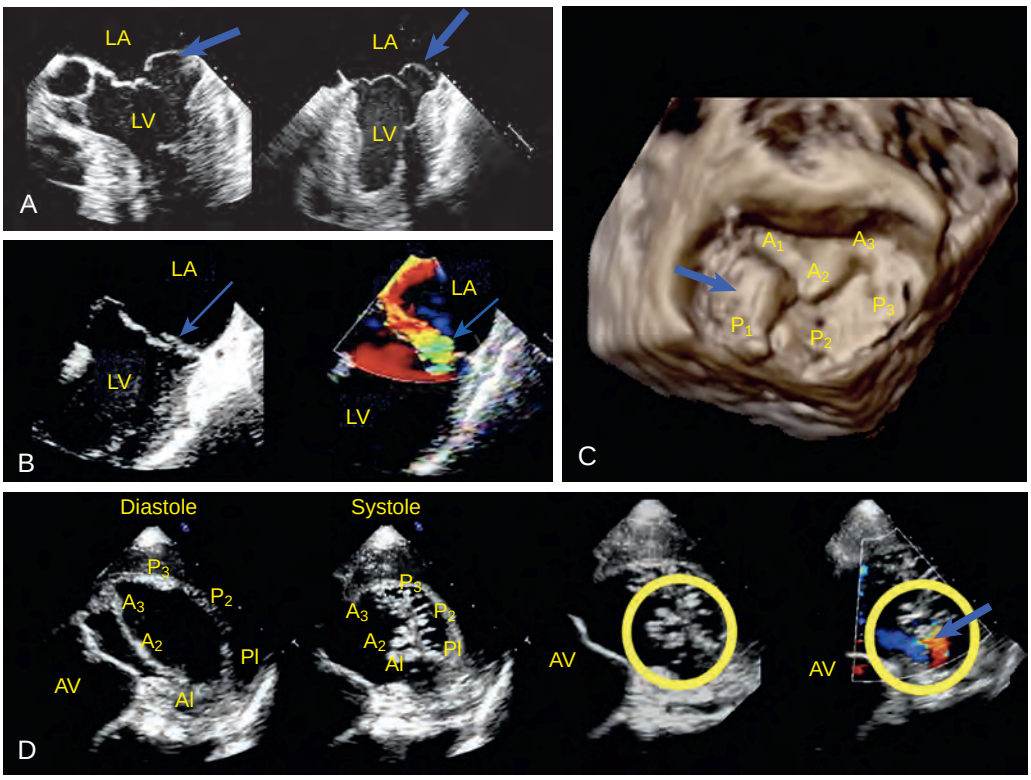

Fig. 15.31 P_1 prolapse: multiple windows. Multiple views of mitral leaflets highlighting a P_1 prolapse. (A) Images obtained at 0 degrees *(left)* and after rotating the transducer to 50 degrees *(right)*, highlighting the prolapsing P_1 *(blue arrows)*. (B) Images obtained after rotating transducer to 80 degrees show the origin of the regurgitant jet from P_1 *(blue arrows)*. (C) Prolapsing P_1 *(blue arrow)* in relation to the other scallops. (D) Series of transgastric images displaying the mitral valve in the short-axis view and showing the prolapsing P_1 *(yellow circle)* and regurgitant jet *(blue arrow)*. *A_1, A_2, A_3,* Anterior leaflet scallops; *AL,* anterior leaflet; *AV,* aortic valve; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *P_1, P_2, P_3,* posterior leaflet scallops; *PL,* posterior leaflet.

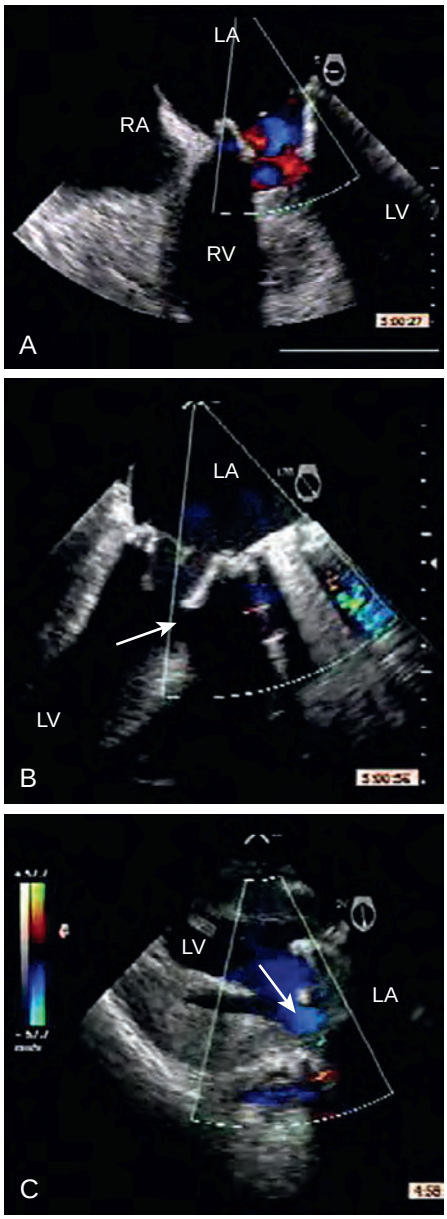

Fig. 15.32 Bioprosthetic mitral valve and the left ventricular outflow tract (LVOT). (A) and (B) Midesophageal views of a bioprosthetic valve for which the struts *(arrow)* appear to be narrowing the LVOT. (C) Transgastric view showing the absence of color Doppler turbulence in the LVOT. Although two-dimensional imaging may be limited, when complemented by Doppler technology, the examiner can adequately formulate a clinical impression and diagnosis. *Arrow* points to color flow. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

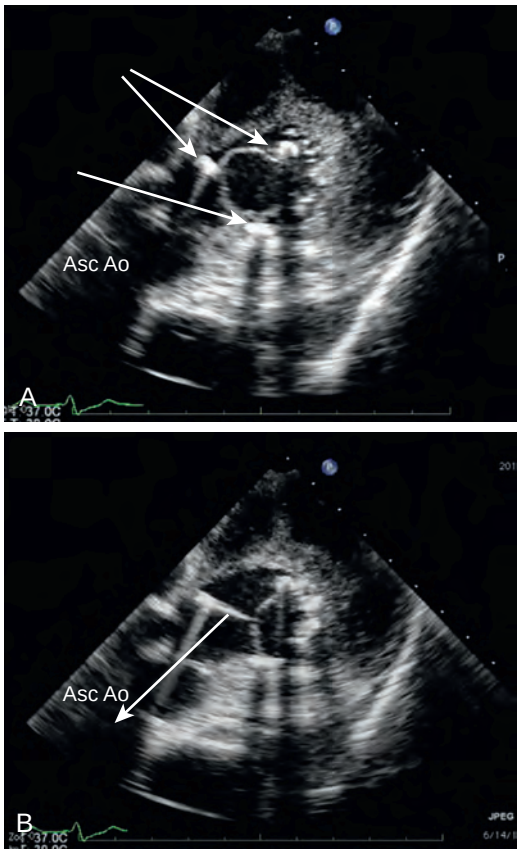

Fig. 15.33 Bioprosthetic mitral valve: transgastric (TG) imaging. This is an example of how a comprehensive exam yields greater information during this two-dimensional imaging from a TG window. (A) Mitral bioprosthetic valve with struts *(white arrows)* not in the left ventricular outflow tract (LVOT). (B) *White arrow* shows an unhindered path through the LVOT and across the aortic valve. *Asc Ao,* Ascending aorta.

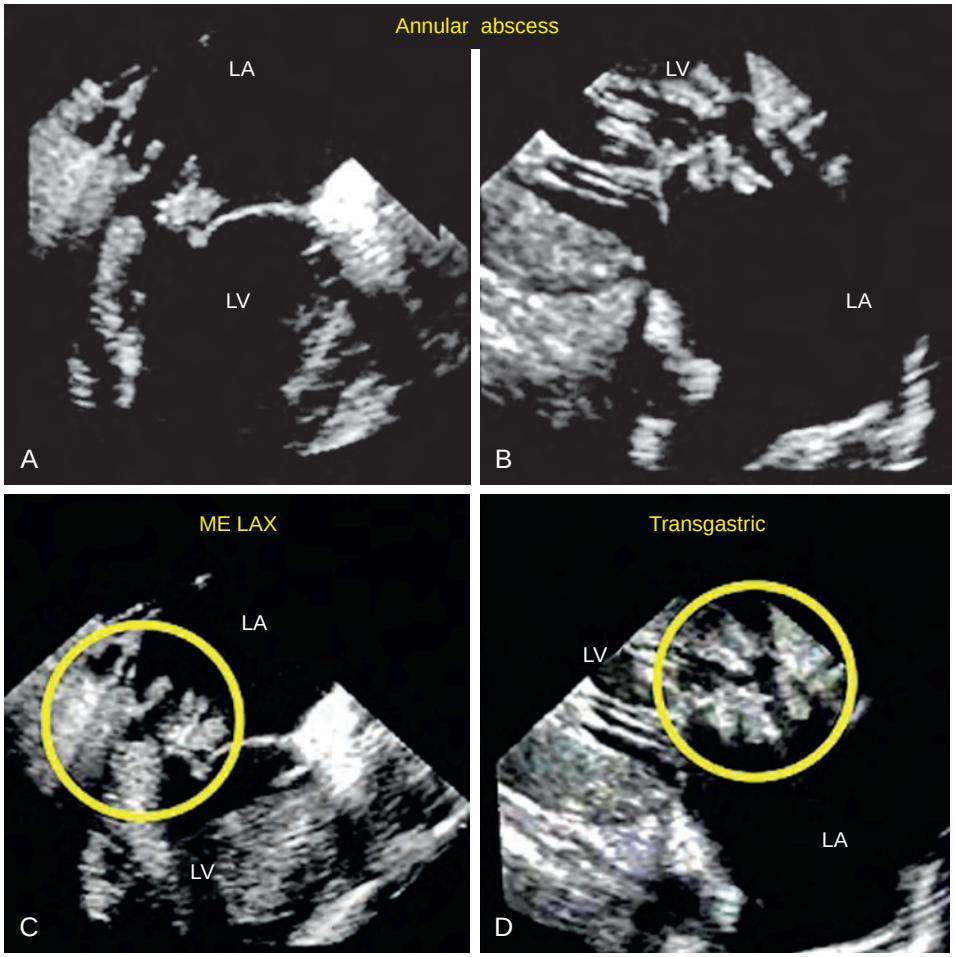

Fig. 15.34 Mitral annular abscess: infection of the mitral valve and surrounding tissues. (A) and (C) Midesophageal and (B) and (D) transgastric windows show a complex combination of echolucency and fragmented valve tissues *(yellow circles)* consistent with endocarditis and annular abscess. *LA,* Left atrium; *LV,* left ventricle; *ME LAX,* midesophageal long-axis (view).

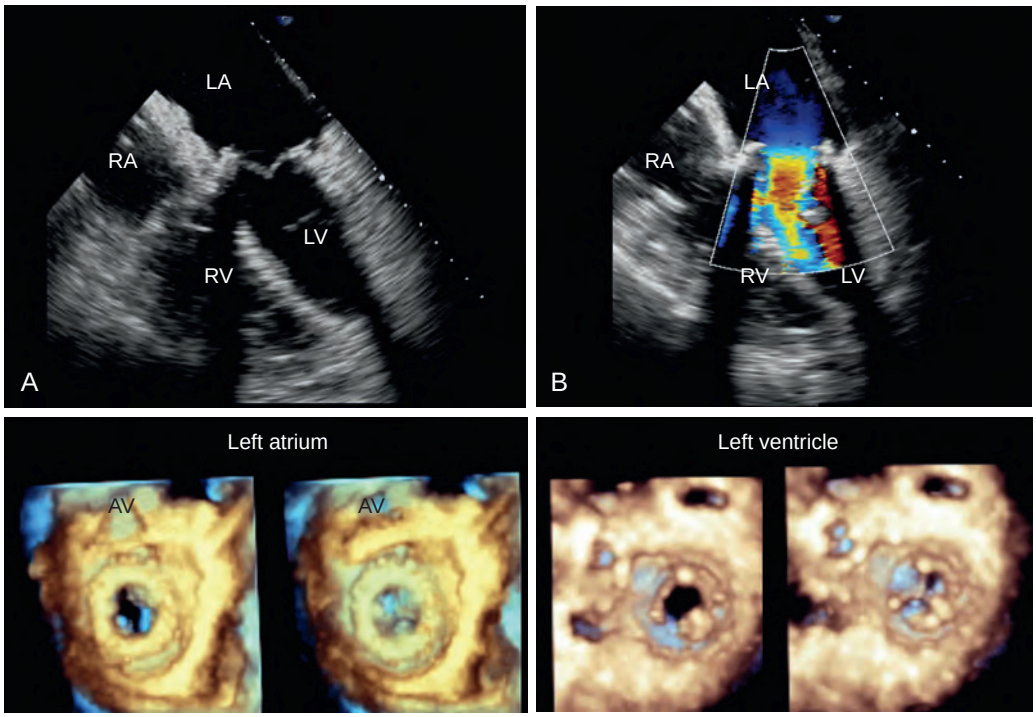

Fig. 15.35 Normal functioning bioprosthetic mitral valve: three-dimensional (3D) imaging. (A) and (B) Normal two-dimensional and Doppler findings of a bioprosthetic valve. Lower images show 3D views of the valve from the LA during diastole and systole from the left atrial (left two images) and left ventricular (right two images) perspectives. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

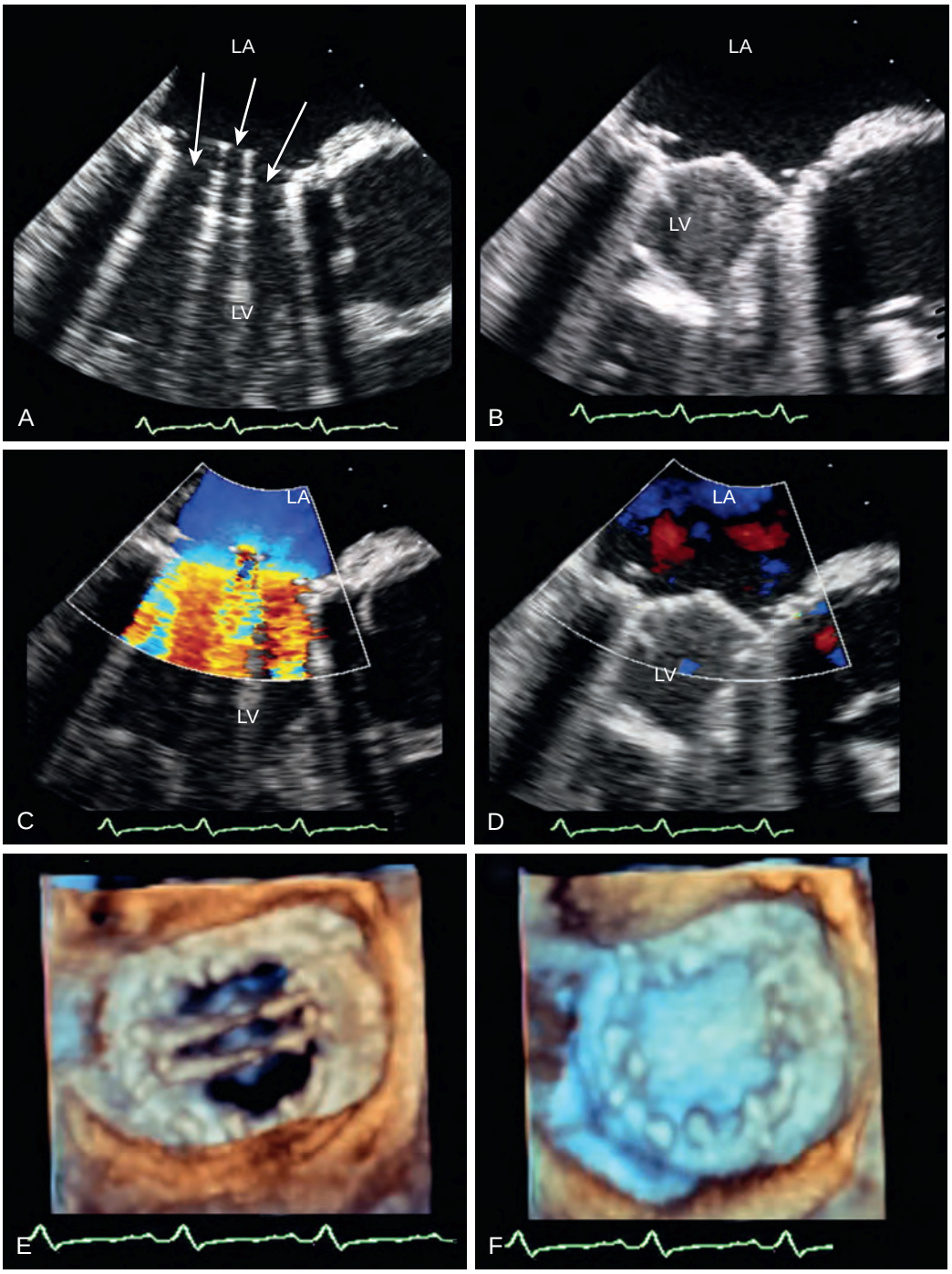

Fig. 15.36 Normal mechanical mitral valve. Multiple images of the bileaflet mechanical valve during diastole (A, C, and E) and systole (B, D, and F) using two-dimensional imaging *(top)*, color Doppler imaging *(middle)*, and three-dimensional imaging *(lower)*, the latter from left atrial perspectives. The *arrows* in (A) point to the three orifices during diastole. *LA*, Left atrium; *LV*, left ventricle.

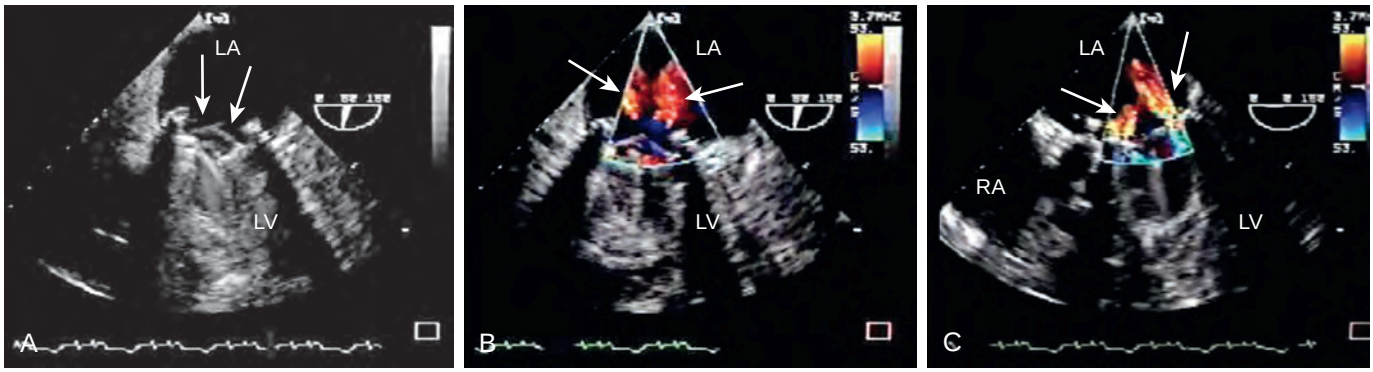

Fig. 15.37 Normal mechanical mitral valve. Images obtained during ventricular systole. (A) and (B) are perpendicular to the valve leaflets, and, while two regurgitant jets *(arrows)* appear in color Doppler imaging, the origin and direction of the two jets are in question. (C) was obtained parallel to the leaflets and more clearly demonstrate the two inwardly directed washing jets *(arrows)* associated with this valve. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

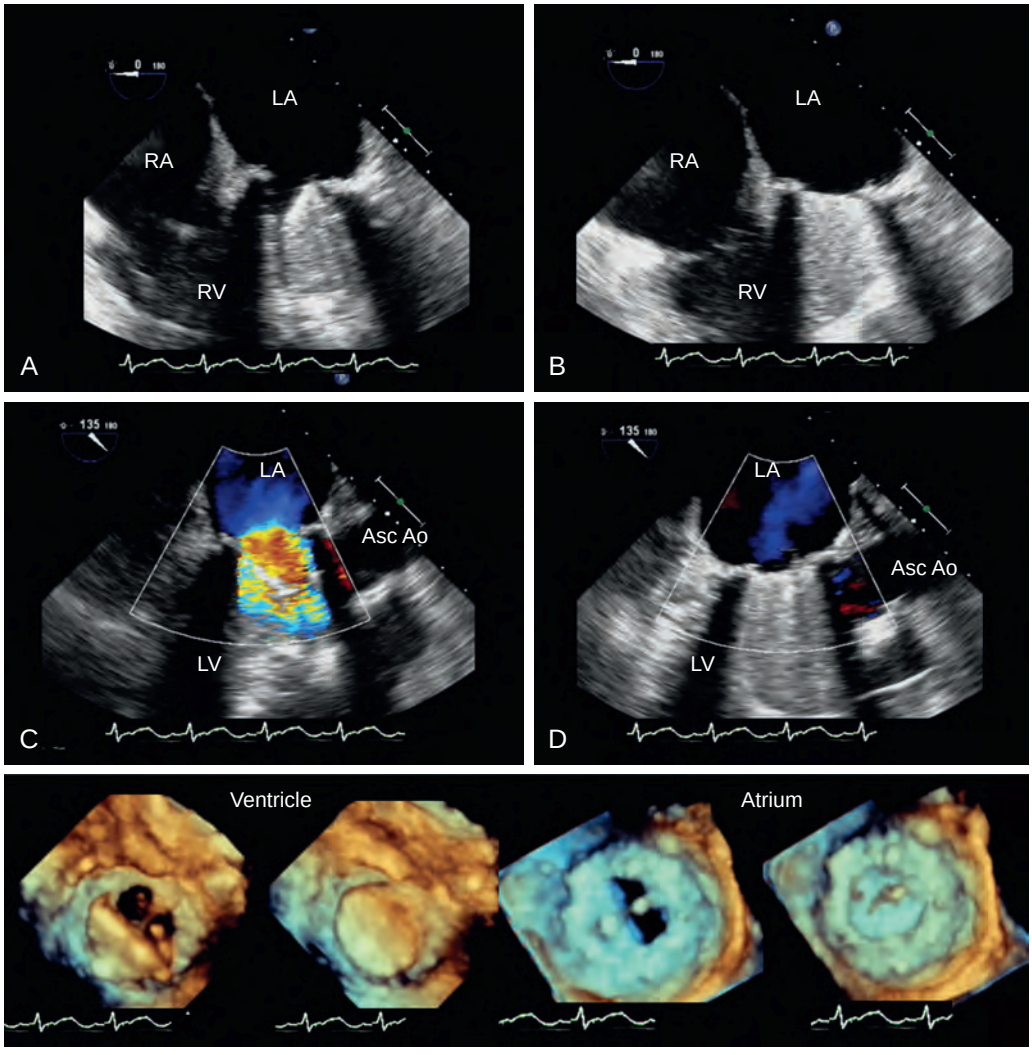

Fig. 15.38 Normal single-leaflet mechanical valve. Two-dimensional views during (A and C) diastole and (B and D) systole. Lower panel shows three-dimensional images from the left ventricular and atrial perspectives during diastole and systole. *Asc Ao,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

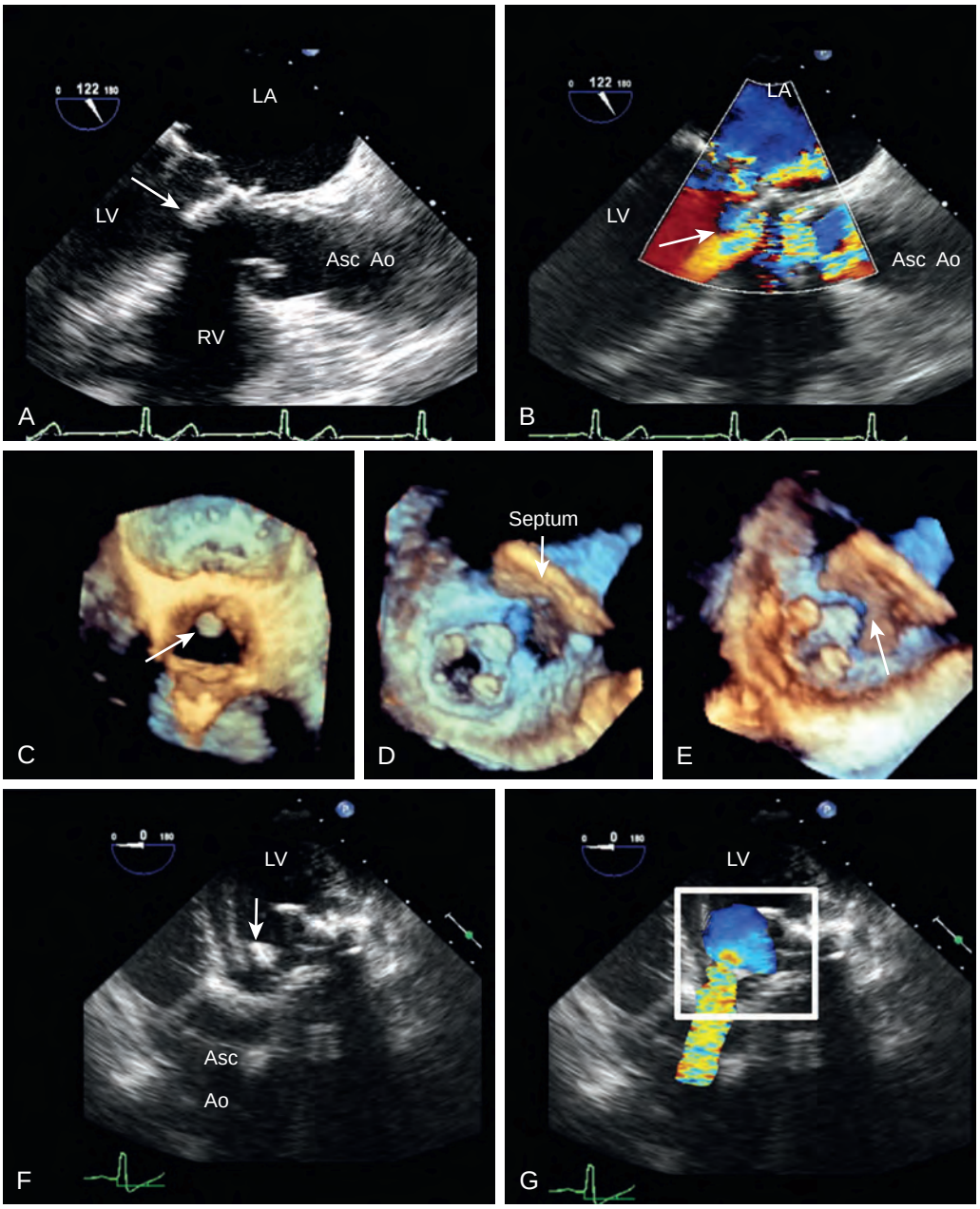

Fig. 15.39 Imaging of the bioprosthetic mitral valve in relation to the left ventricular outflow tract (LVOT). (A) Two-dimensional (2D) and (B) color Doppler midesophageal long-axis views, showing the strut *(arrow)* of a bioprosthetic valve in close proximity to the LVOT. The color Doppler image shows turbulence *(black arrow)* in the LVOT. Three-dimensional views from (C) the aortic side of the aortic valve and from the LV perspective in (D) diastole and (E) systole. (D) shows a circular appearing echo density *(arrow)* on the LVOT side This is the tip of the more anterior prosthetic strut in close proximity to the LVOT. (E) During systole the anterior strut *(arrow)* of the bioprosthetic valve is in close proximity to the ventricular septum. (F) 2D and (G) color Doppler images from transgastric windows, showing both proximity of the strut *(arrow)* to the LVOT and color Doppler turbulence at this site. (G) The narrowing is significant enough to create flow convergence *(white box)*. *Asc Ao,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

TABLE 15.4 Mitral Regurgitation: Degrees of Severity

	Mild	*Moderate*	*Severe*
Angiographic grade	1+	2+	3–4+
Color Doppler jet area (cm^2)	<4 or <25% of LA area		>7 or >50% of LA area
Vena contracta width (cm)	<0.3	0.3–0.69	>0.7
Regurgitant orifice area (cm^2)[a]	<0.20	0.20–0.49	≥0.50
Regurgitant volume (mL)[a]	<30	30–60	>60
Regurgitant fraction (%)[a]	<30	30–50	>50
Pulmonary venous flow	Systolic dominance	Systolic blunting	Systolic flow reversal
Secondary findings	LAE, LVE, LVSD, PHTN		

[a]Measured with proximal isovelocity surface area.
LA, Left atrium; *LAE,* left atrial enlargement; *LVE,* left ventricular enlargement; *LVSD,* left ventricular systolic dysfunction; *PHTN,* pulmonary hypertension.

prostheses, a small central regurgitant jet (see Figs. 15.35 through 15.38). A single tilting disk or bileaflet mechanical valve consists of two or three forward jets and signature regurgitant jets (see Fig. 15.38). Single-leaflet valves typically display one or two small regurgitant jets (one significantly larger than the other) directed centrally. Bileaflet mechanical valves have two centrally directed equal regurgitant jets.

Flow across the repaired valve depends on the repair technique. Typically a large singular jet directed toward the posterior and lateral walls toward the apex followed by flow toward the LVOT along the anterior and septal wall is seen, which is not dissimilar to the normal native valve (see Fig. 15.23). Any other flow pattern may increase risk of systolic anterior motion. Alternatively, a central Alfieri repair, which results in a figure-of-eight orifice, provides two forward moving jets of flow (see Fig. 15.28).

Mitral Regurgitation

Normal native mild MR occurs in up to 75% of patients without clear dysfunction or abnormality of the mitral apparatus, and is, therefore, considered normal. Abnormal MR occurs as a result of dysfunction of one or more of the components of the mitral apparatus (Table 15.4). MR can be grouped into three types: those with normal leaflet mobility (type 1) (see Fig. 14.87; Video 14.64), those with excessive leaflet mobility (type 2) (see Fig. 14.83; Video 14.61), or those with restrictive leaflet mobility (type 3).[31,32,37,38] The latter group can be further distinguished based on the timing of the cardiac cycle to which leaflet mobility is impaired. Type 3a involves restriction during the diastolic phase or during both systole and diastole as seen in rheumatic disease with involvement of leaflet and chordae (see Fig. 14.84; Video 14.62). Type 3b involves restriction during the systolic phase of the cardiac cycle as seen in patients with functional MR as a result of either myocardial ischemia/infarction or cardiomyopathy during which tethering and/or remodeling has occurred (see Fig. 14.85; Video 14.63). The types of MR are summarized in Fig. 14.86.

Type 1 MR can be seen in the presence of annular dilation or leaflet perforation. In the former, the annulus is more likely to dilate along the posterior and lateral annular areas as these are mostly muscle and membranous tissues. As the annulus dilates (>4.0 cm), it becomes more circular and flatter. The regurgitant jet may be centrally or eccentrically directed. The greater the amount of annular dysfunction, the less likely that valve repair will provide long-term freedom from valve replacement. Leaflet perforation occurs in the presence of endocarditis and is more commonly found on the anterior leaflet.

For type 2 MR the leaflets are described by their systolic excursion relative to the annular plane. Prolapse is defined as a greater than 2-mm excursion above the annular plane with the leaflet tip pointing down. Flail is similarly described except with the leaflet tip pointing above the annular plane. Excessive leaflet mobility is often accompanied by redundant or torn chordae or, in the case of myocardial infarction (MI) or trauma, a torn or ruptured papillary muscle. Regurgitation caused by degenerative or myxomatous mitral disease is associated with either prolapse or flail of an isolated scallop or multiple scallops involving one or both leaflets. Excess mobility may result from redundant or torn chordae to leaflet thickening (ie, myxomatous changes). Most commonly, the posterior leaflet is involved with the middle scallop (P_2) being involved in more than 40% to 50% of the cases.[35,48–50] Next in incidence, the middle scallop of the anterior leaflet (A_2) is involved. Both leaflets are involved in up to 40% of cases. The delineation of the scallops is very important in determining the appropriate surgical procedure and whether or not a repair is feasible.

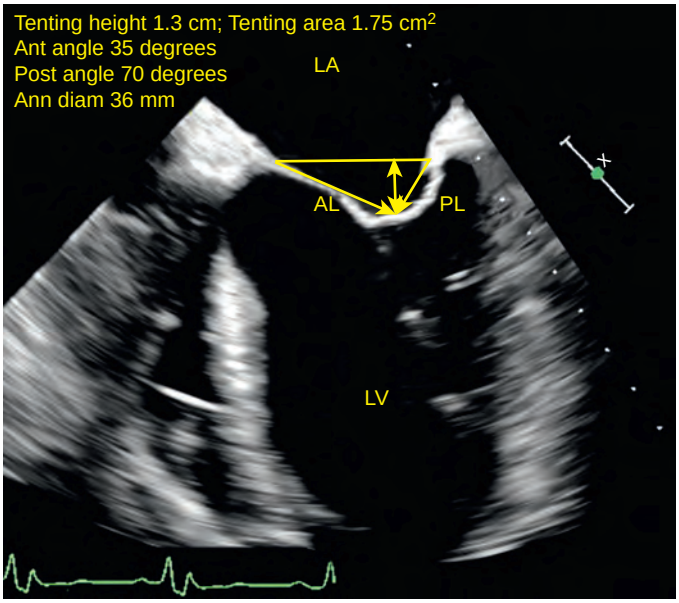

Fig. 15.40 Annular and leaflet measurements. A single view from the midesophageal window allows measurements of tethering and leaflet mobility and excursion. In this case, significant tethering has occurred as denoted by a tethering height greater than 1.0 cm, a tethering area greater than 1.6 cm^2, and a posterior angle greater than 60 degrees. *AL,* Anterior leaflet; *LA,* left atrium; *LV,* left ventricle; *PL,* posterior leaflet.

Type 3b MR seen with dilated cardiomyopathy (DCM) and/or ischemic cardiomyopathy may include normal appearing leaflets; however, reduced systolic return is decreased as a result of tethering.[49] Quantitative assessments help to determine the presence and extent of tethering and may predict outcome after valve repair. These assessments include tethering height and area, and angles of coaptation (Figs. 15.40 and 15.41). Tethering heights greater than 1 cm or tethering areas greater than 1.6 cm^2 are suggestive of severe long-standing changes and greater left ventricular dysfunction, dilation, and remodeling (Figs. 15.41 and 15.42).[51–53] With greater chronicity, leaflet compliance and mobility decline as well. Restriction of abnormal leaflets (type 3a) is seen with rheumatic valves or after radiation therapy. In these cases, the valve leaflets may be thickened, shortened, and/or the subvalvular apparatus (chord and papillary muscle) may be affected. Although rheumatic leaflets (anterior leaflet) may appear like a hockey stick during diastole, this finding is not necessary for the diagnosis to be considered.

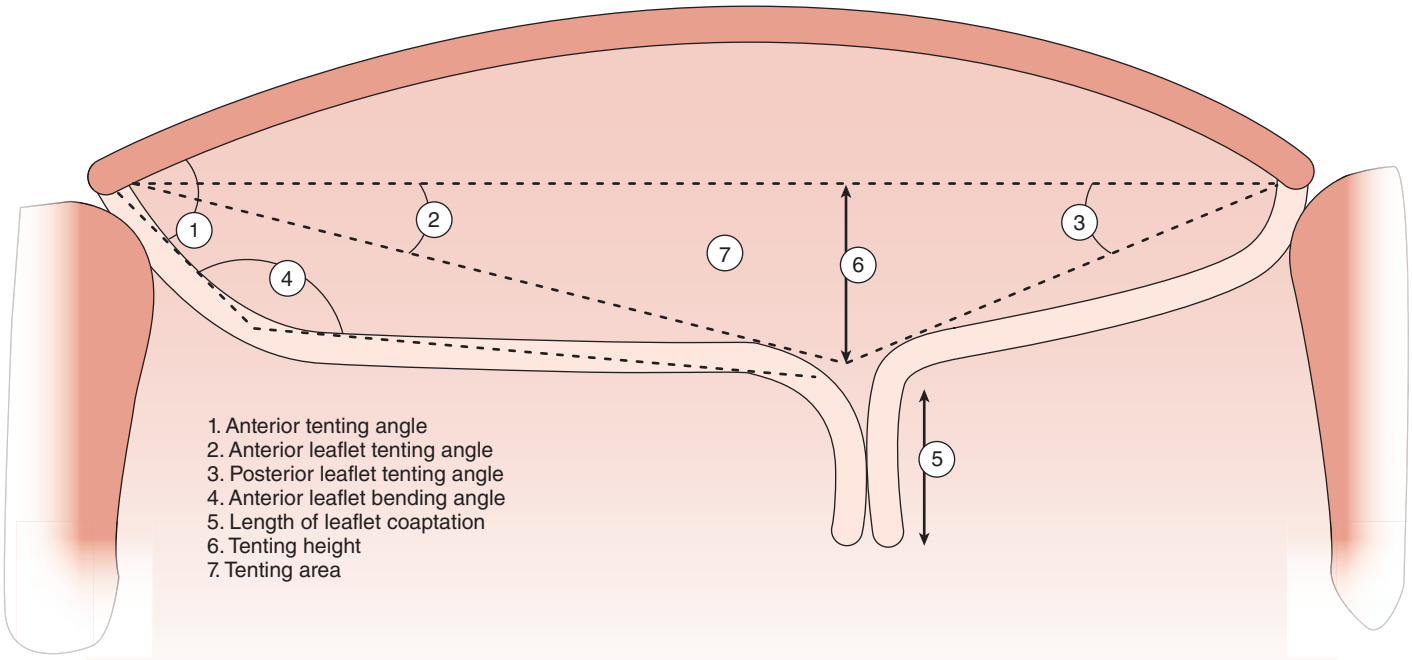

Fig. 15.41 Functional mitral regurgitation (MR): annular measurements. Although these seven annular measurements can be useful for all types of MR, they are particularly relevant for patients with functional MR as they highlight the extent of change in the mitral apparatus resulting from ventricular remodeling. Increases in all measures except for number 5 (coaptation zone/length) result from ventricular remodeling described by apical and lateral displacement of the papillary muscles and resultant tethering of the mitral leaflets. When this happens, the coaptation length or zone decreases in the valve becomes incompetent.

Prosthetic valves are associated with a normal signature of expected regurgitant jets and should be differentiated from abnormal flows (see Figs. 15.17, 15.32, and 15.36 to 15.38).[21,28] Normal or nonproblematic regurgitant jets are less than 3 mm in width and do not extend far from the valve.[54,55] All paravalvular regurgitant jets are considered abnormal. However, regurgitant jets less than 3 mm in width are not likely to pose a long-term problem, especially in the absence of clear disease (Fig. 15.43). Regurgitant jets greater than 3 mm in width and/or are eccentrically directed away from the middle carry a greater risk of MR progression and/or reintervention (Fig. 15.44).[56] These abnormal flows can result from a number of causes, including leaflet restriction or excess mobility, endocarditis, and/or annular dehiscence (Figs. 15.45 to 15.47).[19]

Repair of the MV generally is applied to regurgitant valves.[37,38] Although the goal is to eliminate regurgitation, mild or less is acceptable, while more than mild increases the risk of MR progression and reoperation (see Fig. 15.47). The location and direction of the regurgitant jet depends on the prerepair dysfunction and the repair technique.[31,32,37,38] Determining the cause of MR after repair is essential to decide whether or not additional repair is feasible or if replacement is warranted.

MR can also be described by its acuity. The importance of this distinction is related to the level of compensation or decompensation and clinical presentation. In the acute setting, LA and LV compliance have not adapted; this can result in elevated chamber pressures, which are transmitted backward to the pulmonary vasculature increasing pulmonary vascular pressures, causing pulmonary edema. Ventricular and atrial dilation may not be present. Chronic MR is accompanied by cardiac changes or compensation to allow maintenance of forward flow. Initial compensation includes hypertrophy and dilation of the left ventricle to compensate for MR. Initially, the left ventricle ejects against a lower total resistance as a result of the backward ejection into the low resistance atrial chamber and pulmonary vascular bed. A normal left ventricular ejection fraction (LVEF) in the presence of severe MR is greater than 60%. With continued or worsening MR, dilation becomes more prominent, followed by contractile dysfunction. This is coincident with clinical decompensation. Ultimately, with continued volume overload and increased chamber pressure and stress, LA dysfunction ensues, pulmonary vascular pressures and resistances increase, and, finally, right-sided heart dysfunction occurs. Arrhythmias reflect these cardiac changes and decompensation.

Two-dimensional quantitative analysis of the native valve helps determine outcome for valve procedures.[31,32,34,35,37,38] For regurgitant valves, echocardiographic imaging helps the practitioner predict feasibility and technique of valve repair. For stenotic valves, the examination helps the practitioner determine whether or not valvuloplasty is a viable option.

Measurements guiding valve repair of the regurgitant valve include annular dimensions, leaflet lengths (anterior leaflet, posterior leaflet), coaptation height (tenting height or area), various angles of coaptation, and relations between the leaflets (coaptation) and the ventricular cavity, or specifically, the ventricular septum (see Figs. 15.40 through 15.42, 15.48).[31,32] Data may help the practitioner predict risk of postrepair complications such as SAM and LVOT obstruction (see Fig. 15.48).[57] In general, the more complicated the repair is, the greater is the likelihood of complications and need for reoperation.

Predictors of repair failure differ for patients with functional or ischemic MR versus those with degenerative disease.[31,32,51–53] For all patient types, severe annular dilation (>50 mm) represents prolonged MV dysfunction (ie, end-stage disease) and a greater risk of repair failure. For functional or ischemic MR, the greater the amount of prerepair tethering or remodeling, the more likely that MR will recur (Figs. 15.41, 15.42, and 15.49). These include a tenting height greater than 1.0 cm or area greater than 1.6 cm^2, a posterolateral coaptation angle greater than 45 degrees, inferior and lateral wall motion abnormalities, dilated LV (LV end-diastolic diameter > 65 mm; LV

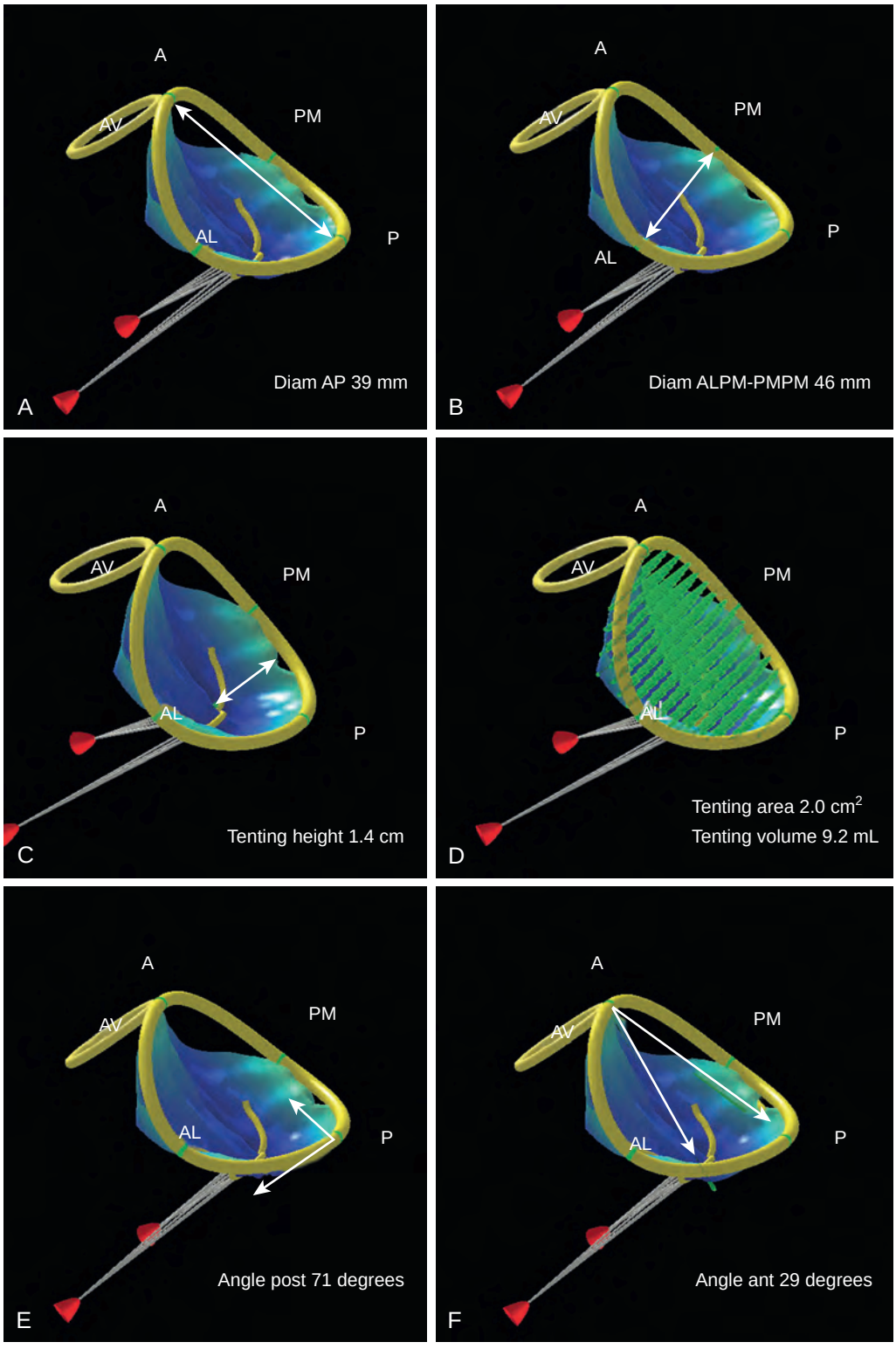

Fig. 15.42 Functional mitral regurgitation QLAB measurements. From the volumetric three-dimensional data set, a number of measurements can be performed using QLAB (Philips Healthcare, Andover, Mass). Measurements that appear in this figure include (A) anteroposterior annular diameter, (B) anterolateral-posteromedial annular diameter, (C) tenting height, (D) tenting area/volume, (E) posterior annular angle, and (F) anterior annular angle. The case depicted in the figure is consistent with severe tethering suggested by the larger annular diameters, a tenting height greater than 1.0 cm, a tenting area greater than 1.6 cm^2, and a posterior annular angle greater than 45 degrees. *A,* Anterior; *AL,* anterolateral; *AV,* aortic valve; *P,* posterior; *PM,* posteromedial.

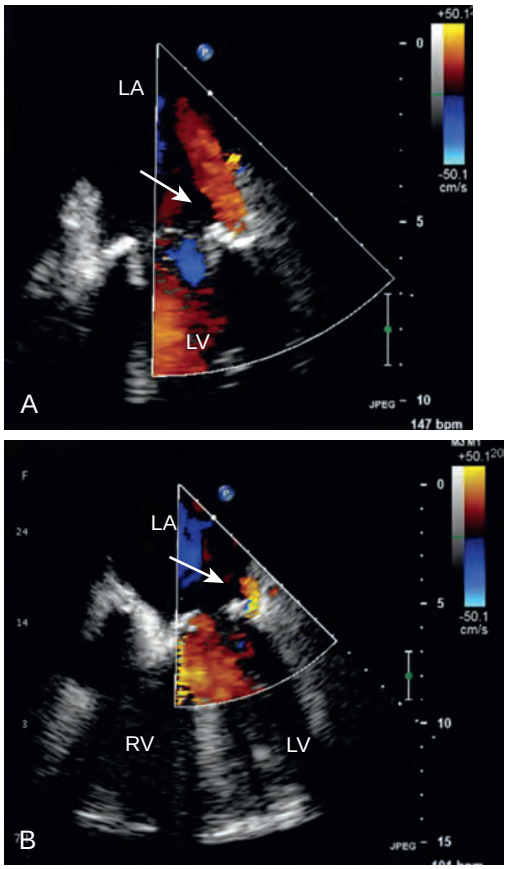

Fig. 15.43 Paravalvular leak after mitral valve replacement. Bioprosthetic valve with a decreasing paravalvular leak (left to right). (A) Jet appears to be nonturbulent or of lower velocity. (B) Color Doppler jet area shows a significant reduction in the regurgitant after administration of protamine. *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

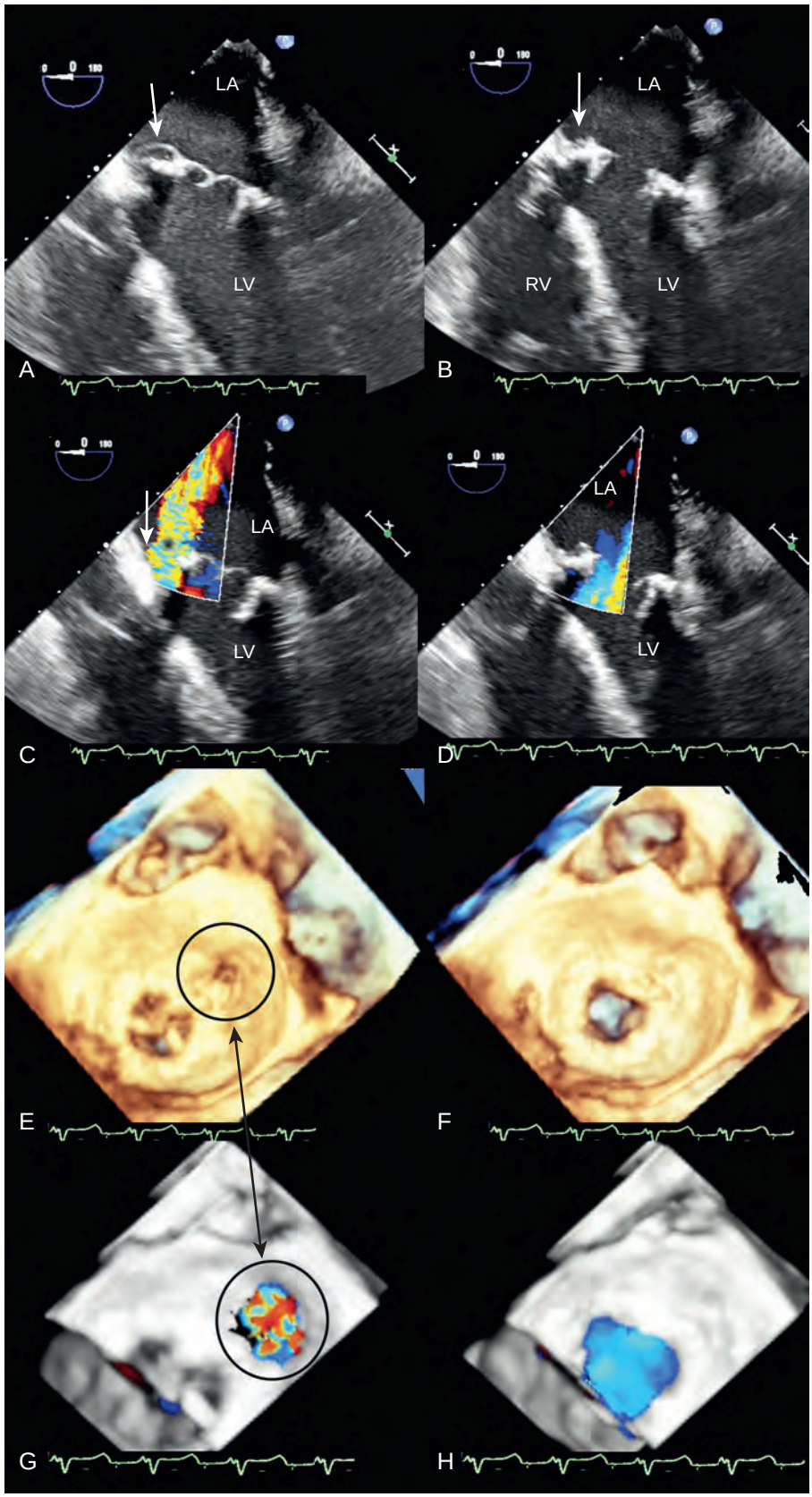

Fig. 15.44 Large paravalvular leak following mitral valve replacement. Large paravalvular regurgitant jet along the septal border *(white and black arrows)* of the prosthetic valve during (A and C) systole and (B and D) diastole. (C) Large jet of regurgitation. (E–H) The defect *(black circle)* is further qualified (and subsequently quantified) in three-dimensional imaging during systole (E) and (F). (F) and (H), obtained during diastole, show that the defect is not seen. *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

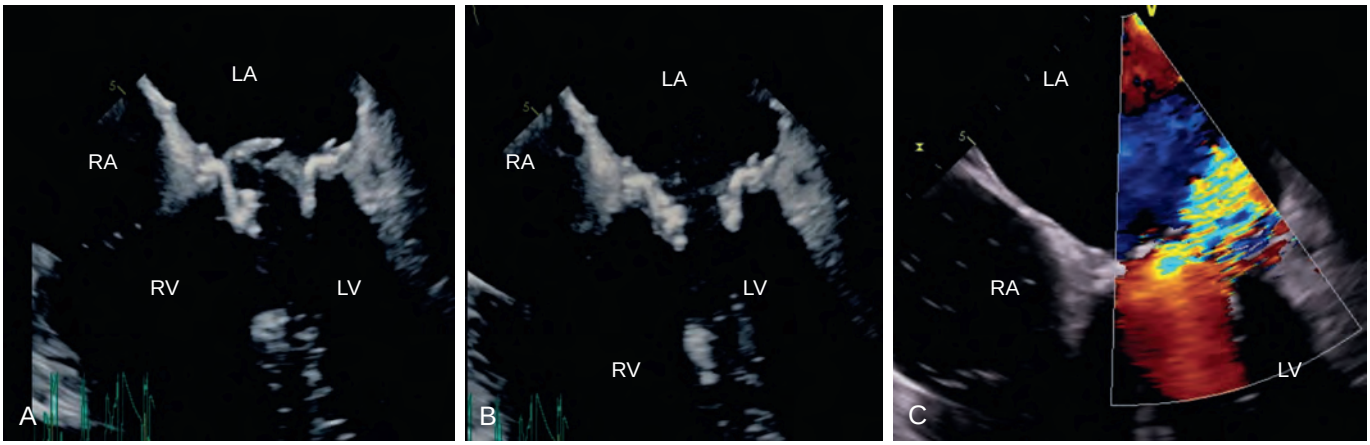

Fig. 15.45 Prosthetic valve endocarditis. (A) and (B) A mobile (above the annular plane) echodensity seen during systole on this bioprosthetic valve is associated with (C) significant mitral regurgitation. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

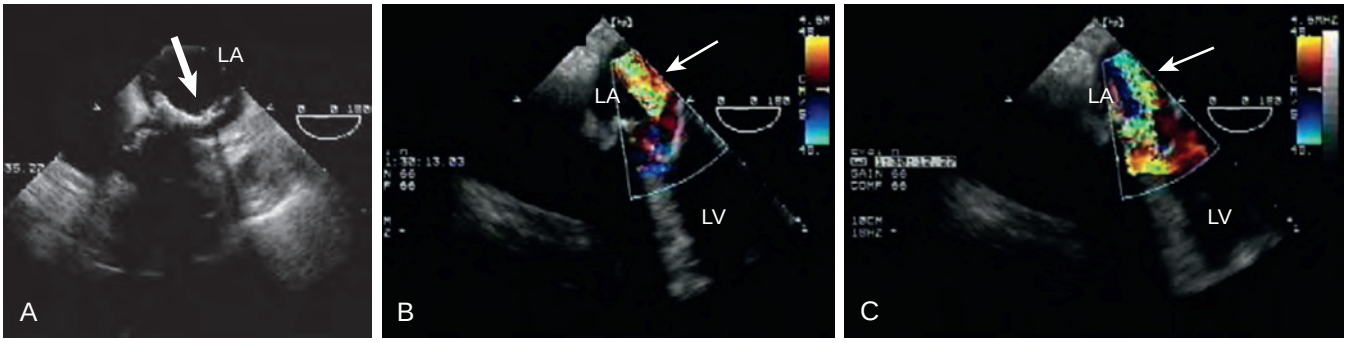

Fig. 15.46 Bioprosthetic valve dehiscence along the posterior mitral annulus. (A) Echo clear *(arrow)* space below the annular prosthesis with advancement of the transesophageal echocardiography probe. (B) and (C) Associated severe mitral regurgitation *(white arrow). LA,* Left atrium; *LV,* left ventricle.

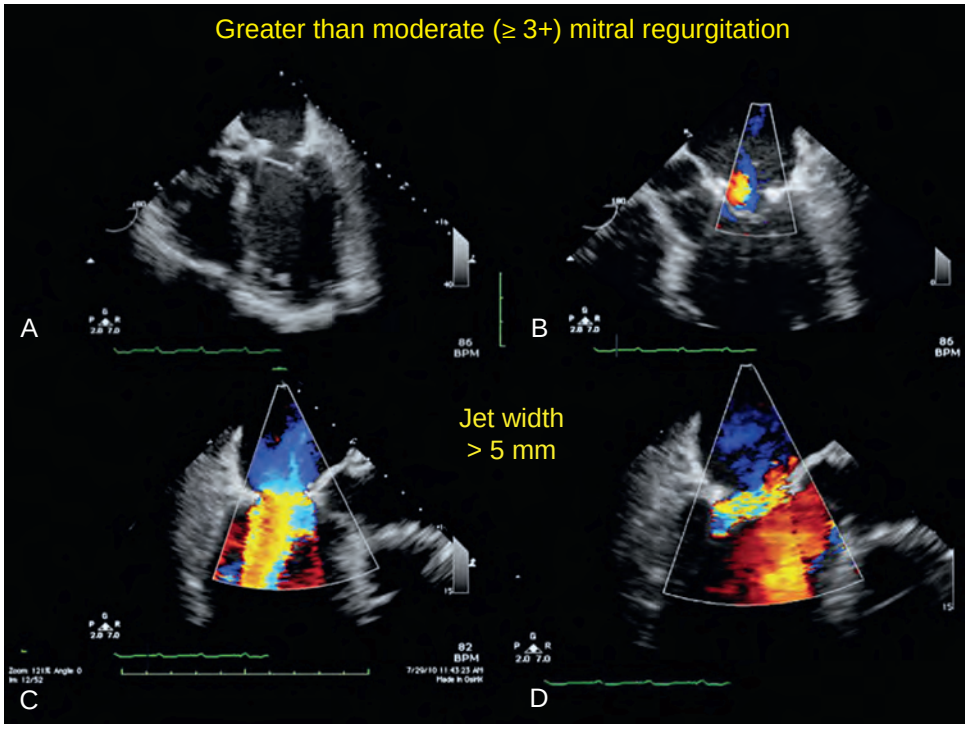

Fig. 15.47 Mitral regurgitation (MR) assessment immediately after mitral valve repair. (A) and (B) Leaflets are seen in the closed position with (B) a mild amount of MR. (C) and (D) Follow-up shows (D) a significant amount of MR defined by a jet width greater than 5 mm.

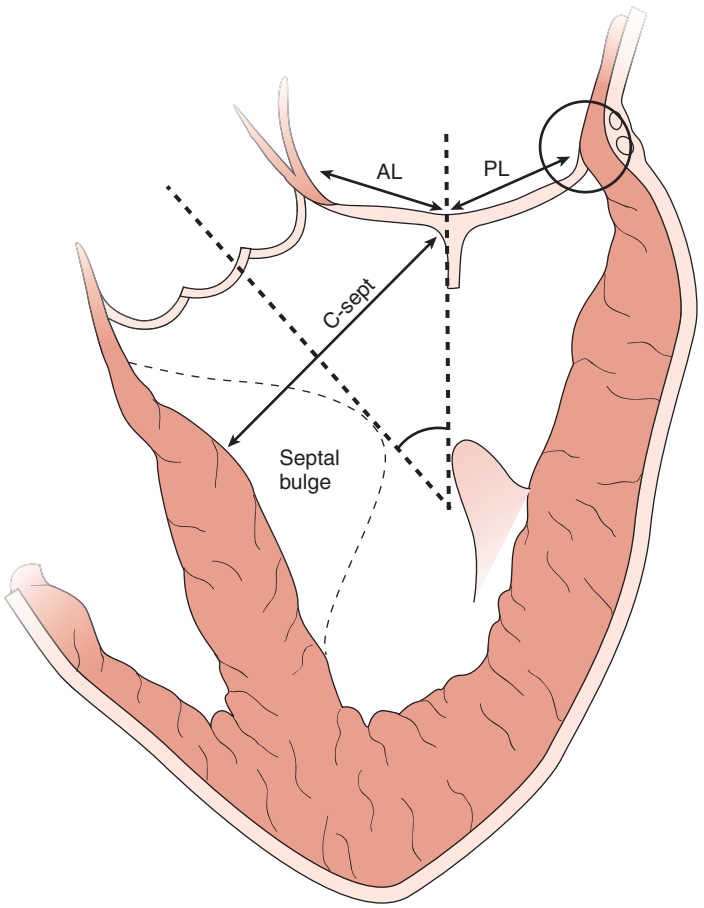

Fig. 15.48 Predictors of systolic anterior motion (SAM). While a greater number of predictors of SAM have been described, the schematic highlights six that seem to be more commonly encountered and/or described. The ratio and heights of the anterior *(AL)* and posterior *(PL)* leaflets contribute toward a greater amount of slack leaflet portions in closer proximity to the left ventricular outflow tract (LVOT). This may also be seen as a shorter distance between the coaptation point and the ventricular septum *(C-sept)*. The presence of a prominent septal bulge also narrows the LVOT, which brings the mitral leaflets closer and/or creates higher jet velocity, which might create a venturi effect to drag the slack mitral leaflet portions toward the LVOT. The mitral inflow: aortic outflow angle *(right dotted lines)* might describe an anatomy that either brings the leaflet tips closer to the LVOT or one that affects transmitral and subsequent intraventricular flow directions such that systolic outflow may (with a greater angle) interact more with mitral leaflets. Finally, impairment of the normal annular systolic motion may decrease the LVOT area and the distance between the mitral leaflets and the LVOT. The *black circle* around the posterior and lateral annulus represents calcification of the annulus and a reduction in posterior and lateral annular contraction.

end-systolic diameter > 50 mm, or LV end-systolic volume > 75 mL/m^2), and/or a sphericity index higher than 0.7. These values reflect significant ventricular dysfunction and remodeling. Although repair of papillary muscle rupture has been reported, such cases are generally managed with valve replacement.

Predictors of repair failure for degenerative valve dysfunction include multiple scallops involved, anterior leaflet disease, bileaflet disease, and endocarditis with leaflet destruction.[48,58–61] These valves may require complicated repair techniques. In addition, severe MR in the presence of a normal annular diameter, or short anterior (<26 mm) and posterior (<10 mm) leaflets, is more difficult to repair. These latter predictors reflect the importance of identifying something repairable and of having adequate leaflet heights after repair.

Other predictors of difficult repair or adverse outcome include rheumatic origin; MR caused by radiation therapy; severe calcification of either the valve, the annulus, and/or the subvalvular apparatus; and atrialization of the coaptation points (Figs. 15.50 and 15.51).[48,59,60] The former three reflect either the absence of repairable tissues or the lack of adequate leaflet lengths. The latter reflects an end-stage degenerative state.

Assessing Severity of Regurgitant Flow

The procedure for assessing severity of regurgitant flow in the native versus the prosthetic MV is similar (see Table 15.4). The examination includes diagnosis, detection, and severity assessment of MR. This is supported by assessing the secondary effects on other cardiac functions, which support the severity assessment as well as determining treatment options. The finding of contractile dysfunction (LVEF < 60%), LA and LV chamber dilation (LV end-systolic volume > 70 mL/m^2), elevation in left-sided heart pressures, the presence of pulmonary hypertension, and right-sided heart dysfunction suggest either more severe, chronic, and/or decompensated MR. The examination demands a comprehensive review using all modes of imaging.

Identifying and determining leaflet anatomy and mobility, as well as assessing the annulus and subvalvular tissues are important to identifying the cause of MR and the possibility of repairing the valve if surgery is necessary. The stability of the valve determines the integrity of the surrounding tissues. A valve that appears to rock or one that has an echocardiographic lucent space within the annulus or between the prosthesis and surrounding tissues might suggest infection or abscess or, in the case of a prosthesis, dehiscence. Dehiscence for an MV prosthesis is more likely to happen along the posterior and lateral annular areas where surgical exposure is less and concern exists over interfering with left circumflex coronary arterial flow (see Fig. 15.46).

The Doppler examination identifies regurgitant jets and determines whether or not they are within normal range for a native valve or are considered the normal (or abnormal) signature for a prosthetic valve. Eccentric jets are considered abnormal.

Severity assessment reflects the regurgitant orifice area (ROA) either indirectly or directly. Measurement of the regurgitant jet area is neither specific nor sensitive enough to diagnose the severity of MR.[62–64] Jet areas of eccentric jets underestimate severity, whereas those of central jets may overestimate severity. However, a regurgitant jet that has a large area (>7 cm^2 vs <4 cm^2), extends toward the posterior wall (>50%), or covers more than 50% of the

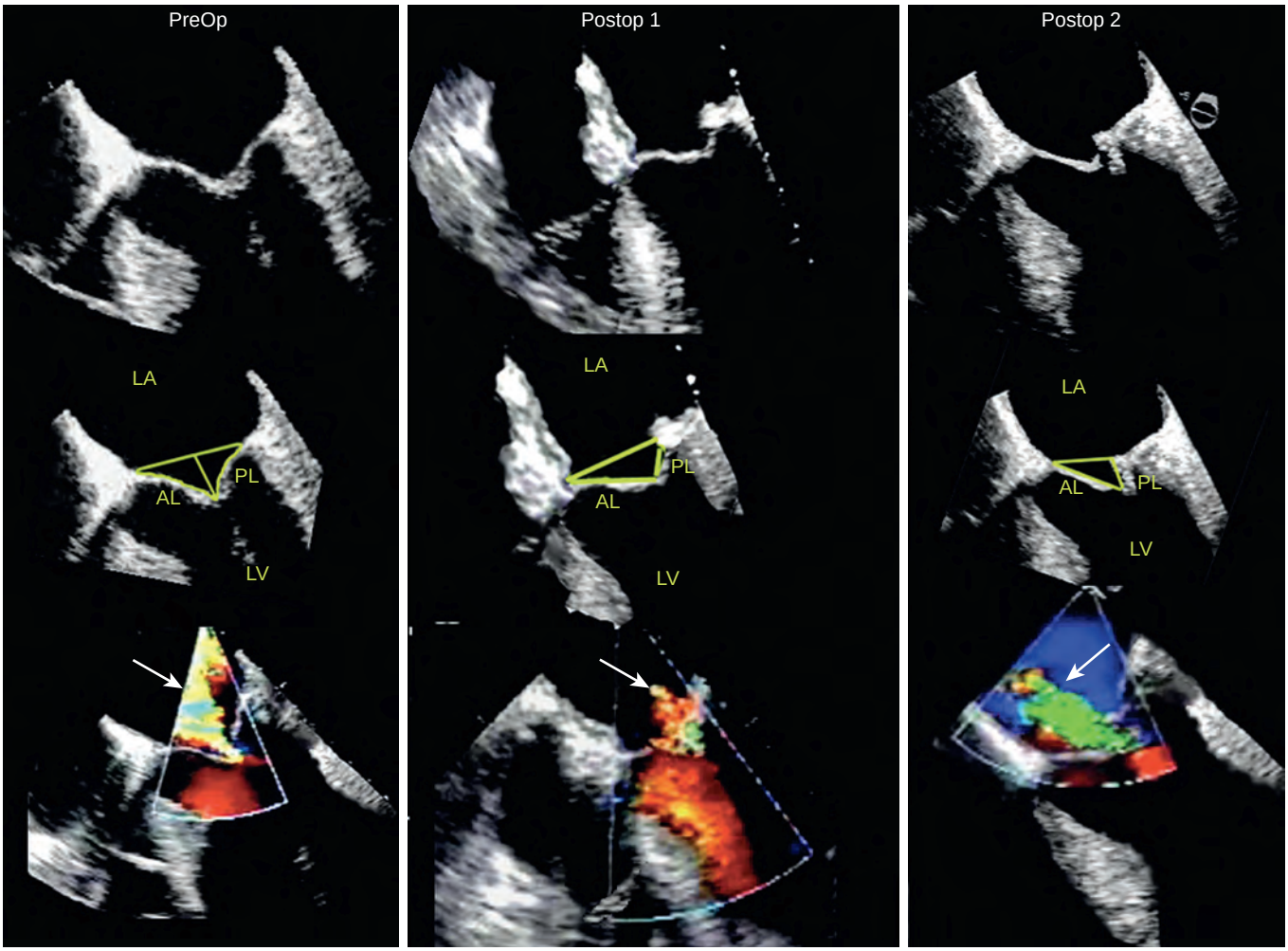

Fig. 15.49 Repair of type IIIb mitral regurgitation (MR): annuloplasty. This case shows the preoperative, intraoperative, and second preoperative (reoperation) echocardiographic images. The preoperative images show the tethered leaflets *(yellow triangle, middle figure)* and MR *(white arrow, lower image)*. After placement of an annuloplasty ring, the intraoperative images show a reduced tethering *(yellow triangle, middle image)* with reduced MR *(white arrow)*. As is reported with repair of type IIIb MR, the images to the right show the recurrence of MR *(white arrow)*. *AL,* Anterior leaflet; *LA,* left atrium; *LV,* left ventricle; *PL,* posterior leaflet.

LA area is considered moderate or greater.[18–21] This determination is further supported by the presence of flow convergence. Moderate or worse MR is suspected by a pulsed-wave Doppler profile of the pulmonary vein showing blunting or reversal of the systolic component (see Fig. 14.91). A dense and more complete continuous-wave Doppler flow profile of the regurgitant jet also supports moderate or greater MR.

More accurate quantitative assessments include measurements of the VC width, ROA, regurgitant volume, and regurgitant fraction, which are detailed in Chapter 14. The latter three are obtained using the flow convergence or PISA method, or the continuity equation. Although the VC measurement is relatively easy to obtain, its accuracy is mainly useful for either mild or severe MR, but it varies for moderate degrees of MR.[20,30,65–70] It is also important to measure the width of the VC perpendicular to the regurgitant jet and not in parallel (see Fig. 15.18). For the native valve, the VC should be obtained either in the ME four- or five-chamber or long-axis windows, but not in the ME two-chamber or bicommissural image, as the latter has been shown to overestimate MR severity. A VC width less than 3 mm or greater than 6 mm is consistent with mild and severe MR, respectively.[20,30,65–70]

The flow convergence method or PISA can be used qualitatively or quantitatively.[17,18,20,21,30,71–73] The absence of a large flow convergence (especially with Nyquist limit of <20 cm/s) supports the determination of moderate or less MR. The corollary is that the presence of a PISA at a Nyquist limit greater than 40 cm/s is consistent with moderate/severe to severe MR.

Flow convergence data that report an ROA greater than 40 mm^2 and/or a regurgitant volume greater than 60 mL is consistent with severe MR. The accuracy of the flow convergence method assumes that the PISA shells are hemispherical and the ROA is circular. Three-dimensional imaging shows that these assumptions are not always correct. A benefit of 3D color imaging is to allow direct measure of the ROA by planimetry.

Simplifications of the flow convergence method can be made if the Nyquist limit is set at 40 cm/s and it is assumed that the peak MR velocity is 5 m/s. If this were the case, then the ROA is equal to:

$$r^2/2$$

If the Nyquist limit were 30 cm/s, then this would be $r^2/3.8$.

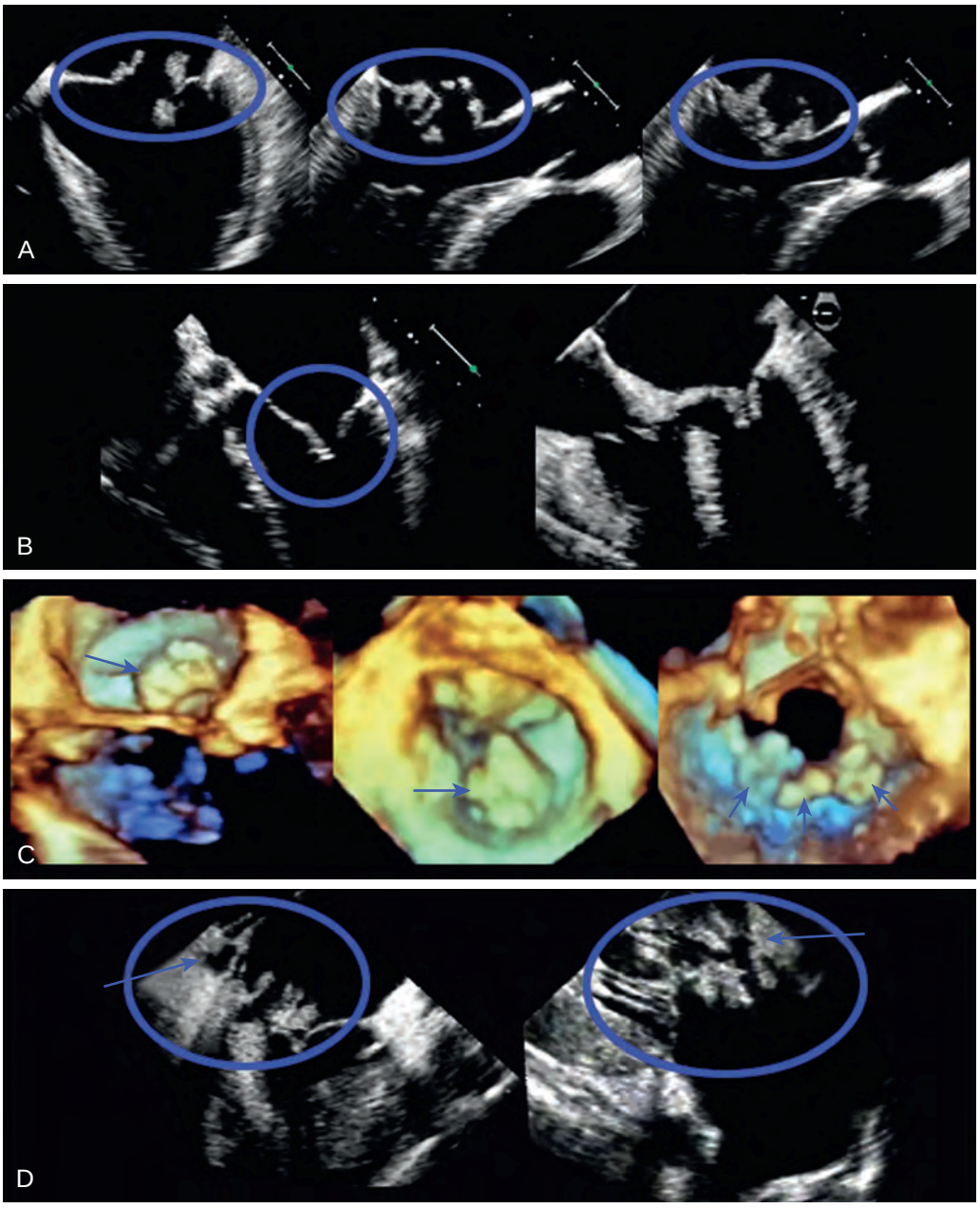

Fig. 15.50 Difficult repair or no repair examples. Although not an absolute contradiction to repair, extensive infection increases the difficulty of repair and reduces the long-term durability. (A) Extensive leaflet destruction. (B) Rheumatic velvets; typically replaced as the risk of mitral regurgitation recurrence and reoperation is high (approximately 25%). (C) Three-dimensional images highlighting extensive annular calcification *(blue arrows)*. (D) Significant leaflet destruction and annular involvement.

A dimensionless index is the ratio of the time-velocity integral (TVI) of the MV to that across the AV.

$$(TVI_{MV}/TVI_{AV})$$

In the absence of significant AI, a value less than 1 or greater than 1.4 is consistent with mild and severe MR, respectively.

Data have been published to predict outcome for varying degrees of MR. Severe MR is defined by an effective ROA greater than 40 mm^2 and is associated with early and late mortality.[64,74] Whereas severe MR requires therapy, it is less clear how milder degrees of MR should be managed. In the same study, an effective ROA (20 to 39 mm^2) was also associated with a worse outcome, but it was not significant until after 2 to 3 years.[64,74]

Surgical Indications

In the presence of severe MR, surgery should be performed if the patient is symptomatic[24–26] (Fig. 15.52). For an asymptomatic patient with severe MR, surgery should be considered if a durable repair is likely; if LV decompensation is present (LVEF <60%; LV end-systolic diameter >45 mm), especially if it is refractory to medical therapy; if it is thought that the MR is causing or contributing to arrhythmias and/or pulmonary hypertension (systolic pulmonary artery [PA] pressure >50 mm Hg); or if LA enlargement is significant and coupled with arrhythmias and pulmonary hypertension. For patients with moderate MR, surgery should be considered if that patient is presenting for other cardiac surgical procedures, especially if it is thought that repair is feasible and to provide long-term reduction in MR (>5–10 years).

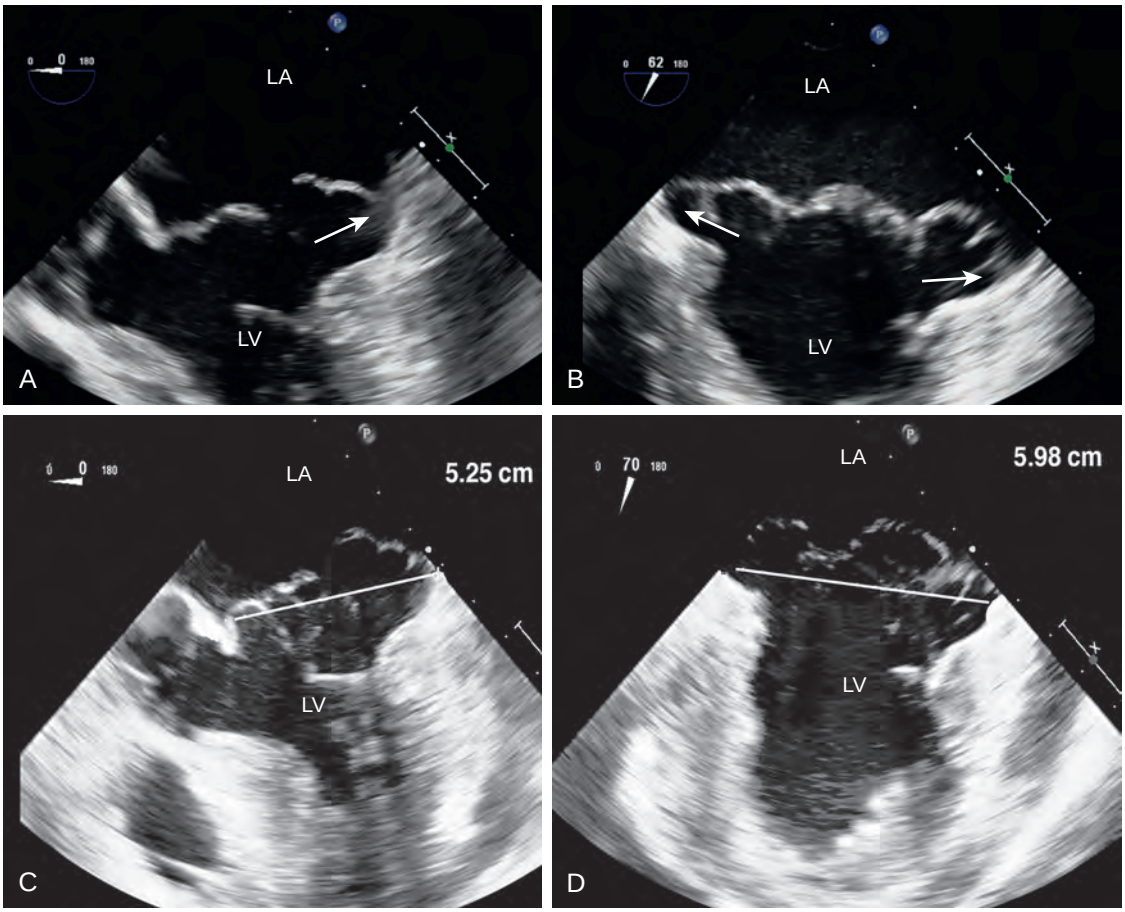

Fig. 15.51 End-stage or atrialization of mitral leaflets. (A–D) Significant bileaflet prolapse, as well as the appearance of atrialization of the leaflet insertion *(arrows)*. When coupled with severe annular enlargement (5.25 cm), these findings are consistent with severe, perhaps late-stage myxomatous disease, with all findings suggesting a difficult repair with questionable durability. *LA,* Left atrium; *LV,* left ventricle.

TABLE 15.5 Mitral Stenosis: Degrees of Severity

	Mild	*Moderate*	*Severe*
Peak jet velocity (m/s)	<1.8	1.8–2.2	≥2.2
Peak pressure gradient (mm Hg)	<12	12–18	>18
Mean pressure gradient (mm Hg)	<6	6–10	>10
MV area (cm^2) pressure half time continuity equation planimetry	>2.0	1–2	<1.0
MV area index (cm^2/m^2)	<1.25		
Velocity ratio (TVI_{MV}/TVI_{LVOT})	<2.2	2.2–2.5	>2.5
Pressure half time (ms)	<130	130–200	>200
Secondary findings	LAE, PHTN, RAE, RVE, TR		

LVOT, Left ventricular outflow tract; *MV,* mitral valve; *PHTN,* pulmonary hypertension; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement; *RVSD,* right ventricular systolic dysfunction; *TVI,* time-velocity integral.

Mitral Stenosis

The normal mitral valve area (MVA) ranges from 4 to 6 cm^2 and transmitral flow velocities are less than 1 m/s (Table 15.5). The more common causes of mitral stenosis (MS) include rheumatic stenosis, calcific MS, and, less commonly, congenital MS. The echocardiographic examination incorporates 2D and Doppler technologies to diagnose and assess for the presence and severity of MS (see Figs. 15.53 and 15.54).

Rheumatic valvitis is the most common cause of MS, causing commissural fusion, chordal shortening/fusion, and leaflet thickening, all complicated by calcification of the structures. The leaflet tips are fused, resulting in stenosis. While stenosis is more common in the rheumatic MV, the leaflet and chordal abnormalities can also be associated with significant MR (Carpentier type IIIa). In addition, involvement of other cardiac tissues and valves are not uncommon, including AV insufficiency and tricuspid regurgitation (TR).

Calcific mitral degeneration mainly affects the mitral annulus and uncommonly results in stenosis unless associated with leaflet thickening.

Patients with MS may be asymptomatic or may have varying degrees of LV and RV failure and arrhythmias depending on the severity and chronicity of the disease. With greater decompensation, forward flow across the valve and into the left ventricle declines, while LA pressure, size, and function continue to deteriorate. With time, the pulmonary vascular pressures and gradient rise, causing pulmonary edema and significant right-sided heart afterload, dilation, and dysfunction. Patients experience fatigue, hemoptysis, and right-sided heart failure. TR may result either from primary rheumatic involvement and/or secondary to pulmonary hypertension. Atrial fibrillation and stroke may be initial presenting signs, the latter, in part, resulting from development of atrial appendage thrombus. The chest x-ray and electrocardiogram show a dilated left atrium and right side of the heart and pulmonary edema.

Part of the assessment of the stenotic MV is geared toward determining the need for and timing of invasive procedures, the latter being either valvuloplasty or valve replacement. The Wilkins score was proposed and now used to predict outcome after valvuloplasty. The score includes assessment of leaflet thickening, mobility, and calcification, as well as subvalvular thickening, each of which is scored from 1

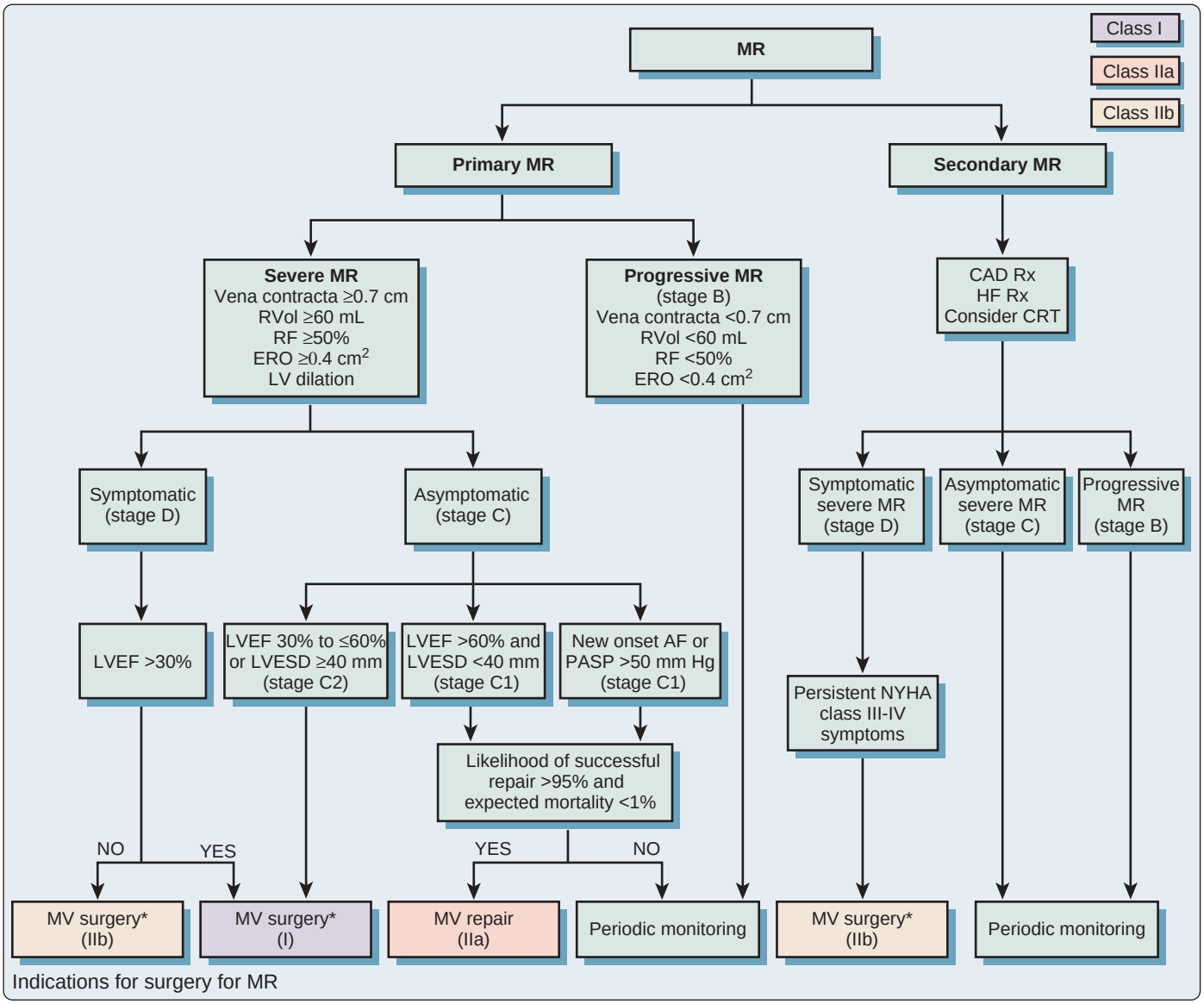

Fig. 15.52 Decision algorithm for mitral regurgitation *(MR)*: timing of intervention. The decision algorithm was taken as a consensus by an expert panel and based on outcome data and interpretation. Decisions are classified as class I, class IIa, class IIb, the former being supported by sufficient evidence such that intervention should be performed, while the latter two are supported by evidence that suggests that the benefits of intervention outweigh the risks and that intervention is reasonable based on multiple (IIa) or isolated trials or nonrandomized data (IIb). Intervention for MR is based on a number of considerations including cause, presentation (symptoms), changes in cardiopulmonary function, and timing (ie, whether other cardiac surgical procedures are scheduled and how repairable the valve is). *AF,* Atrial fibrillation; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *ERO,* effective regurgitant orifice; *HF,* heart failure; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic diameter; *MV,* mitral valve; *NYHA,* New York Heart Association; *PASP,* pulmonary artery systolic pressure; *RF,* regurgitant fraction; *RVol,* regurgitant volume; *Rx,* prescription. *(Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57–e185.)*

to 14.[64] A score less than 8 suggests that the valve is more amenable to valvuloplasty as compared to a score higher than 8. Variations on this score as well as others have been proposed, including one based on 3D imaging. Findings consistently show that the greater the amount of thickening, calcification, and immobility, the worse the outcome after valvuloplasty.[75]

Assessing forward flow across the prosthetic MV, to determine both whether or not it is normal and how severe the dysfunction is, is similar to that for the native valve. As described earlier, different prostheses have different forward flow projections. Bioprosthetic valves have a single forward flow, whereas mechanical valves will have two (single-leaflet) or three (bileaflet) forward projecting jets. The more information known about specific prosthesis, the easier it is to distinguish between normal and abnormal. Prosthetic valve stenosis is caused by leaflet restriction, thickening, and/or thrombosis (Figs. 15.55 and 15.56).

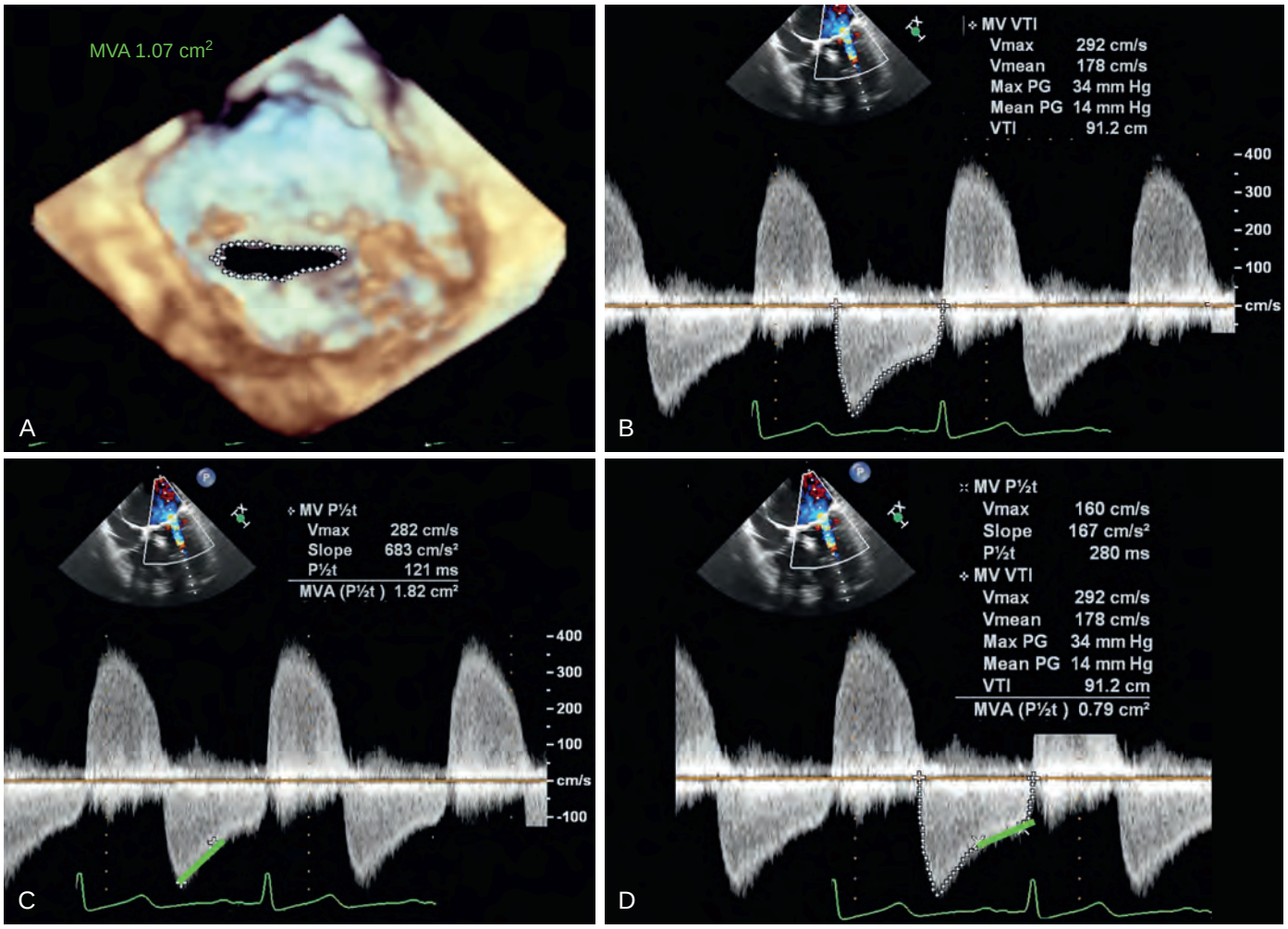

Fig. 15.53 Assessment of mitral stenosis (MS). Pressure gradients, pressure half time (PHT), and planimetry are the common assessments of the mitral valve area *(MVA)*. (A) Planimetry is performed from the three-dimensional view of the mitral opening seen from the left ventricular perspective. (B–D) Doppler profiles of flow across the valve. It is evident that mitral regurgitation coexists as seen by the upward systolic flow. Based on the downward deflection, MS also exists. The peak and mean gradients are 34 and 14 mm Hg, respectively. The forward flow profile across the valve, however, is biphasic. If the PHT were based on the initial phase, the MVA would be 1.82 cm^2. However, if based on the latter phase, the MVA would be 0.79 cm^2. Since the initial phase may represent initial opening velocity resistances, flow, and cardiac output, it is recommended to use the latter phase because it represents a more stable flow state and a better reflection of the effective orifice area.

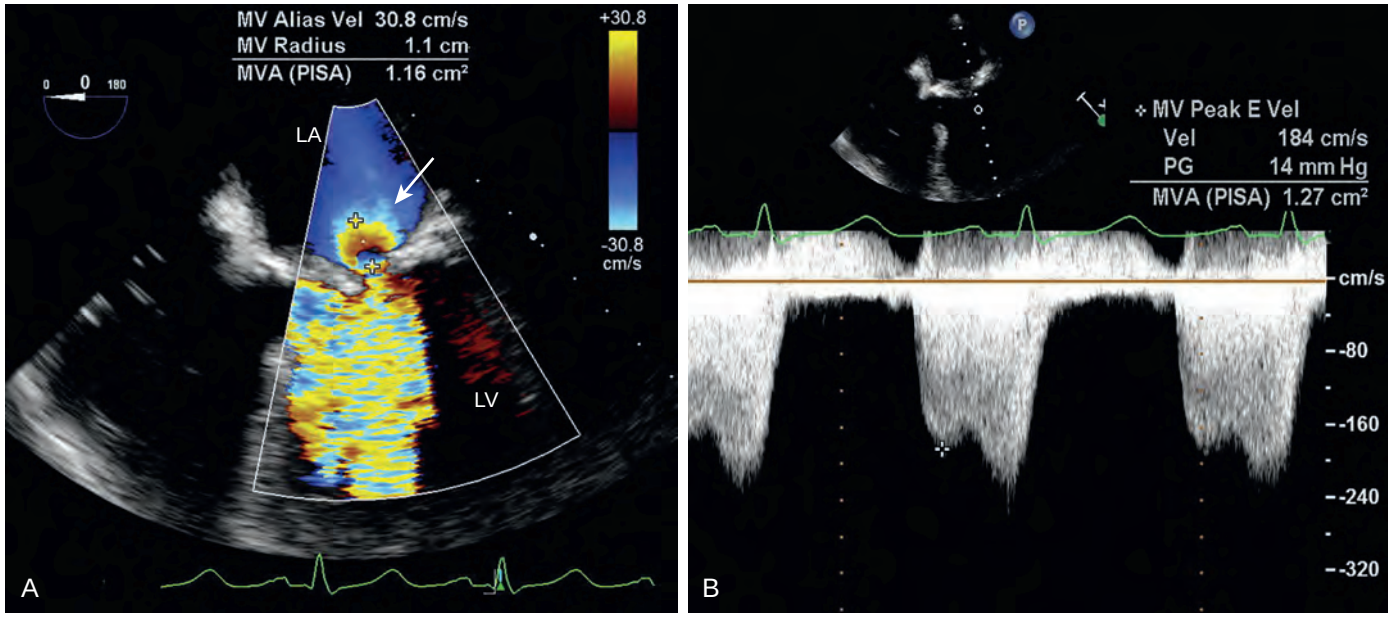

Fig. 15.54 Mitral valve area *(MVA)* with proximal isovelocity surface area (PISA). Flow through a relatively narrow orifice results in flow convergence. This can be the case for stenotic valves as well as regurgitant valves. The PISA method to assess effective orifice area can be employed to calculate the stenotic orifice in the same way it is used to calculate a regurgitant orifice. As shown in this figure the MVA is approximately 1.30 cm^2. *LA,* Left atrium; *LV,* left ventricle.

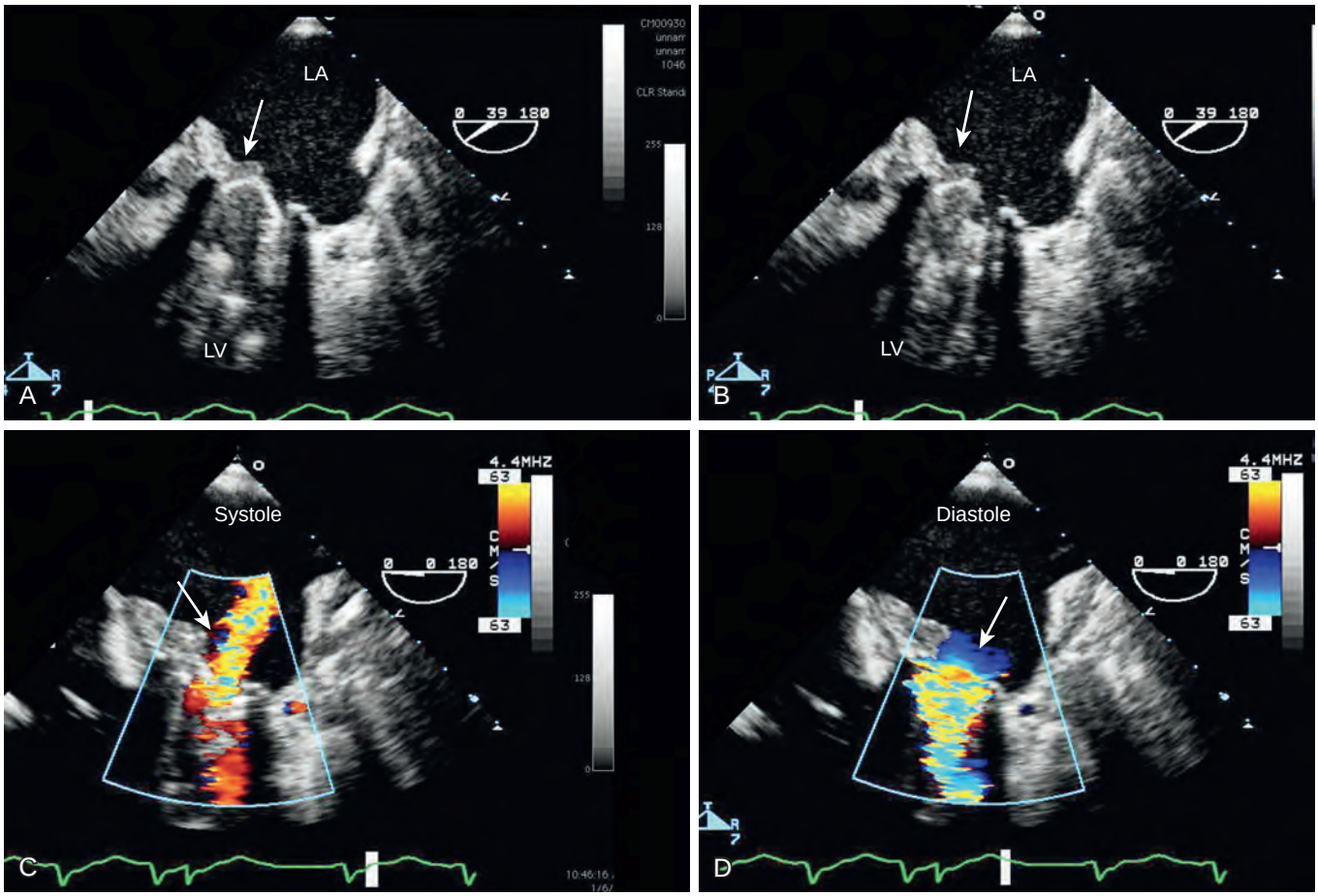

Fig. 15.55 After mechanical mitral valve replacement: stuck leaflet: thrombus. Stuck mechanical leaflet of a bileaflet mechanical valve in the mitral position, probably the result of thrombus. The medial leaflet *(white arrow)* appears to be stuck in a closed position and surrounded by thickening consistent with thrombus formation shown in (A) systole and (B) diastole. Color Doppler imaging demonstrates turbulent flow consistent with both (C) regurgitation and (D) stenosis. *LA,* Left atrium; *LV,* left ventricle.

Quantitative assessment of forward flow across the native versus prosthetic MV is similar and includes all modes of imaging. Measures include both indirect and direct assessment of the MVA (see Table 15.5). The most direct measurement is planimetry made possible by 2D or, more recently, 3D imaging.[76] Identifying and tracing the inner edges of the maximum opening of the MV allow measurement of the anatomic orifice area. This is more feasible and, perhaps, more accurate using 3D imaging.[77] Whereas 2D planimetry is performed from TG MV short-axis imaging, 3D planimetry is obtained using volumetric data from ME windows.

American Society of Echocardiography level 1 recommendations for assessing MV patency include peak transvalvular jet velocity, pressure gradients, and MVA calculated from the pressure half time (PHT) or measured by planimetry (see Figs. 15.53 and 15.54).[17,21,63,77] Peak pressure gradients are obtained from the peak transvalvular jet velocity using the simplified Bernoulli equation. Mean pressure gradients are obtained by tracing the TVI across the MV to integrate the various jet velocities allowing calculation of the mean gradient. Since the peak gradient is influenced more by the net compliance between the left atrium and left ventricle, the mean gradient is of greater importance.[78,79]

The Doppler data are affected by changes in cardiac loading conditions, as well as coexisting valvular or congenital lesions. In addition to changes in cardiac output (CO), these include changes in net compliances, coexistence of MR, AV dysfunction, and an atrial septal defect (ASD).[1,3] Variables that increase the LA pressure or reduce LV pressure and/or increase transmitral flow increase jet velocity and gradient measures and may overestimate MS severity.[24] Doppler measures of MS, including the PHT, are affected by these variables.[78,79] Variables that reduce LA pressure or increase LV pressure do the opposite. For example, an ASD with left-to-right flow, moderate or greater AI, or net positive change in the LV-LA compliance cause an overestimation of MVA by shortening the PHT. The calculation of the MVA from the PHT is done by applying an empirically derived value (see Fig. 14.81).

$$\text{MVA} = 220/\text{PHT}$$

The deceleration time (DT) is an extension of the PHT and is the time from the peak velocity to zero velocity across the orifice. Using the DT to calculate MVA requires knowing that PHT is 29% of the DT.

$$\text{PHT} = 0.29 \times \text{DT}$$

$$\text{Since MVA} = 220/\text{PHT},$$

$$\text{MVA} = 220/0.29 \times \text{DT or } 759/\text{DT}$$

The transmitral TVI may be bimodal with a more rapid initial deceleration followed by a slower decline in gradient. It is recommended to measure the PHT from the slower decline as it better reflects the contribution of the MVA.[80]

Degrees of MS follow similar charts for native and prosthetic valves. Significant (more than mild) MS is considered with a peak velocity greater than 1.8 m/s, a mean transvalvular gradient greater than 6 mm Hg, a peak gradient greater than 12 mm Hg, and/or an

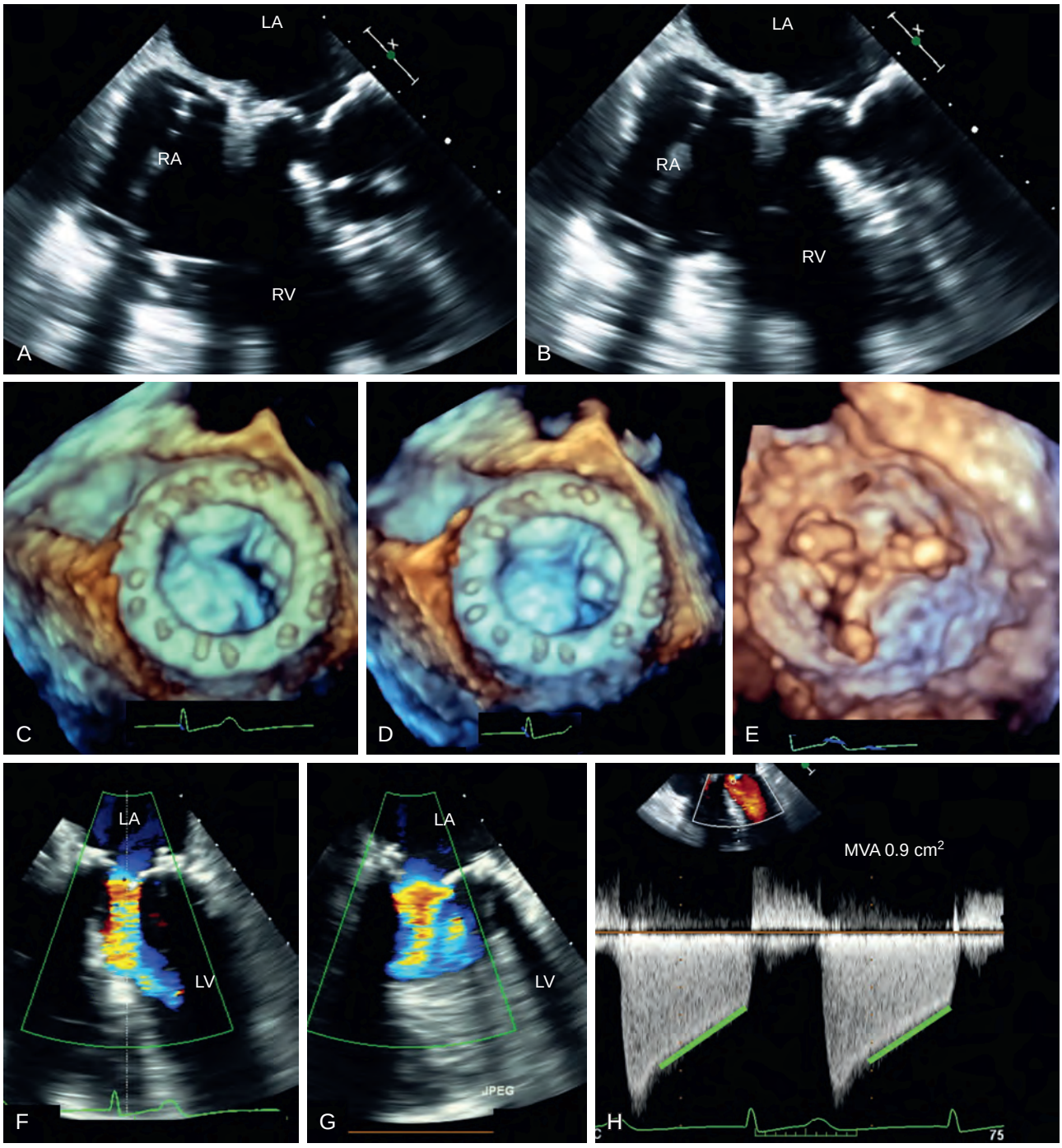

Fig. 15.56 After bioprosthetic mitral valve replacement: degeneration/thickening/restriction. These images demonstrate a complication of bioprosthetic valves in that the leaflets, likely due to inflammation, are thickened, less compliant, and less mobile. This case demonstrates significant mitral stenosis. (A) and (B) Two-dimensional images show echo-bright thickened and immobile prosthetic leaflets during both diastole *(left)* and systole *(right)*. (C) Three-dimensional image showing a very small opening in diastole from the left atrial perspective. (D) Valve in systole. (E) Three-dimensional image showing a very small opening in diastole from ventricular perspective. (F) and (G) Turbulent forward flow during diastole compared with stenosis and confirmed by (H) the continuous-wave Doppler profile. *LA,* Left atrium; *LV,* left ventricle; *MVA,* mitral valve area; *RA,* right atrium; *RV,* right ventricle.

MVA less than 1.5 to 2.0 cm^2. PPM has been described for prosthetic MVs.[81] PPM, for the MV, has been categorized as present or not, based on the indexed valve area (EOAi; $cm^2/BSA\ [m^2]$). PPM for the MV may be considered present when the EOAi is less than 1.25 cm^2/m^2. Different methods are used to assess the EOA, including the PHT, the continuity equation, and the flow convergence method. The continuity equation can be simply described by the following equation (Fig. 15.57)[82]:

$$EOA_{MV} = SV/TVI_{MV}$$

The stroke volume (SV) can be measured from a reference site using Doppler echocardiography (eg, PA or LVOT), a noninvasive

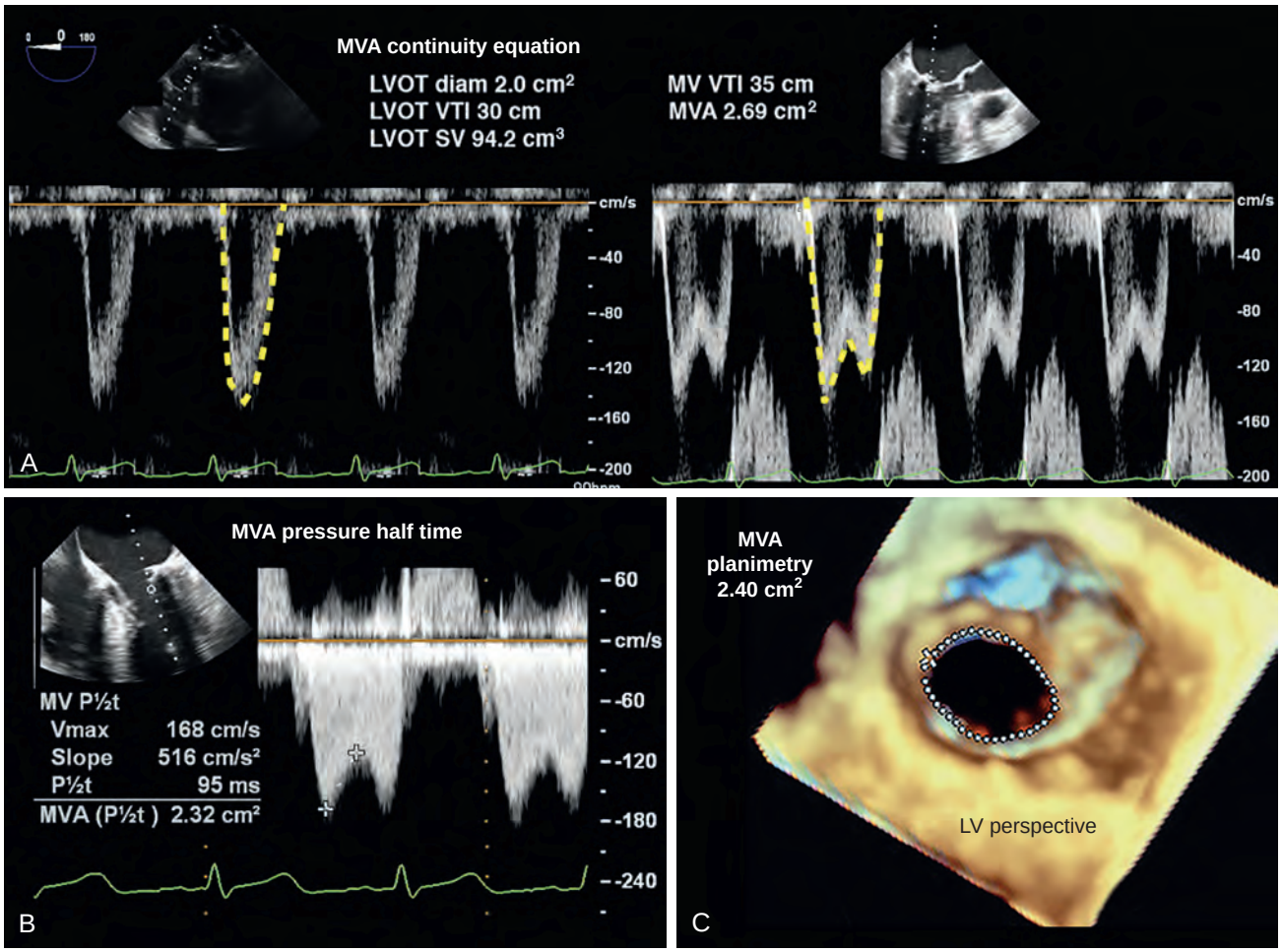

Fig. 15.57 Measures of mitral valve area *(MVA)*. The images show three different methods to measure MVA. (A) employs the continuity equation with the left ventricular outflow tract *(LVOT)* as a reference site. (B) employs the pressure half time equation, while (C) measures MVA by planimetry of the three-dimensional image.

method (eg, arterial waveform), or, in the presence of a PA catheter, can be measured using the thermodilution CO technique. Finally, the PISA, or flow convergence, method has been described in similar principle as above for assessment of MR and is, similarly, based on geometric assumptions that variably exist for native valves; this is perhaps not different for prosthetic valves (see Fig. 15.54).[83]

To avoid geometric assumptions and other variables listed, a Doppler velocity index (DVI) also may be used to assess prosthetic MV patency.[84]

$$TVI_{MV}/TVI_{LVOT}$$

A value < 2.2 is considered normal.

For cases in which imaging is difficult, a modified Gorlin equation can be employed. In this equation, the CO is divided by the square root of the peak transmitral pressure.[74]

Surgical Indications

Surgery, or percutaneous valvuloplasty, is indicated for symptomatic patients with severe MS (MVA< 1.5 cm^2)[24–27] (Fig. 15.58). Percutaneous mitral commissuroplasty (PMC) is preferred to open surgery, and surgery is only performed when PMC is contraindicated, which includes an MVA greater than 1.5cm^2, LA thrombus, significant MR (> 2+), unfavorable anatomy for PMC, and/or when patients are scheduled to undergo other cardiac surgery procedures.

Aortic Valve

Normal Anatomic and Functional Features of the Native Valve

The normal AV is a thin (<2 mm) three-leaflet semilunar valve with a normal EOA ranging from 2–4 cm^2. The three leaflets, or cusps, are equal in size and symmetric and labeled as left, right, and noncoronary cusps, depending on their association with a coronary artery.[17,20,21,85–87] The three leaflets cover an area that is 40% greater than the area of the open orifice, indicating significant overlap. The coapting length (ie, overlap between leaflets) is generally greater than 6 mm. The three leaflets coapt centrally along a thickened nodular area (Nodules of Arantius) above the annular plane (ie, no prolapse).

The AV is a part of the LVOT that extends from the subvalvular to supravalvular area, being defined as the region between the anterior mitral leaflet and the septum immediately below and extending to the sinotubular junction (STJ) within which the AV is attached (Fig. 15.59). The supravalvular tissues include the sinuses of Valsalva, and the STJ, which then extends into the ascending aorta. There are three sinuses of Valsalva: left, right, and non. Each is defined by the presence of the respective coronary ostia (right and left) or its absence (non). The sinuses appear as out-pouches and serve an important role, one of which is to provide a reservoir of blood during diastole to optimize coronary artery filling and flow.

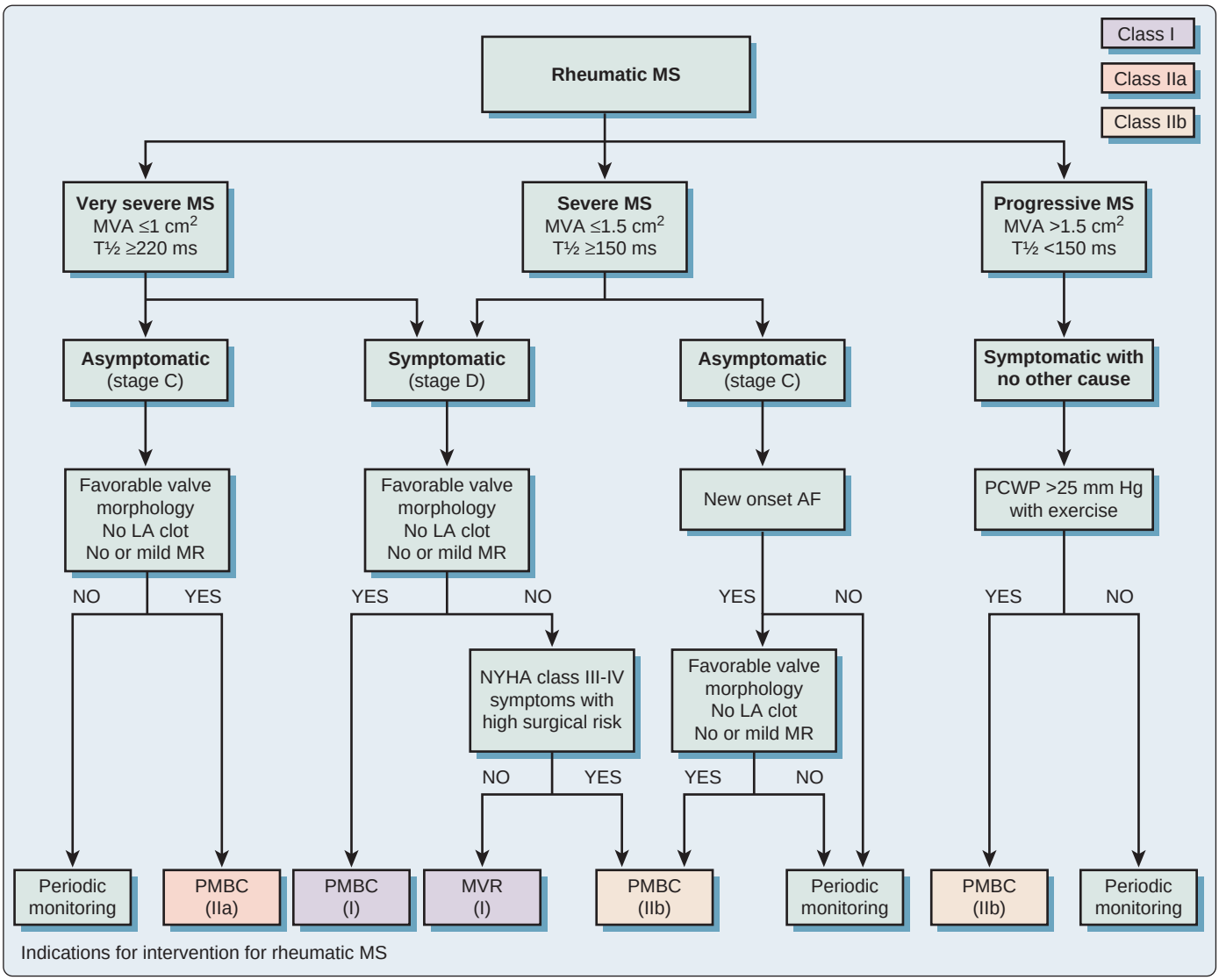

Fig. 15.58 Decision algorithm for mitral stenosis *(MS)*. The decision algorithm was taken as a consensus by an expert panel and based on outcome data and interpretation. Decisions are classified as class I, class IIa, class IIb, the former being supported by sufficient evidence such that intervention should be performed, while the latter two are supported by evidence that suggests that the benefits of intervention outweigh the risks and that intervention is reasonable based on multiple (IIa) or isolated trials or nonrandomized data (IIb). Treatment for MS usually includes percutaneous intervention. The decision is based on a number of considerations including severity, presentation (symptoms), changes in cardiopulmonary function, and whether valvuloplasty is feasible. *AF,* Atrial fibrillation; *LA,* left atrium; *MR,* mitral regurgitation; *MVR,* mitral valve replacement; *NYHA,* New York Heart Association; *PCWP,* pulmonary capillary wedge pressure; *PMBC,* percutaneous mitral balloon commissurotomy. *(Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57–e185.)*

The leaflets open (ventricular systole) and close (ventricular diastole) in accordance with changes in the pressure gradient between the aorta above and the left ventricle below. Although this is the main driving force guiding leaflet motion, the anatomic position and connection between the AV and surrounding tissues also contribute to the opening and closing of the valve. The interplay between the valve leaflets and surrounding tissues/muscle reduce resistance and tension on the leaflets to facilitate both opening and closing. Prior to ventricular ejection, the ascending aorta begins to enlarge and accounts for the initial leaflet separation. Prior to diastole, blood begins to pool in the coronary sinuses creating vortical forces and pressure, which initiate leaflet closure.

Prosthetic or Repaired Aortic Valve

Prior to the evaluation of the prosthetic or repaired AV, it is important to know the details of the surgical procedure, including what kind of valve was placed or how the valve was repaired.[21,22,87] Previous knowledge of normal echocardiographic findings for specific valves and/or successfully repaired valves help delineate what is normal and what is not for the surgical procedures. Knowledge of whether a mechanical or bioprosthetic valve was placed is important to predict what the echocardiographic appearance will look like. Each type of valve has specific appearances. For mechanical valves, the type and number of leaflets are important, while for bioprosthetic valves whether a stented or stentless valve is important to predict appearance

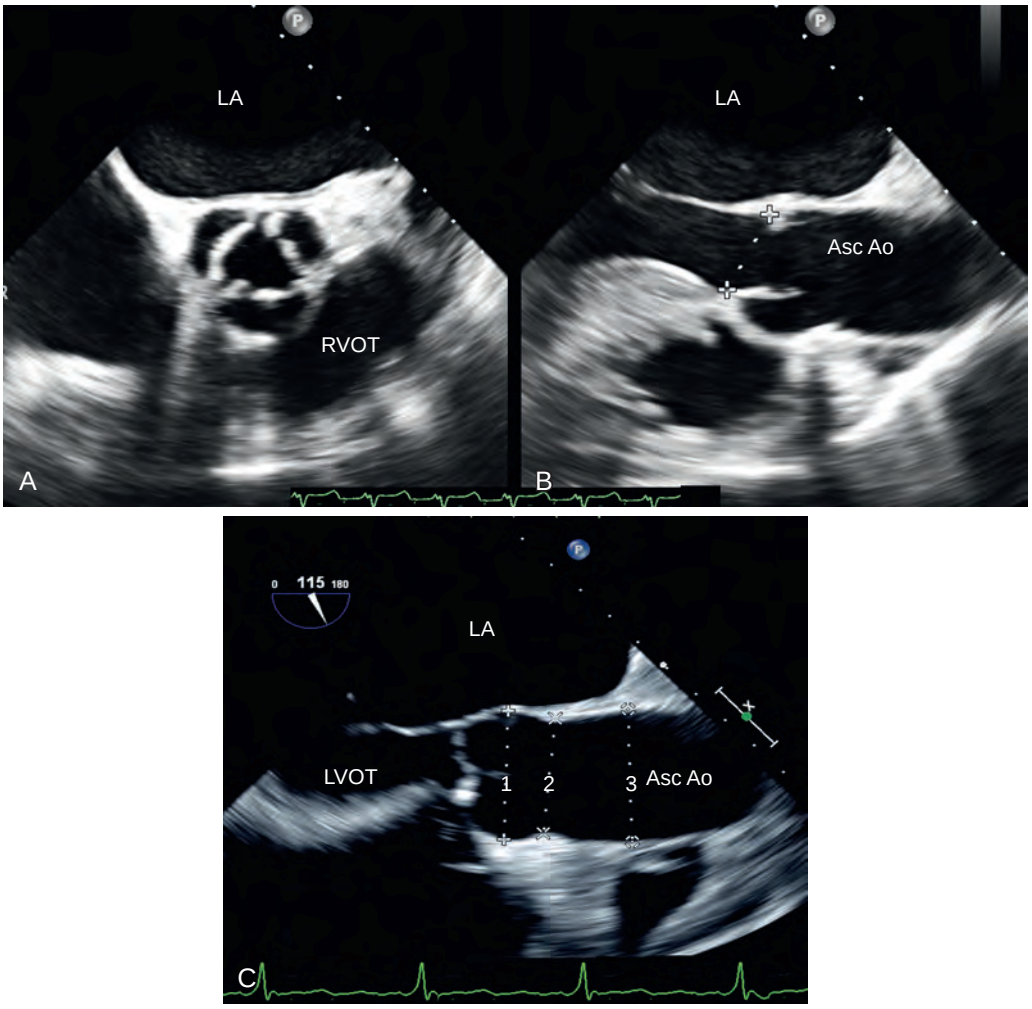

Fig. 15.59 Aortic root diameters. (A–C) The left ventricular outflow tract *(LVOT)* extends from the subvalvular area at the base of the anterior mitral leaflet to the sinotubular junction (STJ). Within this space the aortic valve is attached and distinctly separates the subvalvular from the supravalvular tissues. Important diameters include (B) the annulus, (C1) the sinuses, (C2) the STJ, and the (C3) ascending aorta. These measurements not only explain possible causes of aortic valve insufficiency but also help to guide therapy decisions, including surgical replacement. *Asc Ao,* Ascending aorta; *LA,* left atrium; *RVOT,* right ventricular outflow tract.

and flow profiles. Prosthetic valves are described by their annular size with 19, 21, and 23 mm valves being most commonly placed. In general 19, 21, and 23 mm valves result in EOAs of 1.1, 1.4, and 1.6 cm^2, respectively (see Table 15.3).[21,22,88–91] A normal functioning prosthetic valve yields a smaller EOA compared to a normal native valve in the same anatomic space.

For valve repairs, information of the prerepair disease and the repair itself helps explain the echocardiographic images. Repairs for congenital stenosis are described; however, most repairs are directed toward treating AI, especially for the adult population. Although the appearance of the repaired valve depends on the repair, by and large it should resemble a normal native valve. AV function and prediction of long-term function are the goals of the post- repair imaging. This includes assessment of length and level of leaflet coaptation and Doppler assessment of transvalvular flows. For all echocardiographic assessments, recording of the patient's hemodynamic status improves the perspective at the time of evaluation.

Echocardiographic Examination

The 2D examination of the AV also includes assessment of the supravalvular and subvalvular tissues. This is accomplished from a number of echocardiographic windows. Imaging from multiple sites and angles help to construct a 3D impression of the valve and flows, and helps delineate between normal and abnormal. Particular windows of importance include ME short-axis and ME long-axis windows to image the AV and the tissues above and below in short and long-axis views. Although TG windows are more useful for quantitative Doppler, the TG 2D examination also complements ME images, especially when imaging artifacts limit the latter.

A part of the examination is to determine the feasibility of repair for the regurgitant AV.[87] In doing so, the mechanism of AI has to be determined. Similar to other valves, dysfunction can be divided based either on mobility and/or leaflet pathology. *Type I dysfunction* includes AI due to aortic root dilation (Fig. 15.60). Root dilation includes those tissues extending to the STJ, but not beyond (ie, the ascending aorta).

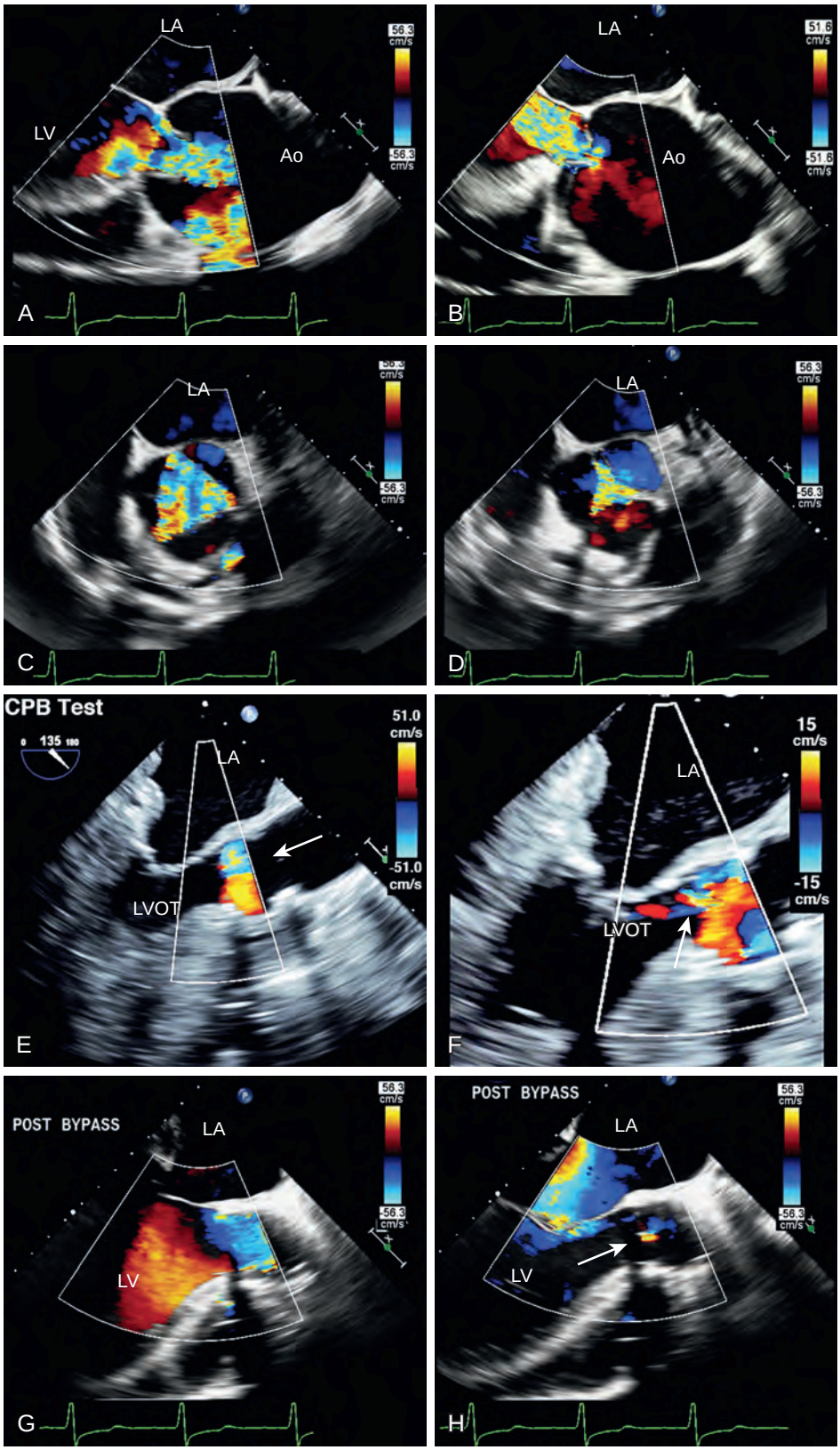

Fig. 15.60 Aortic insufficiency (AI) and repair. (A–D) Prerepair color Doppler images from (A and B) long- and (C and D) short-axis windows depicting severe central AI. Images on the *left* are obtained during systole and those on the *right* are obtained during diastole. (E) and (F) were obtained during cardiopulmonary bypass, after repair of the aortic valve. Color Doppler imaging was used and the color scale was adjusted from 51 to 15 cm/s to increase the sensitivity of detecting residual AI. This is accomplished by infusing cardioplegia into the proximal aortic root under 80 mm Hg of pressure measured from the cardiopulmonary bypass *(CPB)* machine. (G) and (H) were obtained during a stable period after separation from CPB, during (G) systole and (H) diastole and shows trace AI. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

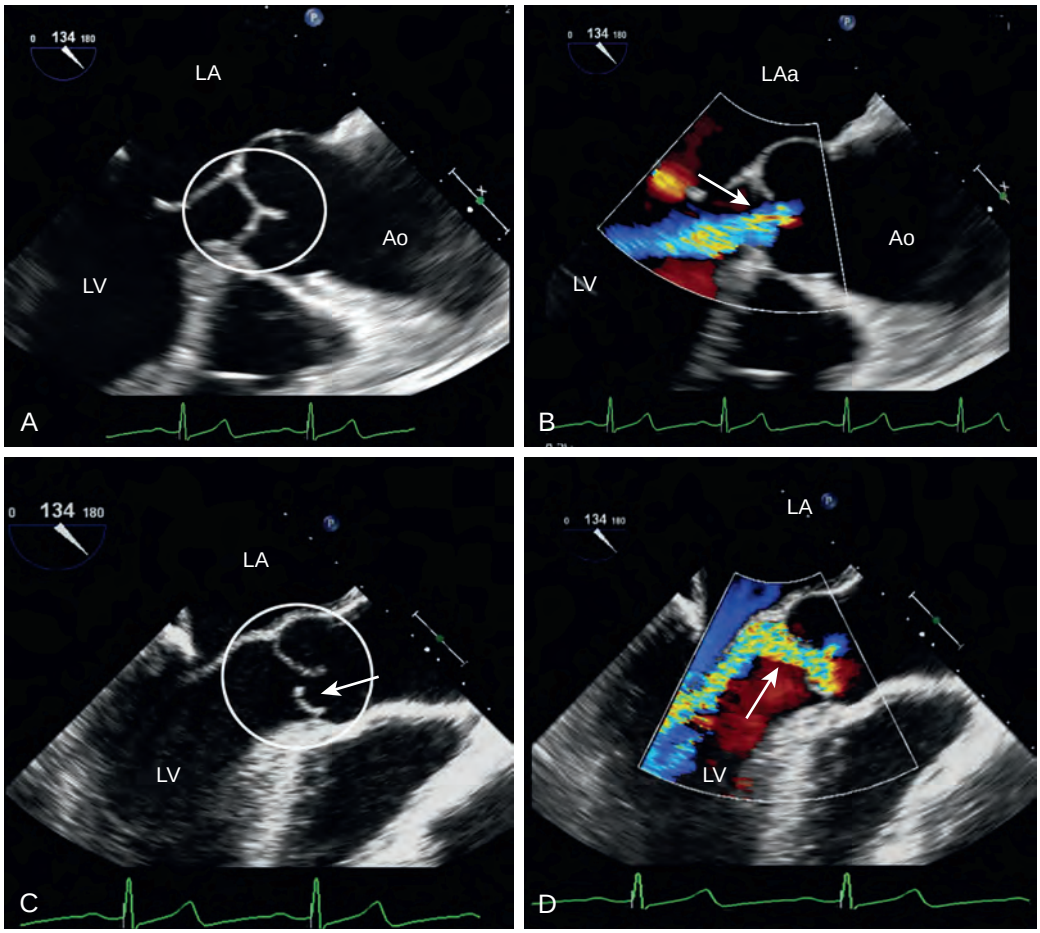

Fig. 15.61 Aortic insufficiency (AI) jet direction. The AI jet may be centrally or eccentrically directed. (A) Centrally directed AI, which might be consistent with equally dysfunctional leaflets. (B) Eccentrically directed insufficiency denoting unequal leaflet dysfunction. (C) and (D) The right coronary cusp prolapses (*circle* in C) and the AI jet (*arrow* in D) is directed away from it. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

Type II dysfunction reflects excess leaflet mobility (Figs. 15.61 and 15.62). Excess mobility is noted by either prolapse or flail of one of more leaflets, while fenestrations are noted by multiple areas in which the integrity of the leaflets is decreased. These causes may reflect fibroelastic deficiency of the leaflet. *Type III dysfunction* also reflects restricting leaflet motion or endocarditis (Fig. 15.63). Repair should be considered for type I and type II dysfunctions.

Imaging of the native and prosthetic AVs are similar. The examination assesses function and pathology including leaflet number, thickness, mobility, and the presence of masses, the latter of which may represent endocarditis, suture materials, or fractured calcium deposits. Any evidence of instability and/or hypolucency within the aortic wall or between the prosthesis and the surrounding tissues/annulus would suggest dehiscence and/or infection/abscess (Figs. 15.64 and 15.65).[21,22] Finally, imaging of the surrounding tissues will point to secondary causes of AI such as root abscess or aortic dissection (see Fig. 15.64). Imaging from multiple planes helps to overcome effects of imaging artifacts and increases the confidence in the diagnosis.[21,22]

After valve surgery, the examination should differentiate between valve repair and replacement, and for the latter, whether or not a mechanical or bioprosthetic valve was placed (Fig. 15.66). The stented and stentless bioprosthetic valves can be differentiated by the presence of both the stent and the supportive struts with the stent (Fig. 15.67). Periprosthetic thickening results from edema or hematoma, which begins to resolve in the early postoperative period.[92] For patients with stentless or repaired valves, this may result in a smaller EOA in the immediate postoperative period followed by a significant increase in EOA over the first 3–6 months with resolution of the perivalvular swelling (see Fig. 15.67).[92] Leaflet mobility, thickness, and integrity, as well as the stability of the valve within the annular area should all be checked.

The Doppler examination allows both qualitative and quantitative evaluations including presence, direction, and width of normal and abnormal blood flow in and around the prosthetic valve.[54,93] Visualization of the three levels of the regurgitant jet is useful to better define the anatomy and severity of AI.[70] While qualitative imaging includes both transesophageal (TE) and gastric windows, most of the quantitative assessment is best achieved from the stomach where blood flow and the Doppler beam can be best aligned to allow measurement of the maximum flow velocities (Figs. 15.66 and 15.68).[17,20–22]

Aortic Regurgitation

AI/AR results from either primary aortic leaflet/valve abnormalities or secondarily from ascending aortic pathology.[21,22,85,87,92,93] Trace or mild AI may be seen in the absence of significant pathology, however, this occurs in the minority or cases (<20%). Similar to the MV, regurgitant lesions can be grouped based on leaflet pathology and mobility (normal, excessive, and restricted). Primary valve pathologies

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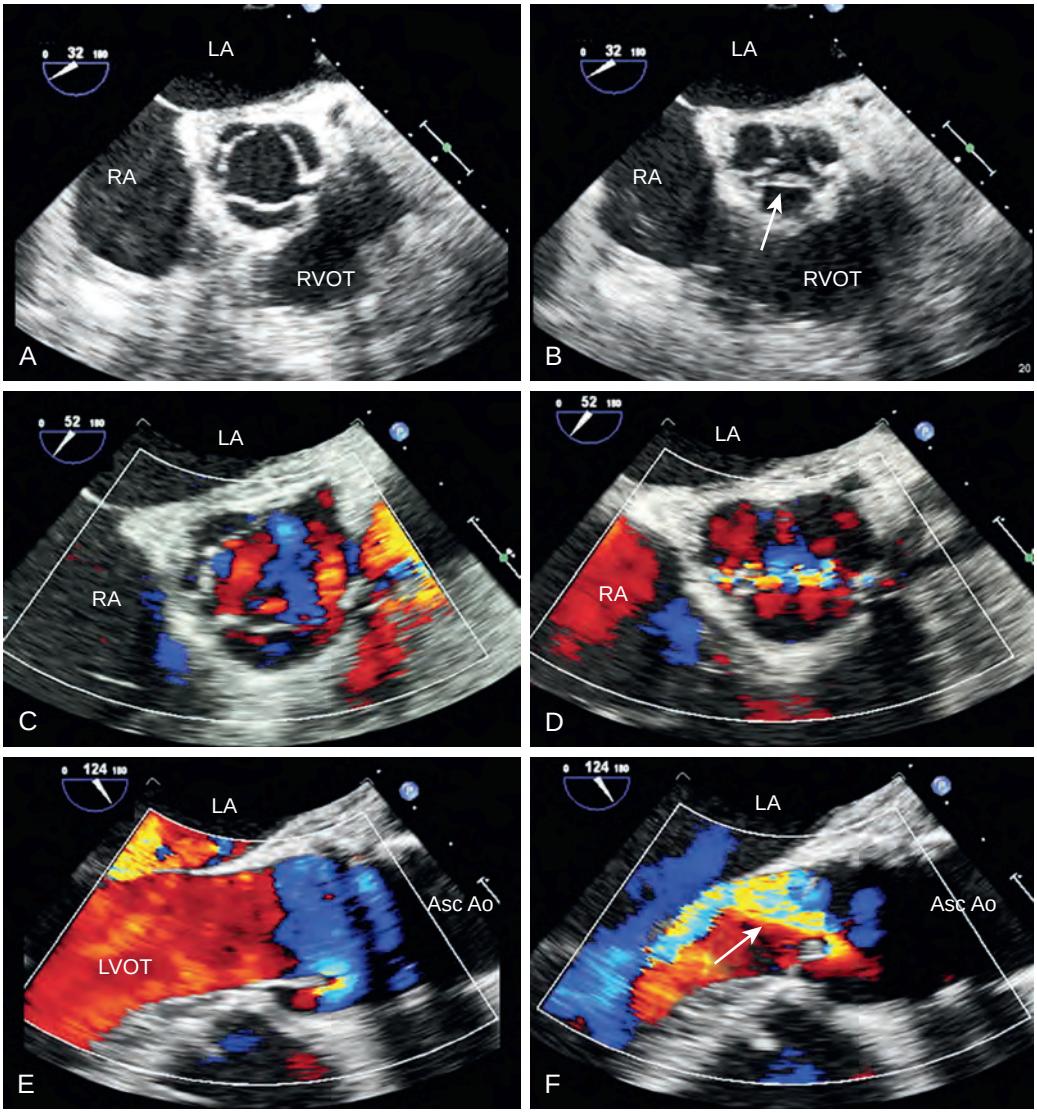

Fig. 15.62 Aortic valve (AV) leaflet fenestrations. AV in (A–D) short- and (E and F) long-axis views during systole *(left column)* and diastole *(right column)*. (B) Right coronary cusp *(arrow)* appears redundant. In the figure immediately below (D) AV insufficiency is seen at the same level where the valve appears redundant (E). (F) shows an eccentric aortic insufficiency jet which appears to be directed away from the right coronary cusp. *Asc Ao,* Ascending aorta; *LA,* left atrium; *LVOT,* left ventricular outflow tract; *RA,* right atrium; *RVOT,* right ventricular outflow tract.

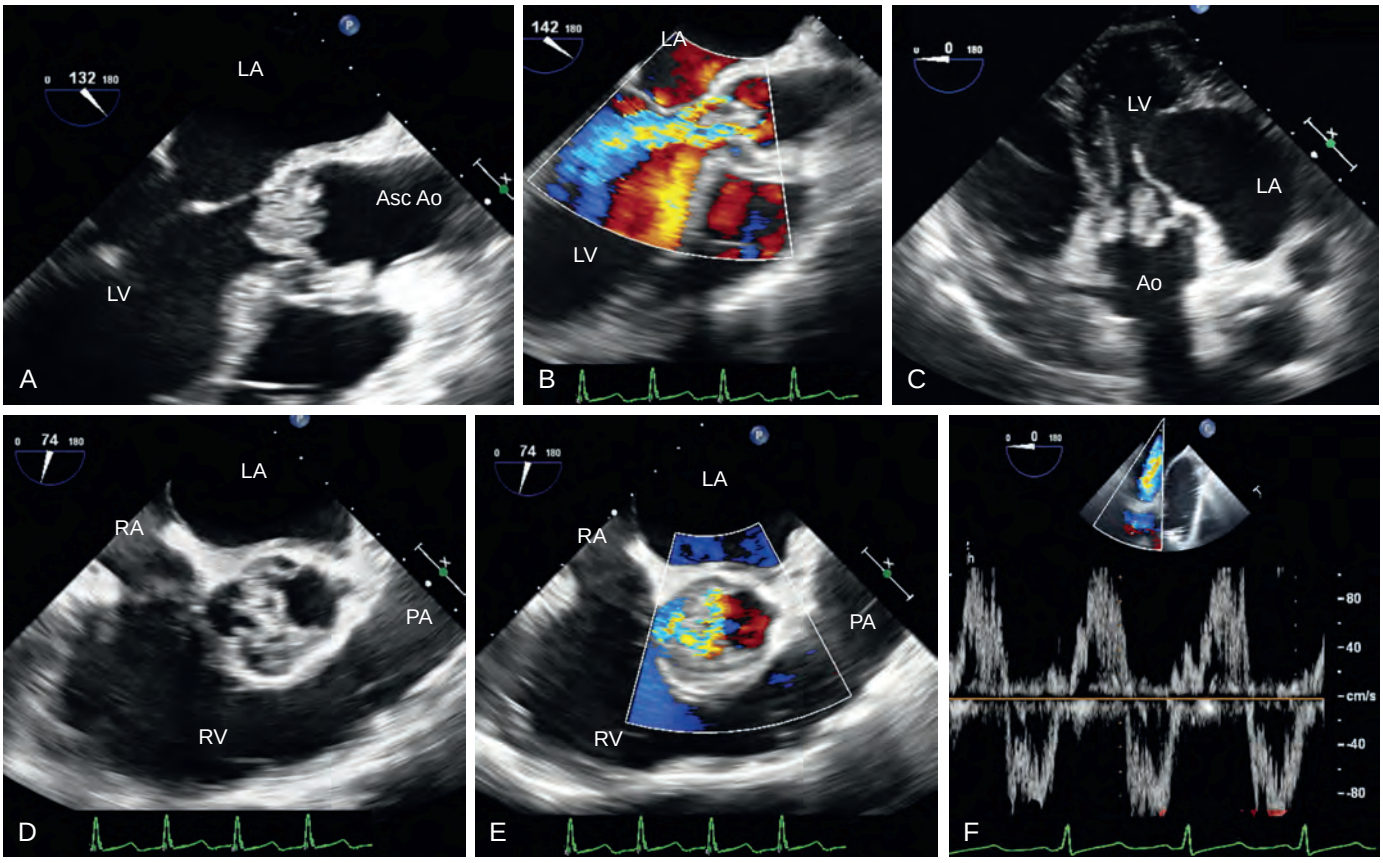

Fig. 15.63 Aortic insufficiency caused by endocarditis. Endocarditis of the aortic valve (AV) can manifest with a range of leaflet/annular/aortic disease and insufficiency. (A) and (B) Significant leaflet involvement and severe insufficiency. (C) Transgastric imaging showing significant involvement of the AV. (A–C) show thickened, irregular, and flail AV leaflets, which are associated with large mobile masses. (D) and (E) AV in short-axis view with and without color Doppler, showing severe insufficiency. (F) Pulsed-wave Doppler of the ascending aorta showing diastolic flow reversal consistent with severe dysfunction. *Asc Ao,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle; *PA,* Pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

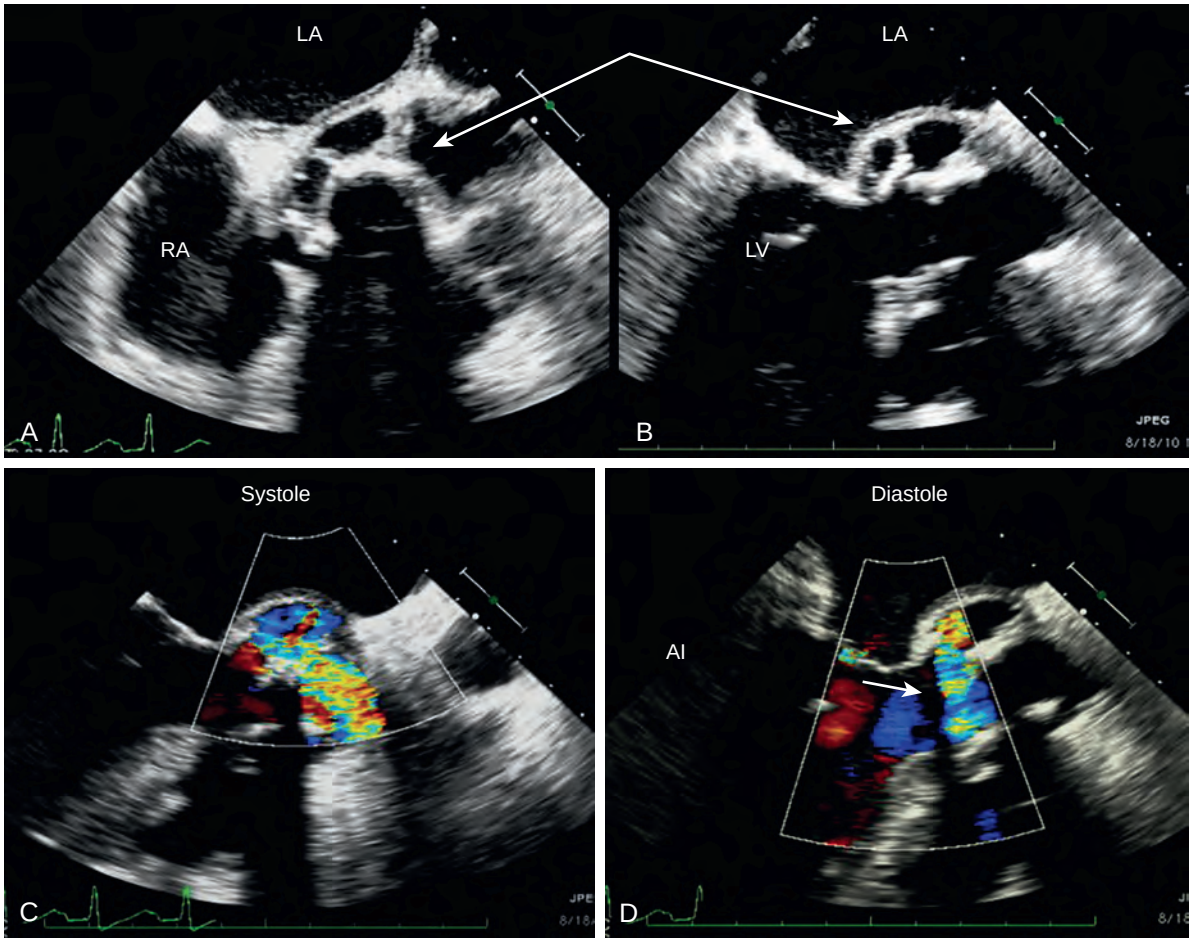

Fig. 15.64 Periaortic abscess. Periprosthetic aortic abscess highlighted by an echolucent space surrounding a previously placed bioprosthetic valve. (A) and (B) Valve in short and long axes. (C) and (D) Color Doppler imaging in the long-axis window during systole and diastole, the latter demonstrating aortic insufficiency *(AI)*. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

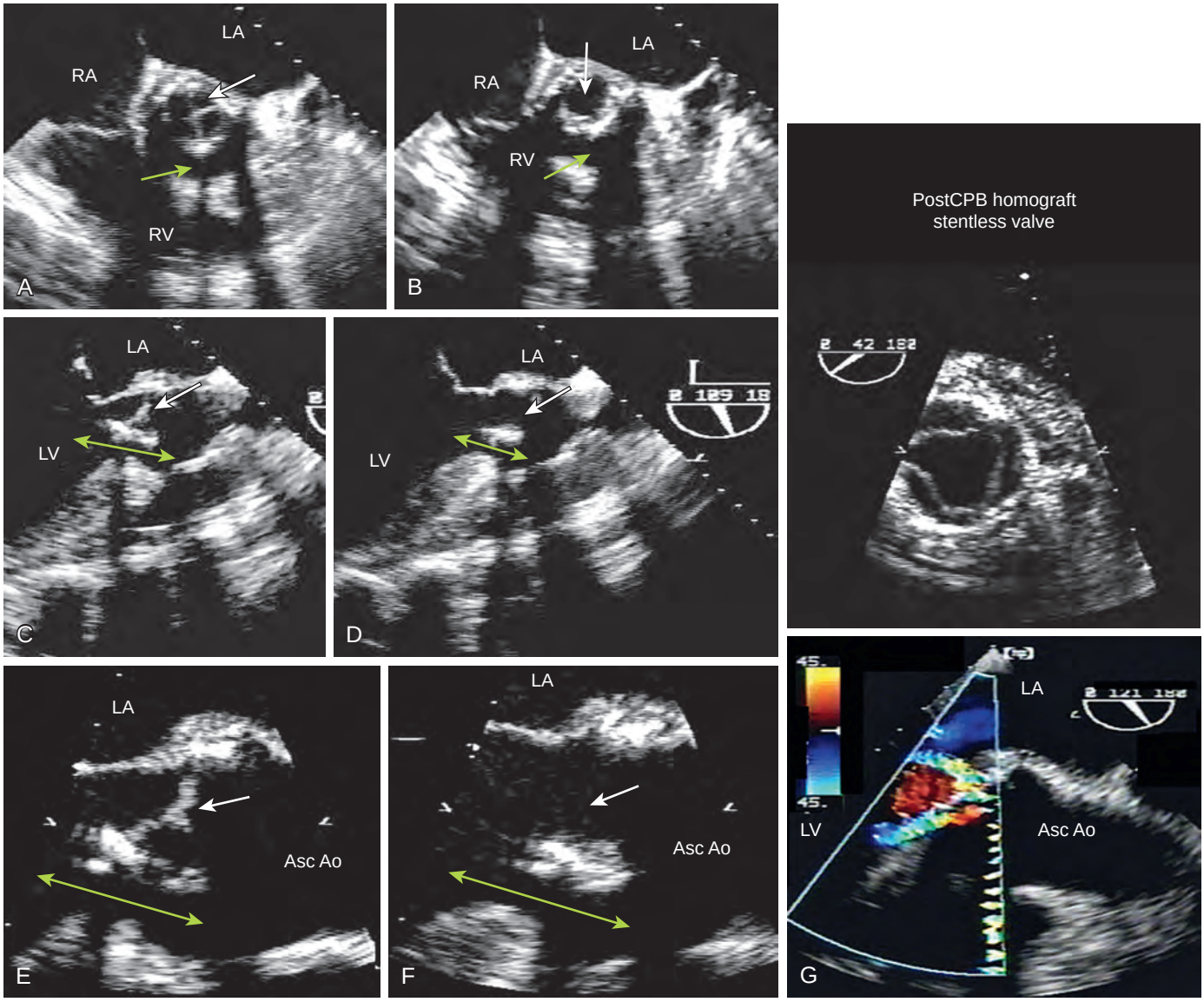

Fig. 15.65 Aortic bioprosthesis dehiscence. Multiple images of a normally functioning bioprosthetic valve that has separated from the anterior part of the native annulus (ie, dehiscence). (A), (C), and (E) were obtained during diastole and (B), (D), and (F) during systole. The *yellow arrows* point to the site of dehiscence. (G) Complicated eccentric regurgitant color Doppler profile. *Top right,* Postbypass *(PostCPB)* homograft that replaced the previous bioprosthetic valve. *Asc Ao,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

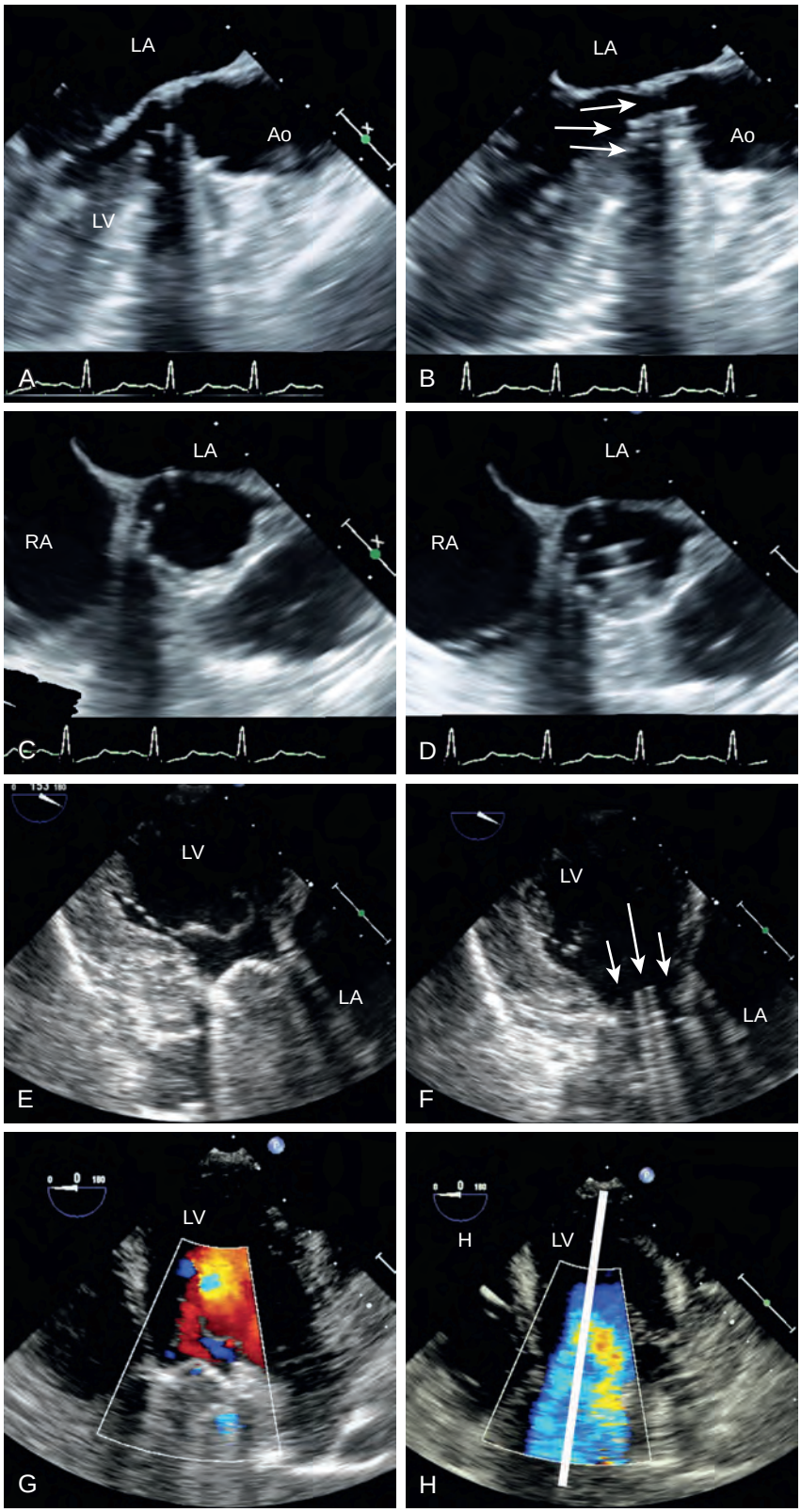

Fig. 15.66 Aortic valve replacement: mechanical valve. Normally functioning bileaflet mechanical valve in the aortic position. Left-sided figures were obtained during diastole and right-sided figures during systole. (A–D) Midesophageal long (A and B) and short (C and D) two-dimensional views of the valve. Normal leaflet mobility is noted by seeing the edges of each leaflet during ventricular systole as seen in (B) and (D). (E–H) Transgastric imaging complements transesophageal imaging. Color Doppler imaging shows (G) insignificant insufficiency and (H) normal Doppler flow during systole. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium.

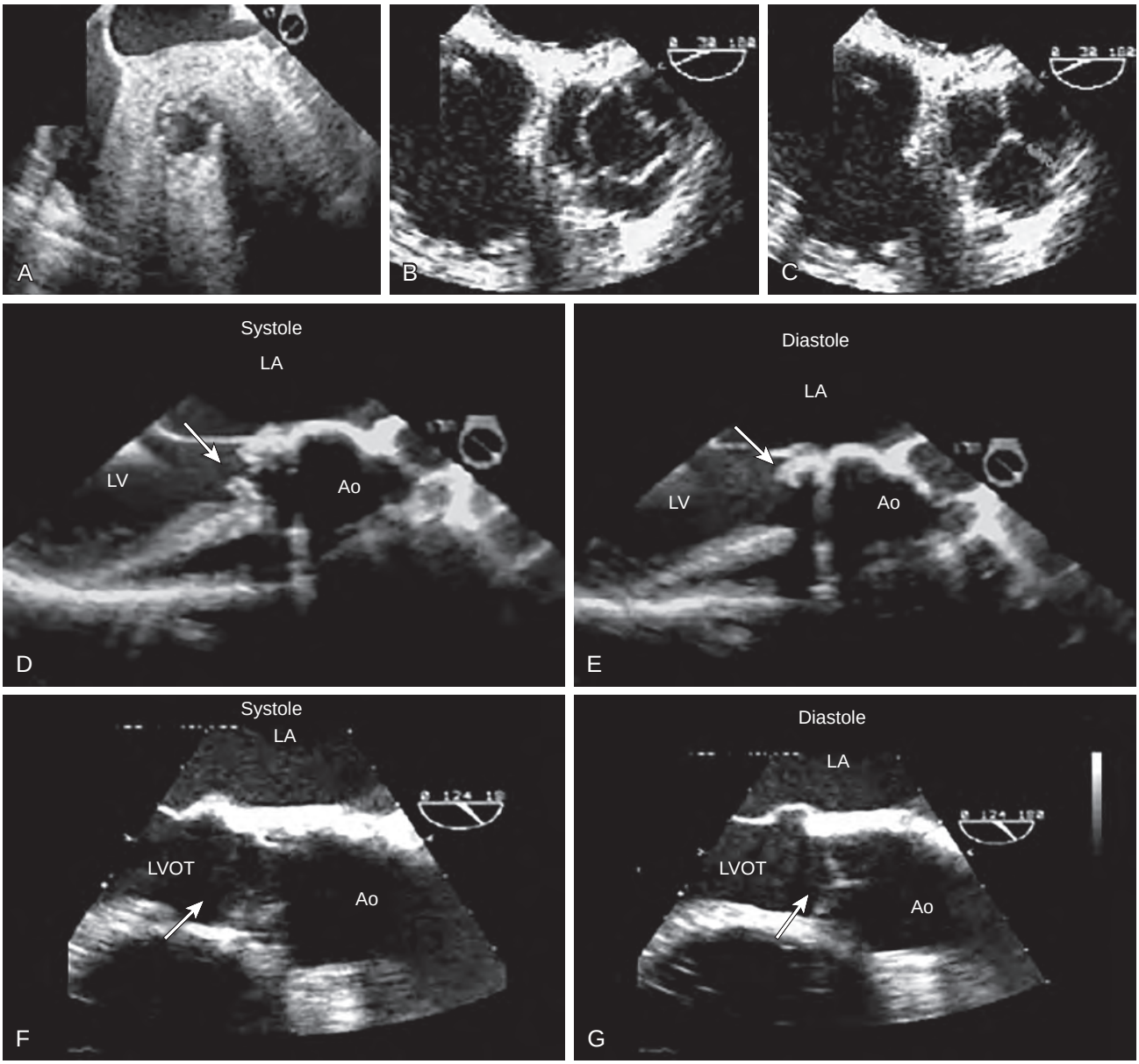

Fig. 15.67 Before and after imaging of a stentless valve in the aortic position. (A–C) Short-axis views of a patient who underwent stentless aortic valve replacement. The period immediately after bypass showed (A) perivalvular thickening caused by either edema or hematoma, which (B and C), within 48 hours was nearly completely resolved. (D–G) Second case, showing long-axis views of a stentless aortic valve. (D) and (E) are immediately after bypass showing the cloth edges of the stentless valve *(white arrows)* in the outflow tract. These were associated with high systolic gradients and systolic obstruction. (F) and (G) At follow-up, 6 months later, showing the cloth edges to have flattened into the LVOT tissues and associated with a reduction in transvalvular pressures and an increase in the calculated effective orifice area. The valvular hemodynamics of the stentless valve is known to improve between 24 hours and 6 months after placement. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *LVOT,* left ventricular outflow tract.

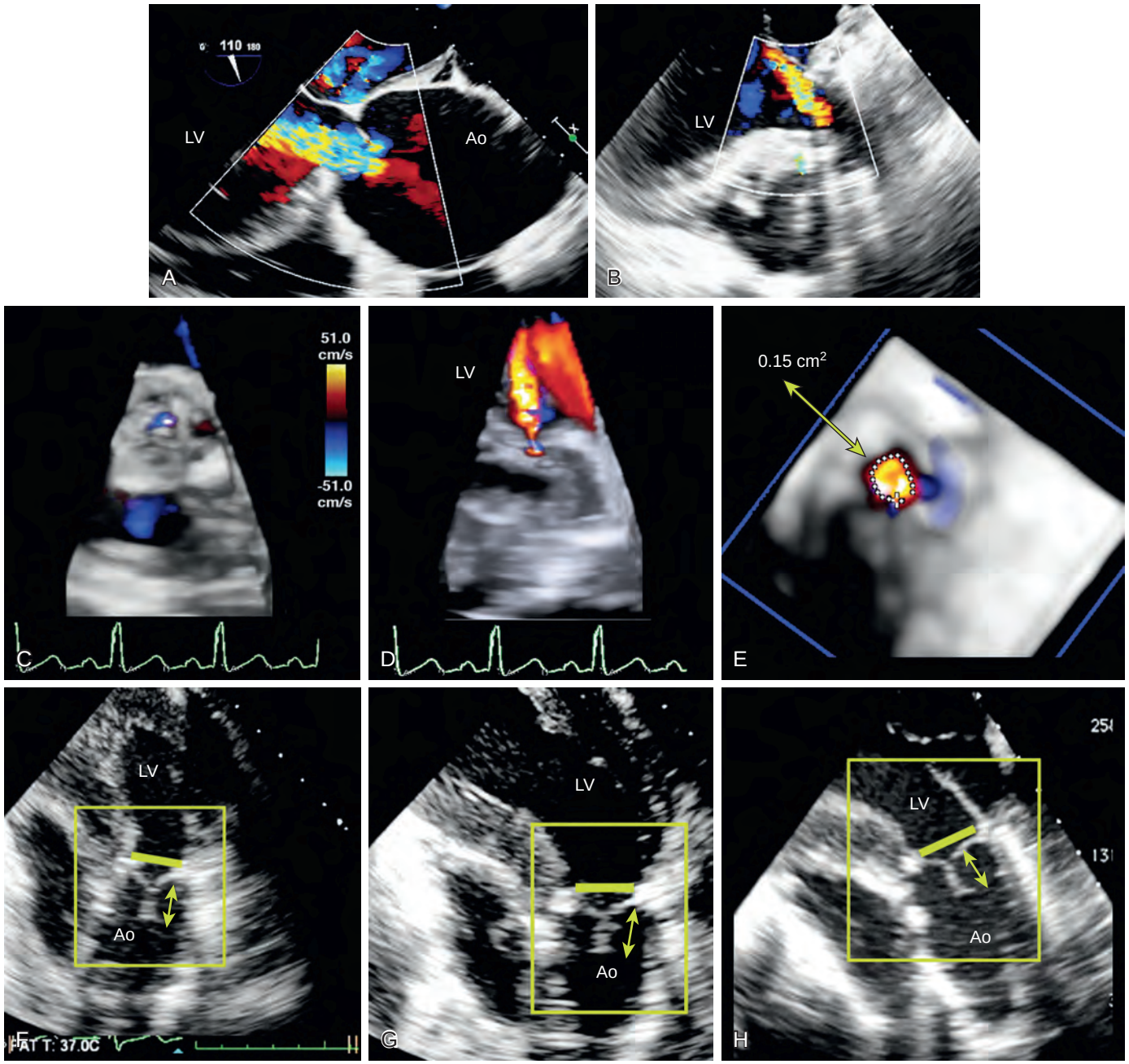

Fig. 15.68 Aortic insufficiency (AI) and repair. These images demonstrate the benefits of performing a comprehensive echocardiographic exam using different ultrasound modalities and both transesophageal and gastric windows. (A) Prerepair and (B) postrepair midesophageal long-axis color Doppler views show significant AI. Postrepair image shows a significant color Doppler profile but the valve is not well seen. (C) Midesophageal and (D) and (E) transgastric windows, three-dimensional volumetric color data sets allow visualizations of the regurgitant jet below, at, and above the valve. (D) Narrow jet of insufficiency at the valvular level, which expands due to entrainment. Editing the data set allows planimetry of the regurgitant jet, which measures 0.15 cm^2 in area consistent with mild AI. (F–H) Transgastric two-dimensional images allowing visualization of the coaptation level (ie, no residual prolapse; *solid line*) and coaptation length *(arrows-line). Ao,* Aorta; *LV,* left ventricle.

include bicuspid AV, quadricuspid AV, myxomatous degeneration (fibroelastic disease), fenestrations, endocarditis, calcification (often associated with AS), radiation therapy, rheumatic disease, and trauma (Figs. 15.61–15.63, 15.69, and Table 15.6). The AV also can be involved in association with a subvalvular membrane or a VSD (Fig. 15.70). Leaflets may prolapse or flail, or display fenestrations, masses, or calcification. Secondary causes include aortic root pathology such as dilation, dissection, and infection in which the aortic leaflets may be involved or appear normal (see Figs. 15.60, 15.64). Determining the cause of AI is important to determine the best mode of therapy and whether or not the valve can be repaired or requires replacement.

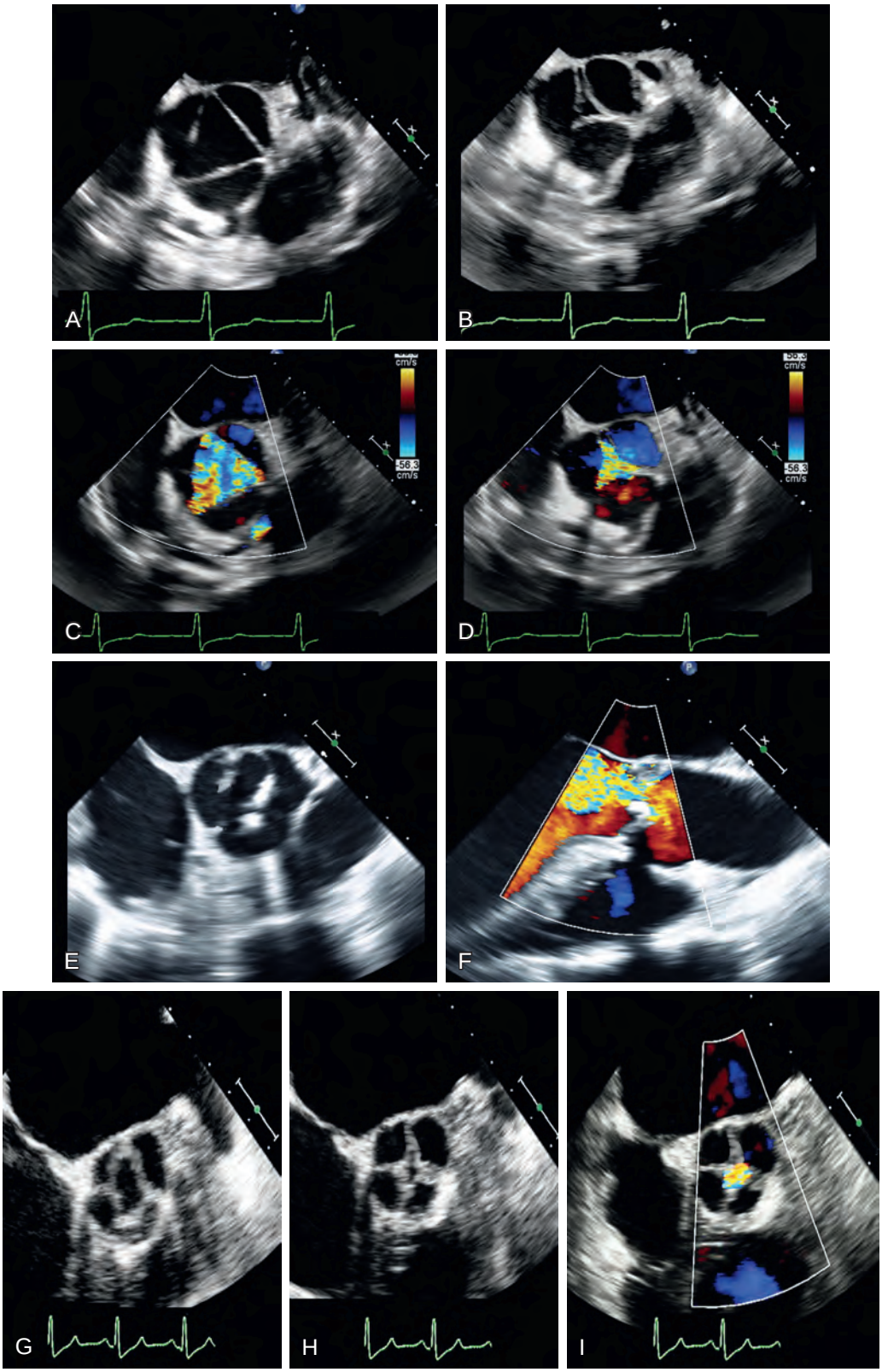

Fig. 15.69 Aortic valve (AV): bicuspid, trileaflet, quadricuspid. (A) and (B) Trileaflet valve associated with a dilated aorta. (C) The same valve during ventricular systole. (D) Centrally directed aortic insufficiency (AI) jet. (E) and (F) Bicuspid valve with AI. Bicuspid valves may manifest with either primary stenosis, regurgitation, or a mixed dysfunction. Associated disorders may include aortic root dilation, aortic coarctation, and/or mitral valve degenerative disease. (G–I) Quadricuspid AV during systole *(left),* and diastole *(middle and right).* The color Doppler analysis shows mild to moderate AV insufficiency. AV insufficiency is the predominant finding/dysfunction for quadricuspid valves. Of note, unicuspid valves (not shown) manifest primarily with stenosis.

TABLE 15.6 Aortic Valve Regurgitation: Degrees of Severity

	Mild	*Moderate*	*Severe*
Angiographic grade	1+	2 +	3–4+
Jet density/appearance	Faint/incomplete	—	Dense/complete
Color Doppler jet width/LVOT width	<0.25	0.25–0.65	>0.65
Doppler vena contracta (cm)	<0.3	0.3–0.6	>0.6
Pressure half time (ms)	>450	250–450	<250
Pulsed-wave Doppler ascending/descending aorta	—	—	Reversal
Regurgitant volume (mL/beat)	<30	30–60	>60
Regurgitant fraction (%)	<30	30–60	>60
Regurgitant orifice area (cm^2)	<0.3	—	>0.3
Secondary findings	LAE, LVE, LVSD, PHTN		

LAE, Left atrial enlargement; *LVE,* left ventricular enlargement; *LVOT,* left ventricular outflow tract; *LVSD,* left ventricular systolic dysfunction; *PHTN,* pulmonary hypertension.

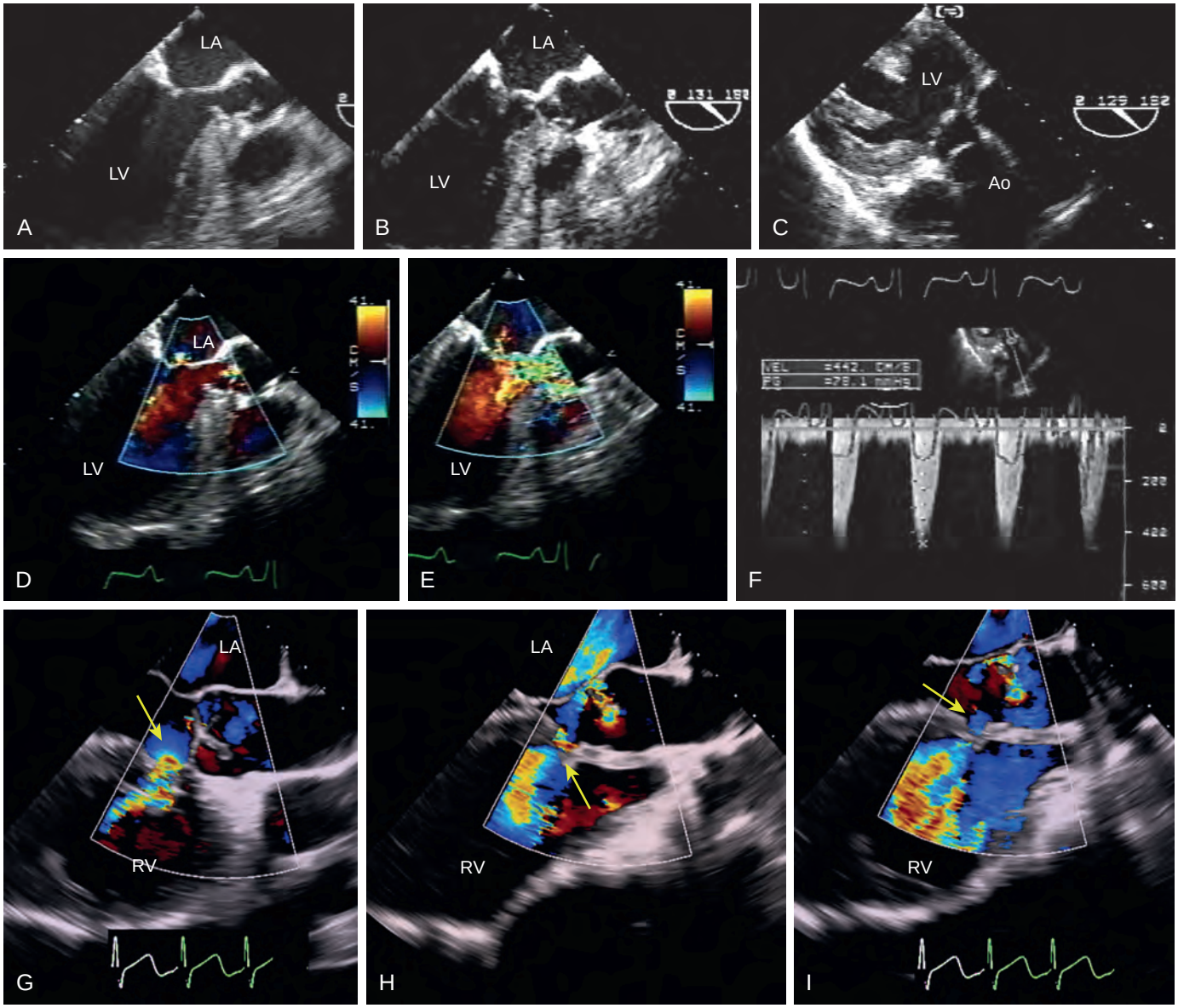

Fig. 15.70 Subaortic valve membrane and ventricular septal defect (VSD). (A) Subaortic valve membrane during systole with evidence of good systolic excursion of the aortic valve (AV) leaflets. (B) Subaortic valve membrane during systole. (C) Transgastric image showing the subaortic valve membrane appearing parallel to the close AV. (D) Color Doppler image showing mild AV insufficiency. (E) Turbulent outflow consistent with a fixed outflow obstruction. Interrogation with continuous-wave Doppler across the left ventricular outflow tract records a gradient greater than 70 mm Hg. Given the normal excursion of the aortic leaflets, the elevated gradient is due to subvalvular obstruction. (G) VSD *(yellow arrow).* (H) and (I) VSD and coexistent (or associated) AV insufficiency. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

Aortic Valve Regurgitation of the Prosthetic or Repaired Valve

Prosthetic valves are associated with a "normal" signature or expected regurgitant jets and should be differentiated from "abnormal" flows. Normal or nonproblematic regurgitant jets are less than 3 mm in width and do not extend far from the valve.[21,22,87,92,93] Bioprosthetic valves typically display a central regurgitant jet, while mechanical leaflets display a variety of regurgitant jets depending on the valve type. Imaging parallel to the valve leaflets will allow better visualization of the normal two regurgitant jets directed centrally. A single-leaflet valve (or tilting disk valve) has one larger and one smaller jet, while the ball-in-cage valve will have a surrounding series of small jets. Abnormal paravalvular regurgitant jets are greater than 3 mm in width and/or are eccentrically directed away from the middle.[56] Smaller jets may also be considered abnormal, but in the absence of obvious pathology (mobile materials; valve instability) these do not tend to progress over time.[54] Abnormal flows can result from a number of causes. Prosthetic valve incompetence is similar to that of native valves with some additional etiologies. These include endocarditis, leaflet deterioration or degeneration, restricted leaflet mobility, or valvular dehiscence/abscess. As with other prosthetic valves, the defect may occur within the aortic prosthesis or around it (paravalvular).

Repair of the AV generally is applied to regurgitant valves.[54,85,87,93] Although the goal is to eliminate regurgitation, mild or less AI is acceptable (see Fig. 15.60).[85,87,92] The location and direction of the regurgitant jet depends on the pre repair pathology and the repair technique. The repair can be assessed before separating from cardiopulmonary bypass by filling up the proximal aorta and generating pressure on the valve (see Fig. 15.60). Either by noting spontaneous echo contrast, or with the color gains adjusted lower, it is possible to assess residual regurgitation. Long-term function (return of AI or need for reoperation) is determined by the coaptation level (no residual prolapse), coaptation length (>6 mm), and severity of residual AI (see Figs. 15.60 and 15.68).[85,87,92]

Hemodynamics and pathophysiologic cardiac changes associated with AI depend on the acuity. Acute AI due to aortic dissection, endocarditis, or trauma causes an acute volume load to the left ventricle causing increased ventricular pressures, myocardial stress, and oxygen consumption. Since the left ventricle has not had time to compensate, the increase in LV end-diastolic volume is relatively less compared to the increase in LV end-diastolic pressure. This is transmitted backward to the left atrium and the pulmonary vasculature, causing pulmonary edema. In order to maintain forward flow, LV contractility and heart rate must increase.

Cardiovascular changes with chronic AI result from a prolonged increase in ventricular volume and pressure overload, ultimately causing myocardial stretch/dilation, and increased myocardial oxygen consumption ($M\dot{V}O_2$). Initially, concentric (or eccentric) hypertrophy occurs and contractility is preserved. With continued progression there is a greater amount of ventricular dilation compared to hypertrophy. The ventricular walls start to thin and LV pressures do not initially increase. The AI causes impairment of isovolumic relaxation and results in a large pulse pressure with a low systemic diastolic blood pressure. Myocardial ischemia occurs due to increases in $M\dot{V}O_2$ (secondary to ventricular stretch and increased LV pressure), as well as lower systemic diastolic blood pressures reducing coronary perfusion. The various changes ultimately result in a reduced LVEF, and increased left heart and pulmonary pressures, the latter two associated with clinical decompensation.

Assessing regurgitant flow of the AV is similar for both native and prosthetic valve disease (see Table 15.6). It is necessary to know what is expected for native valves and acceptable prosthetic valves. For example, a single-leaflet valve (or tilting disk valve) will have a regurgitant jet directed away from the sewing ring from the edge of the major orifice. Homografts should NOT have any regurgitant jets; however, they may be seen depending on the native valve function prior to excision and preparation. 2D imaging identifies the number and mobility and integrity of the leaflets as well as the stability of the valve to determine the integrity of the surrounding tissues. A valve that appears to rock or one that has an echolucent space within the aortic wall, or in between the prosthesis and surrounding tissues, might suggest infection and/or dehiscence.

Assessing AI severity begins with CFD to identify the regurgitant jet, direction, and make an initial qualitative assessment.[20] Although the color Doppler jet area has been described, it is less accurate to quantify AI severity. There are indirect and direct methods that are more accurate to quantify AI severity.[69,94] The former includes assessment of the VC (narrowest jet width just beyond or downstream to the AR orifice), and the ratio of the proximal jet width to the width of the LVOT (see Fig. 14.76). The limitations to the VC and jet width ratio occurs when either the LVOT cannot be seen clearly due to imaging artifact from prosthetic materials, or when the AI jet is either eccentric and/or complex.[62,70] The PHT or DT is used to assess the pressure changes across the regurgitant orifice as a reflection of the ROA.[95,96] A small PHT (<450 ms) reflects significant (more than mild) AI (Fig. 15.71). However, the PHT is affected by net chamber compliance. For a given severity of AI, PHT is shortened with increasing LV end-diastolic pressure, vasodilator therapy, and in patients with a dilated

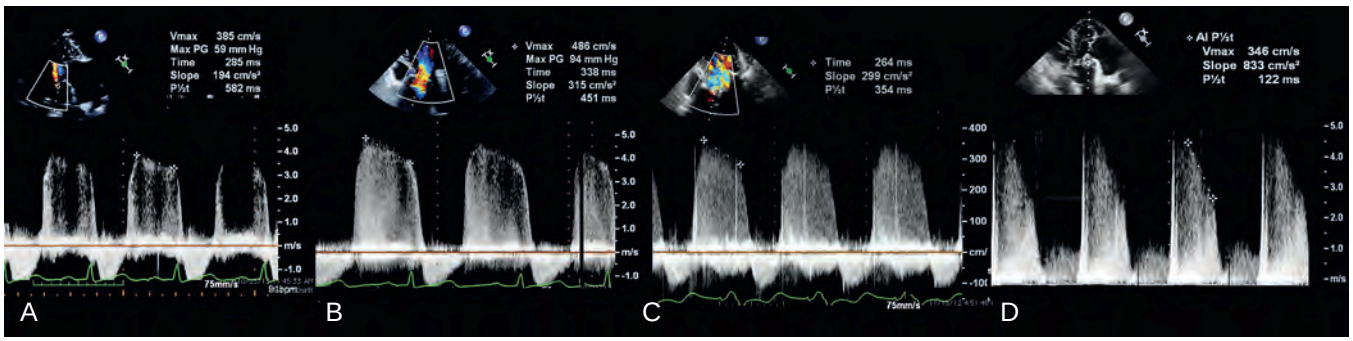

Fig. 15.71 Pressure half time (PHT): aortic insufficiency (AI). (A–D) From *left* to *right* the Doppler profiles show reduction in PHTs from 582 ms to 122 ms, which is consistent with increasing severity of AI. The limitation of the PHT assessment is the impact on net compliance, which in turn is affected by a host of variables including acuity of AI, coexistence of aortic valve stenosis, and a history of hypertension. Although supportive of different degrees of AI, the PHT assessment should not be used as the sole determinant of AI severity. Qualitatively, the Doppler profile in (A) is not as dense or complete as the others, reflecting the regurgitant volume. The more cells that pass through, the more dense the flow profile will be.

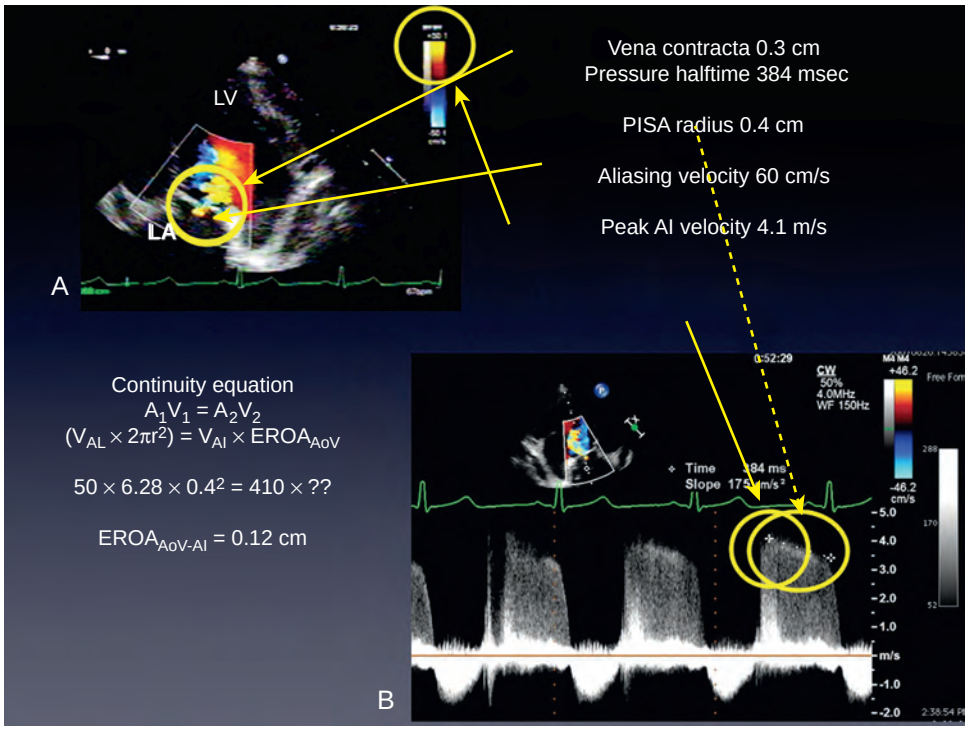

Fig. 15.72 Use of the flow convergence method to assess the severity of aortic insufficiency (AI). In this case the effective regurgitant orifice area *(EROA)* is 0.12 cm^2 and consistent with mild AI. This is also consistent with a vena contracta of 0.3 cm. The pressure half time of 384 ms would suggest moderate AI, but this measure is significantly affected by changes in net chamber compliance between the aorta *(Ao)* and left ventricle *(LV)*. *LA,* left atrium; *PISA,* proximal isovelocity surface area.

compliant aorta, or lengthened in chronic AI.[20,96] Thus, this parameter serves only as a complementary finding for the assessment of AI severity.

The PISA method has been utilized to measure ROA and regurgitant volume (Fig. 15.72).[70]

$$CSA_{AI} \times V_{PeakAIVel} = (2pr_{PISA}{}^2 \times V_{NL})$$
$$CSA_{AI} = (2pr^2 \times V_{NL}) / V_{PeakAIVel}$$

If the EOA were multiplied by the TVI (continuous-wave Doppler), the result would be the volume flowing across the orifice each cardiac cycle. For a regurgitant valve, this would be the regurgitant volume:

$$\text{Regurgitant volume}_{AI} = EOA_{AI} \times TVI_{AI}$$

Other Doppler methods include documentation of diastolic flow reversal (severe AI) in the ascending or descending aorta, the former being more sensitive, while the latter is more specific. The continuity equation may be used to determine the regurgitant volume as the difference between the SV across the PA and the AV.

$$SV_{PA} = SV_{AV} - \text{Regurgitant volume}_{AI}$$

When feasible, either with 2D or 3D imaging, the ROA can be obtained by planimetry.

Quantifying the severity of regurgitant flow[20–22,85] is similar for native and prosthetic AVs (see Table 15.6). For prosthetic valves, regurgitant jet widths less than 3 mm are either consistent with normal regurgitant flows or suggest that such a small abnormal flow is not likely to progress. Findings consistent with significant abnormal (more than moderate) prosthetic AR include dense or complete regurgitant jets, VC greater than 0.3 cm, regurgitant jet width/LVOT diameter ratio higher than 25%, PHT less than 400 ms, ROA greater than 0.3 cm^2, regurgitant volume greater than 30 mL/beat, and a regurgitant fraction greater than 30%. Severe AR may be defined as a VC greater than 0.6 cm and an ROA greater than 0.6 cm^2. Diastolic flow reversal in the aorta is consistent with more than moderate AR. The flow convergence method has been applied to determining AR, but is less studied. Mild, moderate, and severe AR are defined as ROA of less than 15 mm^2, 15.30 mm^2, and greater than 30 mm^2, respectively. These ROAs are associated with regurgitant volumes of less than 30, 30 to 60, and greater than 60 mL/beat. For chronic AR, secondary changes in cardiac geometry and function support the presence of significant (moderate or greater) AR, including ventricular dilation, contractile dysfunction, LA enlargement, and pulmonary hypertension.

Surgical Indications

With the goal of preventing long-term dysfunction, surgical treatment of AI should be performed[24–26] (Fig. 15.73). Indications include symptomatic patients with severe AI. Surgery is also indicated for asymptomatic patients with severe AI and LV systolic dysfunction defined as an LVEF less than 50%, and/or a dilated left ventricle described as an LV systolic diameter larger than 50 mm, LV end-diastolic diameter greater than 70 mm, and/or LV end-diastolic volume index greater than 110 mL/m^2.[97] Surgery is also recommended for asymptomatic severe AI in patients undergoing other cardiac surgical and/or ascending aortic procedures.[24–26]

Aortic Stenosis

Changes in the native AV architecture occur with age and commonly include thickening found in more than 20% of patients older than 65 years and up to a 4% incidence of AS found in patients older than 85 years. The vast majority of fixed native AS is due to elderly (or senile) calcific trileaflet AS.[17] This is followed by bicuspid AS and rheumatic AS (see Figs. 14.64 and 14.65; Video 14.52; Table 15.7). Other less common outflow obstructions include unicuspid valve, supravalvular stenosis (eg, Williams syndrome), and subvalvular obstruction, for example, membrane (see Fig. 15.70). Hypertrophic obstructive cardiomyopathy is a dynamic form of obstruction that should be delineated

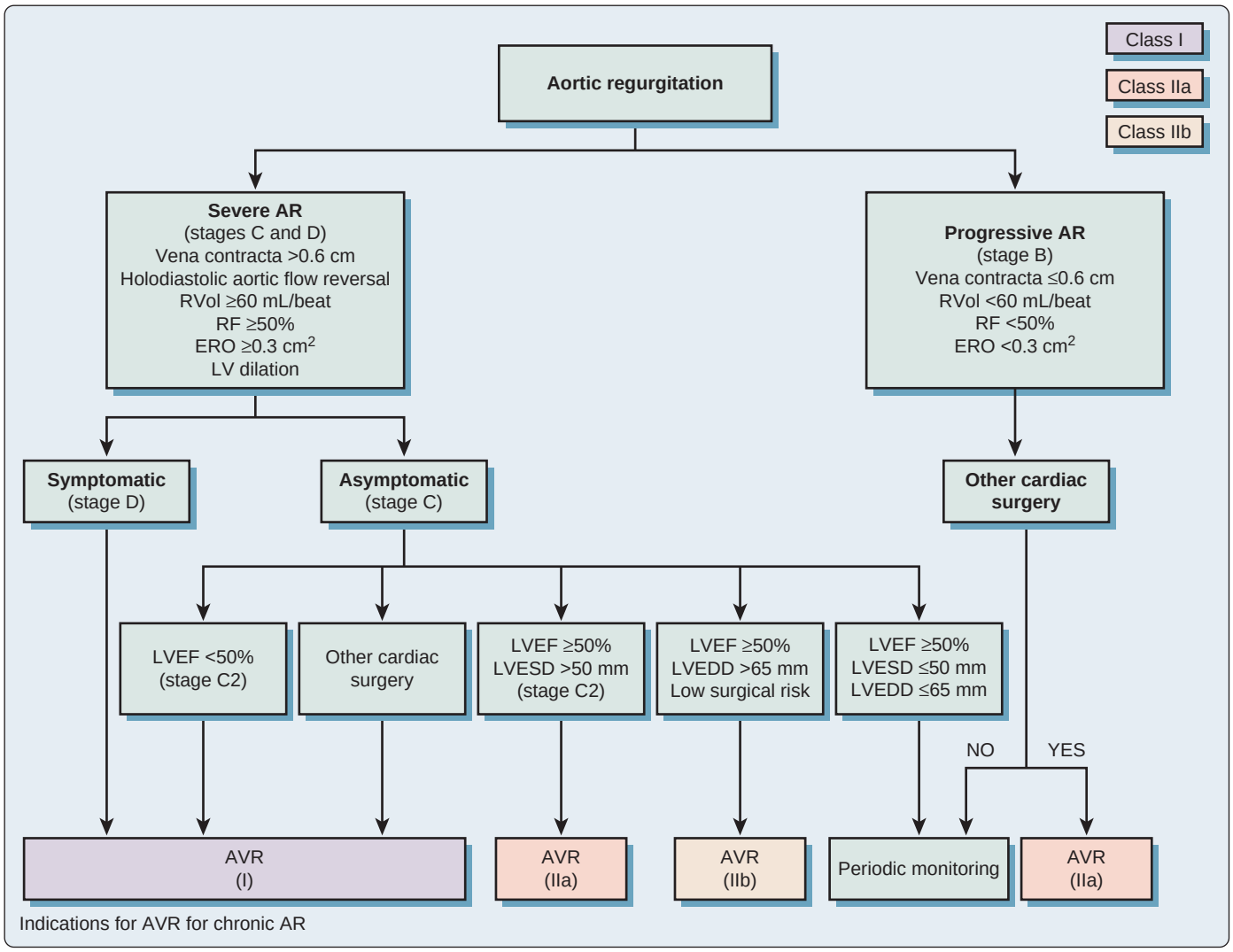

Fig. 15.73 Decision algorithm for aortic insufficiency (AI). The decision algorithm was taken as a consensus by an expert panel and based on outcome data and interpretation. Decisions are classified as class I, class IIa, class IIb, the former being supported by sufficient evidence such that intervention should be performed, while the latter two are supported by evidence that suggests that the benefits of intervention outweigh the risks and that intervention is reasonable based on multiple (IIa) or isolated trials or nonrandomized data (IIb). Treatment for AI usually includes percutaneous intervention. The decision is based on a number of considerations including severity, presentation (symptoms), changes in cardiopulmonary function, repairability, and timing (ie, whether or not another primary cardiac procedure was being performed). *AR,* Aortic regurgitation; *AVR,* aortic valve replacement; *ERO,* effective regurgitant orifice; *LV,* left ventricle; *LVEF,* left ventricular ejection fraction; *LVEDD,* left ventricular end-diastolic diameter; *LVESD,* left ventricular end-systolic diameter; *RF,* regurgitant fraction; *RVol,* regurgitant volume. *(Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57–e185.)*

TABLE 15.7 Aortic Valve Stenosis: Degrees of Severity

	Mild	*Moderate*	*Severe*
Jet velocity (m/s)	<3.0	3.0–4.0	>4.0
Acceleration time (ms)	<100		>100
Mean pressure gradient (mm Hg)	<25	25–40	>40
AV area (cm^2)	>1.5	1.0–1.5	<1.0
AV area index (cm^2/m^2)	>0.85	0.85–0.65	<0.65
Velocity ratio (TVI_{LVOT}/TVI_{AV})	0.35–0.30	0.30–0.25	<0.25
Secondary findings	LAE, LVH, PHTN, RAE, RVE, TR		

AV, Aortic valve; *LAE,* left atrial enlargement; *LVE,* left ventricular enlargement; *LVOT,* left ventricular outflow tract; *PHTN,* pulmonary hypertension; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement; *RVSD,* right ventricular systolic dysfunction; *TR,* tricuspid regurgitation; *TVI,* time-velocity integral.

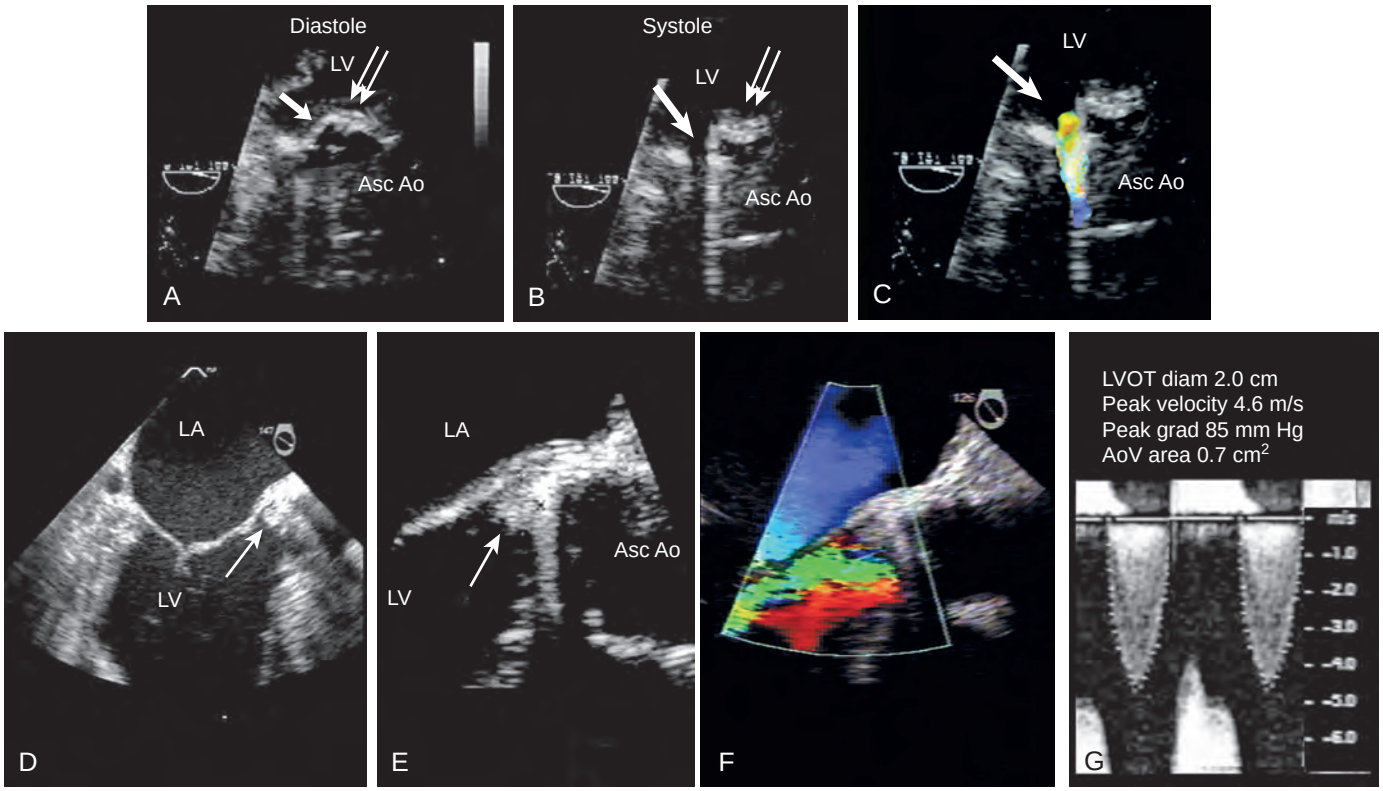

Fig. 15.74 Prosthetic valve stenosis. Two causes of prosthetic valve stenosis include a stuck mechanical leaflet (A-C), and an obstructing mass (D-G) due to thrombus or pannus. The *arrows* in (A) and (B) point to the mechanical leaflets. The transgastric images are obtained during diastole (A) and systole (B). During diastole (A) the *single and double arrows* point to the closed leaflets. During systole (B) the *single arrow* points to the open leaflet while the double arrows point to a persistently closed leaflet, which is confirmed with color Doppler (C) showing flow through the one orifice *(arrow)*. (D)–(G) Echo dense mass obstructing the aortic valve orifice in a patient after aortic valve replacement with a mechanical valve. These masses (*arrows* in D and E) were likely clot given history of recent discontinued coumadin. (F) Color and (G) continuous-wave Doppler imaging show mixed dysfunction of insufficiency and stenosis. *Asc Ao,* Ascending aorta; *AoV,* aortic valve; *LA,* left atrium; *LV,* left ventricle; *LVOT,* left ventricular outflow tract.

from fixed forms of obstruction (see Chapter 24). There is also coexistence of obstruction at different levels.[98]

Trileaflet calcific AS is characterized by calcium collection at the leaflet tips. Rheumatic stenosis is considered with commissural fusion and thickening of the trileaflet valve with a central appearing triangular orifice. Rheumatic AV disease most often occurs in conjunction with MV disease. Bicuspid AS results from fusion of the commissures with or without calcification. The most common configuration of a bicuspid AV is fusion of the right and left commissures with or without a raphe seen. Fusion of the left and noncoronary cusps is least common. A subvalvular membrane may be a simple protrusion of tissue or a circumferential narrowing of the subvalvular space. Supravalvular stenosis appears as an hourglass-shaped deformity in the supravalvular space with or without irregularities of the coronary arteries. Delineating where the obstruction occurs is extremely important to therapy decision making.

Prosthetic Valve Aortic Stenosis

Mild prosthetic AS is not uncommon with the majority of prosthetic valves placed.[21,22] Prosthetic valve areas are less than a normal native AV in the same annular space. Although AVA data vary among different prosthetic valves, in general, a 19-, 21-, or 23-mm prosthetic AV yields an EOA of approximately 1.1, 1.3, and 1.5 cm^2, respectively (see Table 15.3).[88,90,91] Abnormal prosthetic valve stenosis is suspected based on symptoms of heart failure and fatigue, as well as recorded high gradients and/or lower than expected AVA. Causes of prosthetic AS include restricted leaflet motion or mass obstruction (Fig. 15.74).[21,22] Causes of an elevated gradient in the presence of a normally functioning valve include subvalvular obstruction (hypertrophic obstructive cardiomyopathy or a subvalve membrane), supravalvular obstruction, and PPM. Distinguishing flow profiles can identify and differentiate between dynamic outflow tract obstruction, valvular stenosis, and MR (Fig. 15.75).[20,98]

Differences between gradients measured during echocardiography and cardiac catheterization result from pressure recovery phenomena or different techniques to measure peak gradients. The former is the result of energy conversion downstream from the AV, which results in a lower gradient during cardiac catheterization. Doppler echocardiography yields an instantaneous peak gradient while a lower peak-to-peak gradient is measured during invasive catheterization. Regardless, mean gradients remain similar.

Outflow obstruction causes an increase in outflow resistance and an increase in LV stress and pressure. To compensate (ie, maintain forward flow), left ventricular hypertrophy develops and the ventricular contractility increases to overcome the resistance. Although the left ventricular hypertrophy is an important compensation, it also results in diastolic dysfunction. With progression of left ventricular hypertrophy and diastolic dysfunction, hemodynamics become more dependent on a regular heart rate with atrial contraction, diastolic filling time, and maintaining ventricular preload. Over time, increased wall stress, left ventricular hypertrophy, diastolic dysfunction, and increased $M\dot{V}O_2$ with reduced coronary flow reserve result in ischemia, contractile

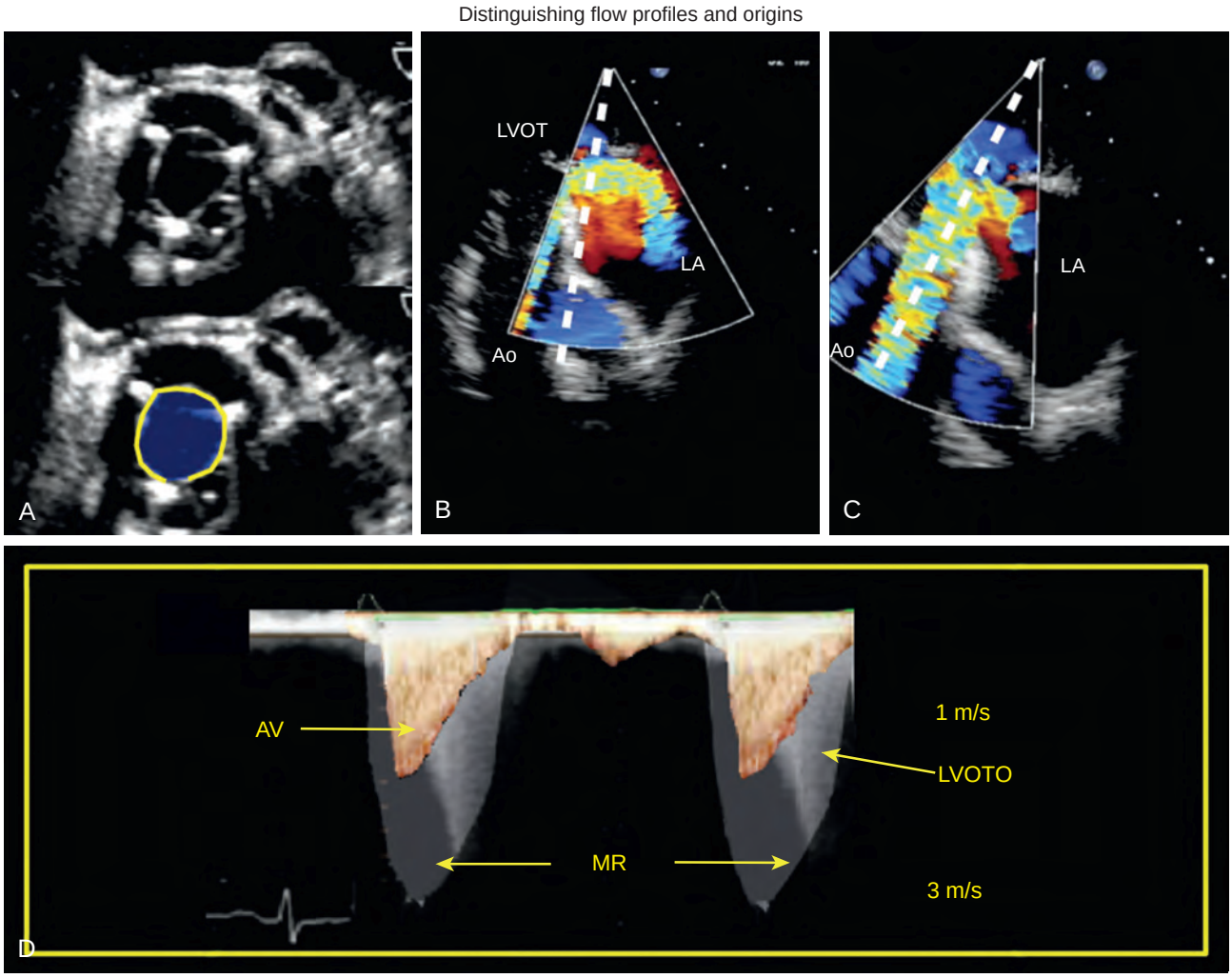

Fig. 15.75 Flow profiles. (A) Short-axis view of a normally functioning bioprosthetic valve immediately after aortic valve replacement. (B) and (C) The period after bypass is complicated by dynamic outflow tract obstruction and mitral regurgitation *(MR)*. (D) Three different Doppler flow profiles recorded during Doppler interrogation from transgastric windows. The valvular profile *(AV)* is lower velocity (approximately 1.5 m/s), early peaking (acceleration time < 80 ms). Left ventricular outflow tract obstruction *(LVOTO)* is a higher velocity late peaking profile. These are distinct from the holosystolic MR profile. *Ao,* Aorta; *LA,* left atrium.

dysfunction, reduced CO, and myocardial fibrosis. Hemodynamic and clinical decompensation occur and regression of left ventricular hypertrophy is less likely to occur despite relief of the obstruction. This is complicated by secondary changes such as increased atrial size and dysfunction with arrhythmias, pulmonary hypertension, and pulmonary edema. Atrial arrhythmias contribute toward further clinical deterioration, and pulmonary vascular changes increase the severity of right-sided heart dysfunction.

Assessing forward flow across the native and prosthetic AV defines valvular hemodynamics and severity of dysfunction[17,21,22] (see Table 15.7). Severity assessment is similar to that of the native AV. Depending on the type of valve, forward blood flow projects in different ways. While bioprosthetic valves have a single forward flow, mechanical valves will have two (single-leaflet) or three (bileaflet) forward projecting jets. Knowledge of expected normal flows helps differentiate them from abnormal valvular flows.

The evaluation includes both qualitative and quantitative assessments, in which the former identifies turbulent or high velocity flows and where to direct the Doppler beams for further quantitative analyses. Although Doppler imaging from ME windows could add to the qualitative assessment, quantitative analysis primarily involves TG imaging in which the ultrasound beam is aligned with transvalvular flow. While stenosis is most commonly a valvular problem, obstruction to ventricular outflow may occur below (subvalvular membrane or hypertrophic obstructive cardiomyopathy) or above the valve (supravalvular stenosis). The coexistence of AI increases flows and, therefore, velocities and gradient.

Qualitatively, AS can be considered based on the presence of turbulence during CFD (exceed Nyquist limit) and/or on the shape of the transvalvular TVI profile[17,21,22] (see Figs. 14-67 and 14-68; Video 14.53) A normal contour of the AV flow velocity profile is an early peaking and triangular shape (see Fig. 15.75). With increasing narrowing or stenosis, the contour peaks later and the shape becomes more round. Along with this change in shape is a respective change in the acceleration time from a relatively short period to the peak velocity (<80 ms) to a more prolonged acceleration phase (>100 ms) consistent with AS.[17,21,22] The profile for AS should be distinguished from those of subvalvular LVOT obstruction and MR, all of which occur in systole (Fig. 15.76).

American Society of Echocardiography level 1 recommendations for assessing AS include measurement of transvalvular jet velocity, calculation of the mean transvalvular gradient, and assessment of the AVA.[17,21,22,88,89] The former two are reflections of AS, and affected by

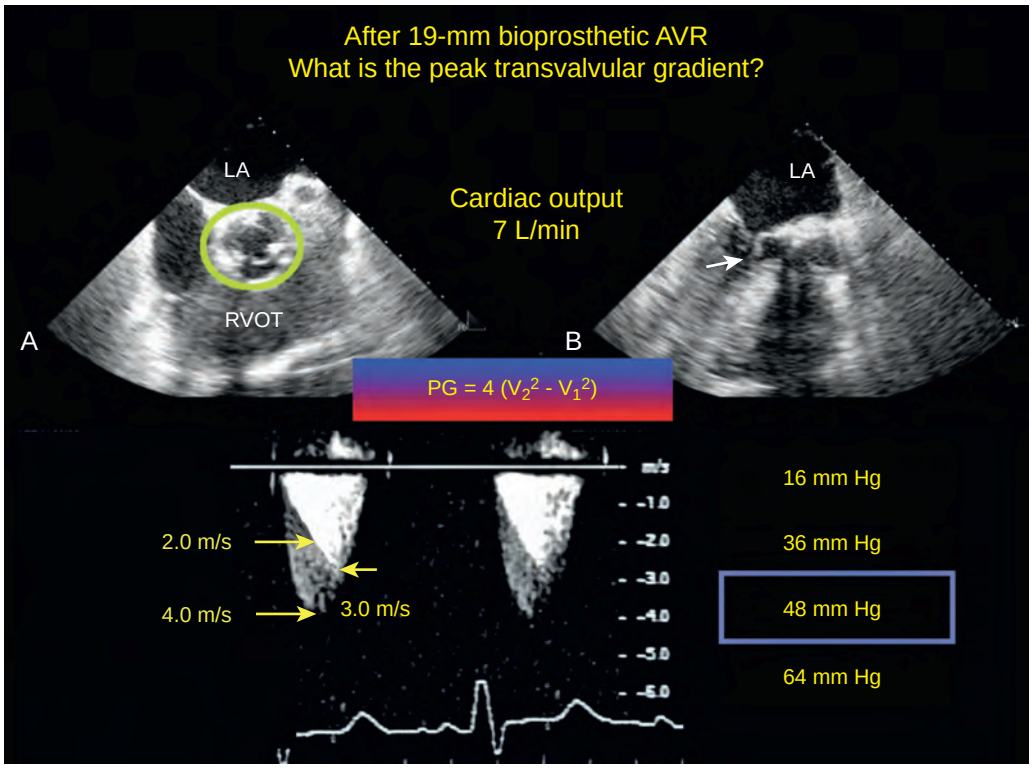

Fig. 15.76 Normal aortic valve *(AV)* and left ventricular outflow tract *(LVOT)*. Short- and long-axis views of the AV during systole. (A) Normally functioning 19-mm bioprosthetic aortic valve. (B) Narrowed LVOT. The continuous-wave Doppler profile shows two distinct flow profiles. The higher peaking profile is generated from the AV while the inner envelope is late peaking and due to dynamic LVOT obstruction. This presents a dilemma when assessing transvalvular gradient, since the subvalvular velocity is high enough it cannot be omitted from the Bernoulli equation. Although the peak velocity is 4 m/s (gradient 64 mm Hg), when considering the subvalvular flows, the more accurate gradient across the valve is closer to 48 mm Hg. *Ao*, aorta; *AVR*, aortic valve replacement; *LA*, left atrium; *PG*, pressure gradient; *RVOT*, right ventricular outflow tract.

chamber pressures and flows.[88,89] The latter can be directly measured, when feasible, using planimetry, or calculated using the continuity equation.

Outcome data and treatment algorithms are based on transvalvular jet velocities and valve area.[99] For velocities less than 3 m/s, AV replacement (AVR) is not recommended and may be of little benefit regarding hemodynamics. A velocity greater than 4 m/s is considered severe and AVR is recommended. For intermediate velocities, other considerations are included in the decision algorithm such as the AVA and amount of AI present. Although simple and reproducible, the evaluator should consider that the jet velocity is dependent on blood flow or CO, as well as the ability to align the ultrasound beam with blood flow.

Peak and mean gradients are calculated from velocities using the Bernoulli equation. Caution must be considered when the subvalvular (LVOT) velocity is elevated (>1.4 m/s) and should be included in the gradient measure. As many as 10% to 15% of AS cases may be associated with subvalvular outflow narrowing or obstruction (see Fig. 15.76). While a mean gradient less than 40 mm Hg does not suggest severe AS, it does not rule it out either. Measuring the AVA by planimetry or calculating it by using the continuity equation may define more accurately the severity of AS by providing an anatomic area or EOA, respectively.[17,21,22] Planimetry is more commonly performed from the ME AV short-axis window. Accurate planimetry may not be possible owing to degree of calcification, imaging artifacts, and the inability to visualize the inner edges of the AV in a planar fashion.[17,88] The continuity equation (conservation of mass) allows calculation of the AVA from Doppler data and a measurement of the LVOT diameter (subvalvular). Clinical data show that peak velocities (V_{LVOT} and V_{AV}) can be substituted for the TVI of the respective sites.[88,89]

The valve area should be considered in the context of each individual case. An AVA of 1.0 has a different impact on a patient with a BSA of 1.5 as compared to one with a BSA of 2.0; indexing the AVA according to the patient size or BSA adds perspective. An indexed AVA (AVAi) less than 0.6 cm^2/m^2 is consistent with severe AS, and an AVAi greater than 0.85 cm^2/m^2 is consistent with mild AS.[29]

A potential source of error in the calculation of AVA by continuity equation is the need to measure the diameter of the LVOT, which is assumed to be circular, which, alone, is a potential error. Two-dimensional measurements have a 5% to 10% error. When the LVOT diameter is halved (radius) and then squared, the total error may be as great 15.20%. An AVA of less than 1.0 cm^2 is considered severe AS.

A simplified dimensionless index (velocity ratio [VR]) that is not affected by the error of 2D measurements or geometric assumptions compares either the TVIs or peak velocities of the LVOT to that across the AV.[17,22,88,89,91]

$$VR = TVI_{LVOT}/TVI_{AV} \text{ or } V_{LVOT}/V_{AV}$$

A value less than 0.25 is consistent with severe AS. This ratio is essentially an abbreviated version of the continuity equation, without the 2D (or 3D) measurements. For the great majority of patients, the LVOT diameter is less than 2.2 cm. If inserted into the continuity equation, a VR of 0.25 would yield an AVA less than 1.0 cm^2. A VR of 0.2 would be consistent with severe AS even for an LVOT diameter as large as 2.5 cm.

Parameters consistent with abnormal (more than mild) prosthetic AV obstruction are similar to that of the native AV and include transvalvular jet velocities greater than 3 m/s, mean gradients greater than 25 mm Hg, and an acceleration time greater than 100 ms.[21,22] Since gradients are affected by hemodynamics, valve function should be more accurately quantified by calculation of the AVA. For all assessments, hemodynamic data should be recorded to help define the meaning of Doppler data.

To avoid error associated with calculating the AVA, a DVI or VR is useful to categorize prosthetic valve opening as normal or not. A VR less than 0.35 is consistent with prosthetic valve stenosis and should prompt further evaluation. The corollary, however, is not as clear. While a VR greater than 0.35 for smaller prosthetic valves (19 and 21 mm) suggests normal opening, larger valves are associated with higher VR (>0.40).[21,22]

Indexing the AVA according to the patient's BSA yields information specific for each patient. Perhaps more clinically relevant is an indexed EOA or AVA (AVA/BSA; cm^2/m^2) of a prosthetic AV. The patient's size or physical needs are considered when determining the size of prosthesis to place. PPM describes the mismatch between the area of the prosthetic valve selection (AVA) and the patient's size (BSA).

$$AVAcm^2/BSAm^2$$

PPM has been categorized as mild, moderate, and severe for EOAi equal to 0.85 to 1.00 cm^2/m^2, 0.65 to 0.85 cm^2/m^2, and less than 0.65 cm^2/m^2, respectively.[29] Outcome data suggest improved short- and long-term outcomes are improved with a properly sized valve. Greater clinically significant outcomes are seen with severe PPM (ie, <0.65 cm^2/m^2). PPM may also have less clinical impact on older adults (older than 75 years) and/or smaller patients (BSA < 1.75 m^2).

Miscellaneous Issues

Analyses should be performed at a time when patient hemodynamics (CO/SV) are optimized, or, at least known. This is especially important for the condition known as low gradient AV stenosis.

$$AVA\ (EOA) < 1.0\ cm^2$$

$$\text{Mean pressure gradient} < 30–40\ \text{mm Hg}$$

Low gradient AV stenosis may be seen in patients with reduced LVEF (<40%) or CO, arrhythmias, and significant MR.[100] In these conditions, reduced flow across the AV is associated with a lower gradient. For such cases, calculation of AVA is necessary. If the AVA is less than 1.0 cm^2, a stress echocardiogram (either exercise or dobutamine) should be considered to differentiate between true AS and pseudo-AV stenosis, the latter being the result of reduced opening forces. Hemodynamic goals of the test include an increase in the heart rate of either 10 to 20 beats/minute, an increase of more than 100 beats/minute, and/or an increase in SV or ejection fraction of 15% to 20%. True AS is characterized by a rise in the mean gradient greater than 40 mm Hg with a persistent AVA less than 1.0 cm^2. An increase in the AVA greater than 1.0 cm^2 supports pseudo-AV stenosis. An absence of a hemodynamic response to stress (ie, no change in LVEF) suggests a lack of contractile reserve, which is associated with increased morbidity and mortality with surgery.

Other conditions that affect the echocardiographic-derived gradient include poor alignment of the ultrasound beam with blood flow, which may underestimate the true flow velocity and subsequently calculated gradient. The presence of AI and/or a high flow state will increase jet velocity and overestimate the severity of AV obstruction. Erroneous measurement of the mitral regurgitant jet will cause overestimation of the true transaortic valve velocity. The former is a holosystolic jet compared to a decrescendo-crescendo flow profile (see Fig. 15.75). Finally, sequential narrowings (subvalvular or supravalvular stenoses or obstructions) affect detection of the true gradient across the AV (see Fig. 15.76).

Differences in pressure gradient between that obtained during cardiac catheterization and echocardiography can occur as a result of poor alignment between the ultrasound beam and blood flow, causing an underestimation during Doppler echocardiography. The peak gradient during echocardiography is an instantaneous peak gradient and is larger than that measured during catheterization, which is the gradient between the peak transvalvular pressure and the peak LV pressure. During catheterization the two peaks occur at different times. A third cause is a phenomenon called *pressure recovery*. When flow crosses the stenotic AV, potential energy is converted to kinetic energy and a high pressure gradient is recorded.[17,21,101,102] However, downstream from the stenotic valve, energy is lost to turbulence and viscous forces. Energy may be converted back to potential energy, causing a rise in pressure or pressure recovery. The amount of pressure recovery is related to the differences in the cross-sectional area (CSA) of the ascending aorta.

$$PR = 4v^2 \times 2EOA/AoA \times (1 - EOA/AoA)$$

Pressure recovery is related to the ratio of the EOA/AoA or the EOA of the AV and the CSA of the ascending aorta. Pressure recovery is most significant for patients with an ascending aortic diameter less than 3.0 cm.

Surgical or Procedural Intervention

Surgical or transcutaneous AVR is indicated for severe AS with symptoms[8–10,24–26] (Fig. 15.77). Surgical AVR also should be considered for asymptomatic patients with severe AS undergoing other cardiac or aortic procedures, or in the presence of LV systolic dysfunction (LVEF <50%) without another cause, an abnormal exercise/stress test result, and/or those who might be suitable candidates for TAVR. AVR can be considered for moderate AS in patients undergoing other cardiac surgical procedures. Other considerations might include asymptomatic patients with very severe AS (peak velocity >5.5 m/s), or low gradient (mean <40 mm Hg) AS if reserve function is documented and it is believed that the AS is true and contributing toward the low flow state.

Tricuspid Valve

Normal Anatomic and Functional Features

The normal TV area is 4 to 6 cm^2 and the normal annular diameter is less than 28 mm. The TV has three unequal-sized leaflets (septal, anterior, posterior). Like the mitral annulus, the TV annulus is a 3D saddle-shaped ellipsoid structure that changes its shape and area during the cardiac cycle.[103,104]

The septal leaflet is attached to the medial or septal wall, which is in continuity with the fibrous trigone of the heart. The posterior leaflet is the smallest of the three leaflets. The anterior leaflet is the largest of the three. The leaflets are attached via chordae to three respective papillary muscles and each papillary muscle gives off chords to at least two leaflets. Congenital variations include two to nine papillary muscles and as many as six leaflets.

In the presence of RV enlargement or failure, tricuspid annular enlargement occurs and the annulus becomes more planar. The septal area is attached to the fibrous trigone and stays relatively stable. Annular dilation tends to occur anteriorly and laterally away from the fibrous skeleton and is associated with the development of TR.

Prosthetic or Repaired Tricuspid Valve

The importance of TV function and its impact on right-sided heart function and patient outcome is increasingly appreciated.[105–109] As a result, TV surgery has increased either alone or in association with surgical procedures on the left side of the heart. The majority of TV surgeries are treating TR, and more than 80% are repaired. However, valve replacement is performed with primary valve disorders (endocarditis, rheumatic valvitis, carcinoid syndrome, traumatic rupture) or for patients in whom recurrent regurgitation is suspected after repair.[110,111]

The TV should be assessed for disease, function, and indications for surgery.[24,25] Severe TV dysfunction is an indication for surgery. Moderate TV dysfunction should receive consideration for surgery

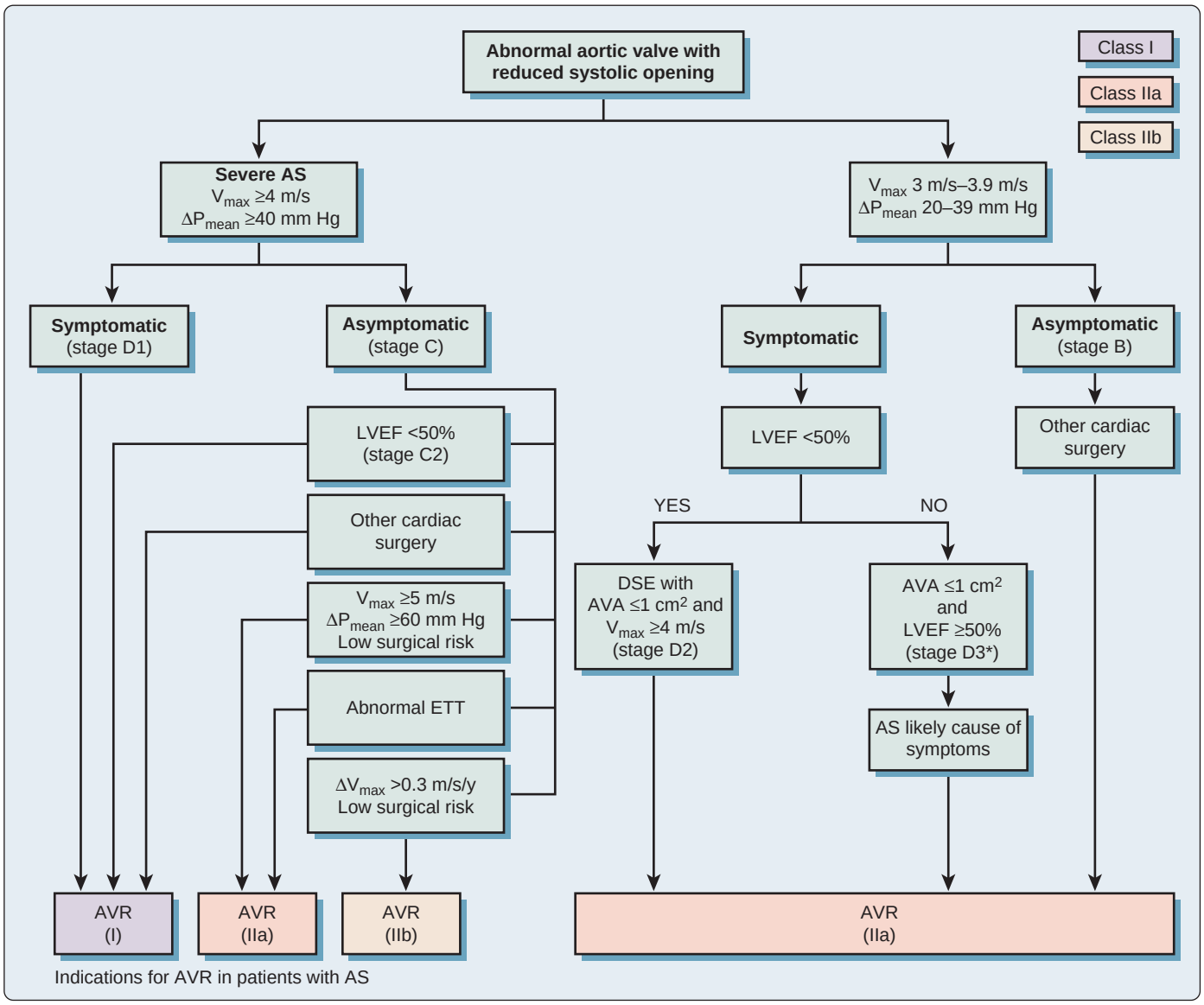

Fig. 15.77 Decision algorithm for AS. The decision algorithm was taken as a consensus by an expert panel and based on outcome data and interpretation. Decisions are classified as class I, class IIa, class IIb, the former being supported by sufficient evidence such that intervention should be performed, while the latter two are supported by evidence that suggests that benefits of intervention outweigh the risks and that intervention is reasonable based on multiple (IIa) or isolated trials or nonrandomized data (IIb). Treatment for AS usually includes percutaneous intervention. The decision is based on a number of considerations including severity, presentation (symptoms), changes in cardiopulmonary function, and timing (ie, whether other cardiac surgical procedures are scheduled). *AS,* aortic stenosis; *AVA,* ; *AVR,* aortic valve replacement; *DSV,* ; *ETT,* ; *LVEF,* left ventricular ejection fraction. *(Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57–e185.)*

when patients are undergoing surgical procedures for the left side of the heart. Primary TV leaflet pathology increases the likelihood that valve replacement may be necessary. Valve repair for regurgitant valves is a first consideration; however, if recurrent dysfunction is predicted and/or primary leaflet pathology is not repairable, then replacement is considered. The value of echocardiography cannot be overstated.

For assessing post-TV repair or replacement, it is important to know the details of the surgical procedure, including what kind of valve was placed or how the valve was repaired. Previous knowledge of normal echocardiographic findings for specific valves and/or successfully repaired valves help delineate what is normal and what is not. Details include whether or not a bioprosthetic or mechanical valve was placed and what kind of valve and how many leaflets are present. For valve repairs, annulus type (flat vs saddle shaped, full vs partial), leaflet resection or repair, or augmentation helps practitioners understand what is seen during imaging. TV repair mainly consists of annular reduction with a prosthetic annuloplasty ring or suture (DeVega procedure). Similar to a repair for MR, more severe functional impairment at baseline increases the likelihood for repair failure; thus, replacement may be necessary. For all echocardiographic assessments,

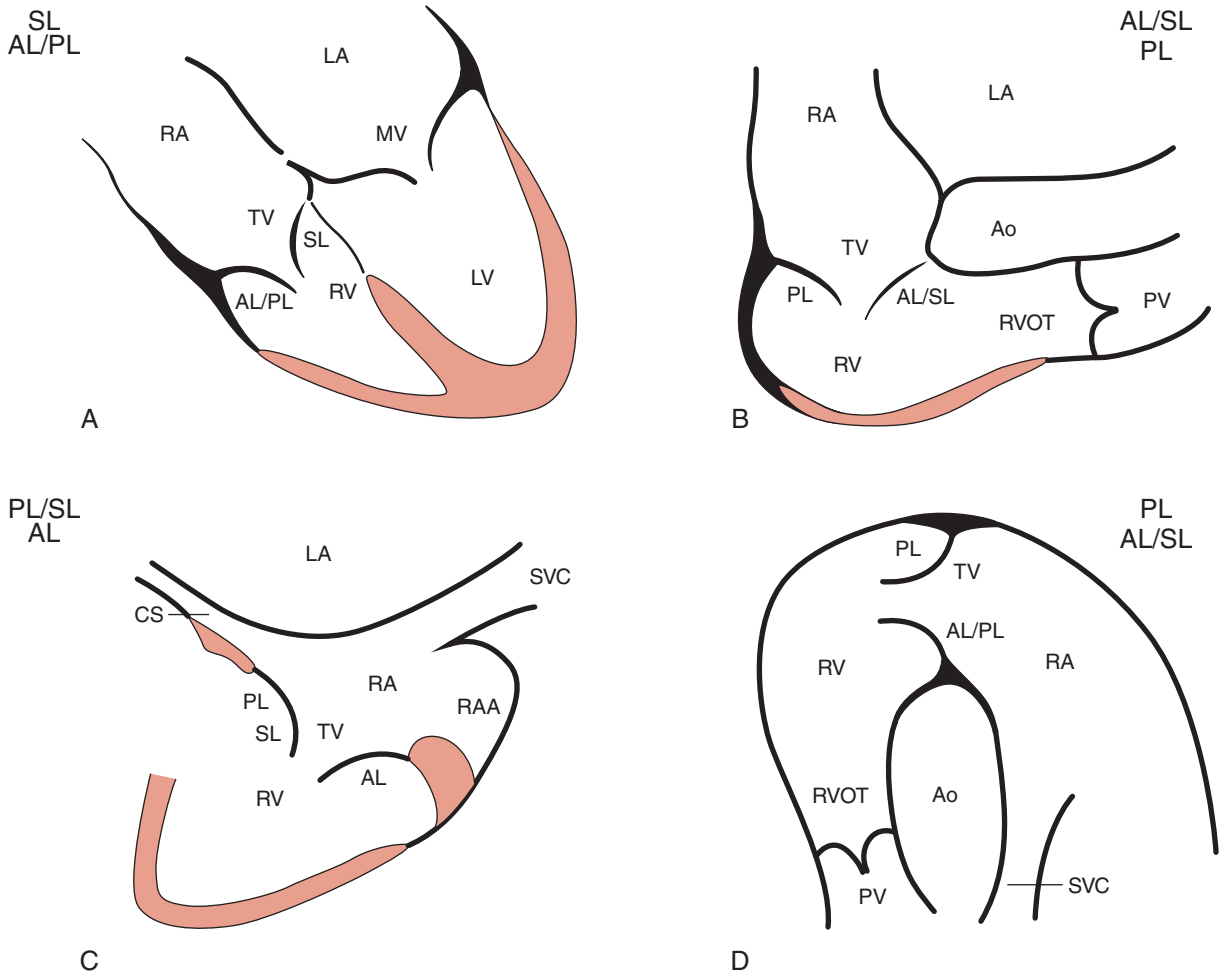

Fig. 15.78 Tricuspid valve *(TV)* imaging windows. The schematics represent the typical echocardiographic windows used to visualize the TV allowing color Doppler assessment (better facilitated from midesophageal windows) and annular measurements, which may be more accurate from the transgastric windows. (A–C) are obtained from midesophageal windows (four-chamber, right ventricular inflow/outflow, and coronary sinus view) while (D) is obtained from a transgastric window with the transducer rotated between 110 and 140 degrees. Depending on the rotation of the transesophageal echocardiography probe, the image may display anterior *(AL)*, septal *(SL)*, or posterior *(PL)* leaflet. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *RA*, right atrium; *RAA*, right atrial appendage; *RV*, right ventricle; *RVOT*, right ventricular outflow tract; *SVC*, superior vena cava.

recording of the patient's hemodynamic status improves the perspective at the time of evaluation.

The Echocardiographic Examination

The 2D examination involves visualization of the TV and its surrounding tissues[112] (Fig. 15.78). The assessment should evaluate leaflet mobility, thickness, integrity, masses, and stability within the annular tissues.[17,18,20] Extraneous mobile structures or materials before and after surgery may represent endocarditis, rupture or tears of the subvalvular apparatus, or suture or retained native tissues after valve surgery. Rocking or unstable annular motion or an echolucent space might suggest abscess or dehiscence of a prosthesis. The greater the amount of leaflet disease there is, the more likely valve replacement will be necessary.

A part of the 2D exam is to determine whether or not the regurgitant TV should and could be repaired, or whether or not valve replacement is warranted. Determining whether or not TR progresses or regresses involves a number of variables. The greater the amount of TV leaflet disease, the less likely that TR will improve and that repair will be feasible.[105,110,111] TR that results from either annular dilation and/or leaflet tethering can be repaired. The long-term success of the repair can be determined by assessing the geometry of the TV apparatus (see Fig. 14-92). Progression of TR is likely with a TV annular diameter larger than 2 cm/m^2, especially if the change in annular diameter during the cardiac cycle is less than 20%.[18–20] These are reflective of significant long-standing regurgitation and less reversibility of annular changes.[113] Similar to the MV, leaflet geometry or tethering can be used to predict successful repair. Tethering heights greater than 0.8 cm and/or tethering areas greater than 1.6 cm^2 reflect significant geometric changes, are associated with severe TR, and are less likely to be successfully repaired with regard to long-term event-free survival[110,114,115] (Figs. 15.79 and 15.80).

Previous data suggest that the TV annulus should be measured from TG and not TE windows.[112] Since the TV annulus is complex, multiple views and measurements yield a more complete assessment, and the largest annular diameter should be measured. More recent 3D data confirm that the annulus dilates anteriorly and that the annulus may be either elliptical or circular, the latter reflecting long-standing and severe TR (Figs. 15.81 and 15.82). Although the 3D data highlight the complexity of the TV annulus, outcome data up until now have been based on 2D imaging during which the largest diameter should be sought.

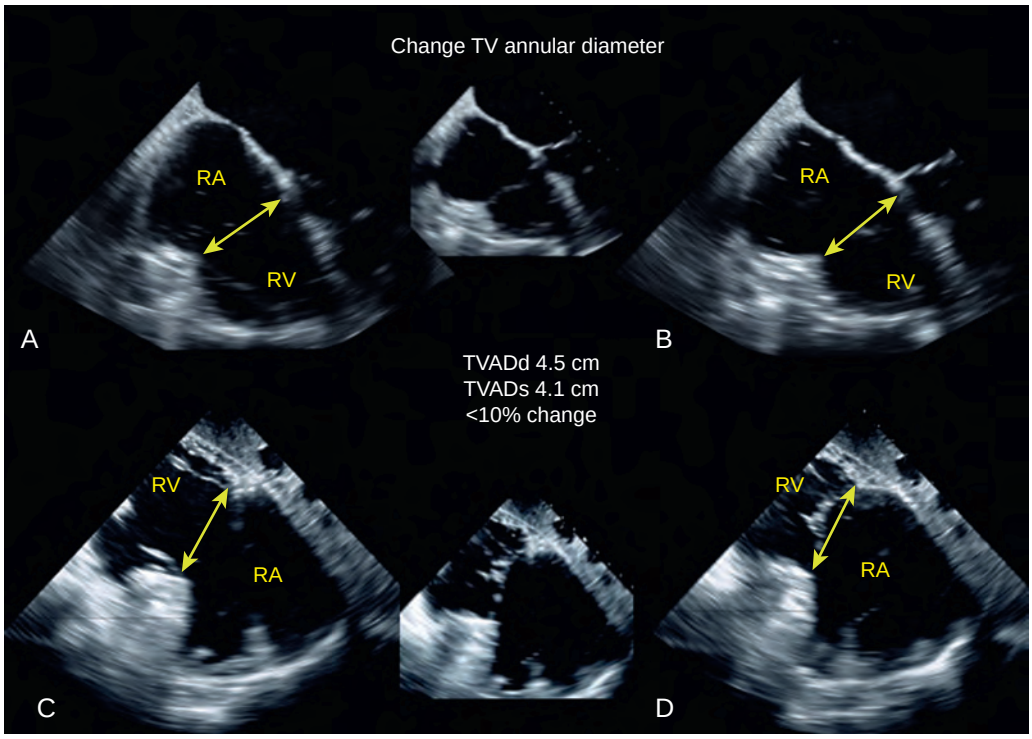

Fig. 15.79 Assessment of tricuspid annular changes. Using two echocardiographic windows, the change in tricuspid valve annular diameter *(TVAD)* is assessed during the cardiac cycle to help determine reversibility of tricuspid regurgitation (TR) in helping to determine whether or not a repair should be considered. (A) and (B) Midesophageal four-chamber views. (C) and (D) Transgastric views. A change less than 10% supports performing tricuspid valve surgery if TR is present. *RA,* Right atrium; *RV,* right ventricle.

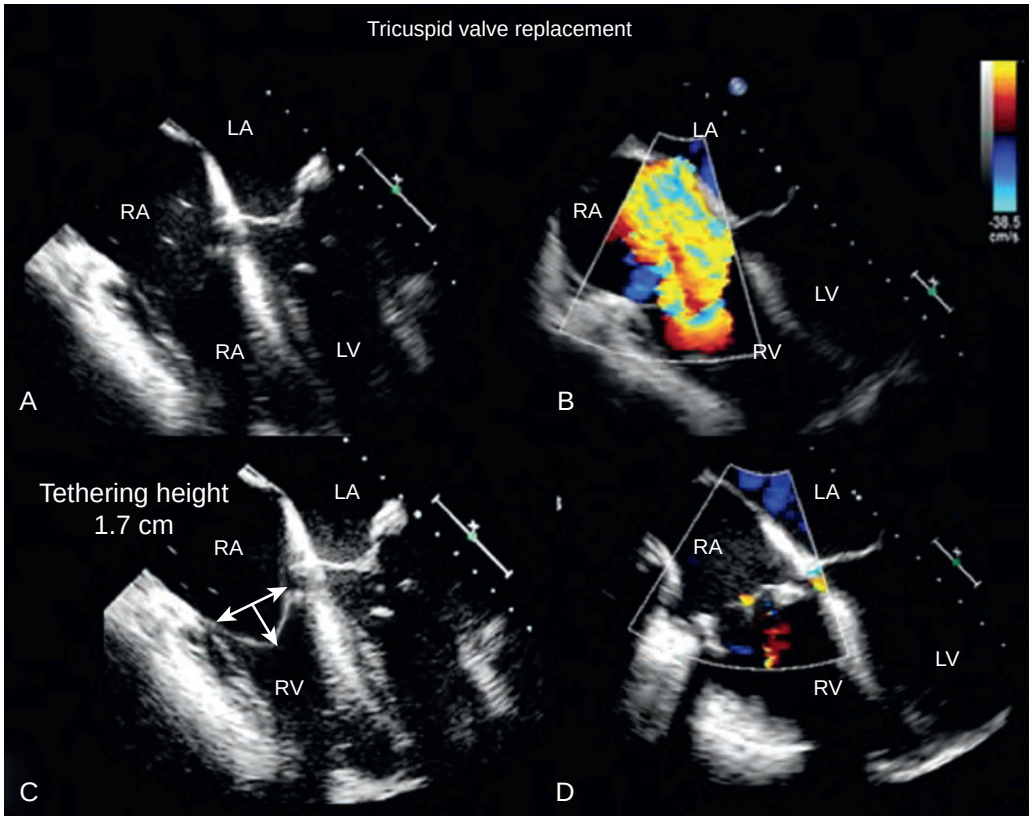

Fig. 15.80 Severe functional tricuspid regurgitation (TR) and tethering. (A) and (B) From the midesophageal four-chamber view, a case of severe functional TR is shown. (C) The annular dimensions and tenting height are measured to assess the severity of tricuspid valve dysfunction. (D) Similar to mitral valve tethering, significant tricuspid valve tethering suggests ventricular remodeling. For the tricuspid valve when the tenting height is greater than 1.0 cm, ventricular changes may be severe enough such that a tricuspid repair may not adequately eliminate regurgitation. For such cases, valve replacement should be considered. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

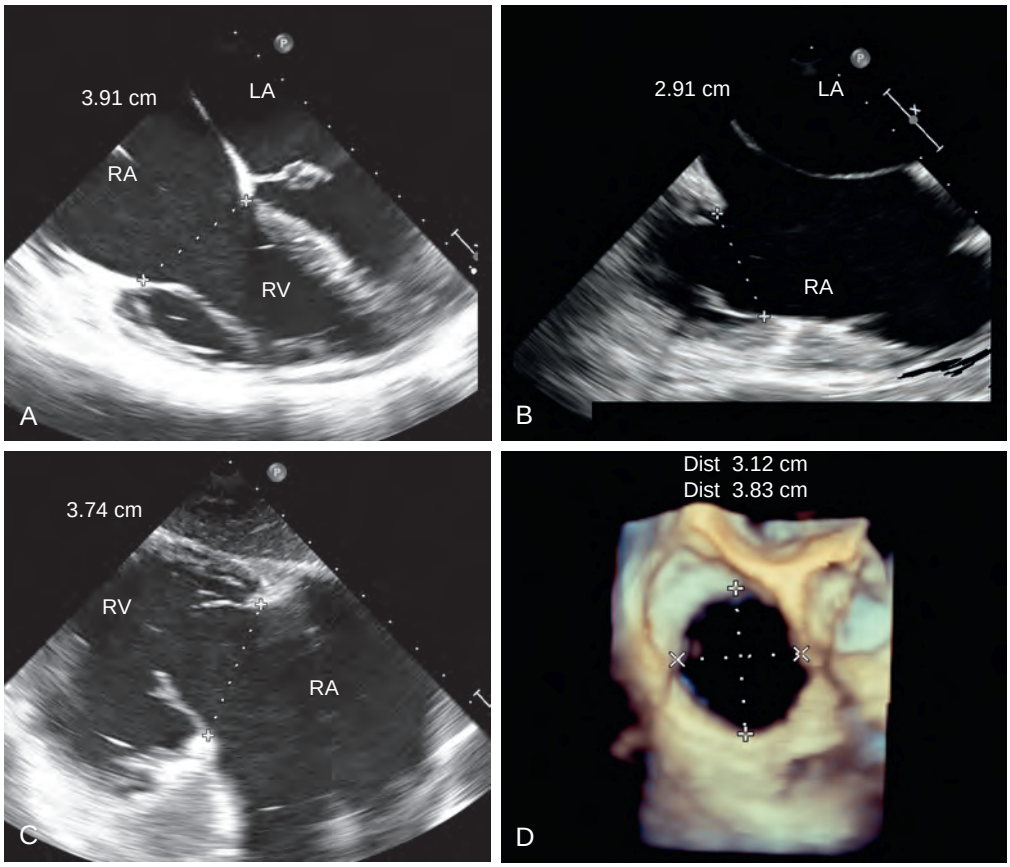

Fig. 15.81 Annular diameter assessment with two- (2D) and three-dimensional (3D) imaging. The introduction of 3D imaging demonstrates that the shape of the tricuspid valve (TV) annulus is not easily predicted. (A–C) Significant variability of the 2D annular diameters likely represents variations of the imaging plane and rotation of the transesophageal echocardiography probe. (D) The 3D image is able to identify these variabilities and perhaps yield a more accurate assessment of TV annular dimensions. However, to this date, tricuspid regurgitation outcomes are still based on 2D imaging. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle.

The Doppler examination includes color (CFD), pulsed-wave, and continuous-wave techniques. The former allows both qualitative and quantitative evaluations, including occurrence, direction, and width of normal and abnormal blood flows in and around the prosthetic valve. The normal transvalvular velocity is less than 0.7 m/s. CFD highlights areas of turbulence, suggesting high velocity flows. Quantitative analyses can be performed from both conventional and CFD imaging of blood across the TV. Additional quantitative Doppler assessment includes tricuspid peak velocities, pulmonary valve insufficiency (PI), and calculation of the RV and PA pressures using the Bernoulli equation.

Prosthetic valve function and appearance are assessed by echocardiography. Images are similar to those of the same valves in other cardiac positions. Assessment includes multiple windows to determine function, assess for disease, and help determine the need for further surgery (Fig. 15.83).

Tricuspid Regurgitation

Normal mild TR is found in up to 75% of patients without clear disease or reason and is considered normal (Fig. 15.84).[116] Pathologic TR either results from a primary valvular disorder or is secondary to either primary RV dysfunction or pulmonary hypertension and increased afterload. Similar to other valvular regurgitations, TR can be described by leaflet mobility (ie, normal, excessive, and restrictive) (Table 15.8).

TR, regardless of it origin, causes a volume overload state that contributes to the progression of right-sided heart failure and greater TR. Patients present for fatigue, atrial fibrillation, and/or signs and symptoms reflecting right-sided heart failure (ascites, hepatomegaly, peripheral edema, jugular venous distention). The echocardiographic examination identifies the presence and origin of TR and assesses the severity of TR. Depending on the echocardiographic findings, the surgeon may decide to repair the valve or replace it. Valve replacement may be preferred if significant tethering of the TV leaflets or primary TV disease is noted and not thought to be adequately managed with a repair (ie, annular reduction alone).

The more common primary causes of TR include rheumatic valvitis (restrictive), myxomatous degeneration (excessive), and endocarditis (excessive).[105] Excess mobility may also result from trauma. Secondary causes account for the majority of TR cases, and the leaflets appear normal with either normal or restricted mobility. Secondary TR is associated with right-sided heart dysfunction, dilation, and annular changes, the latter including dilation, flattening, and development of a circular shape (from an ellipsoid).[113] Depending on the severity of dysfunction, the leaflets may appear restricted or tethered, reflecting either papillary muscle dysfunction or RV remodeling. Other causes of TR include radiation or the presence of catheters or wires passing between the TV leaflets preventing their closure.

The echocardiographic examination helps to determine the diagnosis, severity of dysfunction, and whether or not surgery is indicated. It also determines whether there is excessive mobility, as with myxomatous/degenerative changes, endocarditis, or trauma, or restricted/tethering changes seen with functional TR, or, in the presence of short and thickened leaflets (ie, rheumatic valvitis, radiation,

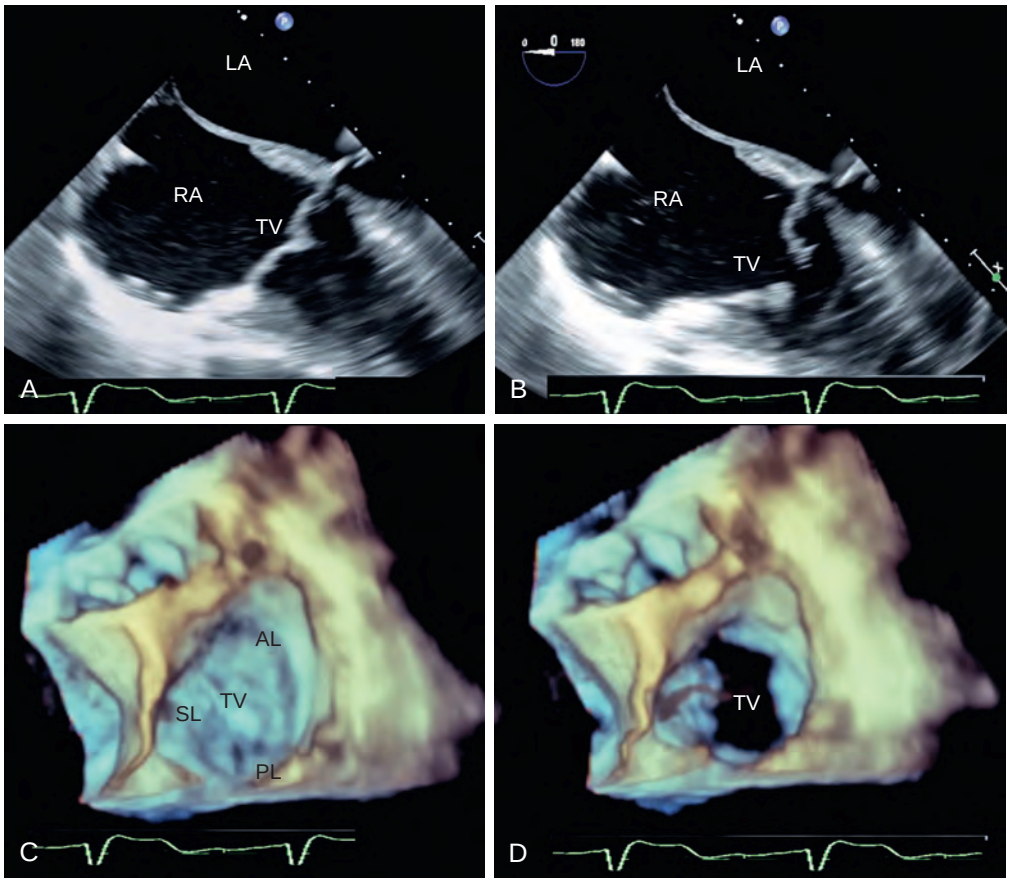

Fig. 15.82 (A) and (B) Two-dimensional and (C) and (D) three-dimensional (3D) images of the tricuspid valve *(TV)* annulus and leaflets during the cardiac cycle. Although the potential for 3D assessment of the TV leaflets is possible, it is our experience that it is not consistent, perhaps owing to the thinness of the leaflets. *AL,* Anterior leaflet; *LA,* left atrium; *PL,* posterior leaflet; *RA,* right atrium; *SL,* septal leaflet.

TABLE 15.8 Tricuspid Regurgitation: Degrees of Severity

	Mild	*Moderate*	*Severe*
Angiographic grade	1	2	3
Color Doppler jet area (cm^2)	<5	5–8	>8
Vena contracta width (cm)	—	<0.7	>0.7
Caval size (cm) with or without respiratory variation	≤1.5 with 50% variation	1.5–2.0 Variable respiratory effects	>2.0 without variation
Cava and/or hepatic vein flow	Systolic predominance	Systolic blunting	Systolic blunting or reversal
Regurgitant orifice area (cm^2)	—	—	>0.4
Regurgitant volume (mL)	—	—	>45
PISA radius (mm; with NL 15–40 cm/s)	<5 mm = mild >9 mm = severe		
Secondary findings	IVC/SVC dilation, PHTN, RAE, RVE		

IVC/SVC, Inferior vena cava/superior vena cava; *NL,* Nyquist limit; *PHTN,* pulmonary hypertension; *PISA,* proximal isovelocity surface area; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement.

carcinoid) (Figs. 15.85–15.87). The presence of normal-appearing leaflets with or without normal mobility points to TR from secondary RV dysfunction and/or pulmonary hypertension.

The echocardiographic findings guide the choice of surgical procedure. Most cases of TR can be repaired (>80%), especially for annular dilation (>2 cm/m^2) with normally appearing and mobile leaflets. However, TR in the presence of significant leaflet pathology and/or restriction suggested by tethering with a tenting height greater than 1.0 cm or tenting area greater than 1.6 cm^2 are less likely to improve with repair and may even progress more (see Figs. 15.79, 15.80, 15.87). The actual goal of reduction annuloplasty may vary from returning the annulus to normal (<3.0 cm) or a 25% reduction from the preoperative baseline (Fig. 15.88).

Prosthetic valve (or repaired valve) regurgitation is assessed in similar fashion to the native TV. Regurgitation is caused by either excessive or restricted leaflet mobility. In the case of prosthetic valves, paravalvular leak can occur. Diagnoses include endocarditis, leaflet deterioration, restricted or stuck leaflet, and/or dehiscence/abscess.

Assessing regurgitant flow of the native and prosthetic TV is similar (see Table 15.8). Analysis of Doppler imaging helps the practitioner detect, describe, and quantify TR. Imaging includes both TE and TG

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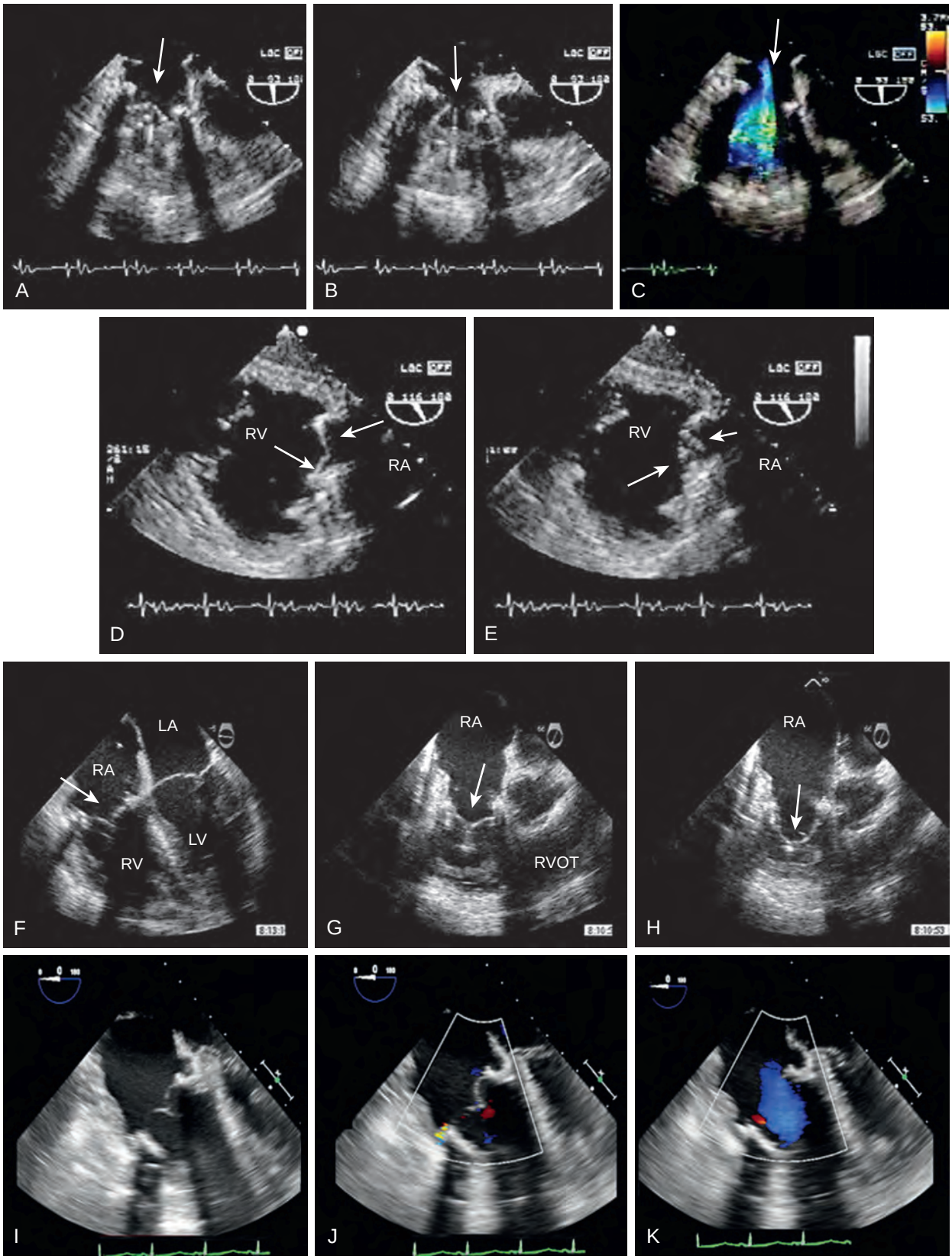


Fig. 15.83 Normal prosthetic valves in the tricuspid position. Normal functioning (A–E) mechanical and (F–K) bioprosthetic valves in the tricuspid position during both two-dimensional and color Doppler imaging. As can be seen, depending on surgical placement and valve rotation, imaging may include a variety of transducer angles and probe positions. *LA,* Left atrium; *LV,* left ventricle; *MV,* mitral valve; *RA,* right atrium; *RV,* right ventricle; *RVOT,* right ventricular outflow tract.

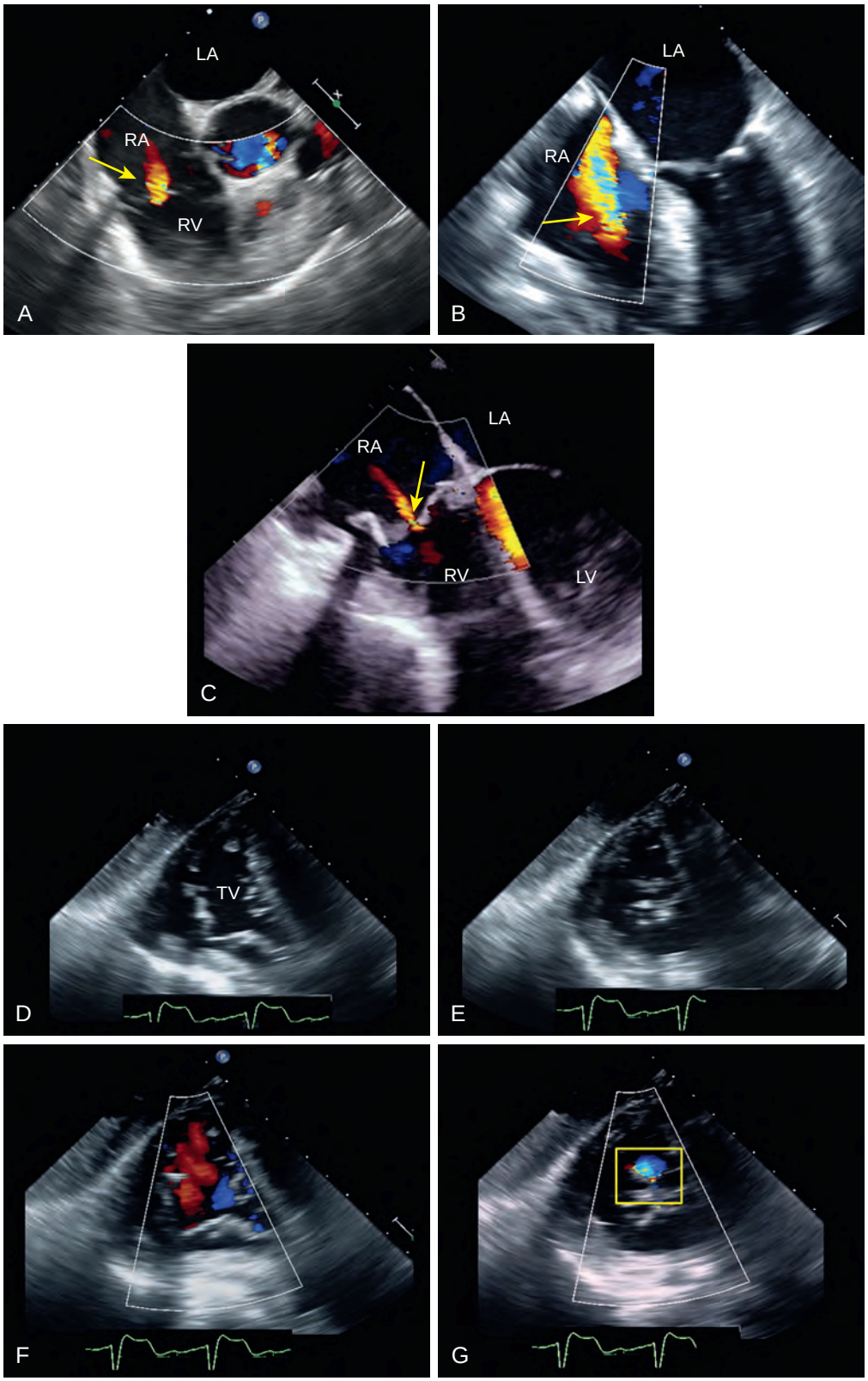


Fig. 15.84 Tricuspid jet width. Views are generated by four different patients. (A) Mild and (B) severe tricuspid regurgitation based on the measured vena contracta. (C) Normal functioning bioprosthetic valve with a small central regurgitant jet *(arrow)*. (D–G) Tricuspid valve *(TV)* and regurgitant jet can be assessed from transgastric images of the TV in a short-axis view. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

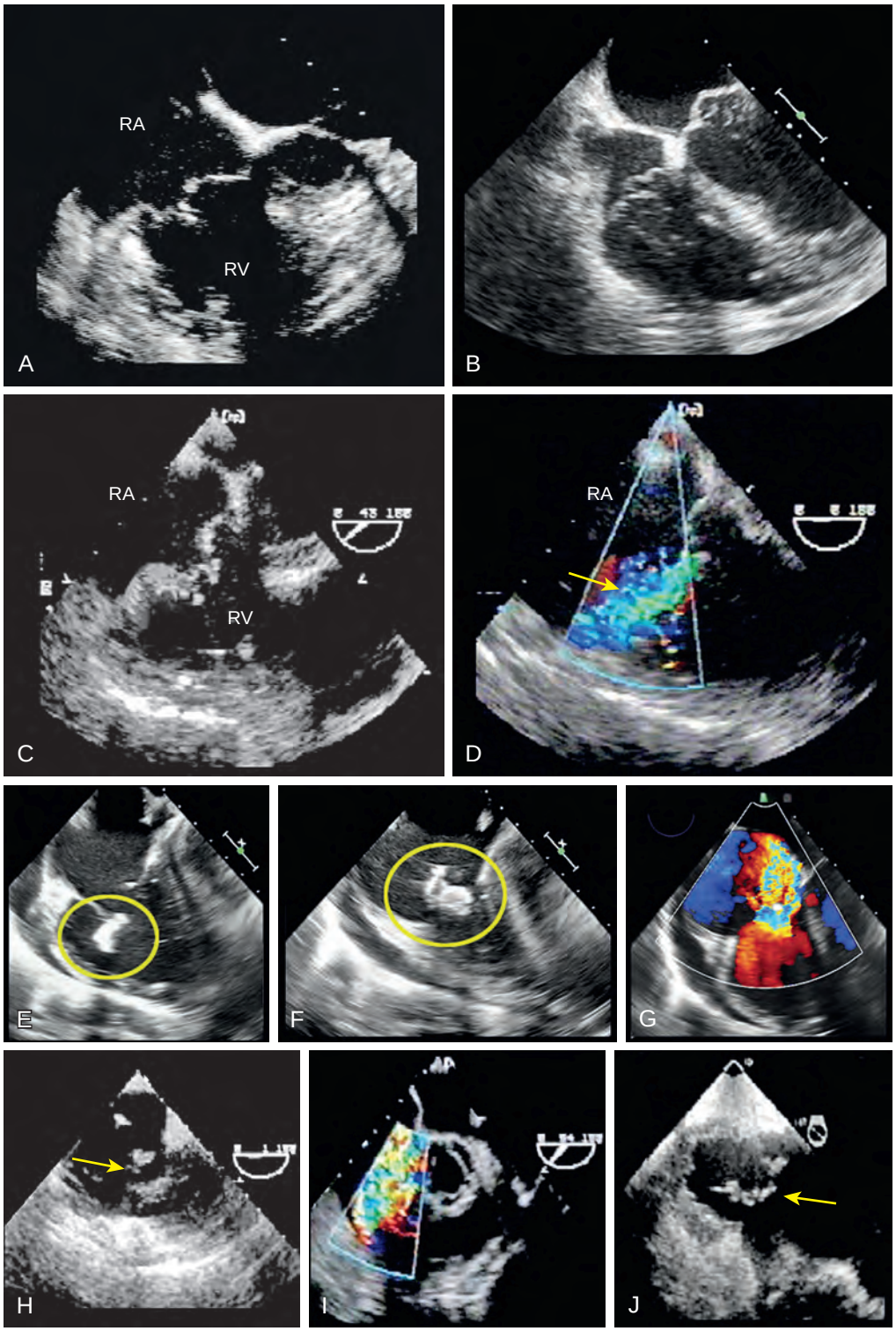


Fig. 15.85 Excessive tricuspid valve leaflet motion. Images are from four different patients. (A) and (B) Myxomatous changes in the tricuspid leaflets. (C) and (D) Severe eccentric tricuspid regurgitation (TR) directed away from the prolapsing septal leaflet *(arrow)*. (E–G) Endocarditis with severe TR *(circles)*. (H–J) Trauma victim with rupture of the anterior leaflet causing severe TR *(arrows)*. *RA,* Right atrium; *RV,* right ventricle.

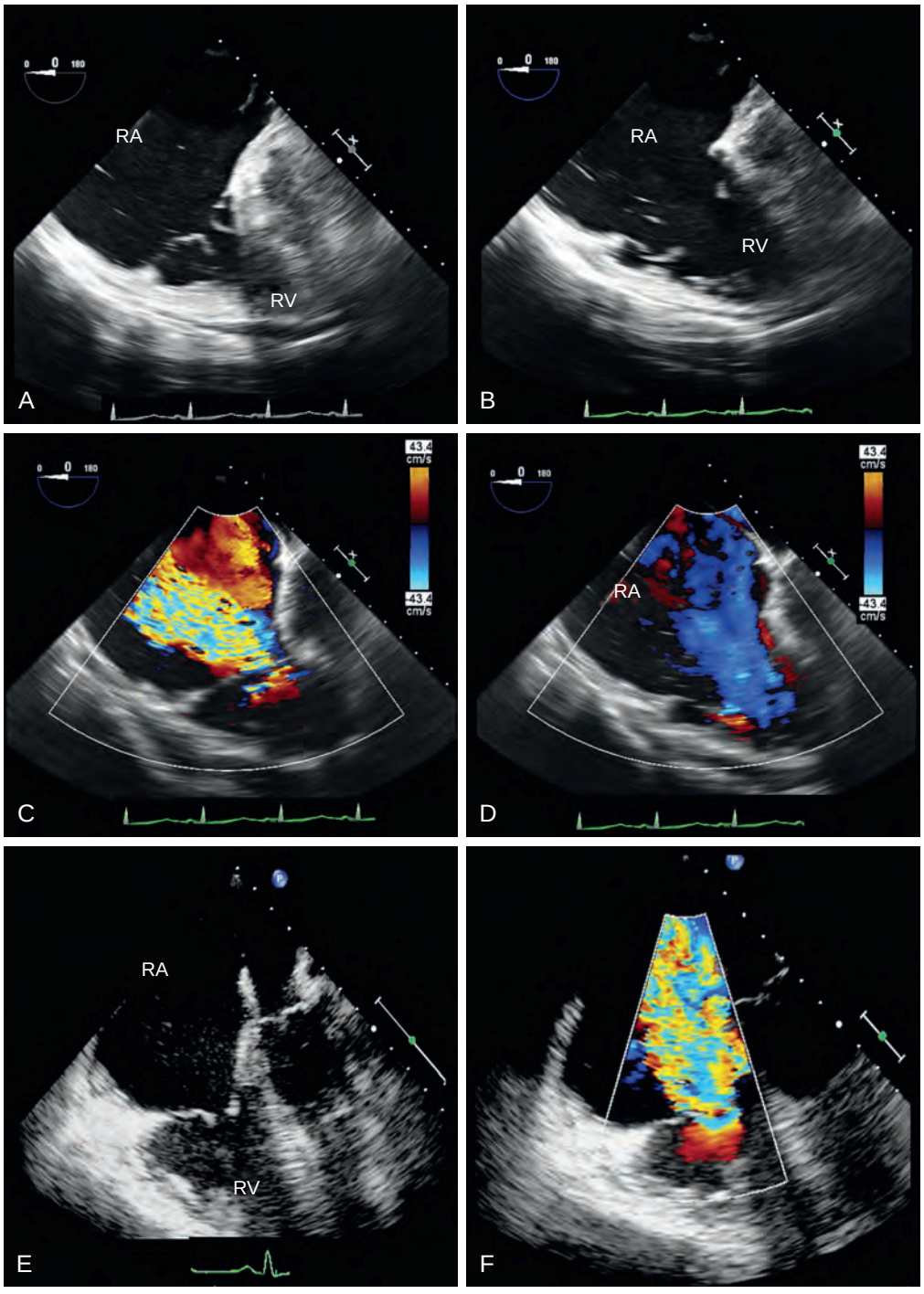


Fig. 15.86 Restricted tricuspid valve (TV) leaflet. Contrasting Fig. 15.85, these images were obtained from two different cases of restricted tricuspid leaflet causing severe tricuspid regurgitation (TR). (A–D) Images from a patient with rheumatic disease (confirmed by pathologic examination) during (A and C) systole and (B and D) diastole with two-dimensional and color Doppler imaging. (C) Severe TR. (E) and (F) Carcinoid involvement (confirmed by pathologic analysis) of the TV. In both cases severe TR was present and both patients underwent valve replacement. *RA*, Right atrium; *RV*, right ventricle.

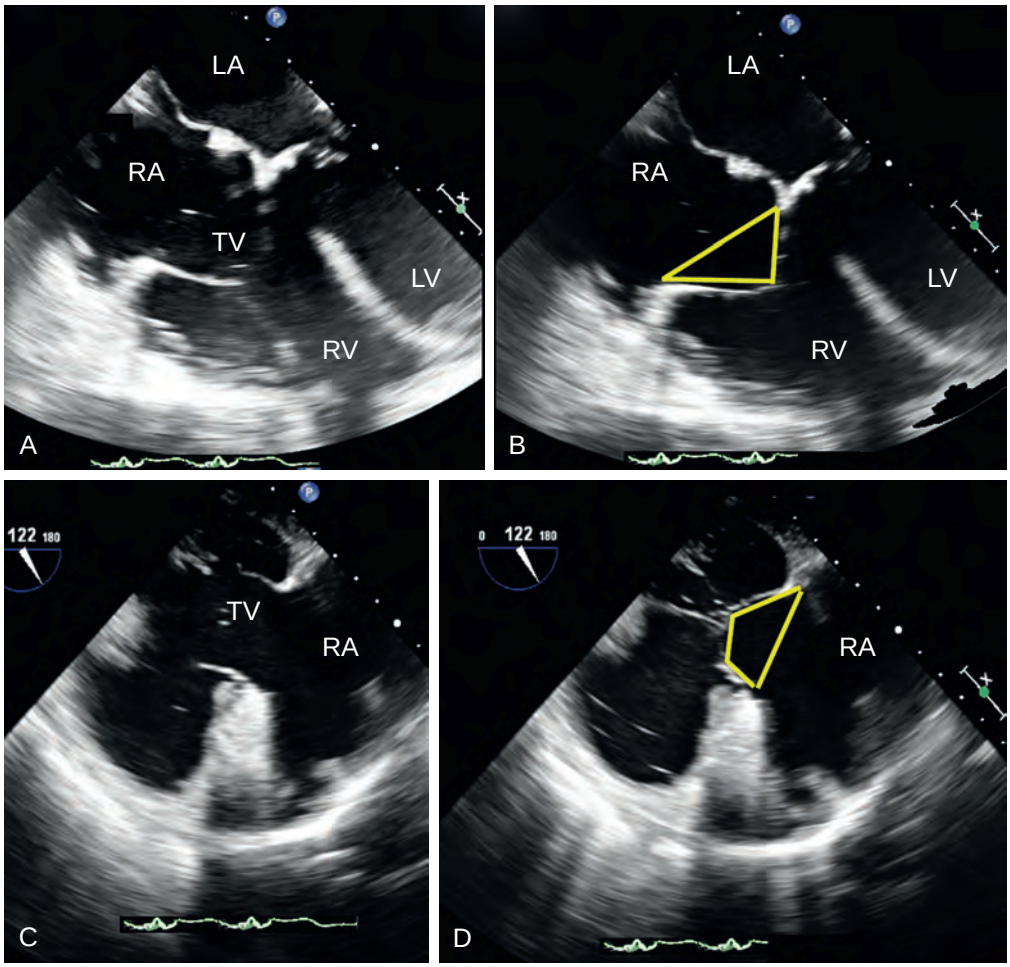


Fig. 15.87 Tricuspid leaflet tethering. (A–D) This patient has severe functional tricuspid regurgitation and significant tethering of the tricuspid valve leaflets resulting from right ventricular dilation and remodeling. The tenting height measured from both (B) midesophageal and (D) transgastric windows was greater than 1.0 cm. Valve replacement was performed. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

windows to assess the presence, severity, and cause of regurgitant flows. Approximately 70% to 80% of patients have mild TR without structural abnormality and, in the absence of disease, may be considered normal.[116] Normal or acceptable regurgitant jets are typically less than 3 mm in width.[69] For prosthetic valves, any paravalvular regurgitant jet is abnormal; however, if the jet is less than 3 mm in width, it is likely to either remain stable or decline on follow-up. Regurgitant jets greater than 3 mm signify greater than mild TR in severity.

Assessing severity of regurgitant flow is similar for native, postrepair, and prosthetic valves (see Table 15.8). Parameters associated with abnormal and more than mild TR include caval diameter greater than 1.5 cm with some amount (<50%) of variation during the respiratory cycle.[105] Specific assessments of the TR jet are not as well studied compared to the MV. Qualitatively, a dense and complete appearance during continuous-wave Doppler is consistent with significant TR. Although the color Doppler jet area is not specific for all levels of severity, a value greater than 8 cm^2 is consistent with severe TR.[18–20,69] A VC greater than 0.3 cm (>3 mm) is abnormal.[69] A VC greater than 7 mm is consistent with severe TR. Although it might be assumed that a VC between 0.3 cm and 0.7 cm suggests moderate TR, the literature reports relatively lower specificity and sensitivity.[69] The presence of flow convergence is considered abnormal. Quantifying effective regurgitant orifice area (EROA), regurgitant volume, and regurgitant fraction are not well studied. However, with the Nyquist limit set between 15 and 40 cm/s, a PISA radius greater than 9 mm is consistent with severe TR, while less than 5 mm is consistent with mild TR.[18–20,69] An EROA greater than 40 mm^2 and a regurgitant volume greater than 45 mL are consistent with severe TR. The value of at least identifying, and perhaps quantifying, flow convergence has been shown for eccentric TR jets, with which the jet area underestimates severity and measures of VC may be difficult.[117]

Additional data that allude to either the cause or the presence of significant TR include RV and right atrial (RA) dysfunction, and increased PA pressures.[118] RA and RV dilation and dysfunction may result in TR via annular dilation and/or leaflet tethering, but also, with continued regurgitation are secondarily affected. If the majority of TR is functional and secondary, then the presence of pulmonary hypertension may allude to the causative factor and may also be a target of medical therapy. Systolic flow reversal in the venae cavae or hepatic veins is consistent with moderate or worse TR. A dilated vena cava that changes little during the cardiac cycle is consistent with a volume and/or pressure overload state found with TV dysfunction.

Surgical Indications[24–26] (Fig. 15.89)

Surgery is indicated for symptomatic patients (right heart failure) with severe TR. Surgery is also indicated for severe TR (with or without symptoms) when the patient is undergoing other cardiac surgical procedures. Surgery should be considered with mild/moderate/or severe

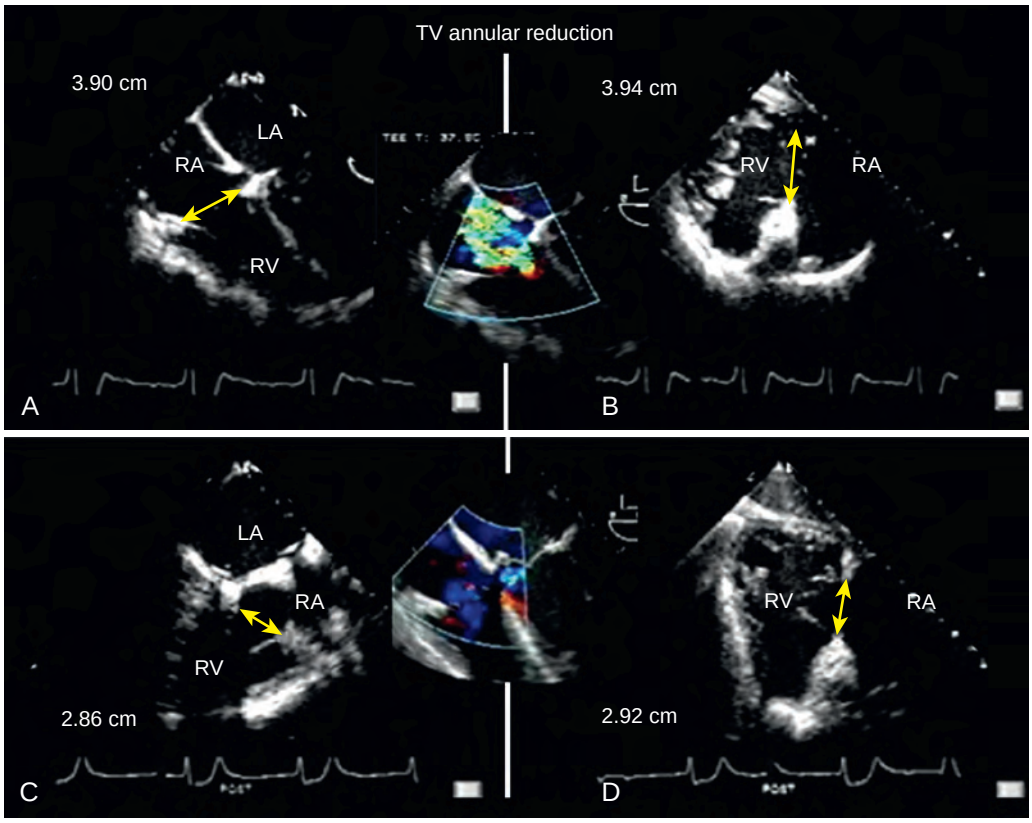


Fig. 15.88 Tricuspid annular reduction. (A) and (B) Dilated annulus with severe regurgitation (before repair). (C) and (D) Significant reduction in annular diameter and regurgitation (immediately after repair). *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle; *TV,* tricuspid valve.

TABLE 15.9 Tricuspid Stenosis: Degrees of Severity

	Mild	*Moderate*	*Severe*
Peak jet velocity (m/s)	≤1.5	—	>1.7
Mean pressure gradient (mm Hg)	<5–6	—	>7
Pressure half time (ms)	<200	≥200	>230
Tricuspid valve area (cm^2)	—	—	<1.0
Vena cava (cm) with or without respiratory variation	≤1.5 with variation	—	2.0 without variation
Secondary findings	IVC/SVC dilation, RAE, right-to-left septal bowing		

IVC/SVC, Inferior and superior vena cava; *RAE,* right atrial enlargement.

TR in the presence of a dilated TV annulus (>40 mm or >20 mm/m^2) who are scheduled for other cardiac surgical procedures.

Tricuspid Stenosis

Tricuspid valve stenosis (TS) is uncommon. Causes include rheumatic valvitis, obstructing tumors or masses, congenital pathology, and infiltrative processes, each of which may also be associated with regurgitation.[105] The most common cause of TS is rheumatic valve disease, but infrequently it occurs in the absence of other rheumatic valvular involvement such as MS/MR (Table 15.9).

Assessment of the stenotic TV demonstrates leaflet findings including restricted mobility, thickening, calcification, masses, and/or diastolic doming (Fig. 15.90). Secondary findings of TV dysfunction include a dilated right atrium and enlarged cavae. Assessments of the RA and RV function and size may indicate the clinical impact of TV dysfunction. As is the case with the MV, valvitis results in leaflet and chordal thickening. Other causes of obstruction are suspected based on both history and echocardiographic findings. Causes of prosthetic valve stenosis depend on the type of valve and are similar to causes of prosthetic valve stenosis at the other cardiac sites. These include deterioration or thickening of tissue valves, restricted or stuck tissue or mechanical leaflets, the presence of clot, or obstructing masses or wires (Fig. 15.91).

Forward flow obstruction results in a very dilated right atrium and vena cava. The risk of atrial fibrillation is high. Although the right ventricle is not necessarily dilated or dysfunctional, the clinical picture is one of right-sided heart failure.[105]

Assessing forward flow across the TV and determining whether or not it is normal depends on whether the valve is native, repaired, or prosthetic (see Table 15.9). Depending on the type of prosthesis, forward blood flow projects in different ways. Similar to bioprosthetic and prosthetic valves in other positions, normal signature flows have been described with bioprosthetic valves having a single forward flow and mechanical valves having two (single-leaflet) or three (bileaflet) forward projecting jets.[119–121] The evaluation of forward flow consists of both qualitative and quantitative assessments, the latter consisting of transvalvular velocities, pressure gradients, and calculation of prosthetic valve area.

A normal transvalvular velocity is significantly lower than the MV. Forward flow velocity is normally less than 0.7 m/s.[105] The mean gradient is typically less than 2 mm Hg. Data for TS report mean gradients between 2 and 10 mm Hg with an average of 5 mm Hg.[23,122–124] A problem with assessing TS with transvalvular velocity and gradients is the dependence on RA function, which, with continued TS, declines such that pressure generation may be compromised. Nevertheless, obstruction is considered when flow velocity exceeds 1 to 2 m/s. The evaluation consists of both qualitative (color Doppler) and quantitative assessments (pulsed-wave and continuous-wave Doppler), the latter consisting of transvalvular flow velocities and pressure gradients.

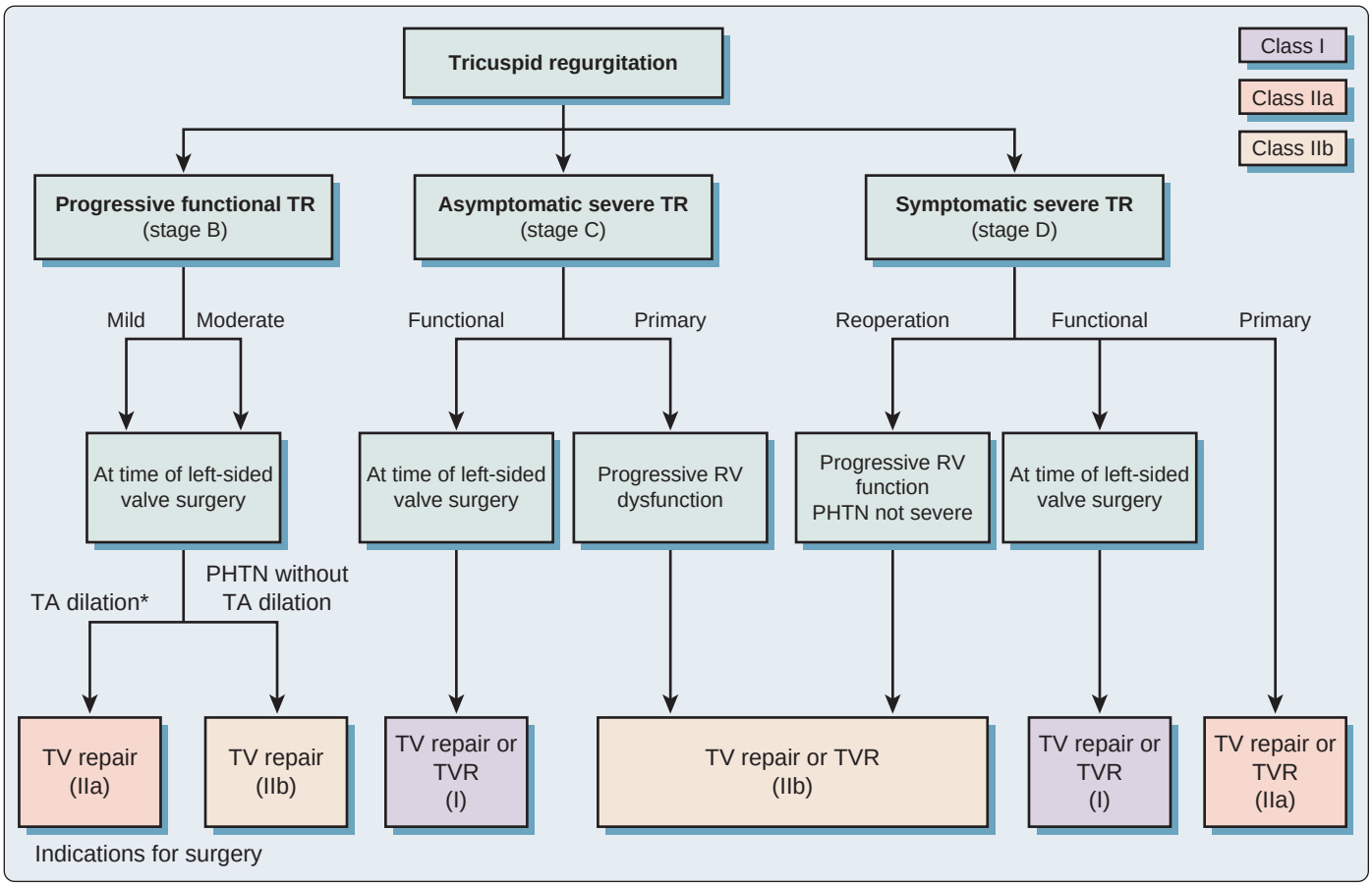


Fig. 15.89 Decision algorithm for intervention of the tricuspid valve *(TV)*. The decision algorithm was taken as a consensus by an expert panel and based on outcome data and interpretation. Decisions are classified as class I, class IIa, class IIb, the former being supported by sufficient evidence such that intervention should be performed, while the latter two are supported by evidence that suggests that the benefits of intervention outweigh the risks and that intervention is reasonable based on multiple (IIa) or isolated trials or nonrandomized data (IIb). Intervention for tricuspid regurgitation is based on a number of considerations including cause, presentation (symptoms), changes in cardiopulmonary function, repairability, and timing (ie, whether other cardiac surgical procedures are scheduled). *PHTN,* Pulmonary hypertension; *RV,* right ventricle; *TA,* tricuspid annular; *TR,* tricuspid regurgitation; *TVR,* tricuspid valve replacement. *(Reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57–e185.)*

Doppler assessment is performed primarily from the TE windows as the Doppler ultrasound beam is more easily aligned with transtricuspid flow. Given the limitations of the Doppler data and the lack of validation, specificity, and sensitivity for different measures, additional analyses of the TV, right heart function, and caval/hepatic flows and diameters might allude to dysfunction and subsequent diagnosis.

Doppler data that are consistent with abnormal forward flow or obstruction include a peak jet velocity greater than 1.5 m/s and a mean gradient greater than 5 mm Hg. Similar application of the PHT for MVs has not been validated for the TV.[17] However, a PHT greater than 190 to 200 ms has been described and is consistent with nonobstructing flow.[24,122] Assessment and calculation of valve area can be performed using the continuity equation or planimetry; the latter may not be feasible because of the difficulty in visualizing the leaflet edges. The continuity equation can be performed assuming that a reference site (PA or LVOT) or method can be assessed or employed to measure an SV, which, when divided by the TV flow profile or TVI, would yield a valve area.[124]

$$\text{TV Area} = \text{SV}/\text{TVI}_{\text{TV}}$$

Other Doppler findings consistent with severe TS are a transvalvular TVI greater than 60 cm and a valve area less than 1.0 cm^2. The presence of moderate or greater TR may cause underestimation of the valve area (overestimate severity) using the continuity equation by elevating the TVI. Normally, the venae cavae are less than 1.5 cm in diameter, which changes more than 50% during spontaneous respiration. A dilated vena cava with less respiratory change would suggest elevated right-sided heart pressures/volumes and dysfunction, which can be caused by TS.

Surgical Indications

Surgery or balloon commissuroplasty is indicated for severe and symptomatic TV stenosis or for severe TS in the presence of right-sided heart failure.[24–26]

Pulmonary Valve

Normal Anatomic and Functional Features

The PV is a three-leaflet valve that is similar in structure to the AV, except that the leaflets tend to be thinner and function in a lower

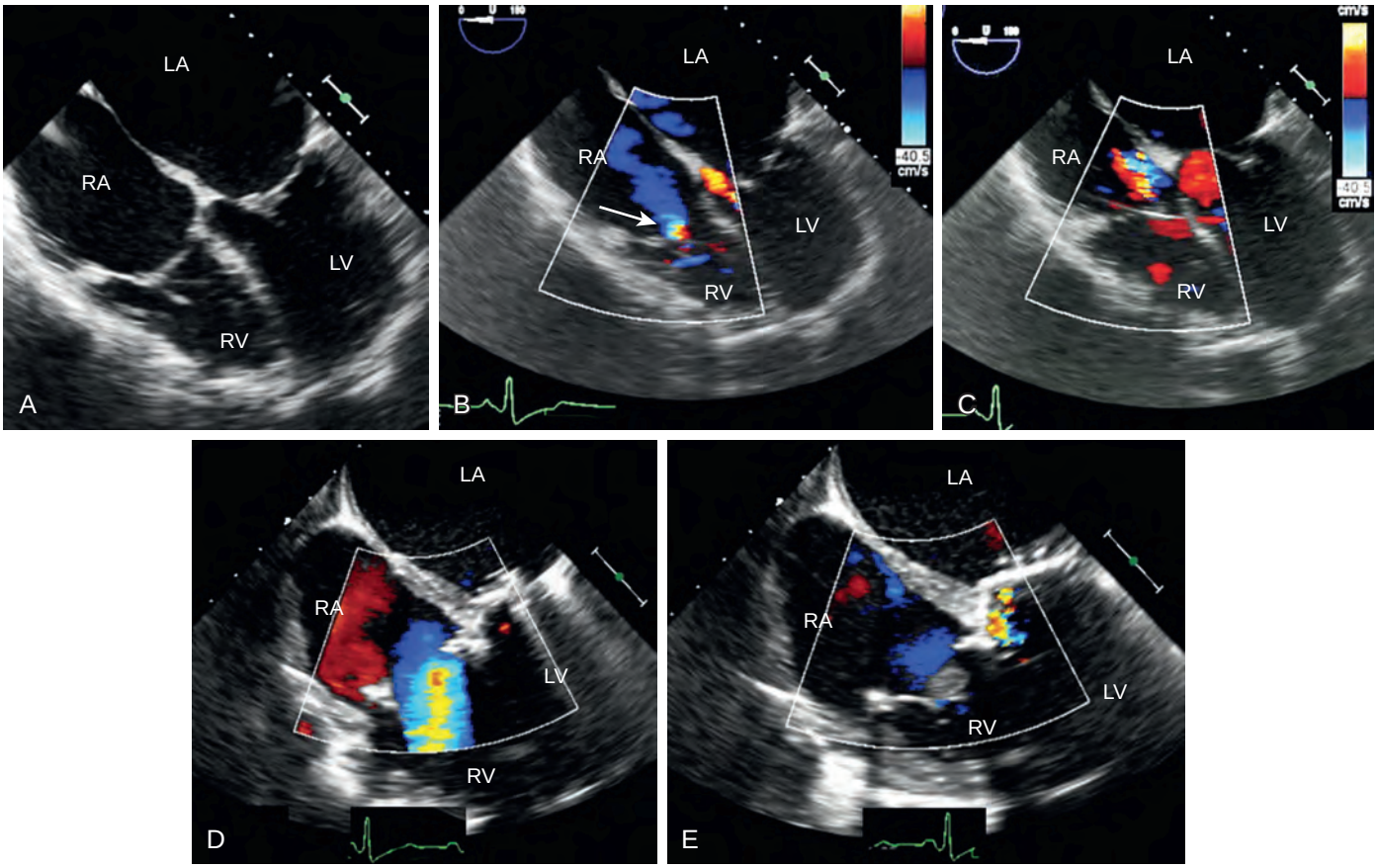


Fig. 15.90 Rheumatic tricuspid valve stenosis. The top panel of images were obtained prior to valve replacement and demonstrate the (A) classic doming of the tricuspid valve (TV) leaflets. The valve also shows fusion of the leaflet tips complicated by (B) tricuspid stenosis and (C) regurgitation. Of interest is the lack of demonstrative turbulent forward flow across the TV. Since flow velocities dictate color Doppler appearance, the lack of turbulent flow may not negate the presence of abnormal flows. The *arrow* in (B) points to a flow convergence area during diastole, which suggests the presence of obstruction or relative narrowing at the valvular level. This patient also had mitral stenosis and had undergone mitral and TV replacements. (D) and (E) Valve replacement with a bioprosthetic valve. *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

pressure system.[18] Similar to the LVOT, the RV outflow tract (RVOT) includes subvalvular, valvular, and supravalvular tissues. The PV lies in the middle of the RVOT. At the ventricular-arterial juncture, the PV is supported by the wall of the circular PA. Surrounding the three-leaflet structure are three smaller sinuses followed by the STJ.

It is important to know what type of valve prosthesis was implanted and to have knowledge of the characteristic 2D and CFD images.[21,22] For all echocardiographic assessments, recording of the patient's hemodynamic status improves the perspective at the time of evaluation. The majority of valves are either stented or stentless (xenografts) bioprosthetic valves. Placement of the prosthetic valve may occur at the annular level or more distal to allow a larger sized valve to be placed. Percutaneous valve replacement has become more popular and may continue to replace surgical placement. Quantitative data regarding prosthetic valve function in the pulmonic position are lacking. Determination of what is normal and abnormal is similar to that of normal native valve function.

Echocardiographic Examination

The 2D and CFD examinations of the PV are accomplished from a number of TE and TG echocardiographic windows. Imaging from multiple sites and angles helps to construct a 3D impression of the prosthetic valve and flows. With regard to Doppler quantitative assessment, both TE and TG windows variably enable alignment between the ultrasound beam and blood flow[125] (Figs. 15.92 through 15.94).

The 2D examination involves visualization of the PV and its surrounding tissues from TE and TG windows. The assessment should evaluate leaflet presence, motion, integrity, masses, and the surrounding tissues. The stability of the valve and whether or not the prosthesis is rocking should be determined. Instability might suggest prosthetic dehiscence and/or infection of the surrounding supportive tissues.

Imaging of the supravalvular and subvalvular areas also should be done to assess for RVOT/subvalvular narrowing, and for PA pathology (see Fig. 15.94). Because of its anterior location, and potential for artifact, the prosthetic PV may be difficult to image using TEE. Epicardial imaging may prove to be the best modality for intraoperative evaluation. Secondary evidence of PV dysfunction includes right-sided heart failure and dilation, elevated RV pressures, and/or significant TR.

The Doppler examination includes CFD, pulsed-wave, and continuous-wave Doppler. The former allows both qualitative and quantitative evaluations including occurrence, direction, and width of normal and abnormal blood flows. Qualitative and quantitative imaging includes both TE and TG windows (Figs. 15.94 and 15.95). It is important to view the PV from multiple windows to increase the chance of aligning the ultrasound beam with the direction of blood flow. Since right heart flows have lower velocity than the left heart

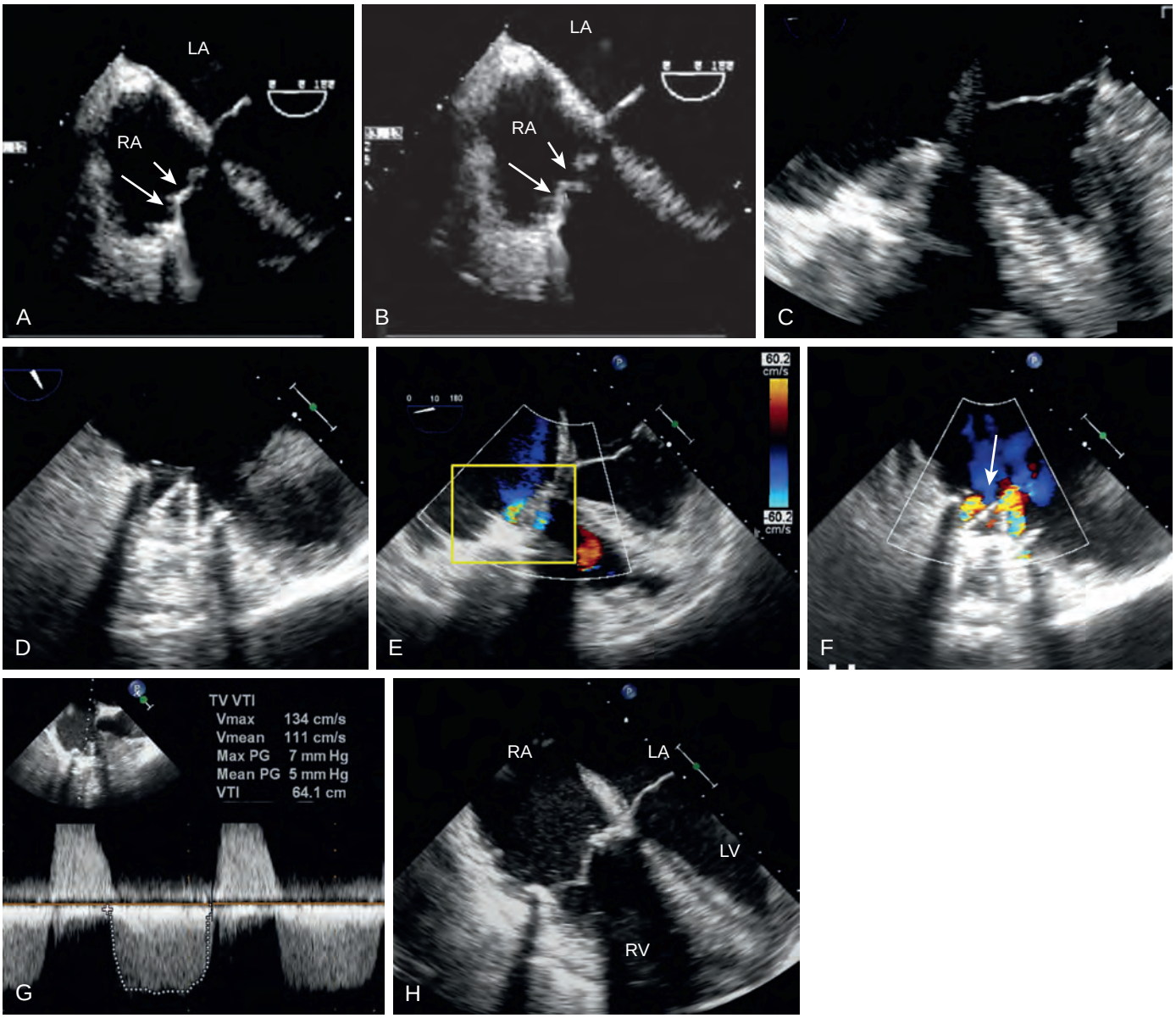


Fig. 15.91 Stuck mechanical valve leaflet in the tricuspid position. Two cases (A/B and C–H) are shown in which one of the mechanical leaflets of a bileaflet mechanical valve is stuck in a closed position (*arrows* in [A] and [B]). (E) and (F) Color Doppler imaging is unrewarding due to imaging artifact *(box* and *arrow);* however, (G) continuous-wave Doppler shows a profile consistent with tricuspid valve stenosis with a mean gradient of 5 mm Hg. In both cases, (H) valve replacement with a bioprosthetic valve was performed. *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

counterparts, it may be necessary to reduce the color scale to highlight turbulent jets and identify potentially abnormal flows.

Pulmonary Valve Insufficiency

PI is found in up to 75% of patients in the absence of any abnormality and is considered normal[18] (see Fig. 15.95). These jets are centrally directed. Abnormal PI has greater proximal jet width, VC greater than 3 mm, and/or eccentrically directed flow (Table 15.10). Mild-to-moderate PI can be seen in patients with moderate-to-severe pulmonary hypertension (ie, functional PI). Otherwise, severe PI is caused by a primary valvular abnormality including bicuspid or quadricuspid valves, leaflet prolapse, hypoplasia, postrepair after tetralogy of Fallot, carcinoid syndrome, endocarditis, or rheumatic valvitis[18,105] (Figs. 15.96 and 15.97).

Prosthetic valve regurgitation results from valve deterioration, infection, dehiscence, or leaflet restriction. In assessing regurgitant flows of prosthetic valves in the pulmonary position, the presence of normal or expected regurgitant jets should be differentiated from abnormal jets. The presence of central trace/mild PI in the absence of disease is a normal finding for bioprosthetic valves, while mechanical valves have two to three washing jets that are known. Findings consistent with abnormal regurgitant jets include jets greater than 3 mm, larger regurgitant jet/RVOT diameter ratio (>25%), an eccentric jet, and/or reversal of diastolic flow in the PA.[21,22]

Two-dimensional imaging of the PV elucidates valvular anatomy, leaflet number, leaflet mobility, and thickening. However, compared to the AV, the PV leaflets are thinner and more difficult to visualize with TTE or TEE. Multiple windows and angles help to obtain the best image of the PV.

PI is sought during CFD interrogation of the RVOT. Its severity is determined by the appearance of the continuous-wave flow profile, the ratio of the proximal jet width to the RVOT diameter, and the PHT.

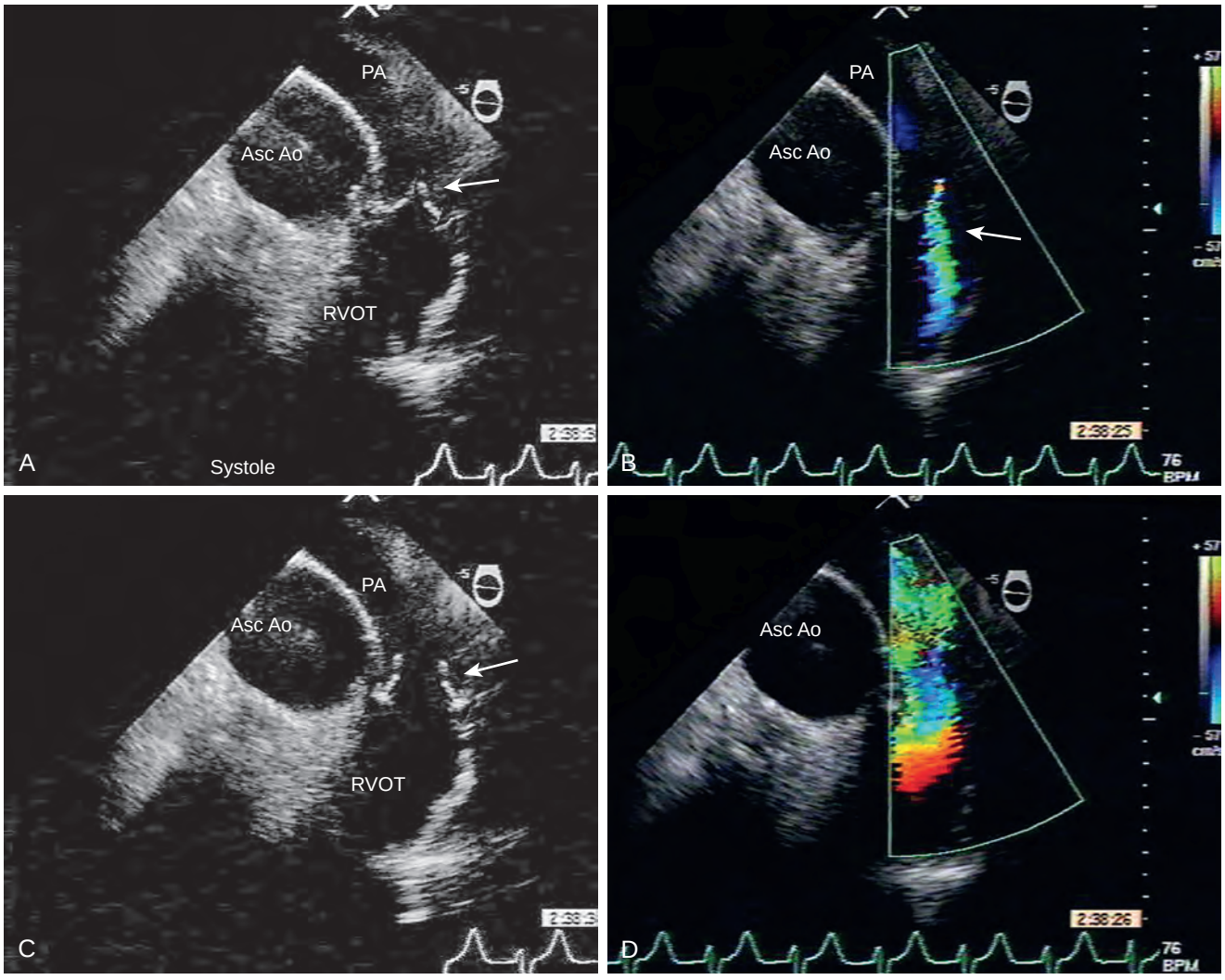


Fig. 15.92 Pulmonary valve replacement: bioprosthetic valve. (A–D) Imaging from the upper esophageal windows of the main pulmonary artery *(PA)* and a cross-section of the ascending aorta *(Asc Ao)*. Color Doppler imaging shows (B) the expected centrally directed regurgitant jet and (D) normal forward flows of a bioprosthetic valve. *RVOT*, right ventricular outflow tract.

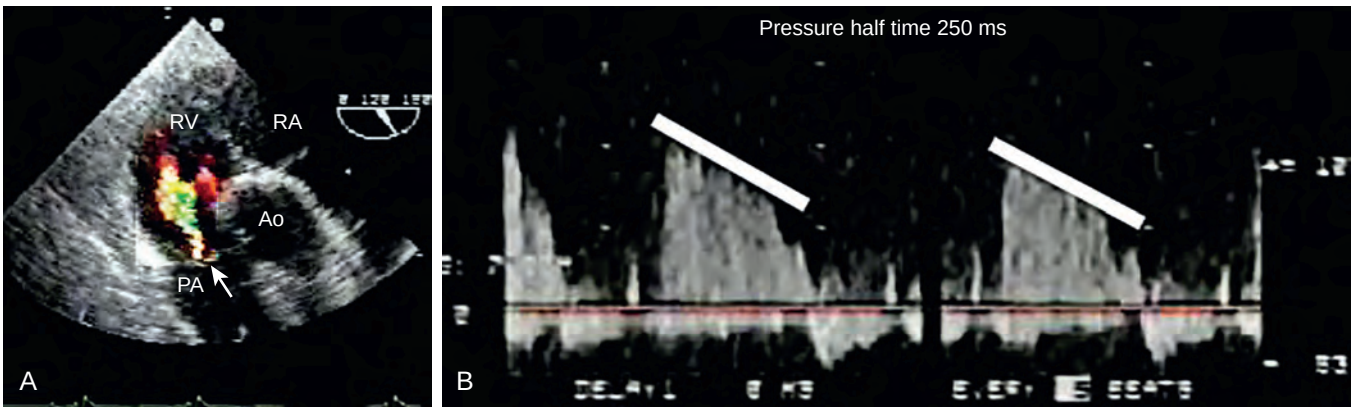


Fig. 15.93 Pulmonary insufficiency. Transgastric imaging shows right ventricular inflow and outflow. (A) Color Doppler applied to the pulmonary valve shows regurgitation as supported by (B) the pressure half time of 250 ms. *Ao*, Aorta; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

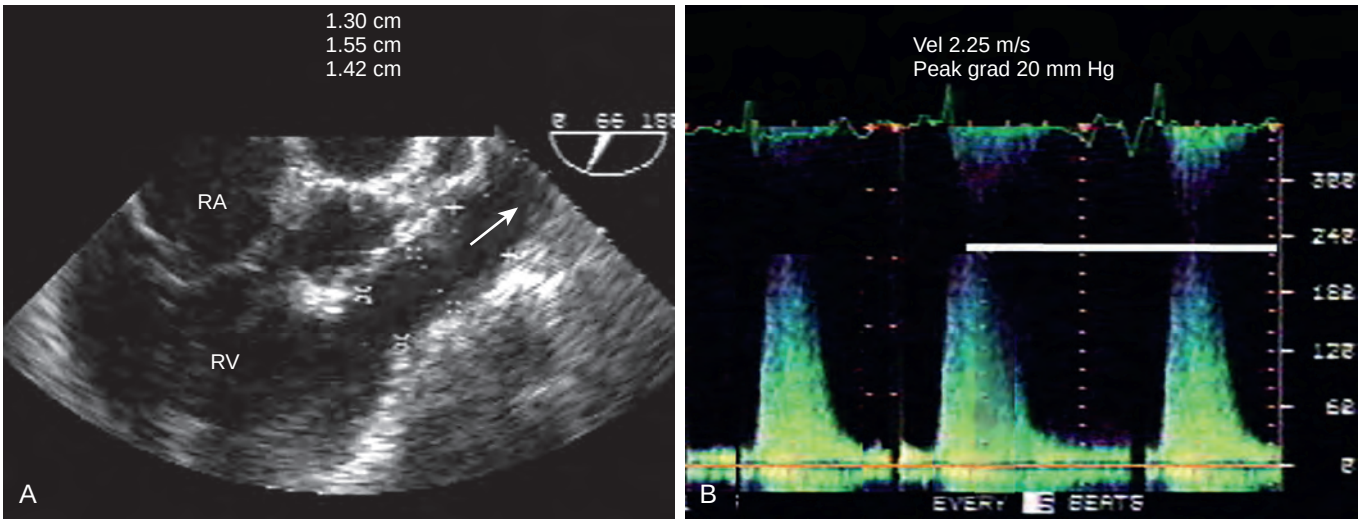


Fig. 15.94 Right ventricular outflow narrowing. From these midesophageal windows (A) the right ventricular outflow tract appears narrow. (B) Continuous-wave Doppler analysis reveals an elevated gradient of 20 mm Hg. Relief of this obstruction requires a prosthetic patch and outflow enlargement. *Peak grad,* Peak gradient; *RA,* right atrium; *RV,* right ventricle; *Vel,* velocity.

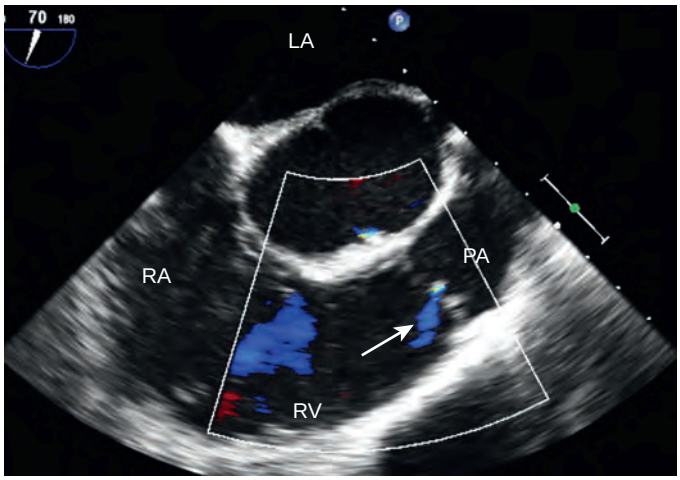


Fig. 15.95 Normal pulmonary valve insufficiency. Approximately 75% of patients have a mild pulmonary insufficiency (considered within the normal range) in the absence of disease. The pulmonary insufficiency jet is narrow *(arrow). LA,* Left atrium; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

Grading of PI (mild, moderate, severe) is less validated compared to AI; however, since PV procedures are not likely to be performed unless severe PI exists, the echocardiography need only differentiate between severe and nonsevere PI.[24] The denser and more complete appearance of the PI TVI suggests more severe dysfunction.[18] Doppler measurements consistent with severe PI include a jet-to-RVOT width ratio of higher than 50% to 65%, PHT less than 100 ms, a regurgitant fraction greater than 60%, and Doppler diastolic flow reversal in the PA.[18,19,105,126,127]

In chronic conditions, the absence of RV dilation or dysfunction suggests that PI may not be severe. While the timing of surgery is typically based on symptomatology (fatigue, syncope, right heart failure, arrhythmias), it has been proposed to time surgery based on RV function and dimensions with the hopes of preventing long-term dysfunction. These include either an RV end-diastolic volume index greater than 163 mL/m^2 or an RV end-systolic volume index greater than 80 mL/m^2.[128]

TABLE 15.10 Pulmonary Valve Regurgitation: Degrees of Severity

	Mild	*Moderate*	*Severe*
Jet density	Incomplete/faint	Dense	Dense
Vena contracta (mm)	—	—	>6
Color Doppler jet width/ RVOT width (%)	≤25	26–50	>50
Pressure half time (ms)	500	200–500	<200
Regurgitant fraction (%)	<30	30–60	>60
Diastolic flow reversal pulmonary artery	Absent/brief	Present	Present/ holodiastolic
Secondary findings	Caval dilation, RAE, RVE, RVSD, TR		

IVC/SVC, Inferior and superior vena cava; *PHTN,* pulmonary hypertension; *RAE,* right atrial enlargement; *RVE,* right ventricular enlargement; *RVOT,* right ventricular outflow tract; *RVSD,* right ventricular systolic dysfunction; *TR,* tricuspid regurgitation.

Pulmonary Valve Stenosis

Pulmonary valve stenosis (PS) is less common than PI (Table 15.11). Stenosis of the native pulmonic valve is most commonly a congenital problem with the valve described as acommissural, unicommissural, bicuspid, or dysplastic.[17,105] The leaflets may appear domed-shaped and tethered to the arterial wall, while the leaflets in the latter are thickened at the leaflets' free edges[129] (Fig. 15.98). PS may also occur as part of a congenital syndrome (tetralogy of Fallot, AV canal defect, double outlet right ventricle, Noonan syndrome, or Williams syndrome). Obstruction to outflow from the right ventricle also may be nonvalvular (ie, subvalvular or supravalvular) and related to VSD, hypertrophic cardiomyopathy (HCM), or secondary to primary valve stenosis.[18,105] Forward flow may be affected by carcinoid tumor/involvement or rheumatic disease; however, these two diseases are associated with other valvular disease. Finally, thrombus or tumor can result in pulmonary outflow obstruction.

Doppler quantification of PS severity is based on transvalvular velocity and gradient.[18,25–27,105,127] A peak velocity less than 3 m/s or greater than 4 m/s is suggestive of nonsevere and severe PS, respectively. These values correlate with pressure gradients of less than 36 or greater than 64 mm Hg. Mean pressure gradients less than 20, 20 to 35, and greater than 35 mm Hg suggest mild, moderate, and severe obstruction to forward flow across the PV (see Fig. 15.98). It is important to distinguish abnormal transvalvular flow from subvalvular (RV hypertrophy), or supravalvular (pulmonary atresia) obstructions (Fig. 15.99).

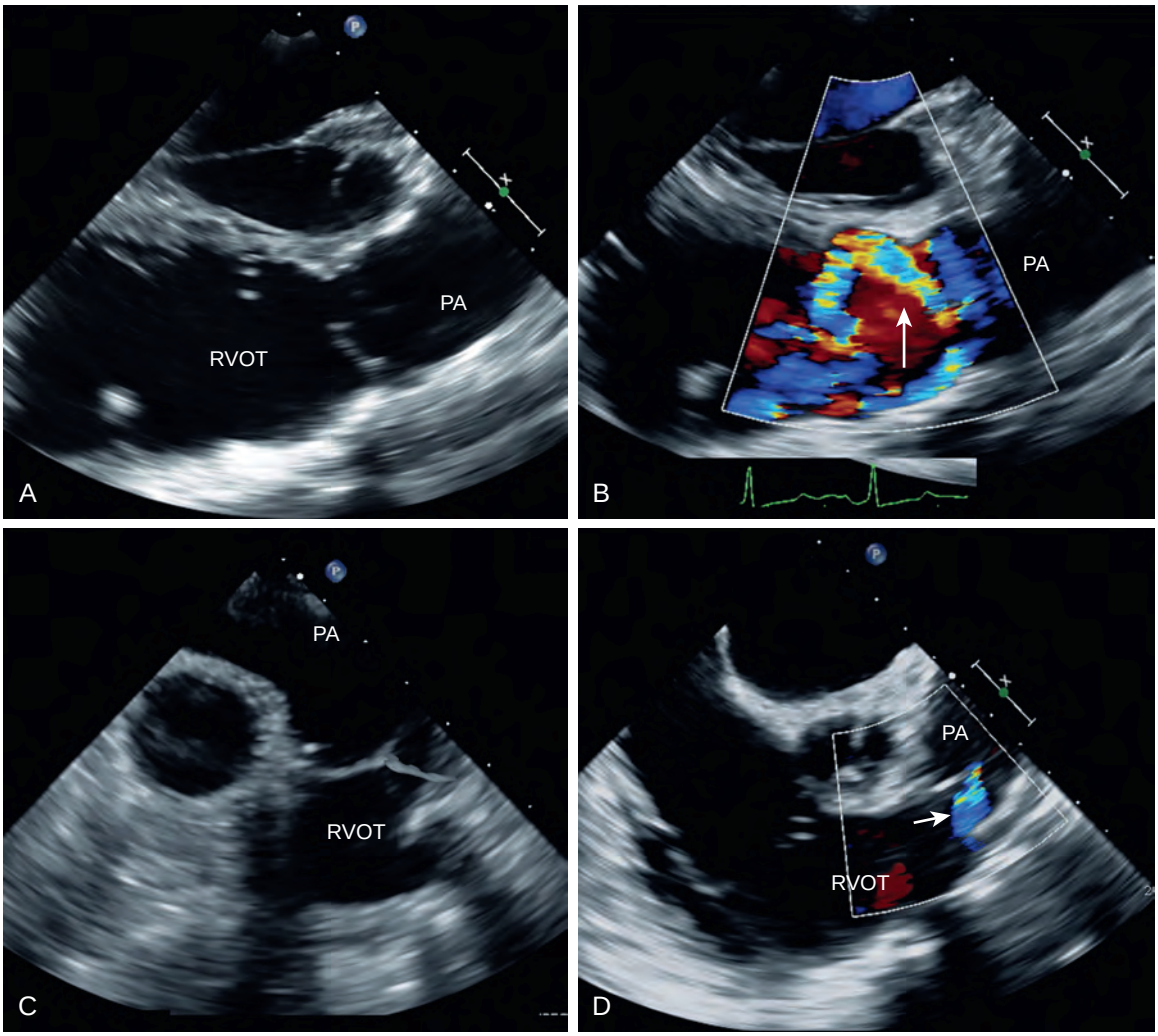


Fig. 15.96 Prolapsing or flail pulmonary valve leaflet. From these midesophageal windows (A) the pulmonary valve leaflet can be seen as prolapsed or flail and is associated with (B) severe eccentric regurgitation *(arrow)*. (C) and (D) After replacement with a bioprosthetic valve. *Arrow* indicates minimal pulmonary regurgitation. *PA,* Pulmonary artery; *RVOT,* right ventricular outflow tract.

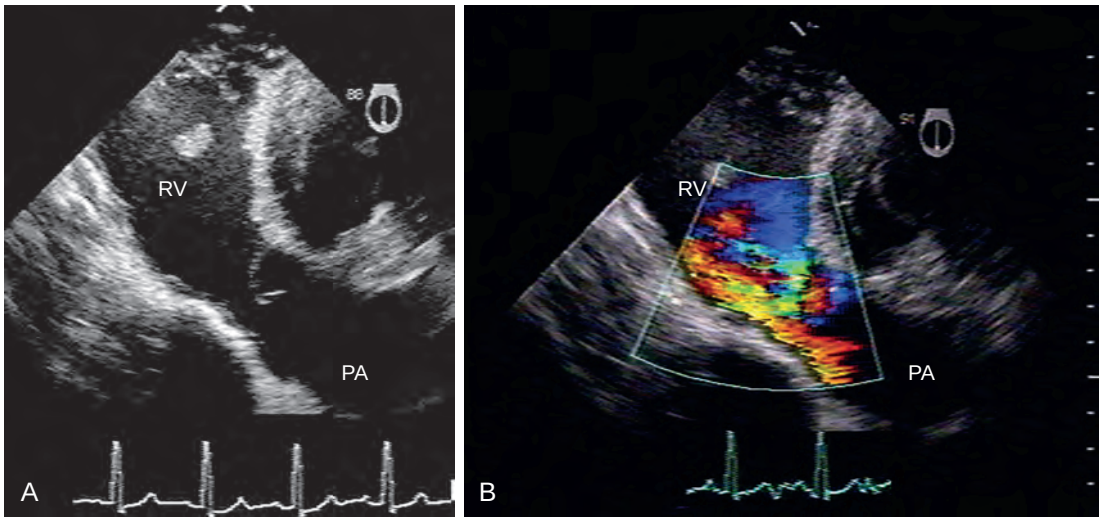


Fig. 15.97 Congenital pulmonary insufficiency. (A) Congenital pulmonary insufficiency and absence of full pulmonary valve associated with (B) severe pulmonary valve insufficiency. *PA,* pulmonary artery; *RV,* right ventricle.

TABLE 15.11 Pulmonary Valve Stenosis: Degrees of Severity

	Mild	*Moderate*	*Severe*
Peak jet velocity (m/s)	<3	3–4	>4.0
Mean pressure gradient (mm Hg)	<20	20–35	>35

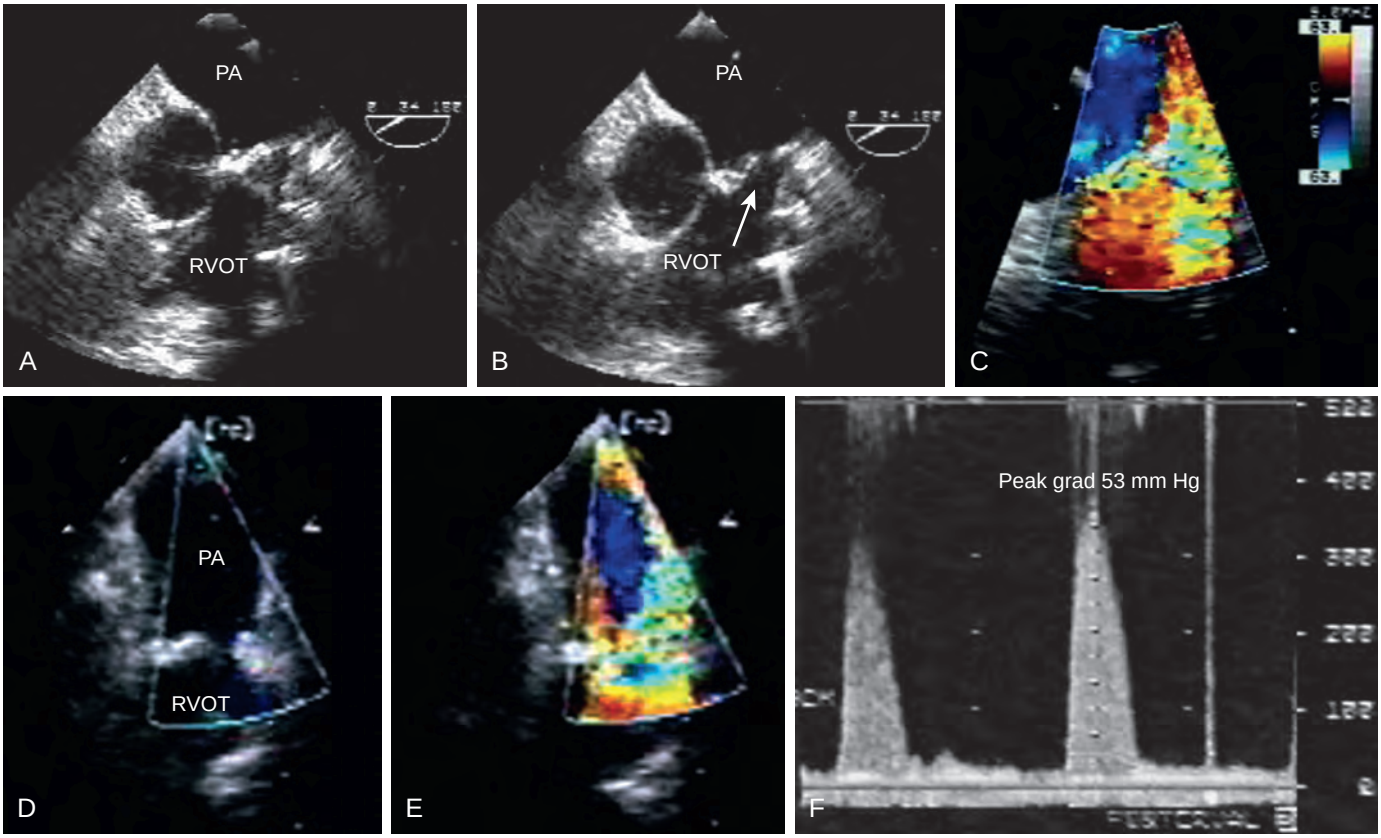


Fig. 15.98 Pulmonary valve stenosis. Images were obtained from midesophageal windows from different angles and probe rotations to visualize flow across the pulmonary valve and to align the Doppler beam with blood flow. (A) and (B) Bioprosthetic valve complicated by obstruction. (C) Color-flow Doppler image of obstruction, showing distorted valve significant turbulence. (D) Thickened leaflets. (E) Abnormal Doppler flow. (F) Continuous-wave Doppler imaging reveals a gradient greater than 50 mm Hg consistent with severe pulmonary valve stenosis. *PA,* Pulmonary artery; *Peak grad,* peak gradient; *RVOT,* right ventricular outflow tract.

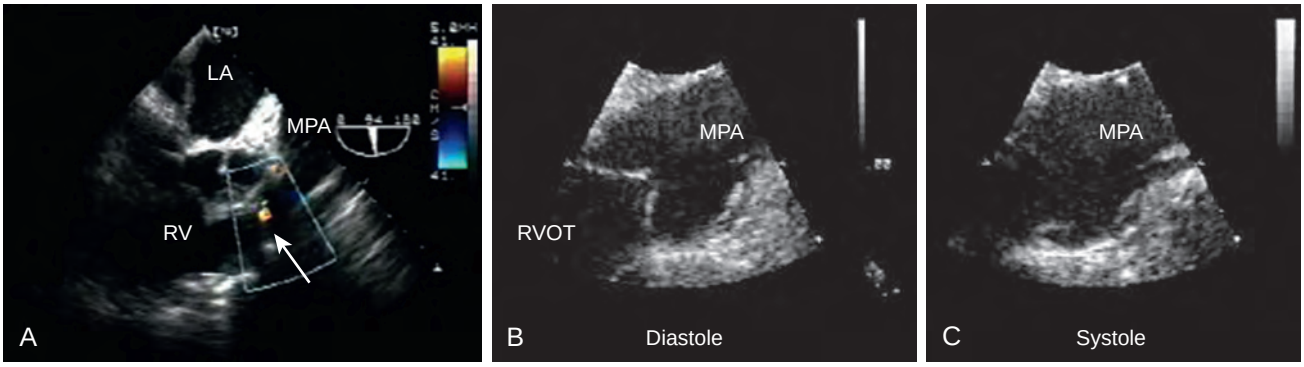


Fig. 15.99 Right ventricular failure: epicardial scanning. The images shown are those obtained after homograft replacement of the pulmonary valve as part of a Ross procedure. There was significant right-sided heart failure. Transesophageal echocardiography imaging was not possible; however, epicardial imaging showed a normal functioning pulmonary valve. Further assessment showed that the pulmonary artery anastomosis created significant narrowing and obstruction to flow.

Secondary effects of PS include RV hypertrophy (RV walls greater than 8 mm), right heart dysfunction, TR, RA enlargement, and dilated venae cavae. There are few data assessing PV area with the continuity equation; therefore, much of the assessment is based on pressure gradients.

The timing of surgery is based on symptomatology, transvalvular gradient, and secondary changes related to PS. A peak velocity greater than 4 m/s or gradient greater than 50 mm Hg predicts a significant reduction in event-free survival and intervention is recommended.[25–27,130] Valvular stenosis less than severe does not warrant intervention.[131] Although balloon valvuloplasty is most commonly performed, patients who are not suitable are considered for surgical intervention. One example is the presence of RV outflow hypertrophy and obstruction requiring enlargement.

Transesophageal Echocardiography for Interventional Procedures

In 1929, Werner Forssmann, a surgical intern (and eventually a Nobel Laureate) described the first cardiac catheterization procedure performed on himself.[132] Interventional cardiology has evolved tremendously after Andreas Gruentzig introduced the balloon angioplasty in 1976, and these procedures can now be used as an alternative or adjunct to cardiac surgery.[133] Long-term data for catheter-based interventions suggests that they may significantly reduce morbidity and mortality rates, and most believe that the need for these procedures, as well as their indications, will increase in the future[134] (see Chapters 3 and 27). Fluoroscopy has been traditionally used to guide interventional procedures, but its use is limited by significant radiation exposure and the need for intravenous contrast, with its associated potential toxicity.[135,136] Emerging interventional cardiac procedures have frequently benefited from TEE guidance, creating the need for interventional echocardiographers.[137] The current role of TEE is being transformed from a monitoring modality into an indispensable procedural adjunct, with the cardiac anesthesiologist becoming an echocardiologist.[138] TEE is now an integral part of the decision-making process during the perioperative care of patients undergoing cardiac surgical procedures.[139]

In cardiac interventional procedures, TEE is routinely used for preoperative assessment, surgical planning, procedural guidance, and evaluation of surgical results. Guidance of septal puncture, evaluation of LA appendage (LAA) thrombi, and closure of paravalvular leaks are some of the potential scenarios where TEE may be helpful in the interventional suite.[137] Some common interventional procedures that benefit from TEE guidance are summarized in Box 15.3. An important advantage of TEE over other imaging modalities is the relatively lower cost, increased portability, and its capacity to provide real-time information.[140] These characteristics make TEE a valuable resource that can enhance the safety and efficiency of percutaneous cardiac interventions.[141]

In this section we discuss the logistics associated with providing TEE service in the interventional suite, examine the implications of specific interventional procedures for the echocardiographer, and discuss the increasing importance of 3D TEE for procedural guidance. However, it is important to clarify that intra-cardiac echocardiography and TTE are also commonly used in interventional procedures.[142]

BOX 15.3 SELECTED INTERVENTIONAL CARDIAC PROCEDURES THAT BENEFIT FROM TRANSESOPHAGEAL ECHOCARDIOGRAPHIC GUIDANCE

Patent foramen ovale closure
Atrial septal defect closure
Ventricular septal defect closure
Mitral valve balloon valvuloplasty
Minimally invasive mitral valve surgery
Robotic mitral valve surgery
MitraClip
Transcatheter aortic valve implantation
Percutaneous closure of paravalvular leaks
Ventricular assist device placement
Left atrial appendage exclusion
Lead extraction

Organizing a Transesophageal Echocardiography Service for the Interventional Suite

Interventional cardiac procedures are performed either in the cardiac catheterization laboratory or in specialized hybrid operating rooms. In a large number of institutions, a cardiac anesthesiologist is responsible for providing both anesthesia and echocardiography services. Knowledge of radiation safety is also important, as interventional procedures significantly increase health care workers' radiation exposure.[143]

Role of the Echocardiographer on the Interventional Team

Echocardiographic evaluation is necessary to confirm the indication for the procedure, evaluate the patient for contraindications, provide real-time guidance during key moments (eg, septal puncture), and confirm the success of the procedure or identify its complications. When using TEE guidance for interventional procedures, the echocardiographer is the eyes of the interventionalist and provides visual and structural guidance that is missing from the fluoroscopy monitors. Therefore, in the hybrid operating room or catheterization laboratory, communication between all members of the team is essential.[144]

Echocardiographic Equipment and Setup

In general, ultrasound systems for a hybrid operating room or catheterization laboratory should have certain characteristics. Systems should have a selection of different probes: a high-frequency linear probe for vascular access, a cardiac probe for TTE, and a TEE probe with 3D imaging capabilities. The 3D imaging probe should be able to provide real-time 3D and biplane imaging, as well as performing R-wave gated reconstruction, and be equipped with on-cart software capable of multiplanar reformatting and 3D quantitative analysis. Lastly, capability of sharing images from the ultrasound system with the interventionalist's display is desirable. The need for fusion imaging capabilities is likely to increase in the future.[145] A typical setup of a hybrid room and catheterization lab with the TEE system is shown in Fig. 15.100.

Fig. 15.100 A typical hybrid operating room.

Transesophageal Echocardiography Evaluation During Specific Procedures

Interatrial Transseptal Puncture

Access to the left atrium is required during several interventional procedures, such as percutaneous MV valvuloplasty, placement of LAA occlusion devices, and radiofrequency ablation for atrial fibrillation. Unfortunately, the left atrium is the most difficult chamber to access percutaneously.[146] Puncture of the interatrial septum (IAS) allows for more direct access to the left atrium from the systemic venous system. Although transseptal puncture is relatively safe, it can be associated with life-threatening complications, especially in inexperienced hands, in repeat procedures, or in patients with difficult IAS anatomy.[147–149] TEE is a frequently used imaging modality for guidance of IAS puncture. Three-dimensional TEE allows for visualization of the IAS en face and appreciation of its spatial relationship with the surrounding structures.[150]

Echocardiographic Assessment

A comprehensive TEE examination is performed to assess cardiac structure and function, as well as the dimensions of both atria. The left atrium and LAA are interrogated to rule out thrombi. It is important to evaluate the presence of IAS aneurysm, Chiari network, eustachian valve, lipomatous IAS hypertrophy, patent foramen ovale (PFO), and ASD, all of which may impact the procedure.

Focused evaluation of the IAS is performed in different planes to identify and select the puncture site (usually in the fossa ovalis). Evaluation for IAS puncture with 3D TEE can start by obtaining an ME bicaval view.[151] After the image is obtained, the wide-angle 3D zoom function is used and the lateral and elevation planes are optimized to visualize the entire IAS. The depth plane is set to include only the left and right sides of the IAS. The relative immobility of the IAS allows for adequate visualization despite the low frame rate of the resulting image.[150] To obtain an en face view of the IAS, the 3D volume is rotated so that the superior vena cava is at the 12 o'clock position. The image can then be turned to visualize the RA or LA perspective as needed.[152] The relationship of the AV and aortic root to the IAS is particularly important to visualize, because of the potentially life-threatening consequences of perforating these structures. After visualization of the IAS, the needle, dilator, and sheath are placed near the superior vena cava and RA junction. The needle is then guided with both TEE and fluoroscopy assistance as it approaches the IAS. A tenting of the IAS is observed as the sheath exerts pressure on the fossa ovalis (Fig. 15.101). The position of the needle inside the left atrium (Fig. 15.102) can then be confirmed with TEE by injection of agitated saline or with fluoroscopy with radiographic contrast.

Regardless of the interventional procedure performed, TEE evaluation after transseptal puncture is performed to rule out pericardial

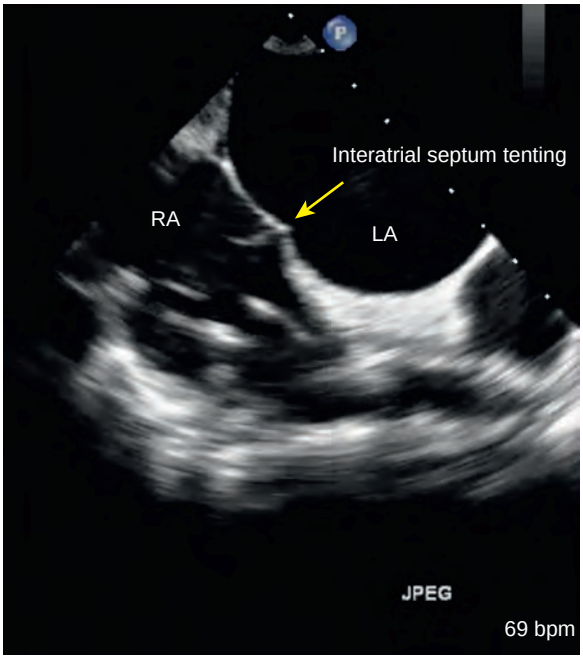


Fig. 15.101 As the needle exerts pressure, tenting of the interatrial septum is observed. *LA*, left atrium; *RA*, right atrium.

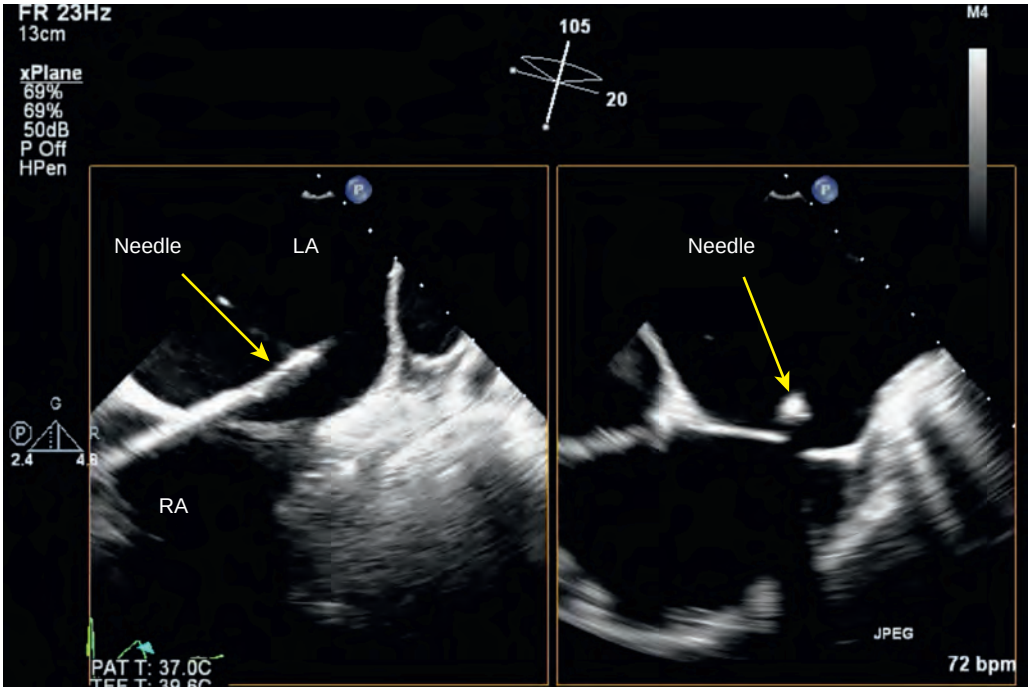


Fig. 15.102 Biplane imaging demonstrates needle position inside the left atrium. *LA*, Left atrium; *RA*, right atrium.

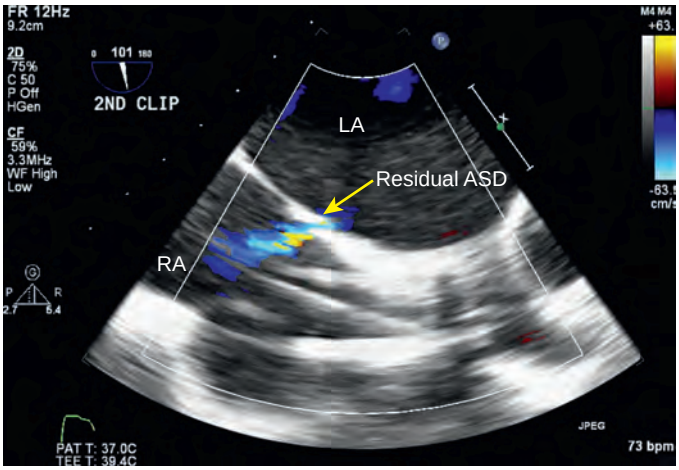


Fig. 15.103 Midesophageal bicaval view demonstrates a small residual atrial septal defect after the puncture. *ASD,* Atrial septal defect; *LA,* left atrium; *RA,* right atrium.

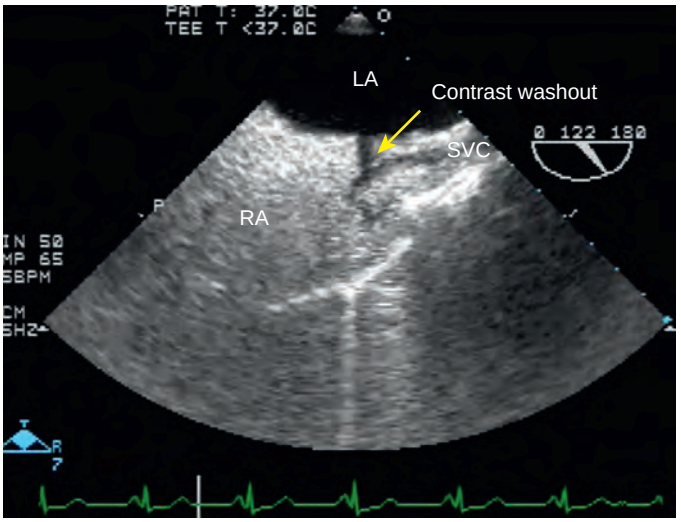


Fig. 15.104 Positive reverse contrast. A midesophageal bicaval view demonstrates washout of contrast on the right atrium *(RA)* as blood enters from the left atrium *(LA). SVC,* Superior vena cava.

effusion or tamponade, and CFD interrogation of the IAS is also performed to evaluate the size and characteristics of the residual ASD created by the transseptal puncture (Fig. 15.103).

Patent Foramen Ovale Closure

The foramen ovale is an opening at the fossa ovalis, where the septum primum and septum secundum overlap. Functional and anatomic closure of the foramen ovale occurs after birth as a result of the difference in pressure between the atrial chambers in the newborn. A PFO occurs in a high proportion of the population.[153] In certain patients, particularly those with a history of cryptogenic stroke or transient ischemic attack, PFO closure may be recommended.[154]

Echocardiographic Assessment

TEE evaluation for PFO closure consists of confirming the diagnosis, quantifying the size of the PFO, evaluating the suitability for closure, and excluding additional disease that may affect the intervention (eg, anomalous pulmonary venous return or large IAS aneurysm).[155] Since these defects have relatively low flow of blood, reducing the Nyquist limit (20–30 cm/s) is useful to aid in their visualization.[156] Injection of agitated saline through a peripheral vein can also be used. In patients with left-to-right shunts, a washout of the contrast in the RA is seen as blood enters from the left atrium (Fig. 15.104). Release of a Valsalva maneuver transiently increases RA pressure and may demonstrate reversal with right-to-left shunting of the contrast medium. The use of agitated saline for this purpose is controversial.[157] The echocardiographic evaluation and guidance for PFO closure is very similar to that of ASD closure and is discussed in the next section.

Atrial Septal Defect Closure

ASDs constitute approximately 50% of hospital admissions for congenital heart disease in the United States.[158] Approximately 75% of ASDs are of the ostium secundum type, which is amenable to percutaneous closure.[159] In fact, percutaneous closure of secundum type ASD has been shown to result in a decreased number of perioperative complications, reduced length of stay, and a benefit in survival.[160,161] Today, the great majority of secundum type ASDs are closed percutaneously.

Echocardiographic guidance is particularly useful for ASD closure, and TEE and intracardiac echocardiography have both been used successfully.[162] Real-time 3D TEE imaging is particularly useful in evaluating ASDs with complex geometries (Fig. 15.105).[163]

Echocardiographic Assessment

CFD interrogation of the IAS with TEE is commonly used to confirm the presence of a secundum ASD or PFO. The ME AV short-axis, ME bicaval, and ME four-chamber views are frequently used to assess ASDs with 2D TEE. An evaluation of all pulmonary veins with exclusion of any congenital abnormalities of location and number should be noted.

Patients who are not suited for percutaneous closure include those with large defects (>38 mm in diameter), anomalous pulmonary venous drainage, or ASDs other than secundum type (ie, primum ASD, sinus venosus ASD, or coronary sinus defects).[164]

Complete TEE examination for ASD closure is important to exclude associated congenital abnormalities, IAS aneurysm, and atrial or LAA thrombi, and to search for signs of LA pressure overload and diastolic dysfunction. During TEE evaluation, it is also important to evaluate the diameter of the ASD rims. An inferior rim (ie, adjacent to the inferior vena cava) of more than 5 mm is required for stable device positioning.[165]

To perform percutaneous closure of the ASD, an interventionalist advances a guidewire via the RA through the ASD and toward the left atrium and anchors it at the left upper pulmonary vein. A balloon is then inflated to gauge the size of the defect (Fig. 15.106). The diameter of the waist of the inflated balloon is measured with TEE to calculate the size of the device that will be placed. CFD examination with the balloon inflated is important to demonstrate absence of flow through the ASD (Fig. 15.107). The device is then loaded on a delivery sheath and advanced. The LA disk is deployed with TEE and fluoroscopic guidance and then abutted against the atrial surface. The alignment of the disk to the IAS is confirmed with TEE and readjusted as necessary. The RA disk is then deployed, maintaining parallel alignment to the septum, and an adequate position of the device is confirmed by TEE. The device is adequately positioned when there is one hemi-disk in each atrium, the ASD ring is between the two hemi-disks, the LA disk does not move past the ASD ring with pulling of the sheath, no erosion of adjacent structures (particularly the roof of the left atrium and aortic root) is found, and no obstruction of the venae cavae inflow, coronary sinus, or right pulmonary veins is found. After the position is confirmed and satisfactory, the release mechanism is activated to liberate the device (Fig. 15.108).[166]

The patient is monitored with TEE for a few minutes after device release to evaluate for complications, such as device embolization, impingement of MV or TV, entrapment of pacing wires, and pericardial effusion or tamponade resulting from erosion of cardiac structures.[167–169] Residual flow through the ASD is evaluated with CFD. A small flow through the mesh of the device can be expected, but it will stop with endothelialization of the device.

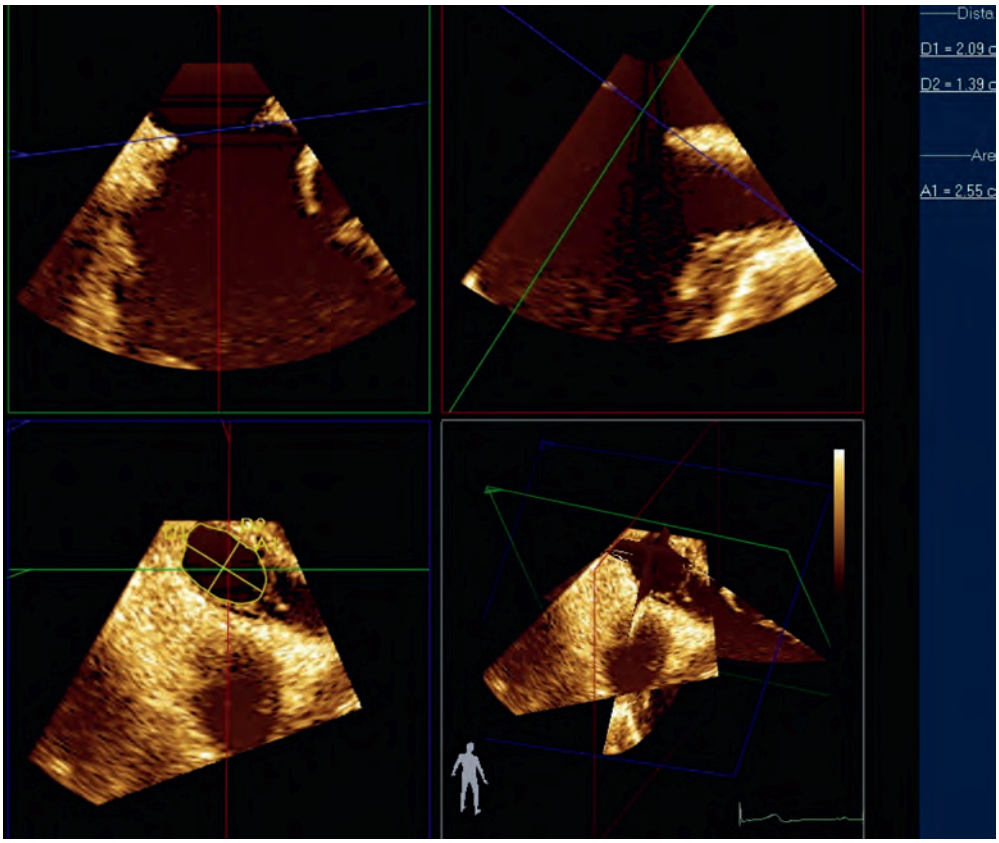


Fig. 15.105 Three-dimensional transesophageal echocardiography with multiplanar reformatting is used to evaluate the irregular, ellipsoid atrial septal defect.

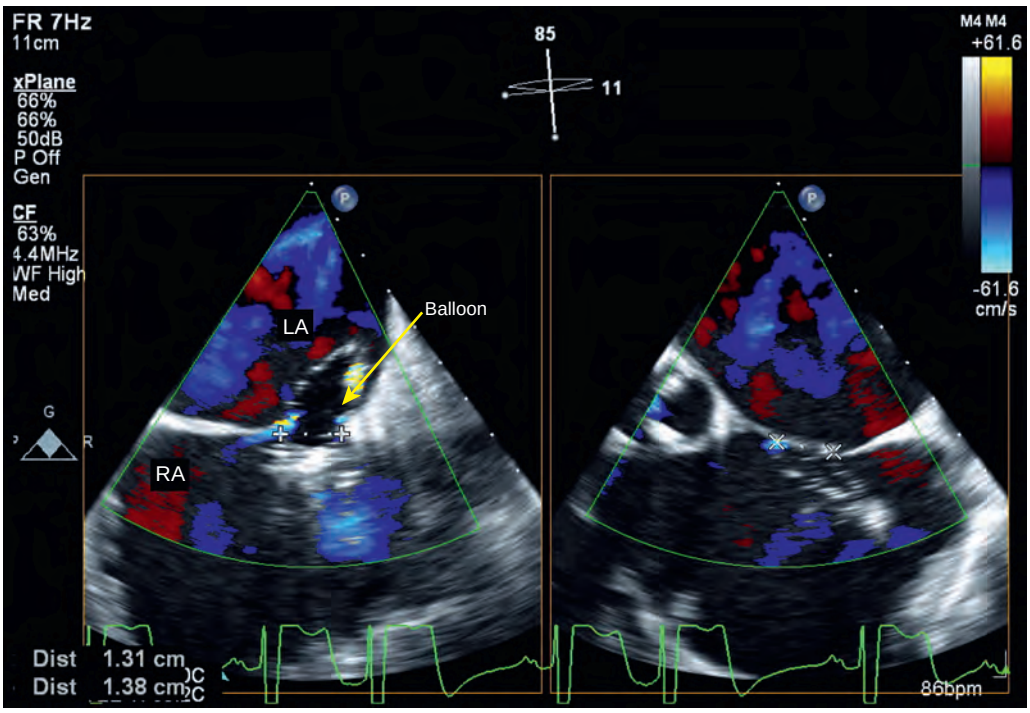


Fig. 15.106 Biplane imaging with color-flow Doppler is used during balloon inflation to measure the size of the interatrial septal defect. *LA*, Left atrium; *RA*, right atrium.

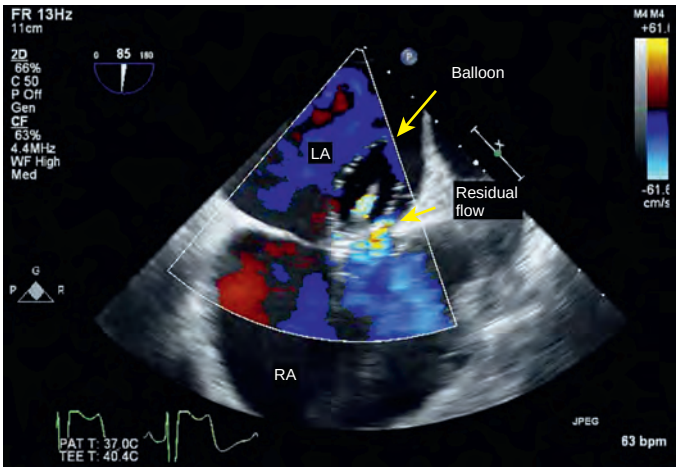


Fig. 15.107 Midesophageal bicaval view with color-flow Doppler demonstrating persistent flow across the atrial septal defect despite balloon inflation. *LA,* Left atrium; *RA,* right atrium.

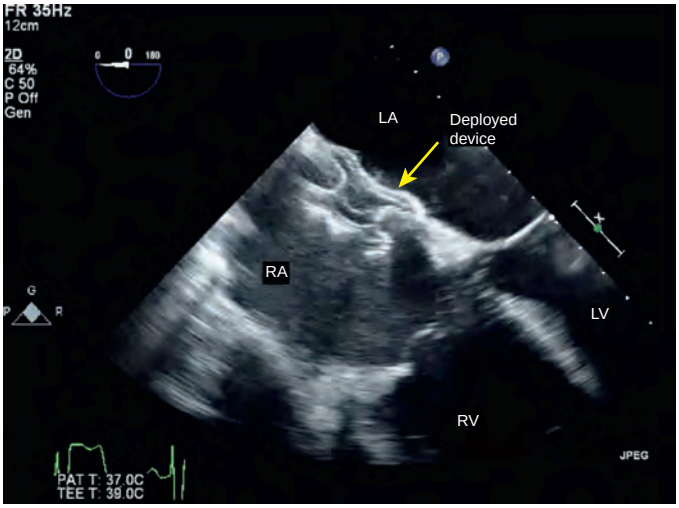


Fig. 15.108 Satisfactory position of the deployed Amplatzer device is shown on a midesophageal four-chamber view. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

Ventricular Septal Defect Closure

In adult patients, percutaneous closure of a VSD is usually performed for acquired postmyocardial infarction defects.[170] In rare cases, adults may require percutaneous closure of congenital muscular or perimembranous VSDs or for defects persisting after surgical repair. Despite being a relatively safe technique, percutaneous VSD closure is still associated with a significant risk of life-threatening perioperative complications and death.[171] This is due, in part, to procedural complications (eg, complete heart block) but also to the high risk of patients requiring these procedures.[172]

Procedural Echocardiographic Assessment

Real-time 2D and 3D TEE evaluation is extremely useful for delineating VSD anatomy. Three-dimensional TEE is particularly useful to assess postmyocardial infarction VSDs because of their irregular shape (Fig. 15.109).[173,174] The location of the defect and its size, as well as the spatial relationship to the tricuspid, mitral, and AVs, are important. Complete assessment of valve dysfunction, pulmonary hypertension, and LV function are some of the advantages of TEE monitoring during the procedure. The most useful views for VSD assessment with TEE are the ME four-chamber, ME long-axis, TG short-axis, and deep TG

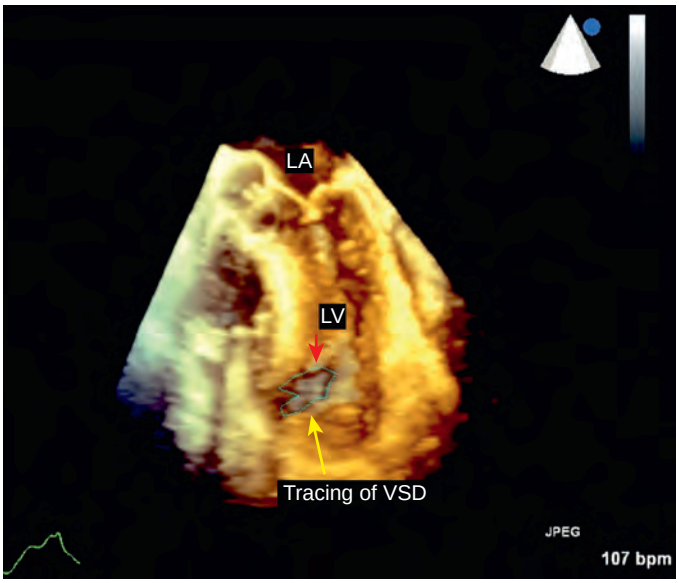


Fig. 15.109 Full volume acquisition with visualization of a postinfarction ventricular septal defect (VSD) from the left ventricular perspective. *LA,* left atrium; *LV,* left ventricle.

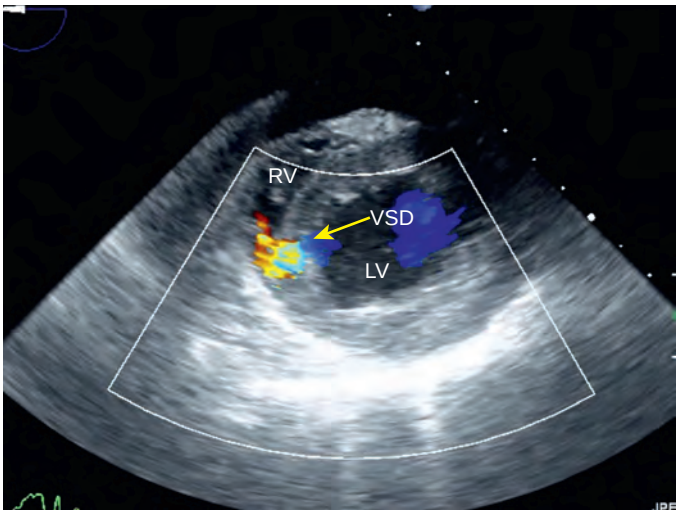


Fig. 15.110 Transgastric mid-short-axis view with color-flow Doppler shows flow across a postinfarction ventricular septal defect *(VSD).* A pericardial effusion is also visualized. *LV,* Left ventricle; *RV,* right ventricle.

views (Fig. 15.110). A surgical patch or other prosthetic material can cause acoustic shadowing and make TEE visualization difficult or impossible.

During the procedure, the left ventricle is accessed with a guidewire through the femoral artery. The wire is then passed toward the venous side of the VSD. Size of the VSD is assessed with TEE or balloon inflation during diastole. Afterward, a snare is introduced through the internal jugular or femoral veins to pull the wire, creating an arteriovenous wire loop that will serve as a rail to deploy the closure device. Over this loop the catheter is introduced through the internal jugular or femoral vein and then advanced under TEE guidance into the left ventricle. Afterward, the LV disk is deployed, avoiding impingement on the MV. After confirming an adequate position, the RV disk is deployed. TEE evaluation is necessary after liberation of the device for assessing residual shunt, device stability, and MV or TV impingement.[175]

Percutaneous Coronary Sinus Catheter Placement

Minimally invasive cardiac surgery has been continuously evolving since the 1990s. Approximately 20% of MV surgery is performed with a minimally invasive approach, with 50% of these cases being robotic surgeries.[176] Although the benefits of minimally invasive cardiac surgery are still under debate, it has definite advantages in patient satisfaction rates and cosmetic appearance.[177] Some studies have also shown a decrease in length of stay, transfusion rates, and earlier return to daily activities.[178] Despite this, a clear mortality benefit has not been proved yet.[179] TEE plays an essential role in the success of minimally invasive cardiac surgery in patients who require administration of retrograde cardioplegia, and it is used to guide cannulation of the coronary sinus (see Chapters 13 and 21).[180]

Echocardiographic Assessment

A comprehensive TEE examination must be performed prior to cannulation during minimally invasive cardiac procedures. Because a great proportion of minimally invasive cardiac surgeries require single-lung ventilation, care must be exercised during probe insertion and manipulation to prevent dislodgement or malposition of lung isolating devices. Special attention should be provided to evaluate the patient for conditions that may complicate or preclude retrograde cardioplegia delivery, such as a thebesian valve, Chiari network, and persistent left-sided superior vena cava.

During minimally invasive cardiac surgery, retrograde cardioplegia is delivered using a coronary sinus catheter, which is placed through the right internal jugular vein. Cannulation of the coronary sinus ostium is performed with TEE guidance as it has been shown to be a useful adjunct to fluoroscopy in guiding coronary sinus cannulation from the right internal jugular vein.[181]

After a sheath is placed in the right internal jugular vein, a retrograde cardioplegia catheter is introduced. This catheter allows for distal pressure measurement and cardioplegia delivery and has a balloon that can be inflated to occlude the coronary sinus. After introducing the catheter, it is advanced to the RA–superior vena cava junction. Advancement of the catheter is monitored with TEE by using the ME bicaval and ME modified bicaval views. Once at the caval-atrial junction, the catheter is slowly advanced in the direction of the coronary sinus ostium, under direct visualization from the ME modified bicaval view (Fig. 15.111). Slight rotation and advancement /withdrawal of the catheter may have to be performed in order to cannulate the coronary sinus.[182] Slight retroflexion and/or advancement of the probe from an ME four-chamber view shows an additional long-axis view of the coronary sinus that may aid in confirmation of catheter position.[183]

In some patients, 3D TEE may aid in the placement of the retrograde cardioplegia catheter, particularly in those in which alignment of the catheter and coronary sinus is repeatedly difficult (Fig. 15.112). To obtain an adequate view of the coronary sinus for this purpose, an ME four-chamber view is first obtained. Centering the image on the TV, the wide-angle 3D zoom function is activated, and the ROI is enlarged to cover the RA toward the region slightly below the TV. Once the 3D image is obtained, it is rotated so that an en face view of the coronary sinus is seen.[184] Despite the advantages of this imaging modality, significant artifacts associated with manipulation of the coronary sinus catheter may obscure the image.

Because visualization of the catheter tip may be difficult with TEE, other methods may be used to confirm coronary sinus cannulation. If the balloon is inflated, a ventricularization of the pressure should occur. Fluoroscopy with injection of contrast also can be used to assess the position of the catheter tip. Success of coronary sinus cannulation is approximately 87.5%, with a relatively low incidence of complications. However, the time to successful cannulation can vary and the procedure has been shown to take approximately as long as 16.1 minutes in experienced hands, and dislodgement of the catheter occurs frequently after placement.[181] The most feared complication of the procedure is coronary sinus perforation, which may present as a new onset pericardial effusion or tamponade. In some patients, visualization of air and fluid in the left posterior atrioventricular groove around the short-axis view of the coronary sinus in the ME two-chamber view may be an early sign of coronary sinus rupture.[184]

Percutaneous Interventions on the Mitral Valve

Balloon Valvuloplasty

Although it is relatively rare in the United States, rheumatic MS occurs frequently in the developing world.[185] Since its development in the mid-1980s, percutaneous balloon mitral valvuloplasty (PBMV) has become the technique of choice for the initial treatment of isolated rheumatic MS.[186,187] In other types of MS (eg, congenital), PBMV may be considered for some specific cases. A successful PBMV results in a significant improvement in both short- and long-term outcomes. Among asymptomatic patients, PBMV is usually performed in those

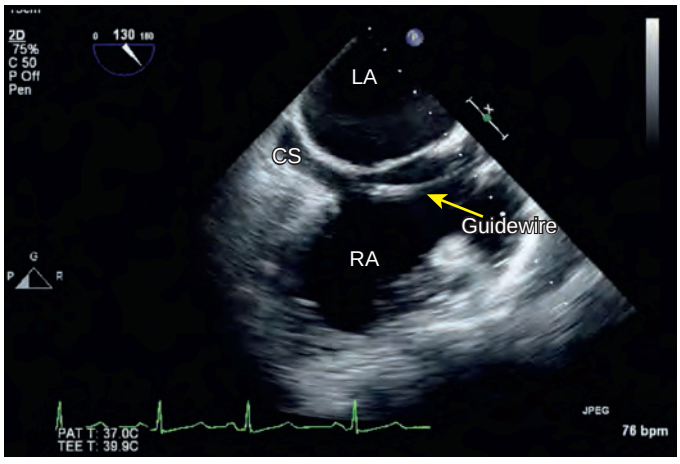


Fig. 15.111 Echocardiographic guidance for cannulation of the coronary sinus *(CS)*. The guidewire is shown advancing toward the CS on a midesophageal modified bicaval view. *LA*, Left atrium; *RA*, right atrium.

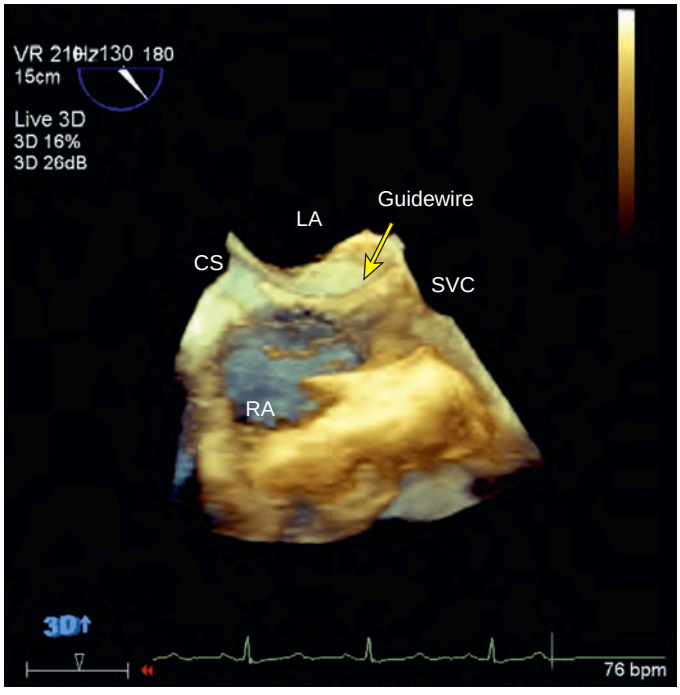


Fig. 15.112 Live three-dimensional (3D) imaging during coronary sinus *(CS)* cannulation. The guidewire is aligned with the CS with real-time 3D echocardiographic guidance. *LA*, Left atrium; *RA*, right atrium; *SVC*, superior vena cava.

TABLE 15.12 Echocardiographic Grading of Mitral Valve Characteristics (Wilkins Score)

Grade	*Mobility*	*Subvalvular Thickening*	*Thickening*	*Calcification*
1	Highly mobile, leaflet tips restricted	Minimal	4–5 mm	Single area of hyperechogenicity
2	Normal in mid and base portions	Chordal thickening up to one-third of length	5–8 mm at margins of leaflets, mid leaflets normal	Scattered hyperechoic areas but confined to leaflet margins
3	Diastolic forward movement from base	Chordal thickening in distal third	Entire leaflet thickening (5–8 mm)	Hyperechoic areas extending to mid portion of leaflets
4	Minimal diastolic leaflet mobility	Extensive thickening up to papillary muscles	Considerable leaflet thickening (>8 mm)	Majority of leaflet is hyperechoic

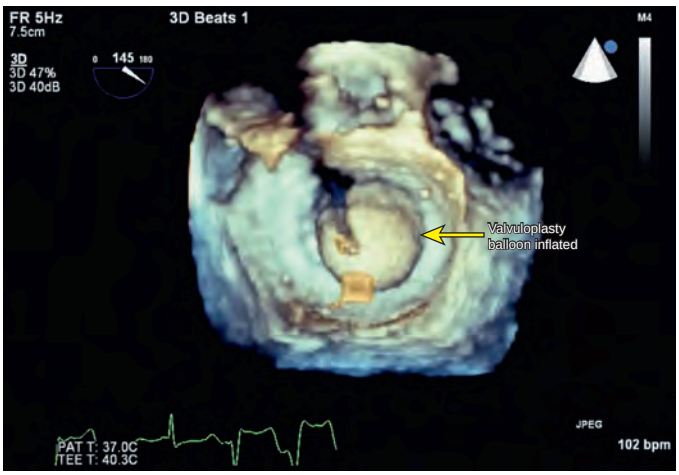


Fig. 15.113 En face view of the mitral valve demonstrating balloon inflation during percutaneous valvuloplasty.

with moderate or severe stenosis (MVA < 1.5 cm^2) with evidence of pulmonary hypertension.[26]

Although not mandatory, TEE is desirable for PBMV, especially to guide IAS puncture. Furthermore, TEE guidance has been shown to improve the placement of the balloon and reduce the total radiation time.[188] In this setting, TEE is frequently performed under mild sedation, so a clear explanation of the procedure to the patient and informed consent are extremely important.

Echocardiographic Evaluation

Intraoperative TEE evaluation should confirm that the patient is an adequate candidate for the procedure. Patients with important mitral annular calcification have poor outcomes with PBMV.[189] Furthermore, patients with LA thrombi, moderate-to-severe MR, and significant TR also are not suitable for PBMV. Three-dimensional TEE may be especially useful for measuring mitral annular diameter and calculating the size of the valvuloplasty balloon.[190] The likelihood of success of PBMV can be predicted using echocardiography-based scores (Table 15.12).[75] These scores have been also shown to correlate with overall costs.[191]

PBMV starts with an IAS puncture, used for gaining access to the left atrium. Real-time 3D TEE guidance is particularly useful for this part of the procedure. After the IAS is punctured, a balloon is advanced from the venous circulation across the IAS and inside the left atrium. The balloon is then guided through the MV orifice into the left ventricle. This portion of the procedure is preferably guided by wide-sector real-time 3D TEE. An ME four-chamber view can be used to evaluate the position of the catheter. TEE is also used to exclude subvalvular apparatus involvement prior to inflating the balloon. Afterward, the balloon is inflated under TEE guidance, ideally with real-time 3D or biplane imaging (Fig. 15.113).[192] After the balloon is inflated, commissural splitting should be confirmed and the MVA should be measured. An MVA greater than 1.5 cm^2 should be present if the procedure is successful. If the MVA is still reduced, balloon inflation may be attempted a second time. CFD imaging of the MV should also be obtained to evaluate the severity of postprocedure MR and to assess the iatrogenic IAS defect.

MitraClip

Severe MR has become an increasingly prevalent disease, with significant impact on survival.[193] Although surgery is beneficial in patients with MR due to MV prolapse or fibroelastic deficiency, the benefit is still under debate for patients with functional regurgitation.[194] Furthermore, several patients are not ideal candidates for surgery because of their increasing age, poor ventricular function, or high number of comorbidities.[195] Although various techniques for percutaneous MV repair have been proposed, the MitraClip (Abbott Vascular, Santa Clara, Calif) is currently the only US Food and Drug Administration (FDA)–approved technique for percutaneous management of MR. This device is indicated in severe (3–4+) primary MR. Inspired originally by the Alfieri edge-to-edge MV repair, it consists of a clip system that grasps the anterior and posterior leaflets together, reducing the regurgitant orifice and creating a double-orifice MV. The device is introduced through the femoral vein, across the IAS (transseptal puncture) through the MV, and into the left ventricle. A combination of TEE and fluoroscopy is used to guide the device into the left ventricle and deploy it (see Chapters 3, 21, and 27).

Echocardiographic Evaluation

Because of the proximity of the probe to the MV, TEE has been shown to be particularly useful for assessing MV structure and function. Furthermore, with 3D TEE many of the geometric assumptions and mental reconstructions required with 2D TEE to assess the complexity of the MV structure are overcome.[196] Because the MV cannot be adequately visualized with fluoroscopy, TEE is an integral part of the MitraClip procedure and the key to its success.

A TEE examination for a MitraClip procedure should first confirm the presence of MR and its severity. Since the procedure is usually performed under general anesthesia, MR severity may be decreased because of a lower peripheral vascular resistance.[197]

Evaluation of the specific scallops involved and the orientation of the regurgitant jet are also important because the MitraClip is better suited for patients with a discrete regurgitant jet originating within the central two-thirds of the line of leaflet coaptation (Fig. 15.114).[194] A planimetered MVA should be confirmed to be greater than 4.0 cm^2, and calcification of the leaflets should be minimal at the point of planned grasping. If a flail leaflet is present, the width of the flail segment should be less than 15 mm.[198] Coexisting conditions that increase the perioperative risk also should be noted, such as a highly calcified aorta or severe pulmonary hypertension.

During the procedure, guidance for IAS puncture is necessary. Once the sheath is advanced into the left atrium, the delivery system is directed perpendicular to the mitral annulus. Alignment may be confirmed with 3D TEE. When the device is perpendicular to the annulus, the grasping arms are opened and it is advanced inside the left ventricle (Fig. 15.115). The device is closed when the leaflets fall into the arms. After closure of the arms, the device's stability should be confirmed, and the MR severity should be evaluated. A successful MitraClip procedure reduces MR to a moderate degree of severity (grade 2+ or less).[199] If greater MR is present, the clip may be reopened and leaflet grasping attempted for a second time, or a second clip may

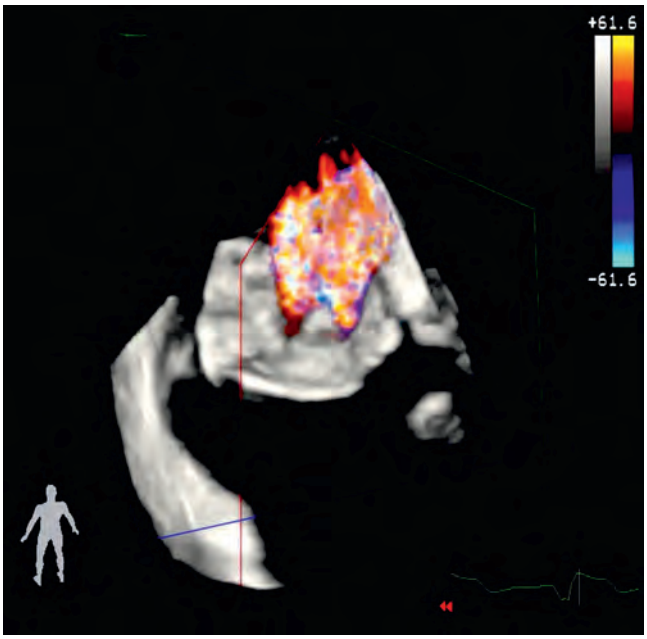


Fig. 15.114 Three-dimensional color-flow Doppler assessment of the mitral valve demonstrates a large regurgitation jet originating within the central two-thirds of the line of coaptation.

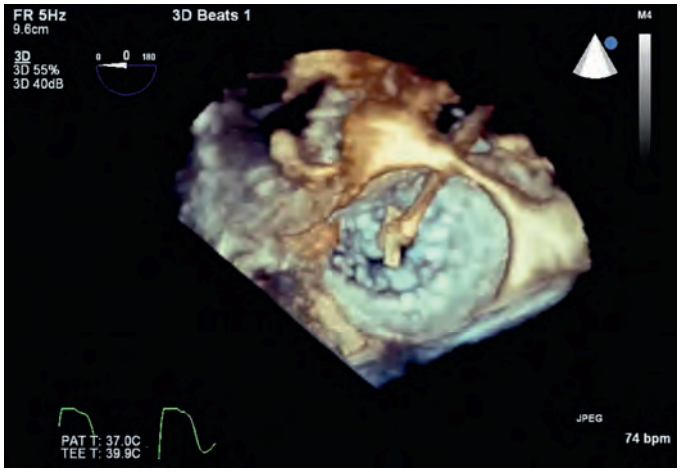


Fig. 15.115 The MitraClip device is seen inside the left atrium with its arms in the open position.

be placed.[200] Evaluation of residual MVA should be performed after clip deployment, confirming adequate transmitral inflow (Fig. 15.116). Certain methods, such as PHT, may be unreliable at this point for quantifying MVA after the MitraClip procedure.[201]

Percutaneous Interventions on the Aortic Valve

Severe AS significantly affects quality of life and is associated with a high mortality rate.[24] AVR is currently the treatment of choice for severe AS. However, AVR is also associated with a high incidence of perioperative complications and mortality in some patients. Transcatheter AVR (TAVR) is a therapeutic option in patients in whom surgery has an unacceptably high risk.[202] Furthermore, in patients in whom AVR may be technically difficult or has a high risk of complications (eg, porcelain aorta), TAVR may also be a suitable alternative.

Currently, there are two transcatheter AVs on the market, the Medtronic CoreValve (Medtronic, Minneapolis, Minn) and the Edwards SAPIEN II valve (Edwards Lifesciences, Irvine, Calif). The main features of both valves are summarized in Table 15.13.

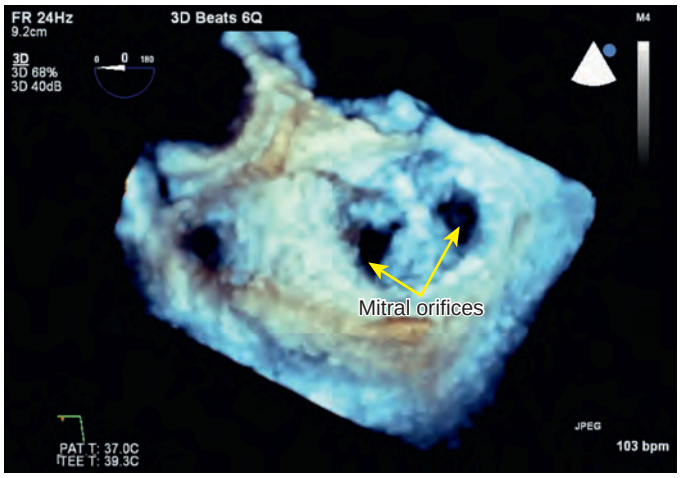


Fig. 15.116 Three-dimensional R-wave gated image demonstrating the repaired mitral valve with the resulting two orifices *(yellow arrows)* during diastole.

TABLE 15.13 Main Features of the Medtronic (Minneapolis, Minn) CoreValve and Edwards Lifesciences (Irvine, Calif) SAPIEN II Transcatheter Aortic Valves

Feature	*CoreValve*	*SAPIEN*
Frame component	Nitinol	Cobalt chromium
Leaflet component	Porcine pericardial	Bovine pericardial
Sizes available	23, 26, 29, and 31 mm	20, 23, 26, and 29 mm
Indicated for patients with annular diameters of	18–29 mm	16–27 mm
Transapical access	No	Yes
Balloon expandable	No	Yes
Self-expandable	Yes	No
Repositioning allowed	Yes	No
Annular fixation	Yes	Yes
Aortic fixation	Yes	No
Pacemaker requirement after implantation	14–40%	3–8%

These devices are usually inserted retrograde through the femoral artery; they also can be inserted through the axillary or subclavian arteries and ascending aorta in case of excessive calcification of the femoral artery. An antegrade transapical approach can also be performed (see Chapters 3, 21, and 27).[203]

Echocardiographic Evaluation

Most institutions usually prefer TEE evaluation during TAVR. In contrast to surgical AVR, during which the surgeon has direct visualization of the operative field, imaging plays an essential role for procedure guidance. A combination of TEE and fluoroscopy is commonly used for TAVR. Because of the need for TEE imaging, general anesthesia is frequently used for these procedures.

During the procedure, TEE evaluation is used to confirm the presence of a tricuspid AV. Original TAVR trials excluded patients with bicuspid AVs. Some investigators found that TAVR in the setting of a bicuspid valve is associated with a higher incidence of postprocedure AI because of the asymmetric shape of the aortic annulus and heavy calcification of aortic leaflets. Recently, this association has been debated.[204]

TEE evaluation is also necessary to accurately measure the aortic annulus diameter, because of the limited availability of valve sizes (see Table 15.13). Patients with aortic annuli less than 18 mm or greater than 27 mm are currently not adequate candidates for TAVR.[205] TEE is more accurate than TTE for aortic annulus sizing, especially in the presence of significant calcification. The aortic annulus is measured

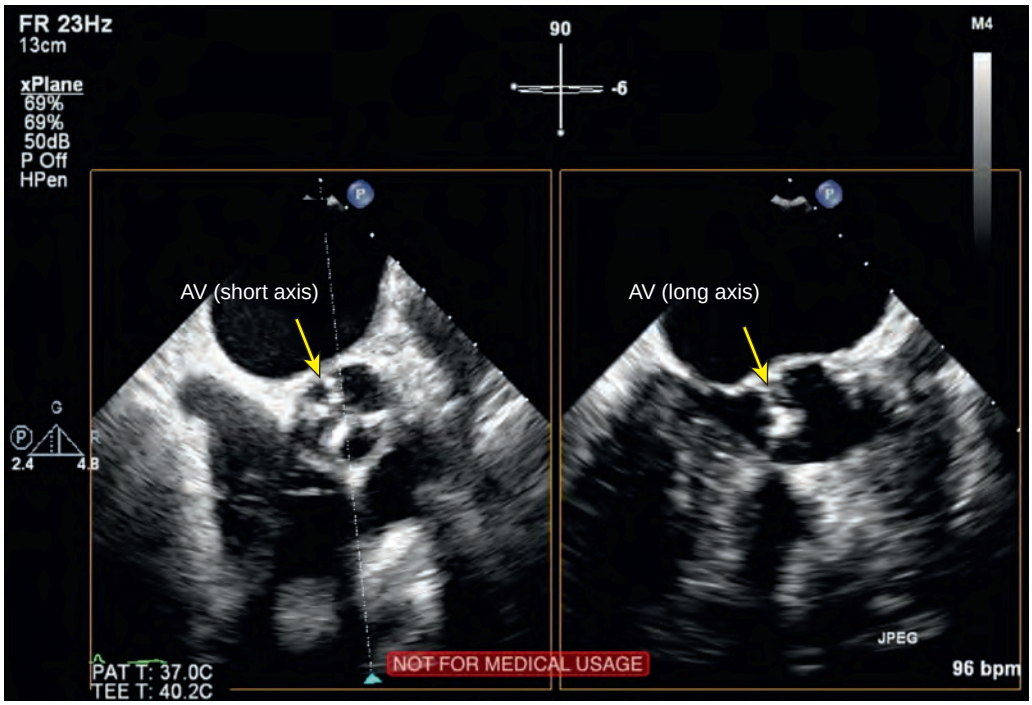


Fig. 15.117 Biplane imaging of the aortic annulus. *AV*, Aortic valve.

during systole in the ME AV long-axis view with 2D TEE between the hinge points of the AV leaflets. Biplane imaging can also be useful to ensure the anteroposterior diameter measurement is not affected by an oblique plane of view (Fig. 15.117). Some echocardiographers also prefer using 3D TEE with orthogonal alignment of multiplanar reformatting planes to obtain a more accurate annular diameter (Fig. 15.118, Video 15.1).[206,207] Some centers have advocated for a 5% to 10% oversizing of the prosthesis to decrease the probability of paravalvular leaks.[208,209]

Besides aortic annular diameter, the aortic root width between the sinuses of Valsalva, the STJ diameter, and the diameter of the ascending aorta should be measured. It is suggested that for TAVR to be successful, the diameter of the ascending aorta within 3 cm of the aortic annulus should be 43 mm or less. The ascending aorta should also be evaluated for atherosclerosis and calcification. The distance from the aortic annulus to the coronary ostia also can be determined with 3D TEE. The distance should be greater than 11 mm to decrease the risk of coronary ostium occlusion by the device after deployment.[210] Careful preprocedure evaluation of the patients' LV function and presence of MR (including severity and mechanism) are also essential so that they can be reassessed after deployment of the valve and compared to baseline.

The TAVR procedure starts by introducing a guidewire through the selected access site. The guidewire is advanced across the stenotic AV under TEE guidance (Fig. 15.119). This guidewire will be used to position the prosthesis. The guidewire should be visualized with TEE to ensure there is no impingement on the MV apparatus. The position of the prosthesis should be carefully selected, because if positioned too low it can embolize into the left ventricle or impinge on the MV, and if positioned too high it may embolize into the aorta, obstruct the coronary arteries, or cause paravalvular leak.[211]

For the SAPIEN valve, once the guidewire is in place, the balloon is advanced and positioned through the AV with fluoroscopic guidance and then confirmed with TEE. Rapid ventricular pacing is used at the time of device deployment to avoid displacement into the aorta. When the CoreValve is used, rapid ventricular pacing is not necessary.[212]

After deployment, TEE is used to ensure the valve stent is centered within the native aortic annulus and there is adequate leaflet opening. CFD is used to evaluate the degree of paravalvular leak (Fig. 15.120). Trace-to-mild central AR is expected to occur while the guidewire is in place (Fig. 15.121). In case of paravalvular leak, the prosthesis can be reballooned, or a second valve can be deployed.[213] LV function is also evaluated, and a new or worsening regional wall motion abnormality (RWMA) may indicate obstruction of a coronary ostium. The presence of pericardial effusion or tamponade and aortic dissection should also be evaluated.

AR has been associated with an increase in mortality rate after TAVR. It is difficult to evaluate AR with traditional methods after a TAVR procedure, because it is usually eccentric and associated with multiple jets (Fig. 15.122). The second Valve Academic Research Consortium described a semiquantitative method to classify AR after TAVR (Table 15.14).[214]

Percutaneous Closure of Paravalvular Leaks

Paravalvular leaks are common complications following MVR and AVR. Even though the majority of leaks are mild, significant leaks occur in 2% to 5% of patients.[215] Paravalvular leaks are twice as common in mitral as aortic prostheses, likely due to preexisting factors, such as endocarditis, mitral annulus calcification, and tissue friability. Paravalvular leaks can cause significant morbidity due to regurgitation and/or hemolysis. Hemolytic anemia is more common in mechanical than bioprosthetic valves. Reoperation after a valve replacement is associated with high morbidity and mortality rates, even greater than those associated with the initial procedure.

Echocardiographic Evaluation

Percutaneous closure of paravalvular leaks has become a suitable alternative for selected patients. As the regurgitant orifices responsible for paravalvular leaks are commonly irregular (crescent shaped or oblong), multiple, and serpiginous, 3D TEE is helpful in assessing the defect size and shape before percutaneous closure is performed.[216–218] The size of the paravalvular leak can be evaluated with 3D TEE by multiplanar reformatting and planimetry. This method measures the anatomic rather than the effective regurgitant orifice (ERO), and the size can vary with different machine settings. Three-dimensional TEE with CFD can be used to improve sizing of the ERO.[216] TEE evaluation

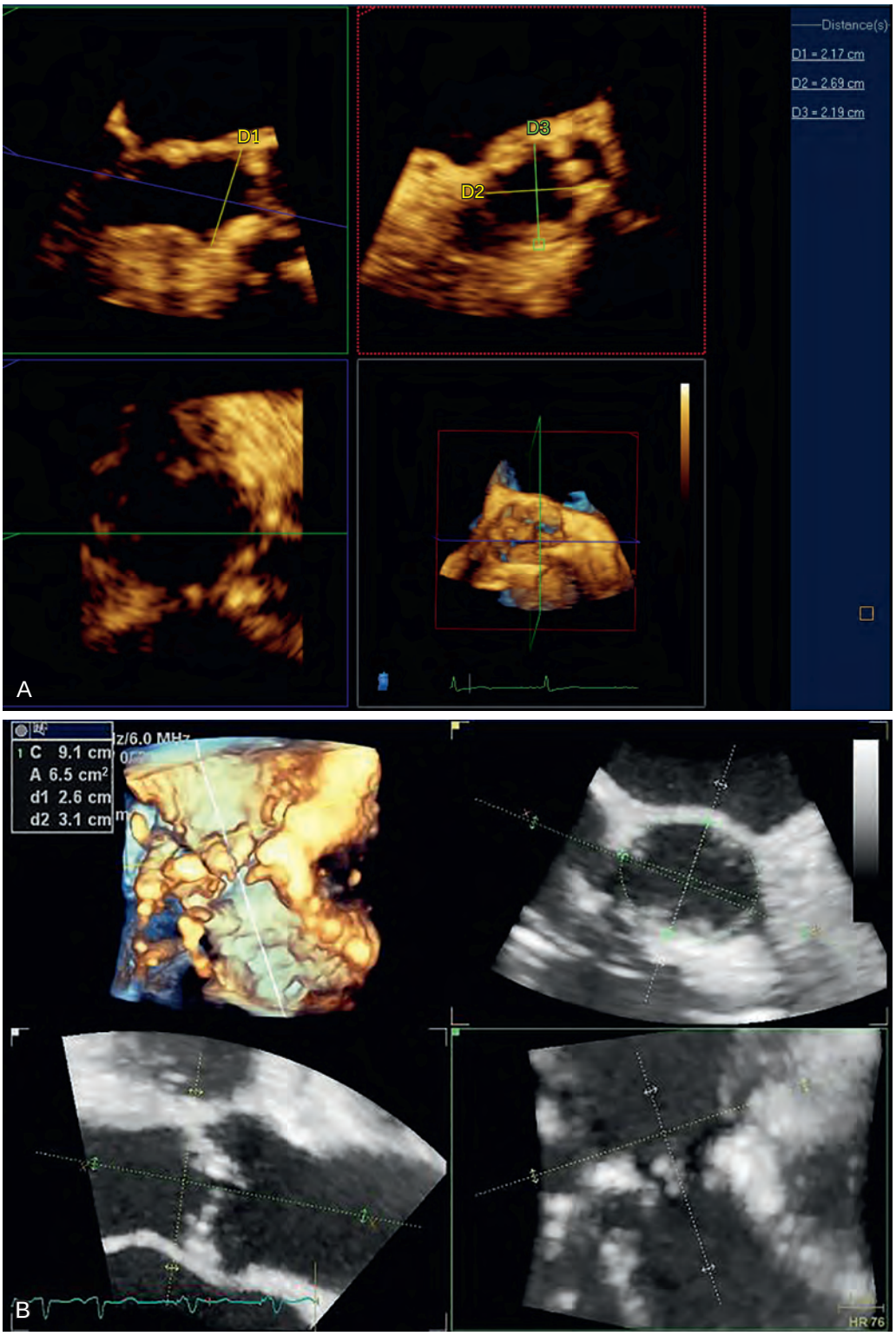


Fig. 15.118 (A) and (B) From two different vendors, multiplanar reformatting planes aligned across the aortic annulus for simultaneous measurement of annular diameters. (See Video 15.1.)

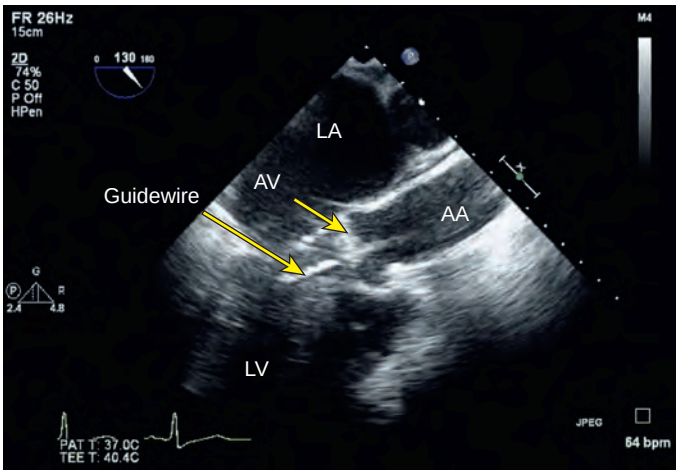


Fig. 15.119 Midesophageal long-axis view. The guidewire is placed through the stenotic aortic valve. *AA,* Ascending aorta; *AV,* aortic valve; *LA,* left atrium; *LV,* left ventricle.

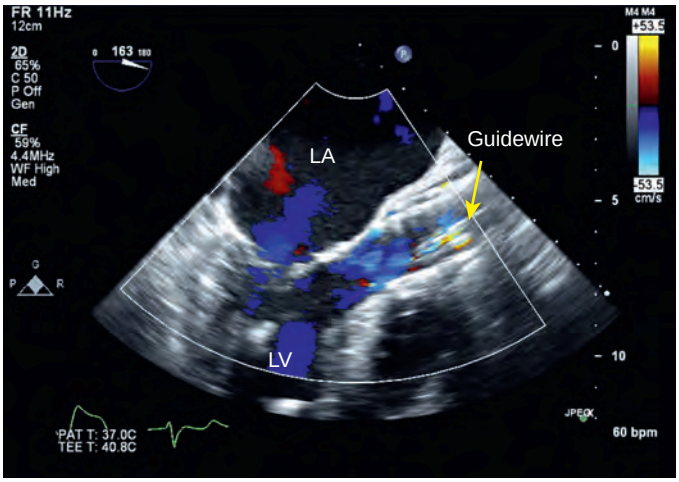


Fig. 15.121 Midesophageal long-axis view demonstrating a trace to mild central aortic regurgitation jet associated with the guidewire. *LA,* Left atrium; *LV,* left ventricle.

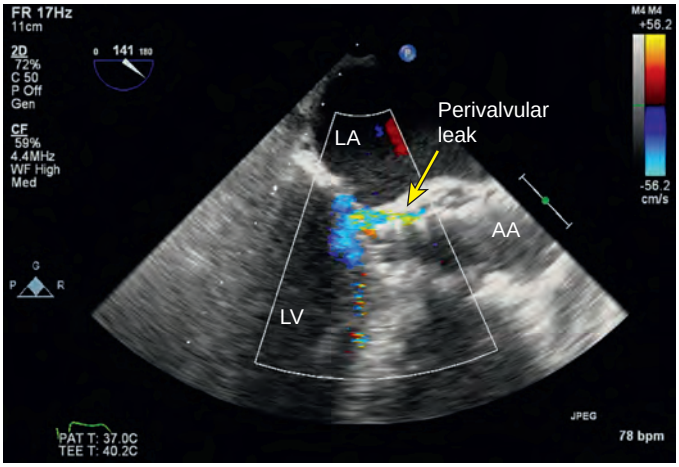


Fig. 15.120 Midesophageal long-axis view demonstrating a paravalvular leak after percutaneous aortic valve placement. *AA,* Ascending aorta; *LA,* left atrium; *LV,* left ventricle.

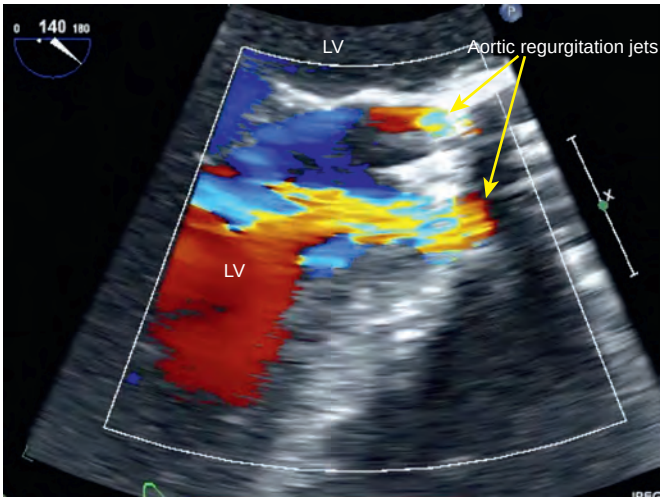


Fig. 15.122 Midesophageal aortic valve long-axis view. Two aortic insufficiency jets can be visualized in association with the aortic prosthesis. *LA,* Left atrium; *LV,* left ventricle.

TABLE 15.14 Semiquantitative Parameters to Grade Aortic Regurgitation Severity After Transcatheter Aortic Valve Replacement

	Mild	*Moderate*	*Severe*
Diastolic flow reversal in the descending aorta with pulsed-wave Doppler	Absent or brief early diastolic	Intermediate	Prominent and holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation	<10%	10–29%	≥30%

must note the location and number of leaks. Patients with paravalvular leaks and a dehiscence more than one-fourth the circumference of the sewing ring are unsuitable for percutaneous closure.[219]

For prosthetic mitral paravalvular leaks, an approach through an IAS puncture is usually selected. TEE is useful to guide IAS puncture and align the guidewire. Positioning of the wire in the left atrium is aided by 3D and multiplane imaging from the LA perspective. For paraaortic defects, the position of the coronary ostia should be carefully measured, as the occluder may obstruct coronary flow. After deployment of the occluding device, adequate function of the valve is reassessed and the presence of RWMAs or tamponade is ruled out.

Ventricular Assist Devices

Ventricular assist devices (VADs) are being used more frequently in patients with heart failure, either as a bridge-to-cardiac transplantation or as destination therapy. Several VADs are currently available, from short-term to long-term systems (see Chapter 28). The HeartMate II (Thoratec Corporation, Pleasanton, Calif) is the only continuous-flow LVAD that is FDA-approved for use as a bridge-to-transplantation or destination therapy; thus, it is the focus of the discussion here, although most of the same general principles apply to other devices.

The HeartMate II VAD is a flow system composed of an inflow cannula placed into the LV apex and an outflow cannula that is placed in the anterior ascending aorta. The pump housing unit is placed in a

subcutaneous pocket in the abdomen, and a percutaneous lead carries an electrical cable to the battery pack and controller that is worn on a belt and shoulder holster. The pump housing unit connects the impeller, which is the only moving part, and the motor. The flow generated depends on the pressure gradient across the device. Flow increases with higher LV pressure and with lower aortic pressures.[220]

Echocardiographic Assessment

Initially, the left ventricle is interrogated and the size and baseline ventricular function are noted. The LA pressure and volume should also be determined, as well as the dimensions of the mitral annulus. If MS is present, it is usually necessary to correct it via commissurotomy or valve replacement before VAD placement, as it could limit LV filling.[221] It is essential to exclude the presence of thrombi at the site where the LV cannula is going to be placed. Thrombosis is a frequent complication of VADs, occurring in approximately 9% to 16% of cases.[222] Preexisting LA or LV thrombi may cause embolism and precipitate pump malfunction, stroke, and end-organ or peripheral ischemia.

Careful evaluation of RV function is important for VAD procedures. Fractional area change, Tei index, and tricuspid annular plane systolic excursion are among the preferred methods for evaluating RV function.[220] Poor RV systolic function and/or the presence of TR must be noted, and the tricuspid annulus should be measured. After VAD activation, RV failure may precipitate underfilling of the left ventricle, with a decrease in LV pressure and the possibility of VAD-generated negative pressure. Collapse of the left ventricle around the inflow cannula may produce air entrainment. This can generate an air embolism to the right coronary artery, further reducing RV function. Also, collapse of the left ventricle can cause leftward shift of the intraventricular septum, exacerbating preexisting TR.[223]

A PFO can precipitate paradoxical embolism or hypoxemia after VAD activation when unloading of the left ventricle causes a reduction in LA pressure.[224] Thus, careful interrogation of the IAS for shunt lesions should be performed before VAD placement. Patients with biventricular failure frequently have an increased pressure in both atria; there may not be a significant gradient between the atria, and flow across a PFO may be undetectable. However, after activation of the device the RA pressure rises as a result of increased venous return, and the LA pressure decreases, so the IAS must be interrogated again to search for a PFO.

AR is detrimental for patients after VAD placement. The AR causes increased LV preload, which increases the pump flow, increasing blood flow through the device and outflow cannula, which in turn increases AR. This causes a futile cycle, with resultant decreased systemic perfusion. Moderate or severe AR requires surgical correction prior to VAD placement. Surgical correction may be performed through primary closure of the AV or bioprosthetic valve replacement.[225,226]

Before VAD activation, careful TEE evaluation to confirm de-airing of the heart is important to prevent air embolism. Volume status should be checked because hypovolemia can also cause LV collapse and cause the VAD to generate negative pressure. The position of the inflow cannula in the LV apex should be assessed (Fig. 15.123). The cannula should be placed immediately below the MV, and it should not impinge on any of the ventricular walls. Continuous-wave Doppler examination of the inflow cannula should demonstrate a velocity of 1 to 2 m/s. Furthermore, the position of the outflow cannula in the aorta should be evaluated. It is difficult to visualize the prosthetic graft material anastomosed to the ascending aorta, but CFD should be used to demonstrate flow inside the aorta. Continuous-wave Doppler interrogation of the outflow cannula should demonstrate a velocity of less than 2 m/s; a higher velocity should arise suspicion of kinking of the cannula.[222]

Exclusion of Left Atrial Appendage Thrombi

LAA exclusion is a percutaneous technique used to prevent systemic embolism in patients with atrial fibrillation. Recently, it has been postulated that LAA exclusion may be as effective as warfarin anticoagulation in stroke prevention.[227]

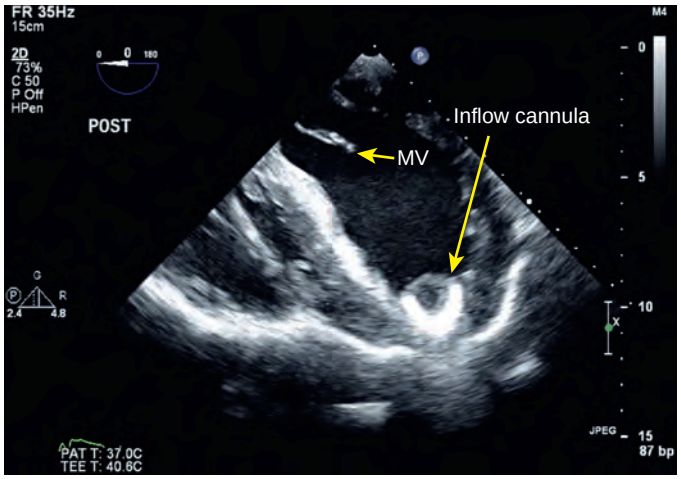


Fig. 15.123 A low midesophageal four-chamber view demonstrates an adequate apical position of the HeartMate II inflow cannula. *MV,* Mitral valve.

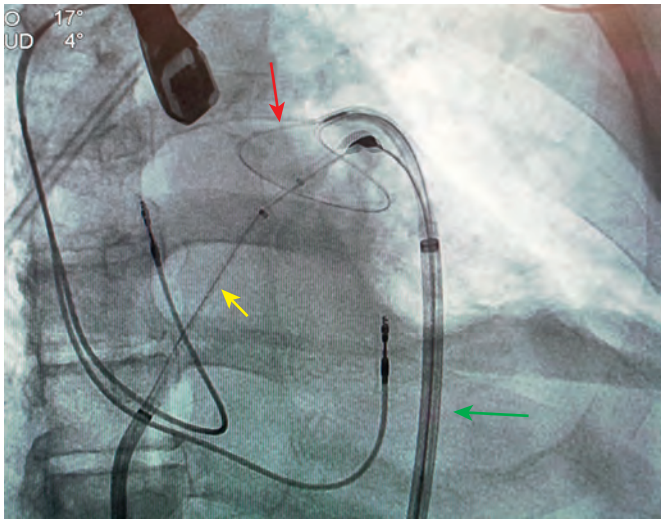


Fig. 15.124 Intraoperative fluoroscopic imaging during Lariat procedure. *Green arrow* denotes epicardial access containing magnet tipped wire near the left atrial appendage. *Yellow arrow* denotes endoluminal left atrial appendage access via a transseptal approach also containing a magnet tipped wire within the appendage. The *red arrow* denotes the LARIAT suture delivery device surrounding the left atrial appendage prior to closure.

TEE examination for LAA exclusion should evaluate LV systolic function, interrogate the IAS for PFO, and evaluate the LAA anatomy. Three-dimensional evaluation may be particularly useful for assessing the LAA morphology. There are four LAA morphologic types: the windsock, chicken wing, cactus, and cauliflower. Of these, the chicken wing is the most difficult to exclude percutaneously.[228]

For LAA exclusion with an endoluminal device (eg, Watchman LAA closure device; Boston Scientific, Marlborough, Mass), a TEE-guided IAS puncture is performed first. The device is then aligned with the LAA under TEE guidance and deployed. For LAA exclusion with an epicardial device (Lariat procedure), a TEE-guided IAS puncture is performed in addition to epicardial access (Fig. 15.124). Via both the trans-IAS access and epicardial access, magnet-tipped wires are inserted to establish continuity. A lasso-styled device (eg, the LARIAT suture delivery device; SentreHEART, Redwood City, Calif) is advanced on the epicardial wire over the appendage (the endoluminal magnet-tipped wire serves as a guide). Once in position, the

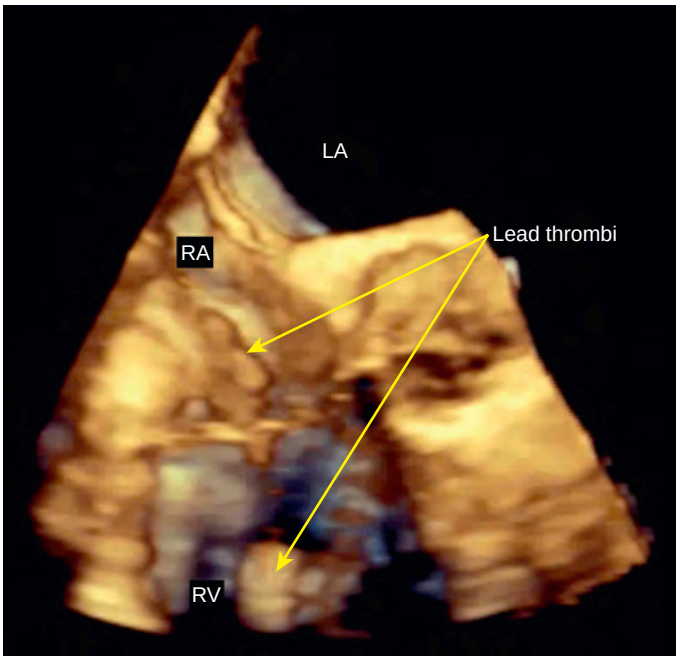


Fig. 15.125 R-wave gated acquisition in a patient presenting for lead extraction. Extensive thrombosis of the pacing lead wire is shown. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle.

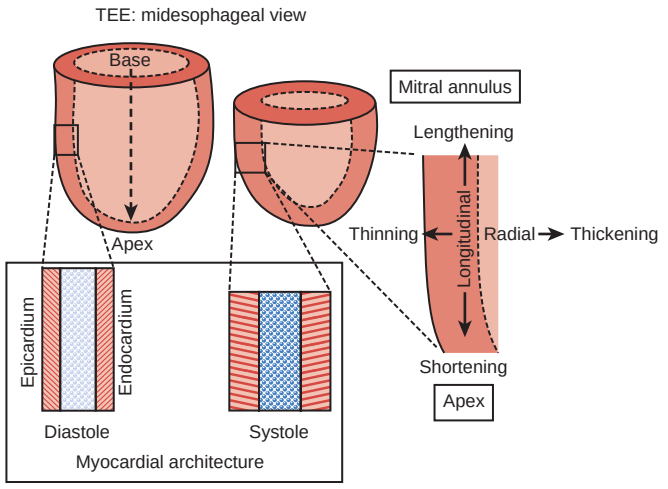


Fig. 15.126 Myocardial architecture consists of helical (left-handed in epicardium and right-handed in endocardium) and circumferential (in midmyocardium) layers of myocardial fibers. This fiber arrangement results in longitudinal (mitral annulus to apex), radial (epicardium to endocardium), and circumferential (tangentially to epicardium) motions during systole and diastole. *TEE,* Transesophageal echocardiogram.

lasso-styled LARIAT suture delivery device is cinched over the appendage. With either technique after deployment, TEE is performed to evaluate the device position and exclude thrombi. CFD examination is then performed to test for residual flow peripheral to the device. Finally, the IAS is interrogated to evaluate the residual ASD at the transseptal puncture site.

Pacing Lead Extraction

A growing number of indications have expanded the use of cardiac implantable electronic devices,[229] and the patient survival rate has increased. As a result, transvenous lead extraction is becoming more frequent for device malfunction or infection (Fig. 15.125).

TEE evaluation during transvenous lead extraction is not mandatory in all institutions. However, the immediate availability to perform TEE, TTE, or intracardiac echocardiography is recommended by the European Heart Rhythm Association and the Heart Rhythm Society.[230] TEE is particularly useful for detecting life-threatening complications of lead extraction, such as ventricular perforation, TR, embolism, and tamponade.[231]

TEE evaluation should include an assessment of RV and LV function. Many of these patients present with severely impaired LV systolic function. Baseline severity of TR and pulmonary hypertension also should be evaluated, because lead extraction can cause injury to the TV and worsen preexisting regurgitation. Evaluation of the patient for PFO or other shunt lesions is also important, particularly when laser-assisted lead extraction is performed. Laser can produce photothermal vaporization of cellular water and produce microbubbles, which may cause paradoxical embolism if a shunt lesion is present.[232] Because laceration of cardiac structures is one of the most feared complications of lead extraction, TEE monitoring can be used to evaluate accumulation of pericardial fluid or tamponade. Early detection of hemopericardium can be life-saving, as it can result in an earlier surgical treatment.

Strain, Strain Rate, and Doppler Tissue Imaging

The recent technologic advances in signal processing in Doppler (Doppler tissue imaging [DTI] and Doppler strain echocardiography) and ultrasound (2D speckle-tracking imaging [STI]) enable measurement of tissue velocity and deformation in one or two dimensions, which provide high-quality, precise, and objective information regarding regional and/or global myocardial function in real time, decrease the subjectivity of the interpretation, and increase the diagnostic accuracy.

Myocardial Structure and Motion

Myocardial fibers are organized in layers, forming a leftward helix in the subepicardium, which transitions to a rightward helix in the subendocardium (Fig. 15.126). Because LV muscle volume remains constant during the cardiac cycle, this myocardial fiber arrangement results in longitudinal (along the major axis) and circumferential (tangent to the periphery) thinning and radial (along the minor axis) thickening during systole, with opposite directed changes in diastole.[233] This 3D global cardiac motion cannot be appreciated during conventional TEE imaging, in which only radial motion (inward endocardial excursion and myocardial thickening in ME or TG views related to midmyocardial function) is evaluated. Longitudinal (ME views) and circumferential motion (TG views) are difficult to evaluate. However, both radial and longitudinal motions are important. In systole, radial thickening predominates; 40% radial thickening is accompanied by 14% longitudinal shortening.[234] On the other hand, the first myocardial layer affected by ischemia is the subendocardium, which provides for longitudinal motion.[235] The subjective evaluation of regional LV motion is also limited during conventional TEE because passive motion of a noncontracting segment, due to tethering to adjacent segments, cannot be reliably excluded. Many of these limitations can be overcome by assessing myocardial deformation (strain).

Deformation

Myocardial strain (S or e) is the (systolic) deformation of a myocardial fiber, normalized to its original length:

$$S = \frac{L_1 - L_0}{L_0} \cdot 100(\%)$$

where L_0 is the baseline (end-diastolic) length, and L_1 is the end-systolic length.[236]

By definition, strain is positive when the systolic dimension increases (the myocardial fiber lengthens or thickens) and negative when the systolic dimension decreases (the myocardial fiber shortens or thins). Therefore, radial thickening is associated with positive strain ($L_1 > L_0$), whereas longitudinal shortening and circumferential thinning are associated with negative strain ($L_1 < L_0$). Radial strain relates to motion from the endocardium to the epicardium; circumferential strain relates to motion along the circumference (curvature) of the left ventricle; and longitudinal strain relates to motion from the base to the LV apex.

Echocardiographically measured strain is measured in relation to time (t) and is called *Lagrangian strain:* $\varepsilon_l(t) = [L(t) - L(t_0)]/L(t_0)$, where $L(t_0)$ is the end-diastolic shape. For a 2D object, there is normal deformation (the motion is normal to the borders of the object and occurs along both the x-axis and y-axis) and shear deformation (motion occurs parallel to the borders of the object). For a 3D object, such as a myocardial segment, there are three *normal* strains (along the x-, y-, z-axes), and six *shear* strains (along the combinations of the different axes).[237] Because fiber contraction causes myocardial deformation, strain is a measure of myocardial contractile function. Echocardiographic deformation can be measured from velocity gradient using DTI (or non-Doppler tracking of speckles [STI]).[238,239]

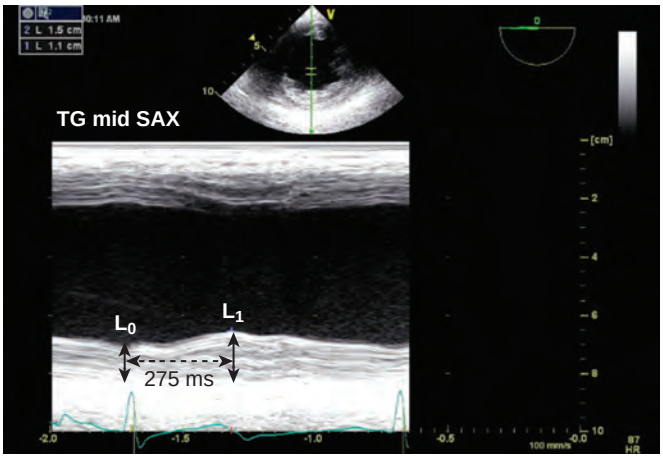
Strain rate (SR) reflects how fast regional myocardial deformation (strain) occurs; that is, SR expresses the speed of deformation:

$$SR = S/t(\%/sec)$$

where t is the time duration of this deformation (Fig. 15.127).

Echocardiographic strain measurements with either technique have been validated against sonomicrometry or MRI, with *r* values of .96 for strain and .94 for SR.[239–243] For normal myocardium, SR reflects regional contractile function because it is relatively independent of heart rate, whereas systolic strain reflects changes in SV.[244,245] Evaluated with DTI or tagged cardiac MRI, LV regional strains increased from base to apex and from endocardium to epicardium.[237,246,247] Normal values are −16% to −24% (longitudinal strain), +48% (radial strain), and −20% (circumferential strain).[248–250] Some have found significantly greater strain values in women than in men.[251] Longitudinal RV strain and SR values are inhomogeneous and greater than those of the left ventricle.[252] Strain and SR offer complementary information, and both should be measured and evaluated. For example, prolonged contraction may yield normal strain despite low SR. As such, SR is considered more sensitive than strain in revealing myocardial disease.

SR showed good correlation with +dP/dt during isovolumic contraction ($r = .74$) and with −dP/dt during isovolumic relaxation ($r = .67$).[252] Strain is load dependent and is not less load-insensitive than ejection fraction, fractional shortening, and other traditional indices of systolic function. For example, acute hypovolemia induced by withdrawal of 500 mL of blood from healthy subjects led to decreased longitudinal DTI strain (−28% ± 8% to −21% ± 4%), whereas SR remained unchanged (−1.5 ± 0.35/s to −1.4 ± 0.4/s).[243,252,253] Similarly, STI strain is preload and afterload dependent; longitudinal strain decreased after hemodialysis in patients with end-stage renal disease (−18.4% ± 2.9% to −16.9% ± 3.2%), and radial strain increased immediately after AVR surgery to treat AS (from 22.7% ± 2% to 23.7% ± 1.8%) and decreased (23.1% ± 3.5% to 21% ± 3.8%) after AVR to treat AR.[254,255] However, others have shown that longitudinal DTI strain (recorded in healthy subjects) remained unchanged during preload manipulation (baseline −18% ± 3%, increased preload with Trendelenburg −18% ± 3%, reduced preload with venodilator −17% ± 3%), whereas myocardial velocities were affected.[256] Discrepancies in previous findings are explained by study design, techniques used for strain measurement, and degrees of preload manipulation. However, it would be safer not to consider strain as a load-independent parameter of systolic function.



$$\text{Strain} = \frac{L_1 - L_0}{L_0} = \frac{1.5 - 1.1}{1.1} = 36\%$$

$$\text{Strain rate} = \frac{\text{Strain}}{\Delta t} = \frac{36}{275} = 0.13/s$$

Fig. 15.127 Illustrative example of estimation of strain and strain rate of midinferior and midanterior left ventricular segments using M-mode. *L_0*, End-diastolic length; *L_1*, end-systolic length; *Δt*, systolic time interval; *SAX*, short axis; *TG*, transgastric.

Principles of Doppler Tissue Imaging and Doppler Strain

As discussed earlier, a shift in frequency is caused when transmitted ultrasound is reflected off a moving target (Doppler effect). In conventional echocardiography, Doppler algorithms are set up to interrogate returning signals from the blood pool only using high-gain settings (to amplify the low-amplitude signal of the fast moving blood) and a high-pass filter (to reject the noise generated by the slow-moving myocardium). Modification of these filter settings (reduction of gain amplification and bypass of the high-pass wall filter) will reject data from moving blood and permit recording of the myocardial motion signal, which is stronger (approximately 40 dB higher amplitude) but slower (<25 cm/s), respectively, thus enabling DTI and measurement of strain.[257] The principles of DTI, together with applications and limitations, have been reviewed recently and are partially summarized in the Diastolic Function section in Chapter 14.[258]

For DTI strain, color DTI is obtained as in conventional CFD, with a color sector positioned over the myocardial wall of interest. The mean myocardial velocities are computed using autocorrelation analysis, displayed in blue if directed away from and in red if directed toward the transducer and are superimposed on a grayscale 2D tomographic view (Fig. 15.128A).[259] While in color DTI mode, placement of a sample volume (see later step-by-step explanation) over the myocardial area of interest (see Fig. 15.128B) will calculate the deformation parameters SR (see Fig. 15.128C) and strain (see Fig. 15.128D) from within this sample volume:

Strain is derived by temporal integration of SR.

SR and strain can be tethered to a functioning adjacent segment that causes a segment with impaired function to give a false impression of contraction. This can be compared to the example of a towed car; although the engine of the towed car is not functioning, the car has velocity. When no velocity gradient exists within the interrogated segment, there will be no deformation and SR (and strain) will be zero.

Strain and SR calculated from myocardial velocity gradients have been validated over a wide range of strain values using sonomicrometry in animals and 3D tagged MRI in humans.[235,241,260,261] However, systolic strain correlates with MRI better in healthy than diseased individuals.[262] DTI strain and SR are strong noninvasive indices of LV contractility; DTI strain and SR increased with dobutamine, decreased

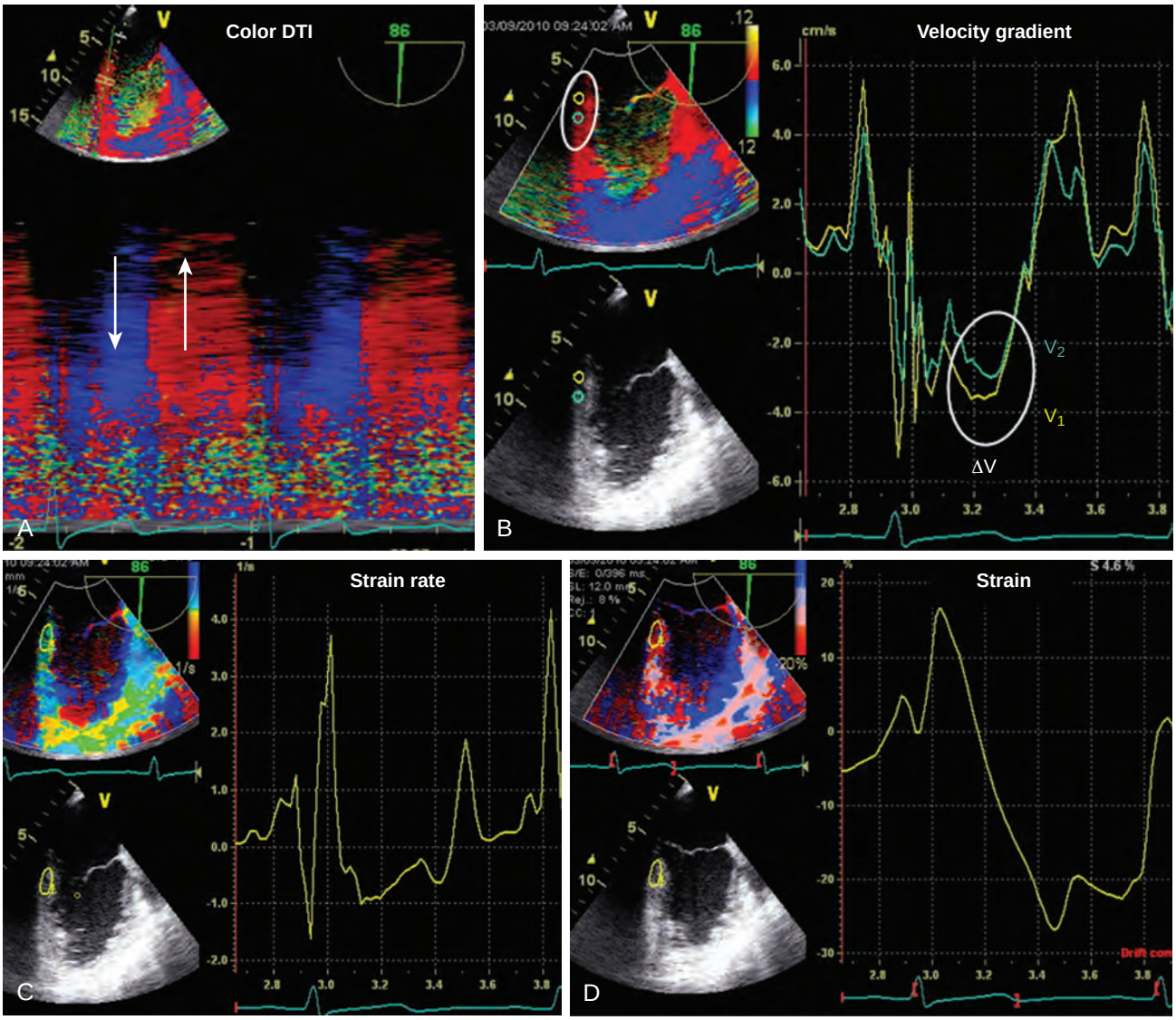


Fig. 15.128 Doppler strain and strain rate. (A) Activation of Doppler tissue imaging *(DTI)* function allows imaging of myocardial velocities in color, here with M-mode (from the inferior wall in a mid-esophageal two-chamber view). The velocities are directed away from the transducer in systole (and colored blue) and toward the transducer in diastole (and colored red). (B) Spectral display of myocardial velocities from within sample volumes (insert panel at left) demonstrates a velocity gradient *(ΔV)*. Basal velocity *(V_1)* is greater than apical velocity *(V_2)* as the inferior wall shortens along its long axis. (C) The velocity gradient (ΔV) of these points is used to calculate strain rate (SR). (D) Integration of SR over time (Δt) derives strain.

with esmolol, and correlated well with peak LV elastance in experimental settings.[245]

DTI strain is time consuming, technically demanding, and has important limitations. Reverberation or dropout artifacts from neighboring structures can affect the measured velocity gradient and interfere with calculation of deformation parameters. Most importantly, DTI strain is a Doppler technique and can display deformation along a single dimension only, that of the ultrasound plane. Therefore, the displayed value (SR and strain) may not relate to the true (longitudinal, radial, or circumferential) deformation. In ME views, when the ultrasound beam is parallel to the myocardial wall, the actual (longitudinal) velocity can be accurately measured, but the velocity of radial (transverse) deformation will be zero because radial motion will be perpendicular to the ultrasound beam. With any angle deviation from 0 degrees, the contribution of radial deformation to the measured velocity increases.[263] As a result, when using TEE, longitudinal strain and SR should be recorded only from ME views, and radial strain and SR from TG views. Furthermore, if the angle between the Doppler and motion plane is greater than 20 degrees, the true myocardial velocity gradient (and the calculated strain and SR) will be underestimated.[261] At an angle of 45 degrees, the measured DTI strain is zero.[243] This becomes more problematic in the presence of RWMAs.[264] Because of this angle dependency, DTI should be used primarily to assess longitudinal deformation parameters.

Step-by-Step Guide on How to Obtain Doppler Strain

The echocardiographic system must have a preset function to image and measure tissue velocity to obtain Doppler strain parameters. Of importance is optimal quality of 2D imaging and clear distinction between blood pool and myocardium (this may be facilitated by using second harmonic imaging, if available). High frame rates are required (usually more than 100 frames per second) to show the subtle changes

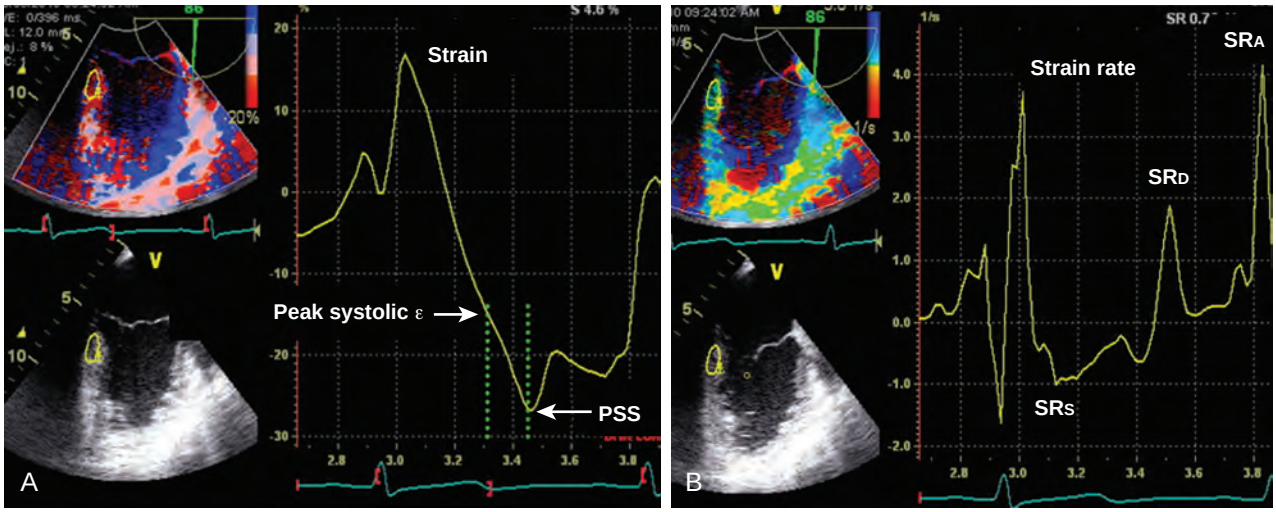


Fig. 15.129 Measurement in Doppler strain echocardiography includes (A) peak systolic *(SR_S)*, early diastolic *(SR_D)*, late diastolic *(SR_A)* strain rates, and (B) end-systolic strain. Strain recorded after aortic valve closure is called *postsystolic strain (PSS)*.

in myocardial velocity. This is accomplished by narrowing the sector width over the myocardial wall of interest. Optimal ECG tracings with clear definition of QRS and P are essential, as well as pulsed-wave or CFD echocardiography of transmitral and aortic flows (for timing of onset and end of systole). These temporal recordings should be concurrent with strain data acquisition.

First, DTI should be activated.[258] The TEE probe then is manipulated in such a way that myocardial motion and ultrasound planes are parallel to each other (or at an angle ≤ 20 degrees). The examination sequence should be standardized and the views labeled because the narrow sector removes neighboring structures used for identification. An adequate Nyquist limit is chosen, usually about ±20 cm/s, to avoid aliasing while increasing spatial and temporal resolution. Next, the sector width and depth are optimized. The operator has two options; either a conventional sector width, which enables side-by-side comparison of diametrically opposite segments/walls, or a narrow sector (with the option of shallow depth), which maximizes the frame rate (DTI strain is optimal at >180 frames per second). The ventilator may be switched off during acquisition of images, which are then reviewed and digitally stored. At least three beats (in sinus rhythm) or up to eight beats (in arrhythmia) should be captured and digitally stored.[265] TEE images used for Doppler strain are the three standard ME views (for long-axis myocardial deformation) and the basal and mid-TG and mid-short-axis views. Selection of these tomographic planes is dictated by the requirement for parallel orientation between the motion plane under examination and ultrasound direction (as described earlier). Addition of an M-mode line to the color DTI velocities displays a vertical line of color tissue velocity pattern along the M-mode beam with good temporal resolution (see Fig. 15.128A).[266]

Further analysis is performed either on the initial echocardiographic system or on a dedicated workstation. Currently, Doppler strain techniques are proprietary software and analyze digitally stored images from the same system only. An appropriately sized sample volume (6 × 10 mm) is placed on the desired LV region, keeping in mind that larger sample volumes result in smoothing of the strain signals, whereas at the same time, temporal and spatial resolution decrease. The size of the sample volume determines the length (L_0) over which the velocity gradient is calculated. To keep the ROI within the myocardial borders, L_0 is typically 10 mm for longitudinal data sets and 5 mm for radial data sets.[267] *Drift compensation* is a default setting that corrects for drift (ie, when myocardium does not return to its original length at end-diastole) in the strain curves, but it can introduce error in the evaluations and should be taken into account as well. Because strain is the temporal integral of SR, strain is a smoother curve than SR. The SR curve should be inspected as a noisy SR curve indicates suboptimal tracking of the ROI and drift. In this case, it is better to reposition the sample volume.

The sample volumes are placed along the length of the myocardial wall (basal, mid, and apical segments) toward the endocardial surface (ME views) or in the middle of the myocardium (TG views) and should track the segment throughout the cardiac cycle. The operator should verify that this happens by scrolling frame by frame and observing the concurrent motion of the sample volume with the myocardial segment. From each sample volume, SR, strain, and timing of peak values with respect to QRS are calculated (Fig. 15.129). The reproducibility of strain measurements is reported to be less than 15%.[265] Suggested measurements and calculations are shown in Table 15.15.

TABLE 15.15 Strain Echocardiography Measurements and Calculations

End-diastole	R wave of electrocardiogram
End-systole	Aortic valve closure (AVC)
End-systolic strain (S_{SYS})	Magnitude of systolic deformation between end-diastole and at end-systole (AVC)
Peak strain (S_{PEAK})	Maximum systolic deformation over a mean RR interval • Lowest value for longitudinal or circumferential strain • Highest value for radial strain
Postsystolic strain (S_{PS} or PSS)	The difference between S_{PEAK} and S_{SYS} $S_{PS} = S_{PEAK} - S_{SYS}$
Postsystolic strain index (PSI)	Represents the relative amount of ischemia-related segment thickening or shortening, found to occur after AVC $PSI = S_{PS}/S_{PEAK} = (S_{PEAK} - S_{SYS})/S_{PEAK}$ $S_{ps} - S_{es}/S_{es}$
Systolic strain rate (SR_{peak})	Maximum SR before end-systole
Peak systolic strain rate (SR_{peak})	Maximum SR
Rotation	Base rotates clockwise (initial, early systolic rotation is counterclockwise): (+)ve ° values Apex rotates counterclockwise (initial, early systolic rotation is clockwise): (−)ve ° values
Torsion	Basal rotation–apical rotation

Principles of Speckle-Tracking Imaging and Two-Dimensional Strain

Interactions of ultrasound with myocardium result in reflection and scattering. These interactions generate a finely gray-shaded, speckled pattern. This speckled pattern is unique for each myocardial region and relatively stable throughout the cardiac cycle. The speckles function as acoustic markers; they are equally distributed within the myocardium and change their position in accordance with the surrounding myocardial deformation or tissue motion. In STI, the speckles within a predefined ROI are followed automatically frame by frame, and the change in their geometric position (which corresponds to local tissue movement) is used to extract strain, SR, velocity, and displacement. Because these acoustic markers can be followed in any direction, STI is a non-Doppler, angle-independent technique for calculation of cardiac deformation along two dimensions. Therefore, radial and longitudinal deformation can be measured in the ME views, and radial and circumferential deformation in the TG short-axis views.[263]

Although considered as the only sound methodology for measuring cardiac deformation,[264] this non-Doppler technique also has limitations: (1) decreased sensitivity because of applied smoothing; (2) incorrect calculation of deformation, which is produced by erroneous tracking of stationary reverberations (when tissue moves, the speckle interference pattern may not move in exact accordance with tissue motion)[266]; (3) the necessity of clear visualization of the endocardial border for reliable radial and transverse tracking; and (4) undersampling in tachycardia because optimal frame rate should be less than 100 frames per second. Equally important, STI algorithms require that the entire myocardium is visualized throughout the cardiac cycle. Echo dropout and mitral annulus calcification attenuate myocardial appearance in the TG or ME views, respectively, and do not allow adequate tracking of echocardiographic speckles.

Shear Strain and Torsion

The myocardial architecture of epicardial and endocardial fibers will produce shear strain during the cardiac cycle (deformation parallel to the reference plane as the myocardial layers slide on each other; see Fig. 15.126). This results in the base and the apex of the heart rotating in opposite directions. From a TEE perspective, the base rotates clockwise (preceded by an early systolic counterclockwise rotation because of earlier activation of subendocardial fibers) and the apex counterclockwise (preceded by an early systolic clockwise rotation). Torsion of the ventricle is the difference in apical and basal rotation, similar to wringing a towel dry.[234] As a result, during the cardiac cycle, there is a systolic twist and an early diastolic untwist of the left ventricle along its long axis because of opposite-directed apical and basal rotations. Rotation angles and torsion can be measured with STI and measurements correlate well with sonomicrometry and tagged MRI.[268,269] Because basal and apical rotations are in opposite directions, somewhere between them is a level (referred to as the *equator*) where rotation changes from one direction to the other.[268]

LV torsion occurs mainly by the counterclockwise apical rotation. Torsion is considered the mechanical link between systolic and diastolic function: systolic twisting stores elastic energy, which, released during the isovolumic phase of diastole, produces untwisting, generates intraventricular pressure gradients, and allows LV filling to proceed at low filling pressure.[233] During systole in healthy subjects, LV torsion increases and LV volume decreases; however, the relation between rapid untwisting (uncoiling) and increasing volume is nonlinear during diastole. Initiation of untwisting is an early and key mechanism that promotes early diastolic relaxation and early diastolic filling, possibly more important than recoil of systolic basal descent.[270]

LV torsion is preload dependent and increases with inotropy.[271] Approximately 40% of LV untwisting occurs during the isovolumic relaxation period, reaching a maximum just after MV opening, when approximately 20% of the SV has entered the left ventricle. By the peak of transmitral early filling (E wave), approximately 80% to 90% of untwisting is completed and essentially finished by the end of transmitral filling E wave, with the subsequent LV volume increase because of expansion in the short and long axes. LV systolic torsion and rapid untwisting increase significantly with exercise, storing additional potential energy that is released as diastolic suction increases. That is why the heart can increase the diastolic filling rate despite the shortened diastolic period during tachycardia. Patients with HCM showed delayed untwisting that was not significantly augmented with exercise.[272] This explains the inability of patients to increase filling during exercise without a significant increase in LA pressure. The magnitude of torsion depends critically on the measurement level relative to the LV base or other reference point. A limitation of STI in recording torsion is the in-out motion of the image plane as the left ventricle moves along its longitudinal axis. Selection of reproducible anatomic landmarks is important for measuring (and reporting) reproducible values. At the basal level, the fibrous mitral ring is used for orientation and reproducible image planes are easier to obtain. For apical recordings, the image plane should be just basal to the level with luminal closure at end-systole (there should be a recognizable apical cavity at end-systole).

Step-by-Step Guide on How to Perform Speckle-Tracking Imaging

The technique of non-Doppler strain analysis has been described for ambulatory cardiac patients.[263,273] As compared with DTI, STI is less demanding and is closer to standard imaging (no Doppler is required and is performed at normal frame rate). The steps to perform STI in the anesthetized cardiac surgical patient are similar and are described in detail later. For the time being, analysis and measurements of 2D speckle strain parameters are possible off-line only, in a dedicated workstation (EchoPAC; GE Vingmed, Holton, Norway). As of this time, analysis is possible only on digitally acquired and stored images of the same vendor (there is no cross-talk between systems from different vendors).

The operator starts by acquiring 2DE images of the left ventricle, which are digitally stored. Three ME views (four-chamber, two-chamber, and long-axis) and three TG views (basal, mid, and apical) are acquired with a frame rate between 40 and 80 per second, with adequate sector width and depth to image both endocardium and epicardium. In the anesthetized patient, it is better to stop ventilating to avoid image translation. Equally important is to acquire optimal quality 2D images and eliminate any myocardial areas with echo dropout (no speckles, no analysis). Timing of systole is based on the ECG-R wave, and end-systole is defined using M-mode tracings of the AV or pulsed-wave Doppler of the trans-AV flow. This interval is used by the software to define the systolic time; therefore, it is practical to initiate postprocessing in an ME long-axis view, in which the AV is seen, and then move to the other ME and TG views. In addition, it is important to acquire images rapidly and ensure that heart rate (and rhythm), as well as hemodynamics, remain stable. Otherwise, the systolic interval needs to be redefined before each strain analysis.

In each LV view stored, the operator manually traces the LV endocardium in a systolic frame, where it is best defined/imaged. Based on this initial endocardial tracing, the software generates an ROI, which encompasses the entire thickness of the cardiac wall between the LV epicardium and endocardium. This ROI may be adjusted manually by the operator so that the inner border is tracing the endocardium and the ROI covers the entire myocardium throughout the cardiac cycle. After approval of the software-generated myocardial wall delineation, speckle-tracking analysis is done from within this region for one cardiac cycle at a time. In each view, the LV myocardium is automatically divided into six segments, and the tracking quality is scored as either acceptable or unacceptable. If more than two segments have unacceptable quality, ROI should be redefined or a different beat should be chosen. Most of the time, the more important reasons for unacceptable segments are myocardial dropout and poor-quality 2D imaging; neither can be corrected after processing.

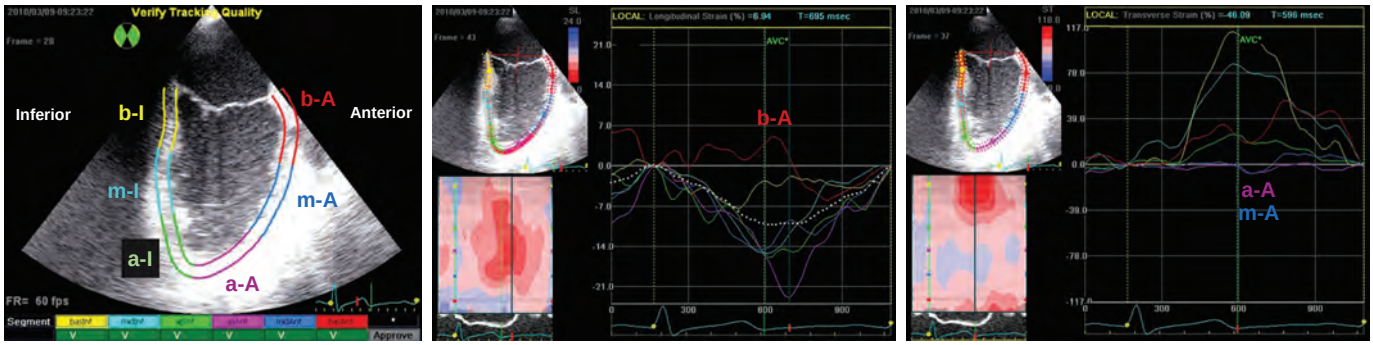


Fig. 15.130 Speckle tissue imaging. (A) Longitudinal strain and (B) transverse strain from a midesophageal four-chamber left ventricular view. *White dotted line* represents the global (average) longitudinal strain. Each myocardial segment is color coded. Longitudinal strain is abnormal in basal inferolateral segment (longitudinal expansion). Transverse strain is normal in only basal and midinferoseptal segments (transverse thickening). (C) Circumferential and (D) radial strain from a transgastric midpapillary short-axis view of the left ventricle. *White dotted line* represents the global (average) circumferential strain. Deformation is uniform (as compared with [A] and [B]). *b-A,* Basal anterior; *a-A,* apical anterior; *a-I,* apical inferior; *b-I,* basal inferior; *m-A,* midanterior; *m-I,* midinferior.

TABLE 15.16 Strain Echocardiography: Imaging Modalities

	Doppler Tissue Imaging	*Speckle-Tracking Imaging*
Technique	Manipulation of Doppler signal • Elimination of wall filter • Low-gain amplification Strain is calculated from velocity gradients, measured against a fixed reference (transducer)	Tracking of acoustic markers • Gray speckles within myocardium are tracked frame by frame Strain is directly measured from tracking of acoustic markers (speckles)
Display	Color map (±M-mode) Pulsed-wave at a specific space (regional values only)	Color map Spectral display (regional and global values)
Measurements	From color map (off-line): • Strain rate • Strain (Lagrangian) • Velocity (mean) • Displacement From pulsed-wave (real-time): • Velocity (peak) • Displacement	• Strain rate • Strain (Lagrangian) • Velocity • Displacement • Torsion
Limitations	Only deformation parallel to ultrasound beam is measured Affected by translation and tethering Requires high frame rate	Requires lower frame rate (time between collection of consecutive image frames ≥ 10 ms)—interpretation may be more reliable if tissue contains some stronger scattering structures Off-line implementation (not real time) Different image resolution in axial and lateral beam directions (long vs radial in midesophageal and radial vs circumferential in transgastric views) Dependent on optimal imaging Basal motion through image plane may result in poor spatial resolution

If tracking quality is acceptable, the operator approves the sampled segments and the software provides various deformation parameters for each segment: strain, strain rate, velocity, displacement, and rotation (torsion).[263,274] Examples of non-Doppler strain measurements are seen in Fig. 15.130. Because acquisition of 2D images (in the ME and TG views) is standard procedure during a comprehensive TEE examination, appropriately stored, good-quality 2D images can be analyzed off-line (provided that the analysis system is of the same manufacturer) and provide STI parameters.

A three-click method (automated function imaging), whereby the operator anchors three points, at each side of the mitral annulus and at the apex of the left ventricle (ME views), further simplifies the process of tracking and analyzing peak systolic strain based on 2D strain. The computerized assessment can present the data in parametric (color), anatomic M-mode, strain curves, and bull's-eye displays. The usefulness of automated function imaging is that deformation data are easily produced and can be comprehended by an inexperienced operator.

The differences between Doppler and non-Doppler strain measurements are summarized in Table 15.16.[263] Deformation values are shown in Table 15.17.[275]

Correlation of Strain Between Doppler Tissue Imaging and Speckle-Tracking Imaging

If either DTI or STI measures deformation accurately, the respective strain values should correlate and give identical values. In 30 patients without acute MI, longitudinal strain values differed only by 0.6% ± 6.0% (r = .53; P <.001), and radial strain values differed by 1.8% ± 13.4% (r = .46; P <.001).[260] Using receiver operating characteristic curves, STI showed greater area under the curve to discriminate among dysfunctional segments compared with DTI strain. Similarly, DTI and STI values were identical in healthy subjects, as well as in patients with cardiomyopathy.[242,246,248,250]

The diagnostic ability of STI (performed with TTE) in patients undergoing dobutamine stress testing was less in the right and left circumflex coronary territory than in the anterior circulation.[276] Contrary to DTI, STI depends on image quality. Poor imaging results in decreased speckled appearance and poor tracking of the myocardium.

Right Ventricular Function

The complex geometric shape and thin wall structure of the right ventricle do not allow quantification of RV function with conventional

TABLE 15.17 Deformation Values

References	*Strain Mode*			*Clinical Point*	
Reisner et al, 2004[250]	STI	$n = 12$ Global longitudinal S = −24.1% ± 2.9% Global longitudinal SR = −1.02 ± 0.09/s	$n = 27$ post-MI Global longitudinal S = −14.7% ± 5.1% Global longitudinal SR = −0.57 ± 0.23/s	WMS correlated well with global longitudinal S and SR	Cutoff: Global longitudinal S < −21% Global longitudinal SR < −0.9/s for detection of post-MI patients
Jamal et al, 2002[307]	DTI	$n = 14$ Regional longitudinal S basal: −18% ± 5% mid: −21% ± 8% apex: −20% ± 9% Regional longitudinal SR basal: −1.1 ± 0.4/s mid: −1.3 ± 0.5/s apex: −1.3 ± 0.3/s	$n = 40$ post-MI Regional longitudinal S (WMS = 2) basal: −10% ± 6% mid: −12% ± 6% apex: −11% ± 9% Regional longitudinal SR basal: −0.7 ± 0.3/s mid: −0.8 ± 0.4/s apex: −0.8 ± 0.5/s Regional S (WMS = 3) basal: −4% ± 4% mid: −7% ± 6% apex: −6% ± 6% Regional SR basal: −0.4 ± 0.2/s mid: −0.6 ± 0.3/s apex: −0.6 ± 0.4/s	—	Cutoff: S < −13% SR < −0.8/s for infarcted segments
Serri et al, 2006[246]	DTI	$n = 45$ Longitudinal S −19.12% ± 3.39%	—	—	—
	STI	$n = 45$ Longitudinal S −18.92% ± 2.19%	—	—	—
Bogaert and Rademakers, 2001[237]	MRI tagged	$n = 87$ Longitudinal S −17% Radial S 38% Circumferential S −40%	—	—	—
Kowalski et al, 2001[248]	DTI	$n = 40$ Longitudinal S −20% Longitudinal SR −1.5–2.0/s Radial S 46% Radial SR 3/s	—	—	Higher long S and SR for RV wall Inhomogeneous values for RV
Hurlburt et al, 2007[251]	STI	$n = 60$ Longitudinal S = −18.4% ± 4% (male) −20.8% ± 4.3% (female) Circumferential S = −20.9% ± 4.3% (male) −25.4% ± 6.3% (female) Radial S = 35% ± 10.2% (male) 40% ± 15.6% (female)	—	—	—
Andersen et al, 2004[256]	DTI	$n = 32$ Longitudinal S = −17.93% ± 2.65%	—	—	—
Abali et al, 2005[253]	DTI	$n = 101$ Longitudinal S = −28% ± 8% Longitudinal SR = −1.5 ± 0.35/s	—	—	—
Zhang et al, 2005[313]	DTI	$n = 720$ segments Longitudinal SR = −1.58 ± 0.38/s	—	—	—
Kukulski et al, 2003[304]	DTI	$n = 20$ Longitudinal S = −18.9% ± 3.7% Radial S = 25% ± 14%	—	—	—
Andersen, 2003[247]	DTI	$n = 55$ Mean longitudinal SR = −1.5 ± 0.3/s	Basal longitudinal SR −1.8 ± 0.6/s Mid longitudinal SR −1.4 ± 0.3/s Apical longitudinal SR −1.4 ± 0.3/s	—	—
Simmons et al, 2002[281]	DTI	$n = 13$ (Septum) Longitudinal S = −0.17% ± 0.04% $n = 11$ (Inferior) Longitudinal S = −0.13% ± 0.04%	—	—	—
Mizuguchi et al, 2008[315]	STI	$n = 30$ Longitudinal S = −22% ± 2.1% Radial S = 73.2% ± 10.5% Circumferential S = 22.1% ± 3.4% Torsion = 19.3 ± 7.2 degrees	—	—	—
Helle-Valle, 2005[268]	STI	$n = 29$ Basal rotation 4.6 ± 1.3 degrees Apical rotation −10.9 ± 3.3 degrees Torsion −14.5 ± 3.2 degrees			
Opdahl et al, 2008[271]	STI	$n = 18$ Basal rotation −5.9 ± 1.3 degrees Apical rotation 12.2 ± 3.8 degrees Torsion 17.8 ± 3.7 degrees	$N = 9$ (EF > 50%) Basal rotation −6 ± 3 degrees Apical rotation 13.6 ± 2.1 degrees Torsion 19.1 ± 4.1 degrees	$N = 18$ (EF < 50%) Basal rotation −4.8 ± 2.9 degrees Apical rotation 7.6 ± 3 degrees Torsion 11.6 ± 3.9 degrees	

Continued

TABLE 15.17 Deformation Values—cont'd

References	*Strain Mode*			*Clinical Point*
Takeuchi et al, 2007[285]	STI	$N = 15$ Radial $S_{base} = 52.8\% \pm 11.5\%$ Radial $S_{apex} = 26.5\% \pm 13.5\%$ Circumferential $S_{base} = -16.2\% \pm 3.4\%$ Circumferential $S_{apex} = -20.6\% \pm 3.3\%$ Torsion = 9.3 ± 3.6 degrees	WMI = 16 (EF > 45%) Radial $S_{base} = 35.8\% \pm 10.7\%$ Radial $S_{apex} = 16.5\% \pm 9\%$ Circumferential $S_{base} = -13.7\% \pm 4\%$ Circumferential $S_{apex} = -13.5\% \pm 4.1\%$ Torsion = 9.8 ± 4 degrees	WMI = 14 (EF < 45%) Radial $S_{base} = 27.4\% \pm 10.3\%$ Radial $S_{apex} = 12.8\% \pm 5.4\%$ Circumferential $S_{base} = -10.7\% \pm 5.1\%$ Circumferential $S_{apex} = -7.3\% \pm 2.6\%$ Torsion = 5.6 ± 2.6 degrees
Teske et al, 2008[280]	DTI	$n = 22$ RV longitudinal S = −30% ± 7.6% RV longitudinal SR = −1.77 ± 0.55/s	STI RV longitudinal S = −29.4 ± 5.6 RV longitudinal SR = −1.75 ± 0.55	—
Chow et al, 2008[275]	STI	$n = 27$ RV global longitudinal S = 26.3% ± 2.9% RV global longitudinal SR = 1.33 ± 0.23/s	—	—

DTI, Doppler tissue imaging; *EF,* ejection fraction; *MI,* myocardial infarction; *RV,* right ventricle; *S,* strain; *SR,* strain rate; *STI,* speckle-tracking imaging; *WMS,* wall motion score.

2D and M-mode techniques. In the experimental setting, systolic strain values obtained by DTI, in either inflow or outflow tract, were found to be comparable with those obtained by sonomicrometry (a method by which the actual length change is measured), whatever the RV loading conditions were.[277] RV longitudinal function is dominant over short-axis function; and RV inflow tract, represented by the basal RV free wall, is the major contributor in global RV systolic and diastolic function. Therefore, measurement of longitudinal RV inflow deformation offers valuable insights to global RV function. DTI longitudinal strain measurements showed an insignificant decline with age (average value of 31%, in 54 healthy adults).[248,278] In laboratory experiments with opened pericardium, increased afterload after PA constriction resulted in a shift of myocardial shortening from early-mid to end-systole or even diastole (postsystolic shortening [PSS]), whereas a reduction in preload caused by inferior vena cava occlusion induced earlier systolic shortening.[277] However, in healthy ambulatory subjects, DTI strain of RV inflow (recorded from the basal segment, lateral to the tricuspid annulus) did not change with preload or afterload increase.[279] DTI and STI RV peak systolic strain values correlate well ($r = .73$), with DTI values always being greater, overestimating peak systolic SR by 0.64%.[280] The correlation for SR was better ($r = .90$).

Deformation in the Operating Room

DTI strain is a sensitive means for detecting and localizing myocardial ischemia, as opposed to myocardial velocities. Intraoperative TEE measurements of DTI strain are comparable with transthoracic assessment, and pericardiotomy does not affect them.[281] As is expected, Doppler strain measurements are not easily obtained in the radial direction because of Doppler angle and translation cardiac motion.[282] DTI strain is better suited for the study of longitudinal cardiac deformation. DTI strain was found to be superior to myocardial velocity measurements in detecting and assessing regional myocardial ischemia during off-pump left anterior descending (LAD) artery revascularization. DTI strain demonstrated systolic lengthening of the apical septum and reduced longitudinal shortening of the midseptum during interrupted LAD flow. These changes occurred with concomitant deterioration of wall motion and were confined to the LAD territory, whereas there were no changes in the basal septum, supplied by the right coronary artery.[283] At the same time, DTI velocities remained unchanged in the apical septum during interrupted LAD flow, probably explained by traction from the basal segments.

Rotation and Twist

Apical rotation (12.2 ± 3.8 degrees) represents the dominant contribution to LV twist (73% ± 15%) and reflects LV twist over a wide range of hemodynamic conditions, making it a noninvasive, feasible clinical index of LV twist.[271] Estimation of LV twist from apical rotation eliminates the requirement of two separate recordings (one for the base and one for the apex) and a possible calculation problem because of beat-to-beat variation in rotation, as well as the move-through of the LV image plane. In patients with chronic ischemia but preserved LVEF, rotation and twist were similar to healthy subjects; but in those with depressed LVEF, apical rotation and twist were reduced.[271]

In patients with diastolic dysfunction (DTI E′ < 8 cm/s), peak LV twist is increased in early-stage diastolic dysfunction, mainly because of more vigorous and increased LV apical rotation.[284] It is unknown whether the mechanism of LV twisting and untwisting is independent of the underlying myocardial relaxation in patients with diastolic heart failure or whether it is dependent on filling pressure (decreased twist with increased filling pressure).[284]

Systolic twist was depressed and diastolic untwisting prolonged in patients with anterior wall MI and abnormal LV systolic function. These abnormalities were related to reduced apical rotation and associated with the reduction of apical circumferential strain.[285] In contrast, systolic twist was maintained in patients with anterior wall MI and LVEF greater than 45%. This is a result of the mild reduction of circumferential strain in the apex that may affect LV twist behavior in a mild manner.

Ventricular Synchronization

In the normal heart, electrical activation of the ventricles occurs after atrial contraction, spreads quickly (within 40 ms) in both ventricles via conduction through the Purkinje fibers, and is associated with synchronous regional mechanical contraction of both ventricles. In mechanical dyssynchrony, there is delay in activation of the ventricles (interventricular dyssynchrony), or there is delay within the different LV segments or regions (intraventricular dyssynchrony; Fig. 15.131). Typically, there is a prolonged QRS complex on the surface electrocardiogram. A classic type of dyssynchrony is left bundle branch block, where there is early electrical activation of the interventricular septum and late activation of the inferolateral LV segments. The early septal contraction causes inferolateral stretching and late inferolateral contraction producing septal stretching. That is, one wall exerts forces on the contralateral wall and results in abnormal systolic performance, because the early septal contraction does not contribute to ejection because it occurs when LV pressure is low. Therefore, dyssynchrony is not innocuous, produces progressive dilation and distortion of the left ventricle, disrupts MV geometry, and results in inefficient LV systolic performance, increased LV end-systolic volume and wall stress, delayed relaxation, and MR. LV dyssynchrony has emerged as an important concept in patients with heart failure. It is present in a significant proportion of patients with heart failure with left bundle branch block and in patients with normal QRS duration. Presence of LV dyssynchrony has been used to predict response to cardiac resynchronization treatment (CRT) in patients with end-stage heart failure.

CRT (by biventricular pacing) results in reverse remodeling, where LV size and function progressively improve over time, with better results in nonischemic patients,[286] and reduces MR by improving temporal coordination of mechanical activation of the papillary

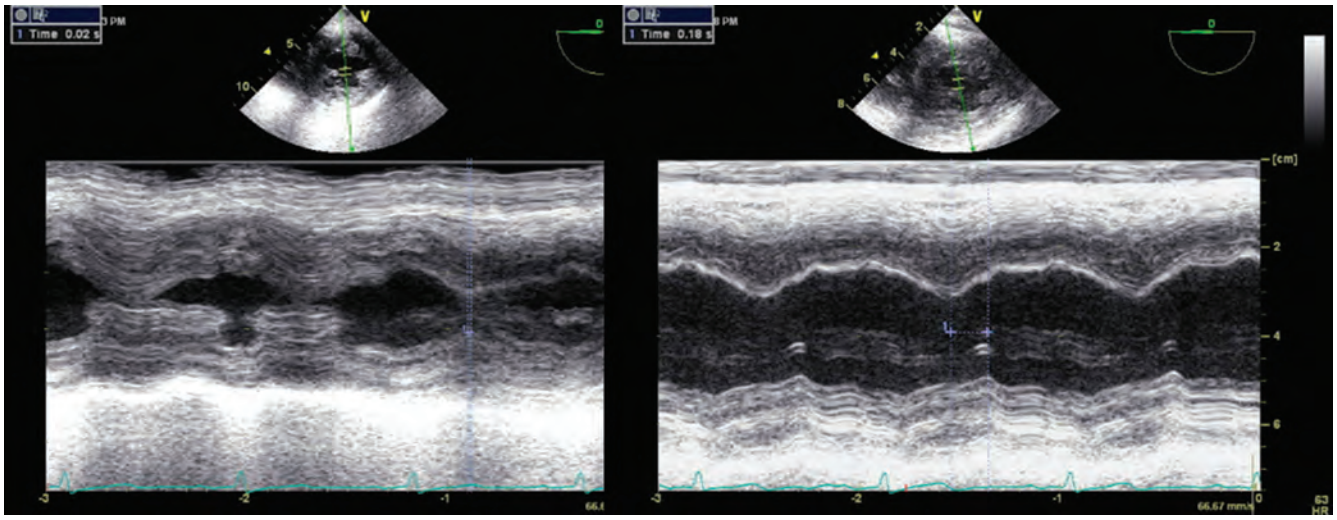


Fig. 15.131 Nonsignificant figure dyssynchrony. *Left,* Interventricular delay: 20 ms. *Right,* Interventricular delay: 180 ms.

muscles.[287] CRT is indicated for patients with severe heart failure (New York Heart Association [NYHA] class III or IV), widened QRS greater than 120 milliseconds, and LVEF less than 35%. However, mechanical dyssynchrony may also exist in patients with depressed LV function and a narrow QRS. As a result, 25% to 35% of patients undergoing CRT fail to improve, and this may be because of widened QRS being a suboptimal marker for dyssynchrony. Additional factors associated with lack of response to CRT are ischemic disease with scar tissue that prohibits reverse remodeling, subsequent MI after CRT, or suboptimal lead placement (see Chapters 4 and 5). Optimization of the techniques used to detect dyssynchrony is important to identify those patients who will respond to CRT because it appears that patients with minimal or no dyssynchrony have a lower probability of response and a poor prognosis after CRT.

Different echocardiographic modes have been used to detect dyssynchrony.[288]

1. M-mode with the cursor across the septal and inferolateral (posterior) segments. A delay between the opposing segments peak systolic excursion, usually longer than 130 milliseconds, was found to be fairly predictive for response to CRT (defined as >15% decrease in LV end-systolic volume and improvement in clinical outcome).[289] However, because of unsatisfactory reproducibility and lack of clear definition of systolic excursion of both septal and posterior walls, M-mode measurements (which are a single-dimensional assessment of LV dyssynchrony) are supplemental means to other echocardiographic modes, such as DTI.[290]
2. DTI of longitudinal myocardial velocities has been the principal method in recent studies and the preferred echocardiographic approach. With color DTI, the direction of motion is color-coded and is used to identify the transition from inward to outward motion in opposing LV segments. Placement of sample volumes in basal, septal, and lateral LV segments produces a spectral display of mean myocardial velocities. The time delay between systolic myocardial excursion is measured (two-site method), and peak systolic delay longer than 65 milliseconds is predictive of clinical response to CRT and reverse remodeling.[291] Subsequent investigators used four or six basal segments as well. A *dyssynchrony index* is the standard deviation of the 12-segment times to peak regional myocardial systolic velocity; greater than 32 milliseconds has been proposed to be the best predictor of response to CRT.[292] An automated color-coding of time-to-peak systolic velocity termed *tissue synchronization imaging* has also been developed. Myocardial systolic velocity spectra can be produced by real-time pulsed-wave DTI. However, the technique is considered time consuming and susceptible to artifacts because of breathing, patient movement, and translation. The major limitation of DTI techniques is that they cannot differentiate a passively moving segment because of tethering from an actively contracting one.
3. Cardiac deformation (strain) can differentiate active myocardial contraction or deformation from passive motion because of translation or tethering and has also been used to study dyssynchrony.[293] Longitudinal (the systolic deformation as imaged in the ME views) or radial (representing radial thickening as seen in TG views) strain can be challenging because it is affected by increased Doppler angle, whereas reproducibility of measurements is limited by the poor signal-to-noise ratio. Some believe that DTI velocities are far better than strain parameters in detecting dyssynchrony amenable to CRT.[294] Deformation studied with STI is a newer modality, which promises to bypass the limitations of DTI deformation.[295] Radial synchrony by STI is independent of clinical and echocardiographic parameters.[296]
4. The full-volume mode is capable of capturing the entire left ventricle in four beats.[297] With the use of integrated software programs, a 3D model of the left ventricle can be created within minutes, allowing the imager to view the 3D dynamics of the entire ventricle, including the timing of regional wall motion independently of its direction (Fig. 15.132). Consequently, 3DE is considered an alternative approach to TDI for the quantification of LV dyssynchrony, showing good correlation against phase analysis of gated single-photon emission computed tomography (SPECT) images.[288,298] Regional wall motion patterns can be visualized and quantified with semiautomatic contour tracing algorithms.[297] Its major limitation stems from the relatively low frame rate.

Optimal AV delay is defined as allowing completion of the atrial contribution to diastolic filling, resulting in the most favorable preload before ventricular contraction. A too-short AV delay will interrupt the late diastolic wave (A), whereas a too-long AV delay results in suboptimal LV preload. Despite these concerns, LV resynchronization is by far more important.[299]

Doppler Tissue Imaging– and Speckle-Tracking Imaging–Derived Strain

DTI-derived strain accurately measures cardiac deformation,[241] is sensitive to early ischemia, and is useful in assessing myocardial viability after MI; it provides more accurate results than DTI velocities or visual wall motion scoring.[300,301] DTI-derived strain in remote from ischemic

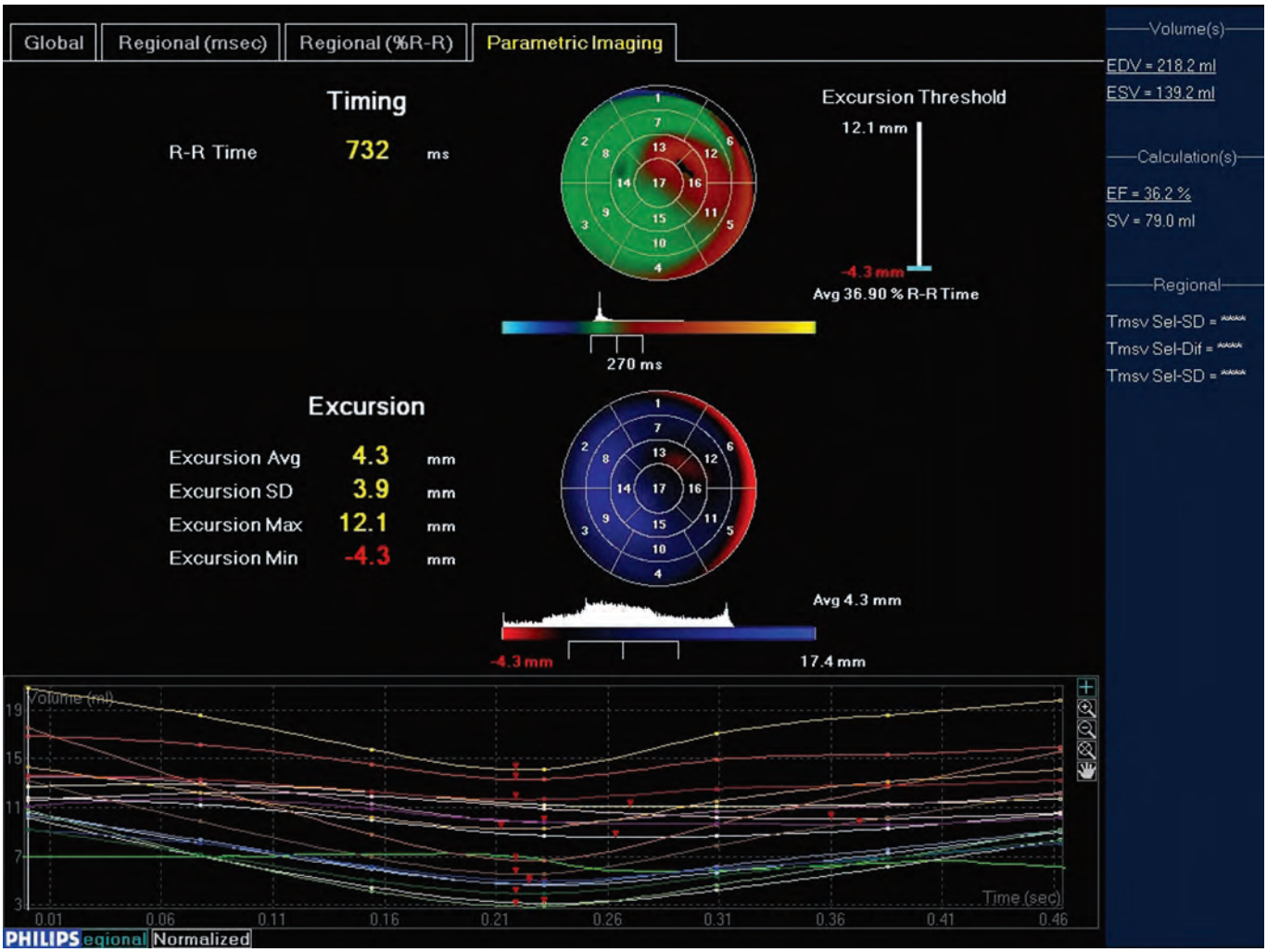


Fig. 15.132 Parametric imaging of the left ventricle. Lateral wall shows severe timing delay in contraction, but only mild decrease in excursion. This technology can be helpful in optimizing ventricular synchrony.

regions will remain normal, contrary to spectral DTI velocities, which are affected because of tethering.[243,261] Acute regional ischemia causes a rapid decrease in segmental contraction during systolic ejection, with the magnitude of regional shortening/thickening reduction in proportion to myocardial blood flow reduction. After systole, myocardial relaxation is delayed as PSS/thickening occurs.

DTI strain may be an important supplement to visual assessment of regional LV dysfunction. DTI strain and SR are more direct measures of regional function than tissue velocities, which are influenced by contractile function of other myocardial regions because of tethering.[243] In 17 patients with LAD disease (>75% obstruction), and normal baseline ejection fraction and wall motion score (WMS), DTI strain detected systolic longitudinal expansion in apical segments (baseline −17.7% ± 7.2% vs 7.5% ± 6.5%) or reduced compression in midseptal segments (baseline −21.8% ± 8.2% vs −13.1% ± 4.1%) in nearly all patients during balloon occlusion of the LAD. Segments not supplied by the LAD did not exhibit any strain changes. DTI strain was more sensitive than DTI velocities in detecting regional ischemia; the latter revealed longitudinal expansion in only two-thirds of the involved segments.[302]

DTI strain indices differentiate acutely ischemic myocardium from normal and dysfunctional myocardium, even in segments that appear visually normal. An acute reduction in regional myocardial blood flow induces a local contractile dysfunction within seconds, which alters the regional deformation pattern. Consequently, during systole, the radial thickening and circumferential/longitudinal shortening of the ischemic segment are decreased. In addition, the segmental relaxation is considerably impaired during the ischemic insult, and the physiologic early diastolic radial thinning and circumferential/longitudinal lengthening are replaced by ongoing postsystolic thickening and shortening, respectively. Such consistent changes in early diastolic deformation have been proposed as an early marker of regional ischemia.

PSS is an important feature of ischemic myocardium. When associated with systolic hypokinesis or akinesis, it indicates actively contracting, potentially viable myocardium. In view of the findings from experimental and clinical studies, PSS should be considered an expression of myocardial asynchrony. A segment that does not deform during contraction, when LV pressure increases, but does so when LV pressure decreases markedly during isovolumic relaxation, is not likely to be passive. DTI can quantify PSS. In an experimental setting, PSS was recorded during moderate (hypokinetic or akinetic myocardium), as well as severe, ischemia (dyskinetic myocardium).[303] During a 50% reduction of LAD flow, hypokinesis was accompanied by decreased longitudinal DTI systolic strain (from −12.3% ± 1.1% to −6.6% ± 1.3%) and substantial PSS (from 0.9% ± 0.2% to 5.1% ± 0.9%). Concurrent LV pressure-segment length and LV stress-segment length loop analysis indicated that PSS was active. Superimposed afterload augments those changes in a manner similar to LAD occlusion; in both cases, dyskinesis accompanied even more marked PSS.[303]

In a population of 90 consecutive patients with coronary artery disease who underwent percutaneous transluminal coronary angioplasty of a coronary artery with more than 90% obstruction, the baseline strain values in the at-risk segments (which had normal WMSs) were similar to those observed in control patients (radial: 49% ± 6.9% vs 56.3% ± 11.7%; longitudinal: −21.2% ± 4.5% vs −23.3% ± 4.7%). At-risk segments with abnormal WMSs had decreased strain values (radial: 21.9% ± 11%; longitudinal: −5.2% ± 4.5%) and increased postsystolic deformation (radial: 0.18 ± 0.14; longitudinal: 0.32 ± 0.26) as compared with normal and at-risk segments with normal WMS. Coronary occlusion resulted in a 50% reduction of radial and longitudinal strain, which peaked early in diastole, and increased postsystolic deformation in all at-risk segments (irrespective of WMS). These changes were reversible, and after 2 minutes of coronary reperfusion, segmental deformation parameters returned to the preocclusion state. Neighboring segments did not exhibit any changes, and presence of collaterals diminished the occlusion-associated strain parameter changes (less PSS).[304] DTI myocardial velocities changed during coronary occlusion only in segments with abnormal baseline function and had lower diagnostic accuracy when compared with strain.[305]

In the clinical setting, RWMAs may not be detected by DTI myocardial velocities because of tethering and translational effects. Only strain and SR offer quantitative and objective parameters indicating ischemia. As observed during dobutamine-exercise testing, DTI strain decreased and PSS markedly increased during ischemia, whereas DTI myocardial velocities did not reveal any changes.[306]

Using STI, global longitudinal strain less than −21% (normal: −24.1% ± 2.9%) and SR less than −0.9/s (normal: −1.02 ± 0.09/s) had good sensitivity and specificity (92% and 89%, and 92% and 96%, respectively) for detection of post-MI patients, with a good linear correlation with WMS index.[250] STI-derived circumferential and radial strain are sensitive to acute reduction of myocardial perfusion. During balloon occlusion, there were significant decreases in circumferential strain (baseline: −18.5% ± 7.2% to −10.5% ± 3.8%) and radial strain (baseline: 46.5% ± 19.4% to 35.7% ± 20.8%), as well as prolongation of the time to peak circumferential and radial strain.[284]

Longitudinal deformation parameters are potentially superior to visual WMS in identification and quantification of subtle ischemia-induced changes in regional contractility. When DTI strain parameters were correlated with the coronary angiogram, systolic strain and SR were significantly reduced in normokinetic segments supplied by a stenosed coronary artery (>70%), but not in normokinetic segments supplied by a coronary artery without significant lumen narrowing.[307] When compared with myocardial velocities, systolic strain and SR differentiated abnormal from normal contracting segments. Infarct-involved segments were differentiated from normal myocardium using cutoff values of less than −13% for strain and less than −0.8/s for SR.[307]

DTI radial SR agrees well with wall motion and is reduced more in hypokinetic and akinetic segments (0.6 ± 0.5/s and 0.008 ± 0.3/s, respectively) than in normokinetic segments (2 ± 0.6/s). SR reflects changes in WMS induced by dobutamine challenge; it increased in those segments that revealed augmented wall motion (from 2 ± 0.7/s to 4.7 ± 1.7/s) and decreased in those segments that showed deteriorating or unchanged wall motion (from 2.1 ± 1 to 1.7 ± 0.8/s).[308]

Radial and circumferential STI strain enable distinction among normokinetic, hypokinetic, and akinetic segments at rest (defined by cardiac MRI), in a highly reproducible manner and with small intraobserver and interobserver variability (5.3% ± 2.6% and 8.4% ± 3.7%, respectively).[309] A cutoff value of radial strain less than 29% defined hypokinetic from normokinetic segments with sensitivity and specificity of 83%, and a cutoff value of radial strain less than 21% akinetic from hypokinetic segments with sensitivity of 83% and specificity of 94%.

Similar discriminatory ability of STI radial strain was found when transmural MIs were analyzed using contrast-enhanced cardiac MRI. Radial strain decreased significantly with increased relative hyperenhancement: 27.7% ± 8% (normal segments) versus 20.5% ± 9.7% (nontransmural infarction segments) versus 11.6% ± 8.5% (transmural infarction segments). Nontransmural infarction was distinguished from transmural infarction segments by radial strain cutoff value greater than 16.5%.[310]

In an experimental model of acute LAD ischemia/reperfusion, extent of infarct correlated well with radial and circumferential STI strain. Myocardial segments with more than 50% area of infarction (verified by postmortem histology) had lower end-systolic radial and circumferential strain and longer time to peak strain versus areas with less than 50% infarction. End-systolic radial strain less than 2% had 88% sensitivity and 95% specificity for detecting infarcted area larger than 50%.[311]

The use of STI strain for combined assessment of long-axis and short-axis cardiac function may allow differentiation of transmurality of chronic infarction and, therefore, overcome DTI strain, which is angle limited and can evaluate only longitudinal function reliably. In subendocardial infarction, STI radial strain (32.4% ± 20%) and circumferential strain (−15.4% ± 6.9%) are preserved, whereas longitudinal strain is reduced (−13.2% ± 5.6%). In contrast, in transmural infarcts, both short-axis and long-axis STI strain are significantly reduced (cutoff value for circumferential strain less than −13.6%, sensitivity 73%, specificity 72%).[312]

Accurate identification of infarcted, nonviable myocardium from viable, hypokinetic segments has important clinical implications; revascularization benefits only patients with a sufficient amount of viable myocardium, whereas it is unlikely to benefit those with transmural MI. In post-MI patients, and in contrast with DTI myocardial velocities, longitudinal DTI SRs of transmural infarcted segments (−0.51 ± 0.17/s) were significantly decreased when compared with nontransmural (−1.06 ± 0.29/s), subendocardial (−1.21 ± 0.41/s) and normal segments (−1.58 ± 0.38/s). SRs also were significantly reduced in subendocardial infarction compared with normal segments. A cutoff value of SR greater than −0.59/s identified transmural from nontransmural and subendocardial MI, and a cutoff value of −0.98/s > SR > −1.26/s identified a subendocardial infarction from normal segments.[313]

STI radial strain can identify myocardial dysfunction and predict recovery of function using a cutoff value of peak radial strain greater than 17.2%. Segments that failed to recover had lower peak radial strain (15.2% ± 7.5%) than those that showed functional improvement after surgical or percutaneous revascularization (22.6% ± 6.3%). This predictive value (sensitivity of 70.2% and specificity of 85.1%) was similar to hyperenhancement by contrast-enhanced MRI.[314]

Among patients with cardiovascular risk factors but no overt cardiac disease, longitudinal strain and SR are decreased, and circumferential strain is increased in those with apparently normal mitral inflow velocities (E/A > 1). This may imply that LV systolic function and filling are compensated by circumferential shortening at ventricular systole.[315]

Myocardial Disease

Myocardial disease and *cardiomyopathies* are broad terms used to describe an array of disease states that are limited to the intrinsic function of the myocardium at a tissue level. These conditions should be separated from causes of dysfunction that are secondary such as ischemia or infarction, changes in myocardial function or mass secondary to valvular diseases, or restriction to normal function because of pericardial or extrapericardial disease.

Evaluating the myocardium can extend past the presence or absence of RWMAs related to ischemic heart disease. The cardiac anesthesiologist is often called to evaluate and assess patients with unknown causes of hemodynamic instability, and possessing a broad differential diagnosis of myocardial dysfunction is crucial. In this section we discuss common causes of myocardial disease that results in ventricular dysfunction and findings on imaging that might assist in the assessment.

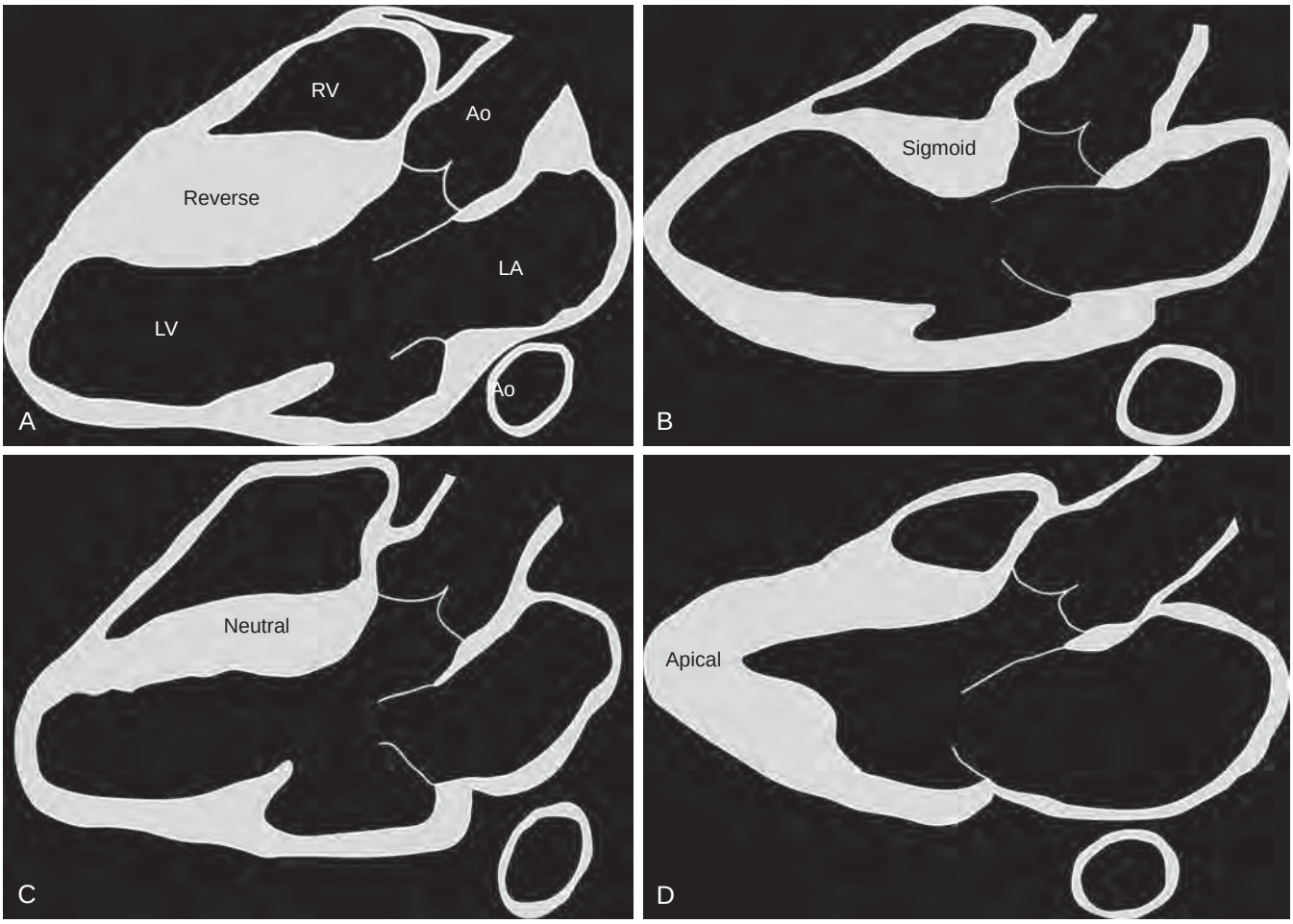


Fig. 15.133 Phenotypic variants seen on echocardiography in patients with hypertrophic cardiomyopathy. (A) The reverse curvature type shows a markedly thickened septum with the endocardial curve convex instead of the expected concave appearance. (B) The sigmoid curvature type shows a discrete region of asymmetric septal thickening near the outflow tract. (C) The neutral septum type demonstrates a uniformly thickened septum with the expected concave appearance of the septum. (D) The apical variant demonstrates asymmetric hypertrophy of the apical segments. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle. *(Adapted from Syed IS, Ommen SR, Breen JF, Tajik AJ. Hypertrophic cardiomyopathy: identification of morphological subtypes by echocardiography and cardiac magnetic resonance imaging.* JACC Cardiovasc Imaging. *2008;1:377–379.)*

Hypertrophic Cardiomyopathy

HCM was initially described in the 1970s, and in addition to the presence of a murmur, syncope, and sudden death, these individuals were found to have asymmetric septal thickening. Early reports found that septal hypertrophy with a ratio of septal (anteroseptal) wall thickness to posterior (inferolateral) wall thickness of greater than 1.3 was indicative of the presence of disease.[316] It was determined that this appeared to be genetic as there were familial tendencies; however, only 30% to 40% of the family members had symptoms associated with the disease.[317] The location of the genetic mutation was first isolated to the long arm of the 14th chromosome (14q1) and encoded a protein for part of the thick chain filament.[318,319] Early evidence of genetic heterogeneity among HCM patients was suspected, and up to 18 different genes with mutations have been identified.[320,321] Overall this is the most common genetically inherited cardiomyopathy with 0.2% of the population (1 in 500) with a genetic mutation at risk for HCM[322] (see Chapters 8 and 24).

Phenotypically this presents as four different types categorized by the appearance of the septal contour, which can be recognized during echocardiography: sigmoid, neutral, reverse, and apical.

Though initially identified with M-mode echocardiography, the appearance of the septum was classified into the three different curves of the septum.[323] Later, Yamaguchi and colleagues identified a fourth phenotypic variant that demonstrates apical hypertrophy.[324] These types are summarized in Fig. 15.133. The apical variant can be confused with LV noncompaction, which appears similar on standard 2D imaging and can be differentiated with the use of microbubble echocardiographic contrast.

Genetic mutations have a more pronounced effect on diastolic filling, resulting in diastolic dysfunction (pseudonormal or restrictive) with the majority of these individuals demonstrating the presence of a diastolic L wave consistent with triphasic filling. Others may have more obstructive symptoms and a relatively thicker septal diameter and these patients tend to have thick filament mutations.

The most serious complication of increased septal thickness is obstruction to LV ejection from SAM of the MV resulting in dynamic LVOT obstruction. This obstruction is both dynamic and variable. The presence of a dynamic LVOT obstruction with a gradient greater than 30 mm Hg is significant and the variations of dynamic LVOT obstruction have been classified as (1) nonobstructive, (2) latent (inducible) obstruction, (3) labile obstruction, and (4) obstruction at rest.[325]

BOX 15.4 DEFINITIONS OF LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN HYPERTROPHIC CARDIOMYOPATHY

Degrees of Obstruction Based on Hemodynamic Findings

Nonobstructive: No LVOT gradient at rest and no inducible gradient with provocation.

Latent Obstruction: No LVOT gradient at rest, but provocative maneuvers result in LVOT obstruction (gradient >30 mm Hg).

Labile Obstruction: Inconsistent LVOT obstruction at rest, occasional obstruction with gradient >30 mm Hg, and provocation provides consistent, high gradient obstruction.

Obstruction at Rest: Consistent LVOT obstruction at rest with gradient >30 mm Hg; no provocative maneuvers recommended.

Qualification of Systolic Anterior Motion of the Mitral Valve

No SAM/Chordal SAM: The anterior mitral leaflet is >10 mm from the septum, and there is no evidence of obstruction or turbulence.

Mild SAM: The anterior leaflet is drawn toward the septum, but it is always >10 mm away.

Moderate SAM: The anterior leaflet is <10 mm from the septum or briefly contacts the septum but for less than 30% of the ejection period.

Severe SAM: The anterior leaflet is in contact with the septum for >30% of the ejection period. There is significant obstruction and associated mitral regurgitation.

LVOT, Left ventricular outflow tract; *SAM,* systolic anterior motion.
Adapted from Gilbert BW, Pollick C, Adelman AG, Wigle ED. Hypertrophic cardiomyopathy: subclassification by M mode echocardiography. *Am J Cardiol.* 1980;45:861–872.

BOX 15.5 CONDITIONS OTHER THAN HYPERTROPHIC CARDIOMYOPATHY WITH THE PRESENCE OR THE APPEARANCE OF SYSTOLIC ANTERIOR MOTION BOTH WITH OBSTRUCTION AND WITHOUT OBSTRUCTION

SAM Without Obstruction

Normal variant
Hyperdynamic state
Aortic regurgitation
Mitral valve prolapse (posterior leaflet)

SAM With Obstruction and Normal Septal Thickness

Hypovolemia
Hyperdynamic state
Low vascular resistance
(Combination of above conditions)

SAM With Obstruction and Increased Septal Thickness

Hypertensive heart disease
D-transposition
Beckwith-Weidemann syndrome
Friedreich ataxia
Pompe disease

SAM, Systolic anterior motion.
Adapted from Gilbert BW, Pollick C, Adelman AG, Wigle ED. Hypertrophic cardiomyopathy: subclassification by M mode echocardiography. *Am J Cardiol.* 1980;45:861–872.

Box 15.4 provides a summary of definitions for LVOT obstruction and grading of SAM.

The majority of symptoms are associated with SAM and the intermittent decrease in CO with dynamic LVOT obstruction. The presence of SAM at rest, a narrow aortomitral angle, and significant septal bulge (sigmoid type) are associated with more symptomatic disease.[326] Care for these patients under anesthesia should focus on improving LV diastolic filling, maintaining low-normal heart rates, and normal vascular impedance as the low vascular resistance state can result in SAM. The presence of SAM not only results in the decrease in forward CO, and therefore, poor cellular perfusion, but also results in more significant MR.[327] This relationship of increased LVOT gradient and increased MR has potential ramifications as acute severe MR results in elevated PA pressures and can promote the formation of pulmonary edema. SAM should be treated aggressively with pharmacologic agents such as α-adrenergic agonists and β-blockade, as well as administration of intravenous fluid.

In addition to dynamic LVOT obstruction, individuals with HCM can demonstrate both systolic and diastolic dysfunction. While diastolic dysfunction is more common since there is increased wall thickness, systolic dysfunction can be seen with chronicity of obstruction. Barac and coworkers demonstrated that the slight decrease in velocity seen within the LVOT during periods of SAM directly prior to the significant rise of the LVOT velocity is an indicator of underlying systolic dysfunction, which may explain the subset of individuals who go on to develop end-stage HCM with LV dilation.[328] HCM can be mimicked by other disease states that result in global and regional increases in myocardial thickness. Box 15.5 lists many of the common diseases that can result in SAM and may mimic HCM.

Guidelines for surveillance and treatment recommend any patient suspected of having HCM should undergo TTE as part of the initial evaluation (class I, level of evidence: B).[329] Individuals with symptoms of lightheadedness and presyncope or syncope should be evaluated with TTE (appropriate use score 9).[330] Additionally, these guidelines suggest that septal wall thickness greater than 30 mm puts individuals at great risk of HCM-related death.[329] A summary of selected recommendations for echocardiography and pharmacologic therapies can be found in Box 15.6. An early nonsurgical treatment that is still used today is DDD pacing. This was demonstrated to be superior to simply pacing the RA, and the use of the RV pacing lead resulted in an improvement of symptoms and dynamic LVOT obstruction from SAM.[331] Amiodarone has shown some benefit in the reduction in sudden cardiac death in patients with HCM, but the use of β-blockers and calcium channel blockers has not shown risk reduction.[332]

Surgical myectomy is a mainstay of treatment for HCM when patients have the presence of an inducible obstruction or obstruction at rest with a gradient of 50 mm Hg or higher.[329,333] First described by Morrow and associates, this technique removes the portion of the septum through an aortotomy that the MV contacts, opening the cross-sectional area of the LVOT and reducing the incidence of SAM.[334,335] The echocardiographer should see both a reduction in the size of the septum in the region of the LVOT and a reduction in SAM. Doppler echocardiography should demonstrate the reduction (<30 mm Hg) or absence of a gradient through the LVOT. This technique can result in iatrogenic VSDs and, therefore, the absence of such a complication should be documented during imaging following cardiopulmonary bypass. Selected recommendations for invasive therapies for HCM are summarized in Box 15.7.

This technique of septal myectomy has shown good durability, especially when individuals with good prognostic factors—presence of asymmetric hypertrophy, severe SAM, and prolonged isovolumic relaxation time—are selected.[336,337] One series found that individuals undergoing surgical myectomy had improved outcomes if they were (1) younger than 50 years of age, (2) had an LA dimension less than 46 mm, and (3) had no history of atrial fibrillation.[338] Another demonstrated 90% of patients undergoing septal myectomy had an improvement of at least one NYHA heart failure class.[339] Intraoperative measurements of reduction of LVOT obstruction and lower Doppler ultrasound gradients provided surgical guidance resulting in 4% of one series returning to cardiopulmonary bypass for additional resection; however, there was a significant (39%) portion of this series that did not have adequate intraoperative imaging to measure a LVOT gradient.[340]

BOX 15.6 SELECTED CLASS I RECOMMENDATIONS FOR ECHOCARDIOGRAPHY AND PHARMACOLOGIC THERAPIES FOR SYMPTOMATIC PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Echocardiography
Class I Recommendations
- TTE is recommended for initial evaluation for all patients with suspected HCM. *(Level of Evidence: B)*
- Repeat TTE is recommended for the evaluation of patients with HCM with a change in clinical status or new CV event. *(Level of Evidence: B)*
- TEE is recommended for the intraoperative guidance of surgical myectomy. *(Level of Evidence: B)*
- TTE or TEE with intracoronary contrast injection of the candidate's septal perforator(s) is recommended for the intraprocedural guidance of alcohol septal ablation *(Level of Evidence: B)*
- TTE should be used to evaluate the effect of surgical myectomy or alcohol septal ablation for obstructive HCM. *(Level of Evidence: C)*

Pharmacologic Management
Class I Recommendations
- β-Blocking drugs are recommended for the treatment of symptoms (angina or dyspnea) in adult patients with obstructive or nonobstructive HCM but should be used with caution in patients with sinus bradycardia or severe conduction disease. *(Level of Evidence: B)*
- If low doses of β-blocking drugs are ineffective for controlling symptoms (angina or dyspnea) in patients with HCM, it is useful to titrate the dose to a resting heart rate of less than 60 to 65 beats/min. *(Level of Evidence: B)*
- Verapamil therapy (starting in low doses and titrating up to 480 mg/d) is recommended for the treatment of symptoms (angina or dyspnea) in patients with obstructive or nonobstructive HCM who do not respond to β-blocking drugs or who have side effects or contraindications to β-blocking drugs. However, verapamil should be used with caution in patients with high gradients, advanced heart failure, or sinus bradycardia. *(Level of Evidence: B)*
- Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration. *(Level of Evidence: B)*

CV, Cardiovascular; *HCM,* hypertrophic cardiomyopathy; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography.
Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;58:e212–e260.

BOX 15.7 SELECTED RECOMMENDATIONS FOR INVASIVE THERAPIES IN HYPERTROPHIC CARDIOMYOPATHY

Class I
- Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: C)*

Class IIa
- Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: B)*
- When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional classes III or IV). *(Level of Evidence: B)*

Class IIb
- Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. *(Level of Evidence: B)*
- The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (ie, >30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. *(Level of Evidence: C)*

Class III: (Harm)
- Septal reduction therapy should not be done for adult patients with HCM who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy. *(Level of Evidence: C)*
- Alcohol septal ablation should not be done in patients with HCM who are younger than 21 years of age and is discouraged in adults younger than 40 years of age if myectomy is a viable option. *(Level of Evidence: C)*

HCM, Hypertrophic cardiomyopathy; *LVOT,* left ventricular outflow tract; *NYHA,* New York Heart Association.
Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2011;58:e212–e260.

Alcohol septal ablation is another option. Target vessel occlusion and echocardiographic contrast agents can assist in preablation confirmation that the target vessel results in necrosis of the desired region without unwanted extension.[341] Successful alcohol septal ablation will show early reduction in LVOT gradient on follow-up TTE.[342]

Myocarditis

Myocarditis is an inflammatory process of the myocardium that can be the result of a direct infection by a virus or can be the result of a host-response to the myocardium as the result of an autoimmune process. The majority of cases are associated with viral origins and the causative agents vary related to regional and temporal differences. Historically, coxsackievirus B was the most common cause until the 1990s when adenovirus became more common.[343,344] More recently, parvovirus B19 has become a more frequently occurring cause, although there is a whole array of viruses that have been related to chronic forms of myocarditis; these include human immunodeficiency virus, hepatitis C virus, cytomegalovirus, human herpesvirus 6, and the Epstein-Barr virus.[4,344,345] Additional causes, both viral and nonviral, are summarized in Box 15.8.

Variability occurs in presentation and the clinicopathologic classification of myocarditis is divided into four distinct groups. These four groups are (1) fulminant, (2) acute, (3) chronic active, and (4) chronic persistent. Table 15.18 includes the clinical findings, natural history, and findings on echocardiography for these four presentations of myocarditis. Fulminant myocarditis and acute myocarditis are the two most commonly presenting forms with acute deterioration of myocardial function, although the two types have distinct characteristics that separate them.

Fulminant myocarditis has a distinct onset of symptoms and the individual presents in extremis as the result of severe LV dysfunction.[346,347] The LV walls are thickened, with severely reduced LV systolic function, and there can be RWMAs on imaging that are not

BOX 15.8 CAUSES OF MYOCARDITIS

Viral
Coxsackievirus B
Adenovirus
Parvovirus B19
Hepatitis C
Human immunodeficiency virus
Cytomegalovirus
Human herpesvirus 6
Epstein-Barr virus
Influenza A virus

Bacterial
Mycobacterium tuberculosis
Staphylococcus
Streptococcus A
Streptococcus pneumonia
Corynebacterium diphtheria
Chlamydia

Fungal
Aspergillus
Actinomyces
Candida
Cryptococcus

Parasitic
Borrelia burgdorferi
Ehrlichia
Babesia
Trypanosoma cruzi
Coxiella burnetii
Rickettsia typhi
Echinococcus granulosus

Medications (Cardiotoxic)
Ethanol
Anthracyclines
Cocaine

Medications (Hypersensitivity)
Penicillins
Sulfonamides
Cephalosporins
Tetracyclines
Tricyclic antidepressants
Clozapine
Loop diuretics
Thiazide diuretics

Hypereosinophilic Conditions
Loeffler's endomyocardial fibrosis
Churg-Strauss syndrome
Postvaccination eosinophilic myocarditis
Acute necrotizing eosinophilic myocarditis

Autoimmune
Cardiac sarcoidosis
Giant-cell myocarditis
Autoimmune antimyosin antibodies (molecular mimicry)
Celiac disease
Crohn disease
Ulcerative colitis
Rheumatoid arthritis
Lupus erythematodes
Kawasaki disease
Copper
Iron

Adapted from Cooper LT. Myocarditis. *New Engl J Med.* 2009;360:1526–1538; Lauer B, Schannwell M, Kühl U, et al. Antimyosin autoantibodies are associated with deterioration of systolic and diastolic left ventricular function in patients with chronic myocarditis. *J Am Coll Cardiol.* 2000;35:11–18; and Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. *J Am Coll Cardiol.* 2012;59:779–792.

TABLE 15.18 Clinical and Echocardiography Features of Myocarditis

	Fulminant	*Acute*	*Chronic Active*	*Chronic Persistent*
Clinical Features				
Onset	Distinct	Variable/indistinct	Indistinct	Indistinct
Presentation	Cardiogenic shock	LV dysfunction	LV dysfunction	Non-CHF symptoms Indistinct
Natural history	Recovery or death	Incomplete recovery or dilated cardiomyopathy	Dilated cardiomyopathy	Persistent non-CHF symptoms with normal LV EF
Echo Features				
Wall thickness	Thickened	Normal	Normal to thin	Normal
LV size	Normal	Dilated	Normal to dilated	Normal
LV systolic function	Severe LV dysfunction	LV dysfunction	LV dysfunction	Normal LV function

CHF, Congestive heart failure; *EF,* ejection fraction; *LV,* left ventricular.
Adapted from Lieberman EB, Hutchins GM, Herskowitz A, et al. Clinicopathologic description of myocarditis. *J Am Coll Cardiol.* 1991;18:1617–1626.

in a standard coronary distribution.[347] One hallmark of fulminant myocarditis is the extremely thickened LV wall with severely reduced systolic function, which is the result of a hyperacute inflammatory process leading to edema of the myocardium. As the myocardium recovers, the edema resolves and there is simultaneous improvement in wall thickness and LV systolic function.[348] Fig. 15.134 demonstrates a patient with fulminant myocarditis; following recovery of systolic function there is improvement in wall thickness. More sophisticated ultrasound techniques, such as the use of integrated backscatter to look at the myocardial architecture, suggest that the backscatter pattern will normalize before systolic function returns, but this has not gained wide application.[349]

The ability of individuals with fulminant myocarditis to recover a significant portion of their cardiac function over a 2- to 4-week period following acute decompensation has led to aggressive interventions. In 2000, McCarthy and colleagues presented a series of 15 patients with fulminant myocarditis; all but one patient had a successful recovery without the need for heart transplantation.[350] While McCarthy's experience showed only one patient required mechanical circulatory support, subsequent series demonstrated the applicability and success of aggressive mechanical circulatory support with fulminant myocarditis.[351] The approach was to initiate mechanical circulatory support for fulminant myocarditis patients and then perform daily serial echocardiograms to evaluate myocardial recovery, both in wall thickness

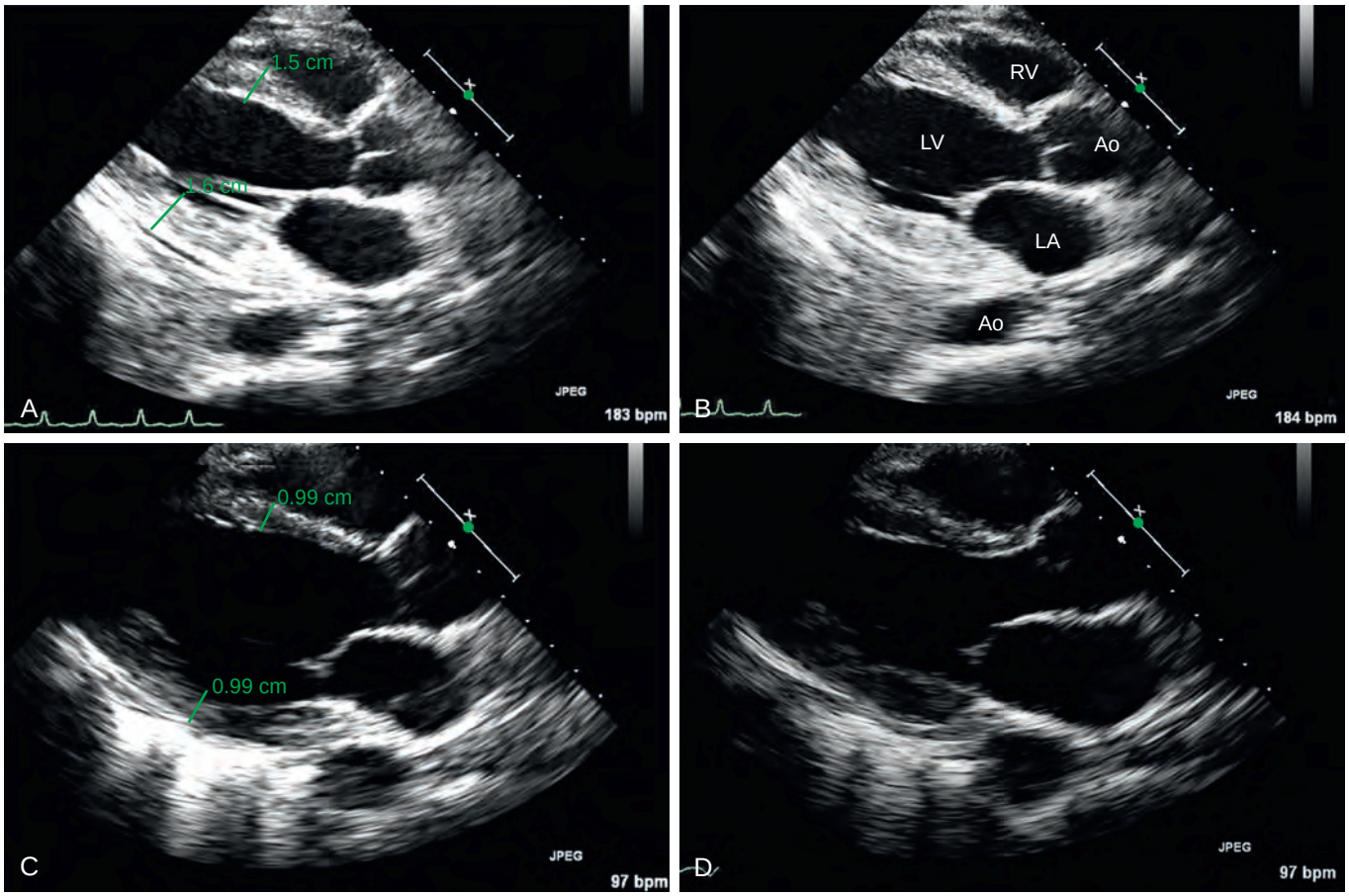


Fig. 15.134 Initial imaging at presentation of a patient with fulminant myocarditis. All images are transthoracic echocardiography images of the parasternal long-axis view. (A) End-diastolic frame with severely thickened myocardium. (B) End-systolic frame of the same clip demonstrating poor systolic function with minimal change in chamber size. (C) End-diastolic frame taken 34 days later demonstrating a resolution of myocardial edema with normal wall thickness. (D) End-systolic frame demonstrating improved systolic function in the form of an improved end-systolic dimension. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

and LV systolic function, and then initiate weaning from mechanical support when myocardial recovery was seen in up to 2 weeks.[351]

In differentiating fulminant myocarditis from acute myocarditis, one series of patients showed that all patients with the fulminant type demonstrated increased septal thickness, normal LV diastolic dimensions, and depressed LVEF.[352] As acute myocarditis is a different clinical entity, the use of imaging can assist in the differentiation. Clinically, acute myocarditis manifests with normal wall thickness, dilation of the LV cavity, and depressed systolic function in which the onset can often be indistinct. It is usually preceded by some infectious process and the recovery is delayed because of poor myocardial performance and heart failure.[346] Unfortunately, recovery from acute myocarditis is often incomplete with less than half of a large group of patients recovering normal myocardial function and avoiding heart transplantation.

The role of imaging in myocarditis is important not only to assist in the care of these often critically ill and decompensated patients, but also to differentiate the cause of deterioration from other common causes. As mentioned, the presence of myocardial edema, normal chamber size, and reduced LVEF should differentiate fulminant from acute myocarditis, but often the diagnosis of myocarditis is unknown or underrecognized. In one series of 45 patients who presented for typical chest pain consistent with acute coronary syndrome but normal coronary angiography, 35 had myocarditis on endomyocardial biopsy.[353] This is further complicated by the fact that within this series, 62% had RWMAs and a depressed LVEF (<50%).[353] Though these findings of RWMAs in the absence of coronary artery disease in the setting of myocarditis have been known since the 1980s, it is not always in a coronary distribution.[354] This has led to a recommendation that multiple imaging modalities, including myocardial strain imaging, cardiac MRI, and the use of antimyosin antibody titers, should be used to evaluate the myocardium if myocarditis is suspected.[355–357]

Despite a much better understanding of the pathophysiology of myocarditis and its clinical progression over the past 2 decades, significant improvement in treatment options and outcomes have not occurred.[358] Biopsy-proven myocarditis has a nearly 20% mortality rate within 5 years despite treatment, which further highlights the need for myocarditis to be on the differential diagnosis of all clinicians when evaluating a patient with abnormal myocardial function.[359] Autoimmune processes involved in myocarditis and diseases such as cardiac sarcoidosis have a better prognosis than other causes of myocarditis, further supporting the need for a broad list of causes of ventricular dysfunction.[360] Causes of myocarditis are summarized in Box 15.8.

One predicative factor associated with postmyocarditis recovery was found to be premyocarditis LV systolic function.[361] Unfortunately, a significant number of individuals do not recover and the long-term result is a transition to a DCM. This dilation is the result of impaired myocardial function and is proposed to be secondary to microvascular spasm within the inflamed myocardium leading to fibrosis and dilation over time.[362]

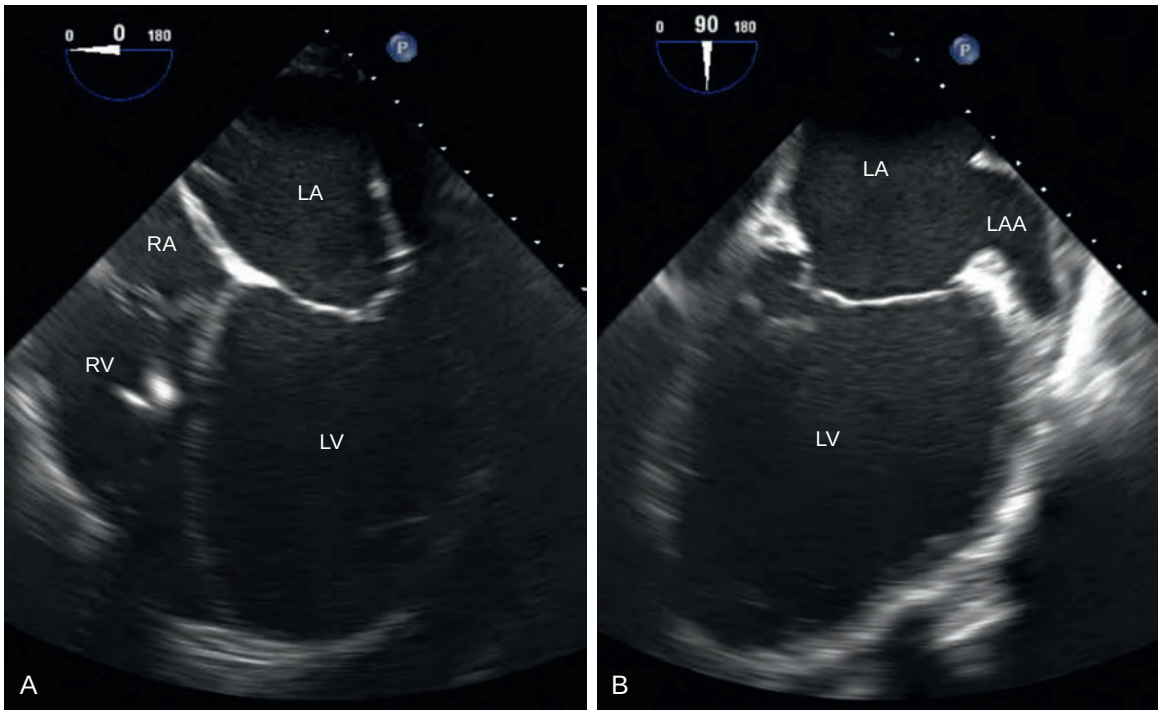


Fig. 15.135 Transesophageal echocardiographic still frames in the (A) midesophageal four-chamber view and (B) midesophageal two-chamber view of a patient with postviral myocarditis dilated cardiomyopathy. Note the large left ventricle *(LV)* with apical tenting of the mitral valve. *LA,* Left atrium; *LAA,* left atrial appendage; *RA,* right atrium; *RV,* right ventricle.

Dilated Cardiomyopathy

DCM is the final common pathway for a number of conditions that result in systolic dysfunction of the left ventricle. Up to 50% of individuals with myocarditis can progress to a DCM, with approximately 20% thought to be the result of viral myocarditis.[362–364] Persistence of certain types of viruses, such as coxsackievirus B, has been seen in one-third of patients with idiopathic DCM.[365] The remaining causes are from ischemic changes, diabetic alterations to the microvasculature, familial causes, and others.

Following an injury to the myocardium (infectious, ischemic, traumatic, metabolic), the remaining viable tissue within the heart begins to remodel and the LV cavity dilates over time.[366] Alterations in myocardial blood flow, myocardial energetics, and the renin-angiotensin-aldosterone system all contribute to elevated LV end-diastolic pressure and subsequent enlargement of the LV chamber with reduction in LV systolic function.[367–369]

The echocardiographer should be aware of the derangements that are associated with DCM as patients will have reduced systolic function and reduced functional reserve. Fig. 15.135 shows a TEE image of a patient with DCM undergoing LVAD implantation as treatment for systolic heart failure. These individuals often have elevated LV end-diastolic pressure that increases the risk for pulmonary edema formation. The derangements to the myocardium that initialed the DCM may not be isolated to the left ventricle, and the right ventricle may have clinical or subclinical dysfunction. Large ventricular chamber size and the relative hypokinesis or RWMAs associated with the cardiomyopathy may support thrombus formation in both the left ventricle and LAA. Dilation of the left ventricle can also promote ventricular and atrial arrhythmias that are often not well tolerated.

Infiltrative Cardiomyopathy

Infiltrative cardiomyopathies are disease processes in which something becomes intercalated within the myocardium that is not expected to be there. Eosinophilic processes can result in infiltration and the deposition of abnormal proteins. Amyloidosis is an infiltrative process that results in cardiac dysfunction from abnormal deposition of amyloid fibrils within tissue. Amyloid is categorized into systemic AA amyloidosis, which traditionally has renal involvement and not much cardiac involvement when compared with the systemic AL amyloidosis, which has 90% cardiac involvement, and the TTR type of amyloidosis, which has 100% cardiac involvement.[370] The deposition of amyloid fibrils within the wall of the ventricles is responsible for the clinical manifestations of amyloidosis. There is impaired diastolic relaxation as a result and subsequent diastolic heart failure in the latter stages.[371] As amyloidosis is generally a progressive diastolic disease it has been named *stiff heart syndrome,* which is characterized by a restrictive process.[372,373] The more the disease infiltrates the myocardium, the worse the diastolic dysfunction becomes, until in the latest stages of disease there also is systolic dysfunction as a result of the infiltration.

Echocardiography has long been a helpful technique to determine the presence and extent of amyloid cardiac disease. In the 1980s, it was shown that any identifiable abnormality of the myocardium on TTE was associated with an increased risk of arrhythmia, especially with the AL variant.[374] Subsequently, it was shown that amyloid has a typical appearance with increased wall thickness, sparkling myocardium, and diastolic dysfunction. When compared to individuals screened for amyloid, but with a negative biopsy, the amyloid patients had smaller end-diastolic and end-systolic sizes, comparable LVEF, and increased rates of restrictive diastolic filling.[375] Common echocardiographic findings in the setting of cardiac amyloidosis are summarized in Table 15.19. The diastolic dysfunction of the myocardium is not isolated to the left ventricle; RV diastolic abnormalities are seen as well.[371] When the LV end-diastolic pressure increases and the LA pressure increases, the pulmonary venous flow becomes diastolic dominant.[376] This is true for the right ventricle as well, but the normal quadriphasic pattern within the hepatic veins make it more challenging to appreciate. The presence of thickened myocardium and diastolic filling abnormalities makes cardiac amyloidosis appear like HCM; this is true for other types of infiltrative cardiomyopathies as well.[372] Infiltrative cardiomyopathies

that mimic HCM presenting with thickened ventricles and increased LV mass are summarized in Table 15.20.

Acute eosinophilic myocarditis is a diagnosis that can be confused clinically with an acute MI because of chest pain and nondescript ST changes on the electrocardiogram.[377] The absolute eosinophil count will help to make the diagnosis, and the administration of steroids should be timely as the mortality rate for this condition approaches 100%.[377] Other diseases that can present with an infarction-like clinical presentation are summarized in Table 15.21. Knowledge of these causal factors are important since prompt diagnosis and treatment of infiltrative cardiomyopathies can be critical to improving their clinical course.

TABLE 15.19 Echocardiographic Findings in Amyloidosis Compared to Suspected but Biopsy-Negative Subjects

Echocardiography Findings	*Amyloidosis (n = 47)*	*Nonamyloid Subjects (n = 115)*
LV diastolic diameter (average)	4.2 cm	5.2 cm
LV systolic diameter (average)	3.1 cm	3.7 cm
LV EF (average)	44%	42%
Anteroseptal wall thickness (average)	1.6 cm	1.2 cm
Inferolateral wall thickness (average)	1.6 cm	1.2 cm
Restrictive diastolic filling	30 % of group	11% of group
Sparkling appearance	26% of group	4 % of group

EF, Ejection fraction; *LV,* left ventricular.
Adapted from Rahman JE, Helou EF, Gelzer-Bell R. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. *ACC Curr J Rev.* 2004;13:43.

Aortic Evaluation

Because of the intimate anatomic relationship of the aorta and the esophagus, TEE is useful in the diagnosis of aortic disease. The normal aorta consists of three layers: intima, media, and adventitia. The intima is a thin endothelial-lined structure that is easily damaged. The media is composed of smooth muscle and multiple layers of elastic laminae that provide tensile strength, distensibility, and elasticity.[378] The adventitia contains primarily collagen and the vasa vasorum. While the aorta may be divided into five main anatomic components (aortic root, tubular ascending aorta, arch, descending thoracic, and abdominal aorta), it is common to divide it into eight segments (Fig. 15.136). Segment I is the aortic root, which consists of the AV annulus, aortic cusps, and the sinuses of Valsalva. The ascending aorta is divided into two segments: IIa extends from the STJ to the level of the pulmonary arteries, and IIb extends to the origin of the brachiocephalic artery. Segment III is the aortic arch. The descending thoracic aorta is divided into two segments: the proximal descending thoracic aorta to the level of the pulmonary arteries is designated as segment IVa, and the more distal portion is designated as IVb. The proximal abdominal aorta to the renal arteries is segment Va and the distal abdominal aorta is Vb (see Chapter 23).

The normal aortic diameters vary according to location and gender and are summarized in Table 15.22. It should be noted that these values are strongly related to BSA and age.[379] Of the aortic segments, aortic root measurements are most plentiful in the literature and are presented in Table 15.23. In addition to their dependence on size and age, aortic root dimensions may also be increased by the hemodynamic

TABLE 15.20 Infiltrative Cardiomyopathies That Mimic Hypertrophic Cardiomyopathy

Diagnosis	*Age at Presentation*	*Clinical Presentation*	*Echocardiography Findings*	*Electrocardiogram Findings*
Amyloid	>30 years	Heart failure, nephrotic syndrome, hepatomegaly	Symmetric biventricular thickening, biatrial enlargement, speckled appearance of myocardium	Decreased QRS voltage
Hypertension	Adult population	Hypertension	Symmetric LV thickening, normal LV EF	Increased QRS voltage
Fabry disease	Male: 11 years Female: 23 years	Neuropathic pain, impaired sweating	Symmetric biventricular thickening, normal LV EF	Normal to increased QRS voltage
Friedreich ataxia	2–50 years	Gait abnormality	Increased LV wall thickness, preserved LV EF	Normal QRS voltage, ventricular tachycardia
Cardiac oxalosis	>20 years	Juvenile urolithiasis, nephrocalcinosis	Speckled appearance, symmetric biventricular thickening, normal LV EF	Normal to increased QRS voltage, complete heart block
Mucopolysaccharidoses	1–24 years	Developmental delay, course facial features, skeletal deformities	Asymmetric septal hypertrophy, normal LV EF	Variable QRS voltage, malignant arrhythmias
Danon disease	<20 years	Mental retardation, skeletal myopathy	Very thick LV (20–60 mm) Variable RV hypertrophy	Normal to increased QRS voltage, delta wave

EF, Ejection fraction; *LV,* left ventricle.
Adapted from Seward JB, Casaclang-Verzosa G. Infiltrative cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:1769–1779.

TABLE 15.21 Infiltrative Cardiomyopathies That Mimic Ischemic or Dilated Cardiomyopathy Patterns

Diagnosis	*Age at Presentation*	*Clinical Presentation*	*Echocardiography Findings*	*Electrocardiogram Findings*
Sarcoidosis	Young adult	Congestive heart failure	Variable wall thickness Global hypokinesis LV aneurysm	Infrahisian block Atypical infarction pattern
Wegener disease	Young adult	Chronic upper and lower respiratory tract infections	Regional hypokinesis LV systolic dysfunction Mitral regurgitation Pericardial effusion	Atrial fibrillation Atrioventricular block
Hemochromatosis	Male: >30 years Female: variable	Hereditary Form: Hepatic dysfunction Hyperpigmentation Diabetes mellitus Secondary Form: Hemolytic anemia Multiple blood transfusions	Dilated LV Global systolic dysfunction	Supraventricular arrhythmia Conduction abnormalities rare
Dilated cardiomyopathy	Adult	Congestive heart failure (often etiology unknown)	Dilated LV Global systolic dysfunction	Atrial fibrillation

EF, Ejection fraction; *LV,* left ventricle.
Adapted from Seward JB, Casaclang-Verzosa G. Infiltrative cardiovascular diseases. *J Am Coll Cardiol.* 2010;55:1769–1779.

effects of training in competitive athletes.[380] This increase in aortic root diameters is relatively small, so marked enlargement should be considered a sign of a pathologic process. The aortic annulus, sinus of Valsalva, and the STJ diameters should be accurately measured (Fig. 15.137). Aortic annular diameters should be performed using the inner diameter along the hinge points of the aortic leaflet during systole.[379] Although the annulus is usually circular, it may become elliptical in older adults; 3D echocardiographic imaging in multiple planes is necessary if accurate measurements are required. Measurements should ensure the maximal aortic diameter in a plane parallel to the long axis of the aorta.[381] In patients with a trileaflet valve, the closure line should be in the center of the aorta and the closed leaflets should be visualized on the aortic side of a line connecting the AV hinge points (Fig. 15.138). If the point of closure is not central, the image is most likely oblique. While some practitioners favor measurements of internal diameters of the remaining aortic segments, both the 2010 European Association of Echocardiography and the 2015 guidelines from the American Society of Echocardiography suggest leading edge to leading edge measurements during end-diastole.[378,379,381] These leading edge to leading edge measurements produce values comparable to the inner edge to inner edge measurements of CT and MRI, are reproducible, and link a large body of historic data.[378] Nonetheless, with recent improvements in echocardiographic imaging and quality, the differences between the

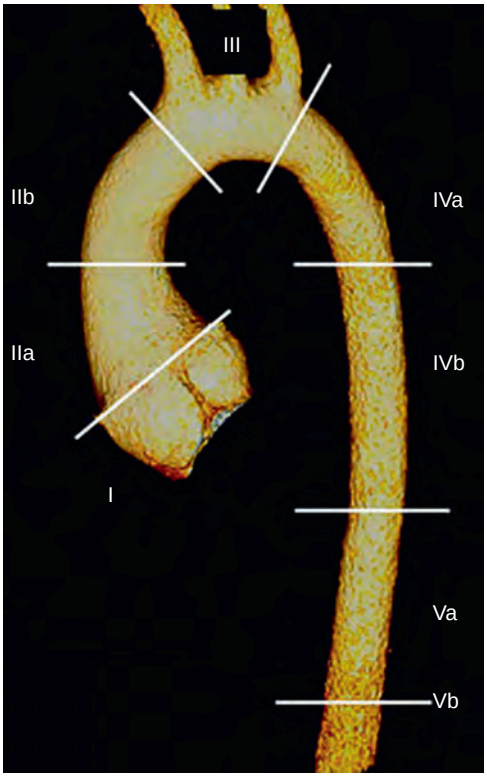


Fig. 15.136 Computed tomographic reconstruction of aorta illustrates the subdivision of aortic segments: segment I, aortic root; segment II, tubular ascending aorta (subdivided into IIa [sinotubular junction to the pulmonary artery (PA) level] and IIb [from the PA level to the brachiocephalic artery]); segment III, aortic arch; segment IV, descending thoracic aorta (subdivided into IVa [from the left subclavian artery to the level of the PA] and IVb [from the level of the PA to the diaphragm]); and segment V, abdominal aorta (subdivided into Va [upper abdominal aorta from the diaphragm to the renal arteries] and Vb [from the renal arteries to the iliac bifurcation]). *(Reproduced with permission from Goldstein SA, Evangelista A, Abbara S, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr. *2015;28[2]:119–182.)*

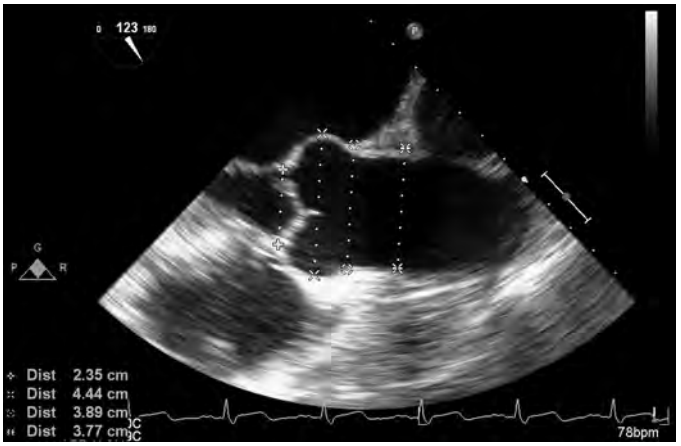


Fig. 15.137 Ascending aortic diameters. The measurements of the aortic annulus, sinus of Valsalva, sinotubular junction (STJ) and ascending aorta diameters are demonstrated. The aortic annular diameter is measured across the inner diameter at the aortic leaflet hinge points. The STJ, sinus of Valsalva, and ascending aorta are measured near edge to near edge.

TABLE 15.22 Normal Aortic Diameters

Location	*Reported Mean Diameters (cm)*
Root (female)	3.50–3.72 ± 0.38
Root (male)	3.63–3.91 ± 0.38
Ascending (male and female)	2.86 (SD not reported)
Middescending (female)	2.45–2.64 ± 0.31
Middescending (male)	2.39–2.98 ± 0.31
Diaphragmatic (female)	2.40–2.44 ± 0.32
Diaphragmatic (male)	2.43–2.69 ± 0.27–0.40

Adapted from Abe S, Ono S, Murata K, et al. Usefulness of transesophageal echocardiographic monitoring in transluminal endovascular stent-graft repair for thoracic aortic aneurysm. *Jpn Circ J.* 2000;64:960–964.

TABLE 15.23 Normal Aortic Root Diameters

		Age (Years)					
		15–29	*30–39*	*40–49*	*50–59*	*60–69*	*>70*
Men (BSA 2.0 m^2)	Mean normal (cm)	3.3	3.4	3.5	3.6	3.7	3.8
	Upper limit normal (cm) (95% CI)	3.7	3.8	3.9	4.0	4.1	4.2
Women (BSA 1.7 m^2)	Mean normal (cm)	2.9	3.0	3.2	3.2	3.3	3.4
	Upper limit normal (cm) (95% CI)	3.3	3.4	3.6	3.6	3.7	3.9

For men, add 0.5 mm per 0.1 m^2 BSA above 2.0 m^2 or subtract 0.5 mm per 0.1 m^2 BSA below 2.0 m^2.
For women, add 0.5 mm per 0.1 m^2 BSA above 1.7 m^2 or subtract 0.5 mm per 0.1 m^2 BSA below 1.7 m^2.
BSA, Body surface area; *CI*, confidence interval.
Adapted from Evangelista A, Flachskampf FA, Erbel R, et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice. *Eur J Echocardiogr.* 2010;11:645–658.

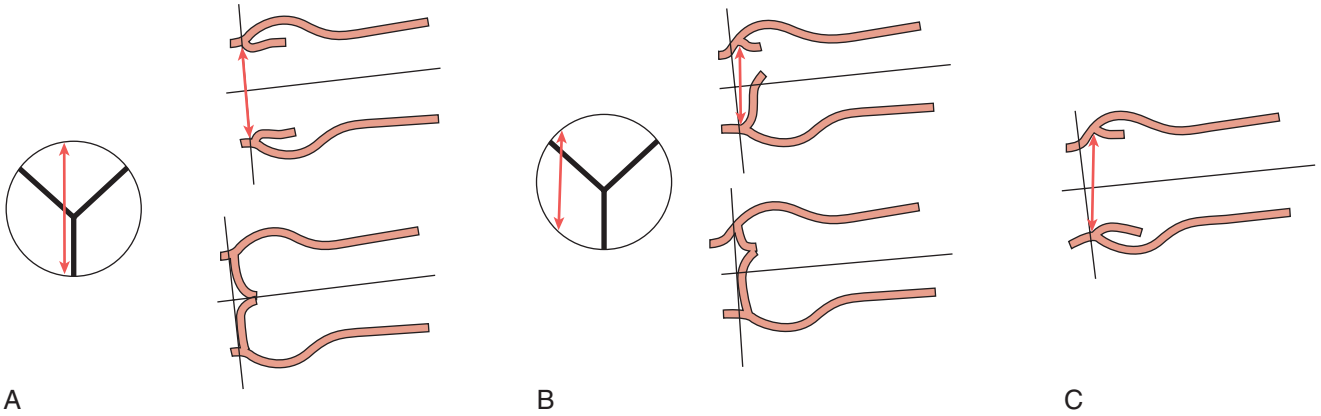


Fig. 15.138 Correct and incorrect measurements of the aortic annulus *(double arrows).* (A) Correct measurement. Centrally positioned diameter and central closure of leaflets. Thin lines correspond to the long axis of the ascending aorta and, orthogonally, to correct orientation of the annular diameter. (B) Incorrect, eccentric annular measurement. The hinge points are slightly displaced upward and do not correspond to the nadir of the cusp attachments, with incomplete opening and closing of leaflets. (C) Incorrect, oblique annular measurement. The annulus is "virtual" and only defined by the hinge points of the three aortic valve leaflets. As such, much of the ring is without a visible anatomic structure. However, its location on any long-axis two-dimensional view can be approximated since the plane of the virtual annulus is approximately perpendicular to the long-axis of the aorta. When bisecting the maximum dimension of the annulus in the sagittal plane, the echocardiographer will image the right coronary cusp (RCC) anteriorly and the fibrous trigone between the left and noncoronary cusps posteriorly. Because only one anatomic marker (the RCC hinge point) is seen, the opposing annulus must be approximated with a measurement that is perpendicular to the long axis of the aorta. Attempting to measure what is believed to be two hinge points typically will measure within the sinuses of Valsalva and overestimate the annulus. *(Reproduced from Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr. *2015;28:1–39.e14.)*

leading edge to leading edge versus internal diameter measurements are becoming minimal.[379] The use of end-diastolic values increase the reproducibility of measurements (since aortic pressure is most stable during this period). All measurements should be performed to the long axis of the aorta. Ideally, measurements should reference other structures such as the STJ or the PA.[378] Sinus of Valsalva diameters should be measured from the anterior right coronary sinus to one of the posterior sinuses (usually the noncoronary). The largest diameter should be sought that is parallel to the aortic annulus and perpendicular to the aortic long axis.

Aortic disease may be classified as aneurysmal, atherosclerotic, dissection, or traumatic. Multiple elements must be included when imaging the aorta (Box 15.9).[382] The location of the aortic abnormality must be accurately identified. In the case of aortic dilation or aneurysmal disease, the maximum diameters should be reported. The array angle should be carefully controlled to ensure that a true short-axis image is obtained; an oblique cut will give a falsely greater diameter. If an acute aortic syndrome is suspected, the extent and character of the dissection should be defined, and the severity and mechanism of AI should be described; there should be a high index of suspicion for evidence of aortic rupture, such as pseudoaneurysm, hemopericardium, or hemothorax.

BOX 15.9 ESSENTIAL ELEMENTS OF ULTRASONOGRAPHIC AORTA IMAGING

- The location of the aortic abnormality
- The maximum diameter of any dilation measured from the internal diameter perpendicular to the direction of flow
- For patients at risk of aortic root disease, measurements of the aortic annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta should be attempted
- Evidence of thrombus or atheroma
- The presence of intramural hematoma, penetrating aortic ulcer, and calcification
- Extension of aortic abnormalities into branch vessels
- Evidence of aortic rupture such as pseudoaneurysm, hemopericardium, or hemothorax

Adapted from Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:1–39.e14.

Aortic Aneurysms

An aneurysm, or true aneurysm, is a localized dilation of at least 50% encompassing all three layers (intima, media, and adventitia) of a given artery. Other accepted terms include *ectasia,* which is arterial dilation less than 50% of the normal artery, and *arteriomegaly,* which is a diffuse arterial dilation of greater than 50% of multiple segments.[382] It is acceptable to use the nonspecific term *aortic dilation* to describe both ectasia and aneurysmal disease. In the ascending aorta, 5 cm is usually considered the threshold for aortic aneurysmal disease, even though it is less than the classical threshold aneurysm definition. In contrast, a pseudoaneurysm or false aneurysm, results in the disruption of the arterial wall with extravasation of blood contained by the periarterial connective tissue; this pseudoaneurysm wall does not contain the normal three arterial layers.

As opposed to other modalities, TEE is considered a third-line recommendation for the evaluation of thoracic aortic aneurysmal disease.[378] While it is an excellent modality for the evaluation of AI mechanisms and the aortic root, proximal ascending aorta, arch, and descending aorta, it has many disadvantages compared with CT and MRI; the distal ascending aorta and arch vessels are poorly visualized,

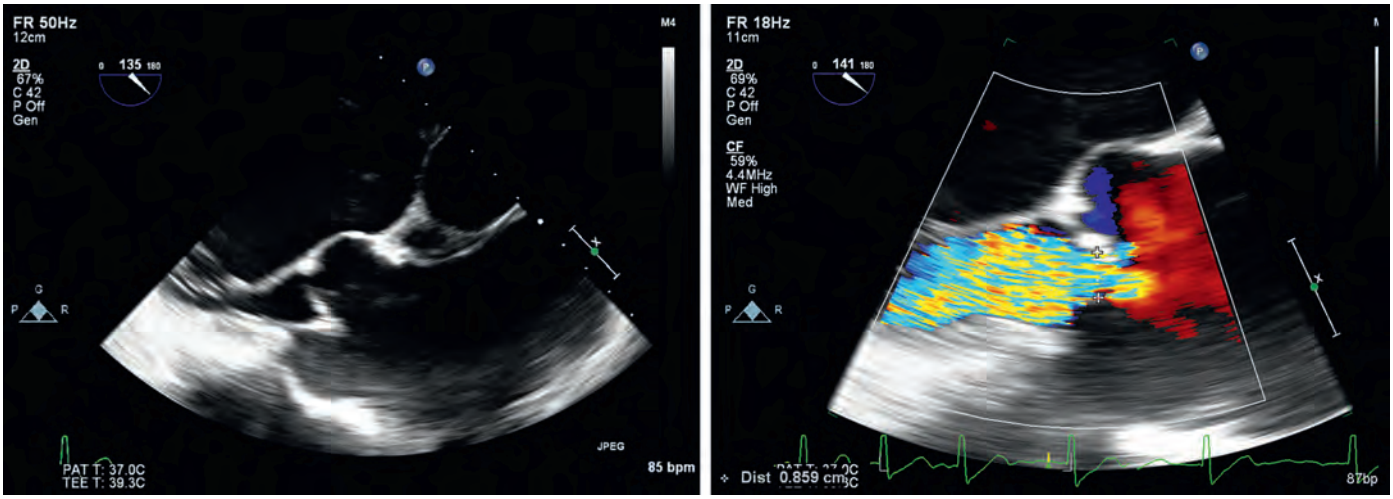


Fig. 15.139 Functional aortic regurgitation (AR) secondary to an ascending aortic aneurysm. Midesophageal aortic valve (AV) long-axis view *(left)*. The sinus of Valsalva is very enlarged with respect to the AV annulus. This enlargement results in tethering of the AV. The coaptation plane of the aortic leaflets is significantly distal to the plane of the aortic annulus *(right)*. Addition of color-flow Doppler demonstrates severe AR.

TABLE 15.24 Quantification of Aortic Atherosclerotic Disease

Grade	*Severity*	*Description Katz et al*[386]	*ASE 2015 Guidelines*[381]
I	Normal	Normal to mild intimal thickening (1–3 mm)	Intimal thickness <2 mm
II	Mild	Severe intimal thickening (3–5 mm) without protruding atheroma	Mild intimal thickness 2–3 mm
III	Moderate	Atheroma protruding <5 mm into lumen	Atheroma 3–5 mm
IV	Severe	Atheroma protruding ≥5 mm into lumen	Atheroma >5 mm
V	Complex	Any thickness with mobile component or components	Grade 2, 3, or 4 plus mobile or ulcerated components

ASE, American Society of Echocardiography.
Adapted from Katz ES, Tunick PA, Rusinek H, et al. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. *J Am Coll Cardiol.* 1992;20:70–77.

and landmarks are limited for serial examinations. If the aorta is tortuous, measurements of diameters may be difficult.

AR may occur as a result of aortic dilation; therefore, if present, the mechanism of AR/AI should be carefully elucidated. A common mechanism for functional AR is tethering of the AV cusps as a result of a mismatch between AV annular and the STJ diameters (Fig. 15.139 and Video 15.2).[383] This tethering results in a retraction of the AV cusps, insufficient leaflet coaptation, and hence regurgitation. The echocardiographic determinants of functional AR with an anatomically normal AV include a coaptation leaflet height (ie, maximum distance between point of cusp coaptation and the annular plane) greater than 8 to 10 mm and a STJ-to-annulus ratio greater than 1.6. With repair of the aortic aneurysm, there may be restoration of aortic root geometry with improved leaflet coaptation and decreases in the severity of AR.

Aortic Atherosclerosis

Neurologic injury after cardiopulmonary bypass remains a devastating complication of cardiac surgery. Possible causes include hypoperfusion and cerebral embolization of gaseous or particulate matter, primarily from atherosclerotic disease. The thoracic aorta is a potential source of such emboli, since it often contains atherosclerotic plaques and may be instrumented multiple times during cardiac operations. Atherosclerosis is normally characterized by the presence of intimal lesions called *atheroma.* These lesions may protrude into the vessel lumen, be calcific, and compromise the integrity of the vessel wall. Abdominal aortic atherosclerosis is more common than descending aortic atherosclerosis, which is more common than ascending aortic atherosclerosis. These atherosclerotic lesions are dynamic, with both progression and regression over time.[384] In addition to defining anatomic locations, TEE may provide information on plaque mobility, ulceration, and composition with excellent interobserver and intraobserver reliability.[385] Grading systems for the severity of atherosclerotic disease rely on the greatest intimal or atheromata thickness, complexity, and presence of an ulcerated or mobile component. Katz and coworkers[386] described a classification system, which was updated by the American Society of Echocardiography in 2015. Both are summarized in Table 15.24 and illustrated in Fig. 15.140. A normal aorta consists of less than 2 mm of intimal thickness and is graded as 1. Increasing degrees of intimal thickening and atheroma are graded from 2 to 4 (ie, mild, moderate, severe) depending on the greatest thickness of the atheroma. If there is a mobile or ulcerated component, it is classified as a grade 5 lesion. The severity of atherosclerotic disease and the presence of a mobile component are highly associated with adverse neurologic outcomes after cardiac surgery.[387] This semiquantitative measurement of plaque thickness was found to be relatively objective and reproducible.

While TEE is a sensitive modality for the proximal ascending aorta, distal arch, and descending aorta, the distal ascending and proximal aorta arch are not consistently well visualized.[388] Nonetheless, TEE can serve as a screen to detect aortic atherosclerotic debris.[389] The presence of atherosclerotic disease in the visualized portions increases the likelihood of finding atherosclerotic changes in the nonvisualized portion of the aorta. The sensitivity of TEE for the detection of distal ascending atherosclerosis may be substantially increased by the introduction of a saline-filled balloon into the trachea and left main bronchus (A-View; Cordatec Inc, Zoersel, Belgium).[390] This technique allows for a significant improvement in the ability to image the distal ascending and

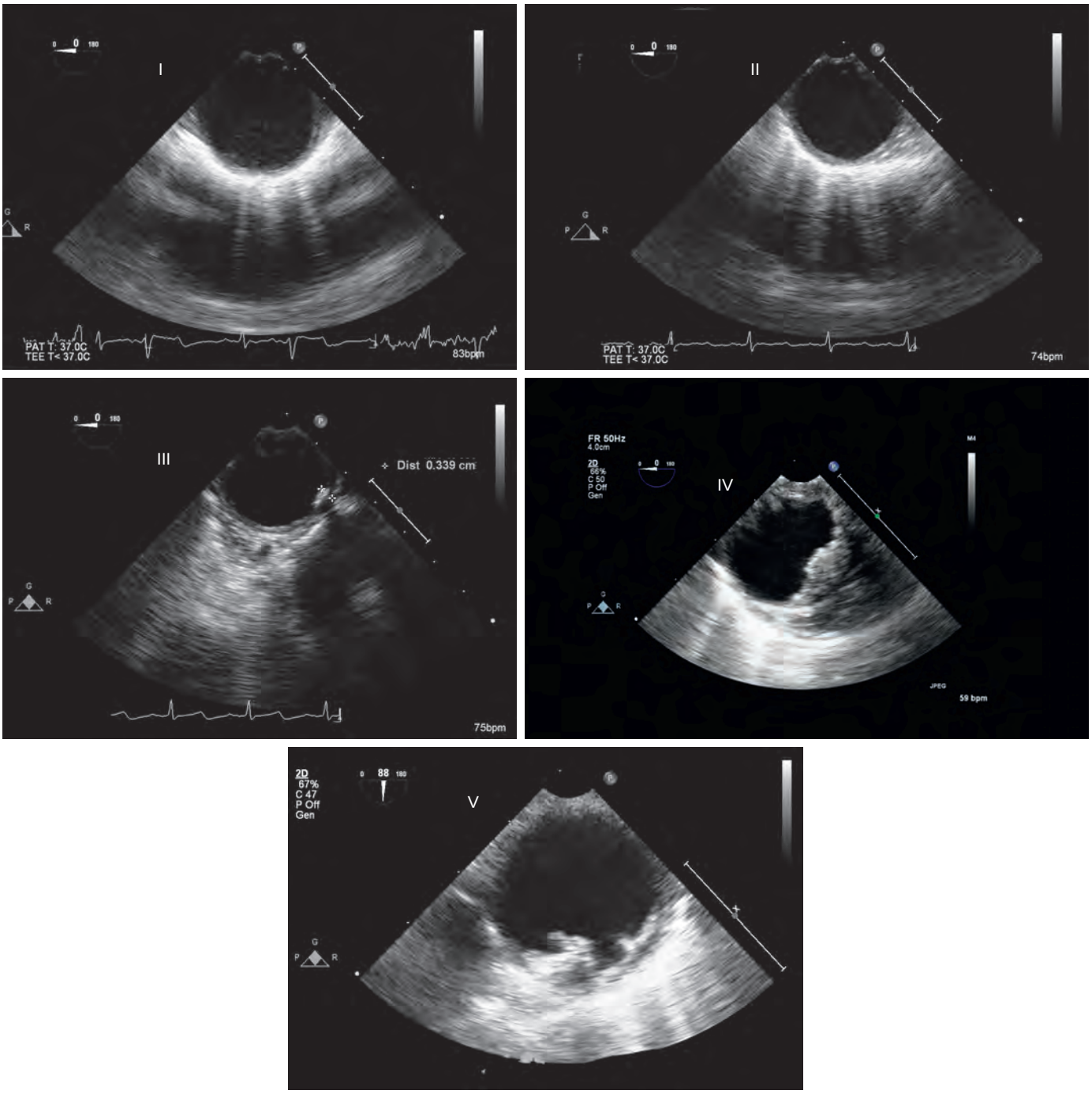


Fig. 15.140 The grading of atherosclerotic disease. I. Normal to mild intimal thickening. II. Mild severity: severe intimal thickening. III. Moderate severity: atheroma protruding less than 5 mm. IV. Severe severity: atheroma greater than 5 mm. V. Complex: large atheroma with a mobile component.

proximal aortic arch. In another study, the right innominate artery was visible in all patients with this saline-filled balloon compared with 5% by TEE without this balloon.[391] This technique is not without complications. Because it requires manipulation of the balloon within the endotracheal tube, there may be minor tracheal mucosal injury. In one case, the endotracheal tube was dislodged with substantial hypoxemia.[391]

Intraoperatively, it is more common to use epiaortic ultrasonography to image potential aortotomy and cross-clamp sites. Compared with TEE, epiaortic scanning provides improved resolution, fewer artifacts, no blind spots, and superior localization of atherosclerotic disease within the middle and distal ascending aorta.[392] Epiaortic scanning is more sensitive than digital palpation in the detection of atherosclerotic disease, and its use has modified surgical management during the conduct of cardiac surgery.[393] While epiaortic scanning may be justified for all patients undergoing cardiac surgical procedures, its use should be seriously considered in those patients with increased risk for embolic stroke (including a history of cerebrovascular or peripheral vascular disease) and evidence of aortic disease by any modality.[394] In a study of 100 patients, 90% of patients had aortic atheroma detected by epiaortic ultrasonography, but only 16% had detectable atheroma by manual palpation.[395] While epiaortic ultrasonography identified 38

separate segments of severe atheroma, manual palpation and TEE were only able to identify severe disease in two and three segments, respectively. In a small study of 105 patients undergoing coronary artery bypass graft surgery, epiaortic ultrasonography changed the conduct of the surgical procedure in 28% of patients,[396] while in a larger study of more than 6000 patients, it changed surgical decisions in 4.1% of cases.[397] These changes included decisions concerning the induction of cardiac arrest, need for atherectomy, requirements for off-pump procedures, and details of aortic cross-clamping and cannulation.

Epiaortic ultrasonography may be performed by placing a sterilely wrapped probe directly on the aorta. Once the disease is defined, it can often be avoided during instrumentation, and hopefully neurologic injury can be prevented. High resolution (ie, greater than 7 MHz) should be used to optimize resolution. Either phase or linear array probes may be used to image the ascending aorta. Phase array probes produce a fan-shaped sector. Because of this fan-shaped sector displayed, the most anterior aspect of the aorta cannot be adequately visualized unless a standoff is used between the transducer and the aorta. This may be accomplished with a dedicated standoff device, but it is usually most convenient to fill the pericardial cradle with saline and hold the probe approximately 1 cm anterior to the aorta while scanning. The entire width of the aorta can usually be seen in the sector. Alternatively, linear array probes may be used. The linear array probes increase the ability to image the near field (ie, the area of the aorta next to the probe itself), while decreasing the need for the standoff required for the phase array probes. Their major disadvantage is the decreased lateral visualization of the aorta; the probe needs to be moved from side to side to visualize the entire area of interest.

A complete epiaortic examination should include short-axis views of the proximal, middle, and distal ascending aorta and long-axis views of both the ascending aorta and arch.[394] These views will allow for evaluation of the 12 areas of the aorta: anterior, posterior, left and right lateral walls of the proximal, middle, and distal ascending aorta. The proximal ascending aorta is defined as the region from the STJ to the proximal intersection of the right PA. The midascending aorta includes that portion of the aorta that is adjacent to the right PA. The distal ascending aorta extends from the distal intersection of the right PA to the origin of the innominate artery.

The epiaortic probe is placed initially on the proximal aspect of the ascending aorta close to the AV.[394] The probe should be manipulated to ensure that the aorta is centered in the field and rotated to ensure a true short-axis view; the anteroposterior and the medial-lateral dimensions should be similar. The probe is advanced cephalad to visualize the middle and distal ascending aorta. During this transit, the probe may need to be rotated clockwise to ensure a true short-axis orientation. After obtaining these short-axis views, the probe is positioned proximally and rotated to obtain a long-axis view of the ascending aorta. The probe is once again advanced cephalad to the aortic arch. The arch as well as the origins of the innominate, left carotid, and left subclavian arteries should be obtained. During the examination, the following should be noted for each segment of the ascending aorta and the arch: (1) the maximal plaque thickness, (2) the location of the maximum plaque within the ascending aorta, and (3) the presence of mobile plaque. The severity of the atherosclerosis should be classified as described in Table 15.24. All information should be communicated with the surgical team.

Aortic Dissection

In the diagnosis of aortic dissection, TEE has overcome some of the major disadvantages of the alternative diagnostic modalities (CT, MRI). The diagnosis of dissection is based on the presence of an intimal flap. In comparison to these other modalities, TEE has been shown to have high sensitivity and specificity.[398,399] According to the 2010 guidelines for the diagnosis and management of aortic disease, TEE, CT, and MRI are recommended as definitive methods for the identification or exclusion of thoracic aortic dissection.[382] Others have recommended that TEE is the modality of choice in the diagnosis of aortic disseccton.[379] The sensitivity for the detection of proximal aortic dissection is 88% to 98% with a specificity of 90% to 95%.[400] With further improvement in technology, the sensitivity of TEE in detecting aortic dissections approaches 100%.[378] As opposed to CT or MRI, it is portable and does not require ionizing radiation or intravenous contrast. An examination can be performed within about 15 to 20 minutes and a diagnosis can usually be obtained at the same time.

TEE should be performed on all patients in the operating room presenting for type A dissections. The diagnostic goals of echocardiography in the evaluation of aortic dissections are summarized in Table 15.25. The hallmark of an aortic dissection is an intimal flap (Fig. 15.141, Video 15.3). Several angles and echocardiographic windows should be used to confirm the flap. Typically, the dissection flap will have an independent motion compared with the surrounding structures, and the intimal flaps should be contained within the aortic lumen. CFD should be used to identify two separate flow patterns within each lumen; flow should not appear to pass easily through the dissection flap. The true and false aortic lumens should be identified (Fig. 15.142, Video 15.4). The false lumen is typically larger, and it expands during diastole. Flow in the false lumen may be absent, delayed, or reversed while the true lumen usually has laminar flow. This slower flow may be seen as spontaneous echo contrast or thrombus. Flow in both true and false lumens may be analyzed with CFD imaging.

The intimal tear appears as a break or discontinuity of the intimal flap (Fig. 15.143, Video 15.5). Ideally the specific locations of the entry and exit sites are also identifiable. During systole, there is flow through

TABLE 15.25 The Role of Echocardiography in the Evaluation of Aortic Dissections

Diagnostic Goals	*Definition by Echocardiography*
Identification of intimal flap	Flap dividing two lumens
Definition of extent of aortic dissection	Extension of the flap and true/false lumens in the aortic root (ascending/arch/descending abdominal aorta)
Identification of true lumen	Systolic expansion, diastolic collapse, systolic jet directed away from the lumen, absence of spontaneous contrast, forward systolic flow
Identification of false lumen	Diastolic diameter increase, spontaneous contrast and or thrombus formation, reverse/delayed or absent flow
Identification of false luminal thrombosis	Mass separated from the intimal flap and aortic wall inside the false lumen
Localize entry and exit tears	Disruption of the flap continuity with fluttering or ruptured intimal borders; color Doppler shows flow through the tear
Assessment presence, severity, and mechanism of aortic insufficiency	Anatomic definition of the valve (bicuspid, degenerated, normal with/without prolapse of one cusp); dilation of different segments of the aorta; flap invagination into the valve; severity by classic echocardiographic criteria
Assessment coronary artery involvement	Flap invaginated into the coronary ostium, flap obstructing the ostium, absence of coronary flow, new regional wall motion abnormalities
Assessment of side-branch involvement	Flap invaginated into the aortic branches
Detection of pericardial or pleural effusion	Echo-free space in the pericardium/pleura
Detection of signs of pericardial tamponade	Classic echocardiographic and Doppler signs of tamponade

Adapted from Goldstein SA, Evangelista A, Abbara S, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:119–182.

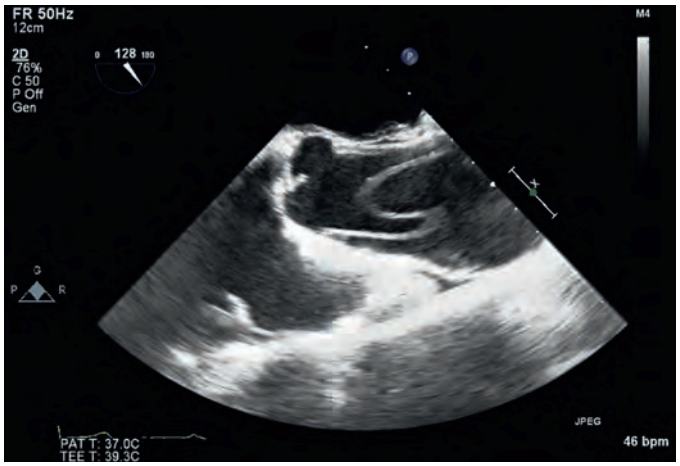


Fig. 15.141 Intimal flap. Midesophageal ascending aorta long-axis view. A large complex intimal flap is seen extending from the sinotubular junction distally through the ascending aorta.

the intimal tear from the true lumen into the false lumen. The identification of the site of the intimal tear may be made in 78% to 100% of cases by TEE.[401] It is important to differentiate the main intimal tear from smaller communications. The primary tear usually has a diameter of over 5 mm.[378] It is frequently located in the proximal part of the ascending aorta in type A dissections and immediately below the origin of the left subclavian artery in type B dissections. Multiple smaller secondary communications may be appreciated in the descending aorta that may correspond to the origin of intercostal or visceral arteries.

TEE is performed in real time allowing for its unique ability to give functional and hemodynamic information. This enables the detection of the common complications of aortic dissection: AR, pericardial and pleural effusions, and LV dysfunction secondary to coronary artery involvement in the dissection process. The mechanism of AR should be defined to assist in the planning of the surgical procedure. These mechanisms are graphically illustrated in Fig. 15.144. There are multiple distinct mechanisms of AR associated with aortic dissection.[402] The most common mechanism is aortic dilation by the false lumen with resultant leaflet tethering resulting in incomplete AV cusp coaptation and secondary or function regurgitation. If the dissection flap extends

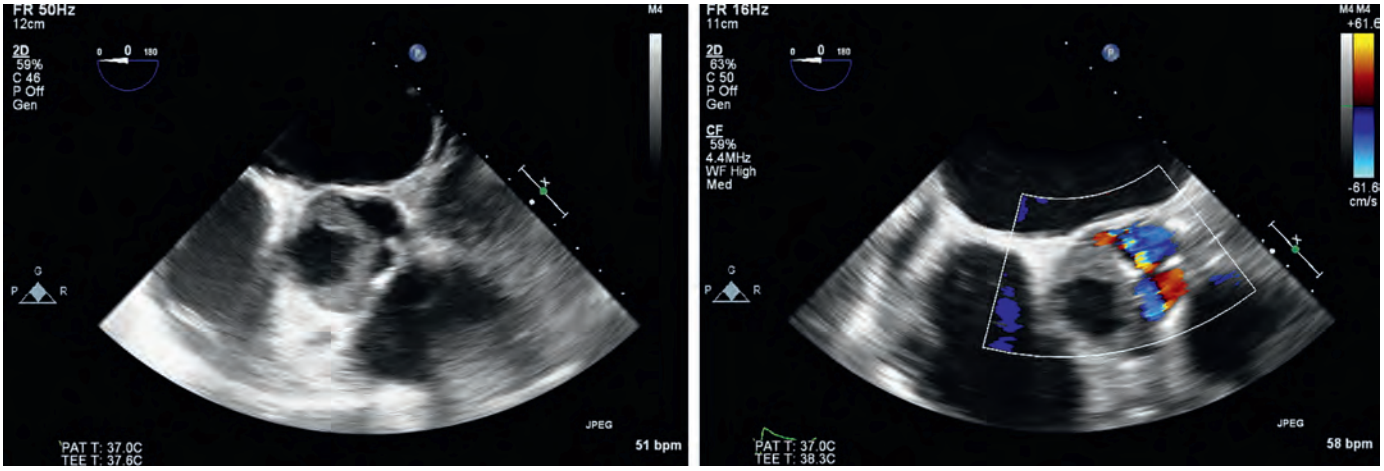


Fig. 15.142 Aortic dissection with demonstration of the true versus false lumen. *Left,* Type A aortic dissection. The larger false lumen is seen on the left of the screen containing thrombus. *Right,* Superimposition of color-flow Doppler demonstrating flow in the true lumen during systole.

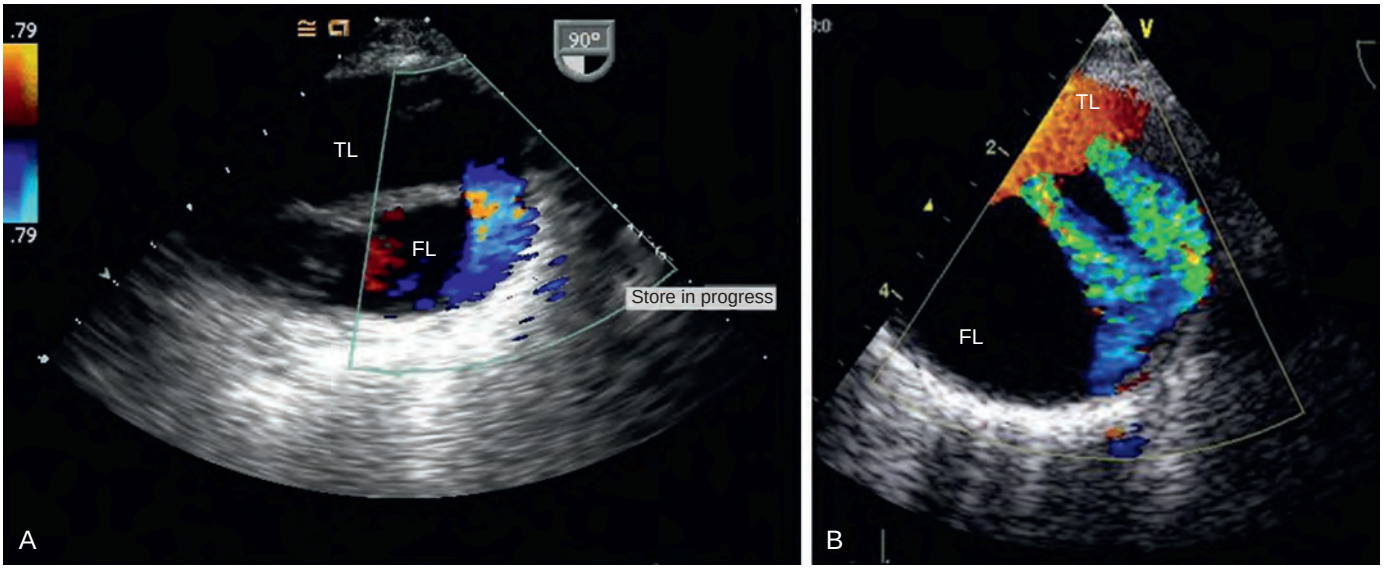


Fig. 15.143 Intimal tear. (A) Primary dissection flap. Descending aortic long-axis view immediately distal to the left subclavian artery. A large dissection flap is visualized with nonrestricted blood flow from the true lumen *(TL)* to the false lumen *(FL).* (B) Secondary communications. Several smaller communications from the TL to the FL are seen from the true to FL, which probably represent the origin of intercostal arteries. *(From Evangelista A, Flachskampf FA, Erbel R, et al. Echocardiography in aortic diseases: EAE recommendations for clinical practice.* Eur J Echocardiogr. *2010;11:645–658.)*

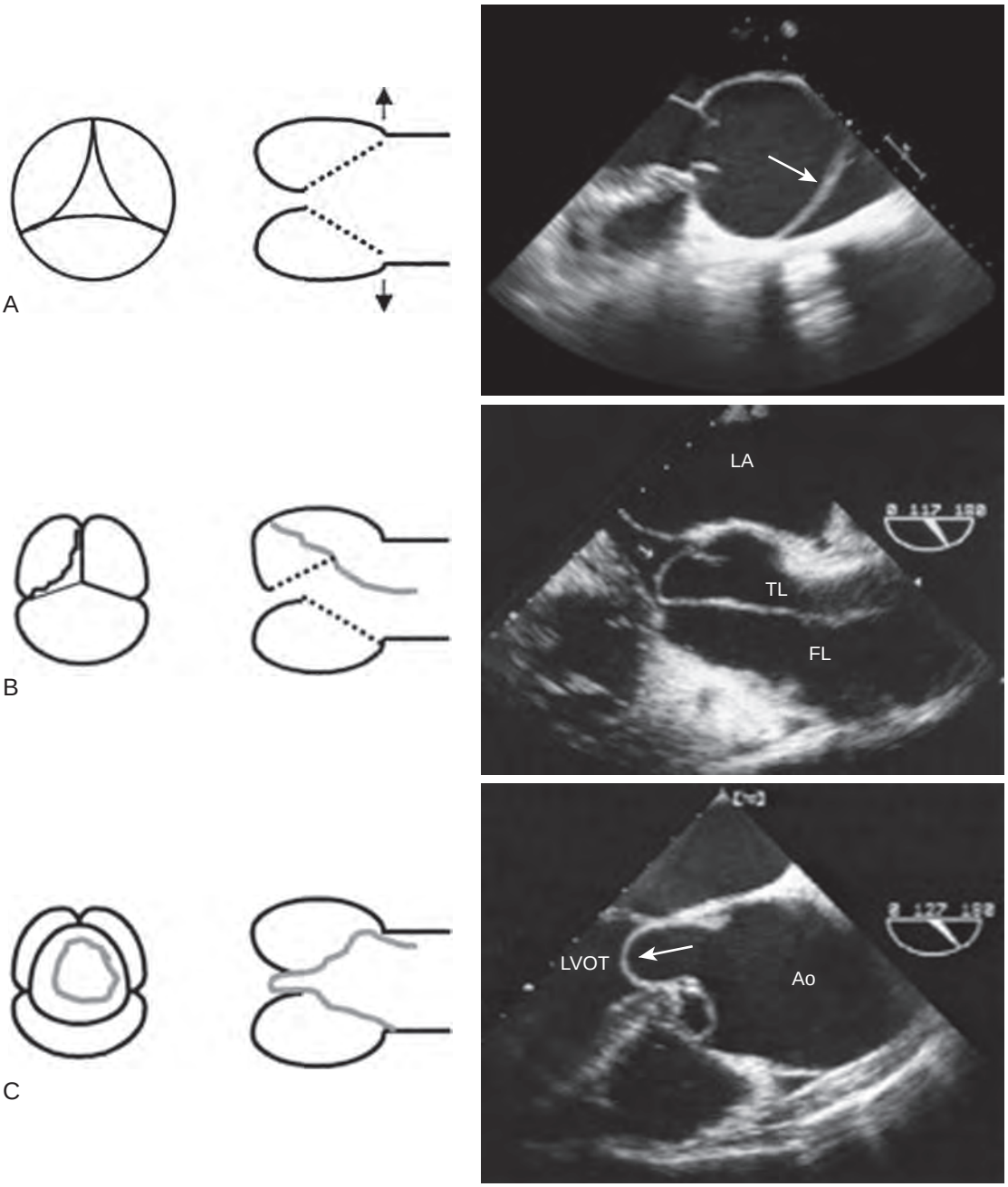


Fig. 15.144 Mechanisms of aortic insufficiency with aortic dissection. Mechanisms of aortic regurgitation (AR) in type A aortic dissection. The *dotted lines* represent the attachment of the leaflet tips to the sinotubular junction (STJ). Normally the leaflet tips coapt fully in diastole (short-axis view) and the diameter of the STJ is similar to that at the base of the annulus. (A) Incomplete leaflet closure when the STJ dilates *(arrows)* relative to the aortic annulus resulting in leaflet tethering and a persistent diastolic orifice. (B) Aortic leaflet prolapse that occurs when the dissection extends into the aortic root and disrupts normal leaflet attachments to the aortic wall, thereby resulting in abnormal leaflet coaptation and eccentric AR. This is usually best visualized in the long-axis view where one or more leaflets are seen prolapsing into the left ventricular outflow tract *(LVOT)* in diastole. (C) Dissection flap prolapse that occurs when a redundant dissection flap prolapses through intrinsically normal aortic leaflets resulting in AR that is often short-lived and may be intermittent. *Ao,* Aorta; *FL,* false lumen; *TL,* true lumen. *(Reproduced with permission from Goldstein SA, Evangelista A, Abbara S, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.* J Am Soc Echocardiogr. *2015;28:119–182; and Movsowitz HD, Levine RA, Hilgenberg AD, Isselbacher EM. Transesophageal echocardiographic description of the mechanisms of aortic regurgitation in acute type A aortic dissection: implications for aortic valve repair.* J Am Coll Cardiol. *2000;36:884–890.)*

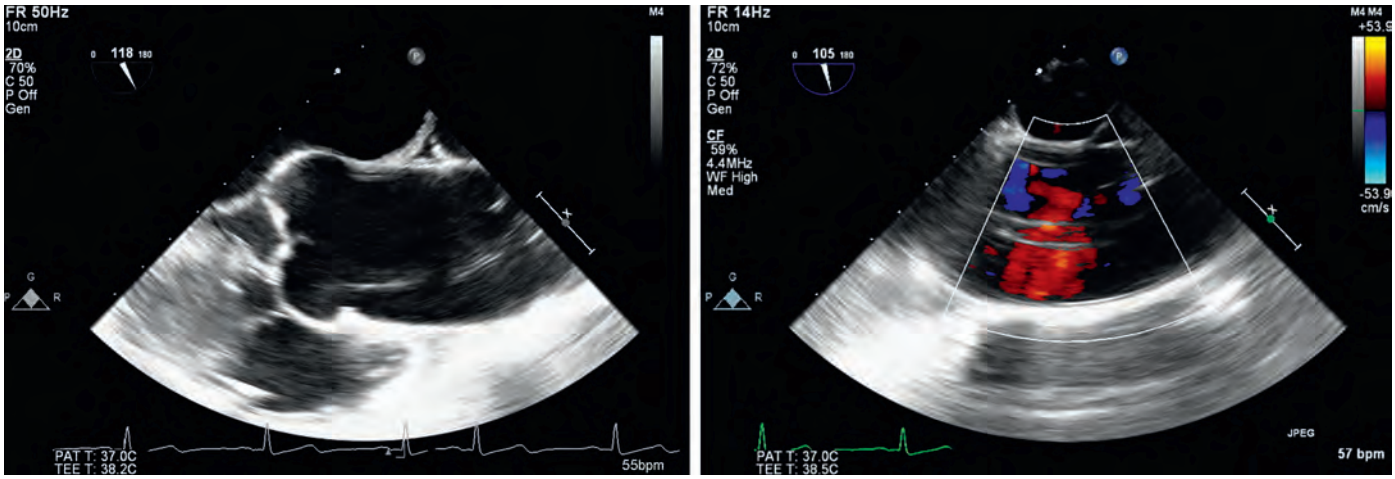


Fig. 15.145 Linear reverberation artifact. Midesophageal ascending aortic long-axis view. A linear reverberation artifact is seen in the ascending aorta. Color-flow Doppler does not demonstrate any effect of the artifact on blood flow patterns.

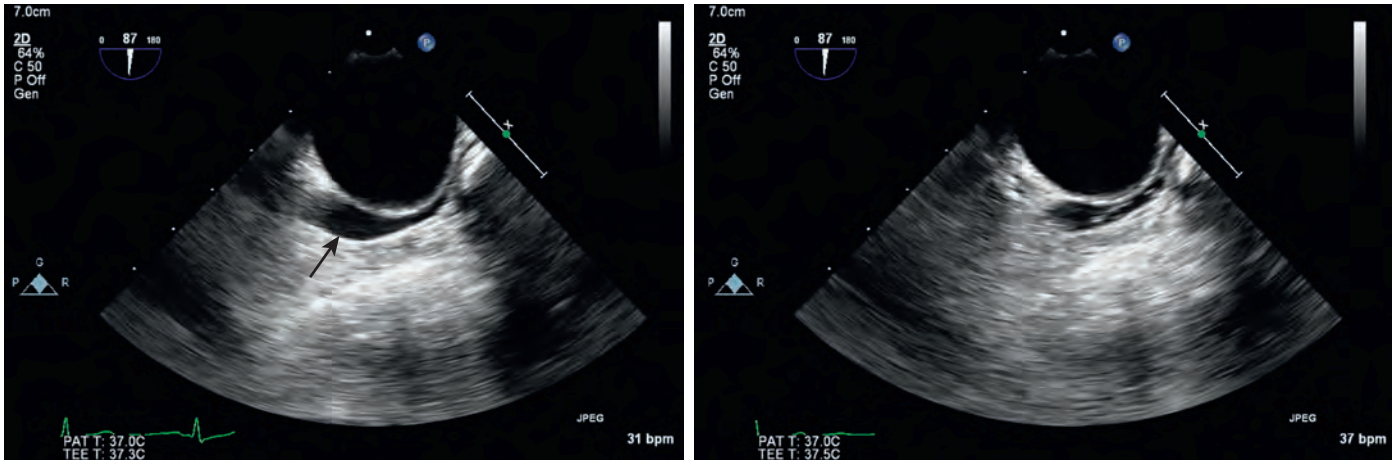


Fig. 15.146 Left innominate vein. Upper esophageal short-axis arch. The left innominate vein *(black arrow)* is visualized along the lesser curvature of the aortic arch. Injection of saline in a left-sided upper extremity vein demonstrates spontaneous echo contrast.

proximal to the STJ into the sinus of Valsalva, the AV commissure may become disrupted from the aortic wall. If the commissure is disrupted, the aortic leaflets are not suspended from the STJ and they prolapse with resultant AR. If there is a long complex proximal dissection flap, the flap itself may prolapse through the AV and interfere with normal AV function. Finally, patients may have preexisting structural AI not related to the dissection.

Pericardial effusions are commonly seen with acute aortic dissection.[382] The most common cause of pericardial effusion is the transudation of fluid across the thin wall false lumen into the pericardium. This transudate is usually mild and does not lead to a hemodynamically significant pericardial effusion. Alternatively, the aorta may rupture directly into the pericardium with resultant pericardial tamponade and hemodynamic collapse. The presence of a significant pericardial effusion carries a poor prognosis. Compromise of coronary blood flow may occur as a result of an expanding false lumen compressing the proximal coronary artery or by extension of the dissection flap into the coronary artery.[403] While challenging, CFD may detect the presence or absence of coronary artery flow. Alternatively, RWMAs may provide information concerning coronary blood flow. In addition to the common sequelae of aortic dissection, TEE can also identify a rare but potentially lethal complication of aortic intimal intussusception.[404] Although TEE may provide information concerning visceral malperfusion, CT is the better diagnostic modality to define this complication.

The major limitation of TEE is the appearance of reverberation or mirroring artifacts that may appear as an intimal flap (Fig. 15.145, Video 15.6). In the ascending aorta, linear reverberation artifacts may be seen in 44% to 55% of TEE studies.[405] These artifacts may mimic the dissection flap, making diagnosis difficult. They are most common in patients with a dilated ascending aorta. In the proximal ascending aorta, these reverberation artifacts may originate from the anterior wall of the left atrium; in the middle aspect of the ascending aorta, they may originate from the posterior wall of the right PA. Intraluminal reverberations in the aortic root are located twice as far from the transducer to the posterior aortic wall; reverberation in the ascending aorta are located twice the distance from the posterior wall of the right PA to the posterior wall of the aorta.[405] The other major limitations of TEE include the potential lack of availability and the operator dependency on accurate diagnosis. Because the left innominate vein runs parallel to the aortic arch, this vein may be mistaken for an arch dissection (Fig. 15.146, Video 15.7). Significant sedation may be necessary; inadequate sedation may result in significant sympathetic

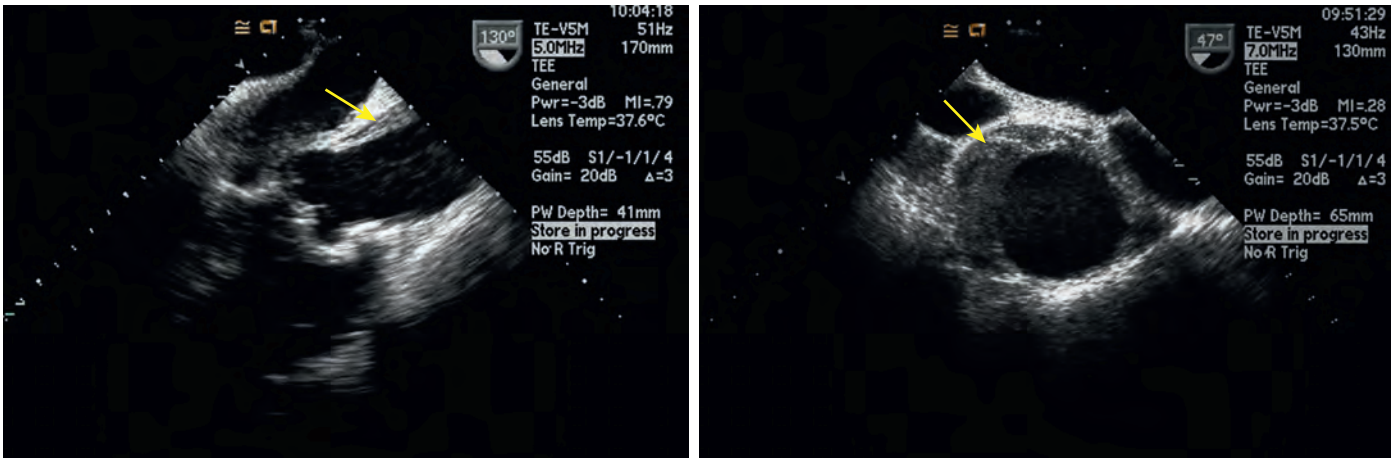


Fig. 15.147 Intramural hematoma (IMH). Midesophageal ascending aorta long-axis *(left)* and short-axis *(right)* views. An IMH *(arrow)* is seen in the posterior and rightward portion of the ascending aorta from the aortic root extending distally. As opposed to atherosclerotic changes, it is crescent shaped with a smooth intimal surface.

outflow. Although isolated cases of aortic rupture have been reported during TEE, the incidence is very low and mostly likely related to the intrinsic disease progression as opposed to the diagnostic modality.[380] The distal ascending aorta and proximal aortic arch may not be adequately visualized because of the interposition of the trachea or left main bronchus between the esophagus and trachea. As opposed to CT or MRI, TEE does not produce consistent visualization of the abdominal branch vessels.

Intramural Hematoma and Penetrating Ulcers

Intramural hematoma (IMH) may be a very challenging echocardiographic diagnosis (Fig. 15.147, Video 15.8). As opposed to classic aortic dissections, a distinct intimal flap is usually not appreciated. These IMHs appear as long echodense crescent-shaped or concentric structures extending along a length of the aortic wall, and in contrast to classical dissections, these IMHs are more localized. Since they appear as areas of aortic thickening, it is sometimes difficult to distinguish IMH from diffuse aortic atherosclerosis or a long aortic mural thrombus. Typically, IMHs greater than 5 mm in thickening of the aortic wall; IMH thickness greater than 10, 12, or 15 mm (depending upon study); and maximal aortic diameter greater than 40 to 50 mm predict risk for progression.[378] The aortic surface of an IMH tends to be smooth, while the internal surface of an aortic atherosclerotic plaque is more irregular. Although there is usually no Doppler evidence of communication between the hematoma and true lumen, some CFD activity may be appreciated in the lumen. In contrast to an IMH, a mural thrombus may have an irregular surface, narrows the aortic lumen, and does not extend as far.

A penetrating atherosclerotic aortic ulcer is characterized as an ulceration of an atherosclerotic lesion that penetrates the internal elastic lamina into the media (Fig. 15.148, Video 15.9).[406,407] Penetrating ulcers appear as crater-like outpouchings of the aortic wall with extensive aortic atherosclerosis. Although the luminal surface of the aorta may appear smooth in some patients, generally there are protruding fibrotic or calcific plaques representing complex atherosclerotic disease. These lesions are associated with a variable degree of IMH formation, either limited or extensive aortic dissection, aneurysmal dilation, pseudoaneurysm, or aortic rupture. The limited aortic dissection secondary to these ulcers are characterized by (1) a markedly thickened dissection flap (0.8 to 1.1 cm), which is calcified, irregular, nonoscillating, or of low motility; (2) a limited longitudinal extension (less than 10 cm); and (3) a true lumen similar to or larger than the false lumen.[407]

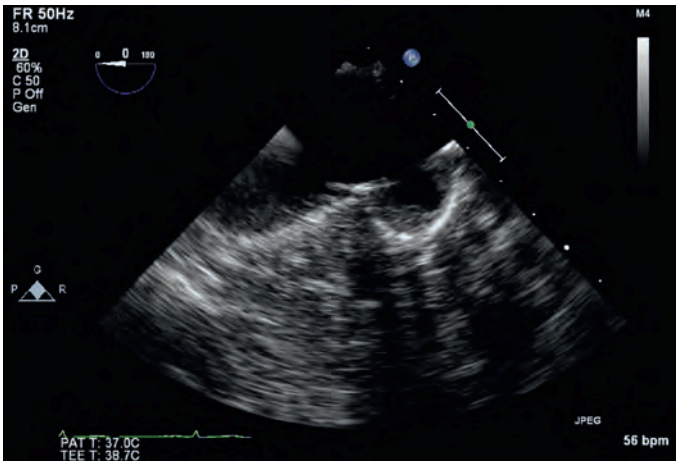


Fig. 15.148 Penetrating aortic ulcer. A penetrating aortic ulcer is seen on the inferior aspect of the aortic arch. It is characterized by an outpouching of the aortic wall, which is filled with thrombus.

Transesophageal Echocardiography During Intraaortic Balloon Pump Placement

The intraaortic balloon pump (IABP) is a catheter-based balloon, which is placed in the descending thoracic aorta distal to the left subclavian artery. The helium-filled balloon inflates during diastole and deflates during systole to increase coronary and visceral blood flow and decrease systemic vascular resistance and ventricular preload. It is important that the distal tip of the catheter does not occlude the arch branch arteries with resultant upper extremity or cerebral ischemia. Ideally, the catheter should be positioned 1 to 2 cm distal to the left subclavian artery.[408] Placement of the IABP farther from the left subclavian artery increases the risk of occlusion of the aortic abdominal branches with resultant visceral ischemia. Whereas fluoroscopy is the standard modality for the position of the IABP, TEE is the more convenient modality during the perioperative period[409] (see Chapters 28 and 36).

Prior to placement of an IABP, contraindications to its placement should be ruled out. The severity of AI should be evaluated carefully. The descending thoracic aorta should be examined for severe atherosclerotic disease that may become dislodged with balloon placement. Furthermore, although reports of IABP placement in the presence of

aortic dissection exist,[410] the presence of an aortic dissection should be considered as a contraindication to balloon placement.

After cannulation of the femoral artery, a wire is advanced into the descending aorta. It may be identified as a thin echogenic structure. Whereas a short-axis descending aortic view accurately shows the presence or absence of the wire, a long-axis image more accurately demonstrates the location of the wire. Aggressive advancement of the wire into the arch branches or the ascending aorta should be avoided. Once the wire is accurately seen in the descending aorta, the IABP may be passed over the wire into the descending aorta (Fig. 15.149, Video 15.10). Since it is difficult to differentiate the balloon from the wire, the wire should be removed before confirmation of the final IABP placement. As discussed earlier, the distal tip of the balloon should be positioned 1 to 2 cm distal to the left subclavian artery. This distance can be measured by identifying the tip of the IABP using the long-axis descending aortic view and withdrawing the TEE probe until the transition to the upper esophageal aortic arch short-axis view with the left subclavian artery is visualized.[403] The distance may be judged based on the distance the TEE probe is withdrawn. Alternatively, the IABP tip may be positioned at the lesser curvature of the aortic arch.[411] In a descending thoracic aortic short-axis view, the IABP is visualized. As the TEE probe is withdrawn, the tip of the IABP should be visualized and then disappear as the aortic arch becomes visible on the patient's right side. In the descending aortic long-axis view, the position of the distal tip may be compared to the level of the lesser curvature by turning the probe to the patient's right side. After placement, the inflating and deflating balloon may be visualized. Because there is a 0.5% incidence of iatrogenic aortic dissection after IABP placement, the descending aorta and aortic arch should be reexamined.[412]

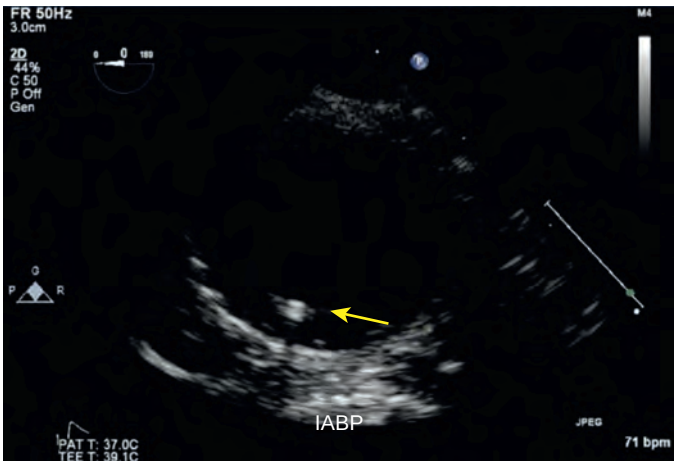


Fig. 15.149 Positioning of an intraaortic balloon pump *(IABP; arrow)*.

Perioperative Transesophageal Echocardiography During Endovascular Thoracic Aortic Stenting

TEE has distinct advantages over perioperative angiography during endovascular thoracic aortic repair.[413] (see Chapters 23 and 48). TEE may provide exact vessel and lesion sizing and localization, which is difficult to obtain during single plane angiography. With the esophagus in close proximity to the aorta, TEE is an excellent tool for diagnosing aortic disease. TEE can provide instantaneous views of the aorta, as well as location of guidewires and endografts prior to deployment in relation to the normal and diseased thoracic aorta. This is particularly important during repair of type B aortic dissections, during which it is critical to ensure that the wire and delivery device remain in the true lumen. The stent-graft delivery system may be distinguished from the guidewire by differences in thickness and echogenicity (Fig. 15.150, Video 15.11). Similarly the stent-graft may be distinguished from the stent-graft delivery system by its unique echogenic pattern and shadow that is cast by the metallic stent. By distinguishing the stent-graft from the delivery system, TEE can be used to ensure that the endograft bridges the diseased aortic segment. Although not imaged in all patients, large intercostal arteries have been imaged, thus avoiding inadvertent obstruction by the aortic stent-graft; however, consistent visualization of intercostal arteries may not be ensured in all patients. Although TEE can visualize the undeployed stent-graft in relation to the aortic disease, there is significant interference by the TEE probe during fluoroscopy; therefore, TEE can only be used between fluoroscopic examinations. After stent-graft placement, exclusion of flow from the aorta into the aneurysm usually can be confirmed with CFD imaging.

Endoleak is the continued pressurization of an aneurysmal sac after endovascular exclusion. This may be a result of a leak at the graft ends (type 1), sac filling via branch arteries (type 2), leak through the graft material secondary to mechanical failure (type 3), an intentionally porous graft (type 4), or endotension (type 5). An example of an endoleak between graft components is illustrated in Fig. 15.151 and Video 15.12. The reported sensitivity and specificity of TEE assessment of endoleak is 100%, which was identical to postoperative CT or angiography.[414] In a series of 25 patients undergoing descending aortic endovascular repair, 8 patients had endoleaks; all of these endoleaks were detected by perioperative TEE, but only 2 of them were detected by angiography.[415] These detected leaks were at the graft ends or between segments of the graft. TEE-diagnosed exclusion was predictive

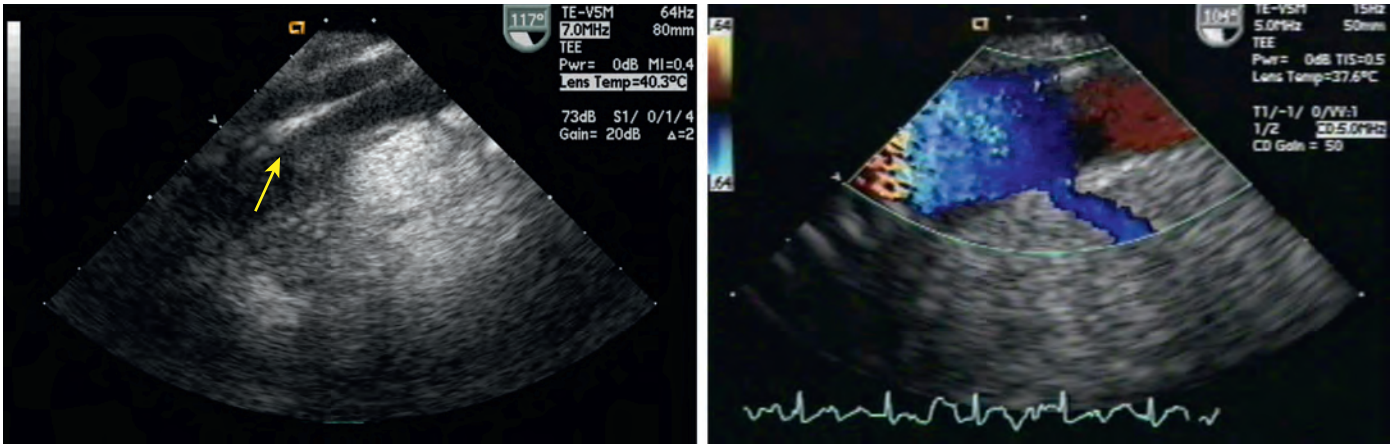


Fig. 15.150 Endovascular stent-graft delivery system. *Left,* An endovascular stent-graft *(arrow)* is seen being advanced into the descending thoracic aorta through a pseudoaneurysm. *Right,* After deployment, there is excellent flow exclusion of the pseudoaneurysm with a patent intercostal artery.

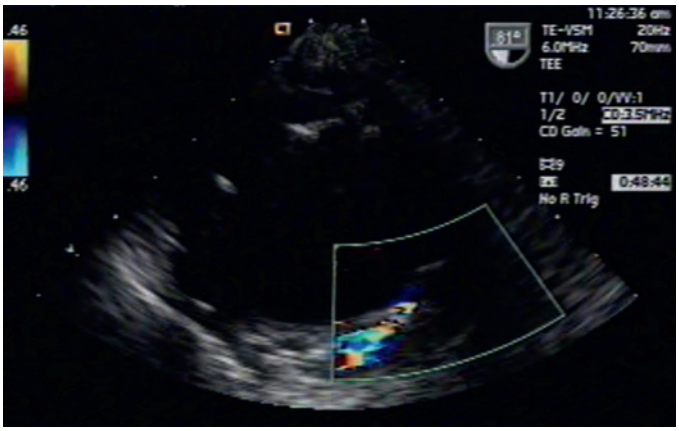


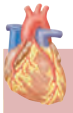
Fig. 15.151 Endoleak. Upper esophageal short-axis aortic arch. An endoleak is demonstrated between two portions of an aortic endograft that was not visualized by angiography. Color-flow Doppler demonstrates flow from the endograft lumen into the aneurysm.

of mid-term aneurysm regression.[414] In a separate study of 9 patients with thoracic aortic aneurysms and 2 with chronic type B dissections, both aortography and TEE detected type 1 endoleak after deployment in 9 of the 11 patients.[416] The use of this technique may be useful for the evaluation of perigraft leakage and thrombus formation, in addition to decreasing the need for intravenous contrast administration.

Blunt Thoracic Aortic Injury

Blunt aortic injury (BAI) occurs as a result of rapid deceleration at an interface of fixed and mobile aortic segments, since they have the greatest exposure to the sheer and hydrostatic forces associated with the trauma.[417] Motor vehicle accidents account for 75% of cases of BAI; other causes include falls from heights, crush injuries, explosions, and direct blows to the chest. The most common location for this injury is the aortic isthmus just distal to the left subclavian artery, followed by the supravalvular portion of the ascending aorta. This injury is usually a damage of the aortic intima with extension to the adventitia. The 2015 guidelines describe a variety of aortic lesions that can result from BAI:[378]

1. Subadventitial aortic rupture involving the intima and media with incomplete circumferential extension. In this most frequent lesion encountered by imagers, there is a discrete tear involving the intima and underlying media. The disrupted aortic wall (intima and media) usually protrudes into the aortic lumen and, through the disrupted wall, the aortic lumen communicates with a cavity (saccular false aneurysm) whose wall is composed only of adventitia. The inner surface of the aorta shows an abrupt discontinuation, and the outer contour is deformed by the false aneurysm. The protrusion of the torn aortic wall into the aortic lumen may produce "stenosis" with flow acceleration and a gradient (pseudocoarctation).
2. Subadventitial aortic rupture involving the intima and media with complete circumferential extension (aortic transection). This lesion results in a fusiform pseudoaneurysm. Because the intima and media tear is circumferential, protrusion into the lumen does not occur. The inner surface of the aneurysm is smooth, formed solely by adventitia. As a consequence, the aortic wall is extremely thin and fragile. Imaging typically reveals an abrupt change in aortic diameter.
3. IMH. Accumulation of blood within the media may result from blunt aortic trauma secondary to disruption of the vasa vasorum or the development of small intimal tears. The aortic wall shows a localized, usually crescent-shaped thickening (usually >5 mm). The inner aortic surface is smooth, the aortic lumen is partially reduced, and the outer aortic contour is unaltered. There is no flap and no flow signals within the hematoma.



BOX 15.10 TRANSESOPHAGEAL ECHOCARDIOGRAPHIC CHARACTERISTICS OF BLUNT AORTIC INJURIES

- Dilatation in the region of the isthmus
- Abnormal aortic contour
- Intraluminal medial flap
- Pseudoaneurysm
- Crescentic or circumferential thickening of the aortic wall (intramural hematoma)
- Mobile linear echodensities attached to the aortic wall consistent with an intimal tear or a thrombus

From Goldstein SA, Evangelista A, Abbara S, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2015;28:119–182.

4. Traumatic aortic dissection. The elastic and collagen fibers of the aortic wall are remarkably strong radially but may be relatively easily split when exposed to transaxial stress. As is true of spontaneous aortic dissection, aortic trauma may produce separation of the media. This lesion is uncommon and can mimic spontaneous aortic dissection but has significant differences. It is usually localized to the area of the aortic injury and does not propagate distally toward the iliac arteries. It typically fails to create two channels and may have a direction transverse to the longitudinal axis of the aorta. Consequently, the resulting "flap" is usually thicker and less mobile than the classical intimal flap. The aorta is usually symmetrically enlarged.
5. Lesion of the aortic branches. Partial or total avulsion, pseudoaneurysm, dissection, and thrombosis may occur as isolated injuries to branch arteries in association with BAI.
6. Superficial lesions involving only the intima. With improvements in imaging technology, ever more subtle lesions are being identified. The term *minimal aortic injury* is often used to describe a lesion that carries a relatively low risk for rupture. Ten percent of patients with BAIs diagnosed through use of high-resolution techniques have minimal aortic injuries. Although most of these intimal injuries heal spontaneously, and, hence, may not require surgical repair, the natural history of these injuries is unknown. Frank tears produced by BAI, but limited to the intima, appear as thin, linear, mobile intraluminal projections from the aortic wall. No alterations of the diameter or external contour of the aorta are present. Thrombi, often mobile, may be present within the aortic lumen, presumably in areas of exposed collagen. Minimal aortic injury from an imaging standpoint is an injury with the intimal flap less than10 mm, accompanied by minimal or no periaortic mediastinal hematoma.

TEE is considered a second-line modality for the evaluation of BAI. The aortic isthmus is usually well visualized. TEE may be useful following small intimal injuries that are not well defined by CT or aortography. As discussed earlier, however, the distal arch and the arch vessels are not easily visualized. The modality is operator dependent and may not be safe in patients with unstable cervical, oropharyngeal, or esophageal injuries. The TEE findings in patients with BAI are summarized in Box 15.10. There are similar findings in patients with spontaneous aortic dissections.[378]

Pericardial Disease

The pericardium is a thin (1 to 2 mm) two-layered structure reflecting from a serosal visceral layer to a fibrous parietal layer. Superiorly, it is approximately 1 to 2 cm distal to the origin of the great vessels and around the pulmonary veins, and inferiorly it is attached to the central tendon of the diaphragm.[418,419] Anteriorly, the pericardium attaches to the sternum by sternopericardial ligaments. The fibrous parietal layer

TABLE 15.26 Strengths and Limitations of Modalities in the Evaluation of Pericardial Disease

	Echocardiography	*Cardiac CT*	*CMR*
Strengths	• First-line imaging for diagnosis and follow-up • Widely available • Low cost • Safe • May be performed at the bedside	• Need for better anatomic description • Evaluation of extracardiac disease • Preoperative planning • Detection of pericardial calcification	• Need for better anatomic description • Superior tissue characterization
Limitations	• Limited windows with narrow field of view • Technical difficulties with obesity, obstructive lung disease • Operator dependent • Low signal-to-noise ratio of the pericardium • Limited tissue characterization	• Use of ionizing radiation • Use of iodinated contrast • Functional studies only possible with retrospectively gated studies • Difficulties with tachyarrhythmias or unstable rhythm • Need for breath-hold • Hemodynamically stable patients only	• Time consuming, high cost • Preferably with stable heart rhythms • Contraindicated with pacemakers or defibrillators • Lung tissue less well visualized • Calcification less well visualized • Use of gadolinium contrast contraindicated with advanced renal dysfunction • Use of some breath-hold sequences • Hemodynamically stable patients only

CMR, Cardiac magnetic resonance (imaging); *CT,* computed tomography.
Modified from Spodick D. Pericardial diseases. In: Braudwald E, Zipes D, Libby P, eds. *Heart Disease: A Textbook of Cardiovascular Medicine.* 6th ed. Philadelphia: Saunders; 2001:1823–1876.

TABLE 15.27 Causes of Pericardial Effusions

Idiopathic	*Infections*	*Inflammatory*	*Postmyocardial Infarction*	*Systemic Disease*	*Malignancy*	*Miscellaneous*
Acute	Viral	Lupus	Dressler syndrome	Uremia	Direct	Posttrauma
Chronic	Bacterial Fungal	Rheumatoid arthritis	Acute after transmural infarct	Cirrhosis Hypothyroidism	Lymphatic obstruction	Postsurgical CHF

is composed of collagen fibers with interspersed short elastic fibrils. The serosal layer, also known as the epicardium, consists of a single layer of mesothelium. Significant amounts of epicardial fat may be found between the visceral pericardium and myocardium and is most abundant along the atrioventricular and interventricular grooves, as well as over the right ventricle.

Under normal circumstances less than 50 mL of fluid is contained within the pericardial sack allowing for practically frictionless motion of the heart during the cardiac cycle.[420] The pericardial fluid is an ultrafiltrate of plasma from the epicardial and parietal capillaries.[421] It also contains prostaglandins secreted by the mesothelial and endothelial cells that modulate cardiac reflexes and coronary tone.[422] In addition, the pericardium limits short-term chamber distention and helps to maintain ventricular chamber geometry.

As discussed earlier, the parietal layer of the pericardium is rich in collagen fibers making it a low compliance structure confining the volume of the four cardiac chambers. The influence of the normal pericardial confinement contributes more than 50% of the normal diastolic pressure of the right-sided structures.[421] This low compliance system results in a ventricular interdependency during systole, where a volume increase of one chamber requires a reduction of volume within another chamber. With normal quantities of pericardial fluid (and hence a normal pericardial pressure), this interdependent ventricular filling is not clinically significant. This interdependence becomes more significant with increases in pericardial fluid volume and serves as an important diagnostic feature.[423]

Although both cardiac CT and cardiac MRI may be used to evaluate pericardial disease, echocardiography is still considered the first-line diagnostic modality.[424] As described in Table 15.26, the major advantages of echocardiography include its wide availability, assessment of both anatomic and physiologic features, low cost, safety, and portability allowing its use at the bedside with hemodynamically unstable patients.[421] With these advantages, TEE is an excellent modality for the screening and follow-up of pericardial effusions and cardiac tamponade and for assessment of constrictive pericarditis.

Pericardial diseases can be grouped into a variety of disease entities, including pericardial effusion and tamponade, acute and recurrent pericarditis, constrictive pericarditis, pericardial masses, and congenital anomalies of the pericardium. The etiologic classification of pericardial diseases includes infectious, autoimmune, post-MI, postsurgical, and autoreactive causes.[425]

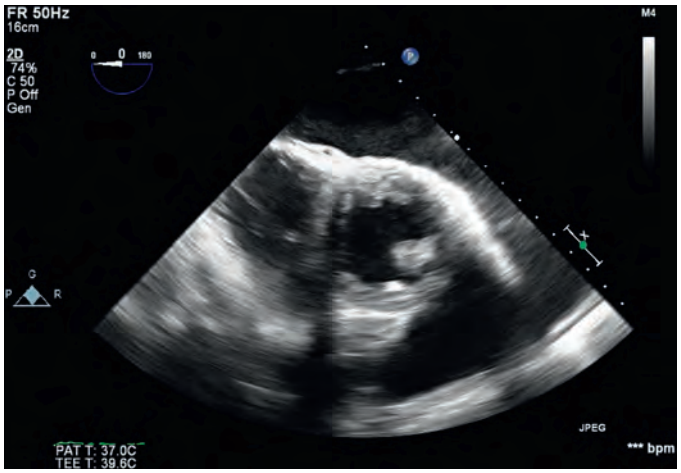


Fig. 15.152 Large pericardial effusion. Transgastric short-axis midpapillary view. There is a large pericardial effusion around the inferior, lateral and anterior aspect of the left ventricle.

Pericardial Effusions

Under normal circumstances, the echocardiographer is unable to visualize the fluid film between the two layers. Under disease conditions, fluid accumulation can occur resulting in the development of a pericardial effusion (Fig. 15.152 and Video 15.13) Typical causes leading to pericardial effusions are listed in Table 15.27. These effusions may be transudates, exudates, hemopericardium, or pyopericardium. An exudative effusion may show stranding, adhesions, or an uneven distribution. According to the 2013 guidelines, small effusions are usually defined as 50 to 100 mL, moderate as 100 to 500 mL, and large as more than 500 mL.[421] The size of the effusion correlates poorly with its hemodynamic effect; the rapidity of accumulation has a greater effect on hemodynamics. Pericardial effusions of different origins

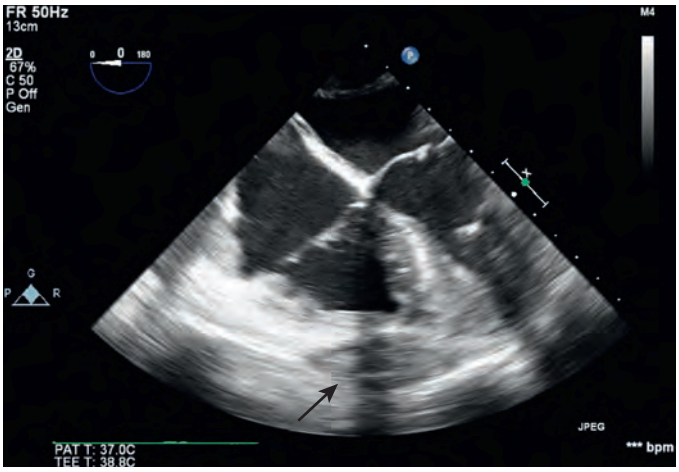


Fig. 15.153 Loculated pericardial effusion. Midesophageal four-chamber view. After cardiac surgery, a pericardial thrombus *(black arrow)* is visualized compressing the lateral and inferior free wall of the right ventricle.

TABLE 15.28 Severity of Pericardial Effusions

Severity	*Width of Effusion*
Trivial	Only seen during systole
Mild	<10 mm
Moderate	10–20 mm
Large	>20 mm
Very large	>25 mm

Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr.* 2013;26:965–1012.e1015.

have characteristic sizes and progression. Idiopathic or viral infections may result in small pericardial effusions, while large effusions may be associated with hypothyroidism, tuberculosis, or neoplasms. Rapid pericardial blood accumulation may be from blunt trauma, ascending aortic dissection, or cardiac rupture (either secondary to MI or iatrogenic, such as during invasive cardiac procedures).[426] Free effusions are more typically seen in medical conditions, whereas loculated effusions are seen after surgery or inflammatory processes (Fig. 15.153, Video 15.14). In many patients, however, the origin of pericardial effusions must be classified as idiopathic.

A qualitative grading system is often used to characterize the quantity of the pericardial effusion present. This qualitative grading uses the diameter of the effusion in two dimensions. The 2013 guidelines are summarized in Table 15.28. Trivial effusions are only seen during systole, mild effusions are less than 1 cm, and large effusions are greater than 2 cm in diameter. Additionally, the effusion can either encompass the entire heart (free) or be loculated. TEE has been demonstrated to be a more sensitive modality for the detection of loculated effusions or intrapericardial clots compared with TTE.[427] It is important to define the anatomic relationship of the effusion. A loculated effusion found primarily at the inferior aspect of the heart can lead to inadvertent injury of the right ventricle if a subxiphoid approach is chosen for drainage.

It can be difficult to differentiate a left-sided pleural effusion from a pericardial effusion. A left pleural effusion may be identified as fluid between the descending aorta and the heart. A good clue is to identify the descending thoracic aorta; since the reflection of the pericardium is typically anterior to the descending thoracic aorta, pericardial effusions are generally seen anterior and to the right of the aorta. A dilated thoracic aorta, giant atrium or atrial appendage, or an enlarged coronary sinus must be considered as part of the differential diagnosis.[428]

Cardiac Tamponade

Cardiac tamponade and pericardial effusion are not synonymous. A pericardial effusion is an anatomic diagnosis that may or may not lead to hemodynamic alterations. Cardiac tamponade is a pathophysiologic diagnosis.

The fibrous pericardium constrains the cardiac chambers. This fibrous constriction results in a nonlinear intrapericardial pressure-volume relationship. The normal pericardium has a 150- to 250-mL capacitance reserve, where initial increases in pericardial sac volume produce negligible increases in intrapericardial pressure.[428,429] At low volumes, the curve is flat with minor increases in pericardial pressure. At a given inflection point, the curve becomes steeper; further small increases in fluid result in a significant increase in pericardial pressure. Acutely, small increases in pericardial fluid may result in clinically significant cardiac tamponade. In contrast, if pericardial fluid accumulation is gradual, the pericardium may stretch, increasing the compliance and shifting this pressure-volume curve to the right. This slow accumulation of fluid can go undetected for long periods of time resulting in volumes exceeding one liter. However, once the limits of pericardial stretch are exceeded, the rise in pericardial pressures will limit diastolic filling.[429]

Intrapericardial pressure is usually similar to pleural pressure; during spontaneous ventilation, it may be −6 mm Hg during end-inspiration and −3 mm Hg during end-expiration.[423] This decrease in pericardial pressure during inspiration increases the transmural pressure on the right side of the heart, thus increasing RV inflow (ie, transtricuspid flow). There is a slight decrease in LV inflow (ie, transmitral flow) due to increased aortic transmitral pressures and delayed pulmonary transit. The opposite changes occur with positive-pressure ventilation.

As the pressure increases within the pericardial sac, the total blood volume within the heart becomes limited, leading to an exaggerated response to the respiratory cycle. Because of the low compliance of the pericardial sac, any increases in ventricular size result in a significant increase in pericardial pressure limiting contralateral ventricular filling: increases in RV filling limits LV filling and vice versa. Under normal circumstances respiratory variation of arterial pressure is less than 10 mm Hg. *Pulsus paradoxus* is a more than 10 mm Hg change in systolic arterial pressure with respiration. If the intrapericardial fluid is not relieved, an equalization will occur among diastolic pressures within the heart. With increasing pericardial pressures, LA and RA pressures must increase to maintain ventricular filling. When compensatory mechanisms are unable to support preload with higher filling pressures, decompensation occurs (see Chapters 24 and 38).

Echocardiographically, cardiac tamponade may be identified as RA and RV collapse during the relaxation phase. This collapse occurs when the intrapericardial pressure exceeds the intrachamber pressure. Maximum RA collapse occurs during early ventricular systole after discharging the atrial kick near the QRS complex, when the RA pressure is lowest. RV collapse is greatest during early ventricular relaxation after the T wave. The severity and duration of this collapse increase with further increases in the pericardial pressure. RA collapse duration that exceeds one-third of the cardiac cycle is nearly 100% sensitive and specific for clinical cardiac tamponade.[430] Since the right ventricle is thicker than the RA, a higher pericardial pressure is required for RV diastolic collapse; RV collapse is a more specific but less sensitive sign of pericardial tamponade.[431] Hypovolemia may result in chamber collapse without tamponade, and significant RV hypertrophy with decreased compliance or pulmonary hypertension may prevent chamber collapse in the presence of high pericardial pressures.[418] A loculated or isolated effusion may also result in local tamponade. This local tamponade is most commonly seen after cardiac surgery or MI. In addition to the presence of a pericardial effusion, other signs of tamponade include a dilated inferior vena cava, hepatic venous fullness with systolic blunting of hepatic blood flow velocities, excessive ventricular septal movement with respiration, and a small left ventricle. An inferior vena cava greater than 2.1 cm with less than a 50% reduction

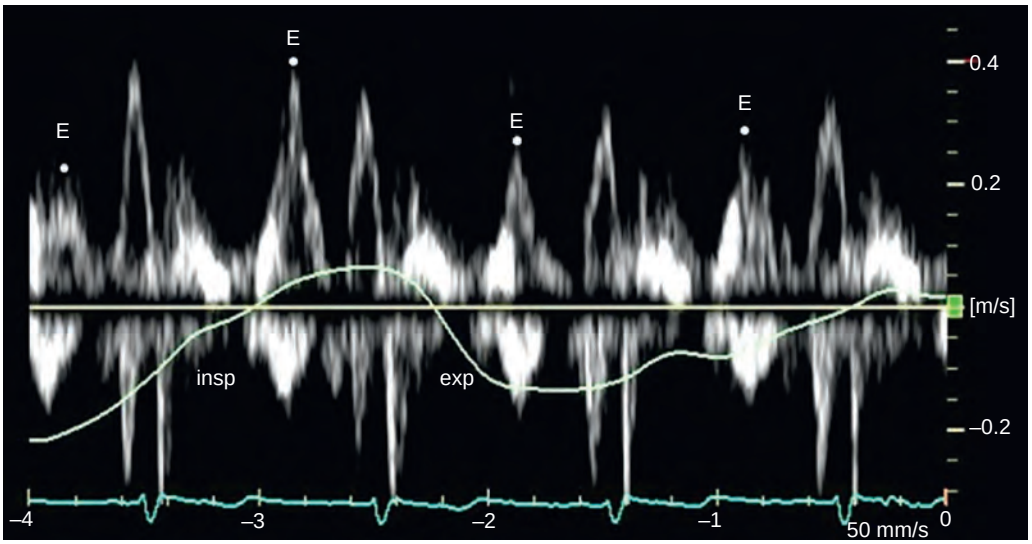


Fig. 15.154 Doppler spectrum of through tricuspid valve during spontaneous respiration during cardiac tamponade. Since transthoracic imaging is used, flows are in the opposite direction compared with transesophageal echocardiography. There is increased E-wave velocity during inspiration *(insp)* compared with the lower velocity E waves during expiration *(exp)*. (*From Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease.* J Am Soc Echocardiogr. *2013;26:965–1012.e1015.)*

in diameter during inspiration is indicative of an elevation in systemic venous pressure that occurs with increases in pericardial pressure.[432]

More subtle signs of pericardial tamponade can be detected with Doppler modalities (Fig. 15.154). As discussed earlier, with cardiac tamponade, filling of one side of the heart will only occur at the expense of the other side. This phenomenon may be demonstrated by significant respiratory variation of transmitral or tricuspid inflow velocities. Respiratory variation should be calculated by:

(E wave expiration – E wave inspiration)/E wave expiration

Normally, the respiratory variation is 5% with spontaneous ventilation. The 2013 guidelines from the American Society of Echocardiography suggest that a respiratory variation of 30% or more in peak early transmitral flow or a 60% or more variation in transtricuspid diastolic valve flow velocity is diagnostic of cardiac tamponade.[421] This measurement can be achieved by positioning the pulse wave gate just at the leaflet tips of the MV or TV. Although a large pericardial effusion is associated frequently with pericardial tamponade, other factors can be responsible for respiratory variation in transvalvular flow velocities (eg, high airway pressures, hematoma, hypovolemia); the diagnosis of pericardial tamponade should not be made in the presence of respiratory variation without other supporting evidence of tamponade.

In addition to Doppler changes in transtricuspid and transmitral flow, associated changes with hepatic venous blood flow velocities can be found. Normally, hepatic systolic venous flow is approximately 50 cm/s and is greater than hepatic diastolic venous flow.[433] With inhibition of filling, systolic venous flow decreases to 20 to 40 cm/s.[421] With moderate tamponade, diastolic flow is nearly absent but still may display respiratory variation. With severe tamponade, diastolic flow disappears completely. When no hepatic flow is seen except during inspiration (with spontaneous ventilation) or expiration (during controlled ventilation), cardiac arrest is imminent.

Pericarditis

Echocardiographic signs of pericarditis are nonspecific. Many patients with acute pericarditis have normal echocardiographic examinations.[421] More commonly, patients may have pericardial effusions that are small, large, generalized, or localized. In some patients, this pericardial effusion may result in tamponade. Intrapericardial fibrinous strands suggest either an inflammatory cause or clotted blood, while intrapericardial masses may be seen with primary or secondary pericardial tumors or with inflammatory processes. Approximately 5% of patients with acute pericarditis will have RWMAs.

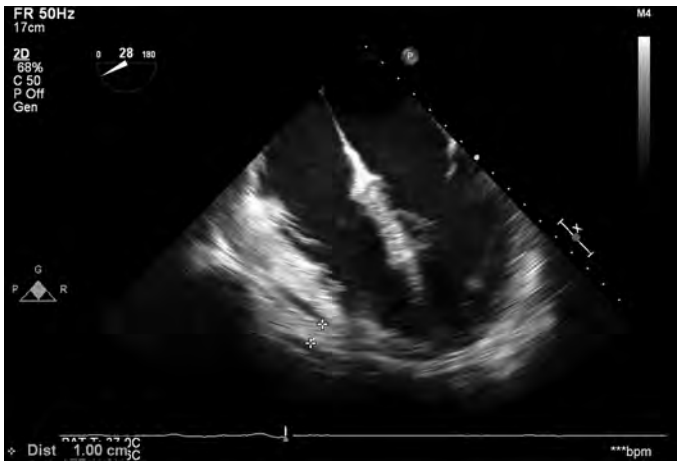


Fig. 15.155 Constrictive pericarditis. Midesophageal four-chamber view. A thickened pericardium is indicated between the curser crosshairs, resulting in constrictive pericarditis.

Constrictive Pericarditis

Constrictive pericarditis is defined as a chronic fibrous thickening and calcification of the pericardium (Fig. 15.155, Video 15.15). This thickening results in a decrease in pericardial compliance, which limits ventricular filling with raised filling pressures.[434] Although commonly idiopathic, other causes of constrictive pericarditis in developed countries include previous cardiac surgery, mediastinal radiation, and hemorrhagic pericarditis. In developing countries, scarring from tuberculous pericarditis is more common. Myocardial encasement by the pericardium isolates the heart from the normal intrathoracic pressure changes during respiration. This ventricular isolation results in both the dissociation of intracardiac and intrathoracic pressures

TABLE 15.29 Differentiation of Constrictive Pericarditis From Restrictive Cardiomyopathy

Variable	*Restriction*	*Constriction*
Septal motion	Normal	Respiratory shift
Mitral E/A ratio	>1.5	>1.5
Mitral DT (ms)	<160	<160
Mitral inflow respiratory variation	Absent	Usually present
Hepatic vein Doppler	Inspiratory diastolic flow reversal	Expiratory diastolic flow reversal
Mitral septal annular e′	Usually <7 cm/s	Usually >7 cm/s
Mitral lateral annular e′	Higher than septal e′	Lower than septal e′
Ventricular septal strain	Reduced	Usually normal

Adapted from Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009;22:107–133.

during respiration and the interdependence of ventricular filling.[435,436] According to Troughton and coworkers, "on inspiration, intrathoracic pressure decreases, but is not transmitted to the left atrium. A reduced pulmonary vein to LA pressure gradient produces a fall in flow into the left atrium, and across the MV into the left ventricle. Decreased LV filling during diastole allows more room for RV filling, which leads to a septal shift and an increase in right-sided inflow. The exact opposite sequence occurs in expiration."[418] Similar to cardiac tamponade physiology, constrictive pericarditis results in an exaggerated respiratory variation during ventricular inflow in diastole. Unlike cardiac tamponade, early diastolic filling in constrictive pericarditis is more rapid than normal, because the restraining effects of the pericardium do not occur until middiastole, after which little ventricular filling is seen, even with atrial contraction. The comparison of cardiac tamponade and constrictive pericarditis are summarized in Table 15.29.[376] Other characteristic features include pericardial thickening, myocardial tethering, a septal bounce, and inferior vena cava plethora.[437] Precise measurement of pericardial thickness may be challenging by TTE; however, measurement by TEE correlates strongly with CT measurements.[398] Transmitral flow patterns are similar to those seen with restrictive cardiomyopathy: high velocity E waves with very short duration times are observed with a reduced A-wave velocity. In contrast to restrictive disease, there is usually a prominent e′ velocity (ie, tissue Doppler velocity during early diastole), and the color M-mode propagation velocity during early systole is either normal or increased. In a study of 122 patients, 89% of patients with surgically proven constrictive pericarditis had normal e′ velocities, and 73% of patients with restrictive disease had reduced e′ velocities.[438] Because of the tethering of the lateral mitral annulus to the pericardium, the lateral mitral annular e′ is usually lower than e′ from the medial annulus ("annulus reversus") in patients with constrictive pericarditis. The echocardiographic differentiation between constrictive pericardial physiology and restrictive disease is summarized in Table 15.30.

Pericardial Cysts and Masses

Pericardial cysts may be congenital, inflammatory, or echinococcal.[425] Congenital pericardial cysts can be unilocular or multilocular with diameters from 1 to 5 cm. Inflammatory cysts may be pseudocysts or alternatively encapsulated or loculated pericardial effusions. Causes of these inflammatory cysts include rheumatic pericarditis, bacterial infection, trauma, or cardiac surgery. Finally, echinococcal cysts may be caused by ruptured hydatid cysts from the liver or lung. In contrast, pericardial diverticula are outpouchings or herniations through a pericardial defect. As opposed to pericardial cysts, these diverticula may rapidly change in size within a short period of time. As opposed to cysts, diverticula communicate with the pericardial sac. On echocardiograms they appear as a distinct echogenic space adjacent to the pericardium. They are commonly adjacent to and compressing the right atrium.

TABLE 15.30 Comparison of Constrictive Pericarditis and Cardiac Tamponade

Cardiac Tamponade	*Constrictive Pericarditis*
Fixed cardiac volume limiting cardiac filling (respiratory variation of ventricular filling)	Fixed cardiac volume limiting cardiac filling (respiratory variation of ventricular filling)
Ventricular interdependence (septal shift)	Ventricular interdependence (septal shift)
Elevated and equalized central venous, pulmonary venous, and ventricular diastolic pressures	Elevated and equalized central venous, pulmonary venous, and ventricular diastolic pressures
Prominent systolic filling (attenuated Y descent)	Prominent early diastolic filling (exaggerated Y descent)
Inspiratory Y in intrathoracic pressure not transmitted to heart (dissociation of intracardiac and intrathoracic pressures)	Inspiratory Y in intrathoracic pressure not transmitted to heart (dissociation of intracardiac and intrathoracic pressures)
Pulsus paradoxus common	Pulsus paradoxus uncommon
Kussmaul sign not present	Kussmaul sign

Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr.* 2013;26:965–1012.e1015.

Pericardial tumors can be benign or malignant. Primary pericardial tumors are significantly less common than metastatic tumors.[425] The most common primary benign tumors of the pericardium are teratoma, lipoma, fibroma, hemangioma, and lymphangioma. These tumors may be small or very large, causing compression, and may be found either in the parietal or the epicardial pericardium. The most common malignant primary tumor of the pericardium is mesothelioma, followed by angiosarcoma, whereas the most common source of the metastatic tumors are lung, breast, malignant melanomas, lymphomas, and leukemia. These malignancies may cause either small or large serosanguineous pericardial effusions with resultant pericardial tamponade (see Chapter 24).

Although pericardial masses may be easily appreciated by echocardiography, other modalities are generally used for further tissue classification and delineation. Generally they appear as echodense masses on the pericardium. They may either be nodules or result in general pericardial thickening. Malignant tumors tend to have a diffuse growth pattern. The masses can be homo- or heterogeneous, cystic, or have a more complex septated pattern.

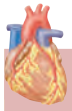
Evaluation of Cardiac Masses

A cardiac mass is defined as an abnormal structure within or immediately adjacent to the heart. Cardiac masses are typically divided into three categories: thrombus, vegetation, and tumor. Identification of an unfamiliar structure during echocardiography should lead to further analysis and differentiation from normal anatomy. In addition, the presence of intracardiac catheters (central venous or PA catheters, dialysis catheters) and cardiac pacing wires need to be considered.

Unfamiliar structures should be evaluated for location, anatomic characteristics (shape, mobility), spatial relationship with other known cardiac structures throughout the entire cardiac cycle, and impact on blood flow dynamics. All masses should be evaluated in two or more imaging planes with optimized frequency and depth to avoid the possibility of misdiagnosis of an artifact.[439] Intracardiac structures that frequently lead to incorrect diagnosis of intracardiac masses can be found in Box 15.11.

Thrombus

When a cardiac mass is identified, it is frequently a thrombus or vegetation.[440] Intracardiac thrombus formation occurs when there is low velocity or stasis of blood. Conditions predisposing patients to thrombus formation in the left atrium include LA enlargement, MS, and atrial fibrillation (Video 15.16). LA enlargement secondary to severe



BOX 15.11 NORMAL ANATOMIC STRUCTURES AND DEVICES THAT ARE OFTEN CONFUSED FOR INTRACARDIAC MASSES

Right Atrium
Pacer wires, catheters, Chiari network, crista terminalis, eustachian valve, right atrial appendage, lipomatous hypertrophy of the intraatrial septum

Left Atrium
Left atrial appendage variants, pectinate muscles, Coumadin ridge (raphe between the left atrial appendage and the left superior pulmonary vein)

Right Ventricle
Pacer wires, pulmonary artery catheters, trabeculae, moderator band

Left Ventricle
False tendons, papillary muscles, calcified mitral valve chordae

Aortic Valve
Nodules of Arantius, Lambl excrescences

MR does not predispose patients to thrombus formation. The turbulent blood flow of the regurgitant jet and subsequent lack of blood stasis make thrombus formation unlikely. LA thrombi are frequently homogenous, well-demarcated, and typically located in the LAA; they must be distinguished from pectinate muscles. Particular attention should be given to patients with spontaneous echo contrast in the left atrium. Pulsed-wave Doppler should be placed 1 cm into the LAA to determine blood velocity. A velocity less than 40 cm/s indicates low flow and increased likelihood of thrombus formation. Three-dimensional TEE and biplane evaluation greatly enhances imaging of the LAA and has been shown to aid in the diagnosis of thrombus.

Thrombus formation in the left ventricle is typically seen in the presence of severe global systolic dysfunction, LV aneurysms, and areas of significant RWMAs, particularly in the apical regions. Although apical thrombi are seen best using TTE, detection using TEE is possible if foreshortening of the left ventricle is avoided. A thrombus in the left ventricle may be sessile, smooth walled, and challenging to differentiate from the myocardium, or may be large, irregular, and mobile (Video 15.17). The use of left-sided contrast agents can aid in detection of a LV thrombus if suspicions are high. Just as with artifacts, evaluation of a thrombus in multiple imaging views and throughout the cardiac cycle is necessary to ensure correct diagnosis.

Thrombus formation in the right atrium or right ventricle is rare and is frequently associated with indwelling catheters or pacing wires. If no associated foreign material is present, the thrombus likely originated in the systemic venous system and is in transit to the PA.

Vegetations

Vegetations are highly mobile, irregularly shaped masses that occur on a valve or subvalvular apparatus. They can be infectious resulting in bacterial or fungal endocarditis, or noninfectious. They are frequently found on the upstream (low-pressure) side of valves in the path of regurgitant jets. The echogenicity resembles soft tissue or myocardium in contrast to the bright connective tissue appearance of the valve or chordae (Video 15.18). If a catheter or pacing wire is present, vegetations may be adherent to the foreign material. In this instance, it would be challenging to distinguish from a thrombus using echocardiography.

Intracardiac Tumors

Although many intracardiac tumors have characteristic appearances, the goal of using echocardiography in the evaluation is not to gain pathologic diagnoses but rather to evaluate the location, anatomic extent, and physiologic consequences of the tumor (see Chapter 24).

Primary Cardiac Tumors

Primary cardiac tumors are rare, occurring about 20 times less frequently than nonprimary cardiac tumors.[440] Pathologically, 75% of these tumors are benign. The majority of benign cardiac tumors are myxomas, which represent more than 85% of the cardiac masses that are surgically excised. Myxomas are typically single, pedunculated, and smooth-walled in appearance, but occasionally they have an irregular, grape cluster appearance (see Fig. 24-3, Video 15.19). They often have inhomogenous echogenicity and can have areas of calcification. More than 75% of myxomas arise from the LA side of the IAS. Other sites of origination include the RA and, infrequently, the right ventricle or left ventricle. Although benign, these tumors can be quite large and result in obstruction to LV filling if they prolapse across the MV in diastole.

Papillary fibroelastomas are the second most common type of benign intracardiac tumor and are typically associated with cardiac valves. Often mistaken for valvular vegetations, papillary fibroelastomas arise from native valve tissue. These tumors are often less than 1 cm in diameter and are highly mobile. Typically they are located on the mitral and AVs; however, they can be seen on the right-sided heart valves or, rarely, arising from nonvalvular sites.[441] It is controversial as to whether or not large papillary fibroelastomas provide a source of systemic embolization and therefore whether excision or anticoagulation is necessary. The most common benign cardiac tumors in the pediatric population are rhabdomyomas and LV fibromas.

Malignant primary cardiac tumors are far less common than benign ones. The most common malignant primary cardiac tumors in the adult population are angiosarcomas, rhabdomyosarcomas, mesotheliomas, and fibrosarcomas.[442] Malignant tumors are often immobile because of their tendency to infiltrate adjacent cardiac anatomy. Similar to metastatic disease, malignant primary cardiac tumors often cause pericardial effusions.

Nonprimary Cardiac Tumors

Nonprimary tumors consist of four categories: metastases from distant primary tumors (liver, colon), metastases by lymphatic spread (lymphoma), direct invasion of adjacent malignancy (lung, breast), or through direct extension from distant malignancy through the inferior vena cava (renal cell carcinoma). Lung cancer, lymphoma, breast cancer, and leukemia represent the top four sources of metastatic cardiac tumors in adults.[441] Nonprimary tumors affect the pericardium more commonly than the myocardium, causing pericardial effusions that may lead to cardiac tamponade. Myocardial involvement is more common with melanoma or lymphoma.[441]

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Decision Making and Perioperative Transesophageal Echocardiography

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KEY POINTS

1. The first step in decision making is to frame the problem by defining the parameters, priorities, and pertinent criteria.
2. The second step is the directed acquisition of data, "data collection," which includes all pertinent information, regardless of whether it is confirmatory or contradictory. The supplemental information from the preoperative evaluation should always be taken into consideration.
3. A comprehensive systematic transesophageal echocardiography (TEE) examination permits the acquisition and interpretation of both qualitative and quantitative echocardiographic data for most cardiovascular diseases. The greatest risk and source of error are omission and misinterpretation of data that lead to mismanagement.
4. The decision regarding management of a specific anatomic abnormality in an individual patient should take an evidence-based approach reflecting the severity of the lesion, coexisting factors, the patient's wishes, and the current literature.
5. Intraoperative findings should be objectively and effectively characterized and discussed with the pertinent clinicians, surgeon, or cardiologist and the patient's family.
6. The decision and recommendations should be formally communicated through a reporting document that is accessible to other health care providers.
7. A systematic process for learning from the results of past decisions (quality improvement program) and continued education are critical for the future success of any intraoperative TEE program.

"In the affair of so much importance, wherein you ask my advice, I cannot make for want of sufficient premises advise you what to determine, but if it please I will tell you how."

Benjamin Franklin

All too often in medicine, critical decisions are made without the benefit of a thorough consideration of data, evidence, and framework. The paucity of clinical outcomes research in echocardiography, especially in the perioperative period, dampens the prospects for evidence-based decision making. In the absence of evidence-directed practice, decision making often devolves into a reliance on anecdote, clinical impression, and tradition. With this lack of clear evidence-based guidelines, combined with the ever-increasing flow of information that physicians must process on a daily basis, it becomes imperative to develop a systematic approach to handling data streams, organizing ideas and thoughts, defining and prioritizing problems, and effecting care through a well-thought-out decision. Such a formalized approach (Fig. 16.1) enhances the quality of the intraoperative echocardiogram, its interpretation, and the confidence with which the findings are communicated to other members of the operative and nonoperative teams. Poor decisions are not made with bad intentions. Rather, they are the result of relying on limited medical knowledge, narrow framing, and false or tenuous anchors (eg, an echocardiographer who is overly confident in the abilities of his or her surgeon may not interrogate a repaired valve to the same extent as one without such preconceived notions).

The lack of a structured paradigm for decision making is most worrisome when clinicians with lesser ability or experience are making the decisions. The least accomplished clinicians often have the most inflated estimate of their own abilities, thus lending themselves to the vulnerabilities of both limited skills and a lack of a decision-making process.[1]

Expertise is gained from experience and enhances the repertoire of experiences from which a practitioner can draw, but it does not alter cognition and does not immunize the practitioner from errors in decision making. Intuition and experience are not reliable predictors of success, and even experienced physicians can fall prey to heuristic methods of decision making that create a systematic and predictable bias. It is acceptable to be wrong. It is unacceptable to be consistently wrong in the same direction. A structured process of assessing all the data and weighing various alternatives (cognitive engine) enables the physician to formulate a concise, organized approach to problem solving, communicating the findings, and managing alternatives. For the echocardiographer confronted with multiple channels of information, including data specific to providers, operations, and patients (Boxes 16.1 to 16.3), the best approach is through a systematic transesophageal echocardiography (TEE) examination of the heart and great vessels. Such an approach helps prevent the practitioner from missing important information that may be overlooked as a result of bias or intuition.

Decision making can also be encumbered by cognitive and emotional attachments that limit clinicians' intellectual flexibility. Poor problem solving and an unfavorable outcome can follow a single poor decision of great magnitude. However, the "creep effect" of a series of small poor decisions can insidiously lead to an unfavorable outcome. The adherence to a poor course of action because of an attachment to the original decision is common in medicine. In the perioperative setting, this process is most vivid in the care of critically ill patients with little or no hope for survival. Continued commitment of resources and intervention often contribute to a patient's discomfort and cost without benefit in quality of life or longevity. The previous commitment of resources often encourages further commitment and investment in a losing cause. The echocardiographic decisions during surgical procedures may become part of an intraoperative sequence of

BOX 16.1 PATIENT HISTORY AND PHYSICAL SIGNS

- Symptoms: shortness of breath
- New York Heart Association classification for heart failure
- Level of activity
- Functional disability
- Age
- Signs: vital signs, rales, peripheral edema, peripheral circulation
- Cardiac and noncardiac comorbidities, including esophageal disease
- Patient's preferences (eg, Jehovah's Witness, long-term anticoagulation)

BOX 16.2 PATIENT-RELATED DATA

- Intraoperative transesophageal echocardiography
- Left ventricle: systolic or diastolic function, ejection fraction, chamber size, wall thickness, regional wall motion
- Valvular function: pathologic process, severity, location, vena contracta, annular size, size of donor chamber, pressure gradient, flow-velocity profiles
- Cardiac catheterization
- Chest radiographs, electrocardiogram, blood tests, radionucleotide studies, positron emission tomography scans, stress test, transthoracic echocardiography
- Hemodynamics
- Surgical inspection of the pathologic features

BOX 16.3 OPERATIVE FACTORS

- Complexity of planned surgical procedure (eg, redo sternotomy, previous valve repair, infectious process)
- Alternatives to the planned surgical procedure
- Anticipated risk for a failed intervention
- Alternatives if the original procedure is unsuccessful
- Equipment availability (eg, ventricular assist device backup, special retractors, specific valves, homografts)
- Expertise and experience of the operating team

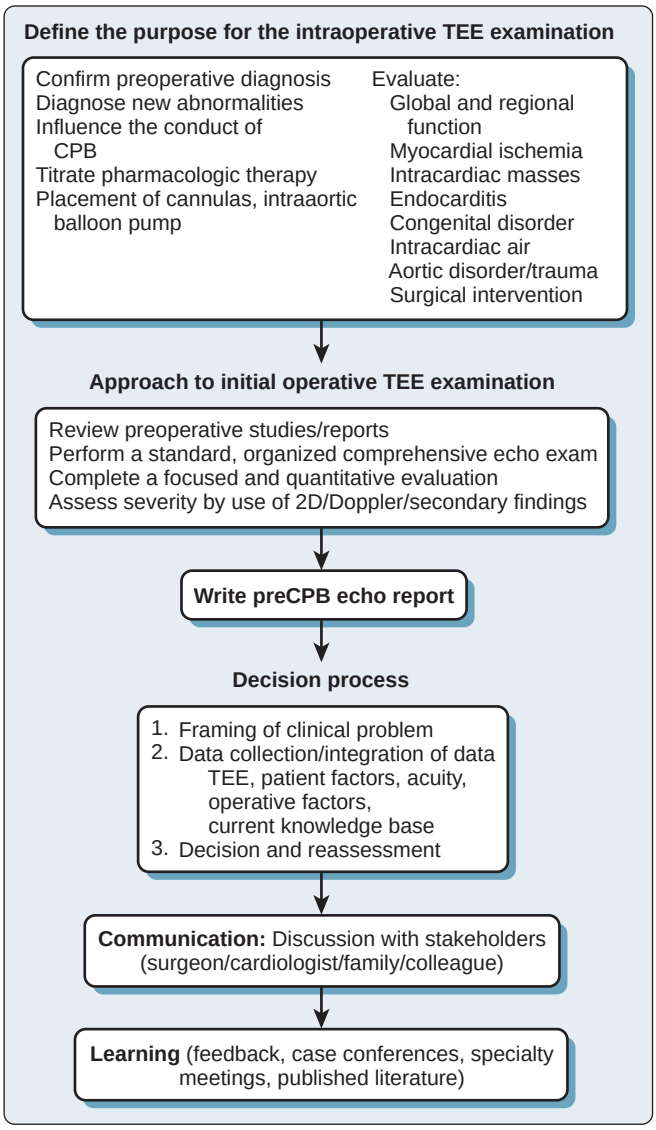


Fig. 16.1 An algorithm for the decision-making process. *CPB*, Cardiopulmonary bypass; *TEE*, transesophageal echocardiography; *2D*, two-dimensional.

diagnostic and therapeutic interventions in which the best course of action is a complete reversal of direction. Repeated attempts at repairing a mitral valve (MV) may follow an initial unsuccessful repair. The decision to replace the valve instead of repairing it often is not considered until late in the course. Repeated intervals of cardiopulmonary bypass (CPB) and aortic cross-clamping are not without their complications and associated morbidities. It often is difficult to retain an open mind and to consider alternative diagnoses or therapeutic alternatives. Effective decision makers are able, if necessary, to abandon the original decision to repair an MV and move toward valve replacement.

A thorough intraoperative TEE examination can correct preoperative inaccuracies in diagnosis or detect occult disease. With increasing emphasis on decreasing preoperative testing, avoiding redundant testing, and decreasing costs, accurate diagnoses of disease may not occur until the time of surgical intervention. The increased reliance on the intraoperative TEE is fiscally wise, but it places greater responsibility and impact on the intraoperative echocardiographer. The detection of occult disease not appreciated during the preoperative evaluation often affects operative management. It is necessary to reframe a problem when the data acquired provide new insights. For example, the detection of mobile atheroma in the ascending aorta may influence positioning of an aortic infusion cannula or cross-clamp, hence changing circulatory management and the operation.[2–4] A change in clinical management with respect to otherwise asymptomatic and silent findings is often controversial. The change in the operation has typically not been discussed with the patient because the findings were unanticipated. The intraoperative diagnosis of moderate aortic regurgitation (AR) that was not detected preoperatively creates a clinical challenge for the surgical team regarding administration of cardioplegia and the decision whether to replace the aortic valve (AV). Hence, the decision to proceed with an unplanned AV replacement (AVR) relies on the ability of the echocardiographer to establish the diagnosis and mechanism of valvular disease, define the pertinent factors that sway the decision (preoperative symptoms of congestive heart failure, ventricular size and function, pulmonary hypertension), and communicate with the surgeon and the other pertinent stakeholders. The decision

to recommend AVR to a patient is not often guided by the degree of AR, but rather by the degree of corresponding ventricular dilatation and dysfunction. The finding of moderate AR with normal ventricular systolic function and chamber size, normal left atrial pressure, and no preoperative history of congestive heart failure may sway the operative team to proceed with the originally planned surgical procedure and to treat the occult finding medically with postoperative afterload reduction and follow-up serial echocardiograms. In contrast, in a patient with otherwise unexplained shortness of breath, pulmonary hypertension, and a dilated left ventricle, the presence of moderate AR typically leads to AVR. The introduction of new findings to the operative team warrants a "time-out" approach to determine the impact of the findings on the intraoperative care.

Decision-Making Process

The process of decision making is, in essence, "deciding how to decide."[5] What is the primary issue that must be addressed? What are the pitfalls in the decision? What are the consequences of the decision? What tools and resources does the decision maker require? What information is needed to make an informed decision? Does evidence support one decision over another? How much time does the decision maker need to make the decision? Rarely does a valid reason exist for not taking enough time to make a well-thought-out decision, even in the high-productivity, high-throughput environment of the operating room. The anchor to a "last case" experience creates bias and is all too prevalent in medicine; the experience from the previous case dictates decision making on the subsequent case. If physicians are to remain the dispensers of medical care and resources, then they must be cognizant of the effects of their decisions on all patients, not just the one lying on the operating room table. It is inappropriate to accrue health care costs without evidence that such financial investment provides any health care benefit. We have applied the methods of Russo and Schoemaker[5] to decision making in medicine: framing, data collection, decision and implementation, and learning from knowledge to wisdom.

Framing

Framing defines the question and the factors that influence or sway the decision maker. Framing sets the vantage point of the decision maker and defines the boundaries, parameters, and priorities. Framing a question in the early stages of problem solving permits focus and bounded rationality. However, the price of focusing on a specific issue may be loss of peripheral vision. Adopting a narrowed vantage point can inadvertently impose significant bias and limitation. The decision should be addressed from a variety of vantage points so that all aspects of the decision can be considered. Failure to work beyond a single conceptual frame can lead to difficulties in communication among the different participants of the care team. In the setting of a complex MV repair, the intraoperative echocardiographer often is focused on performance of the TEE, successful remedy of hemodynamic disturbances, surgical intervention, and documentation. If the echocardiographer is also the anesthesiologist, his or her frame is broadened to include the patient's safety and comfort, vigilance, and maintenance of body homeostasis. The surgeon's frame includes his or her abilities and limitations in achieving a competent surgical repair, alternatives in surgical management, the covenant with the patient and family regarding surgical management (eg, repair vs replacement, bioprosthesis vs mechanical prosthesis), the patient's overall outcome, and the surgeon's own reputation. The patient's vantage point may differ from those of the operative team. The patient wants the mitral regurgitation (MR) to be fixed, for the symptoms to be resolved, to return to a "normal routine," for the remedy to be long lasting, and to be able to ride a Harley Davidson, which he or she would otherwise have to forfeit if lifelong warfarin (Coumadin) is required. Hence as a decision maker, broadening the understanding of the issues and considering multiple frames will account for the interests of multiple parties.

Data Collection

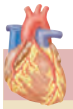
Data collection is aimed at reducing uncertainty. Uncertainty is never eliminated and hence must be managed. The perioperative echocardiographer manages uncertainty not through pinpoint predictions but by uncertainty estimates. It is imperative in the decision-making process to identify the causes systematically that could lead to decision failure and to quantify the likelihood that such causes will occur.

The ability to render a sound conclusion often is predicated on the performance of a complete and quantitative echocardiographic examination. Incomplete and qualitative assessments may be subject to missed or inaccurate diagnoses. The "soft" interpretation of the "mild-to-moderate" category is not always avoidable. The ability to "nail down" a diagnosis and establish a quantifiable measure of dysfunction allows for serial follow-up and comparison before and after treatment. The imperative for quantitative measures is directed at producing reproducible conclusions and trackable results.

The importance and impact of TEE decisions have been generally recognized and accepted. The ability to make an appropriate decision is predicated on a comprehensive examination. Confirmatory information is useful, as is contradictory information. The process of decision making also includes defining what information not to collect. Collecting as many data as possible typically leads to confusion and loss of direction in the reasoning process. A common hazard for the echocardiographer is the performance of an abridged examination because of either increased clinical demands or reliance on a preoperative examination. The conclusions drawn from an intraoperative examination and associated decisions should not be hurried and should be based on all aspects of the examination. Although physical injury from the TEE examination is a serious matter, the greatest risk of TEE is that of errors of omission or misinterpretation, leading to mismanagement and poor outcome.[6–11] Guidelines describing the comprehensive TEE examination have been published jointly by the American Society of Echocardiography and the Society of Cardiovascular Anesthesia, most recently in 2013.[12] Time permitting, the echocardiographer is encouraged to document in writing the prebypass TEE findings at the time they are discovered. It is acceptable to document a finding only to discover later that it has poor agreement with the surgical findings. This practice fosters learning and a systematic process. The process of writing a report ensures a formalized approach to evaluating the TEE examination.

Decision and Implementation

A clinical decision is made based on the integration of knowledge, framing, and information (Box 16.4). Primary knowledge is "knowing



BOX 16.4 DECISION PROCESS

Projecting the Impact of:
- Progression of disease
- Risk for redo operation
- Short- and long-term outcomes
- Associated risks (eg, anticoagulation)
- Size mismatch of the prosthesis
- Effect of prolonged cardiopulmonary bypass on the immediate postoperative outcome

Does the Decision Account for:
- Inconsistencies (among two-dimensional images, Doppler images, patient's symptoms, preoperative evaluation)
- Plausibility of an alternate explanation
- Alternate therapy
- Current literature
- Preoperative evaluations
- Patient-related factors (eg, age, cardiac status, ability to tolerate anticoagulation)

what you know" and "knowing what you do not know," with the latter prompting a practitioner to seek assistance. Second-order knowledge is "not knowing what you do not know"; hence diagnoses are missed rather than misinterpreted. The broader the repertoire of primary knowledge, the more informed is the decision maker and the more reliable is the decision. The echocardiographer is an intraoperative consultant who generates vital information that has a direct impact on intraoperative care and decision making. As consultants, echocardiographers offer suggestions and recommendations, but rarely does the echocardiographer dictate the management to the operative team. The suggestion or recommendation is shared with the stakeholders (surgeons, perfusionists, nurses, referring cardiologists, postoperative intensivists, family, and patient) and is communicated verbally and by written report. Decisions often are accompanied by discussion and sometimes persuasion. Making a sound decision concerning the surgical approach to an anatomic problem can benefit the patient only if the recommendation is effectively communicated to the operating surgeon. However, clinical judgment must take into account the skill set of the operative team and the pitfalls associated with each intervention. Persuading a surgeon to proceed with a complex reconstruction may appear to be the appropriate course of action according to an echocardiographer, but it may be the wrong thing to do if the surgeon is unfamiliar with the recommended repair (ie, poor framing).

Learning From Knowledge to Wisdom

A systematic process for learning from the results of past decisions is designed to increase the decision maker's primary knowledge base and defines an effective clinical quality improvement program. The ability to achieve success or failure may depend on the ability of the decision maker to learn from past decisions and the decisions of others.[5] A fund of knowledge gained through training, continuous medical education, readings, and the performance of echocardiograms on a regular basis maintain the skills of the echocardiographer. Although it is often difficult to obtain feedback on the impact of decisions on long-term outcome, the increment in effort to seek such insight always renders the echocardiographer better prepared for the next clinical case that shares common cardiovascular themes (wisdom). Feedback can be sought from a variety of sources: the surgeon, the cardiologist, and outpatient echocardiography data files, among others. Participation in quality improvement forums with cardiovascular anesthesiologists, cardiologists, and cardiac surgeons who tend to follow the patients longitudinally is a useful learning tool.

A significant limitation of assessing performance during uncertainty is that it is often judged not by the decision-making process, but by single case results. If the decision is followed by a good outcome, the decision maker often is applauded with little regard to the ability to reach an intelligent conclusion. An unfavorable outcome does not necessarily imply a poor process or a poor decision. High-risk surgical intervention leads to poor outcomes in many cases despite robust decisions. As a result, in medicine, practitioners are often reluctant to make any decision at all because they know that a poor outcome is likely and that it will be linked to their decision making. The reality of performance assessment is that even if the decision to proceed with therapy is substantiated, a poor outcome often will reflect negatively on the abilities of the echocardiographer, the anesthesiologist, the surgeon, and the operative team. Conversely, a favorable outcome does not imply a good process or a good decision.[5] The surgeon's decision to perform a posterior sliding mitral valvuloplasty and quadrilateral resection of the posterior leaflet based on a dilated mitral annulus with normal leaflet motion as defined by TEE may result in a technically competent MV repair and good long-term results. The decision to perform a posterior sliding valvuloplasty may or may not have been a wise decision. Equally good results may have occurred with the insertion of an annular ring without leaflet resection. The measure of an outcome by recording a metric is a valid assessment of quality only if the metric is a function of the actions of the provider.[13] The outcome cannot be random; otherwise, no basis exists for estimating quality.

Case Study 1: The Regurgitant Carpenter

A 48-year-old asymptomatic woman presented for elective MV repair secondary to MR. She was otherwise healthy, except for mild pulmonary hypertension and rapidly increasing left ventricular (LV) dimensions. The woman was a union carpenter and absolutely refused to be subjected to lifelong anticoagulation. Physical examination was notable for a loud holosystolic murmur from the apex to the axilla. The lungs were clear. The baseline electrocardiogram (ECG) was normal, as were all laboratory blood tests. The preoperative chest wall echocardiogram demonstrated severe MR, no segmental wall motion abnormalities (SWMAs), and a flail MV. Intraoperatively, after induction of general anesthesia and tracheal intubation, two-dimensional (2D) and three-dimensional (3D) TEE was performed and showed a severely dilated left atrium, a dilated left ventricle, a flail and thickened middle scallop of the posterior leaflet with multiple ruptured primary and secondary chordae to all scallops of the posterior leaflet, prolapse of the anterior leaflet, and a small perforation. The short-axis and bicommissural views, along with 3D color acquisition of the MV, suggested three regurgitant orifices. The surgeon was experienced in complex mitral repairs and chordal transfer. Consultation between the surgeon and the echocardiographer resulted in the surgeon proceeding with an MV repair, resection of excessive leaflet tissue of the posterior leaflet, chordal transfer from the anterior leaflet, and patch closure of the perforation, in addition to a mitral annular ring. Separation from CPB was facilitated with epinephrine, but the postrepair TEE demonstrated residual moderate central MR and residual anterior leaflet prolapse. No systolic anterior motion (SAM) of the MV was evident. No gradient existed between the left ventricle and the aorta. CPB was reinstituted. The surgeon elected to replace the MV with a pericardial bioprosthesis, despite the patient's young age. The patient required the transfusion of blood, plasma, and platelets, as well as return to the operating room on the evening of the operation because of mediastinal bleeding. The patient emerged from anesthesia and operation on postoperative day 1 edematous and confused. Heart function showed a cardiac index of 2.4 L/m^2 per minute, mild pulmonary hypertension, and bounding peripheral pulses. Neurologic function recovered fully before discharge on postoperative day 7. Was the initial decision to repair the MV a sound decision? Do the poor initial results of the operation suggest that the decision was poor? Would it have been wise to attempt a second repair after the initial attempt failed? Was the better decision to proceed directly to an MV replacement, thereby decreasing the CPB and aortic cross-clamp times?

Myxomatous Degeneration of the Mitral Valve and Mitral Regurgitation

Framing

Myxomatous degeneration of the MV is a common cause of MR. Patients often are young and otherwise quite healthy. The diagnosis is commonly established preoperatively, and patients are scheduled for elective surgical procedures unless acute leaflet or chordal rupture leads to acute pulmonary edema and emergency operation. The decisions to be addressed in this setting include the following: Can the surgeon perform the MV repair to address the MR, or is valve replacement necessary? If MV replacement is necessary, would the patient prefer a mechanical or a bioprosthetic valve? What does the surgeon need to know to assess the possibility of repair and how to accomplish it? What are the possible complications of MV repair? Is the MV repair acceptable?

Data Collection

The first decision by the echocardiographer is whether TEE is indicated. Application of intraoperative TEE in the care of the patient with mitral disease is widely accepted. Even in this area, however, data supporting an improved outcome for intraoperative patients cared

BOX 16.5 INDICATIONS FOR THE USE OF TRANSESOPHAGEAL ECHOCARDIOGRAPHY

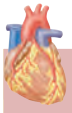
Category I
- Heart valve repair
- Congenital heart condition procedures
- Hypertrophic obstructive cardiomyopathy
- Endocarditis
- Acute aortic dissection
- Acute, unstable aortic aneurysm
- Aortic valve function in the setting of aortic dissection
- Traumatic thoracic aortic disruption
- Pericardial tamponade

Category II
- Myocardial ischemia and coronary artery disease
- Increased risk for hemodynamic disturbances
- Heart valve replacement
- Aneurysms of the heart
- Intracardiac masses
- Intracardiac foreign bodies
- Air emboli
- Intracardiac thrombi
- Massive pulmonary emboli
- Traumatic cardiac injury
- Chronic aortic dissection
- Chronic aortic aneurysm
- Detection of aortic atheromatous disease as a source of emboli
- Evaluating the effectiveness of pericardiectomies
- Heart-lung transplantation
- Mechanical circulatory support

Category III
- Other types of cardiomyopathy
- Emboli during orthopedic procedures
- Uncomplicated pericarditis
- Pleuropulmonary disease
- Placement of an intraaortic balloon pump or a pulmonary artery catheter
- Monitoring the administration of cardioplegia

Modified from Practice guidelines for perioperative transesophageal echocardiography: a report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology*. 1996;84:986.

for with TEE compared with no TEE are few. The decision to perform TEE during cardiac surgical procedures is substantiated by practice expectations and consensus opinion. In an attempt to develop an evidence-based approach to this expanding technology, the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists cosponsored a task force to develop guidelines for defining the indications for perioperative TEE. Despite the scarcity of outcome data to support the application of TEE in the perioperative period, TEE had rapidly been adopted by cardiac surgeons and cardiac anesthesiologists as a routine monitoring and diagnostic modality during cardiac surgical procedures. In 1996, the task force published their guidelines, designed to establish the scientific merit of TEE and the justification of its use in defined cohorts of patients.[14] The indications were grouped into three categories based on the strength of the supporting evidence or expert opinion that TEE improves outcome (Box 16.5). Category I indications suggested strong evidence or expert opinion that TEE was useful in improving clinical outcome. Category II indications suggested weak evidence or expert opinion that TEE improves outcome in these settings. Category III indications suggested little or no scientific merit or expert support for the application of TEE in these settings (see Chapters 14, 15, and 17). These guidelines were further updated in 2010 to include virtually all adult cardiac surgical procedures (Box 16.6).[15]



BOX 16.6 2010 UPDATED RECOMMENDATIONS FOR TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Cardiac and Thoracic Aortic Surgery
- *All* adult open-heart (eg, valves) and thoracic aortic surgical procedures
- Consider in coronary artery bypass grafting procedures
- Transcatheter intracardiac procedures

Critical Care
- When diagnostic information that is expected to alter management cannot be obtained by transthoracic echocardiography or other modalities

Modified from Practice guidelines for perioperative transesophageal echocardiography: an updated report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology*. 2010;112:1084.

TEE is not without its serious complications. The risks of intraoperative TEE include physical injury to the mouth, dentition, and esophagus, in addition to the misinterpretation of a finding leading to mismanagement. When deciding whether to perform intraoperative TEE, the physician should consider the cumulative effects of the indications and risks. TEE should not be performed if the appropriate equipment, safety precautions, and skilled examiners are not available. In this instance, the surgeon cannot rely on visual inspection of the native MV in the flaccid, arrested heart to discern the mechanism of MR. As such, intraoperative TEE is often critical in assisting the surgeon to plan the appropriate surgical correction, as well as evaluate the repair during separation from CPB.

The intraoperative TEE examination targets the MR, left atrium, left ventricle, and right ventricle. The 2D and color-flow Doppler examinations have long been the standard assessment tools, but more recently 3D echocardiography has become a recommended modality for examining MV disorders.[16] The TEE examination of MR should first quantify the degree of regurgitation, which may differ significantly from that seen in the preoperative echocardiogram as a result of changes in hemodynamics and loading conditions. This examination is traditionally done using a 2D color-Doppler method,[17] although 3D echocardiographic techniques have shown promise in several studies.[18–21]

Following the establishment of regurgitation severity, the anatomy of the regurgitant MV must be interrogated and the cause of the regurgitation identified. Typical findings of myxomatous valves include excessive leaflet motion, redundant leaflet tissue, and a dilated mitral annulus. Leaflets commonly prolapse into a dilated left atrium, the degree of which is based on the chronicity of the illness. Chordal rupture is common and leads to flail leaflets and severe MR. The imperative is to be exact in the descriptive anatomy of MV disorders, including the location of any flail or prolapsing leaflet segments, as well as any coexisting leaflet perforations or clefts. Mounting evidence indicates that 3D echocardiography may be more accurate than 2D echocardiography, especially in the hands of less experienced users, in identifying these disorders.[22–24] The width of the anterior and posterior leaflets, the bisecting widths of the mitral annulus (minor and major axes), the severity of annular calcification (less common in isolated ischemic or myxomatous disease), and the size of the left atrium also contribute significantly to the planned repair and should be accurately communicated to the surgeon.

SAM risk should also be assessed before any MV repair. Maslow and colleagues[25] examined the predictors of LV outflow tract (LVOT) obstruction after MV repair. In this study of patients who were undergoing repair for myxomatous valve disease, 11 of 33 patients experienced development of SAM and outflow tract obstruction. The major predictive factors were a smaller anteroposterior length ratio (annulus

to coaptation; 0.99 vs 1.95) and a short distance from the septum to the MV coaptation point (2.53 vs 3.00 cm). The surgeon may elect to perform a posterior sliding valvuloplasty to move the point of coaptation laterally, thereby decreasing the risk for outflow obstruction and mitral incompetence associated with SAM (see Chapter 21).

The repaired MV is scrutinized closely, with the ventricular vent removed at the discontinuation of CPB under typical loading conditions. The systolic and diastolic functions of the valve are examined for residual regurgitation, stenosis, and the presence of outflow tract obstruction. The examination after bypass is critical for determining the acceptability of the repair or for guiding subsequent revision should the initial repair be unacceptable. Systolic valve dysfunction after repair typically produces residual MR. Residual MR after mitral repair is not uncommon and may not necessitate revision if the grade is trace or mild. Diastolic mitral function is ascertained by Doppler flow measurements across the mitral orifice to provide assurance that the repaired valve has not been rendered stenotic. Peak transvalvular blood-flow velocities and pressure half-times are measured to calculate valve gradients and valve areas.

Discussion

The growing imperative is to repair instead of replace myxomatous MVs. The intraoperative echocardiographer soon becomes familiar with the abilities and limitations of his or her surgical counterparts. Outcomes of valve repair may depend on the ability of the individual surgeon, more so than in valve replacement operations. Hence it may be prudent to track short-term (intraoperative) results of these operations because outcomes may be defined less by national databases and more by individual providers. In general, the likelihood of a successful repair is based on the severity and extent of involvement of the mitral leaflets. Isolated prolapse of the middle scallop of the posterior mitral leaflet in an eccentric MR that overrides an otherwise normal anterior leaflet is associated with a high success rate. However, cases of extensive leaflet degeneration with bileaflet prolapse, multiple chordal ruptures from both leaflets, leaflet destruction from preceding endocarditis, the presence of two or more regurgitant orifices, and extensive calcification are associated with a significantly lower success rate for repair.[26] Many patients leave the operating room with a prosthetic MV replacement with preservation of the subchordal apparatus, with excellent long-term results. Retention of the subvalvular apparatus preserves longitudinal shortening of the left ventricle and decreases the incidence of heart failure in the long term.[27,28] In a comparative study, the ejection fraction (EF) of patients without chordal transfer decreased 24% postoperatively compared with patients having chordal transfer who maintained preoperative function.[28]

Some degree of residual MR after repair is common. Most surgeons do not accept residual MR of 2+ or greater and readdress the valve surgically. Assessment of valve function after bypass under unloaded conditions (decreased afterload with relative hypovolemia) may not accurately reflect MR under normal hemodynamic parameters. Similarly, a left ventricle that is struggling with hypokinesis and dilation immediately after bypass often responds well to the introduction or escalation of inotropes, with concomitant improvement in the degree of MR.

If the valve is left with significant regurgitation after the optimization of LV function and loading conditions, then the repair has failed and the mechanism of failure must be determined. Residual mild regurgitation associated with persistent leaflet prolapse may warrant further leaflet resection. Mild residual regurgitation in the setting of a "normal" MV may sway the surgeon to accept it. The presence of a central jet of MR may require resizing (ie, smaller) of the annuloplasty ring or consideration of an edge-to-edge repair (ie, Alfieri stitch). The decision to repeat a repair or valve replacement often is difficult and requires weighing the balance between the risks for reoperation and the risk for residual MR. The final decision of what constitutes acceptable residual valvular regurgitation is patient specific (eg, age, anticipated level of activity, ability to tolerate a return to CPB).

In addition to residual regurgitation, the presence or absence of LVOT obstruction caused by SAM must be assessed after MV repair. This phenomenon is the result of displacement of leaflet coaptation toward the septum that causes the anterior leaflet paradoxically to move into the LVOT, rather than toward the left atrium late in systole (Fig. 16.2).[29] Displacing the anterior leaflet into the LVOT during ventricular ejection (Venturi effect) produces outflow tract obstruction, early closure of the AV, and worsened MR. The incidence of postoperative SAM and the need to revise the surgical repair have decreased as understanding of the predisposing factors and management strategies have improved. SAM may be intermittent and dependent on loading conditions. If possible, patients should be examined after adequate volume resuscitation and with minimal inotropic support. Most cases of SAM resolve with conservative measures including β-blockade, vasoconstriction, and fluid administration to augment preload. In a single-center retrospective study of 2076 patients who underwent MV repair, the incidence rate of intraoperative SAM was 8.4% (174 cases).[30] Revision of repair or valve replacement related to SAM during initial operation was undertaken in only 2 of these patients. However, in the case of persistent severe SAM with a high left ventricle–to-aorta gradient, returning to CPB and revising the mitral repair (eg, posterior sliding mitral valvuloplasty to shift the locus of coaptation laterally), performing an edge-to-edge repair, or possibly replacing the MV should be considered. Patients who transiently demonstrate SAM or turbulence in the outflow tract in the operating room may be at increased risk during the immediate postoperative period (Fig. 16.3). An important role of the clinical echocardiographer is to recognize potentially important findings that may have an impact on subsequent patient care and long-term follow-up (see Chapters 14, 15, 21, and 24).

Management of Ischemic Mitral Regurgitation During Coronary Artery Bypass Grafting

Framing

Ischemic heart disease is the most common cause of mitral insufficiency in the United States. Mechanisms of valve incompetence are varied and include annular dilatation, papillary muscle dysfunction from active ischemia, papillary muscle rupture, or LV remodeling and papillary muscle displacement, thus leading to a tethering effect of the subvalvular apparatus. MR leads to pulmonary hypertension, pulmonary vascular congestion, and pulmonary edema with functional disability. Ventricular function deteriorates as the left ventricle becomes volume overloaded with corresponding chamber dilatation. Left untreated, severe MR from ischemic heart disease has a poor prognosis, hence the imperative for diagnosis and treatment.[31–33] Less certain is the impact of lesser degrees of mitral insufficiency on functional status and long-term morbidity and mortality. Patients presenting for coronary artery bypass grafting (CABG) often have concomitant MR of a mild or moderate degree.[34] The intraoperative team is confronted with the decision whether to address the MV surgically during the coronary artery operation.

Does MR warrant mitral surgical treatment? What is the mechanism of the regurgitation? What are the grade and chronicity of the MR? Is the MR likely to improve by coronary revascularization alone?

Data Collection

Pertinent data, including preoperative functional status and evaluation, must be considered to interpret and place the intraoperative data in context appropriately. The preoperative echocardiogram and ventriculogram must be reviewed. The intraoperative hemodynamic data are coupled with TEE information to complete the data set needed to move forward with the decision-making process. The severity of MR on TEE is assessed by conventional methods (eg, vena contracta width or area, regurgitant jet area, regurgitant orifice area, and pulmonary vein inflow velocities), although 3D echocardiography is becoming

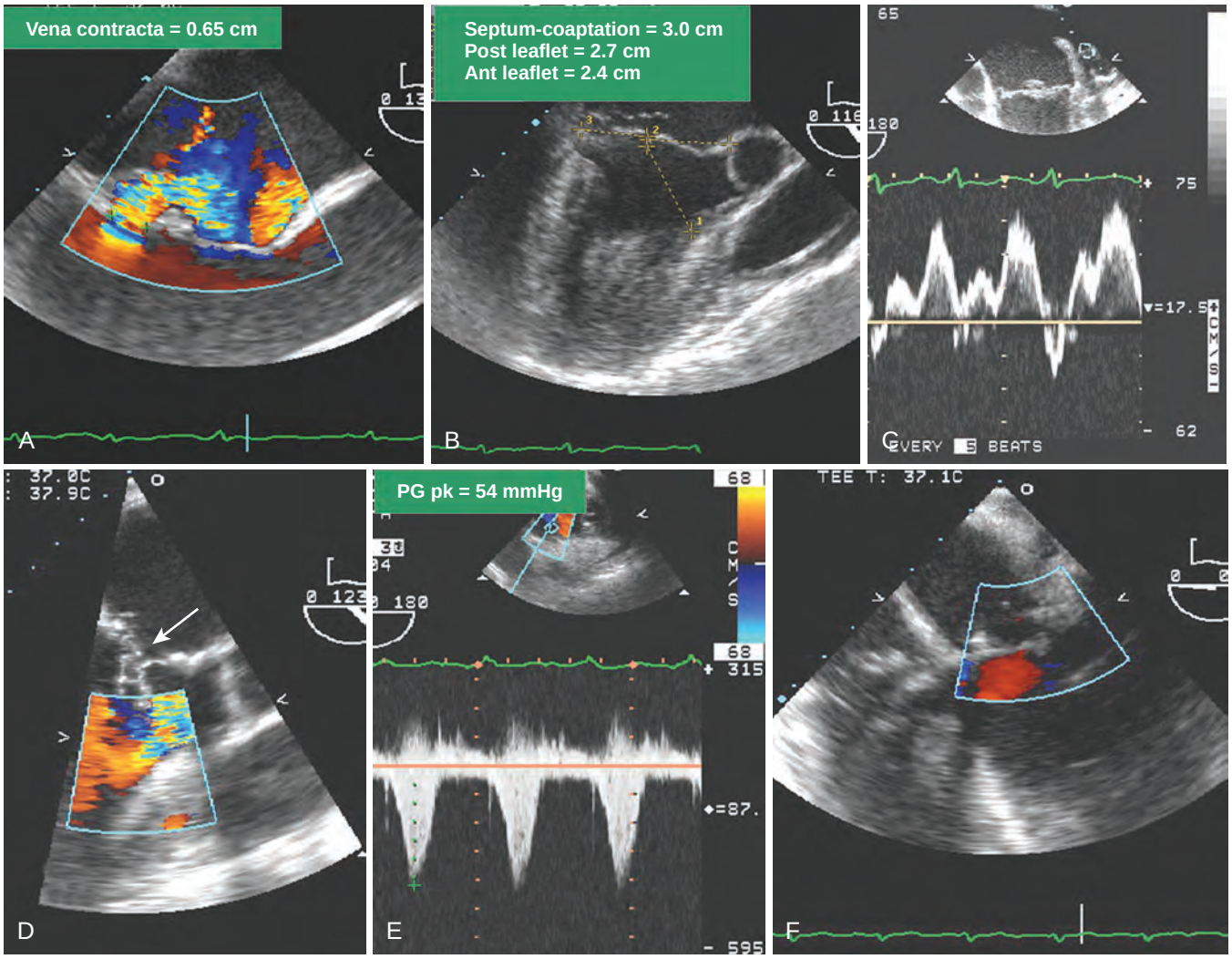


Fig. 16.2 Complex mitral valve (MV) replacement or repair revision. A 58-year-old woman with severe mitral regurgitation (MR) and a history of congestive heart failure, pulmonary edema, and hypertension was scheduled for surgical repair of mitral insufficiency. (A) The prebypass transesophageal echocardiogram characterized the MV as having severe MR with mildly thickened, myxomatous leaflets and several ruptured chordae tendineae. The markedly dilated annulus was consistent with the chronic disease process. Prolapse of the posterior leaflet caused the MR jet to override the anterior leaflet. (B) Although the distance from the septum to the coaptation point of the MV was greater than the value cited by Maslow as predictive of postbypass systolic anterior motion, the ratio of the length of the anterior *(Ant)* and posterior *(Post)* leaflets (0.89) suggested a risk for left ventricular (LV) outflow obstruction.[39] The midesophageal long-axis view demonstrates several ruptured chordae that resulted in MR having a vena contracta of 0.65 cm. (C) Blunting of the systolic component of pulmonary vein blood flow velocity corroborated the diagnosis of significant MR. The surgeon performed a quadrangular resection of the posterior leaflet and secured the annulus with a no. 30 Physio ring. (D) Postbypass imaging of the midesophageal long-axis view demonstrated a coaptation defect, designated by the *arrow,* and nonlaminar flow in the LV outflow tract. Shift of the coaptation point medially created laxity of the redundant chordae that were drawn into the outflow tract by systolic LV ejection. (E) The outflow tract obstruction was characterized by peak pressure gradient *(PG pk)* of 54 mm Hg as determined by continuous-wave Doppler through the outflow tract by using the transgastric long-axis view. Neither the MR nor the outflow tract obstruction was effectively addressed by volume loading and decreasing the inotropic support. Circulatory bypass was reinstituted, and the surgeon revised the previous repair by further resecting the posterior leaflet and enlarging the annular ring to a no. 34. (F) The patient was successfully separated from bypass by using minimal support and had resolution of LV outflow tract obstruction, return of normal hemodynamics, and reduction of MR to trace severity (F).

more frequently used for this purpose.[18–21] The degree and angle of leaflet tethering should also be determined. Long-standing ischemic MR often causes changes in other cardiac structures and may be associated with a dilated left atrium, pulmonary hypertension, and right ventricular (RV) dysfunction. Wall motion assessment and the ECG are used for detecting reversible myocardial dysfunction that may benefit from revascularization. The hemodynamic and TEE data are coupled with provocative testing of the MV in an attempt to emulate the working conditions of the MV in an awake, unanesthetized state. It is not uncommon that preoperative mild-to-moderate MR with a structurally normal valve totally resolves under the unloading conditions of general anesthesia.[35–37]

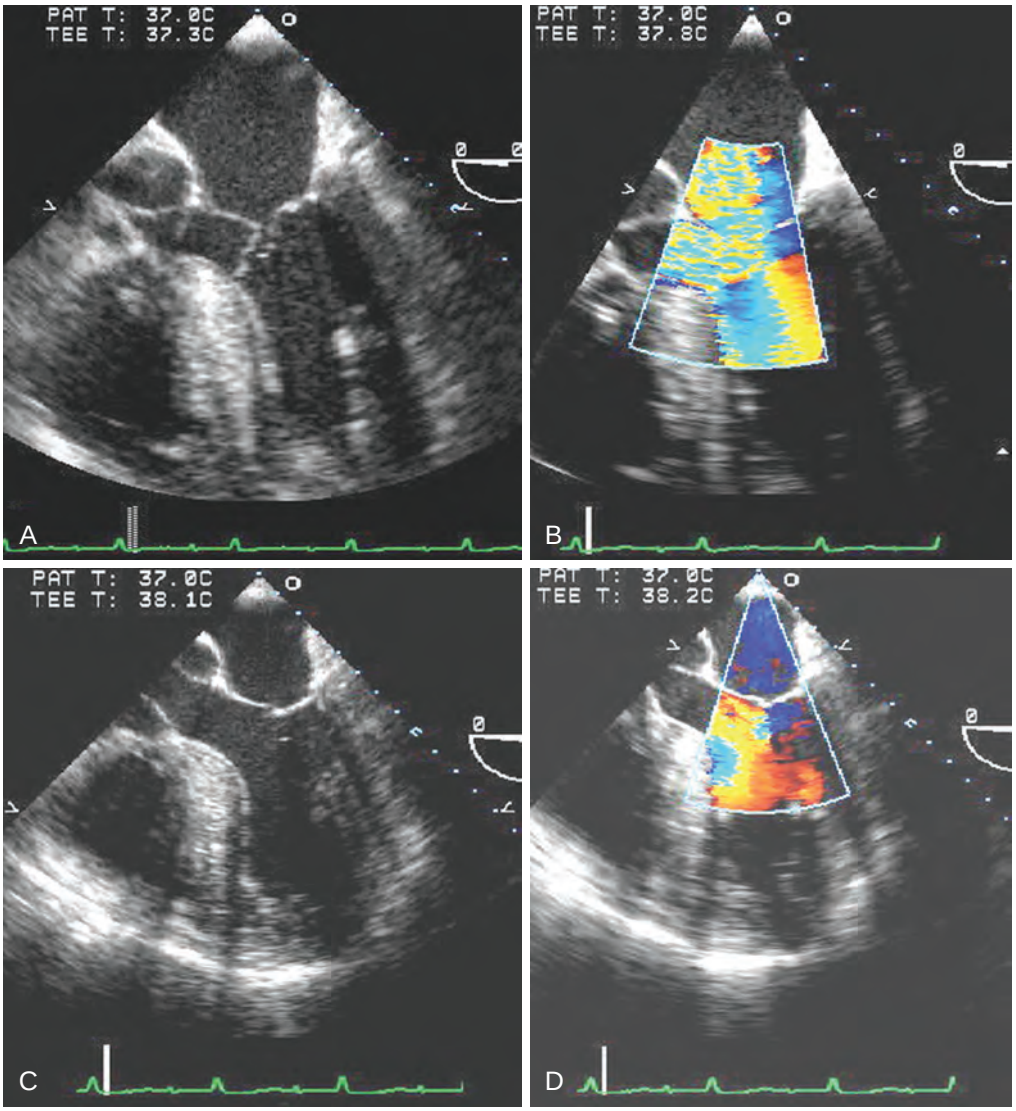


Fig. 16.3 Acute intraoperative hemodynamic deterioration. A 65-year-old man with a medical history of hypertension, sleep apnea, and smoking was scheduled for resection of colon cancer. During the bowel resection, the patient had a profound episode of hypotension and new-onset hypoxia. Although the patient's hemodynamic condition initially improved after administration of phenylephrine and ephedrine, the patient became more hypotensive and hypoxic with evidence of pulmonary edema. Transesophageal echocardiography was requested and was performed on an emergency basis to diagnose the cause of cardiovascular collapse and to guide management. (A) The midesophageal four-chamber view showed a moderately hypertrophied left ventricle. Left ventricular (LV) systole was associated with displacement of the mitral leaflet and chordae tendineae down into the outflow tract. The resulting defect in leaflet coaptation of the mitral valve (MV) and the abnormal chordal position noted in (A) were associated with overwhelming mitral regurgitation (MR) and LV outflow tract obstruction. (B) Administration of inotropes (epinephrine and ephedrine) was discontinued; the management strategy was changed to volume resuscitation and pressor administration. (C) and (D) The hemodynamics normalized, and the examination was repeated 10 minutes later. Displacement of the mitral leaflet and chordae had resolved, together with the findings of MR and outflow tract obstruction. The patient was believed to have experienced a profound acute decline in systemic vascular resistance in response to the release of vasoactive substances during bowel manipulation. The initial exacerbation of the hemodynamics was created by the relative hypovolemia and the use of inotrope, thus leading to dynamic LV outflow tract obstruction. The concomitant episodes of hypoxia and pulmonary edema, which were attributed to the severe MR and increased left atrial pressures, resolved with the decrease in MR. The application of transesophageal echocardiography was critical in making the correct diagnosis, altering management strategies, and initiating the appropriate therapy.

Discussion

Most cases of ischemic MR are categorized as "functional" rather than structural. In a study of 482 patients with ischemic MR, 76% had functional ischemic MR, compared with 24% of patients with significant papillary muscle dysfunction.[38] The mechanism of ischemic MR is attributed to annular dilatation secondary to LV enlargement and regional LV remodeling with papillary muscle displacement, thereby causing apical tethering and restricted systolic leaflet motion.[39] The importance of local LV remodeling with papillary muscle displacement as a mechanism for ischemic MR was reproduced in an animal model.[40]

Severe MR in a patient presenting for CABG is almost always addressed through valve repair or replacement, and cases of trace or mild MR are usually left alone. However, the question of what to do with moderate ischemic MR in patients undergoing CABG is more difficult. Evidence indicates that patients with mild-to-moderate ischemic MR have an increased risk of cardiovascular death if the condition is left untreated,[41] but it remains unclear whether revascularization alone will provide enough improvement in the degree regurgitation to alter mortality rates. Multiple studies looked at this issue without any clear resolution. Following CABG alone, the degree of MR often improves in the immediate postoperative period, but many patients have residual moderate or greater MR after several weeks.[42,43] A study by Penicka and associates[44] identified characteristics (more than five segments of viable myocardium, absence of papillary muscle dysfunction) that help predict improvement in the degree of ischemic MR with revascularization alone (Fig. 16.4).

If MV repair is elected, the most common technique is the use of a restrictive (ie, downsized) annuloplasty ring. Unfortunately, despite this repair, some patients have recurrence of moderate or greater MR postoperatively, especially patients with an LV end-diastolic dimension greater than 65 mm, a coaptation depth greater than 10 mm, or a posterior leaflet tethering angle greater than 45 degrees.[45–47] The first major randomized controlled trial examining this issue was performed by the National Heart, Lung, and Blood Institute Cardiothoracic Surgical Trials Network. This study involved 301 patients from 26 centers across the United States and Canada who had moderate ischemic MR and randomized them to CABG alone or CABG with mitral annuloplasty. The study found no differences in mortality rates or LV systolic volumes after 1 year (subsequent 3- and 5-year follow-up results will be of great interest). Those patients who were randomized to the annuloplasty group had longer CPB times, longer hospital stays, and worse neurologic outcomes, but they did have a reduction in residual moderate or severe MR (11% vs 31% for CABG alone).[48] A second randomized trial, Moderate Mitral Regurgitation in Patients Undergoing CABG (MoMIC) is also under way and should shed additional needed light on this topic.[49,50] Without definitive evidence in either direction, the most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines from 2014 state that MV repair should be considered on a case by case basis in patients with moderate secondary MR who are undergoing other cardiac surgical procedures (class IIb recommendation, evidence level C). Adjunctive techniques to restrictive annuloplasty, including papillary muscle relocation, secondary chordae resection, and posterior leaflet extension, as well as percutaneous techniques such as the MitraClip device (Abbott Vascular, Santa Clara, CA), require further study to determine what role, if any, they may play in reducing the rates of residual ischemic MR after valve repair.[51]

Functional Mitral Regurgitation in the Setting of Aortic Stenosis

Framing

Valvular diseases do not often occur in isolation. Other anatomic structures may be influenced, either by the same pathophysiologic process or as a secondary consequence of the primary valvular lesion. Mitral insufficiency is a common finding, occurring in approximately two-thirds of the patients having significant AS.[52] Patients presenting for AVR commonly have MR, and the question is whether to repair or replace the MV in addition to the AV (Fig. 16.5). Such an undertaking is not without risk. Patients undergoing double-valve replacement have increased mortality rates compared with patients undergoing isolated AVR.[53,54]

Should moderate MR be surgically addressed in patients undergoing AVR for aortic stenosis (AS)? Does the severity of MR regress after AVR? Can it be predicted which cohort of patients with AS would benefit from concomitant MV repair? In which patient cohort would the MR be expected to regress with the unloading effects of replacing a stenotic AV?

Data Collection

The most important data for these decisions are the grade of MV, AV area, anatomy of the MV, and cause of MR (ie, rheumatic disease, ischemic, myxomatous degeneration). Patients are likely to have the signs and symptoms of AS, MR, and pulmonary hypertension. The grade of MR is often not evident until TEE is performed and may be underestimated by a preoperative transthoracic examination. An enlarged left atrium suggests that the MR is chronic, rather than acute.

Discussion

MR is a maladaptive consequence of increasing AS. More significant MR is associated with greater trans-AV pressure gradients, as well as more progressive dilatation and worsening systolic function.[55,56] If the anatomic features of the MV are markedly abnormal and the regurgitation is severe, the decision is relatively obvious: MV repair or replacement at the time of AVR. If the MV is anatomically normal (no leaflet prolapse, no perforation, no rheumatic changes) and the regurgitation is trace or mild, the decision is also relatively obvious: correct the AS and do not surgically address the MV.

The more controversial decision is whether to surgically address the MV that has mild-to-moderate regurgitation when a patient presents for AVR for AS. The evidence currently available on this issue is conflicting. Some studies have shown unchanged or worsened mortality rates in patients who received a concomitant MV repair with their AVR,[57,58] a finding suggests that AVR alone may be the prudent decision. Other investigators, however, have shown an increase in mortality rates for patients left with residual moderate or greater MR following AVR alone and no real effect on mortality rates of concomitant valve repair.[59,60] In general, functional MR of moderate severity usually regresses at least one grade after AVR for severe AS (see Fig. 16.5). Mild-to-moderate MR that improves after AVR for AS seems to be a lasting phenomenon.[61] Harris and colleagues[62] ascribed the decrease in the severity of MR after AVR to several anatomic changes: decreases in mitral annular area, left atrial size, and LV length. Together with the decrease in driving pressure that occurs with resolution of AS, all three of these anatomic changes alter the architecture of the MV and ventricle and contribute to decreasing functional MR.

Coexisting moderate or greater MR is also extremely common in patients presenting for transcatheter AVR (TAVR), with an incidence approaching 20%. As with open AVR, evidence of the effect of untreated significant MR on outcomes following TAVR is conflicting. Data from the Italian and German TAVR registries indicate that moderate or greater MR is an independent predictor of late death following TAVR. In contrast, the Placement of Aortic Transcatheter Valves (PARTNER) trial showed no difference in mortality rates between these patients and those with no or mild MR. Approximately 50% of patients will have an improvement in the degree of MR following TAVR, whereas the remainder will have unchanged or even worsened MR. Some evidence also indicates that MR improvement is greater with the balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, CA) than with the self-expanding CoreValve (Medtronic,

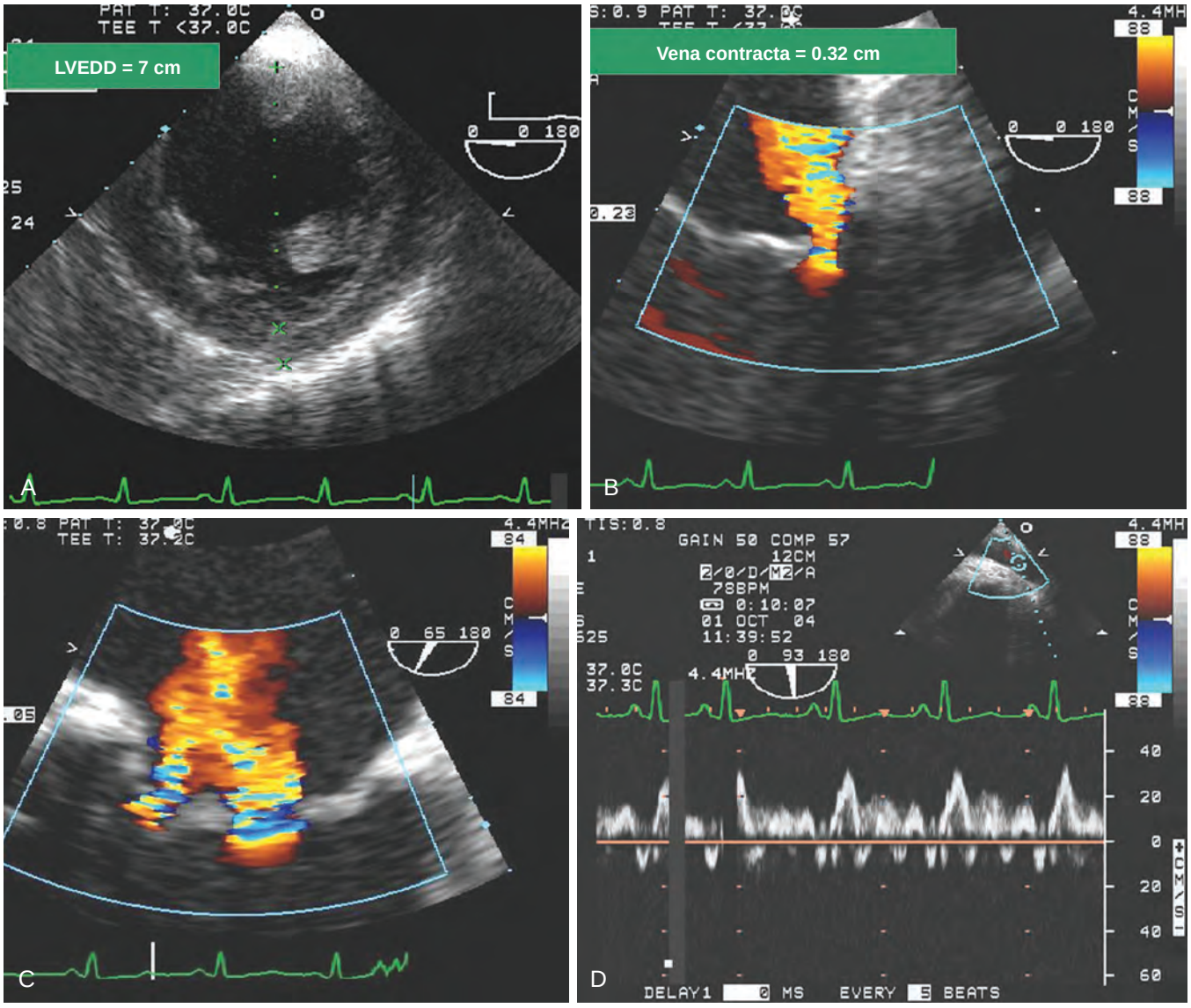


Fig. 16.4 Evaluation of mitral regurgitation (MR) in a patient undergoing coronary artery bypass grafting. A 63-year-old man was scheduled to undergo off-pump coronary artery revascularization. The patient had a history of progressive congestive heart failure without evidence of acute pulmonary edema. The physical examination was significant for a diffuse, laterally displaced point of maximum impulse and a systolic murmur at the apex that radiated to the axilla. (A) The patient received an intraoperative transesophageal echocardiography examination to evaluate the severity of MR. The left ventricle was significantly dilated with a left ventricular end-diastolic dimension *(LVEDD)* of 7 cm and had depressed systolic function with an estimated ejection fraction of 40%. (B) The MR was characterized by color-flow Doppler imaging to be a central jet of mild-to-moderate severity. The grading of MR was based on the area of the regurgitant jet and the vena contracta viewed in a long axis view. The pathogenesis of MR was believed to be functional and resulted from restricted leaflet mobility caused by the dilated left ventricle. (C) The coaptation of the anterior and posterior leaflets was below the valve plane. (D) The absence of reversal of pulmonary vein blood flow measured in the left lower pulmonary vein supported the assessment of moderate MR. Because the annulus was not significantly dilated (the minor axis measured 2.97 cm) and the MR was graded as only mild to moderate, the surgeon proceeded with the initial plan of off-pump coronary artery bypass grafting. The MR decreased immediately after revascularization, and the patient's symptoms were expected to improve further with afterload reduction.

Minneapolis, MN), although this difference must be studied further for confirmation[63] (see Chapter 27).

Factors that may predict an improvement in the severity of MR following both open AVR and TAVR for AS include a functional (as opposed to structural) origin of the regurgitation, poorer LV ejection fraction, greater LV dimensions, and higher aortic transvalvular gradients.[64–66] Negative predictors for the regression of MR after AVR alone include structural MV disease, significant mitral annular calcification, an enlarged left atrium (>5 mm), pulmonary hypertension, and atrial fibrillation.[67,68]

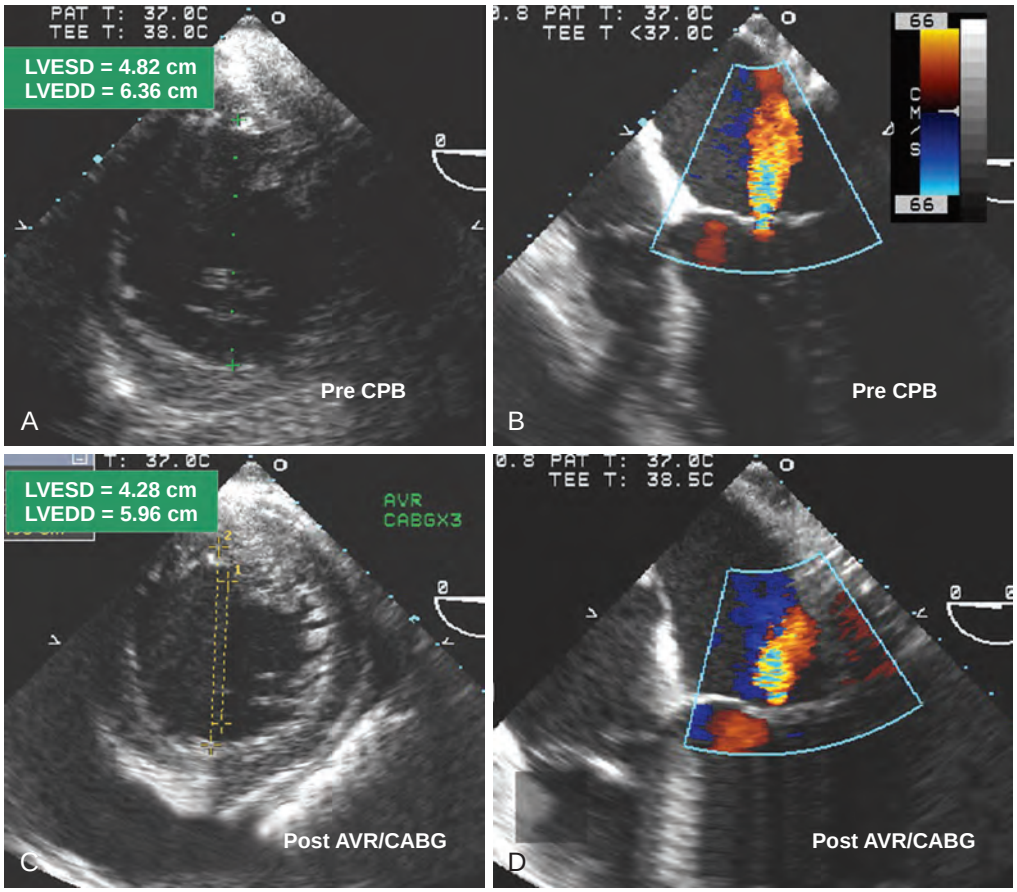


Fig. 16.5 Management of concurrent mitral regurgitation (MR) in a patient undergoing aortic valve replacement (AVR) for aortic stenosis (AS). This 70-year-old patient underwent an AVR for critical AS. The patient had history of hypertension, moderate MR, congestive heart failure, and episodes of shortness of breath. (A) Left ventricular (LV) function was moderately depressed, and the chamber size was dilated (LV end-diastolic dimension *[LVEDD]* = 6.36 cm). (B) The patient had a central jet of MR that was graded as mild; the annulus was mildly dilated, and the pathologic features of the leaflets and apparatus were only mildly thickened. The pulmonary vein blood flow showed minimal blunting of the systolic component, consistent with increased left atrial pressures but not clinically significant MR. The discrepancy in the severity of MR between the preoperative study and intraoperative transesophageal echocardiography (TEE) reflects the effect of general anesthesia on loading conditions. After reviewing the prebypass TEE examination and the patient's history, it was decided to perform only an AVR. A bioprosthetic valve was chosen by the surgeon because of the patient's age, thus eliminating the requirement for anticoagulation. Because the MR was believed to be more functional, the replacement of the severely stenotic AV, the major pathologic lesion, was anticipated to decrease MR over time. The choice of implanting a no. 23 pericardial prosthetic valve was based on the annular size that was measured before initiation of bypass. (C) and (D) The postbypass TEE examination documented that the gradient across the AV decreased from 74 to 18 mm Hg, and (C) cardiac function and (D) MR improved after AVR.

Management of Previously Undiagnosed Aortic Valve Disease

Framing

A relatively common clinical situation for the echocardiographer is to assess the significance of previously unrecognized AV disease. This discussion has pertinence for the echocardiographer faced with the new diagnosis of bicuspid AV, AS, or AR.

What are the symptoms that brought the patient to medical attention? What is the patient's baseline function? What is the anatomy of the AV? What is the severity of AR or AS? How do the intraoperative findings of AV disease differ from the preoperative assessment? Would surgical repair or replacement of the AV benefit the patient's short-term or long-term outcome? What is the planned procedure, and how would the risks be changed if the procedure is altered to address the new finding? Does another health care provider need to be involved in the decision whether to address the valve surgically? Is the disorder of the AV significant enough to require surgical intervention at this time?

Data Collection and Characterization of the Aortic Valve

Multiplane TEE permits an accurate assessment of AV area, valvular disease, severity of regurgitation and stenosis, and detection of secondary cardiac changes. In the case of AS, the severity of valvular dysfunction is determined by measuring the transvalvular pressure gradient, calculating the AV area using the continuity equation, and performing planimetry of the AV systolic orifice. Planimetry of the AV orifice with TEE is more closely correlated with the catheter-derived valve area (using the Gorlin formula) than the value derived from transthoracic

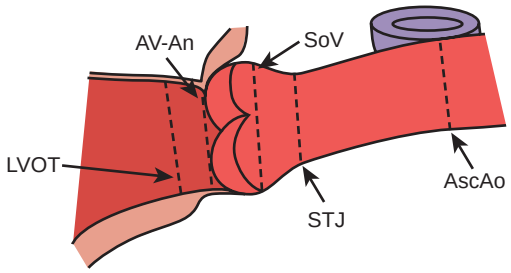


Fig. 16.6 Anatomy of the aortic root. The aortic valve in long axis shows the components of the aortic root, which include the sinotubular junction *(STJ)*, the sinus of Valsalva *(SoV)*, and the annulus of the aortic valve *(AV-An)*. *AscAo*, Ascending aorta; *LVOT*, left ventricular outflow tract.

echocardiography (TTE) ($r = 0.91$ vs 0.84), and 3D TEE assessments of AV area may be more accurate than those obtained by 2D methods.[69,70] The presence of subvalvular disease, such as a discrete fibrous subaortic membrane, should also be excluded, and the aortic root and ascending aorta should be inspected for any pathologic features (Fig. 16.6). Secondary findings associated with AS depend on where the patient's condition is along the natural course of the disease. AS is commonly associated with LV hypertrophy and abnormal filling of the left ventricle. The diastolic function is often impaired in response to a thickened, noncompliant left ventricle. Hence MV and pulmonary vein blood flow velocities would demonstrate a blunted passive filling phase of the ventricle. Systolic function often is normal or hyperdynamic. The LV chamber size is normal or small. However, long-standing AS results in progressive ventricular systolic dysfunction and heart failure. The left ventricle becomes dilated with compromised contractile function. As the ventricle fails, cardiac output (CO) decreases with a resultant decrease in transvalvular pressure gradient. Hence the pressure gradient across the AV may be misleading as a measure for severity of AS.

The severity of AR as seen on TEE generally is graded with color-flow Doppler imaging, with measurement of the width of the regurgitant jet relative to the width of the LVOT. TEE is sensitive to even the most trivial amount of AR. Jet areas measured by TEE tend to be larger, and their severity is graded as greater compared with AR assessed by TTE.[71] The structure of the AV leaflets themselves should also be examined for the presence of any vegetations, perforation, thickening or calcification, or prolapse. The aortic root and ascending aorta should be examined and assessed for any dilation or other structural abnormality that may be contributing to the AR.

The presence of a bicuspid AV presents its own set of associated disorders because it is at increased risk for degeneration and calcification that lead to AR and calcific AS. Bicuspid AVs predispose patients to ascending aortic and arch aneurysm formation,[72,73] and these valves are associated with increased incidences of aortic coarctation and atrial septal defect (ASD). As such, the diagnosis of bicuspid AV should prompt the echocardiographer to search for other commonly associated findings. The presence of isolated asymptomatic bicuspid AV without AS or AR does not mandate surgical correction. Bicuspid AVs can function without major hemodynamic abnormality well into the seventh decade of life.[74] In contrast, many patients experience either progressive dilatation of the aortic root, which produces AR, or premature calcification of the valve, which produces AS.[75–78] For patients in their fourth decade of life, the predominant lesion at operation is AR, which is increasingly treated with surgical repair of the bicuspid AV in young patients.[79–82] With increasing age, the predominant lesion associated with bicuspid AVs becomes AS.[83] The decision-making process with regard to surgical correction of a bicuspid AV must account for the size of the aortic root and the likelihood the patient will return for an aortic root operation in the not-too-distant future. The rate of ascending aortic dilatation in patients with a bicuspid AV may be as high as 0.9 mm/year.[84]

Discussion: Unexpected Mild-to-Moderate Aortic Stenosis

The intraoperative management of mild-to-moderate AS at the time of cardiac operation remains controversial. A patient arrives in the operating room scheduled for CABG but is discovered also to have mild or moderate AS that was unappreciated preoperatively. The operative team must decide whether to address the AV surgically. The ACC/AHA Task Force recommends valve replacement at the time of coronary artery operation if the asymptomatic patient has severe AS but also acknowledges that data to support intervention in the case of mild or moderate AS are limited. In this exact situation, the rate of progression of AS is of value but is rarely obtainable. A rapidly calcifying valve in a young patient that is becoming rapidly stenotic would sway the operative team to perform AVR. A combined double cardiac procedure (CABG/AVR) increases the initial perioperative risk, as well as those risks associated with long-term prosthetic valve implantation. A delay in AVR and a commitment to a second cardiac operation in the future subject the patient to the risk for a redo sternotomy in the setting of patent coronary grafts and its associated morbidities. If the AV is not operated on during the initial presentation for CABG, the development of symptomatic AS may be quite delayed or may not happen.

A review in the national database of The Society of Thoracic Surgeons of 1,344,100 patients who had CABG, CABG/AVR, or AVR alone culminated in a decision paradigm recommendation.[85] The study assumed rates of AV disease progression (pressure gradient of 5 mm Hg/year), valve-related morbidity, and age-adjusted mortality rates that were obtained from published reports. These investigators proposed three factors in the consideration of CABG or AVR/CABG: age (life expectancy), peak pressure gradient, and rate of progression of the AS (if known). Because the rate of AS progression is difficult to discern, the analysis assumed an average rate of disease progression and recommended that patients should undergo AVR/CABG when the peak pressure gradient exceeds 30 mm Hg. The threshold (AS pressure gradient) to perform both procedures is increased for patients older than 70 years of age because the reduced life expectancy diminishes the likelihood that these patients will become symptomatic from the AV disease. Whether to perform concomitant AVR at the time of revascularization was also addressed by Rahimtoola,[86] who advocated a less aggressive approach. All this is beginning to change, however, with the widespread adoption of TAVR. TAVR not only offers a valve replacement option to older or otherwise high-risk patients who previously would have been denied open surgical AVR but also is increasingly being held out as a future treatment option to patients undergoing a needed cardiac procedure who have coexisting mild-to-moderate AS. Rather than add AVR onto a CABG or other procedure, which increases mortality rates, a patient can be referred for TAVR 5 to 10 years down the line when his or her AS becomes symptomatic, without the added morbidity of a redo sternotomy. Thus far the outcomes of TAVR have been quite good, although the long-term outcomes remain uncertain.

The transvalvular pressure gradient, heretofore used as a grading tool for AS severity, may be a misleading measure of the degree of stenosis of the AV because its value depends on CO. A low CO and flow rate produce a low transvalvular pressure gradient, even in the setting of a severely stenotic AV. Patients with LV dysfunction and decreased CO in the setting of AS often present with only modest transvalvular pressure gradients (<30 mm Hg). Distinguishing patients with a low CO and severe AS from patients with mild-to-moderate AS can be challenging (Fig. 16.7). The standard for assessing the severity of AS is AV area, typically calculated using either a continuity method or by planimetry. Patients with low-gradient AS with severe LV dysfunction who underwent AVR had improved survival and functional status compared with patients who did not have a valve replacement.[87–89]

Dobutamine challenge in a patient with low-pressure gradient AS can be useful in establishing the true AV area. The ability to distinguish

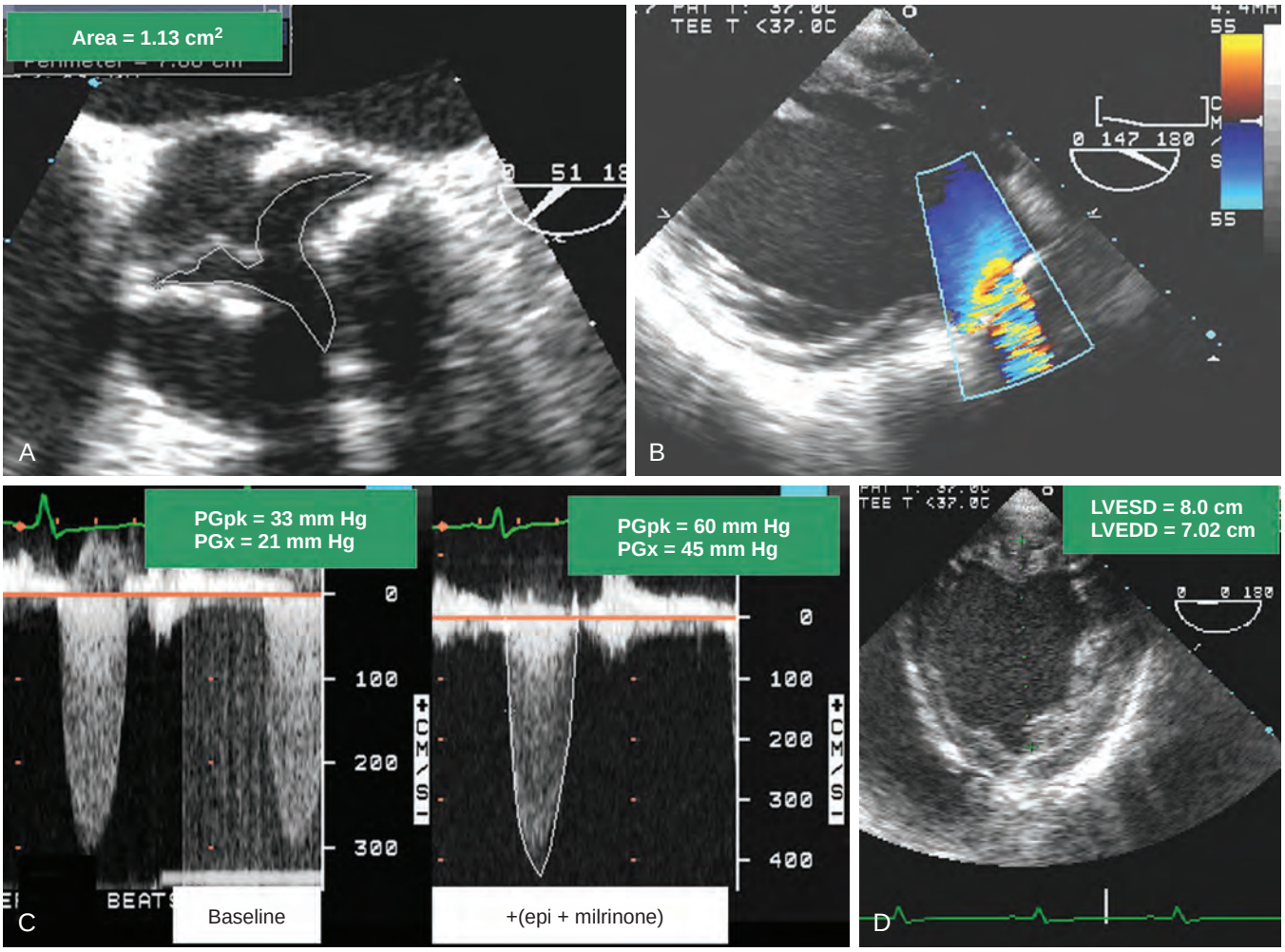


Fig. 16.7 Low-pressure gradient severe aortic stenosis (AS). A 76-year-old cachectic man was scheduled to undergo a corrective surgical procedure for severe mitral regurgitation (MR) and possibly clinically significant AS. (A) The midesophageal short-axis view of the aortic valve (AV) showed a highly calcified trileaflet valve with restricted mobility. The measurement of AV area, 1.13 cm^2, which was obtained by planimetry, was believed to underestimate the severity of AS because of the shadowing artifacts related to the severity of calcification. (B) The transgastric long axis of the left ventricle was obtained, and the velocity profiles of blood flow within the left ventricular (LV) outflow tract and the AV were measured. (C) Although the patient had a diagnosis of severe AS, the maximal pressure gradient *(PGpk)* and mean pressure gradient *(PGx)* were 33 and 21 mm Hg, respectively. The area of the AV was calculated to be 0.83 cm^2 using the continuity equation. (D) LV function was characterized by severe dilated cardiomyopathy with an ejection fraction of 8%, an LV end-systolic dimension *(LVESD)* of 7 cm, and an LV end-diastolic dimension *(LVEDD)* of 8 cm. The diagnosis of low-pressure gradient AS was considered, and infusions of epinephrine and milrinone were started. Cardiac performance improved from 2.4 to 4.5 L/minute, and the pressured gradients (C) increased to 60 mm Hg peak and 41 mm Hg mean. Although the calculated valve area that was recorded under conditions of inotrope support slightly increased to 0.9 cm^2, transesophageal echocardiography clarified that the marked increase in the pressure gradient was consistent with a diagnosis of low-gradient AS and confirmed the presence of cardiac reserve.

between true AS and a state of "pseudostenosis" relies on characteristic changes in hemodynamic and structural measurements in response to the augmented CO. The test is not usually performed in the operative setting but rather is used in the preoperative evaluation. The increase in calculated AV area is related to the increase in the CO and is attributed to partial reversal of primary cardiac dysfunction.[90–93] If dobutamine improves CO and increases the AV area, it is likely that the baseline calculations overestimated the severity of the AS. The dobutamine challenge is conducted as follows: patients with low-gradient AS receive intravenous dobutamine at 5 μg/kg per minute with stepwise increases in dose.[91] Patients may exhibit a significant increase in AV area (0.8 to 1.1 cm^2) and a decline in valve resistance after dobutamine challenge. Patients with fixed, high-grade AS would demonstrate no change in valve area and an increase in valve resistance.

Although most patients who exhibit low-gradient AS have reduced EFs, a subset of patients with low-gradient AS (as defined by a mean gradient <40 mm Hg and an AV area <1 cm^2) has preserved EFs. These patients often have small ventricular cavities, severe concentric LV hypertrophy, increased afterload, restrictive physiology, and/or increased subendocardial myocardial fibrosis.[94] The need for valve replacement in this subgroup of patients is still unclear, but early data suggest that outcomes of medical management alone are better than those in high-gradient AS or low-gradient, low-EF AS, and outcomes may be similar to those in patients with mild-to-moderate AS.[95]

Discussion: Unexpected Aortic Regurgitation

Many older patients undergoing cardiac surgical procedures have some degree of AR. In most cases, the patients are asymptomatic, and the severity of AR is graded as trace to mild. The presence of AR has implications regarding the conduct of circulatory management, administration of cardioplegia, management of hemodynamics, and possible alteration of the surgical plan. The presence of AR requires the echocardiographer to monitor for distention of the left ventricle during CPB and cardiac arrest, as well as during the administration of antegrade cardioplegia. On release of the aortic cross-clamp, the heart may not instantaneously revert to an organized rhythm, thus precluding ejection of LV blood and predisposing to ventricular distention. Ventricular distention is particularly problematic in the setting of AR. The decision whether to address the valvular dysfunction surgically should not be based on LV distention during CPB but considered in the context of the data set that includes the natural history of AR in adults, established guidelines, and published outcomes, in addition to individual patient-related variables, as previously described.

Chronic AR generally evolves in a slow and insidious manner with very low morbidity during a long asymptomatic phase. Some patients with mild AR may remain asymptomatic for decades. Others exhibit progressive worsening of the regurgitant lesion and develop LV systolic dysfunction, leading eventually to heart failure. Evaluation of LV size and function is important because of the poor correlation between symptoms and severity of cardiac disease. The nature of the transition between the compensated and uncompensated periods is poorly understood. Clinicians should be reluctant to consider valve replacement in an asymptomatic patient with preserved LV function (Fig. 16.8). Early operation exposes the patient to perioperative death and morbidity, as well as to the long-term complications of a prosthetic valve. The most recent guidelines for AV operations in patients with AR were published in 2014 by the ACC/AHA Task Force.[49] AVR is clearly indicated for symptomatic patients with chronic, severe

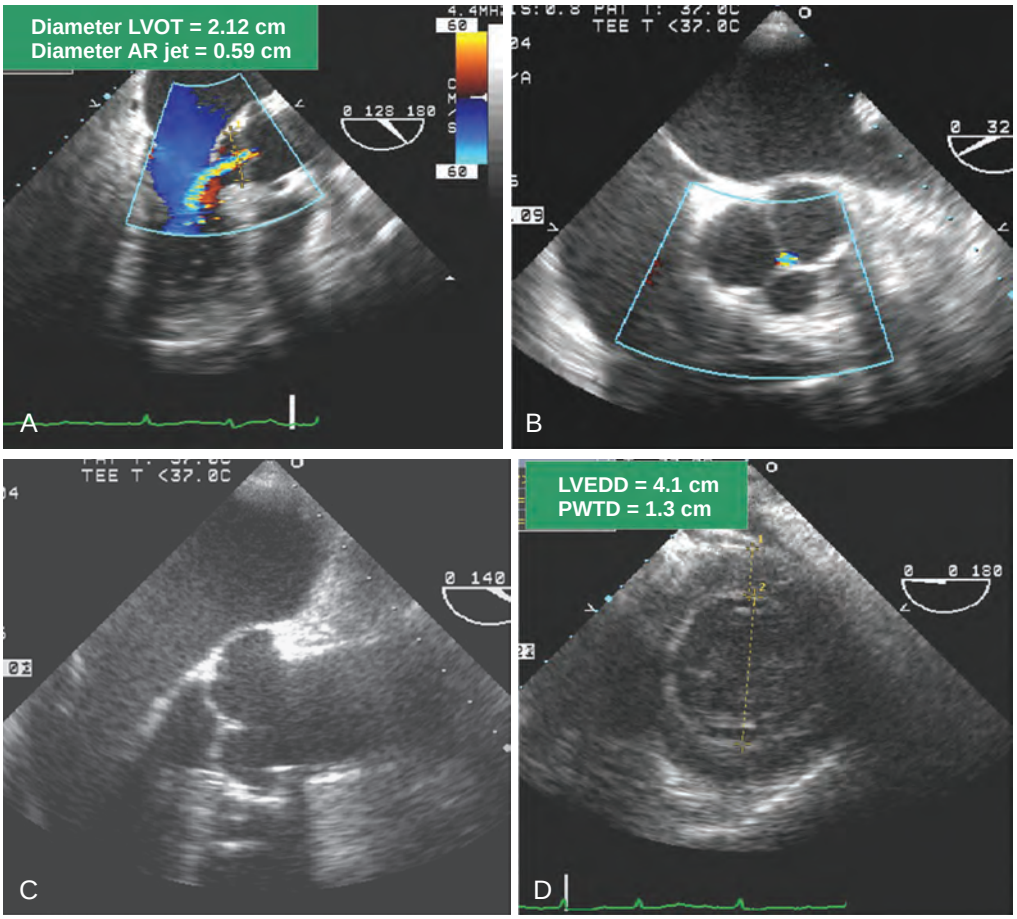


Fig. 16.8 Detection of occult aortic regurgitation *(AR)* during a nonvalvular cardiac surgical procedure. A 66-year-old woman was scheduled to undergo coronary artery bypass grafting using extracorporeal circulatory support. (A) An intraoperative transesophageal echocardiography examination detected the presence of a central AR jet that extended halfway into the left ventricle. The severity of AR, which was graded as mild, was based on assessing the retrograde flow in the left ventricular (LV) outflow tract *(LVOT)* by using color-flow Doppler imaging in midesophageal long-axis plane. The severity of AR is determined by comparing the width of the AR jet, 0.59 cm, with the diameter of the LVOT, 2.12 cm; the ratio of 0.28 is graded as mild. (B) and (C) The anatomy of the valve was that of a normal trileaflet structure with mildly thickened leaflets. No leaflet prolapse, vegetations, or annular or root dilation was present. In addition, no significant aortic stenosis was detected by Doppler examination or calcification of the leaflets. (D) LV chamber size was normal, LV end-diastolic dimension *(LVEDD)* was 4.14 cm, and the presence of LV hypertrophy was consistent with hypertension. Because the severity of AR was not clinically significant and it was not expected to increase markedly, surgical intervention in the aortic valve was deferred. However, the diagnosis of AR altered circulatory management by increasing the vigilance of the echocardiographer to monitor LV chamber size during antegrade cardioplegia and initiate supplemental retrograde cardioplegia. *PWTD,* Pulsed-wave tissue Doppler.

AR, as well as for asymptomatic patients with systolic dysfunction that has no other cause. However, the decision to perform valve replacement is less apparent for asymptomatic patients with moderate AR. The published recommendations suggest that it is reasonable (class IIa recommendation) to perform a valve replacement in asymptomatic patients with moderate AR who are undergoing a surgical procedure for another reason or in patients with an LV end-systolic dimension greater than 50 mm.

Cardiac Function and New Regional Wall Motion Abnormalities

Framing

Ventricular function is a predictor of outcome after cardiac surgical procedures and a predictor of long-term outcome in patients with cardiovascular disease. Patients with compensated congestive heart failure may have a severely decreased EF with minimal symptoms. Regional ventricular dysfunction most commonly is caused by myocardial ischemia or infarction. Hence an imperative exists to detect ventricular dysfunction and institute treatment in an attempt to prevent acute or long-term consequences.

Is ventricular function normal or abnormal? Is the abnormal function global or regional? What is the coronary artery distribution that relates to an SWMA? Is the ventricle large or small? Is the myocardium thinned or hypertrophied? Is the abnormal function new or old? Does the medical or surgical intervention improve or decrease ventricular function?

Data Collection

LV systolic function is assessed echocardiographically based on regional and global wall motion. Methods of assessment include changes in regional wall thickness, radial shortening with endocardial excursion, fractional area change, and systolic apical displacement of the mitral annulus. Quantitative assessments of EF and LV volumes can be made using software built into most modern echocardiography machines by using either 2D (Simpson's equation) or 3D data sets. The 3D techniques in particular have demonstrated accurate results in LV chamber quantification when compared with cardiac magnetic resonance imaging (MRI).[96] Speckle-tracking and measurement of LV strain have also shown promise as newer modalities to assess LV function.

Regional assessment of LV wall motion provides an index of myocardial well-being that can be linked to coronary anatomy and blood flow. Although the measurement of coronary blood flow is not achieved by TEE, the perfusion beds and corresponding myocardium for the left anterior descending, left circumflex, and right coronary arteries are relatively distinct and can be scrutinized by TEE using multiplane imaging. The transgastric short-axis and long-axis imaging views of the left ventricle are the most widely used for evaluating wall motion abnormalities. Regional myocardial ischemia produces focal changes in the corresponding ventricular walls before changes occur on the ECG.[97] Changes progress from normal wall motion to hypokinesis or akinesis. Dyskinesis, thinning, and calcification of the myocardium suggest a nonacute process, likely a previous infarction.

Assessment of RV systolic function is more problematic because it is less quantifiable. The crescent-shaped right ventricle is not amenable to quantitative measures of differences in chamber size during the cardiac cycle. Characterization of the right ventricle is accomplished by comparing the size of the RV chamber with that of the left ventricle and assessing the relative contractile function of the RV free wall and that of the interventricular septum. Early research on 3D echocardiographic techniques to assess RV function was promising,[98,99] but these findings largely relied on off-line analysis of data sets by third party or proprietary software and are thus impractical for use in real time in the operating room.

Ventricular failure can be caused by diastolic dysfunction: the compromised ability of the ventricle to accommodate diastolic filling. Diastolic dysfunction is assessed echocardiographically by examining volumetric filling of the ventricle at the mitral or tricuspid valves and annular excursion using tissue Doppler. Abnormalities of ventricular filling (eg, impaired ventricular relaxation, restriction, constriction) produce characteristic changes in the spectral recordings of Doppler inflow velocities. Abnormalities of diastolic function can lend insight into the mechanisms of circulatory instability (see Chapters 14 and 15).

Discussion

Preexisting ventricular dysfunction suggests an increased surgical risk and a poorer long-term outcome. Such ventricular dysfunction may deteriorate intraoperatively and require marked pharmacologic or mechanical support. A patient with a preoperative EF of 10% who is scheduled for CABG and MV repair is at increased risk for intraoperative ischemia, acute heart failure, and difficulty maintaining hemodynamic stability during the period immediately after bypass. Anticipating such problems, consider placement of an intraaortic balloon pump or femoral arterial catheter during the period before bypass (Fig. 16.9). The same patient is likely to benefit from the administration of inotropic agents during separation from CPB (see Chapter 36).

A marked decrement or unexpected decrease in global cardiac function after release of the aortic cross-clamp can be caused by poor myocardial preservation during cross-clamping or distention of the heart during bypass. The risk for such incidents can be reduced by monitoring of the electrical activity of the heart and pulmonary artery pressures, as well as monitoring for distention of the right and left ventricles. Effective venting of the heart is often difficult to discern by visual inspection alone, especially with the use of minimally invasive surgery through small incisions. TEE can detect ventricular distention produced by AV insufficiency.

Not all preexisting SWMAs benefit from coronary revascularization. Regions of akinesia and dyskinesia usually are the result of a myocardial infarction and may reflect nonviable myocardium, although "hibernating" myocardium is possible. Hypokinetic segments generally are viable and may represent active ischemia.[100] Preoperative positron emission tomographic scanning can detect hibernating myocardium and may be cost effective to guide CABG.[101–103] The detection of hibernating myocardium in an area of chronic ischemia and regional hypokinesis directs the surgeon to revascularize the corresponding stenosed coronary artery. In contrast, an occluded coronary artery with downstream infarction may not benefit from revascularization because contractile function may be irreversibly lost. However, in this latter situation, revascularization after infarction may provide some benefit in decreasing the risk for ventricular aneurysm formation.[104]

Diastolic dysfunction is associated with significant increases in mortality rates during long-term follow-up.[105] Characterization of abnormalities of diastolic function lends insight into the mechanisms of circulatory instability and hypotension. Severe LV hypertrophy with a noncompliant left ventricle and hyperdynamic systolic function may produce severe heart failure if adequate loading is not achieved. Hemodynamic indices obtained from a pulmonary artery catheter may be misleading. The findings of a small LV chamber size, blunted transmitral filling velocities, and an increased fractional area change demonstrate the cause of the hypotension. The decision to administer volume may be appropriate despite the increased pulmonary artery pressures.

If the intraoperative examination reveals new ventricular dysfunction, the intraoperative team must determine the cause and severity and then plan a treatment. Other causes of SWMAs such as conduction abnormalities (left bundle branch block or ventricular pacing) may be difficult to distinguish. Is the decrement in function potentially reversible with conservative therapy, or should additional intervention be considered? Treatment of myocardial ischemia may include

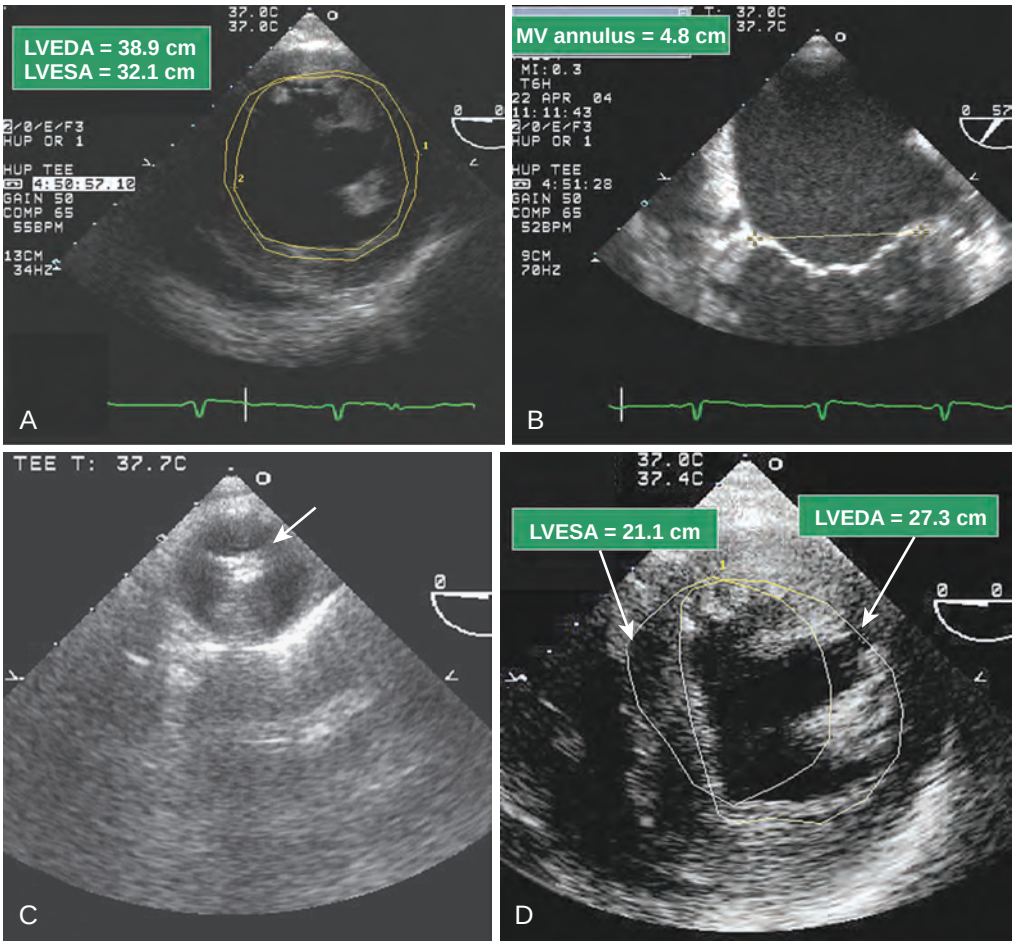


Fig. 16.9 The prebypass transesophageal echocardiography (TEE) examination may have predictive value for postbypass circulatory management. A 63-year-old woman with a medical history of hypertension, congestive heart failure, pulmonary edema, dilated cardiomyopathy, diabetes, and obesity was scheduled for coronary artery bypass grafting (CABG) and mitral valve (MV) repair. The preoperative evaluation documented moderate-to-severe mitral regurgitation (MR) with reversal of systolic pulmonary vein blood flow velocity. (A) The prebypass TEE midesophageal four-chamber view showed a markedly dilated left ventricle (LV) and mildly dilated right ventricle (RV) with mildly decreased global dysfunction. The transgastric view was characterized by severe global dysfunction and an LV end-diastolic diameter of 6.6 cm. The fractional area change (FAC) was 17% [FAC = (left ventricular end-diastolic area [LVEDA] – left ventricular end-systolic area [LVESA])/LVEDA × 100]. Revascularization alone was unlikely to significantly improve MV function. (B) The midesophageal bicommissural view of the MV demonstrated marked dilation of the MV annulus (major axis = 4.8 cm) and tethering of the leaflets below the valve plane that was caused by LV chamber dilation. A femoral arterial line was inserted for monitoring of central aortic pressure and/or possibly placing an intraaortic balloon pump. The patient underwent a CABG × 3 and MV annuloplasty for moderate MR. The separation from bypass was difficult, requiring milrinone, epinephrine, vasopressin, and placement of an intra-aortic balloon pump. (C) TEE, which was used to initially confirm the location of the femoral guidewire, was later used to position the balloon pump just downstream to the left subclavian artery. (D) Worsening of RV function that was characterized by increased central venous pressure, new-onset tricuspid regurgitation, and a hypokinetic RV can be appreciated by ventricular septal flattening and dilation of the RV. The LV ejection fraction did not decrease as might be expected; after correcting MR, the FAC improved slightly from 17% to 22% after bypass. Cardiac function continued to improve, and the counterpulsation device was removed without complication on the first day after surgery. The infusions of milrinone and epinephrine were continued for several days.

the following: optimizing hemodynamics; administering anticoagulants, nitrates, calcium channel blockers, or β-blockers; inserting an intraaortic balloon pump; or instituting CPB and coronary revascularization. The presence of new-onset SWMAs after separation from CPB is worrisome for myocardial ischemia. Even the patient without coronary artery disease remains at risk because of hypotension, a shower of air or debris into the coronary circulation, or coronary spasm. The patient with coronary artery disease who is undergoing CABG may have all the foregoing risks, technical difficulties at the anastomotic site, injury to the native coronary artery (eg, stitch caught the back wall or occlusion of the circumflex artery during MV operation), or occlusion of the coronary graft by thrombosis or aortic dissection. The coronary arteries, grafts, and anastomoses should be carefully inspected for patency and flow. Graft patency in the operating room is

difficult to determine. Techniques include manual stripping and refill, measurement of coronary flow by handheld Doppler, or administration of echocardiographic contrast agents (see Chapters 14 and 15). Hybrid operating rooms have been increasing in number with the intent of providing advanced imaging of the coronary circulation at the time of operation.[106] A new SWMA in the distribution of a new coronary graft can prompt the decision-making strategies listed in Table 16.1 (see Chapters 20, 36, and 38).

Transesophageal Echocardiography as a Rescue Device: Management of Marked Hemodynamic Instability

Framing

In many instances during the perioperative period, the patient may exhibit progressive, unremitting hemodynamic deterioration or acute cardiovascular collapse. Echocardiography offers a versatile modality to diagnose the cause of hypotension and develop management strategies quickly and accurately (see Chapters 15 and 46).

The echocardiographer may be summoned to evaluate an unstable patient in the operating room, intensive care unit, or emergency department with little or no preceding knowledge of the patient. Typically, no consent for the TEE procedure will have been obtained; occasionally, a family member may be available to provide consent on the patient's behalf. TEE may need to be postponed in the trauma patient with suspected cervical spine injury or esophageal injury. The trauma patient with an unstable cervical spine is at increased risk for spinal cord injury with passive movement of the head and neck. Until the cervical spine has been documented to be stable, TEE should be avoided, and TTE is the alternative. The risk for further esophageal injury in patients with penetrating trauma poses an additional challenge. Esophagoscopy is performed before TEE in patients with suspected esophageal injury. However, delay in diagnosis is not without cost. Time must be used efficiently because permanent vital organ injury relates to the magnitude and duration of hypotension and malperfusion. Several issues should be considered to guide the discussion and development of rational management strategies.

What is the cause of the hypotension? Does the cardiac or vascular disorder detected by TEE explain the decrease in blood pressure? Is the heart large or small? Is it full or empty? What is the global function of both ventricles? Are SWMAs present? Is fluid present in the pericardium? Is the observed decrease in cardiac function the primary cause, or is it a consequence of the decreased blood pressure? Is this event related to the patient's medical history or current operative procedure?

TABLE 16.1 Management Strategies for New-Onset Myocardial Ischemia After Bypass

Cause of Ischemia	*Diagnosis*	*Plausible Treatment*
Coronary graft occlusion	ECG changes, new wall motion abnormality, systolic dysfunction	Revise coronary graft
Coronary air emboli	ECG changes, new wall motion abnormality, systolic dysfunction, increased echogenicity of myocardium	Increase coronary perfusion pressure
Coronary calcium or atheroma emboli	ECG changes, new wall motion abnormality, systolic dysfunction	Support circulation, increase coronary perfusion pressure
Dissection of the aortic root	Dissection or hematoma in ascending aorta or aortic root	Repair dissection
Coronary spasm	ECG changes, systolic dysfunction, new wall motion abnormality	Administer coronary dilators

ECG, Electocardiography.

What specific parameters of the ventricle may help explain the current episode of hypotension? What interventions or therapy can be performed to improve hemodynamics? Once therapy is initiated, what index or parameter should be monitored to guide management?

Data Collection

Clinicians must not underestimate the importance of medical history, chief complaint, and operative course when attempting to discern the causes of hemodynamic instability in the acute setting. Important hemodynamic indices include heart rhythm, heart rate, blood pressure, concentration of exhaled carbon dioxide, and central venous or pulmonary artery pressure, if available. Echocardiography can be used to develop a rational approach based on the critical factors of cardiac performance. The determinants of cardiac performance include stroke volume and heart rate, as elucidated by the following equation: CO = Stroke volume × Heart rate. The three components of SV that can be affected are preload, afterload, and myocardial contractility. Although quantitative analysis is possible, qualitative online analysis generally yields sufficient information to form the basis of initial therapeutic intervention. Preload of the ventricle can be determined by assessing the end-diastolic area, afterload can be estimated by assessing the end-systolic area, and contractility can be estimated by the velocity of circumferential shortening, fractional area change, or EF. Mechanical causes of hypotension must be considered (eg, pericardial effusion).

Discussion

Initial inspection determines heart size and overall contractile function of both ventricles. Estimates of end-diastolic area and EF of the LV provide an index of ventricular load and global function. Attention to both RV and LV size and function helps distinguish among different inciting events.

The common causes of intraoperative or perioperative hypotension include intravascular hypovolemia, myocardial ischemia, myocardial infarction, and systemic vasodilatation, either pathologic from infection or inflammation or iatrogenic from drug administration (eg, vancomycin). Mechanical causes of hypotension typically are related to compressive forces impairing the heart's ability to fill or eject (eg, pericardial fluid, tension pneumothorax). The MV is inspected for incompetence. Acute MR is rare in the absence of myocardial ischemia or infarction. A diagnosis of dynamic LVOT obstruction, an uncommon cause during the perioperative period, is difficult to establish in the absence of more invasive monitoring such as TEE (see Fig. 16.3). Systemic hypotension with a dilated right ventricle and a small, underfilled left ventricle implies either primary RV failure (eg, myocardial ischemia or infarction in the distribution of the right coronary artery) or secondary RV failure from acute increases in pulmonary vascular resistance (eg, pulmonary embolus [Fig. 16.10], pneumothorax, or protamine reaction).

Decreased systemic vascular resistance during sepsis or a systemic inflammatory reaction is associated with decreased end-systolic area and increased ventricular contractility (increased velocity of circumferential shortening), with concomitant elevations in the EF and fractional area change. The increase in cardiac performance can be quantified by measuring the CO. In cases of hypotension associated with a markedly heightened CO, the treatment of choice would be the administration of a vasopressor, such as phenylephrine or vasopressin. If decreased systemic vascular resistance and CO are present, administration of a positive inotrope having vasopressor actions, such as epinephrine or norepinephrine, may be more appropriate.

The distribution of the right coronary arterial system of most patients (right-dominant system) includes the right ventricle and the posterior descending coronary artery, which provides blood supply to the inferior and inferoseptal walls of the left ventricle. Acute RV dysfunction is not uncommon after the release of the aortic cross-clamp. Preservation of the right ventricle is less reliable compared with the

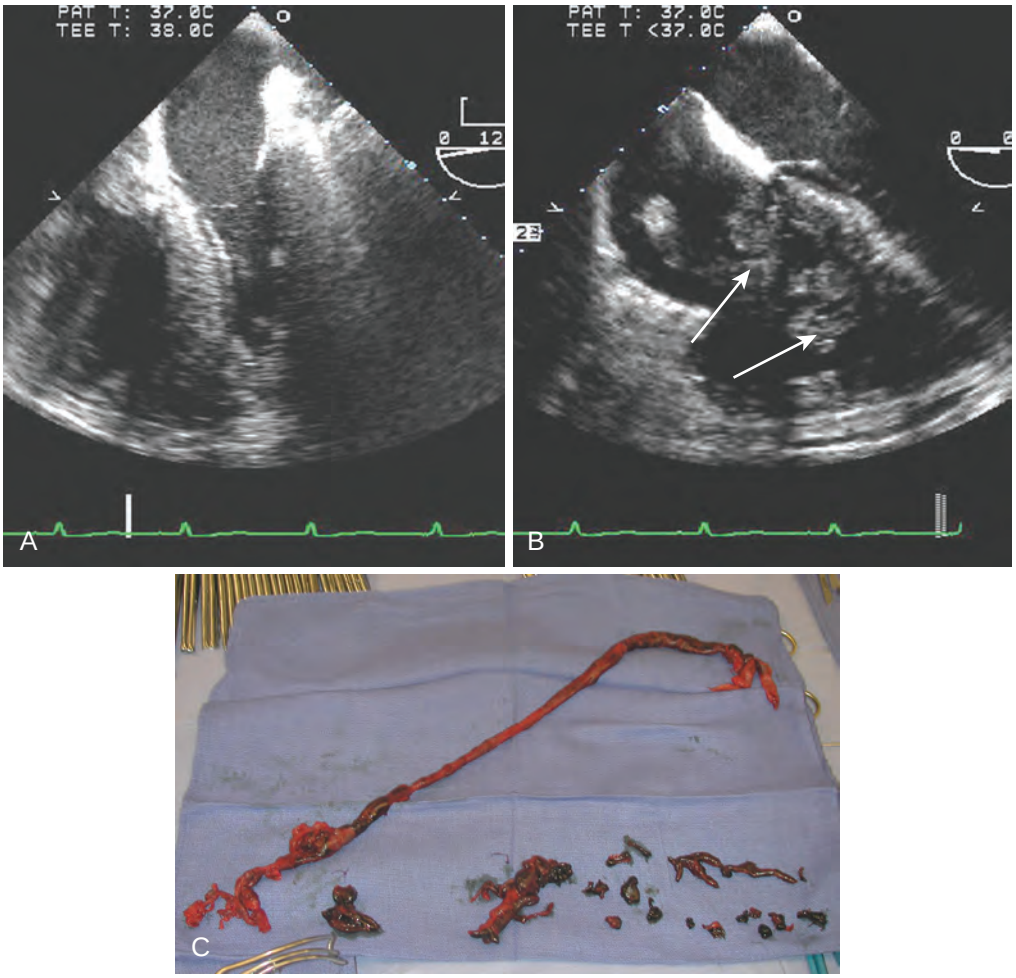


Fig. 16.10 Progressive hypoxia and hypotension after cardiac surgery. A 58-year-old morbidly obese patient with a medical history of hypertension, diabetes, and smoking had recently undergone coronary artery bypass grafting × 3. Five days after surgery, the patient experienced development of new-onset atrial fibrillation together with progressive hypoxia and hypotension requiring readmission to the intensive care unit. The patient's condition continued to deteriorate and required tracheal intubation, ventilator support, and infusions of vasoactive agents. Transesophageal echocardiography (TEE) was performed to evaluate cardiac function and rule out a pericardial effusion. (A) The midesophageal four-chamber view showed a dilated right ventricle (RV) coincident with a relatively underfilled left ventricle (LV) and abnormal positioning of the ventricular septum. The displacement of the septum into the LV was consistent with RV dysfunction and RV volume overload. (B) Inspection of the right heart revealed a dilated hypokinetic RV and a serpiginous density that extended from the right atrium into the RV. The thrombus appeared to be entangled in the chordal structure of the tricuspid valve. Although no thrombus was noted in the pulmonary arteries, the diagnosis of pulmonary embolism was made and the patient underwent an emergent embolectomy. (C) A right atriotomy was performed, and a 64-cm thrombus was extracted from the RV together with additional clots from both the right and left pulmonary arteries. The postbypass TEE documented improved right ventricular function and filling of the LV. TEE was critical in making the diagnosis and the decisions to institute and guide therapy.

left ventricle because of its exposure to ambient room temperature and variability in its coronary circulation. Open-chamber procedures increase the risk for RV dysfunction because of retained intracardiac air. In the supine patient, the right coronary ostium is located in the least-dependent portion of the aortic root, thus predisposing it to embolization of air bubbles. Air embolization to the right coronary artery produces acute ST-segment changes, marked global RV dysfunction, and SWMAs of the inferior wall of the left ventricle (Fig. 16.11). Conservative treatment includes increasing the blood pressure to promote coronary perfusion while continuing CPB.

Pericardial Effusion and Cardiac Tamponade

Framing

Small effusions are common after cardiac operations, especially after removal of chest tubes. In isolation, pericardial effusion may not require surgical intervention. Cardiac tamponade occurs when the pressure exerted by the presence of a pericardial effusion (or any structure adjacent to the heart) compresses the heart, limits diastolic filling of any of the chambers of the heart, and impairs CO. Cardiac

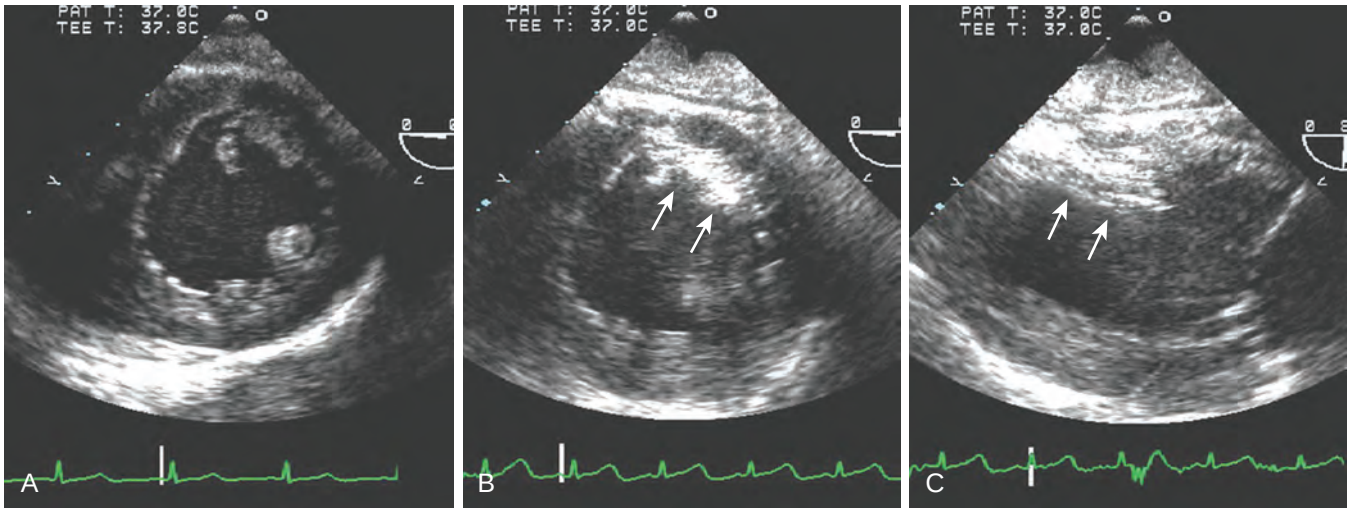


Fig. 16.11 Air embolism after open-chamber procedure. A 57-year-old patient underwent surgical intervention to treat severe mitral regurgitation (MR) and two-vessel coronary artery disease. After performing the mitral valve (MV) repair, the right superior pulmonary vein vent catheter was advanced through the mitral valve to facilitate deairing. The patient was positioned in Trendelenburg and the aortic cross-clamp removed. After ventricular ejection, the left atrium and ventricle (LV) were relatively clear of air and the left atrial vent was removed. An aortic vent that had previously served as the cardioplegia cannula was used to vent the residual air from the ascending aorta. The patient was separated from bypass in normal sinus rhythm and maintained good hemodynamics. (A) The initial postbypass transesophageal echocardiogram (TEE) showed normal ventricular function and filling. Shortly after starting administration of protamine, the blood pressure decreased and the electrocardiogram demonstrated ST-segment changes consistent with ischemia. The protamine administration was stopped, and vasopressors and inotropes were quickly administered. The TEE documented reduced cardiac function in the right ventricle and hypokinesis in the inferior and inferoseptal walls of the LV. (B and C) The transgastric short- and long-axis views of the LV showed that the myocardium in the distribution of the right coronary artery, as designated by the arrows, was characterized by increased echogenicity. Note the significantly elevated ST segments observed in B and C compared with the baseline (A). The absence of pulmonary hypertension and adequate diastolic filling of the LV supported a diagnosis other than acute anaphylactic protamine response or pulmonary embolism. The most likely culprit was air embolization causing transient myocardial ischemia. Air bubbles that migrated from the LV chamber embolized into the ostium of the right coronary artery, which lies at the most anterior aspect of the sinus of Valsalva. TEE served a crucial role in quickly evaluating and diagnosing the cause of hypotension. The hemodynamics, which were temporarily supported by boluses of vasopressors and inotropes, stabilized, and the protamine dose was completed. The patient was transferred to the intensive care unit without any further incident.

tamponade is an emergency, necessitating immediate diagnosis and intervention (see Chapters 24 and 29).

Is a pericardial effusion present? If so, does it contribute to cardiac dysfunction and the patient's present hemodynamic distress? What is the cause of the effusion (acute or chronic)? Is the pericardial effusion the sequela of another cardiovascular event or process (ie, aortic dissection or cardiac catheterization)? Are invaginations of the free walls of the right atrium, right ventricle, or left atrium present? Is the effusion free flowing or loculated? Where is it located? Is echocardiographic assessment consistent with tamponade? What is the coagulation status?

Data Collection

Echocardiography is the standard modality for diagnosis of pericardial fluid. However, the diagnosis of cardiac tamponade is a clinical diagnosis based on hemodynamics and the patient's condition. Low CO, hypotension, equalization of pressures, and high venous pressures are all signs of cardiac tamponade. Echocardiographic findings consistent with tamponade include the presence of pericardial fluid, compression of the atria, compression of the right ventricle, and loss of normal respiratory variability of ventricular inflow velocities.

The TEE examination quickly determines whether pericardial effusion is present, the location of the effusion (loculated, free-flowing), and the impact on chamber filling. Location of the effusion is paramount should pericardiocentesis be deemed necessary for acute decompression. Right atrial and RV collapse are the most sensitive signs of increased pericardial pressure. The effusion need not be a large circumferential effusion to affect cardiac function significantly. Postcardiotomy pericardial clot may be smaller and more compartmentalized than a chronic circumferential effusion, which may be free flowing. Interpreting the clinical significance of cardiac hemodynamics may be complicated by factors such as lability of hemodynamics, decreased intravascular volume, depressed cardiac function, mechanical ventilation and pulmonary dysfunction, soft tissue changes, and chest tubes that obstruct some of the echocardiographic windows. Doppler imaging is used as a complementary method of demonstrating the hemodynamic derangements of tamponade and to determine the clinical significance of an effusion. The echocardiographer should interrogate the phasic respiratory variation of blood flow through the tricuspid valve and MV. Although not specific for tamponade, the changes in respiratory variation of inflow velocity are the hallmarks of increased pericardial pressure. Significant respiratory variation of blood inflow velocities also may be seen in constrictive pericarditis or conditions associated with changes in intrathoracic pressure, such as

increased work of breathing, asthma, or positive-pressure ventilation, and it may be exacerbated in patients receiving positive end-expiratory pressure. Other important data pertaining to the cause and possible intervention include coagulation status.

Discussion

The ACC/AHA/American Society of Echocardiography (ACC/AHA/ASE) Task Force assigned a class I recommendation to the use of echocardiography in patients with suspected bleeding in the pericardial space. Echocardiography is portable, quick, and noninvasive, yet it is a sensitive and specific modality for the detection and assessment of a pericardial effusion. Pericardial effusions can be diagnosed and cardiovascular effects determined by TTE or TEE. However, during the period after cardiac operation, the presence of positive-pressure ventilation, chest tubes, and bandages may severely limit the capability of TTE to assess fluid in the pericardium.

The effusion need not be a large circumferential effusion to affect heart function significantly. Loculated effusion may impinge only on the left atrium and may not be discernible by the traditional acoustic windows used by TTE. A hemodynamically significant localized hematoma compressing only the left atrium may not produce right atrial and RV collapse or the constellation of equalization of pressures. Small effusions are common after cardiac surgical procedures, especially after removal of chest tubes, and in heart transplant recipients with a mismatch between heart size and pericardial cradle. The presence of a pericardial effusion in the patient who has not undergone cardiotomy must lead to a search for the cause of the effusion. Pericardial effusion mandates close scrutiny of the aortic root for possible aortic dissection. Pericardial effusion in a trauma patient is worrisome for cardiac rupture, ventricular contusion, or foreign body injury.

Acute cardiac tamponade in the patient who has not undergone cardiotomy can develop after introduction of as little as 60 to 100 mL of blood. Causes may include type A aortic dissection, myocardial infarction with rupture, acute pericarditis, bleeding from malignant disease, myocardial contusion, or myocardial perforation from penetrating trauma. These life-threatening conditions may manifest with hypotension, tachycardia, plethora, and jugular venous distention. Other classic findings include narrowed pulse pressure, pulsus paradoxus, widening of the mediastinum on chest radiography, and electrical alternans on the ECG. Treatment consists of immediate decrease in pericardial pressure, which can be accomplished through the removal of a relatively small volume of fluid. This temporizing measure can be lifesaving until more definitive therapy is instituted.

Not all pericardial effusions require immediate intervention. Development of cardiac tamponade is related to the rate of accumulation of pericardial fluid and the capacity for the pericardium to stretch and accommodate fluid. Chronic pericardial effusions, which occur in cases of malignant disease, uremia, connective tissue disease, Dressler syndrome, and postinfection pericarditis, uncommonly require emergency intervention. Acute pericardial effusions that occur after cardiotomy are usually more ominous and often result in hemodynamic compromise requiring treatment (see Chapters 24 and 38).

Hemodynamics may improve temporarily with the administration of volume, thus altering intrathoracic pressure (decreasing peak inflation pressure), but the patient still may require drainage of the effusion. Chronic malignant effusions improve after pericardiocentesis but often require a pericardial window for more definitive therapy. Effusions resulting from acute aortic syndromes or cardiac trauma require timely surgical intervention. Postoperative cardiac surgical patients may require urgent reexploration for evacuation of pericardial hematoma and to address the cause of continued bleeding. If hemodynamics improve after sternotomy but minimal clot is found, the physiologic tamponade may be related to generalized tissue edema and pulmonary dysfunction. In cases of poor cardiac function, the sternal incision may need to remain open and covered with a sterile dressing until edema recedes and cardiac function improves.

Occult Congenital Abnormalities: Persistent Left-Sided Superior Vena Cava

Framing

The finding of a persistent left-sided superior vena cava (SVC) is not a common incidental finding, but its diagnosis has important implications for the conduct of circulatory management during CPB.

What echocardiographic findings suggest persistent left-sided SVC? What confirmatory test can be performed? Does the finding of an anomalous left-sided SVC have implications for the conduct of CPB?

Data Collection

The echocardiographer should suspect a persistent left-sided SVC if the coronary sinus is significantly dilated or if significant difficulty was encountered while attempting to place a pulmonary artery catheter. Because the differential diagnosis of a dilated coronary sinus includes disorders associated with increased right-sided pressures, confirmation should be obtained by injecting agitated saline contrast into an intravenous catheter in the left arm. In the case of a persistent left-sided SVC, opacification of the coronary sinus occurs before that of the right atrium or right ventricle. Once the diagnosis is confirmed, the echocardiographer should look for other associated congenital anomalies, including ASDs or an unroofed coronary sinus with communication between the coronary sinus and the floor of the left atrium.

Discussion

Left-sided SVC is the consequence of arrested embryologic development that causes the left brachiocephalic vein to empty into the coronary sinus with subsequent flow into the right atrial return of blood (see Chapter 22). As a consequence, cannulation of the coronary sinus with administration of retrograde cardioplegia is ineffective for providing cardiac protection during cardiac arrest. Once the diagnosis is confirmed, the surgeon is informed to modify the conduct of cardiac protection during CPB. If TEE is unable to confirm the diagnosis (absence of venous access in the left arm to inject contrast material), the surgeon can confirm its presence by direct inspection.

Occult Congenital Abnormalities: Atrial Septal Defects and Patent Foramen Ovale

Framing

The incidental diagnosis of an ASD or a patent foramen ovale (PFO) during a TEE performed for other reasons is a common occurrence because TEE is extremely sensitive at detecting these anomalies.[107] The clinical implications of an intracardiac defect can include shunting, stroke, headaches, pulmonary hypertension, RV dysfunction, and paradoxical embolization. If transseptal flow is present across the defect, it is generally from left to right because left atrial pressure is generally greater throughout the cardiac cycle. Bidirectional flow is possible with transient increases of right atrial pressure that can be observed during normal respiratory maneuvers (ie, Valsalva, coughing, and physical straining).[108,109] Although uncommon, right-to-left shunting can produce episodes of relative hypoxia and paradoxical embolization. In most patients, an ASD or PFO is well tolerated and often remains asymptomatic into adulthood.

When a septal defect is discovered, several questions must be answered. What type of ASD is present: primum, secundum, sinus venosus, or PFO? What is the size of the defect? Does the defect produce transseptal blood flow? What is the shunt fraction: Q_s/Q_t? Does the patient have any symptoms such as congestive heart failure, increased shortness of breath, history of stroke or transient ischemic

attack, or refractory hypoxia? What are the pulmonary artery pressure and RV function? Does the patient have any associated congenital abnormalities, such as a cleft MV with a primum ASD? Does the operation as initially planned require the use of CPB? If so, was single or bicaval cannulation planned? Perhaps most importantly, does the interatrial defect need to be closed?

Data Collection

The application of 2D echocardiography, color-flow Doppler imaging, and contrast administration in the midesophageal four-chamber and midesophageal bicaval views provides for high sensitivity of detection and diagnosis of ASDs and PFOs. The clinical implication of these findings is determined by the type of disorder. The PFO may be detected in approximately 25% of adults; it occurs when the secundum septum fails to close or is stretched open because of elevated pressures in the left atrium (Fig. 16.12). Ostium secundum defects, which account for 70% of ASDs, are located in the area of the foramen ovale. The cause of this lesion is attributed to poor growth of the secundum septum or excessive absorption of the primum septum. MV prolapse is present in up to 70% of patients with this abnormality and may be related to a change in LV geometry resulting from RV volume overload. The primum ASD develops when the septum fails to fuse with the endocardial cushion at the base of the interatrial septum. A primum ASD commonly is associated with cleft anterior leaflet of the MV and MR. The tricuspid valve also may be abnormal. The final type of ASD is a sinus venosus defect, which comprises only 10% of ASDs. It commonly is associated with abnormal insertion of the pulmonary veins into the right atrium or SVC.

Discussion

In general, patients benefit from ASD closure. Although often asymptomatic, ASDs may manifest with atrial arrhythmias, heart murmur, abnormal ECG, dyspnea, cerebrovascular injury or stroke, or migraine headaches. Medical management and surgical closure of secundum ASDs were compared in randomized trials; surgical closure was associated with significantly decreased morbidity and mortality.[110] However, data concerning treatment strategies and outcomes for occult ASD or PFO detected intraoperatively are scarce. In the absence of recognized consensus guidelines, the decision to proceed with definitive closure should be based on the following factors: history of a neurologic event without a definite cause, recurrent stroke while receiving anticoagulation, significant shunting through the defect, a previous episode of hypoxia that may be related to intracardiac shunting, RV dysfunction, or a previous paradoxical embolism. Detection of a primum or sinus venosus defect requires a more involved surgical procedure, and associated anomalies must be addressed. Alternatives to operative closure are increasing as transvenous percutaneous closure devices become increasingly applicable. Transvenous catheter–based closure of an ASD by interventional cardiologists can be performed only on a secundum ASD or a PFO (Fig. 16.13). Approximately 30% of secundum ASDs are amenable to percutaneous closure.[111] The technique optimally requires a defect with limited size and a rim of tissue surrounding the defect of at least 5 mm, to prevent obstruction of the coronary sinus or impingement of the AV (see Chapters 3 and 22).

A PFO is the most common congenital finding and usually is asymptomatic. However, several studies found an increased prevalence

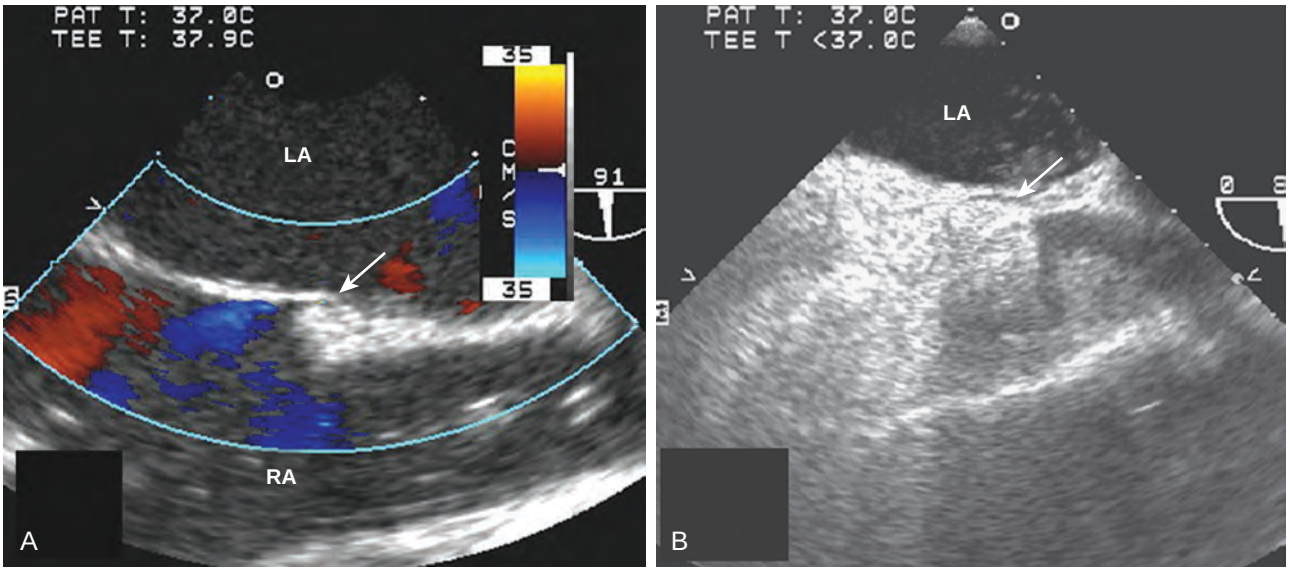


Fig. 16.12 Detection of a patent foramen ovale (PFO) in a patient undergoing cardiac surgery. A 68-year-old patient was undergoing two-vessel off-pump coronary artery bypass grafting. In addition to coronary artery disease, the patient had a medical history of hypertension, non–insulin-dependent diabetes, and a stroke of unknown cause. (A) The intraoperative transesophageal echocardiographic examination that included an inspection of the interatrial septum in the midesophageal four-chamber, and bicaval imaging planes showed a new finding of an aneurysmal interatrial septum with a PFO (*arrows*). Color-flow Doppler showed minimal shunt flow from the left atrium *(LA)* to the right atrium *(RA)*. (B) The presence of the PFO *(arrow)*, which was initially diagnosed by color-flow Doppler imaging (A), was confirmed by the transient flow of injected contrast *(arrow)* into the LA after it was injected into the venous circulation. A provocative maneuver such as Valsalva transiently increases pressure of the RA more than that of the LA, thus increasing the sensitivity of PFO detection.[47] Because of the patient's history of a cryptogenic stroke, the surgical plan and circulatory management were altered. The patient was fully heparinized and circulation was supported by an extracorporeal pump while the coronary artery bypass graft was performed and the PFO was closed.

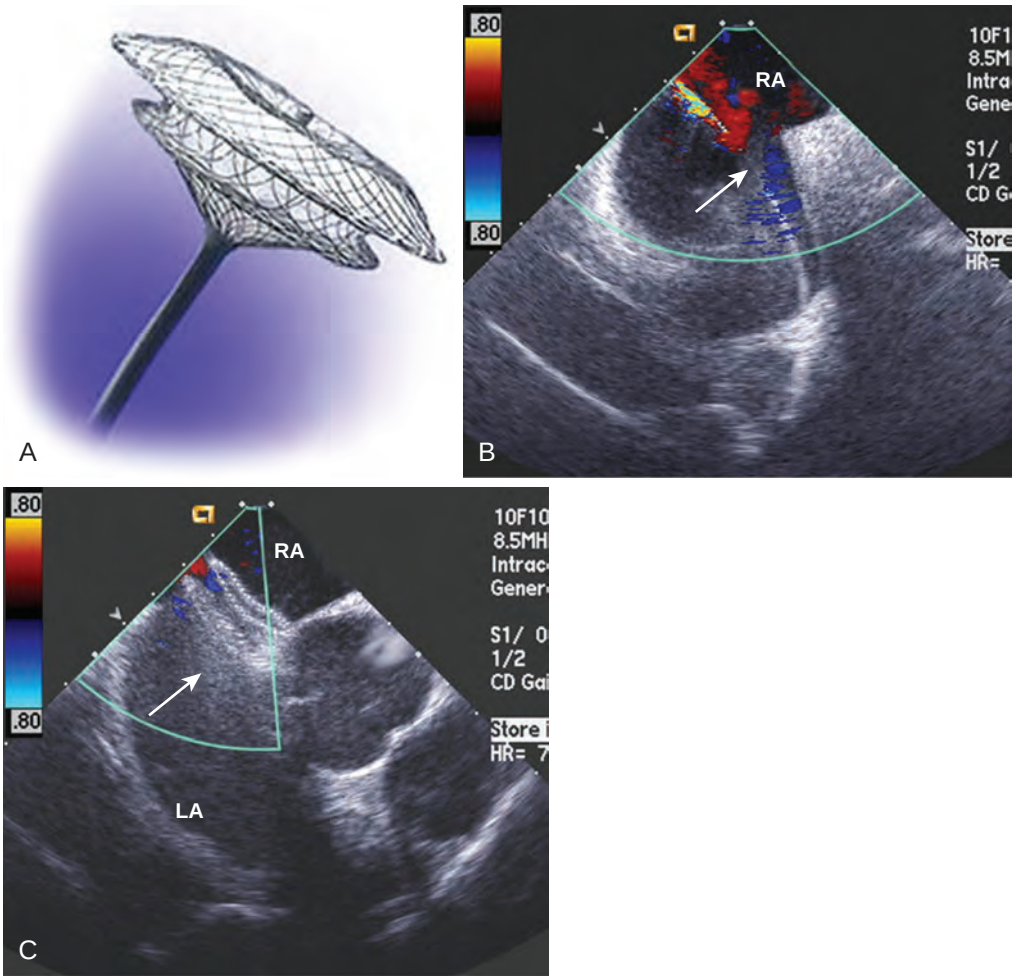


Fig. 16.13 Transvenous approach to closure of atrial septal defects (ASDs). Patent foreman ovale and secundum ASDs can be closed by deploying a transvenous closure device as an alternative to surgical intervention. (A) Self-expanding Amplatzer occlusion device (AGA Medical Corporation, Plymouth, MN) that is made of wires tightly woven into two interconnected disks. The device is deployed from the femoral vein and is positioned using transesophageal echocardiography or intravascular ultrasound. (B) Color-flow Doppler image from an intravascular ultrasound scan that shows the deployment catheter as it enters through the right atrium *(RA)* and spans the secundum ASD *(arrow)*. (C) Color-flow Doppler ultrasound image showing the Amplatzer device *(arrow)* in position across the interatrial septum, thus preventing shunt flow across the ASD. *LA,* Left atrium.

of PFO and atrial septal aneurysms in patients who had cryptogenic strokes (ie, no identified cardioembolic or large vessel source).[112–118] A metaanalysis of these case-control studies found that PFOs, atrial septal aneurysms, or both were significantly associated with ischemic stroke in patients younger than 55 years of age.[119] However, the relationship between septal disease and neurologic events in patients older than 55 years of age is less clear. Evidence also indicates that the morphology of PFOs in patient who suffer cryptogenic strokes may be different from that in patients without a history of stroke; the former tend to be larger (3.9 vs 2.9 mm) with longer tunnels and a greater incidence of atrial septal aneurysm.[120] The data on treating patients with atrial septal abnormalities for either primary or secondary prevention of stroke are limited. The Patent Foramen Ovale in Cryptogenic Stroke Study and a metaanalysis by Orgera and colleagues[121] found that warfarin treatment was superior to other antiplatelet therapy and was comparable to surgical PFO closure for the prevention of recurrent cerebral events.

A survey of cardiothoracic surgeons in the United States noted a high degree of variability in management of intraoperatively discovered PFO.[122] During planned on-pump CABG surgical procedures, 27.9% of responders stated that they always closed intraoperatively discovered PFOs, whereas 10.3% did not. Only 11% of surgeons converted a planned off-pump procedure to an on-pump procedure to close the defect, but the rate of closure increased to 96% if the patient had a history of possible paradoxical embolism. In a large, retrospective study of 13,092 cardiac surgical patients at the Cleveland Clinic in Cleveland, Ohio, 2277 (17%) were found to have a PFO during intraoperative TEE. Of these patients, 639 went on to have their PFO closed. Survival was similar between the closure and nonclosure groups, although the risk of stroke was higher in those patients who had their PFO closed (2.8% vs 1.2%).[123] Some evidence indicates that the presence of a PFO may increase the risk of postoperative atrial fibrillation after cardiac surgical procedures.[124]

The benefit of aggressive management of a PFO in the absence of other interatrial septal abnormalities is less clear than with ASD closure and is more controversial. Sometimes surgical intervention requires a significant alteration of the surgical plan that may significantly increase operative risk. If PFO detection occurs during off-pump coronary artery bypass, surgical intervention necessitates marked changes in the conduct of both the operation and circulatory management. The patient who is undergoing off-pump coronary artery bypass and who has a small PFO typically remains untreated. In the absence of recognized consensus guidelines, the decision to proceed with definitive

closure should be based on the following factors: history of a neurologic event without a definite cause, recurrent stroke while receiving anticoagulation, the morphology of the defect, significant shunting through the defect, a previous episode of hypoxia that may be related to intracardiac shunting, RV dysfunction, or a previous paradoxical embolism.

Ascending Aorta: A Source of Embolization

Framing

The most disabling complication after cardiac operations is stroke. Major focal and nonfocal neurologic deficits, cognitive decline, and coma are common postoperatively. The pathogenesis of cerebral damage is multifactorial, with embolism considered a major contributor. Other factors include hypotension, low flow, reperfusion injury, and inflammation. Embolic events are strongly associated with the severity of atherosclerotic disease, characterized by plaque thickness of greater than 4 mm, ulcerated plaques, and mobile protruding plaques in the aorta.[125,126] The severity of atherosclerosis of the descending aorta, as determined by TEE, is a significant risk factor and an independent predictor of adverse cardiac and neurologic outcomes in patients undergoing CABG.[127] Surgical manipulation of the thoracic aorta may liberate debris from diseased aortic tissue. The process of microembolization has been detected by transcranial Doppler imaging during aortic cannulation, application and removal of the aortic cross-clamp, commencement of CPB, and initiation of ventricular ejection. The clinical consequence of distal embolization depends on the number, composition (eg, air bubbles, fat particles, platelet aggregates, and calcium deposits), size, and location of the emboli (see Chapters 14, 15, 18, 20, 21, 23, 31, and 40).

Is the patient at increased risk for postoperative neurologic dysfunction? Would epiaortic ultrasound examination or TEE improve detection of significant atheromatous disease? What modifications to the conduct of the general anesthesia, monitoring, CPB, or cardiac surgical procedure could be implemented in a risk-reduction effort? Is epiaortic scanning necessary?

Data Collection

TEE imaging of the anterior wall of the ascending aorta is limited by far-field imaging resolution and its juxtaposition to air in the open chest. Imaging of the middle and distal ascending aorta by TEE is limited by the interposition of the airway with the esophagus and aorta. Epiaortic ultrasound examination can provide high-definition imaging of these otherwise hidden portions of the aorta. Epiaortic scanning offers higher sensitivity for detection of atheroma of the ascending aorta, as compared with TEE, especially in the middle and distal segments.[3,128] The descending aorta is immediately adjacent to the esophagus and is easily imaged using conventional TEE. A common practice is the interrogation of the descending thoracic aorta for high-grade atheroma. In the absence of atheromatous disease in the descending aorta, the ascending aorta and locus of aortic cannulation are significantly less likely to have high-grade disease. If the descending aorta contains high-grade or mobile atheroma, it may be prudent to examine the ascending aorta with epiaortic scanning for potential sites for aortic cannulation and clamping (Fig. 16.14).

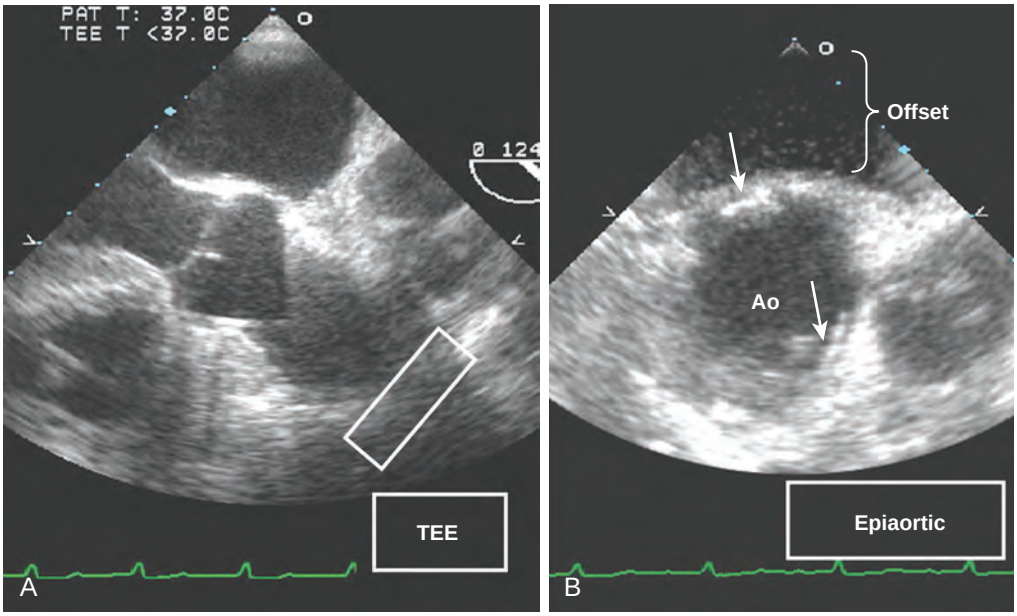


Fig. 16.14 Detection of atheromatous plaque by epiaortic ultrasound. A 67-year-old patient was scheduled to undergo triple coronary artery bypass grafting. Transesophageal echocardiographic *(TEE)* examination was performed to evaluate the mitral valve for mitral regurgitation that could necessitate surgical intervention. Routine examination of the descending thoracic aorta detected severe atherosclerotic disease characterized by several ulcerated areas and plaques with a thickness of 4 mm. Because the severity of atherosclerotic disease in the descending aorta predicts significant disease in the ascending aorta,[127] examination of the ascending aorta was attempted. (A) TEE examination of the ascending aorta at the site of aortic cross-clamp and cannulation *(white rectangle)* was limited by poor resolution in the far field and interposition of the trachea. (B) A handheld probe that was placed in a sterile sleeve was used to examine the aorta. The bottom of the sleeve was filled with saline solution as an offset to image the anterior surface of the aorta *(Ao)* more clearly. Several calcified plaques *(arrows)* were detected. Based on findings of the epiaortic scanning, the surgeon modified the site of cannulation and used a single cross-clamp technique to avoid a second clamping of the aorta during the proximal anastomosis.

Discussion

Historically, surgeons palpate the ascending aorta to determine the extent of intraluminal atherosclerotic disease in an effort to choose an appropriate location for cannulation, cross-clamping, and proximal graft anastomosis. However, palpation is a notoriously poor predictor of atheromatous disease.[129–131] The occurrence of atheroma in the ascending aorta of cardiac surgical patients may be as high as 60% to 90%.[130,132] Advanced age, hypertension, and diabetes are risk factors for atheromatous disease of the aorta and stroke after cardiac operations.[133] The information provided by ultrasound imaging of the aorta defines the location and severity of atheromatous disease and can guide the surgeon to choose the cannulation, cross-clamp, and anastomotic sites more strategically.

Possible modifications to the conduct of cardiac surgery and CPB include the following:

1. Altering the site of cannulation
2. Aborting CPB altogether and performing the CABG operation as an off-bypass procedure
3. Performing the operation on a fibrillating heart without aortic cross-clamping
4. Performing aortic atherectomy or replacement of the ascending aorta
5. Attempting a "no-touch" technique using deep hypothermic circulatory arrest.

Epiaortic scanning combined with a modification of surgical techniques in patients undergoing CABG decreased the number of emboli as detected by transcranial Doppler imaging and significantly reduced neurologic behavioral changes at 1 week and 1 month postoperatively.[134] Modifications in the methods used in CABG revascularization, including the avoidance of proximal aortic graft anastomoses after detection of atheroma by echocardiography, resulted in a lower incidence of late neurologic complications.[2]

The application of epiaortic scanning for all patients undergoing cardiac surgical procedures is controversial. Epiaortic scanning takes time and expertise in its interpretation and poses the potential risk for wound contamination. Data are insufficient to support its use in all cardiac patients, although high-risk patients (advanced age, diabetes, hypertension) are the most likely to benefit.[135,136] As the population of patients undergoing cardiac operations ages, these patients will have a greater incidence of atherosclerosis of the aorta and the presence of concomitant risk factors for postoperative complications. Echocardiographers working in the operating room need the skill set to interrogate the aorta by handheld ultrasound scanning and the ability to guide the surgeon in performing the examination. Such scanning could be potentially lifesaving in high-risk patients. A diagnostic scan of the ascending aorta and arch to evaluate the location of possible cannulation and clamp sites can be performed in several minutes. Standardized approaches to a comprehensive organized intraoperative epiaortic and epicardial examination are useful guides.[137]

Case Study 2: Putting It All Together: A Case Study in Acute Aortic Syndromes

It is midnight on a gloomy, rainy night. The hospital helicopter calls in "… young woman, unrestrained driver, deceleration injury, steering wheel impact, chest contusion, unconscious, hypotensive. She is intubated with bilateral breath sounds. Her blood pressure is 70/40 mm Hg with a heart rate of 125 beats/minute and sinus tachycardia. She is being fluid resuscitated and being transported directly to the cardiac operating room." The patient is too unstable for MRI or computed tomography (CT) scanning. The patient arrives in the operating room with a portable chest radiograph obtained as she was whisked through the emergency department; the radiograph shows a widened mediastinum. The vital signs have not changed except that she is receiving dopamine at 10 μg/kg per minute. Pulses are palpable in the groin and the neck. The patient is transferred to the operating room table, and everyone turns to the anesthesiologist-echocardiographer for guidance. The attending surgeon asks, "I need to know is this an anterior injury with heart contusion, injury to the ascending aorta, tamponade with blood in the pericardium, or a transected aorta at the isthmus or arch, or is this a nonoperable injury?" An injury to the ascending aorta will require a sternotomy, while a transection of the descending aorta or isthmus will require a left thoracotomy. "If we make the incorrect decision, the patient will surely die." The patient is stabilized in the operating room, and the TEE probe is inserted. TEE reveals no blood in the pericardium, an intact aortic root with no evidence of type A dissection, a step-up in the intima at the site of the left subclavian artery, and a small left pleural effusion. The patient is positioned in the left lateral decubitus position, and the operation proceeds to save a young life.

Framing

The unstable patient with suspected acute aortic disease or injury is often the most challenging of TEE cases. Few more crucially important decisions are posed to the intraoperative echocardiographer than to diagnose the nature and extent of acute aortic injury quickly and accurately. Hypotension and respiratory distress may prevent a complete and comprehensive evaluation preoperatively (Fig. 16.15). The patient's history often is unobtainable. The echocardiographer becomes a detective. Clues are quickly gathered from the available clinical presentation, history, and associated physical findings. TEE is often the only modality used to establish the diagnosis and define the surgical plan.

The sensitivity and specificity of TEE to detect and diagnose injury or disease of the thoracic aorta are significantly better than the sensitivity and specificity of TTE and are comparable to CT scan and MRI.[138,139] TEE provides information on cardiac performance and the presence of other critically important sequelae that may be important in determining the approach and timing for surgical intervention. Hence TEE is indicated even if MRI or CT scanning has confirmed the diagnosis.

Can consent be obtained from the patient or family members? In these emergency circumstances, it may be more prudent to proceed with the TEE examination rather than delaying diagnosis and treatment in an attempt to find family members. What is the differential diagnosis of a widened mediastinum? How does TEE discriminate among the different causes of a widened mediastinum? Is TEE performed in the awake distressed patient, or is the examination done under more controlled conditions of an anesthetized, intubated patient? Does a risk exist for cervical spine injury? Does a risk exist for esophageal injury? Can insertion of the TEE probe further compromise the patency of mediastinal structures? Is fluid present in the pericardium? What is the biventricular function? Is myocardial rupture present? Is aortic rupture present? Is the thoracic aorta intact? Are an intimal flap and a dissection present? Is a transection present? Is a pleural or periaortic effusion or hematoma present? Is an intramural hematoma (IMH) present? What factors determine the urgency of intervention and strategies for management?

Data Collection

Because the diagnosis and cause of instability are not established, the entire mediastinum, including the left pleural space, is interrogated before definitive therapy is initiated. Rarely does the echocardiographer have enough time to do a complete TEE examination. The operative team can often proceed with confidence in the management of these critically ill patients with only TEE to guide the treatment. The primary events in aortic dissection are a tear and separation of the aortic intima. It is uncertain whether the inciting event is a primary rupture of the intima with secondary dissection of the media or hemorrhage within the media and subsequent rupture of the overlying intima. Systolic ejection forces blood into the aortic media through a tear that leads to

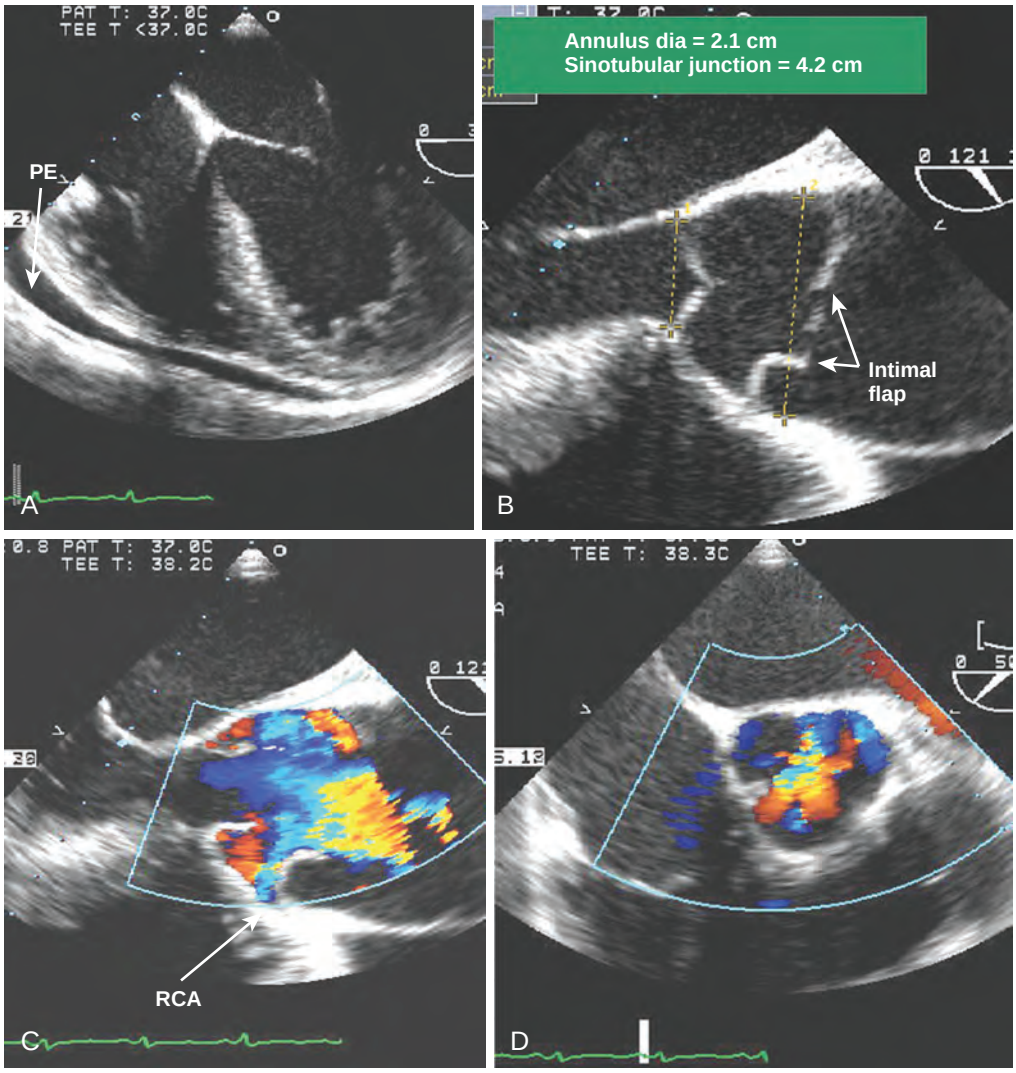


Fig. 16.15 Acute aortic syndrome as the cause of hemodynamic compromise. A 62-year-old previously healthy, unrestrained driver had a motor vehicle accident. On arrival to the emergency department, the patient was hypotensive (blood pressure = 90/45 mm Hg) and tachycardic (heart rate = 120 beats/minute). He described an episode of loss of consciousness that was associated with severe chest pain but could not recall whether the syncopal episode preceded the accident. The chest radiograph was significant for several fractured ribs, a widened mediastinum, and a pleural effusion. The patient became progressively more unstable and was transferred to the operating room to perform diagnostic transesophageal echocardiography and a definitive surgical procedure if necessary. The echocardiographer performed a quick transthoracic echocardiographic examination that confirmed the presence of pericardial effusion with findings that were consistent for tamponade. After fluid resuscitation and induction of anesthesia, a transesophageal echocardiographic examination was performed. (A) The midesophageal four-chamber view showed the presence of a pericardial effusion *(PE)* that compromised right atrial filling. (B) The midesophageal long-axis view of the aortic valve showed a type A dissection that was characterized by intimal flaps within the aortic root and that extended distally into the descending thoracic aorta. The annulus of the aortic valve was of normal size, but the sinus and root were markedly enlarged (diameter *[dia]* of sinotubular junction = 4.22 cm). (C) The dissection extended into the noncoronary and right coronary sinus segments, narrowing blood flow at the right coronary ostia *(arrow)*. Although the electrocardiogram did not show acute ischemia, the right ventricular function and inferior wall of the left ventricle were mildly hypokinetic. (D) Although an effaced aortic root, ascending aortic aneurysm, and acute dissection in this age group are suggestive of a congenital bicuspid aortic valve, the short-axis view of the aortic valve showed a trileaflet valve with a coaptation defect with aortic insufficiency at the noncoronary cusp. The surgeon resuspended the aortic valve and replaced the ascending aorta and hemiarch with a tube graft. The valve repair was successful with only +1 aortic insufficiency and cardiac return to normal postoperatively. *RCA*, Right coronary artery.

the separation of the intima from the surrounding media, thus creating a false lumen. Blood flow may exist in both the false and true lumina through communicating fenestrations. Elucidating which lumen is the true lumen and which is the false lumen is of utmost importance in an aortic dissection and has important implications for arterial cannulation for CPB. Traditionally, the true lumen expands during systole, has earlier and more robust blood flow in systole, and is smaller than the false lumen, but each of these characteristics may be misleading in individual cases. When possible, it may be most accurate to find the separation point of the intima from the aortic wall and follow it circumferentially, thereby identifying which lumen is bordered on all sides by intima (true lumen). Aortic dissections are classified by one of two anatomic schemes (the DeBakey and Stanford classifications). Transection is diagnosed through the detection of paraaortic hematoma near the isthmus and a "step-up" in the internal media wall (see Chapter 23).

Discussion

Acute dissections (Stanford type A or DeBakey type I or type II) involving the ascending aorta or arch are considered acute surgical emergencies because of the high risk for a life-threatening complication such as AR, cardiac tamponade, myocardial infarction, rupture, and stroke. The mortality rate is as high as 1% to 2% per hour early after symptom onset.[140] Neither acute myocardial ischemia nor cerebral infarction should contraindicate urgent intervention. Although patients with stroke in progress may be at increased risk for hemorrhagic cerebral infarction because of intraoperative anticoagulation, leading to hemorrhagic stroke, we have seen several patients who experienced dramatic neurologic recovery. Operative mortality for ascending aortic dissections at experienced centers varies from 7% to 36%, much lower than the greater than 50% mortality rate with medical therapy.[141–147]

In contrast, dissections confined to the descending aorta (distal to the left subclavian artery; Stanford type B or DeBakey type III) are treated medically unless the patient demonstrates proximal extension, hemorrhage, or malperfusion. From the International Registry of Acute Aortic Dissection, 73% of the 384 patients with type B dissections were managed medically with an in-hospital mortality rate of 10% (compared with 32% for those patients managed surgically).[148] The long-term survival rate after applying medical therapy was approximately 60% to 80% at 4 to 5 years and 40% to 45% at 10 years.[148–152] In those patients who present with an acute complicated type B dissection (characterized by aneurysmal enlargement, rupture, or malperfusion), thoracic endovascular aortic repair (TEVAR) with a stent graft has become the standard of care, with relatively low rates of both mortality (5–6%) and spinal cord ischemia (2–3%).[152] TEVAR is also starting to gain traction as a therapy for uncomplicated type B dissections because one study showed reduced 5-year mortality and progression of disease rates compared with medical therapy alone[153] (see Chapter 48).

Aortic IMH is often considered a variant of aortic dissection.[154] Although many patients present with chest or back pain, many of the associated sequelae, such as pericardial or pleural effusions, stroke, and myocardial infarction, are absent.[155,156] Aortic IMH is characterized by the absence of a detectable intimal tear. The hematoma is likely produced by a hemorrhage of the vasa vasorum into the aortic wall. In a metaanalysis, acute aortic IMH was most often associated with long-standing hypertension; trauma was a significant factor in 6% of cases.[157] In a metaanalysis of 143 cases, 81% were diagnosed by CT, and in the remaining patients aortic IMH was diagnosed by MRI, TEE, or both; the sensitivity and specificity of TEE to detect IMH were reported to be 100% and 91%, respectively.[155,157] The diagnosis is characterized by the absence of a dissecting flap or intimal disruption with specific regional thickening of the aortic wall of greater than 7 mm in a crescent or circular shape. When seen in the ascending aorta (involved in 33–57% of cases), IMH appeared to represent the early stage of a classic dissection,[156–160] whereas traumatic IMHs typically involved the descending thoracic aorta.[159] Acute management is similar to that of classic aortic dissection.

Traumatic aortic rupture is a life-threatening vascular injury that often results in lethal hemorrhage. In a multicenter trial of 274 patients, the overall mortality rate reached 31%, with 63% of deaths attributable to aortic rupture.[161] Aortic transection and rupture usually occurred at the aortic isthmus (between the left subclavian and the first intercostal arteries) and resulted from shear forces generated by unrestrained frontal collisions.[162] Although aortography had been considered the gold standard for the diagnosis of transection, TEE and contrast-enhanced spiral CT and MRI are currently favored, especially for patients with renal insufficiency.[163–166] Intravascular ultrasonography has been proposed as a potential diagnostic tool for the identification of limited aortic injuries.[167] Traumatic aortic rupture must be distinguished from aortic dissection. Imaging of a dissected aorta typically reveals true and false lumina at multiple levels. The focal aortic injury of aortic transection is localized and may be overlooked during a cursory examination. A second potential diagnostic problem is that protuberant atherosclerotic changes of the aorta may be difficult to differentiate from partial aortic tears. The thick and irregular intraluminal flap, which corresponds to disruption of both intimal and medial aortic layers, can be imaged in both the short-axis and long-axis planes in the vicinity of the isthmus. In the longitudinal view, the medial flap is nearly perpendicular to the aortic wall because traumatic lesions are usually confined within a few centimeters distal to the left subclavian. The formation of a localized contained rupture of the false aneurysm is common.[164,168] Color-flow Doppler imaging and spectral Doppler imaging can be used to detect turbulence associated with nonlaminar flow at the aortic defect and the presence of a pressure gradient. Traditional treatment includes immediate surgical invention using a right lateral decubitus approach and resection of the aorta with insertion of a tube graft, but TEVAR is increasingly becoming the treatment of choice because it avoids the need for a major open surgical procedure, one-lung ventilation, and high-dose anticoagulation in patients who often have significant coexisting injuries.[152]

In conclusion, the intraoperative echocardiographer is confronted with a broad array of diseases that require on-site decision making in the perioperative setting. The key ingredients to sound decision making are a broad fund of knowledge (database), a systematic approach with attention to all vantage points and frames, and the identification, addressing, and prioritization of the pertinent questions.

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17

Education and Simulation in Echocardiography

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KEY POINTS

1. Transesophageal echocardiography is invasive, yet it requires repetition and practice for gaining proficiency, thus making it an ideal target for simulation training.
2. Current echocardiography simulators evolved in a stepwise development process over a span of 2 decades with incremental improvements in quality of simulation and features.
3. Substantial evidence supports the utility of echocardiography simulation in its current form; however, new features and their applications will continue to require ongoing research to refine best practices.
4. An understanding of key definitions, terms, and features across different simulation platforms is important for both education and research in this area.
5. In the future, echocardiography simulation is likely to be formally incorporated into training curricula, assessment protocols, and accreditation processes.

Patients are necessary for medical trainees to hone their skills just as airplanes are for pilots to fly. However, the need to ensure safety in both these situations conflicts with the need for new operators to practice new skills. Simulation plays a key role in uncoupling these two goals. Although the aviation industry has systematically and thoroughly embraced the learning opportunity presented by modern simulation, medical training has been relatively slow to adapt. For a long time, clinical educators were content with employing low-tech simulators such as mannequin models and role-playing actors.[1] However, technologic advances in clinical procedures have elicited the development of simulation systems to keep pace with the needs of health care providers.[2]

The introduction of minimally invasive surgery in the 1990s heralded the development of simulators to "rehearse" procedures. The rationale was based on the understanding that repetitive exposure of novices to the task at hand could significantly decrease the initial learning curve.[3] Early simulators in this category consisted of anatomic models on which to practice laparoscopic surgical skills. These simulators were quickly incorporated into training programs for purposes of both "task training" and "warming up." UltraSim (MedSim, Fort Lauderdale, FL), for example, was the first ultrasound-based teaching simulator, and it consisted of data sets of normal and pathologic anatomy from actual patients[4] (Fig. 17.1).

Traditionally, echocardiography education has been imparted incidental to patient care. This model presents several challenges to ideal training. First, the principle of "do no harm" asserts that patients take precedence over trainees in any given situation. With the hospitals' and physicians' primary responsibility being to their patients, medical training is a desirable byproduct of the patient-physician interaction. Second, a patient can undergo a procedure only so many times, thus limiting the number of examinations available for trainees to conduct. This is especially problematic for tasks requiring repetition to achieve manual dexterity. Moreover, in clinical settings, the complexity of disease cannot be purposefully graduated from basic to advanced levels to suit the trainees' learning requirements at particular points in time. In fact, the clinical experience can vary significantly from day to day and among different settings. In addition, expert echocardiographers often conduct examinations incorporating significant mental reconstruction and imagination based on their experience, gliding seamlessly and quickly through different views, and making it difficult for the operator to explain and the observer to follow.[5,6]

In the Halstedian model of medical education, these roadblocks were addressed by the assumption that a sufficiently long period of time enables all trainees to attain a minimum level of proficiency required for independent practice. However, more recent developments in medical education advocate moving from a duration-based *assumption* to a competency-based *proof* of proficiency.[7] With the incorporation of work-hour regulations in training programs, residents and fellows today are expected to learn more in less time and demonstrate acquisition of competency and proficiency. These challenges have led to the development of rigorous simulation training programs to shorten the learning curves associated with routinely performed tasks in the course of patient care. Fundamentals of endoscopic surgery, laparoscopic surgery, and anesthesia crisis resource management are examples of simulation programs that have been incorporated into training curricula with demonstrable benefit.[8]

The expanding role of echocardiography within and outside the operating room has also necessitated the development of efficient training tools for echocardiographers.[9] Unlike other imaging modalities, echocardiography requires that its operators be adept at both obtaining and interpreting images. The complex geometry of the heart and the nonintuitive orientation of images make echocardiography a difficult task to master cognitively. For example, images on both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are flipped from left to right on the screen. Anterior structures figure at the apex of the sector on TTE, whereas the reverse is true for TEE. Furthermore, mastery of probe handling and manipulation adds a significant manual dexterity component that must be developed alongside abilities of three-dimensional (3D) mental reconstruction.

At present, an accredited cardiac anesthesia fellowship is the only route to obtaining advanced certification in perioperative TEE.[5] The educational opportunities offered by national organizations (American Society of Anesthesiologists, Society of Critical Care Medicine) mainly consist of didactic courses without hands-on training. The introduction of the Basic TEE Certification by the National Board of Echocardiography for noncardiac anesthesiologists has further underscored the paucity of clinical training resources in this area.[5] The availability of high-fidelity echocardiography simulators has the potential

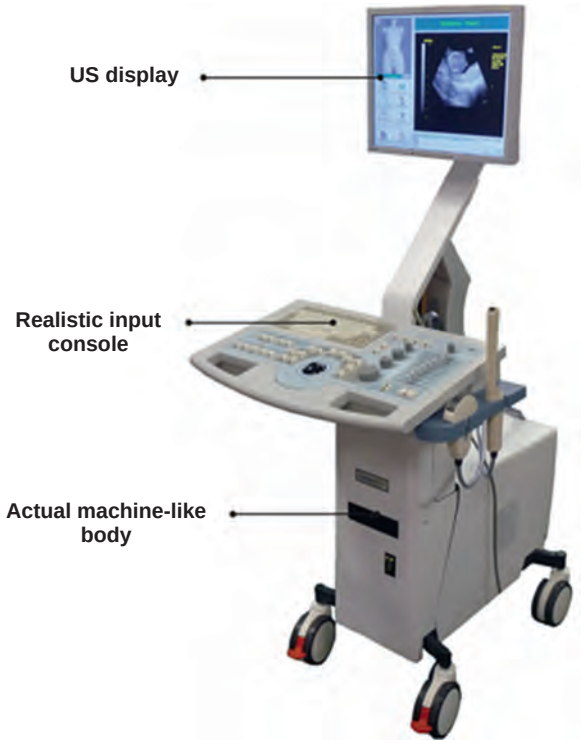

Fig. 17.1 The latest version of UltraSim, the first ultrasound simulator to hit the market. Note that with continued development, the simulator hardware and software interfaces have fully embraced the look and feel of an actual ultrasound machine. *(Courtesy MedSim, Fort Lauderdale, FL.)*

to train not only anesthesiologists, but also other health care providers who frequently use this imaging modality, including cardiologists, intensivists, emergency physicians, and nurses who practice in similar settings. This chapter reviews the history of simulators for echocardiography training, tracks the progression of technology, assesses the current state of simulation in echocardiography, and examines its future direction.

Early Development

For an echocardiography simulator to be effective the images displayed by the simulator must mimic those a trainee can expect in a real patient. Before the advent of the digital graphics revolution, achieving realistic depictions of medical images constituted a major hurdle to developing reliable simulators. One solution to this problem was to use real data and display images from actual patients on the screen in response to the trainees' actions. An arrangement that allows the operator to access and manipulate real-world data as part of a broader device is ordinarily referred to as *augmented reality*. In contrast, *virtual reality* refers to a completely computer-generated environment that mimics the real world and allows the user to perform tasks virtually as they would in reality. A simulator that allows augmented or virtual realities to be manipulated by physical, or *haptic*, controls is referred to as a *mixed* simulator. A simulation cockpit that allows a pilot to fly through a virtual city by using a physical control stick is an example of a mixed simulator.

Using the same concepts, the first TTE simulator developed and reported by Weidenbach and colleagues[10] in 2000 was based on a 3D virtual model of the heart (virtual reality), computationally registered to real, two-dimensional (2D) echocardiographic images (augmented reality). This virtual heart model could be sliced using a virtual scan plane to yield the corresponding 2D image on the screen.[10] The virtual scan plane, in turn, was coregistered to an actual, physical probe equipped with tracking sensors to detect its motion (Fig. 17.2). Although much progress has since been made, the basic idea behind echocardiography simulators has remarkably remained the same ever since: a virtual heart model, sliced by a virtual scan plane coupled to a tracked, physical probe.

In subsequent developments, Weidenbach's group equipped the physical probe and a dummy torso with a 3D electromagnetic tracking system. This allowed for the echocardiographic data set from the computer to be projected and registered to a reference area within the torso. Users of this system were able to move the probe on a plastic torso and see echocardiographic representations of their imaging planes on the screen in real time. This system allowed the operator to develop an understanding of the anatomy as seen in the scan plane and on the torso, as well as hand-eye coordination for probe movements.[11]

Although the invention of a TTE simulator was a sentinel step in echocardiography education, a similar tool for TEE held greater promise on account of the semiinvasive nature of TEE. The EchoComTEE simulator first appeared in 2007 and drew on the same technology as the TTE simulator reported earlier.[12] This simulator allowed the operator to practice conducting a TEE examination without the time-limiting pressures of a cardiac operating room or the inability to perform examinations repeatedly. The virtual heart model used in the EchoComTEE simulator was the same model as the one stitched together using real TTE data sets. Because only apical views were used to construct that model, it did not include upper esophageal views or the great vessels. Including those views would require either a model based on TEE images or a different approach altogether (ie, a completely virtual system based on computer-generated representations of real and echocardiographic anatomy).

Commercialization

Soon after the successful development of EchoComTTE and EchoComTEE simulators for research purposes, commercial vendors entered the fray to address the need for simulation in echocardiography. Today, several different vendors, including Inventive Medical, CAE Healthcare, Simbionix, and Blue Phantom, offer mannequin-based devices for TTE and TEE training. Scan planes through beating, virtual heart models are processed into 2D echocardiographic images, displayed simultaneously on the screen. These "echocardiographic images" are in fact graphic renderings of what an ultrasound image would look like on a real heart. Hence the key difference in the software interface of the new simulators and that of the earlier EchoComTEE and EchoComTTE devices is the complete replacement of augmented reality by virtual reality. As the trainee moves from one position to the other within the virtual heart, the corresponding changes in virtual echocardiographic imagery can be followed on the screen.

All simulators afford multiple display options to the operator, who can choose to view the virtual model alone, the ultrasound image alone, or both side by side. Newer versions of these simulators also incorporate quantitative echocardiography modules and physical foot switches to enable image capture and other controls by the operator while the same operator performs a bimanual examination such as TEE. Excluding the "body-simulator" by Blue Phantom, currently available TEE and TTE trainers are more alike than they are different. However, each one incorporates certain salient features, as described here.

HeartWorks

Manufactured by Inventive Medical (London, United Kingdom), the HeartWorks TEE simulator was the first commercially available echocardiography simulator to hit the market, in 2008[13] (Fig. 17.3). The cardinal feature of this system is a realistic model of the heart and great vessels that facilitates an easy suspension of disbelief. This high-fidelity model was constructed using state-of-the-art animation technology, and its use was made possible by advances in graphics processing units for personal computers. Since the initial TEE-only module, the

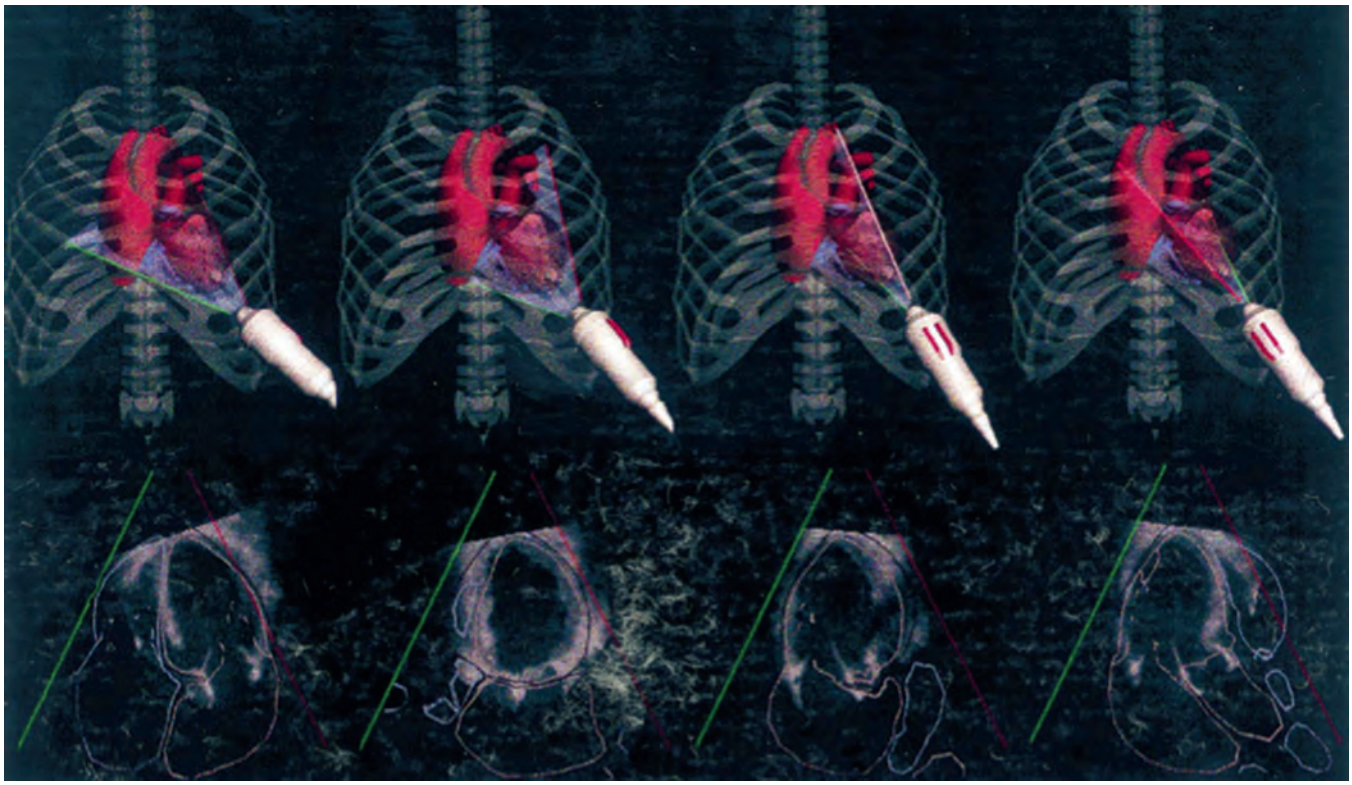

Fig. 17.2 Images obtained from different probe positions within the first EchoComTTE echocardiography simulator. The *top section* displays the virtual heart model and a virtual probe and scan plane (virtual reality). The *bottom section* shows actual echocardiographic images that are expected at the corresponding probe position. These images are also labeled with outlines and colored scan plane boundaries to facilitate comprehension of image orientation and underlying and overlying anatomy (augmented reality).

Fig. 17.3 The HeartWorks echocardiographic simulation system by Inventive Medical *(Courtesy Inventive Medical, London, United Kingdom. © Inventive Medical Ltd.)*

simulator has been marketed in different forms including a combined TTE-TEE simulator, individual TEE and TTE simulators coupled to mannequins, and a laptop-only station for demonstration purposes. The mannequin-based package includes a rubber-torso mannequin with TTE or TEE probes, or both. All packages are shipped loaded with the simulation software.

Imaging on the station can be controlled by keyboard and mouse or by mannequin-based probe motions. Although rarely used, a comprehensive descriptive text is available for quick reference for independent learners. The ability to add labels and individually highlight as well as visualize as many as 160 cardiac structures in isolation from the rest of the heart significantly increases the simulator's educational value (Fig. 17.4). More recent updates to the system have incorporated the ability to simulate color-flow Doppler, continuous-wave Doppler, and pulse-wave Doppler imaging. Although the manufacturer has provided regular upgrades since the first release, the process of upgrading requires uninstalling and reinstalling the software using DVD drives, thus making the upgrade process time consuming and cumbersome.

CAE Vimedix

Vimedix was initially created as a stand-alone company, but the Vimedix simulation system was later acquired and is currently sold by CAE Healthcare (Montreal, Canada; Fig. 17.5). Like HeartWorks, the simulator is based on a digital heart model. In addition, it includes virtual intrathoracic and intraabdominal structures that allow the operator greater orientation to surrounding anatomy such as ribs, lung, liver, stomach, and as far down as the urinary bladder. In fact, Vimedix is not only capable of simulating cardiac ultrasound imaging (TTE and TEE), but it also doubles up for intraabdominal ultrasound.[14] For that purpose, the simulator can be bundled with a curvilinear probe to simulate abdominal imaging if required. This makes the device especially suitable for training emergency room health care providers.

The current version allows users to perform the following functions: run M-mode and Doppler examinations; disable lung and rib artifacts if required; vary the level of noise on ultrasound images through gain and depth settings; enable the display of ideal probe positions to obtain an echocardiographic window; and, finally, generate echocardiography reports as done on actual machines. Although the update process on the Vimedix system is cloud based, automatic, and seamless, the quality of the virtual heart model and the corresponding gray-scale echocardiographic renderings need further improvement to mimic real anatomy and images more closely.

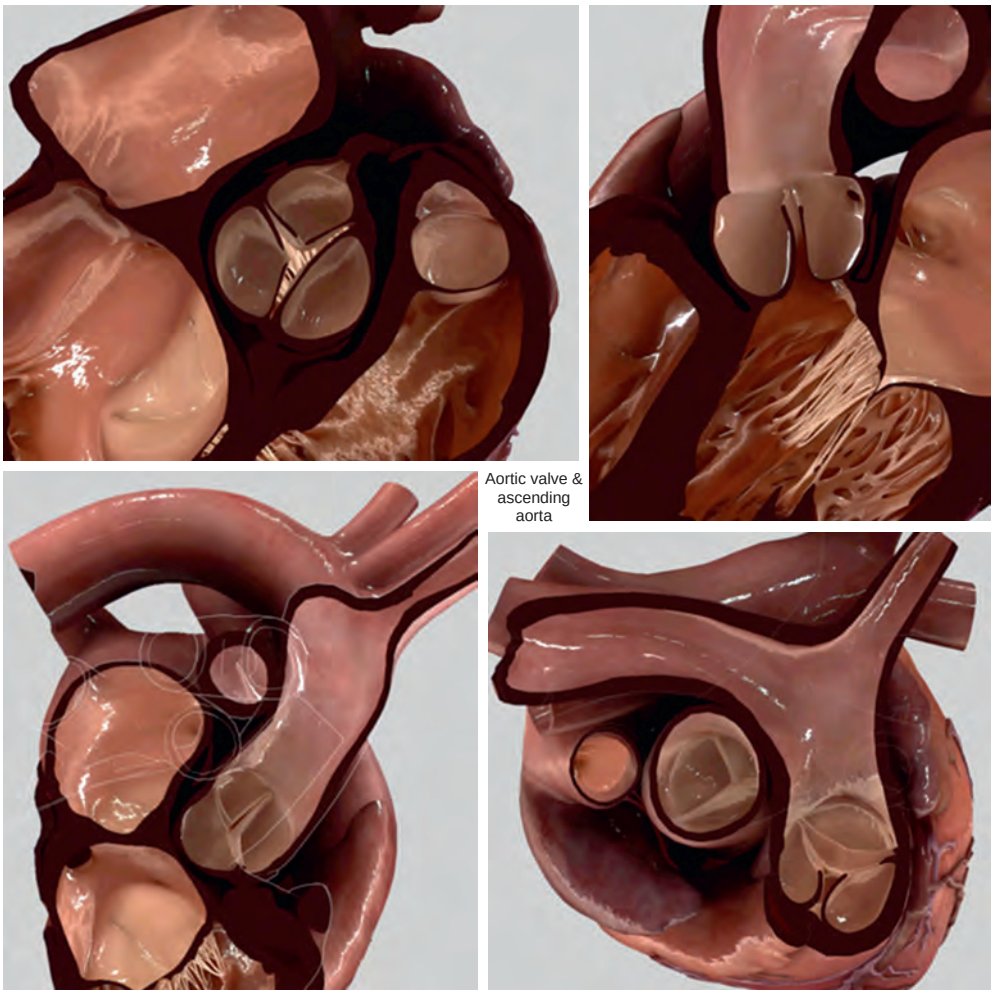

Fig. 17.4 Sections through the virtual heart model built into the HeartWorks echocardiography simulation center. The *top two panels* demonstrate the aortic valve short-axis *(left)* and long-axis *(right)* views. The *bottom panels* showcase the ascending aorta short-axis *(left)* and long-axis *(right)* views. Note the dimmed margins of overlying structures that have been removed to ease visualization. *(Courtesy Inventive Medical, London, United Kingdom.)*

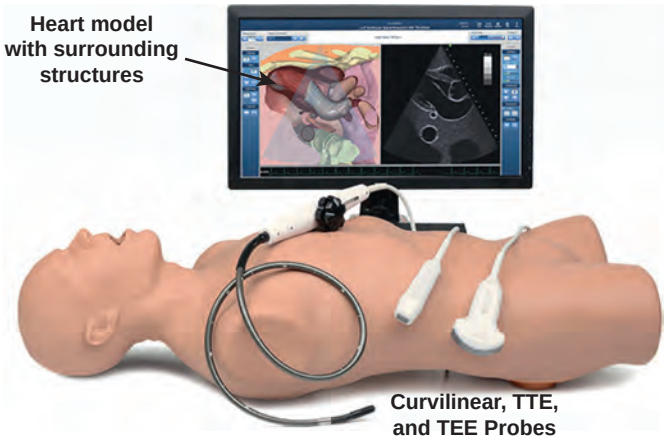

Fig. 17.5 The Vimedix echocardiography simulation system by CAE Healthcare. The virtual heart model built into this simulator is surrounded by models of adjacent structures, including ribs, stomach, lung, spine, and others. The simulator also includes a curvilinear probe and virtual abdominal anatomy for abdominal ultrasonography simulation. *TEE*, Transesophageal echocardiography; *TTE*, transthoracic echocardiography. *(Courtesy CAE Healthcare, Montreal, Canada. © CAE Healthcare, Inc.)*

Simbionix

The Simbionix simulator sold by 3D Systems (Cleveland, OH) is the most recent entry into the echocardiography simulation market (Fig. 17.6). This system offers some new features that differentiate it from other devices, and it delivers most of the functionalities already mentioned and in a fashion similar to that described earlier. Some distinct features include the following: preset step-by-step instructions for a complete examination; recording and browsing capability, including freeze and cine-loop; and pressure-sensitive mannequin-probe interaction. This simulator also includes modules for both echocardiography and abdominal ultrasound imaging, thereby enabling its use for a wider set of health care providers in a given educational setting. Specific to echocardiography, the modules are divided into bedside echocardiography, advanced TTE, and TEE. In general, the Simbionix system offers more options for independent learning, compared with its older cousins.

Blue Phantom Training Model

Also sold by CAE Healthcare, the Blue Phantom training model consists of a life-sized mannequin with an oral cavity and esophageal conduit built in tissue-like consistency, an anatomically correct nonbeating model of the heart made of a composite material suspended in the thoracic cavity, and accurate surface anatomy on the outside

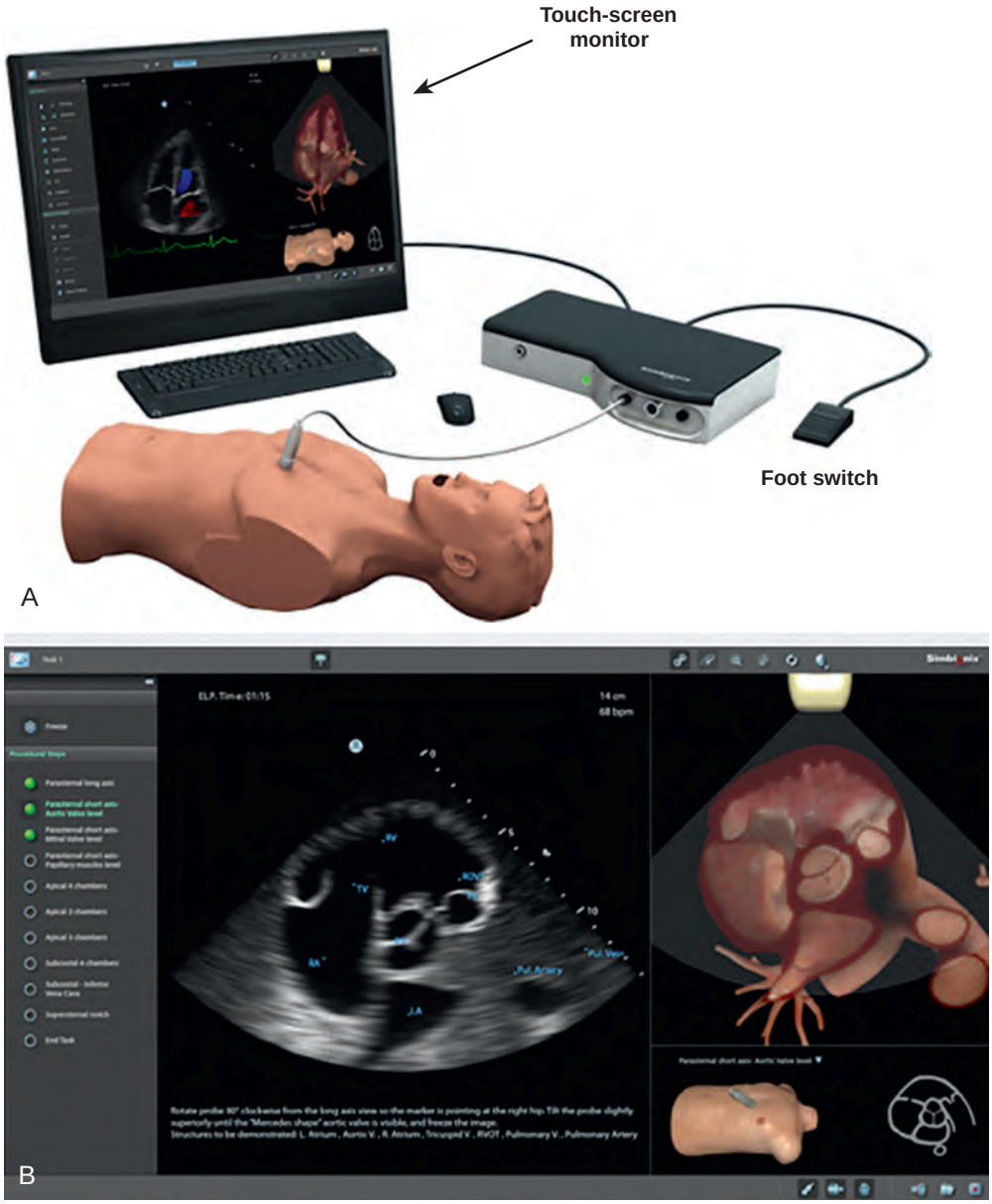

Fig. 17.6 The Simbionix echocardiography simulator by 3D Systems. (A) The simulator hardware includes an all-touch monitor and a foot switch to allow image capture functionality during bimanual transesophageal echocardiography examination. (B) Features include the ability to turn on labels for cardiac structures on the gray-scale–rendered images and a step-by-step, self-administrable examination that requires the examinee to acquire different views in succession, thereby capturing their windows through the footswitch. The list of views can be seen on the *left,* with the *green dots* representing accurate acquisitions. *(Courtesy 3D Systems, Cleveland, Ohio. © 3D Systems, Inc.)*

(Fig. 17.7). The main advantage of this simulator is the ability of trainees to use actual ultrasound systems and TEE probes for an echocardiographic examination.[5] Additionally, trainees can practice and learn image optimization and manipulation techniques on the actual ultrasound system that they would be using intraoperatively, thus facilitating clinical transferability. The ability to inject fluid into the pericardial space to practice image-guided pericardiocentesis is an additional feature that can be very useful for intensivists and cardiology fellows.

These properties make the Blue Phantom training model especially suitable for training in the latest developments in echocardiography (eg, 3D imaging, to learn and master workflow of the examination). The current echocardiography simulators lack the technologic interface to simulate 3D echocardiographic imaging, and the Blue Phantom simulator provides a relatively low-cost, but effective training tool for teaching 3D imaging. Similarly, the exigencies of the cardiac operating room environment preclude the training of a large number of physicians in 3D echocardiography during the course of patient care.

Although the images obtained are not completely representative of actual echocardiographic pictures, they enable the user to practice operating the machine. This model delivers on realistically mimicking some key aspects of echocardiography that are missed by other simulators (eg, probe insertion, image optimization on real machines, and knobology).

Online Learning

The period of early development of echocardiography simulators was also a time of rapid growth in information technology. Being an

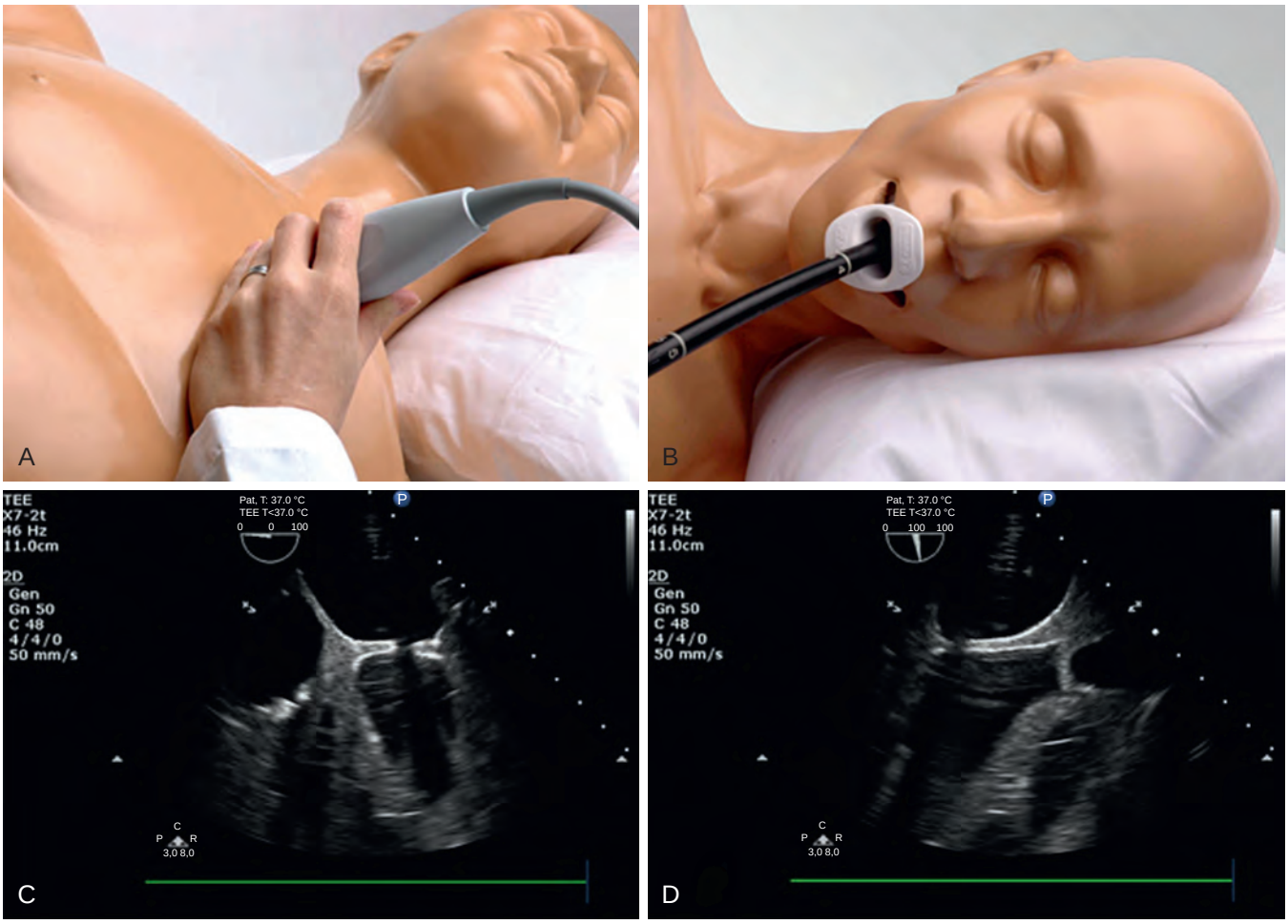

Fig. 17.7 The Blue Phantom model by CAE Healthcare. The model includes a plastic heart. (A) and (B) The ability to use both transthoracic echocardiography and transesophageal echocardiography probes to practice image acquisition and optimization skills on a real machine. (C) and (D) Image quality obtained on transesophageal echocardiography midesophageal four-chamber and aortic valve long-axis views. *(Courtesy CAE Healthcare, Montreal, Canada.)*

operator-dependent imaging modality, echocardiography lends itself to superior comprehension through vivid, interactive imagery as opposed to textual discourse. Realizing this potential, the Internet was identified early on as a useful medium of interactive instruction for purposes of echocardiography education. One of the first such efforts was the development of a computer application consisting of a static heart model, a virtual TEE probe, and representative knobs on the computer screen that could be controlled using a computer mouse (Fig. 17.8). Developed by Hartman and associates,[15] the interface permitted full manipulation of the probe relative to the heart (depth of insertion, retroflexion or anteflexion, rotation, left or right deflection, transducer angle advancement). The user could also control the viewing vantage point, by choosing either a cephalad-posterior view (top of the table; standard for most anesthesiologists) or an anterior-posterior approach (facing the patient; standard for most cardiologists).[15] Although ahead of the curve at the time, the project failed to come to fruition because the application never came online.

A similar echocardiography learning tool under the name of CT2TEE came online in 2009 as a noncommercial research project.[16] Built by Aleksander Kempny and Adam Piórkowski, the program is freely available online (http://www.ct2tee.agh.edu.pl; flash version is also available for download). This simulator is different in that it draws on computed tomography (CT) data to showcase the anatomy as seen on a particular echocardiographic scan plane (Fig. 17.9A). Because the CT data set is a complete 3D model of internal anatomy, the user can

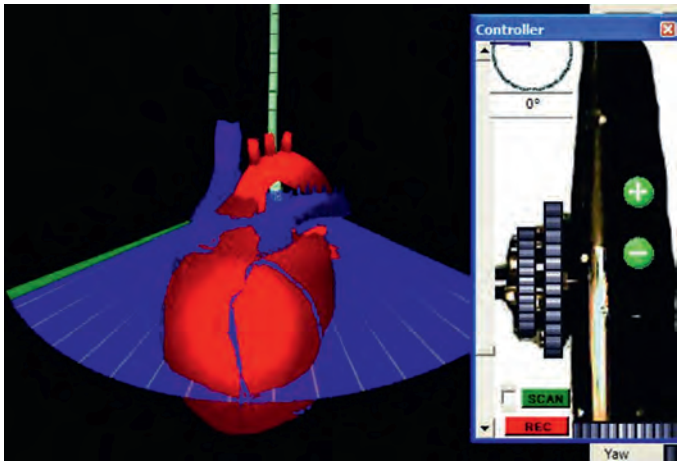

Fig. 17.8 Early virtual transesophageal echocardiography simulator developed by Hartman and colleagues. *(From Hartman GS, Christopher W, Mullin M. A virtual reality transesophageal echocardiography (TEE) simulator to facilitate understanding of TEE scan planes. Anesthesiology. 2001;95:A545.)*

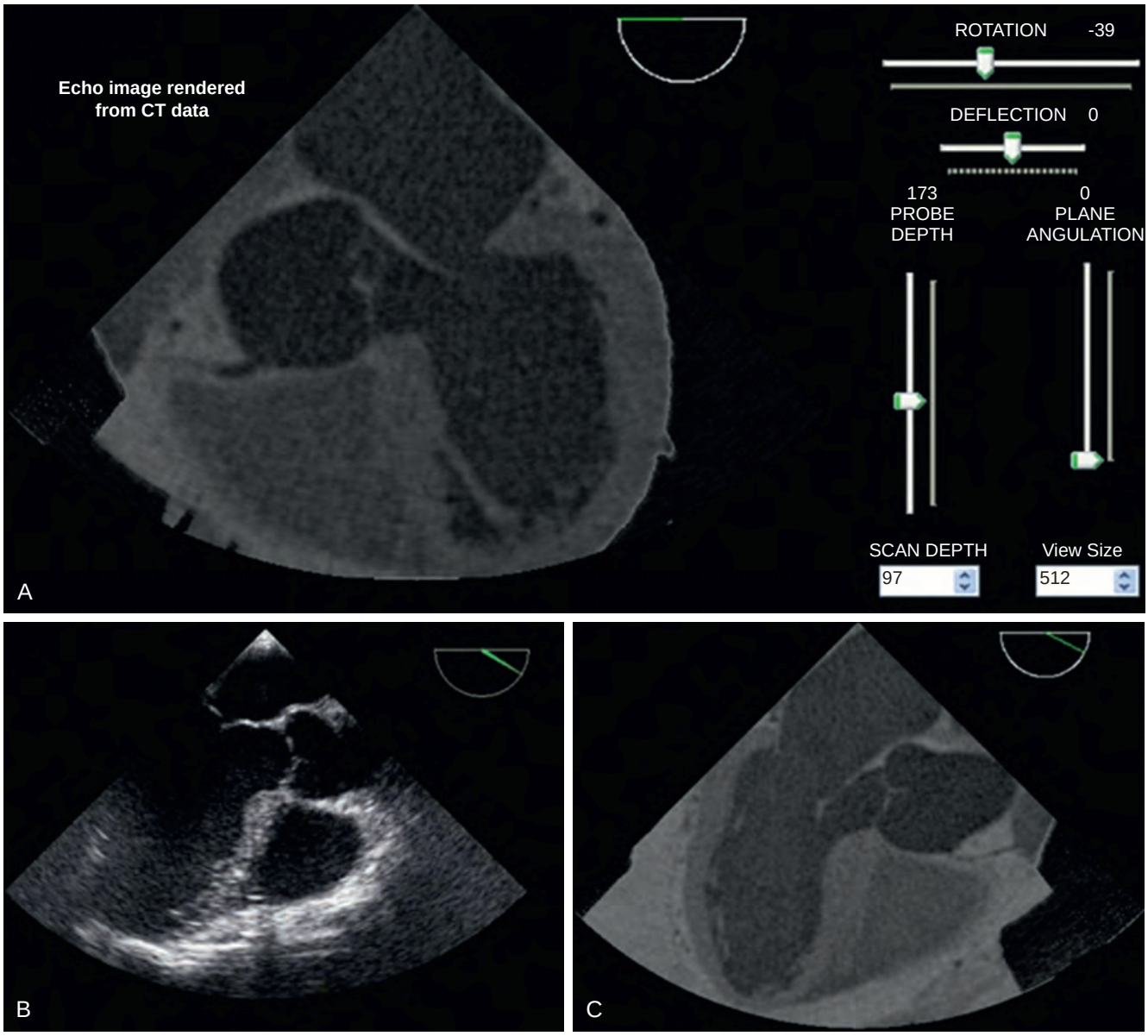

Fig. 17.9 CT2TEE virtual simulator. (A) Note that by manipulating the controls such as probe depth, plane angulations and rotation, the corresponding echocardiographic *(Echo)* window is rendered using computed tomography *(CT)* data. (B) and (C) Comparison of the same view obtained using actual transesophageal echocardiography and the CT2TEE simulator, respectively.

virtually "move" and "rotate" the probe in any direction to view the anatomic features expected on the corresponding echocardiographic window. The slider buttons within the simulator interface can be controlled by keyboard and mouse, thus enabling the user to "glide" the probe into the esophagus and angulate it into a scan plane position. The application then generates a corresponding 2D image from the corresponding CT data sets. Although CT and echocardiograms yield significantly different pixel gray values for the same tissue, the simulator does a good job of orienting the user to the anatomic features, and the images generated are comparable to TEE images (Fig. 17.9B–C).

Perhaps the most comprehensive, freely available online resource for echocardiography education is the TEE simulator developed by Michael Corrin at the University of Toronto (http://pie.med.utoronto.ca/TEE/). This interface includes a static heart model, a virtual TEE probe, and a scan plane. The scan plane can be rotated and the TEE probe manipulated using keyboard and mouse controls. Users can also select specific training modules or switch to 3D TEE views. The Standard Views module includes the 20 standard TEE views illustrated with the scan plane through the heart model along with the corresponding echocardiographic images (Fig. 17.10). It is possible to rotate the heart model and remove portions of the anatomy to visualize the structures that fall within a given TEE view.

The Alternative Views module includes the 19 nonstandard TEE views, whereas the TEE simulation module allows a virtual TEE examination, starting from probe insertion to positioning and maneuvering in reference to the virtual heart model. Standard assessment of the heart structures with spectral and color Doppler imaging is covered in the Spectral and Color Doppler modules. A descriptive text and an interactive quiz also help the user learn about disorders detectable on TEE. The Standard, Alternative, and Color Doppler TEE modules are also available on an iPad application. Overall, the virtual TEE trainer is a robust learning tool that can be accessed by novices on the go as they orient themselves to echocardiographic anatomy, even before they have access to a simulator.[17–19]

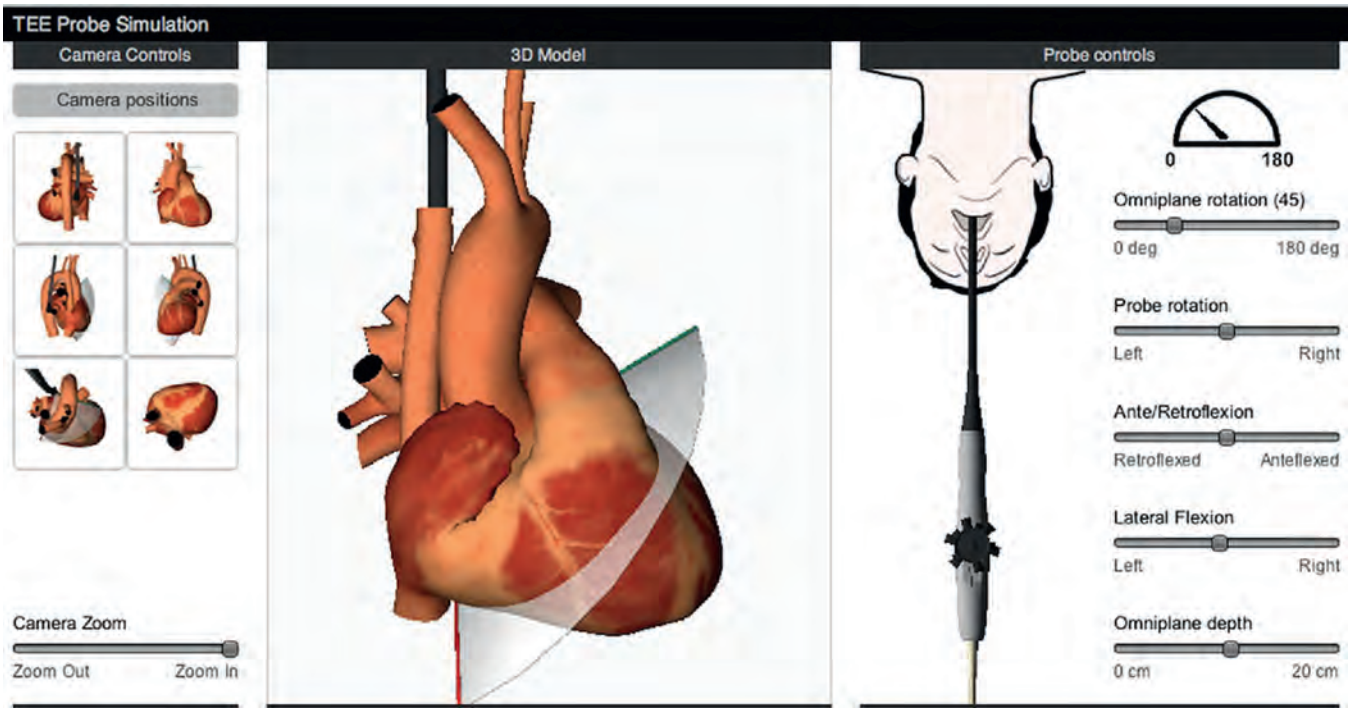

Fig. 17.10 The virtual transesophageal echocardiography simulator developed by University of Toronto physicians. The simulator offers views from multiple vantage points (camera position, *left*) to visualize a particular probe position. The probe control section *(right)* allows the user to manipulate different controls and see the corresponding effects on the three-dimensional model *(middle)*. *3D,* Three-dimensional. *(Courtesy University of Toronto, Perioperative Interactive Education: https://pie.med.utoronto.ca/TEE/.)*

Commercial Online Courses

Both Inventive Medical and CAE Healthcare, the makers of HeartWorks and Vimedix simulators, respectively, currently offer e-learning courses for echocardiography (accessible online at http://www.inventivemedical.com/elearn-a-complete-introduction-to-tee/ and http://www.caeiccu.com/lms). Although the HeartWorks course includes only TEE, the CAE HealthCare course offers both TTE and TEE modules, which must be purchased separately. The courses include audiovisual resources, animations, vivid illustrations, tutorials, and quizzes on topics in basic TTE and TEE. Being major participants in the echocardiography simulation market, these companies offer professionally designed, robust tools for remote learning for individual trainees and institutions that may not have access to their mannequin-based simulators. In this regard, they may be cost-effective alternative actual simulators for individual trainees or centers with a small number of trainees. Importantly, these courses are accredited by the American Society of Echocardiography, and candidates can redeem continuing medical education credits for successful completion of these courses.

Simulating Pathologic Conditions

The ability to simulate abnormal and pathologic variants of anatomy is a critical piece in making simulation-based medical education realistic. After orienting the trainees to normal anatomy, a simulation program must also introduce them to abnormal structure and function. This is vital for the newly acquired skills to be applicable to the clinical realm. Simulation of pathologic conditions can be instrumental in training the uninitiated eye to register an abnormality and pursue a suitable course of action accordingly.

Since the introduction of echocardiography simulators, incorporating pathologic features within various modules and programs has been a work in progress. The early EchoComTEE simulator included pathologic states (eg, pericardial effusion, mitral valve prolapse, left ventricular thrombus, and thrombus in the left atrial appendage).[12] The TTE version of the same simulator also incorporated congenital heart defects, including transposition of the great arteries, tetralogy of Fallot, ventricular septal defect, and atrial septal defect.[20] Currently, all three mannequin-based simulators available on the market include packages that simulate various adult and congenital disorders (Fig. 17.11). The Vimedix system, for example, can simulate up to 50 disease states that can be loaded on the system for a trainee to diagnose by either TTE or TEE. However, the base module includes only a few: dilated cardiomyopathy, hyperdynamic left ventricle, and recent myocardial infarction. Modules containing further pathologic conditions must be purchased separately in packages of 10. Similarly, the HeartWorks device can be loaded with several disease modules, one each for ventricular, valvular, vascular, and structural dysfunctions.

The Simbionix system also offers the ability to simulate pathologic conditions, notably allowing for variation in the severity. From a clinical standpoint, this is an important distinction and one that ideally needs to be further developed toward dynamic pathologic variation. In real patients, a disease spectrum often changes over the course of a surgical case. However, abnormal findings in current simulators do not dynamically vary (ie, tamponade does not worsen, wall motion does not change).[21] In the future, simulators that showcase worsening or improving disorders in response to trainees' actions (eg, crisis management simulations) may prove to be important tools in preparing clinicians for the stresses of a challenging clinical environment.

Evidence for Simulation

To date, numerous studies have been undertaken to investigate the utility and efficacy of echocardiography simulation as an educational tool. Some investigators have assessed the use of simulators as adjuncts to traditional didactic learning.[19,22–29] Yet others have explored the noninferiority of simulators to both live instructors as well as live volunteer models.[26,30] A comprehensive description of studies on the subject is included in Table 17.1.

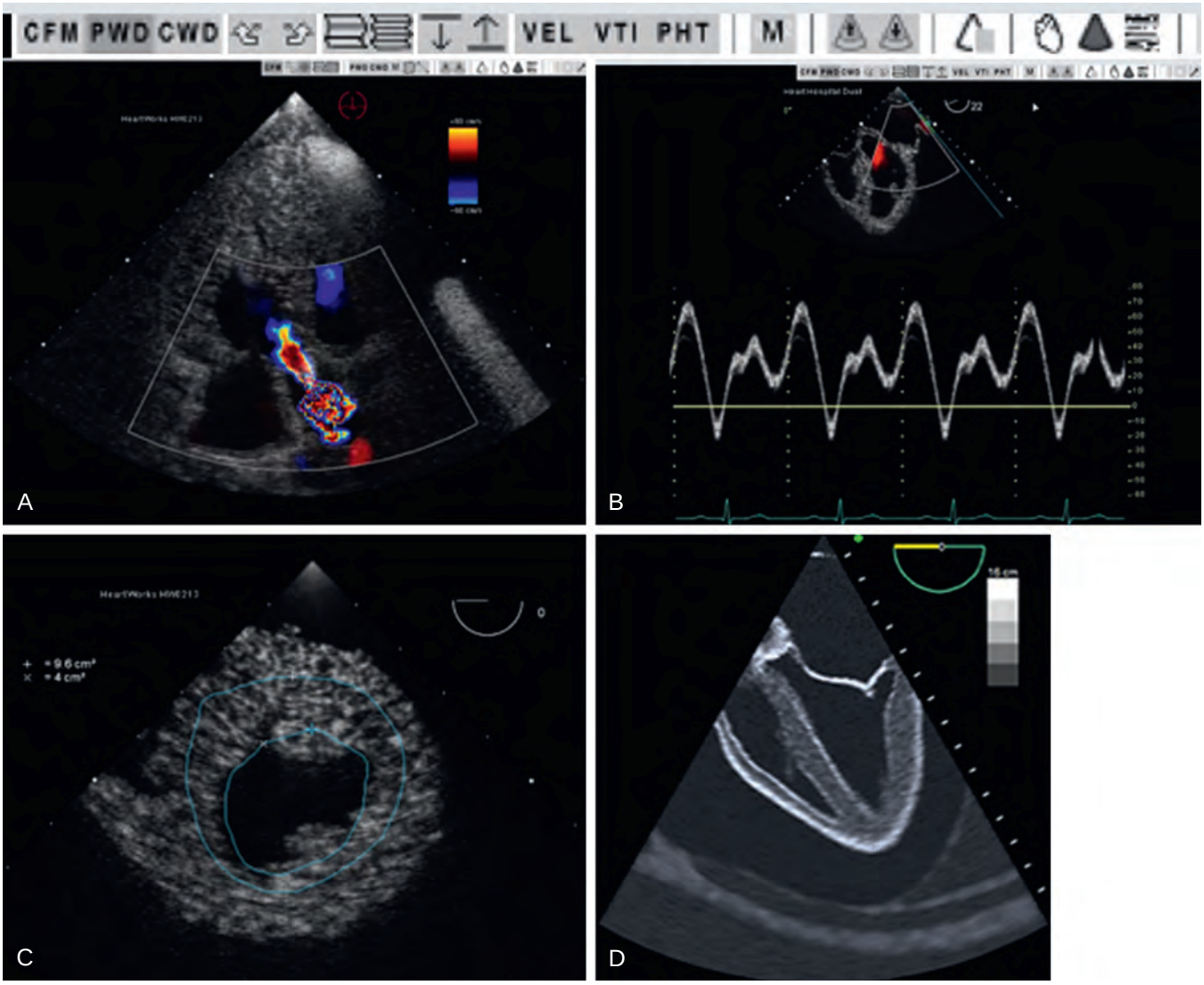

Fig. 17.11 Disorders as seen on different simulators. Current simulators offer ample opportunity to practice Doppler and M-mode *(M)*, as well as quantitative echocardiography skills such as computation of velocity time integral *(VTI)* and pressure half-time *(PHT)*. The *top strip* shows the control bar in the Doppler module of a HeartWorks simulator. (A) Aortic stenosis with color-flow Doppler imaging (HeartWorks). (B). Global left-ventricular dysfunction (HeartWorks). (C) Planimetry of left ventricle in the midpapillary view at systole and diastole showing areas of 4 and 9.6 cm^2, respectively, with significant anterior wall dysfunction (HeartWorks). (D) Cardiac tamponade with significant fluid accumulation in the pericardium (CAE Vimedix). *CFM*, color flow mapping; *CWD*, continuous-wave Doppler; *PWD*, pulsed-wave Doppler; *VEL*, velocity. *(A–C, Courtesy Inventive Medical, London, United Kingdom; D, Courtesy CAE Healthcare, Montreal, Canada.)*

A major limiting factor of most studies is the low number of participants because of constraints of program sizes, as well as the precedence taken by clinical work, especially for trainees who serve as subjects for these studies. However, a high degree of correlation is seen in the results, which are in line with the generally accepted notion that simulator training improves task performance. Most participants in these studies also report satisfaction with the quality of simulators and welcome the idea of simulation itself as part of their training.

A key element identified is that simulation delivers the greatest benefit for trainees at the beginning of their careers.[29] In other words, simulation is especially instrumental in helping echocardiography-naive residents and fellows through the initial learning curve as they first become oriented to echocardiographic anatomy. For more experienced echocardiographers, the law of diminishing returns sets in, and the benefits offered by simulators dwindle.

Assessment

The utility of simulators as task training and educational tools in echocardiography has been sufficiently established, especially for the new learner. Going forward, the use of simulation use in performance assessment would constitute a quantum jump in its role as a holistic educational and credentialing tool in echocardiography.[31] Fundamentals of laparoscopic surgery comprise one example in which successful completion of a simulation course as part of the broader curriculum fulfills an accreditation requirement. For a similar course in echocardiography, a need exists for assessment metrics that can be used to verify proficiency and be objectively applied across the board for all trainees. So far, written pretests and posttests have been the mainstays of assessing trainee performance in response to simulation. Although such tests provide some insight into the theoretic know-how

TABLE 17.1 Studies Carried Out to Date That Investigate the Realism, Feasibility, and Efficacy of Simulation-Based Echocardiography Training

Author (year)	*N*	*Study Type*	*Simulator Studied*	*Results and Conclusions*
Weidenbach et al[12] (2007)	56	Questionnaire-based survey of opinions after using the simulator (25 experts and 31 novices)	EchoComTEE[a]	The simulator was graded as "realistic" by experts; novices felt an improvement in spatial orientation, which may be especially important when starting out
Weidenbach et al[20] (2008)	43	Prospective observational (12 experts, 16 intermediates, 15 beginners); validity assessed by accuracy of diagnosis of congenital defects	EchoComTEE[a]	Construct validities were significantly different among the three groups; experts diagnosed almost all data sets correctly
Bose et al[22] (2011)	14	First-year anesthesia residents prospectively randomized into two groups and assessed using pretests and posttests	HeartWorks TEE[b]	A statistically significant difference between two groups was noted, with the simulation group scoring higher on the posttest; simulation is superior in teaching anatomic correlation, structure identification, and image acquisition
Jerath et al[17] (2011)	10	Prospective observational; benefit assessed using pretests and posttests after an average of 130-min access over 3-day period.	UofT virtual TEE; standard module	Significant improvement in knowledge of cardiac anatomy on TEE occurred after review of an online application; significant increases in posttest scores compared with pretest were seen after a short training period
Platts et al[23] (2012)	82	40 trainee sonographers; 42 TEE workshop attendees; prospective observational survey assessing usability and realism	Vimedix TTE and TEE[c]	Simulation provides a realistic method of training in image acquisition and improves spatial orientation
Neelankavil et al[24] (2012)	61	Anesthesia residents prospectively randomized; assessed using pretests and posttests and TTE examination on volunteers	HeartWorks TTE[b]	Simulation group scored higher on all criteria: written posttest, subject image quality, anatomy identification, and percentage of correct views; simulation is superior to lecture-based methods of TTE instruction
Vegas et al[18] (2013)	10	Prospective observational among novice echocardiographers; benefit assessed using pretests and posttests after 1 h of simulation	UofT virtual TEE; standard module	A 1-h exposure to the virtual TEE simulation produced a significant improvement in the posttest score; use of online simulation improves knowledge of navigating the 20 standard TEE views
Damp et al[25] (2013)	27	Prospective randomized; assessed by checklist for 37 different views and self-assessment questionnaire	HeartWorks TEE[b]	TEE simulator training improves proficiency and helps speed learning and comfort with TEE among cardiology fellows
Sohmer et al[26] (2013)	30	Prospective randomized; TEE novices underwent simulation and a human instructor or simulation and a slide presentation	Vimedix TEE[c]	Regardless of the method of instruction, scores on simulator based image-acquisition posttest improved significantly and similarly in both groups; a simulation-based curriculum may obviate the need for faculty
Sharma et al[45] (2013)	28	Prospective randomized; benefit assessed by pretests and posttests following Internet-based and simulation-based training	UofT virtual TEE; HeartWorks TEE[b]	Internet- and simulation-based teaching significantly improves TEE knowledge when compared with traditional methods among echocardiography-naive anesthesia residents
Jelacic et al[27] (2013)	30	Prospective observational; senior anesthesiology residents assessed by MCQs before and after simulator instruction	HeartWorks TEE[b] (normal version; no disorders)	Echocardiography-naive residents showed significant improvement in echocardiographic anatomy score on posttest, but not in patient safety, clinical application, probe manipulation, or pathology
Wagner et al[28] (2013)	10	Prospective observational among pediatric residents; benefit assessed using MCQs and performance-based pretests and posttests	EchoComTEE[a] (pediatric mannequin)	Scores showed significant improvement in both MCQs and performance tests assessing image orientation and ability to identify and diagnose congenital heart defects
Ferrero et al[29] (2014)	42	Prospective randomized between didactic and simulator training; assessed by examination on anesthetized patient	HeartWorks TEE[b]	Simulator-trained anesthesia residents demonstrated superior image acquisition skills; mean difference in image quality scores was greatest for junior and echocardiography-naive residents
Edrich et al[30] (2014)	46	Prospective randomized between simulator and live volunteer training; written pretest followed by written and practical posttests	Vimedix TTE[c]	Practical image acquisition and written test scores improved similarly and significantly after both simulator- and volunteer-based instructions; simulators are noninferior to live models for echocardiography education
Matyal et al[37] (2014)	18	Prospective observational; trainee performance tracked using kinematic analysis during the simulation course	Vimedix TEE[c]	Novices demonstrated reduction in the time taken to acquire images and greater economy of motion over the course; benefits of simulation can be quantified for assessment purposes; clinical transferability was demonstrated

[a]EchoComTEE, developed by Weidenbach et al.[12]
[b]HeartWorks, Inventive Medical, London, United Kingdom.
[c]Vimedix, CAE Healthcare, Montreal, Canada.
MCQs, multiple-choice questions; *TEE,* transesophageal echocardiography; *TTE,* transthoracic echocardiography; *UofT,* University of Toronto.

a trainee has achieved, they offer little information on the image acquisition and interpretation skills or on manual dexterity components of echocardiographic ability. Other indicators of proficiency reported in earlier studies have largely drawn on binary measures of ability, or lack thereof, to achieve a certain view or subjective assessments of image quality.[25]

Some of the currently available simulators have also sought to integrate subjective assessments of image acquisition and quality within their software platforms. In the HeartWorks' START (Student Assessment and Reporting Tool), for example, a tutor can set up student profiles and assign different tests such as basic TTE, TEE, or mitral valve examination to individual students depending on their level of proficiency. Students, in turn, access their respective user accounts (on the same simulator) and record what they believe is an accurate representation of each of the views within that examination. The tutor logs back into the students' accounts (in their own time), reviews the images as obtained and uploaded by each student, and grades them on a scale of 0 to 2. Although this arrangement eliminates the need for a tutor and a pupil to stand side by side simultaneously to enable trainee evaluation, it does not fundamentally alter the subjectivity in assessing proficiency in proper probe positioning, economy of motion, or the time taken to achieve the results. A video recording feature is planned for the future, but it may offer only yet another subjective measure of how comfortable a trainee appears visually.

The Simbionix system takes a step further and offers the ability to "automatically adjudicate" whether a trainee has acquired a correct image in response to a task assignment. For example, in test mode, the software can ask a trainee to acquire images, one by one, for the standard TEE views on the mannequin (see Fig. 17.6B). The trainee then acquires each image as directed, by using a foot switch to signal

final acquisition for that particular view. Based on the preset image for that view stored within the application, the software determines whether the trainee-acquired image is good enough to progress or not. Although the system allows for setting "difficulty" (or tolerance) levels of easy, medium, and hard, it can be difficult to achieve the exact image as stored within the application. This difficulty makes the particular assessment tool unrealistic, despite the advantage of allowing self-directed assessment by the trainee alone. Moreover, the extent of assessment is once again limited to the quality of image obtained and ignores other yardsticks of echocardiographic ability.

For simulation-based assessment to be broadly valid and applicable, a paradigm shift from subjective assessment of image quality is required. Quantification of measures of echocardiographic proficiency can help remediate this situation. Objective measurement of skills can also help overcome challenges posed by nonuniform clinical experiences by enabling verification of echocardiographic competency among trainees. In general, it is reasonable to define *echocardiographic competency* as the ability to perform a complete echocardiographic examination, including all standard views, in a time-limited and safe fashion. Achievement of such competency is meant to "prime" echocardiography-naive trainees for clinical exposure before their first, actual echocardiographic examination, as opposed to replacing clinical experience in any form.[6] More recent years have seen significant development in the arena of objective performance measurement, with the greatest progress stemming from the introduction of kinematic analysis in echocardiography simulation.[32,33]

Automated Kinematics

Kinematics refers to the study of motion and moving objects. In the context of echocardiography, it can be defined as the study of probe motion as an operator attempts to acquire a certain image. In purely physical terms, motion can be described by parameters such as acceleration and velocity. Recall that both these measures take certain other parameters into account: time, direction (or angle), and distance. It follows that probe motion can be broken down into several different parts, hence giving rise to the term *kinematic analysis.* Previously, such analysis of motion was used to evaluate training for endoscopic procedures and identify trainees requiring further instruction.[34,35] Setting benchmarks and hard targets in the context of simulation is associated with improved resident motivation to participate in a curriculum by *gamification* of their learning experience.[36]

For an echocardiography simulator to achieve kinematic capability, it would need to document the starting point precisely and track the change in position in the x, y, and z positions of the probe during its motion. The angular rotation of the scan plane as well as the roll, pitch, and yaw of the TEE probe would also need to be recorded over time. The z-axis refers to the distance of the probe from the chest wall; the x-axis and y-axis refer to the horizontal and vertical (cephalad-to caudad) motion of the probe in the chest. Roll, pitch, and yaw refer to angular motion of the probe along the x-axis, y-axis, and z-axis, respectively[37] (Fig. 17.12).

The electromagnetic technology that detects and records probe motion in a given field has existed since the very first simulators. Indeed, were it not for this technology, probe-responsive echocardiography simulation would not have existed. However, the idea to use this technology as a means of recording, measuring, and tracking trainee performance is a relatively late development. The starting point for this arrangement to work is the creation of a "target." In case of echocardiography, this would imply a "target image" or a *target cut plane* (TCP) that the trainee must acquire. Ordinarily, the TCP is an expert-acquired "ideal" 2D echocardiographic image, which can be stored on the system for use if and when required. Once a particular TCP is loaded, the "motion recording" option can be activated. "Motion recording" begins documenting the trainees' probe movements as they start, stop, turn, rotate, stop again, start again, accelerate, and finally refine their acquisition into a final image corresponding to the originally loaded TCP. Once the image acquisition is complete, the recording is stopped, and a report is generated with all the measurements obtained during the exercise.[33]

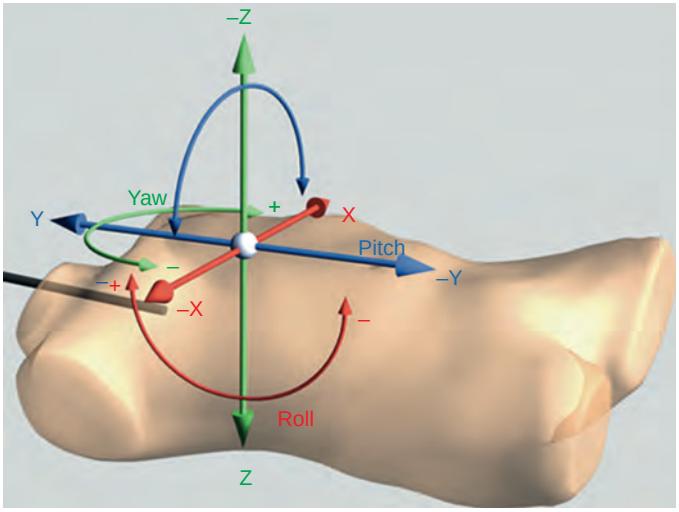

Fig. 17.12 The geometric dimensions measured by the CAE Vimedix system during motion tracking. *(Courtesy CAE Healthcare, Montreal, Canada. © CAE Healthcare, Inc.)*

At present, this feature is offered by the Vimedix system alone. On this simulator, the motion metrics interface has four different windows (Fig. 17.13):

1. The virtual reality 3D heart model with two superimposed scan planes: the red, static plane representing TCP; and the blue, dynamic scan plane that moves in response to trainee probe movements
2. The 2D computer-rendered target echocardiographic image, as defined by the TCP
3. The computer-rendered 2D ultrasound image corresponding to the trainee's scan plane, which changes with the trainee's probe manipulations
4. The target plane in relation to the body's surface anatomy

The system allows motion metrics to be used for both training and evaluation. In the training mode, the trainees are able to visualize the TCP on the screen, along with the ideal probe position in relation to the body to help guide them as they move and rotate the probe. In the evaluation mode, the trainees can be asked to acquire the desired image by using only their own memory, cognition, and manual dexterity to guide the probe to the correct position without the visual cue from an onscreen target image. Once a desired echocardiographic image has been acquired, the 3D tracking of the probe manipulation can be terminated. At the end of the tracking, the simulator automatically displays a detailed report with measurements for each of the recorded parameters (Fig. 17.14). This report can also be exported by a universal serial bus drive.

In their article on kinematic analysis, Matyal and colleagues[37] described the utility of motion metrics in measuring and tracking trainee performance. These investigators identified and reported parameters that show improvement in response to a simulation-based curriculum. These parameters include the following:

- The total time required to acquire the image measured in seconds from the time of activation of tracking until such time as the learner feels confident of the acquisition (and verified by an instructor)
- The sum of all linear and angular movements of the probe measured as centimeters of total distance moved
- The time before initiation of the first motion of the TEE probe after being instructed to acquire a specific image
- The number of times the subject performed accelerations as evidenced by sudden changes in speed or direction of the TEE probe
- Area under the curve of total distance plotted against total time for the acquisition (ie, economy of both time and motion)

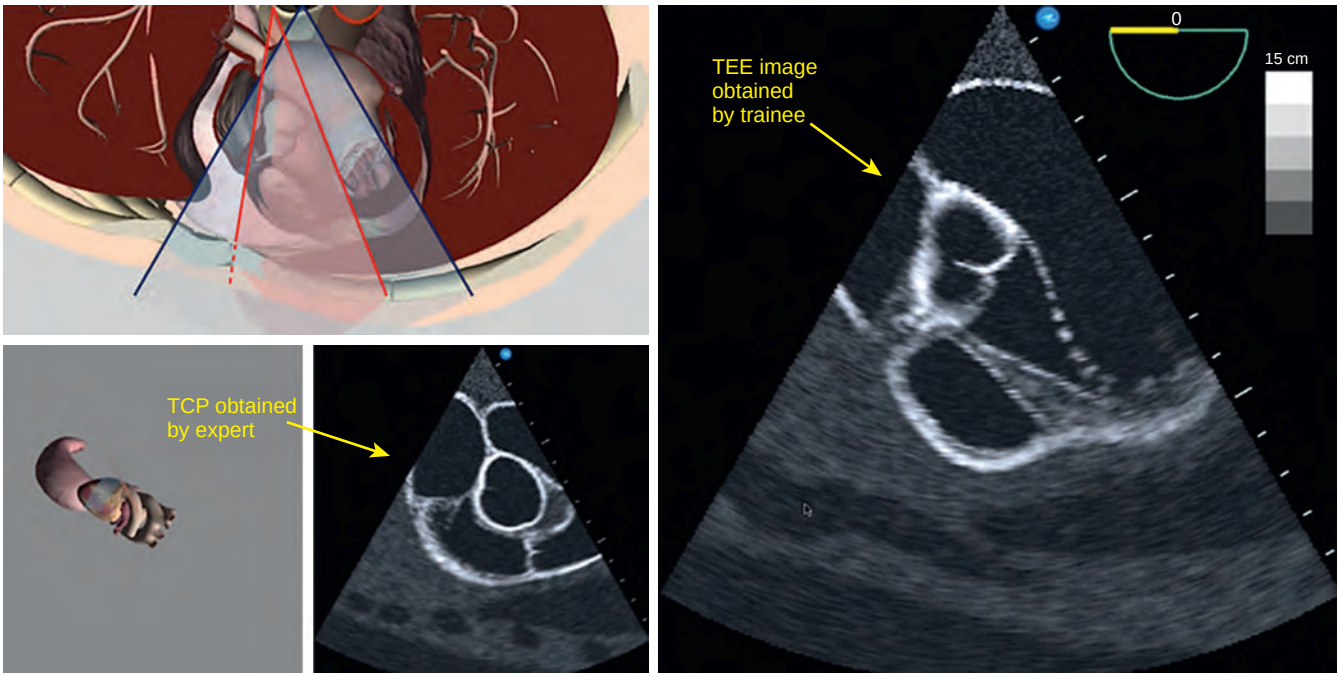

Fig. 17.13 A screenshot showing the different windows visible during a motion tracking acquisition. *TCP,* Target cut plane; *TEE,* transesophageal echocardiography.

Comparison of Captured vs. Target Cut Plane	
Total position difference (cm)	16.8535
Total angle difference (cm)	165.3490
Time (sec)	20.4999
Time until initial movement (sec)	5.1580
Total distance travelled (cm)	11.6659
Total angular movement (degree)	183.6045
Number of acceleration from Rest	19
Lateral(x) Position difference (cm)	-10.4056
Longitudinal(y) position difference (cm)	8.5449
Anteroposterior(z) postion difference (cm)	10.1366
Roll difference (degree)	-82.2843
Pitch difference (degree)	-8.5513
Yaw difference (degree)	-126.8527
Beam depth of field difference (cm)	-1.0000
Beam angle difference(degree)	0.0000

Fig. 17.14 Data generated by CAE Vimedix motion tracking algorithm at the end of a metrics acquisition for a single view.

The total distance traveled (path length) and the number of accelerations (Fig. 17.15) also helped differentiate between novices and experts, thus underscoring the importance of these parameters as potential metrics to establish competency for accreditation purposes. Importantly, progress on these parameters was shown to indicate readiness for clinical echocardiography, as evidenced by the ability to perform a complete, standard TEE examination on a real patient in the operating room. Meanwhile, another important concept that could be useful in context of echocardiography is that of *automaticity*, or the ability to engage in a process without devoting significant attention.[38] Surgical residents who demonstrate automaticity in tasks during simulation training have been reported to demonstrate a more complete transfer of skills to the clinical setting compared with surgical residents who do not.[39] A similar association for echocardiography education and practice is worth exploring in the future.

Future of Echocardiography Education

In recent years, the field of ultrasonography in general has witnessed a steep increase in the use of ultrasound as a diagnostic, guidance, and monitoring tool. Echocardiography has also had tremendous growth as an integral tool for perioperative physicians. Given this increase in number of users, the need for effective education in echocardiography has never been greater.[40] More importantly, given the current and evolving role of echocardiography in acute diagnosis and clinical decision making, adequate education in echocardiographic technique and operation carries direct implications for patient safety and potentially improved outcomes.[41,42] Given these requirements, the appearance of simulation in echocardiography education has been a timely and welcome development. To address the growing requirements of effective and large-scale echocardiography education, current simulators must keep improving and evolving in their roles as adjuncts to clinical experience, particularly in reducing the initial learning curve, as well as validating logbook scorings through objective assessment for basic and advanced certifications.

Despite technologic progress, the role of simulation in formal echocardiography education is yet to be defined. Moving forward, a curriculum-based approach including a combination of didactic lectures, online instruction, and hands-on simulation training holds significant promise.[43] Simultaneous use of multiple modalities can help provide a uniform, graduated, and coordinated learning experience to large numbers of trainees at the same time. For example, trainees can learn the basics of hemodynamics by didactic or online lectures and then practice quantitative echocardiography and its use in valve area calculations. The same coordinated learning strategy can be applied across all areas of initial echocardiography learning including wall motion assessment and aortic valve, mitral valve, and tricuspid valve evaluations.[44] At present, echocardiography education relies on a "top-down" approach with set milestones for achievement of final certifications. Adoption of simulation technology in training curricula can

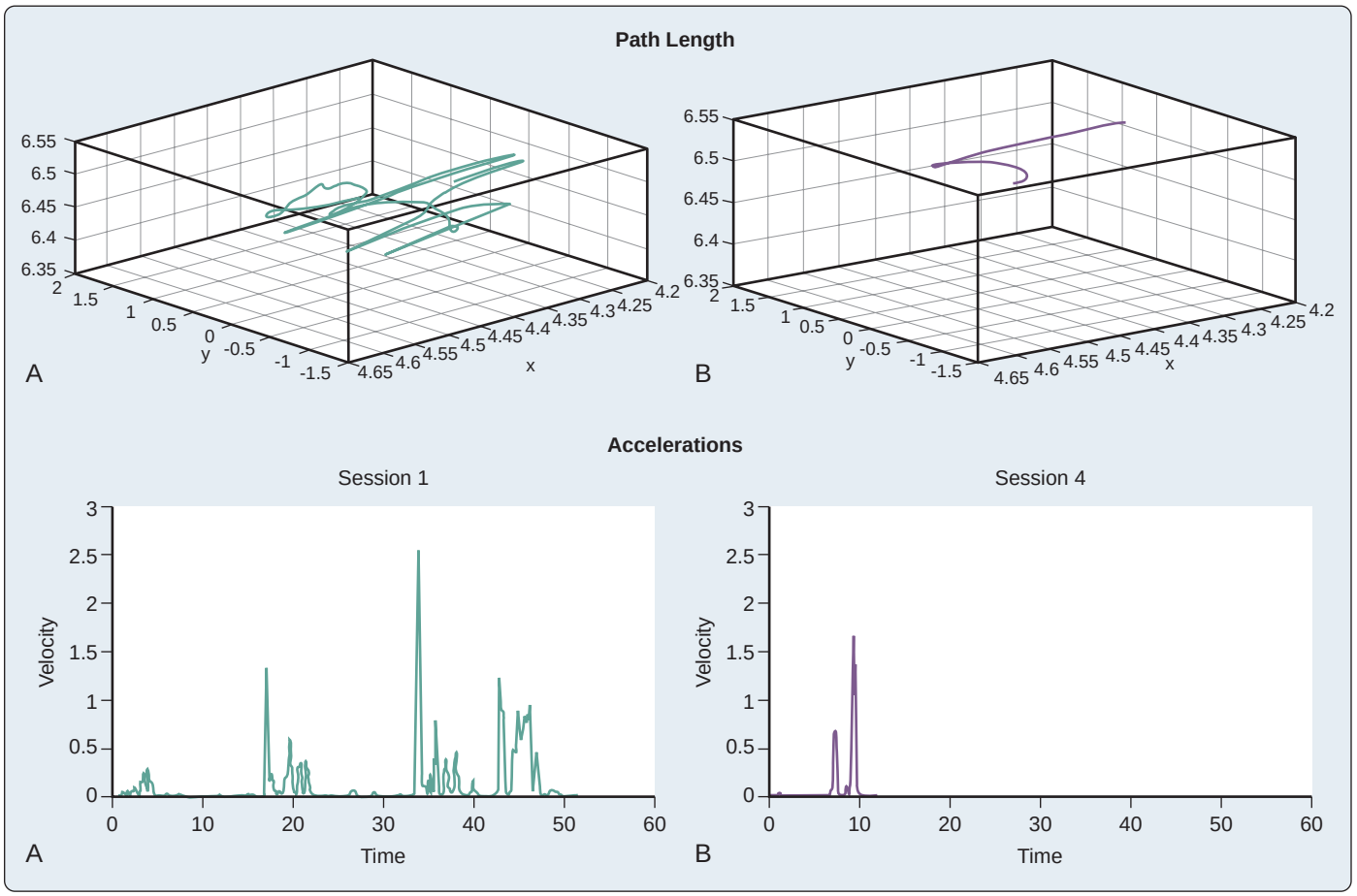

Fig. 17.15 The progress noted among simulation training sessions during a curriculum-based simulation course. *(Top)* The reduction in total distance moved by the probe by a particular trainee in an attempt to acquire a midesophageal four-chamber view. *(Bottom)* The number of accelerations, as evidenced by changes in velocity (speed or direction of the probe) over the course of an acquisition. The final session shows a decrease in both the number of accelerations and the time taken to acquire the image.

enable a "bottom-up" approach, with prerequisites specified for initiation of clinical echocardiography training.[6] Having attained comfort in areas such as basic ultrasound principles, echocardiographic anatomic orientation, and machine knobology in the simulation center, the trainees can acquire more meaningful and wholesome learning experiences right from their very first exposure.

One important caveat for echocardiography simulation going forward is its cost. Currently available simulators typically cost upward of $55,000 in the United States, with additional costs for annual software and hardware upgrades and service contracts. Moreover, storage costs, time devoted to teaching, and trainee time are also substantial. Streamlining simulation within the broader training program can help mitigate some of the personnel cost and clinical time lost in the simulation center.[21] Evidence suggests that echocardiography simulation may be at the cusp of widespread adoption as part of broader ultrasound curricula. However, the onus to achieve economy of scale remains on device vendors, who can pave the way for widespread adoption by price control. In case of failure to do so, virtual simulation could be a viable, cost-effective alternative to explore. Several studies have evaluated and demonstrated the effectiveness of virtual tools in reducing the learning curve for student echocardiographers.[17,18,45] Although such tools lack a manual dexterity component, they do address gaps in theoretic and cognitive knowledge in the absence of physical mannequin-based simulators.

Finally, although current simulators have come a long way since their earlier cousins, numerous areas of potential improvements remain. Building machine-like simulation consoles with knobs and buttons (eg, the current version of UltraSim; see Fig. 17.1), integrating data obtained from other monitors, deploying dynamic pathophysiologic changes, and eliciting diagnosis for evolving conditions are all features that future simulators could include to evaluate technical, cognitive, and behavioral responses to acutely unstable patients, as in a real environment. Further development of quantitative echocardiography tools and their role in diagnosis and decision making could also be helpful in filling gaps in clinical experience as well as accreditation-related assessment. Such high-fidelity simulation would serve to train not merely good "image acquirers," but rather *perioperative echocardiologists.*[46]

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18 Central Nervous System Monitoring

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KEY POINTS

1. Cardiac surgery–associated brain injury is common, multifactorial, and often preventable.
2. Electroencephalography can detect both cerebral ischemia or hypoxia and seizures and can measure hypnotic effect.
3. Middle-latency auditory-evoked potentials objectively document inadequate hypnosis.
4. Brainstem auditory-evoked potentials measure the effects of cooling and rewarming on deep brain structures.
5. Somatosensory-evoked potentials may detect developing injury in cortical and subcortical brain structures and peripheral nerves.
6. Transcranial electric motor-evoked potentials monitor function of the descending motor pathways.
7. Transcranial Doppler ultrasound examination assesses the direction and character of blood flow through large intracranial arteries and identifies microemboli.
8. Cerebral oximetry, using spatially resolved transcranial near-infrared spectroscopy, provides a continuous measure of change in the balance of cerebral oxygen supply and demand.
9. Used in concert, these technologies can reduce the incidence of brain injury and ensure the adequacy of hypnosis.

Yearly, nearly one-half of the 1 million patients undergoing cardiac surgical procedures worldwide will likely experience transient neurologic, cognitive, or neuropsychological dysfunction; in one-quarter of these patients, the changes will be persistent.[1] The direct annual cost to US insurers for brain injury from just one type of cardiac operation, myocardial revascularization, is estimated at $2 billion.[2] Furthermore, the same processes that injure the central nervous system (CNS) also appear to influence dysfunction of other vital organs. Thus, enormous clinical and economic incentives exist to improve CNS protection during cardiac surgical procedures.

Historically, neurophysiologic monitoring during cardiac surgical procedures has elicited little enthusiasm because of the presumed key role of macroembolization. It is widely assumed that most brain injuries during cardiac operations in adults result from cerebral embolization of atheromatous or calcified material dislodged from sclerotic blood vessels during the manipulation of these vessels. Until the introduction of myocardial revascularization without cardiopulmonary bypass (CPB) or aortic clamp application, these injuries often were viewed as unavoidable and untreatable.

Technical developments are altering this perception. First, CNS injuries still occur despite reductions in aortic manipulation with the newer approaches to coronary artery bypass grafting (CABG) and aortic surgical procedures.[3] Second, neurophysiologic studies have implicated hypoperfusion and dysoxygenation as major causative factors in CNS injury[4,5] (Box 18.1). Because these functional disturbances are often detectable and correctable, the impetus is to examine the role of neurophysiologic monitoring in organ protection (see Chapter 40).

The familiarity of cardiac anesthesiologists with neuromonitoring is becoming increasingly important. The information from compact and simplified monitors of brain electrical activity, blood flow velocity, and oxygenation can now be integrated into a unified display to facilitate cardiac anesthetic management. The goal of this chapter is to highlight the practical issues involved with each of these neuromonitoring technologies. This emphasis on practicality limits discussion to devices cleared for use by the US Food and Drug Administration (FDA). Because many of the practical issues in the application of these technologies are similar, the technical and physiologic underpinnings are presented first, with the later portion of the chapter devoted to clinical applications.

Electroencephalography

Electroencephalographic (EEG) monitoring for ischemia detection has been performed since the first CPB procedures.[6] However, in contrast to its widespread use during carotid endarterectomy (CEA), EEG monitoring of cardiac operations has been performed primarily in academic centers or those specializing in pediatric surgery. This limited use appears to have several causes.

First, small, practical, and affordable EEG monitors have only recently become available. For example, using a book-sized box of electronics and a notebook computer, it is now possible concurrently to display multichannel conventional and processed EEG findings, as well as bilateral transcranial Doppler (TCD) ultrasonic spectra and cerebral oxygen saturation. All the resulting data can be easily transmitted over high-speed data lines for Internet-based consultation or archival or post hoc analysis.

Second, the traditional diagnostic approach to EEG analysis depended on complex pattern recognition of 21-channel analog waveforms to identify focal ischemic changes.[7] This analytic format necessitated extensive training and constant vigilance. As a result, the direct monitoring of EEG findings during cardiac operations by anesthesia providers was viewed as impractical. However, reduced electrode array perioperative EEG recordings that include bilateral activity appear to be effective in identifying cortical ischemia and seizure activity in the perioperative and critical care settings.[8] Anesthesia-oriented training materials now permit providers to learn the basics of EEG artifact recognition[9] and waveform interpretation[10–12] quickly. In addition, computerized processing of EEG signals provides simplified trend displays that have helped to overcome many of the earlier interpretational complexities.[13]

Third, EEG analysis during cardiac surgical procedures was often confounded by anesthetic agents, hypothermia, and roller pump artifacts.[14] Fortunately, these technical problems have now been overcome by (1) elimination or replacement of the troublesome roller pumps with centrifugal pumps, (2) routine use of mild hypothermic or normothermic bypass, and (3) adoption of fast-track anesthesia protocols that avoid marked EEG suppression.

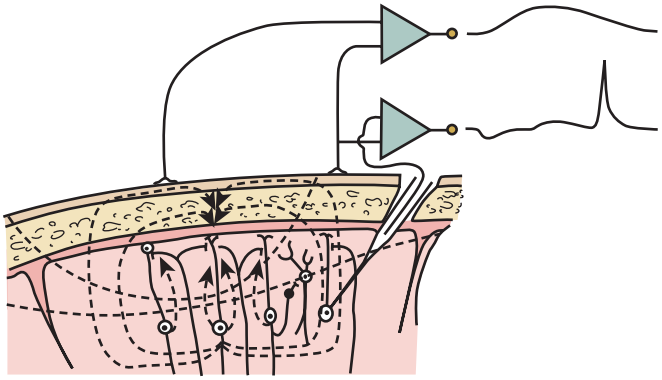
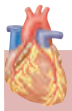


Fig. 18.1 Production of electroencephalographic (EEG) waves. Scalp electrodes record potential differences that are caused by postsynaptic potentials in the cell membrane of cortical neurons. The *closed loop dashed lines* represent the summation of extracellular currents produced by the postsynaptic potentials. *Open segment dashed lines* connect all points having the same voltage level. The two scalp electrodes record changes in the voltage difference over time *(top trace at upper right).* The *lower trace* from a microelectrode inserted in a single cortical neuron has little direct relationship with the summated EEG wave. *(Modified from Fisch BJ.* EEG Primer. *3rd ed. New York: Elsevier, 1999:6.)*



BOX 18.1 FACTORS CONTRIBUTING TO BRAIN INJURY DURING CARDIAC SURGICAL PROCEDURES

- Atheromatous emboli from aorta manipulation
- Lipid microemboli from recirculation of unwashed cardiotomy suction
- Gaseous microemboli from air leakage and cavitation
- Cerebral hypoperfusion or hyperperfusion
- Cerebral hyperthermia
- Cerebral dysoxygenation

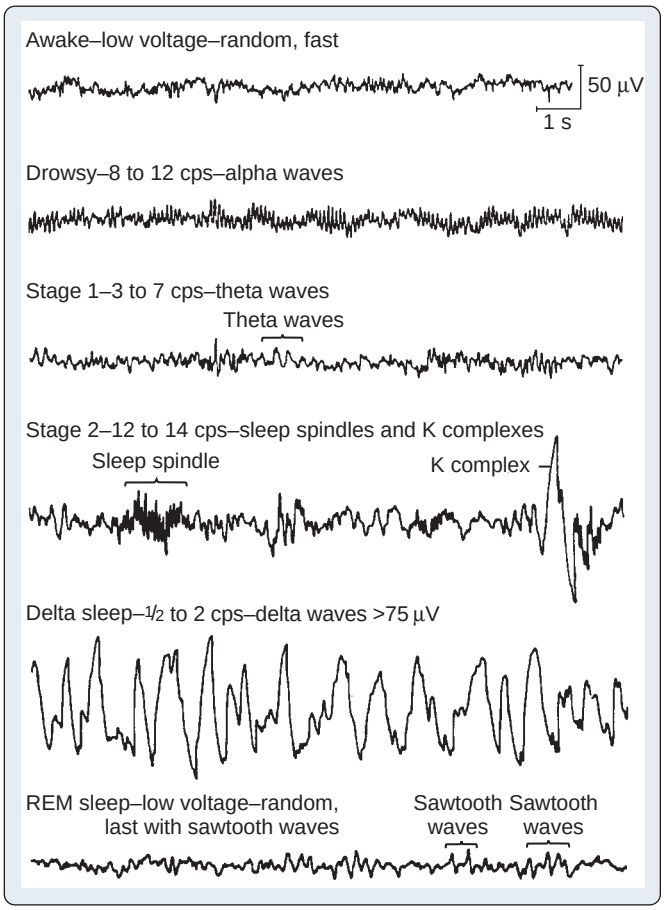


Fig. 18.2 Specific electroencephalographic characteristics of human sleep-wakefulness cycle stages. Note the appearance of the four most common frequency bands, from the lowest frequency delta through theta and alpha to high-frequency beta. An even higher gamma frequency band (25 to 55 cps) is also described. *REM,* Rapid-eye-movement. *(Modified from Yli-Hankala A, ed.* Handbook of Four-Channel EEG in Anesthesia and Critical Care. *Helsinki, Finland: GE Medical Datex-Ohmeda Division; 2004:5, with permission of the publisher.)*

Physiologic Basis of Electroencephalography

Electroencephalographically directed interventions designed to correct cerebral hypoperfusion during cardiac surgical procedures require an appreciation of the underlying neurophysiologic substrate. Scalp-recorded EEG signals reflect the temporal and spatial summation of long-lasting (10–100 milliseconds) postsynaptic potentials that arise from columnar cortical pyramidal neurons (Fig. 18.1). These potentials are produced by dipoles distributed over soma-dendritic surfaces. Pyramidal neurons have a long, vertically oriented apical dendrite and shorter basal dendrites radiating from the soma base. Near-synchronous excitation (or inhibition) of neighboring dendritic membranes produces large-amplitude spatially summating vertical dipoles, whereas radial current layers are generated in the somatic region. Simultaneous current generation in the two regions may appear to be self-canceling at distant surface electrodes. In addition, traditional EEG tracings depict only voltage change, not absolute voltage. Thus, sustained high-frequency neuronal activity may result in a large but nonvarying surface voltage deviation that would be invisible on the conventional EEG tracing. These important EEG characteristics should be appreciated when interpreting low-amplitude signals; they do not necessarily indicate synaptic quiescence.

EEG rhythms represent regularly recurring waveforms of similar shape and duration. These signal oscillations depend on the synchronous excitation of a neuronal population. The descriptive nature of conventional EEG findings characterizes the oscillations (measured in cycles per second [cps] or Hertz [Hz]) as sinusoids that were classified according to their amplitude and frequency. The terminology used to describe the frequency bands of the most common oscillatory patterns is illustrated in Fig. 18.2. In addition, a high-frequency (25–55 Hz) gamma band is recognized (Table 18.1).

TABLE 18.1 Electroencephalographic Frequency Bands

Delta (δ)	0.1–4 Hz
Theta (θ)	4–8 Hz
Alpha (α)	8–14 Hz
Beta (β)	14–25 Hz
Gamma (γ)	25–55 Hz

EEG oscillatory patterns are functional manifestations of specific intraneuronal networks. The extent of cortical processing among neighboring neuronal columns influences the extent of scalp-recorded EEG waveform synchronization and does not necessarily depend on the subcortically mediated arousal level. At a high level of cortical processing, each neuronal palisade may function in relative independence. The resultant EEG signal will be of low amplitude, representing the distance-weighted average of many desynchronized micropotentials. The large number of small potentials is reflected in an EEG pattern characterized by a high dominant frequency (14- to 25-Hz beta waves). Such a pattern may be seen during very different vigilance states, such

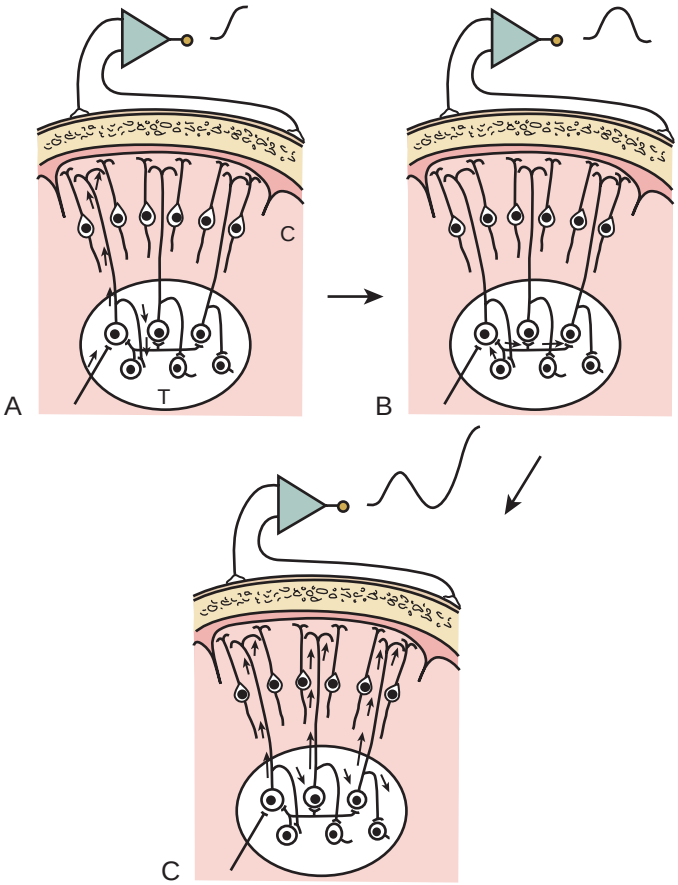


Fig. 18.3 Steps involved in the production of rhythmic electroencephalographic (EEG) activity. (A) Initiation of an EEG wave results from afferent excitation of a thalamocortical relay neuron (TCR) in the thalamus *(T)* and subsequent simultaneous transmission to a cortical and inhibitory thalamic interneuron. (B) Output from the thalamic inhibitory interneuron suppresses neighboring TCR neurons, thus leading to the termination of the first EEG wave. (C) Following the inhibitory phase, additional TCR depolarization produces another EEG wave. *(Modified from Fisch BJ.* EEG Primer. *3rd ed. New York: Elsevier, 1999:10.)*

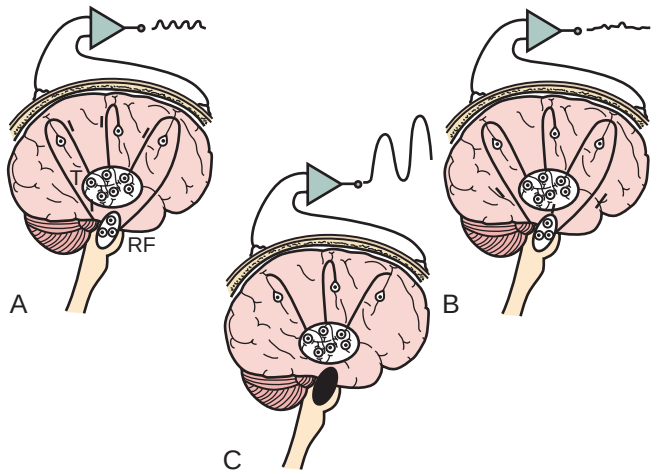


Fig. 18.4 Role of the mesencephalic reticular formation *(RF)* in the generation of rhythmic electroencephalographic (EEG) activity. (A) In the absence of strong RF input, the thalamic pacemaker cells produce rhythmic EEG activity. (B) RF activation sends inhibitory signals to the thalamus, thereby suppressing rhythmic EEG and leading to a desynchronized pattern. (C) In contrast, anesthetic or hypnotic RF suppression augments cortical EEG rhythms. *(Modified from Fisch BJ.* EEG Primer. *3rd ed. New York: Elsevier, 1999:12.)*

as awake and mentally alert status (see Fig. 18.2, top trace) versus rapid-eye-movement (ie, dream) sleep (see Fig. 18.2, bottom trace). Partial cortical columnar synchronization develops with a reduction in information processing, thus resulting in higher-amplitude and lower-frequency EEG oscillations associated with a relaxed, drowsy state (see Fig. 18.2; 8- to 14-Hz alpha rhythm). Progressive suppression is associated with lower-frequency 4- to 8-Hz theta waves. Minimal processing leads to the very high-amplitude, low-frequency hypersynchronous 0.1- to 4-Hz delta waves seen during the low-vigilance states of deep coma, deepest sleep, hypoxia, ischemia, and some forms of surgical anesthesia.

Synchronization of cortical columns is influenced by subcortical structures, including the thalamus (Fig. 18.3) and reticular activating system (Fig. 18.4). Reticular inhibition can block the passage of sensory information to the cortex that is routed through thalamic relays. This state of functional deafferentation results in unconsciousness, an essential component of both natural sleep and surgical anesthesia.[15] However, the individual components of a modern balanced anesthetic technique may differentially affect the separate control mechanisms for sensory processing and vigilance. Thus an EEG pattern suggestive of a low-vigilance state (ie, surgical hypnosis) does not necessarily guarantee the absence of subcortical (ie, unconscious) sensory perception (ie, reflexive response to painful stimuli).[16] Furthermore, because the neuronal basis for the electroencephalogram is primarily of cortical origin, it is not surprising that many univariate (ie, single variable) EEG amplitude or frequency descriptors are only weakly correlated with clinical measures of anesthetic effect or developing disease involving primarily or exclusively subcortical structures.

Practical Considerations of Electroencephalographic Recording and Signal Processing

The process of converting these tiny potentials into interpretable EEG displays begins with choice of scalp electrodes (subdermal needle, metallic disk, or silver-silver chloride gel self-adhesive patch) and their location. All three electrode types provide high-quality signals. Single-use sterile needle electrodes are easy to apply but are invasive, relatively expensive, and not well tolerated by conscious patients. They also predispose to hematoma formation or bleeding in heparinized patients. Reusable disk electrodes, held in place with conductive gel, gel-free self-abrading plastic retainers or built into a nylon mesh cap, may be used on conscious patients and are the least costly option. Adhesive patch electrodes are generally used only on glabrous skin and have a cost midway between the other options.

Standardized electrode placement is based on the International 10–20 System (Fig. 18.5). It permits uniform spacing of electrodes, independent of head circumference, in scalp regions known to correlate with specific areas of cerebral cortex. Four anatomic landmarks are used—the nasion, inion, and preauricular points. Electrodes are located at 10% or 20% segments of the distance between two of these landmarks. The alphanumeric label for each site uses an initial upper case letter to signify the skull region (ie, frontal, central, temporal, parietal, occipital, auricular, and mastoid). Second and sometimes third letters, in lowercase, further delineate position (eg, "p" represents frontal pole, whereas "z" indicates zero or midline). Subscripted numbers represent left (odd) or right (even) and specific hemispheric location, with the lowest numbers closest to the midline. The prime notation (′) is used to signify specialized locations designed for certain evoked potential applications (eg, C_3' and C_4' represent 2 cm posterior to C_3 and C_4, directly over the upper limb sensory cortex).

The differential amplifiers used in EEG recording measure the voltage difference between two inputs. By convention, a negative voltage at input 1 relative to input 2 results in an upward deflection of the tracing. With a referential arrangement (montage) of recording channel selections (Fig. 18.6, left), the input 2 connections from a

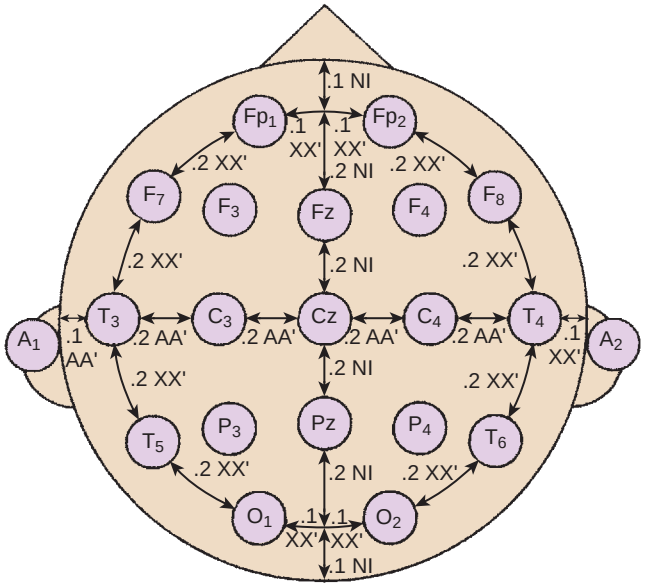


Fig. 18.5 Electroencephalographic electrode positions in the International 10–20 system. The sagittal hemicircumference (labeled *AA′*) is measured from the root of one zygoma (just anterior to the ear) to the other, across the vertex. The third measurement is the ipsilateral hemicircumference *(XX′)* measured from a point 10% of the coronal hemicircumference above the zygoma. Through these intersecting lines all the scalp electrodes may be located, except the frontal *(F_3, F_4)* and parietal (P_3, P_4). The frontal and parietal electrodes are placed along the frontal or parietal coronal line midway between the middle electrode and the electrode marked in the circumferential ring.

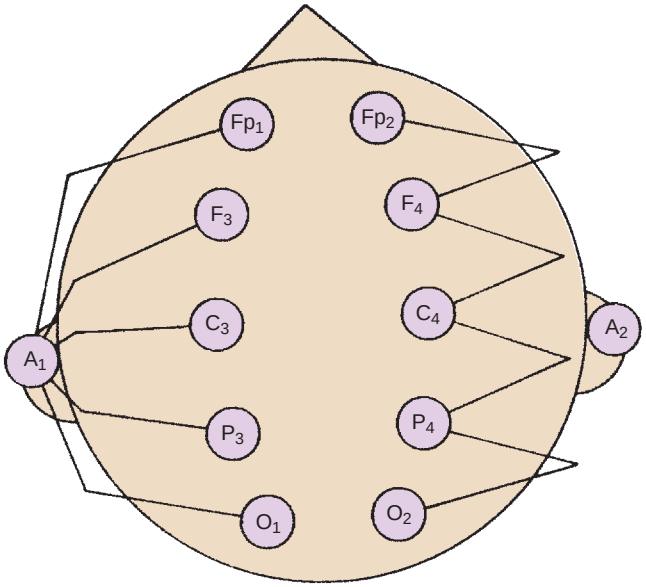


Fig. 18.6 Bipolar and common reference electroencephalographic (EEG) montages. The left parasagittal electrodes are connected in a common reference montage using the left earlobe *(A_1)* as the common reference electrode. Five channels are recorded, each of them between the parasagittal electrode and the ear electrode. Differences among these channels represent differences in cerebral activity among the various parasagittal electrodes because each channel is recorded as the difference between the activity at the parasagittal electrode and the activity at the ear electrode. For comparison, the right parasagittal electrodes are connected in a bipolar chain. In this configuration, only four channels of EEG data are recorded. Each channel of data represents the electrical difference between the two electrodes.

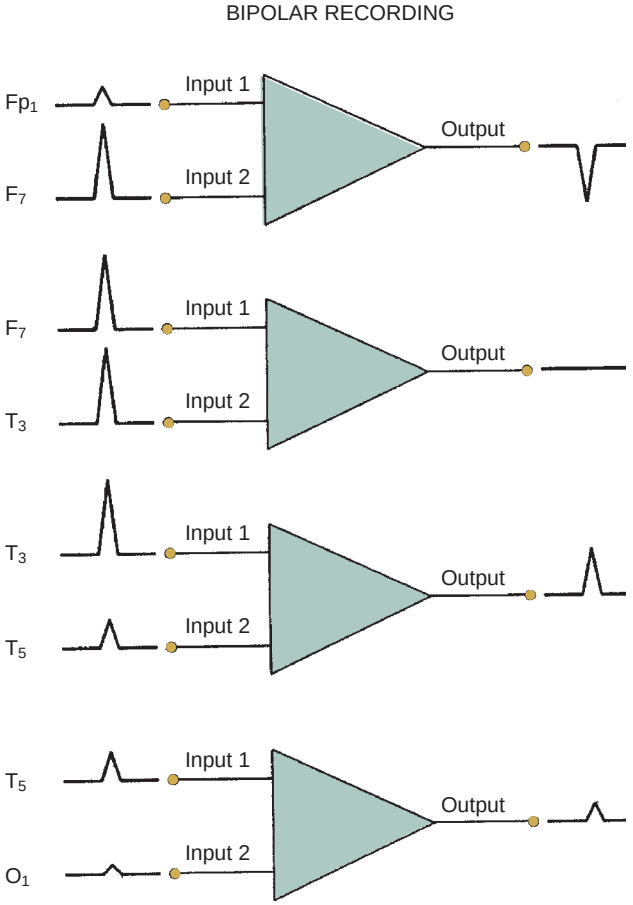


Fig. 18.7 Detection of focal electroencephalographic (EEG) abnormalities. Their accurate characterization requires that one of the amplifier's inputs be outside the field distribution of the transient EEG abnormality. If both inputs lie within the transient field, the signal may become invisible because of in-phase cancellation. (*Modified from Goldensohn ES, Legatt AD, Koszer S, et al, eds.* Goldensohn's EEG Interpretation. *2nd ed. Armonk, NY: Futura; 1999:16 with permission of the publisher.)*

series of channels are connected to a single electrode, whereas input 1 electrode connections all differ. (This approach is occasionally and erroneously referenced as "unipolar.") Alternatively, in bipolar recordings, a common reference is not used (see Fig. 18.6, right).

Although an array of scalp electrodes theoretically permits many possible montages to be used, the capability to change montage quickly varies greatly among different EEG monitors. This ability to change recording montage quickly may be important in the detection and characterization of both focal and diffuse abnormalities. With bipolar montages (Fig. 18.7), the transient will be distorted if both amplifier inputs lie within the transient electric field.

Montage choice also influences susceptibility to artifact. For example, millivolt ECG potentials may contaminate the thousand-fold smaller EEG signal, and cardiac pacing is often readily identifiable even in high-quality recordings. Contamination is often problematic with an ear or mastoid reference montage, but it may be invisible with an anterior-to-posterior bipolar montage. The extreme lateral placement of ear or mastoid references maximizes contamination by the perpendicularly oriented high-voltage dipole generated by the heart.

The frequency range involved in production of the EEG waveform is termed its *bandwidth*. The upper and lower bandwidth boundaries are controlled by filters that reject frequencies above and below the EEG bandwidth. Both the appearance of the unprocessed EEG waveform and the value of univariate numeric EEG descriptors such as the mean dominant frequency (MDF) may be heavily influenced by signal bandwidth that is often user controlled by high- and low-frequency

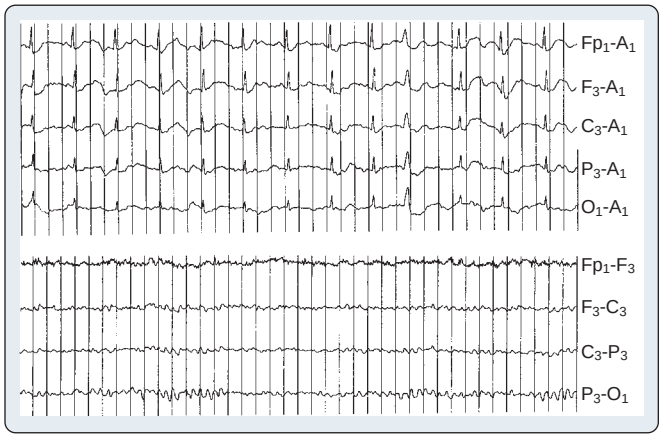


Fig. 18.8 Electroencephalographic (EEG) waveform notable features and the bispectral index (BIS). (A) Two EEG traces and corresponding BIS values are shown. These traces reflect a hypothetic situation in which bilateral frontal EEG recordings are taken. The right channel shows an underlying slow delta wave pattern with higher-frequency waves (eg, faster delta, theta, and alpha waves) also apparent. The left channel shows a burst suppression pattern. Such asymmetry could occur with unilateral *(left)* frontal hypoperfusion. (B) The EEG traces are obtained from a BIS monitor. Cardiopulmonary bypass had been initiated, and the patient's electroencephalogram was persistently suppressed. Marked electrocardiographic (ECG) artifact is evident in the persistently suppressed EEG trace. Automated analysis may not recognize the ECG signal as readily as a trained anesthesia provider. (C) The results of EEG filtering are depicted. The first trace shows a typical EEG epoch during general anesthesia, with an underlying slow delta pattern. Also apparent are higher-frequency waves (eg, faster delta, theta, and alpha waves). In the second trace, the higher-frequency waves are still apparent, but the underlying slow delta pattern has been attenuated by a user-selectable low-frequency filter. The default BIS setting automatically outputs a filtered EEG trace; these filters may obscure useful information. In this case, large delta waves consistent with deep anesthesia were filtered out, thus potentially preventing the anesthesia provider from appreciating the true anesthetic depth. EEG tracings were obtained using a BIS Quatro Sensor (version XP; Covidien, Boulder, Colo.). (*From Kertai MD, Whitlock EL, Avidan MS. Brain monitoring with electroencephalography and the electroencephalogram-derived bispectral index during cardiac surgery.* Anesth Analg. *2012;114:533, with permission of the publisher, Lippincott Williams & Wilkins, Baltimore.)*

filter settings (Fig. 18.8). Similarly, the same cerebral biopotential recorded by different EEG devices may result in dissimilar waveforms and numeric values.

Modern EEG monitors use digital microprocessors to analyze the amplified analog biopotentials. Yet analog-to-digital conversion imposes limitations on signal processing. Digitization converts a continuously varying biopotential into a series (ie, sample) of discrete quantal values. To minimize conversion inaccuracies, at least two samples per period are required. Sampling (Nyquist) frequency must be greater than twice the highest frequency of interest. For example, with an EEG bandwidth of 50 Hz, the minimum acceptable sampling frequency is 100 Hz (eg, 10-millisecond sampling interval). Aliasing, the counting of high-frequency signals as low-frequency input, may occur if the complex biopotential contains frequencies above the Nyquist frequency. Therefore most EEG monitors contain antialiasing filters that sharply attenuate waveform components above the Nyquist frequency. The details of filtering further add to the manufacturer-specific characteristics of processed electroencephalograms.

The continuous analog signal is also simplified into a (usually) discontinuous set of segments of a fixed duration (ie, epoch). Window functions can minimize, but not totally eliminate, digital distortion produced by the abrupt truncation of a continuously varying waveform. These window functions are numeric series containing the same number of elements as the epoch. Their purpose is to reduce the value

BOX 18.2 LAW OF THE ELECTROENCEPHALOGRAM

- In the absence of disease, electroencephalographic amplitude and frequency are inversely related.
- Simultaneous decrease may indicate ischemia, anoxia, or excessive hypnosis.
- Simultaneous increase may indicate seizure or artifact.

of epoch terminal elements. In addition to windowing, commercial EEG analyzers often use another form of signal conditioning called *whitening*. The energy content of the electroencephalogram is not uniform at all frequencies but instead is heavily skewed to the lower range. Whitening mathematically alters the momentary frequency-amplitude relationships to achieve nearly equal energy per octave and may improve pattern recognition in processed waveforms. Antialiasing, windowing, and whitening may vary not only among different devices but also among software versions used with a single device. The user should be aware that a standard unprocessed analog EEG signal may generate digitally processed displays and numeric descriptors that are unique for each monitor design and software version.

Display of Electroencephalographic Information

Time-Domain Analysis

Traditional display of the electroencephalogram is a graph of biopotential voltage (y-axis) as a function of time and consequently is described as a time-domain process. The objective of a diagnostic electroencephalogram is to identify the most likely cause of a detected abnormality at one moment in time. Typically, a diagnostic electroencephalogram is obtained under controlled conditions, using precisely defined protocols. Recorded EEG appearance is visually compared with reference patterns. Interpretation is based on recognition of unique waveform patterns that are pathognomonic for specific clinical conditions. In contrast, the goal of EEG monitoring is to identify clinically important change from an individualized baseline. Unlike diagnostic EEG interpretation, monitoring requires immediate assessment of continuously fluctuating signals in an electronically hostile, complex, and poorly controlled recording environment. Therefore, of necessity, interpretation relies less on pattern recognition and more on statistical characterization of change. Numeric descriptors thus may appropriately form an integral part of EEG monitoring.

Both EEG diagnostic and monitoring interpretations are based in part on the "law of the electroencephalogram" (Box 18.2). It states that amplitude and dominant frequency are inversely related. As described earlier, synchronously generated postsynaptic potentials may produce large-amplitude biopotentials. However, long membrane time constants limit the number of changes that may occur per second (eg, high amplitude, low frequency). Conversely, summation of spatially distributed asynchronous potentials results in EEG signals of low amplitude but relatively high frequency. Thus the inverse relationship between amplitude and frequency generally is maintained during unchanging cerebral metabolic states. Parallel increases in both may occur in some hypermetabolic states such as seizure activity, whereas decreases may be seen in hypometabolic states such as hypothermia. In the absence of these influences, simultaneous decreases in both amplitude and frequency may indicate ischemia or anoxia (Fig. 18.9); a parallel increase may represent artifact (Fig. 18.10).

Time-domain analysis of traditional electroencephalography uses linear signal amplitude (ie, voltage) and time scales. The amplitude range of EEG signals is quite large (several hundred microvolts), and univariate statistical measures of its central tendency and dispersion may contain clinically useful information.[17] Furthermore, amplitude variation may show clinically significant changes in reactivity that can be obscured by frequency-domain analysis. Advances in the technology

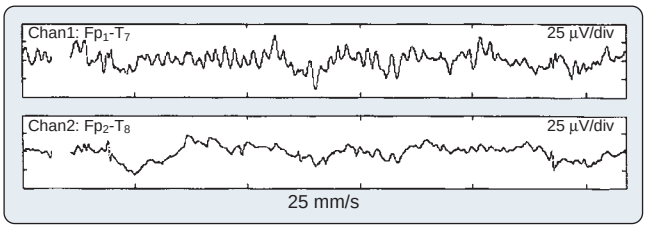


Fig. 18.9 The importance of electroencephalographic (EEG) baseline recording. This two-channel EEG recording was made immediately after induction of anesthesia, before head repositioning for insertion of a central venous catheter. Anesthetic induction apparently uncovered a preexisting asymmetry that was not evident in the waking electroencephalogram. Although the patient had a history of an earlier mild cerebrovascular accident and transient ischemic attacks, he appeared neurologically normal at preoperative assessment. *(Modified from Yli-Hankala A, ed.* Handbook of Four-Channel EEG in Anesthesia and Critical Care. *Helsinki, Finland: GE Medical Datex-Ohmeda Division; 2004:31, with permission of the publisher.)*

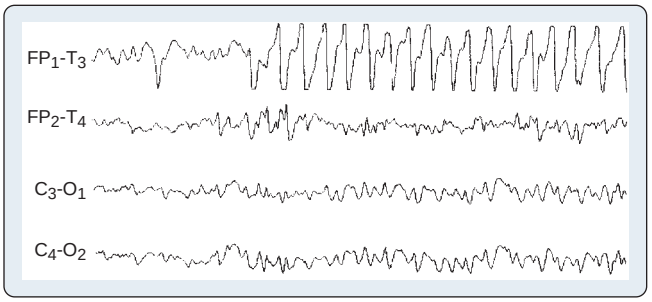


Fig. 18.10 Electroencephalographic (EEG) contamination by electrical artifact. The large-amplitude 2-Hz triangular waves in the left frontotemporal derivation *(top trace)* are the result of temporalis muscle activation with a nerve stimulator. Current spread from the stimulating to the EEG recording electrodes may be minimized with use of the appropriate facial nerve stimulation site at the jaw angle. *(Modified from Yli-Hankala A, ed.* Handbook of Four-Channel EEG in Anesthesia and Critical Care. *Helsinki, Finland: GE Medical Datex-Ohmeda Division; 2004:18, with permission of the publisher.)*

of EEG amplitude integration have prompted a resurgent interest in this attractively simple approach, particularly in pediatrics.[18]

Frequency-Domain Analysis

An alternative method, frequency-domain analysis, is exemplified by the prismatic decomposition of white light into its component frequencies (ie, color spectrum). As the basis of spectral analysis, the Fourier theorem states that a periodic function can be represented in part by a sinusoid at the fundamental frequency and an infinite series of integer multiples (ie, harmonics). The Fourier function at a specific frequency equals the amplitude and phase angle of the associated sinusoid. Graphs of amplitude and phase angle as functions of frequency are called Fourier spectra (ie, spectral analysis). The EEG amplitude spectral scale (Fig. 18.11) squares voltage values to eliminate troublesome negative values. Squaring changes the unit of amplitude measure from microvolts to either picowatts (pW) or nanowatts (nW). However, a power amplitude scale tends to overemphasize large-amplitude changes. Clinically important changes in low-amplitude components that are readily discernible in the linearly scaled unprocessed EEG waveform may become invisible in power spectral displays.

Simplification of the large amount of spectral information generally has been achieved through the use of univariate numeric descriptors. Most commonly, the power contained in a specified traditional EEG frequency band (delta, theta, alpha, or beta) is calculated in absolute, relative, or normalized terms. Relative amplitude represents the fraction of total power (TP; 0.1–55 Hz) contained in a specified frequency band (relative delta power = [delta power / TP] × 100). Normalization equalizes the TP of successive epochs to that of some arbitrary reference before the calculation of relative power (the delta power is described as z-score change from a previous individualized baseline). The latter two derived measures are particularly useful in minimizing misinterpretation of spectral changes. For example, during the production of hypothermia, absolute delta power declines in parallel with cerebral metabolism, although the fraction of the TP in the delta band remains unchanged. In this circumstance, exclusive focus on absolute delta power may lead to the erroneous conclusion that the hypnotic state is decreasing.

The most widely used univariate frequency descriptors (Box 18.3) are as follows:

1. TP
2. Peak power frequency (PPF), the single frequency of the spectrum that contains the highest amplitude
3. MDF, the sum of power contained at each frequency of the spectrum times its frequency divided by the TP
4. Spectral edge frequency (SEF), the frequency below which a predetermined fraction, usually 90% or 95%, of the spectral power occurs
5. Suppression ratio (SR), the percentage of flat-line electroencephalogram contained within sampled epochs

Trended changes in three of the foregoing descriptors (PPF, MDF, and SEF) occurring during total CPB are shown in Fig. 18.12.

Pronk[19] evaluated computer-processed univariate descriptors of EEG changes occurring before, during, and after CPB. MDF alone was sufficient to describe all EEG changes adequately except those changes occurring at very low amplitudes. Addition of a single-amplitude factor improved agreement with visual interpretation to 90%. Further factor addition did not improve agreement.

Multivariate (ie, composed of several variables) descriptors have been developed to improve simple numeric characterization of clinically important EEG changes. With this approach, algorithms are used to generate a single number that represents the pattern of amplitude-frequency-phase relationships occurring in a single epoch. Several commercially available monitors provide unitless numbers that have been transformed to arbitrary (ie, 0–100) scales. Each monitor provides a different probability estimate of a patient's response to verbal instruction. Current monitors designed for use by anesthesia providers are listed in Table 18.2. BIS (bispectral index, Covidien, Boulder, Colo), NT (NarcoTrend, Monitor Technik, Bad Bramstedt, Germany), PSI (Sedline, Masimo, Irvine, Calif), and SNAP II (Stryker Instruments, Kalamazoo, Mich) are rule-based proprietary indices empirically derived from patients' data. In contrast, CSI (Danmeter A/S, Odense, Denmark) uses a fuzzy logic-based algorithm, whereas SE applies standard entropy equations to EEG analysis. Each product is designed to require the use of proprietary self-adhesive forehead sensors. Collectively, these products are now in widespread use as objective measures of hypnotic effect.

Scalp-recorded cerebral biopotentials are complex physiologic signals. They represent the algebraic summation of voltage changes produced from cortical synaptic activity (ie, electroencephalogram), upper facial muscle activity (ie, facial electromyogram [fEMG]), and eye movement (ie, electro-oculogram [EOG]). During consciousness and light sedation, high-frequency gamma power (ie, 25–55 Hz) is a mixture of electroencephalography and subcortically influenced facial electromyography. Muscle activity makes a larger contribution because of the closer proximity of signal generators to the recording electrodes. Hypnotic and analgesic agents typically suppress both cerebral and muscle activities, with resulting reduced gamma power. Because the upper facial muscles are relatively insensitive to moderate neuromuscular blockade, they may remain reactive to noxious stimuli.[20] Nociception results in sudden gamma power increase, independent of activity in the lower-frequency classic EEG bands.

The EEG analyzers just described either provide separate quantitative estimates of the high-frequency information or incorporate this information into the hypnotic index. For example, the Datex-Ohmeda Entropy Module (GE Healthcare/Datex-Ohmeda, Helsinki,

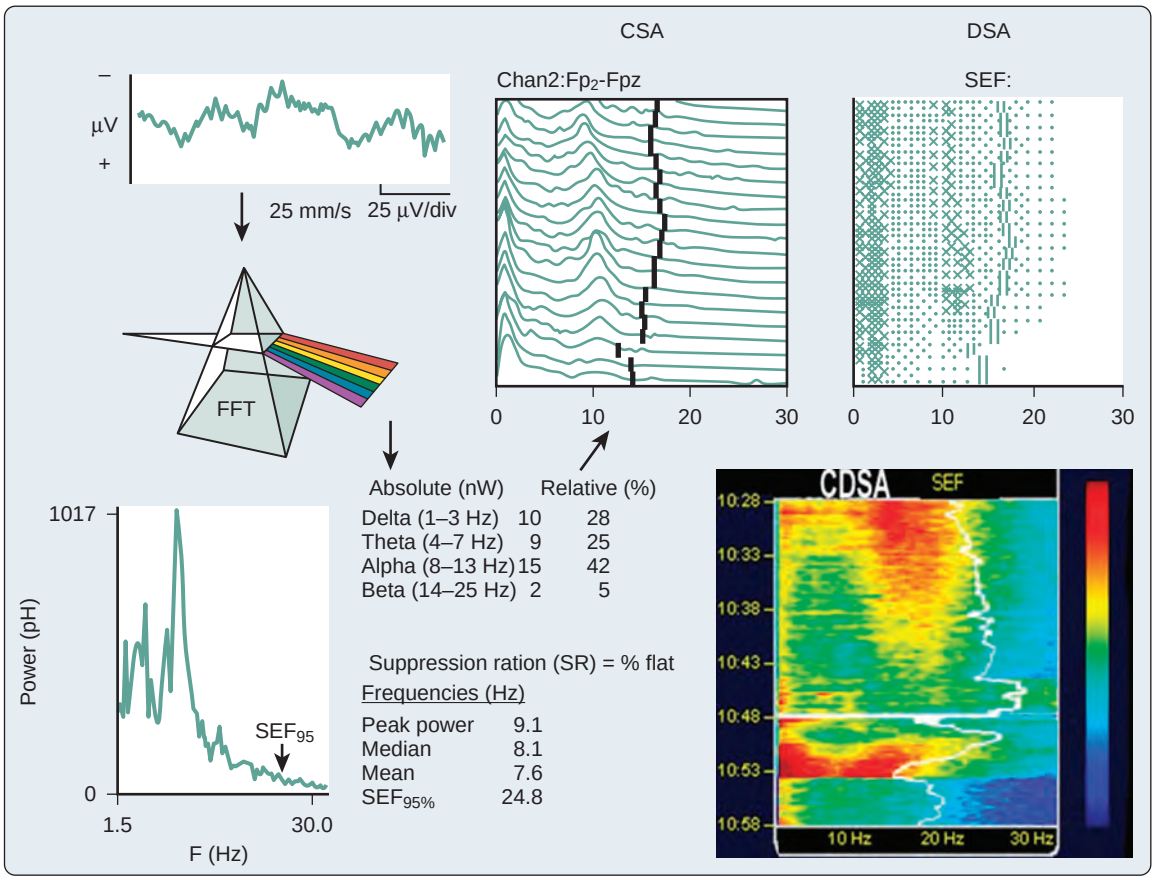
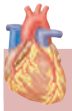


Fig. 18.11 Comparison of time- and frequency-domain electroencephalographic (EEG) displays. The traditional analog EEG signal shown in the *upper left* is a time-domain graph of scalp-recorded amplitude *(μV)* as a function of time. Digitized EEG segments (epochs) are computer processed using the fast Fourier transform *(FFT),* which, like a prism, decomposes a complex electromagnetic signal into a series of sinusoids, each with a discrete frequency. The instantaneous relationship is then graphically depicted by the power spectrum *(lower left),* a frequency-domain plot of power (μV^2 or *pW*) as a function of frequency. The spectral edge frequency *(SEF)* defines the signal amplitude upper boundary. The three-dimensional compressed spectral array *(CSA)* plots successive power spectra with time on the z-axis *(upper middle).* The density-modulated spectral array *(DSA; upper right*) improves data compression by using dot density to represent signal amplitude (ie, power). Amplitude resolution is improved through color coding in the color density spectral array *(CDSA)* shown at the *lower right.* The SEF is shown as the *white vertical line.* Note the EEG suppression at the bottom of each spectral trend.



BOX 18.3 COMMON UNIVARIATE ELECTROENCEPHALOGRAPHIC DESCRIPTORS DETECTING ISCHEMIA

- Total power (TP)
- Peak power frequency (PPF)
- Mean dominant frequency (MDF)
- 95% spectral edge frequency (SEF)
- Suppression ratio (SR)

TABLE 18.2 Commercial Multivariate Quantitative Electroencephalographic Descriptors of Hypnotic Effect

Acronym	*Index Name*	*Mode*	*Manufacturer*
BIS	Bispectral	Bilateral	Covidien, Boulder, Colo
CSI	Cerebral state	Unilateral	Danmeter A/S, Odense, Denmark
NT	Narcotrend	Bilateral	MonitorTechnik, Bad Bramstedt, Germany
PSI	Patient state	Bilateral	Masimo, Irvine, Calif
SE	State entropy	Unilateral	GE Healthcare/Datex-Ohmeda, Helsinki, Finland
SNAP II	SNAP II	Unilateral	Stryker Instruments, Kalamazoo, Mich

Finland) separately analyzes the 32- to 47-Hz band and terms the signal Response Entropy (RE). Addition of RE to the lower-frequency state entropy (SE) is claimed by the manufacturer to facilitate distinction between changes in hypnosis and analgesia, although supporting evidence for this proposition awaits carefully designed and adequately powered randomized, prospective studies. EEG suppression decreases both entropy indices because noise-free flat-line EEG segments are generally thought to have near-zero entropy. However, during cardiac surgical procedures, EEG signals that appear to be totally suppressed may be associated with paradoxically very high entropy values. To minimize this problem, SE uses a special algorithm that assigns zero entropy to totally suppressed EEG epochs.

In addition to the quantitative EEG numeric indices, many monitors also display pseudo-three-dimensional plots of successive power spectra as a function of time. This frequency-domain approach was

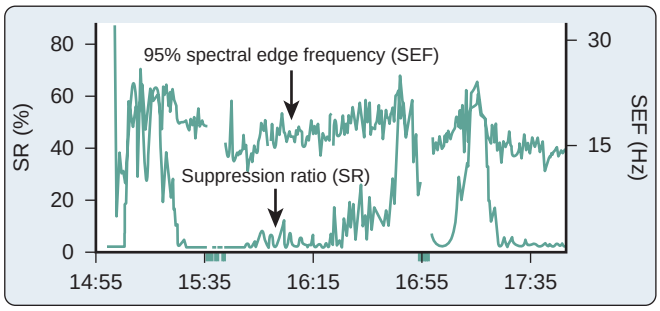


Fig. 18.12 Certain univariate electroencephalographic descriptors are particularly susceptible to the confounding influence of electronic interference. Note the peak in the suppression ratio *(SR)* trend at 17:00, correctly identifying marked EEG suppression. In contrast, the spectral edge frequency remains unchanged because of the presence of low-intensity electronic noise.

originated by Joy[21] and was popularized by Bickford, who coined the term "compressed spectral array" (CSA).[22] Its popularity stems in part from enormous data compression. For example, the essential information contained in a 4-hour traditional EEG recording consuming more than 1000 pages of unprocessed waveforms can be displayed in CSA format on a single page.

With CSA (see Figs. 18.11 and 18.12), successive power spectra of brief (2- to 60-second) EEG epochs are displayed as smoothed histograms of amplitude as a function of frequency. Spectral compression is achieved by partially overlaying successive spectra, with time represented on the z-axis. Hidden-line suppression improves clarity by avoiding overlap of successive traces. Although the display is esthetically attractive, it has limitations. The extent of data loss resulting from spectral overlapping depends on the nonstandard axial rotation that varies among EEG monitors. More important, epoch duration and the frequency with which each is measured (ie, update rate) may critically affect the presentation of clinically important change. For example, three distinctly different burst-suppression CSA patterns are recognized: high-amplitude bursts, flat line, or a combination of the two.[23]

Fleming and Smith[24] designed an alternative to the CSA display to reduce data loss. Density-modulated spectral array (DSA) uses a two-dimensional monochrome dot matrix plot of time as a function of frequency (see Fig. 18.11). The density of dots indicates the amplitude at a particular time-frequency intersection (eg, an intense large spot indicates high amplitude). Clinically significant shifts in frequency may be detected earlier and more easily than with CSA. However, the resolution of amplitude changes is reduced. Therefore color DSA (CDSA) was developed to enhance amplitude resolution (see Fig. 18.11). The CSA, DSA, and CDSA displays are not well suited for the detection of nonstationary or transient phenomena such as burst suppression or epileptiform activity.

In summary, a quick assessment of EEG change in either the time or frequency domain focuses on (1) maximal peak-to-peak amplitude, (2) relation of maximal amplitude to dominant frequency, (3) amplitude and frequency variability, and (4) new or growing asymmetry between homotopic (ie, same position on each cerebral hemisphere) EEG derivations. These objectives are generally best achieved through the viewing of both unprocessed and processed displays with a clear understanding of the characteristics and limitations of each (Box 18.4).

Auditory-Evoked Potentials

Auditory-evoked potentials (AEPs) assess specific areas of the brainstem, midbrain, and auditory cortices. Because of their simplicity and reproducibility, AEPs are suitable for monitoring patients during cardiovascular surgical procedures. Specific applications of AEP monitoring in this environment are the assessment of temperature effects

BOX 18.4 MEASURES THAT DEFINE ELECTROENCEPHALOGRAPHIC CHANGES

- Maximum peak-to-peak amplitude (or total power)
- Relation of maximum amplitude to dominant frequency
- Amplitude and frequency variability
- Right-to-left symmetry

on brainstem function and the evaluation of hypnotic effect. Direct involvement of cardiac anesthesia providers with AEP monitoring is likely to increase following the introduction of EEG/AEP modules designed for use with available operating room physiologic monitors.

Acoustic stimuli trigger a neural response integrated by a synchronized neuronal depolarization that travels from the auditory nerve to the cerebral cortex. Scalp-recorded signals, obtained from electrodes located at the vertex and ear lobe, contain both the AEPs and other unrelated EEG and electromyographic activity. Extraction of the relatively low-amplitude AEP from the larger-amplitude background activity requires signal-averaging techniques.[25] Because the AEP character remains constant for each stimulus repetition, averaging of many repetitions increases the signal amplitude linearly, whereas the inconstant background voltages are increased by the square root of the number of signals averaged. Thus increases in the signal-to-noise ratio of 10-fold to 30-fold are commonly achieved. For the AEP sensory stimulus, acoustic clicks are the most commonly used. These broadband signals are generated by unidirectional rectangular short pulses (40–500 microseconds) with frequency spectra lower than 10 KHz.

The AEPs comprise a series of biopotentials generated at all levels of the auditory system in response to an acoustic stimulus (Fig. 18.13). Using scalp electrodes, a dozen peaks have been identified within the first 100 milliseconds after stimulus onset. Each peak is described by its poststimulus latency and peak-to-peak amplitude. AEPs are commonly classified as early or middle-latency potentials. Fig. 18.14 is a schematic representation of the AEPs most commonly used for surgical monitoring. Early AEPs are generated from the auditory nerve and the brainstem and include a series of wavelets recorded within the first 10 milliseconds after stimulus. These evoked responses have been designated brainstem AEPs (BAEPs). Seven waves (I–VII) characterize the adult BAEPs. Peaks I and II are generally thought to originate from the distal and proximal parts of the eighth nerve, and peak III arises from the cochlear nucleus. Peak IV sources include the superior olivary complex, cochlear nucleus, and nucleus of the lateral lemniscus. Peak V contributors seem to include both the lateral lemniscus and the inferior colliculus. Peak VI and VII origins are not well defined, but these peaks may arise from the medial geniculate body and the acoustic radiations. BAEPs are useful in assessing brainstem and subcortical function during surgical procedures, in part because of their relative resistance to the suppressant effects of most anesthetic agents.[26]

The middle-latency AEPs (MLAEPs), with poststimulus latencies between 10 and 100 milliseconds, are generated in the midbrain and primary auditory cortex. In an awake adult subject, the MLAEPs usually consist of three main peaks: Na, Pa, and Nb, with respective latencies near 15, 28, and 40 milliseconds (see Fig. 18.14). Children under general anesthesia commonly display the trimodal configuration of the adult MLAEP waveform (Na, Pa, Nb waves), although neonates may exhibit only a small Pa wave.[27] Many agents with hypnotic effects prolong the latency and suppress the amplitude of Pa and Nb in a concentration-dependent manner.[26] It appears that the latency and amplitude changes allow reliable detection of consciousness and nociception during cardiac surgical procedures.[28] In addition, parallel monitoring of MLAEP and quantitative EEG descriptors (ie, BIS) may permit distinction between the hypnotic and antinociceptive anesthetic components.[28] This approach has also been used successfully

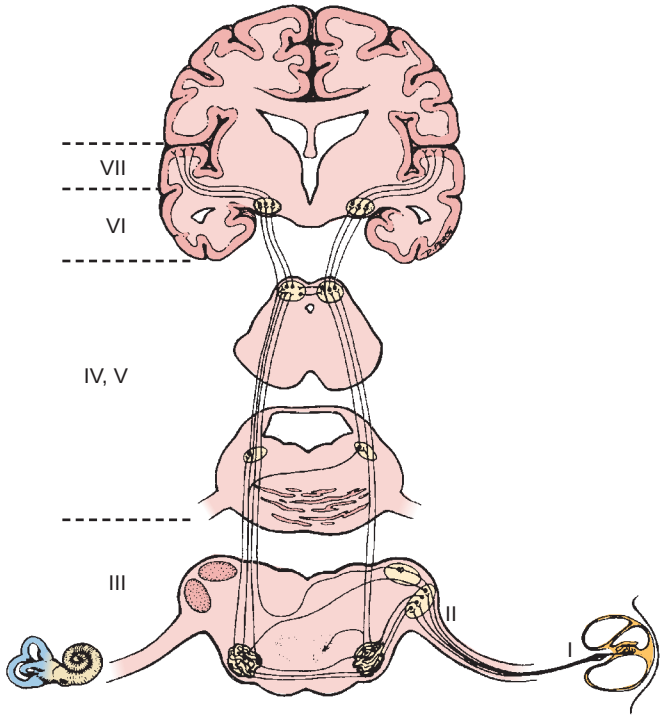


Fig. 18.13 Putative sites at which the brainstem auditory-evoked potential is generated include the cochlear nerve, cochlear nucleus, trapezoid complex, lateral lemniscus, inferior colliculus, medial geniculate nucleus, and auditory radiations. Wave I is generated in the distal cochlear nerve near the spiral ganglion, and wave II is generated in the proximal cochlear nerve near the brainstem. All other waveforms are generated in multiple brainstem sites and do not bear a one-to-one relation to any particular structures, although the later waveforms do tend to be generated in more rostral sites. *(Modified from Friedman WA, et al:* Advances in anesthesia. *Chicago: Yearbook Medical Publishers, 1989, p 244.)*

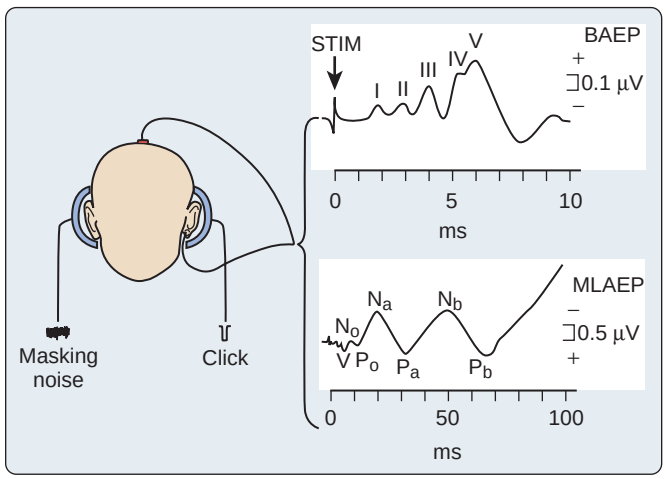


Fig. 18.14 Brainstem auditory-evoked potential *(BAEP)* and middle-latency auditory-evoked potential (MLAEP) waveforms. Stimulation *(STIM)* of one ear and recording between the ipsilateral earlobe and vertex produce sequences of peaks that can be displayed at two different recording speeds and gain settings. Recording with a short 10-millisecond time base at a high gain reveals the first five peaks that comprise the BAEP. With a longer 100-millisecond time base and lower gain, the MLAEP peaks become evident. By a rather confusing convention, BAEP peaks represent positive deflections, whereas MLAEP peaks indicate negative deflections. *(Modified from Spehlmann R.* Evoked Potential Primer. *Boston: Butterworth; 1985:196, with permission of the publisher.)*

in pediatric cardiac surgical patients to assess postoperative sedation objectively.[29]

To facilitate continuous perioperative monitoring, amplitude and latency from each of the primary MLAEP components have been integrated into a proprietary autoregressive linear function (A-Line Danmeter A/S, Odense, Denmark).[30] Subsequently, this metric was expanded to the A-Line Autoregressive Index, AAI, which included the quantitative EEG descriptors: (1) percentage of burst suppression and (2) beta ratio (ie, percentage of total EEG power contained in the high-frequency beta-frequency band).[31]

Somatosensory-Evoked Potentials

In many ways, the somatosensory-evoked potential (SSEP) is similar to the AEP. An electrical stimulus is applied peripherally to the arms or legs, or both, and the progression of the neuronal transmission through the spinal cord and subcortical structures is tracked, with various neurogenerators producing specific positive or negative deflection of the recorded signal at various times. In this way, SSEPs provide an objective measure of ascending sensory pathway function. Like AEPs, they are recorded by signal averaging over a large number of stimuli, with the duration of recording after each stimulus being somewhat longer and thus the frequency of stimulation somewhat lower. SSEPs are moderately sensitive to depression from inhaled anesthetic agents, but they do not generally preclude the use of potent agents in a balanced technique or as supplement to a high-dose narcotic approach. Fig. 18.15A illustrates the key neural structures involved in a prominent upper limb sensory pathway suitable for cardiac surgical neuromonitoring.

Motor-Evoked Potentials

By relying on the delivery of a rapid stimulus pulse train, it is now possible to monitor the integrity of descending motor pathways continuously by using transcranial electric motor-evoked potentials (MEPs).[32] The most frequent application of this emerging monitoring modality for cardiothoracic surgical procedures currently is during open surgical or endovascular repair of the descending aorta.[33] The need for improved spinal cord protection remains critical because, even with modern spinal cord preservation techniques, the infarction rate during type I and II aneurysm repairs in patients remains disturbingly high.[33]

The neurophysiologic basis for the MEP is illustrated in Fig. 18.16. Individual high-intensity transcranial stimuli depolarize cortical motor neurons directly in the axon hillock region or indirectly by activation of interneurons. Synaptic transmission of individual impulses to segmental α-motor neurons lowers the postsynaptic membrane potential, but it is often insufficient to initiate cell firing. Instead, this goal is achieved through use of a pulse train that triggers lower motor neuron discharge by temporal summation of individual subthreshold responses.

Precise placement of subdermal stimulating electrodes (Fig. 18.17A) is important because of the influence on motor pathway activation. The transcranial electric current generated from closely spaced electrodes depolarizes a discrete cortical region that may control only a restricted muscle group. In contrast, current produced using wide electrode separation bypasses the anesthetic-susceptible cortical neurons. This results in direct depolarization of descending motor tracts that affects both upper and lower limb muscles (Fig. 18.17B). Even though lower limb MEPs are necessary to document the functional integrity of motor pathways in the thoracolumbar spinal cord, upper limb recording is also important. The upper limb responses identify generalized MEP suppression. Its causes include anesthetic-induced synaptic inhibition, hypocapnia, and hypothermia, as well as position-related ischemia involving cerebral or upper limb motor pathways, or both (Fig. 18.18). The effects of anesthetic agents on evoked potentials are summarized in Table 18.3. In addition to these generalized effects, volatile anesthetic agents suppress both cortical and spinal cord motor

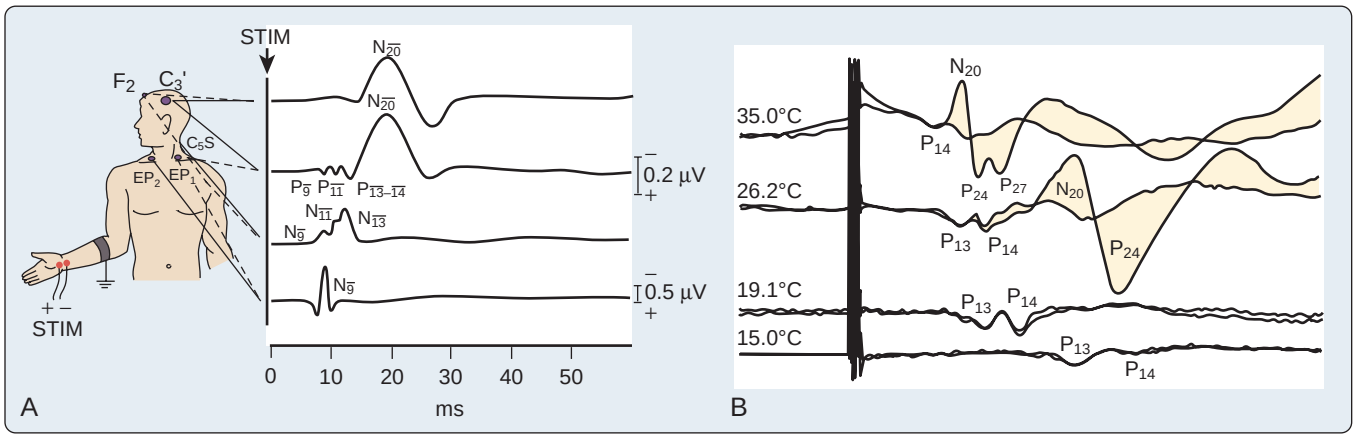


Fig. 18.15 Upper limb somatosensory-evoked potential (SSEP) waveforms. (A) The waveforms show ascending responses to median nerve electrical stimulation. With the aid of noncephalic reference electrodes, the N_9 clavicular (Erb point) potential reflects signal passage through the brachial plexus, whereas the N_{13} potential represents activation of the cervical and brainstem lemniscal structures. Signals passing through the cortical radiations and sensory cortex result in the N_{20} potential when recorded between a scalp active electrode and cephalic reference. (B) Each pair of upper limb SSEP waveforms is created by the superimposition of parietal recordings ipsilateral and contralateral to single limb median nerve stimulation. The *shaded area* represents signal generated within the cortical mantle. Cooling to 26.2°C increases the latency of both subcortical and cortical waveform components and results in the emergence of a second (ie, P_{13}) brainstem potential. Although that deep hypothermia at 19.1°C suppressed cortical activity, brainstem P_{13} and P_{14} responsiveness persists. *(A, From Misulis KE, Fakhoury T. Spehlmann's Evoked Potential Primer. 3rd ed. Boston: Butterworth-Heinemann; 2001:98, with permission of the publisher. B, Modified from Guérit JM. Intraoperative monitoring during cardiac surgery. In: Nuwer MR, ed.* Handbook of Clinical Neurophysiology. *Vol. 8.* Intraoperative Monitoring of Neural Function. *New York: Elsevier; 2008:834.)*

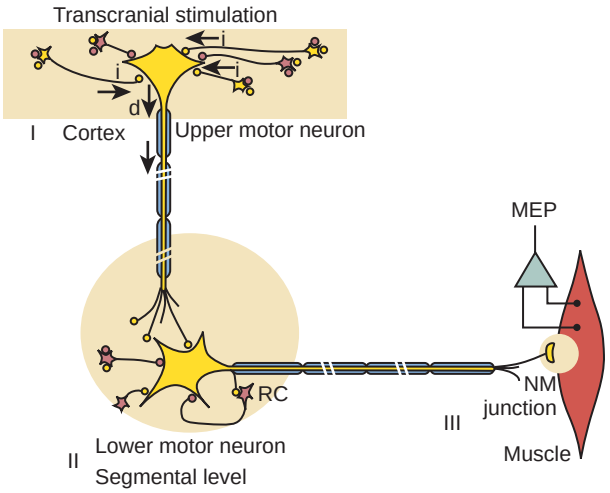


Fig. 18.16 Neural generators of transcranial motor-evoked potentials *(MEP)*. High-intensity transcranial electric or magnetic stimulation results in direct *(d)* activation of upper motor neurons. In addition, indirect motor neuron activation *(i)* results from transcranial activation of horizontally oriented excitatory (light) and inhibitory (dark) neuronal axons. Descending motor potentials are conducted unidirectionally through the corticospinal, rubrospinal, tectospinal, vestibulospinal, and cerebellospinal tracts to lower (alpha) motor neurons in the lateral and anterior spinal cord. In the absence of complete pharmacologic neuromuscular *(NM)* blockade, alpha motor neuron action potentials then produce muscle fiber contraction that is recorded by electromyography. *(Modified from Journee JL. Motor EP physiology, risks and specific anesthetic effects. In: Nuwer MR, ed.* Handbook of Clinical Neurophysiology. *Vol. 8.* Intraoperative Monitoring of Neural Function. *New York: Elsevier; 2008:219.)*

neurons. Thus the use of these drugs should be avoided or minimized during attempted MEP monitoring.[34]

In contrast to AEPs and SSEPs, the large amplitude of MEP electromyographic responses obviates the need for signal averaging. However, the inherent variability of these individual responses (see Fig. 18.18) means that precise measurement of peak amplitude and latency is more difficult to achieve than with the more stable averaged sensory-evoked potentials. Nevertheless, Kawanishi and colleagues[35] found 100% sensitivity and 98% specificity for MEP detection of motor pathway dysfunction. Their criterion for noteworthy change was a persistent 25% peak-to-peak amplitude decline. Correct interpretation of MEP amplitude change requires precise monitoring and control of neuromuscular blockade.[36] Information on the extent of neuromuscular blockade obtained from evoked electromyographic train-of-four responses in both upper and lower limb muscles bilaterally helps guide relaxant administration and detects limb ischemia.

Transcranial Doppler Ultrasound

Ultrasound Technology

Ultrasonic probes of a clinical TCD sonograph contain an electrically activated piezoelectric crystal that transmits low-power 1- to 2-MHz acoustic vibrations (ie, insonation) through the thinnest portion of temporal bone (ie, acoustic window) into brain tissue. Consequently, variations in cranial anatomy influenced by age, sex, and race may preclude TCD monitoring in a substantial fraction of certain demographic groups (eg, older African American women).[37] Overall, bilateral functional cranial windows may be anticipated in approximately three-quarters of older patients.[37] Blood constituents (predominantly erythrocytes) contained in large arteries and veins reflect these ultrasonic waves back to the probe, which also serves as a receiver. Because of laminar blood flow, erythrocytes traveling in the central region of a large blood vessel move with higher velocity than those near the vessel wall (Fig. 18.19). Thus, within each vascular segment (ie,

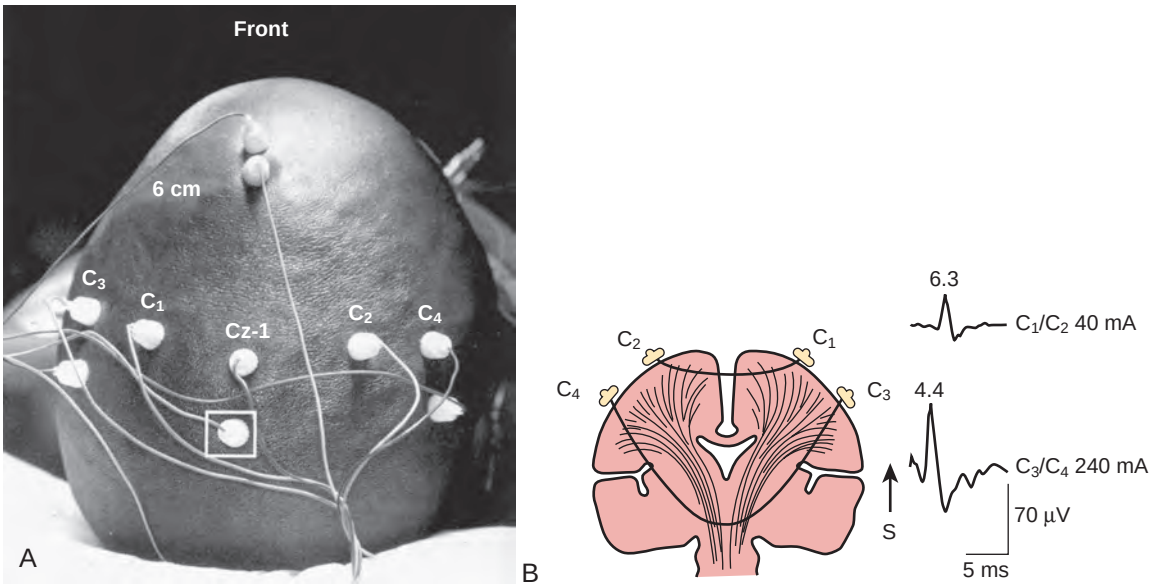


Fig. 18.17 Motor-evoked potential (MEP) transcranial stimulation. (A) Placement of transdermal electrodes for generation of MEP by transcranial electrical stimulation. (B) Transcranial electric current paths following cortical (C_1/C_2) and subcortical (C_3/C_4) stimulation. The direct MEP responses were obtained from an electrode placed adjacent to exposed upper thoracic spinal cord. Note the large 240-mA current required for subcortical stimulation and the shorter latency between the stimulus *(S)* and C_3/C_4 response because of the reduced distance between stimulating and recording electrodes. *(A and B, Modified from Deletis V, Sala F. Corticospinal tract monitoring with D- and I-waves from the spinal cord and muscle MEPs from limb muscles. In: Nuwer MR, ed.* Handbook of Clinical Neurophysiology. *Vol. 8.* Intraoperative Monitoring of Neural Function. *New York: Elsevier; 2008:236–237.)*

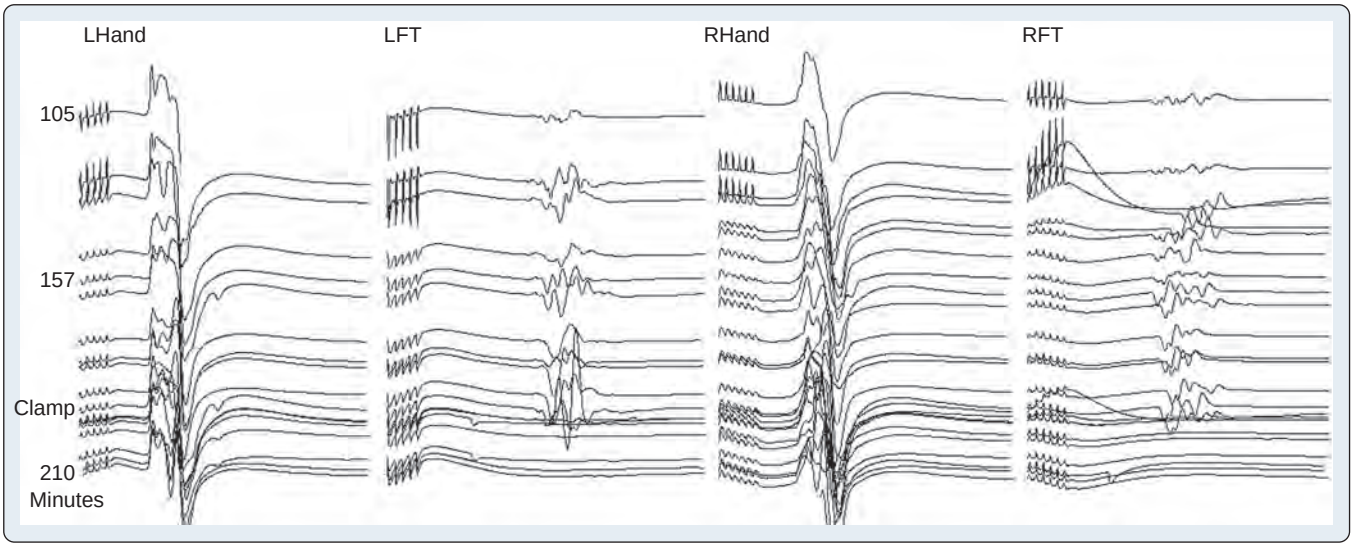


Fig. 18.18 Motor-evoked potential (MEP) detection of spinal cord hypoperfusion. Changes are shown in hand (*LHand* and *RHand*) and foot (*LFT* and *RFT*) MEP responses to clamping of the descending aorta during surgical repair of a thoracoabdominal aneurysm. Note the bilateral loss of lower limb MEP with clamp application. MEP monitoring helped guide management of left-sided heart bypass and reimplantation of the superior mesenteric and renal arteries into the aortic graft.

sample volume), a series of echoes associated with varying velocities is created. The frequency differences between the insonation signal and each echo in the series are proportional to the associated velocity, and this velocity is determined from the Doppler equation (see Fig. 18.19). Although several large intracranial arteries may be insonated through the temporal window, the middle cerebral artery is generally monitored during cardiac operations because it carries approximately 40% of the hemispheric blood flow.

Pulsed-Wave Spectral Display

Pulsed-wave Doppler examination samples the ultrasonic echoes at a user-selected distance (ie, single gate) below the scalp. The frequency composition of these Doppler-shifted echoes is analyzed by Fourier analysis, the same technique used to quantify EEG frequency patterns (see Fig. 18.19). The analysis produces a momentary amplitude spectrum displayed as a function of blood flow velocity (eg, Doppler-shift frequency). This relationship is mapped as one vertical strip in the

TABLE 18.3 Anesthetic Effects on Sensory- and Motor-Evoked Responses

Pharmacologic Class	*Agent*	*SSEP*	*AEP*	*MEP*
Nonspecific inhibitor	Isoflurane	Suppression	Suppression	Suppression
	Sevoflurane	Suppression	Suppression	Suppression
	Desflurane	Suppression	Suppression	Suppression
	Barbiturates	Suppression	Suppression	Suppression
GABA-specific agonist	Propofol	Suppression[b]	Suppression	Suppression[b]
α_2 Agonist	Clonidine	Suppression[b]	?	Suppression[b]
	Dexmedetomidine	Suppression[b]	?	Suppression[b]
NMDA antagonist	Nitrous oxide	Suppression	—	Suppression
	Ketamine	Increase	—	Suppression[b]
	Xenon	Suppression[b]	Suppression[b]	Suppression[b]

[a]1 MAC-equivalent dose.
[b]Slight to minimal effect.
AEP, Auditory-evoked potential; *GABA,* γ-aminobutyric acid; *MAC,* minimum alveolar concentration; *MEP,* motor-evoked potential; *NMDA, N*-methyl-D-aspartate; *SSEP,* somatosensory-evoked potential.
Modified from Sloan TB, Jäntti V. Anesthetic effects on evoked potentials. In: Nuwer MR, ed. *Handbook of Clinical Neurophysiology.* Vol. 8. *Intraoperative Monitoring of Neural Function.* New York: Elsevier; 2008:94–126.

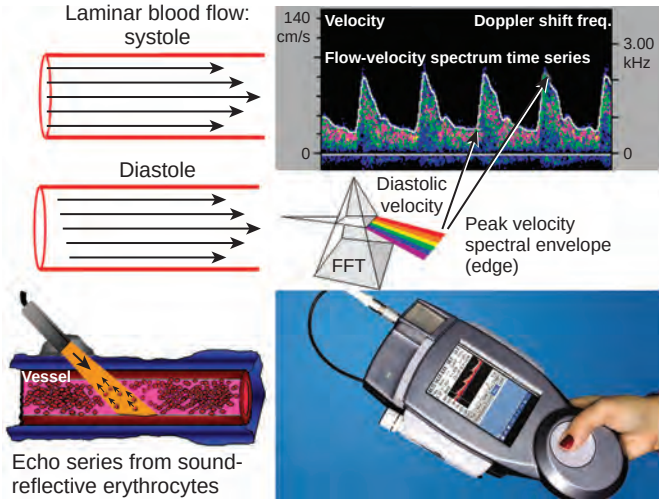


Fig. 18.19 Physiologic basis of the transcranial Doppler (TCD) ultrasound display. Large-vessel laminar flow results in a cross-sectional series of erythrocyte velocities, with the lowest values nearest the vessel wall. Ultrasonic vessel insonation produces a series of erythrocyte echoes. The frequency differences (ie, Doppler-shift frequencies) between the insonating signal and its echoes are proportional to erythrocyte velocity and flow direction. Fast Fourier transform *(FFT)* analysis of this complex echo produces an instantaneous power spectrum analogous to that used in electroencephalographic analysis. The time-series of successive Doppler-shift spectra (*upper right)* resembles an arterial pressure waveform but represents fluctuating erythrocyte velocities during each cardiac cycle. Some modern TCD sonographs are small enough to be handheld or incorporated into multimodal neurophysiologic signal analyzers. *(Image of the 500P Pocket Transcranial Doppler courtesy Multigon Industries, Inc, Yonkers, NY.)*

spectrogram display (see Fig. 18.19, upper right). Amplitude at each frequency is expressed as log change (ie, dB) from the background composed of random echoes. The momentary analysis is repeated 100 times per second to produce a scrolling spectrogram of time-related changes in flow velocity.

Signal amplitude at each frequency shift–time intersection is indicated by monochromatic dot density or color coding. The maximum velocity, the upper edge (envelope) of the velocity spectrum (analogous to the EEG SEF), represents the maximum Doppler shift (erythrocyte velocity) in the vessel center. Peak-systolic and end-diastolic velocities are derived from this spectral edge. Intensity-weighted mean velocity is calculated by weighted averaging of the intensity of all Doppler spectral signals in a vessel cross-section. Sampling echoes at multiple loci (multigating) produces spectrograms for each of the different probe-to-sample site distances (Fig. 18.20).

Power M-Mode Doppler Display

An alternative method for processing pulsed-wave Doppler echoes is nonspectral power M-mode Doppler (PMD) (Fig. 18.21). Unlike the series of spectra generated with multigating, PMD creates one image with each depth represented by a plot of signal amplitude (ie, power) and depth as functions of time. A color scale signifies flow direction (red is flow directed toward the probe; blue is flow away from the probe), whereas color intensity is directly related to signal power.

Embolus Detection

Erythrocytes (approximately 5 million/mL) are the most acoustically reflective nonpathologic blood elements (ie, have the greatest acoustic impedance). However, gaseous and particulate emboli are better reflectors of sound than are erythrocytes. The presence of high-intensity transient signals (HITS) within either the PMD or spectral TCD display may signify the presence of an embolus.[38] Because a gaseous or particulate embolus cannot simultaneously appear at all distances from the probe, either PMD or a multigated spectral display may be used to distinguish them from acoustic artifact (tapping on the ultrasonic probe produces a high-intensity transient acoustic artifact at all distances).

Fig. 18.22 illustrates the appearance of HITS in the two TCD display formats. The bottom spectral displays are generated from a small vascular segment at a distance of 50 ± 3 mm (6-mm sample volume) from the probe surface. The midpoint of the spectral sample is indicated on the top PMD displays as a light horizontal line at a 50-mm depth. An embolic track labeled "*a*" is a single embolus that is shown in the top PMD display moving toward the probe (ie, decreasing distance from the probe face over time). Embolic tracks "*b*" and "*d*" display the characteristic "lambda" acoustic signature in the spectral display. The PMD shows that this pattern reflects embolus direction reversal within the spectral sample volume. The true behavior of the spectrally paradoxical track "*c*" (start and end points of the single acoustic signature are not connected) becomes clear in the PMD view. Track "*c*" direction reversal is invisible on the spectral display because it occurs outside the sampling region. Currently available spectral or PMD TCD monitors can determine neither the size nor the composition of embolic form material responsible for HITS. TCD devices designed for surgical monitoring typically provide a semiquantitative estimate of aggregate HITS, irrespective of their origin (Box 18.5). Nevertheless, the HITS aggregate has been shown to be predictive of neurodeficit following aortic surgical procedures.[39]

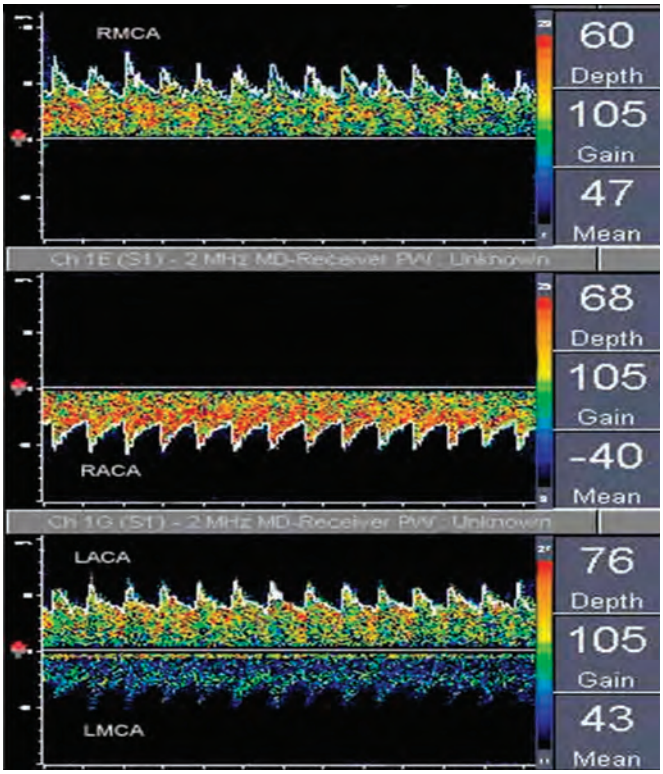


Fig. 18.20 Multigated transcranial Doppler ultrasound display. Multigating of pulsed-wave Doppler signals permits simultaneous display of echo spectra generated at several different intracranial loci. *LACA,* Left anterior cerebral artery; *LMCA,* left middle cerebral artery; *RACA,* right anterior cerebral artery; *RMCA,* right middle cerebral artery.

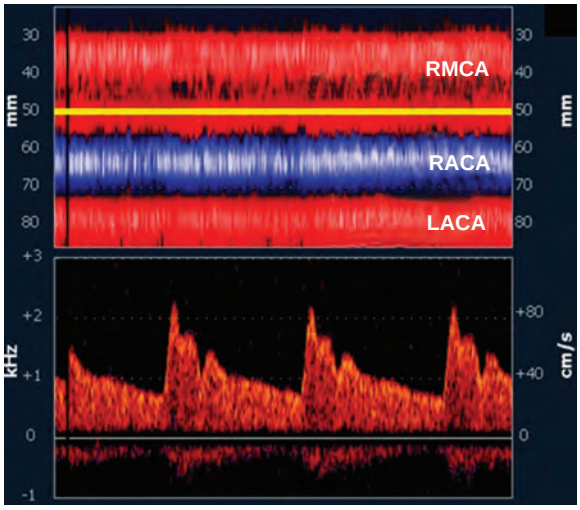
Intervention Threshold

Because erythrocyte velocity and flow may be differentially influenced by vessel diameter,[40] blood viscosity,[41] and pH,[41] as well as temperature,[41] TCD does not provide a reliable measure of cerebral blood flow. However, in the absence of hemodilution, *change* in TCD velocity does correlate closely with *change* in blood flow.[41] Sudden large changes in velocity or direction are readily detected by continuous TCD monitoring. The clinical significance of velocity changes has been assessed in conscious patients during implantable cardioverter-defibrillator and tilt-table testing.[42] In both circumstances, clinical evidence of cerebral hypoperfusion was accompanied by a mean velocity decline of greater than 60% and absent diastolic velocity. During vascular operations, the ischemia threshold appears to be an 80% decrease below the preincision baseline.[43]

In general, reduction of flow velocity indicating severe ischemia is associated with profound depression of EEG activity.[42] However, with adequate leptomeningeal collateral flow, cerebral function may remain unchanged in the presence of a severely decreased or absent middle cerebral artery flow velocity.[43] Together, these findings form the rationale for a TCD-based intervention threshold. During cardiac surgical procedures, mean velocity reductions of greater than 80% or velocity losses during diastole suggest clinically significant cerebral hypoperfusion.

BOX 18.5 TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

- Detects change in intracranial blood flow
- Detects particulate or gaseous emboli



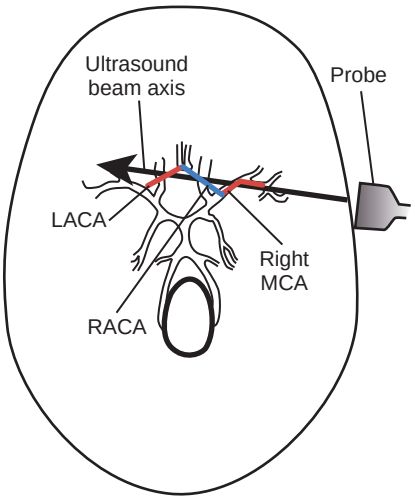


Fig. 18.21 Comparison of the transcranial Doppler (TCD) M-mode and spectral displays. The TCD continuous wave M-mode *(upper left)* and pulsed-wave spectral *(lower left)* displays are compared. The horizontal bands of the M-mode display represent a series of Doppler-shift echoes. Signals in the 30- to 50-mm depth range *(upper red band)* represent flow in the right middle cerebral artery *(right MCA)* ipsilateral to the ultrasonic probe. The *red color* signifies flow directed toward the probe *(right diagram).* Echoes arising between 55 and 70 mm from the probe emanate from the ipsilateral (right) anterior cerebral artery (RACA) are shown in the *middle blue band* of the M-mode display. Signals in the 72- to 85-mm range arise from the contralateral (left) ACA (LACA) with flow directed toward the probe *(lower red band).* The M-mode *yellow line* at a depth of 50 mm indicates the measurement site for the TCD frequency spectral display shown at the *lower left. (Courtesy Dr. Mark Moehring, Spencer Technologies, Seattle, Wash.)*

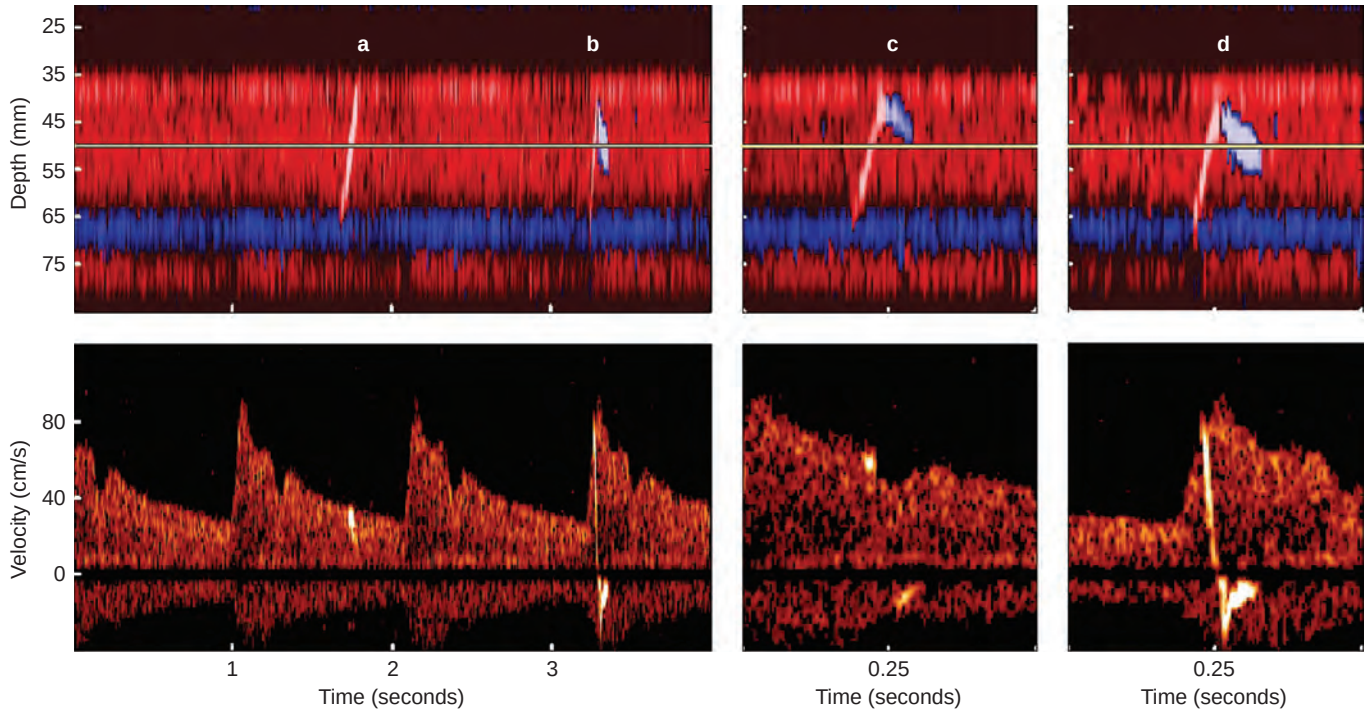


Fig. 18.22 Embolic signals detected by the transcranial Doppler M-mode and spectral displays. The appearance of emboliform high-intensity transient signals (HITS) is compared using the M-mode and frequency spectral displays. The *white horizontal line* at a depth of 50 mm depicts the site of the spectral measurement along the axis of the vessel. HITS *(white transient)* represents linear migration of an embolus in the M2 segment of the ipsilateral middle cerebral artery. HITS *(white dot)* is noted on the spectral display as the embolus passes through the 50-mm measurement site. In contrast, emboli in the remaining panels suddenly change direction as they pass into a smaller branch vessel. HITS *b* and HITS *d* direction changes are noted on the spectral displays as the characteristic "lambda" sign. However, the HITS *c* behavior is misidentified as two emboli because the direction change occurs outside the spectral sample volume. *(Courtesy Dr. Mark Moehring, Spencer Technologies, Seattle, Wash.)*

Jugular Bulb Oximetry

Oximeter catheters transmitting three wavelengths of light may be inserted into the cerebral venous circulation to measure cerebral (jugular) venous oxygen saturation ($SjvO_2$) directly and continuously. Commercially available devices are modifications of the catheter oximeter originally developed for the pulmonary circulation. External pre-insertion calibration of the catheter and documentation of catheter position in the jugular bulb are required for accurate measurements. In vivo calibrations against co-oximeter samples can also be performed. Reflected light signals are averaged, filtered, and displayed. Conditions affecting the accuracy of these measurements include catheter kinking, blood flow around the catheter, changes in hematocrit, fibrin deposition on the catheter, and changes in temperature. The normal $SjvO_2$ range is widely assumed to be between 55% and 70%.[44] However, a study using radiographically confirmed catheter placement observed a much wider 45% to 70% range in healthy subjects.[45]

This technology has two major limitations. First, $SjvO_2$ represents a global measure of venous drainage from unspecified cranial compartments. Because cerebral and extracranial venous anatomy is notoriously varied, clinical interpretation of measured change is a major challenge. The difficulty is exemplified by the study of Guo and Wong.[46] These investigators used a new magnetic resonance imaging technique called velocity-selective excitation and arterial nulling to image cerebral venous oxygen saturation quantitatively. The average saturation value obtained from the large veins (ie, $SjvO_2$) differed substantially from the checkerboard pattern of regional hemoglobin oxygen saturation (rSO_2) values representing the microcirculation. Second, accurate measurement using jugular oximetry requires continuous adequate flow past the catheter. Low-flow or no-flow states such as profound hypoperfusion or complete ischemia render $SjvO_2$ unreliable.[47] Despite these limitations, the global measure of brain oxygen balance has been used successfully (1) as a transfusion trigger,[48] (2) to document the deleterious effect of even modest cerebral hyperthermia,[49] and (3) to compare the frequency of cerebral oxygen desaturation during myocardial revascularization with and without CPB.[50]

Cerebral Oximetry

Near-Infrared Technology

Because the human skull is translucent to infrared light, intracranial intravascular rSO_2 may be measured noninvasively with transcranial near-infrared spectroscopy (NIRS) (Fig. 18.23). An infrared light source contained in a self-adhesive patch affixed to glabrous skin of the scalp transmits photons through underlying tissues to the outer layers of the cerebral cortex. Adjacent sensors separate photons reflected from the skin, muscle, skull, and dura from those of the brain tissue (Fig. 18.24). NIRS measures all hemoglobin, pulsatile and nonpulsatile, in a mixed microvascular bed composed of gas-exchanging vessels with a diameter of less than 1 mm.[51] The measurement is thought to reflect approximately 70% venous blood.[51] Cerebral oximetry appears both to quantify change reliably from an individualized baseline and to offer an objective measure of regional hypoperfusion.[52] Unlike pulse and jugular bulb oximetry, cerebral oximetry may be used during nonpulsatile CPB and circulatory arrest.

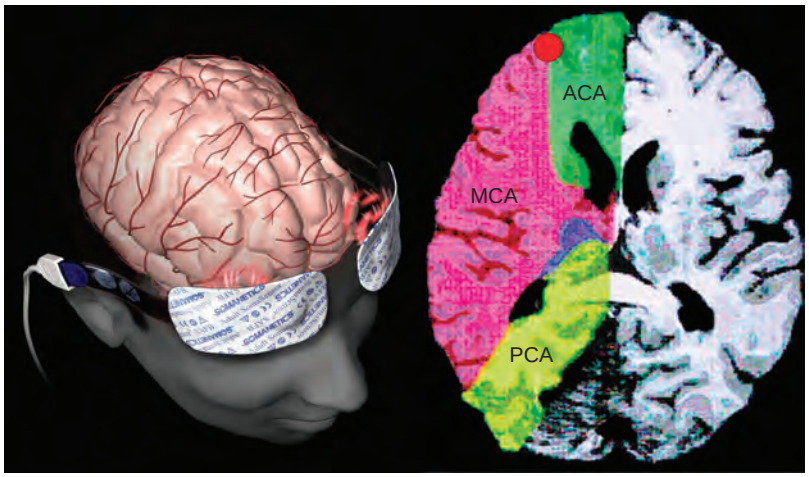


Fig. 18.23 Cerebral oximetry monitors the anterior arterial watershed region. The frontal cortex anterior cerebral artery (ACA) and middle cerebral artery (MCA) watershed region may be sampled bilaterally by cerebral oximeter sensors located on the forehead above each eye. The diagram at the *right* illustrates the anterior *(green)* and middle cerebral artery *(pink)* flow-distributions and the approximate size and location of the oximetric sampling region *(red dot). PCA,* Posterior cerebral artery. *(Courtesy Covidien, Boulder, Colo.)*

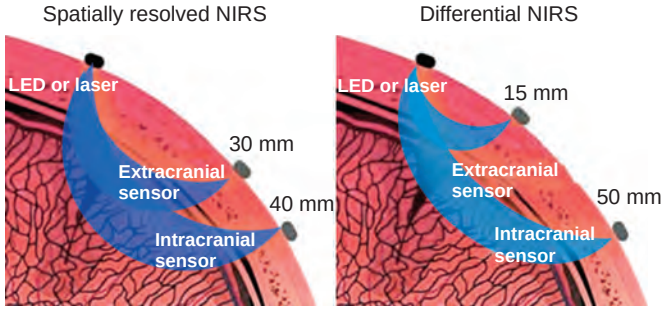


Fig. 18.24 Comparison of transcranial spatially resolved near-infrared spectroscopy *(spatially resolved NIRS)* and differential NIRS. Unabsorbed photons travel a parabolic (ie, banana-shaped) path through the adult cranium from scalp-mounted infrared sources to nearby sensors. The average penetration depth of these reflected photons is given by the square root of the source-detector separation. Spatially resolved NIRS uses a pair of sensors located at sufficient distances from the light source to ensure that both signals detect photons reflected from extracranial and intracranial tissue (*left panel*). Two-point extracranial and intracranial measurement permits partial suppression of both the extracranial signal and the interpatient variance in intracranial photon scatter. The resultant cerebral oxygen saturation measurement appears to be approximately 65% intracranial.[50a] In contrast, differential NIRS uses a sensor placed very near the light source to record exclusively extracranial signal and another more distant sensor for extracranial and intracranial measurement *(right panel)*. Single-point subtraction suppresses much of the extracranial signal, but not the intersubject variation in intracranial photon scatter. Mitigation of this confounding influence is attempted through the use of additional infrared wavelengths.[77] The proportion of the differential regional hemoglobin oxygen saturation signal that represents intracranial tissue has not been established. *LED,* Light-emitting diode. *(Spatially resolved NIRS diagram courtesy Covidien, Boulder, Colo.)*

Similar to TCD monitoring, cerebral oximetry is primarily used to quantify change because the substantial NIRS intersubject baseline variability makes it difficult to establish a reliable threshold value signifying tissue injury.[53] An adverse shift in oxygen supply-demand balance is indicated by a decreasing oxyhemoglobin fraction. The clinical significance of the decline has been demonstrated in conscious subjects and patients during G-force studies with high-speed centrifugation,[54] implantable cardioverter-defibrillator testing,[42] tilt-table testing,[42] carotid artery occlusion,[55] and intracranial artery balloon occlusion.[56] In each setting, a decline of greater than 20% was associated with syncope or signs of focal cerebral ischemia. During adult[52,57] and pediatric[58,59] cardiac surgical procedures, the magnitude and duration of cerebral dysoxygenation are associated with hospital cost-driver increase as well as the incidence and severity of adverse clinical outcomes.

The first commercial device to receive FDA clearance for measurement of rSO_2 was the single-channel INVOS 3100 cerebral oximeter (Somanetics Corporation, Troy, Mich). The latest model, 5100C (Covidien, Boulder, Colo), is a four-channel device that is approved for monitoring of cerebral and somatic tissue oxygenation in patients larger than 2.5 kg. Measurement is achieved with self-adhesive patches (ie, optodes), each of which contains a light-emitting diode (LED) infrared light source and two infrared sensors. Because unabsorbed photons are known to traverse a parabolic course through chromophore-containing media, light source-sensor separations of 30 mm or more ensure that both signals represent extracranial and intracranial tissue.[51] Two wavelengths of infrared light are sufficient to determine oxygen saturation, the oxyhemoglobin fraction of total hemoglobin.[51] The process of spatial resolution uses the sensor signal ratio to suppress influences of extracranial hemoglobin absorption and intersubject variation in intracranial photon scatter.[51] The resultant rSO_2 metric is approximately 65% intracranial[60] (see Fig. 18.24, left panel).

Three other cerebral oximeters also have received FDA clearance. Like INVOS, the CAS Medical (Branford, Conn) Fore-Sight also uses an optode containing an LED light source and two infrared sensors.[61] A small, 15-mm light source-proximal sensor separation is used to detect extracranial photon migration exclusively, whereas a larger, 50-mm distal separation measures photons arising from both extracranial and intracranial tissues (see Fig. 18.24, right panel). Cerebral saturation is determined from the proximal-distal differential signal. Although this approach appears to suppress extracranial contamination, the single-point intracranial measurement may be influenced by individual variations in intracranial photon scatter. Additional wavelengths of infrared light are used in an attempt to mitigate the influence of photon scatter variations on the rSO_2 measurement.[62]

Nonin (Minneapolis, Minn) manufacturers the EquanOX 7600 cerebral oximeter. This device relies on dual LED light sources and four wavelengths of infrared light.[63] The rSO_2 value appears to represent the average of two neighboring extracranial versus intracranial differential measurements.[64] Reports are now available that describe its performance in a variety of clinical applications including cardiac operations.[65]

The Ornim Medical (Foxborough, Mass) CerOx measures microcirculatory rSO_2 and blood flow in brain or peripheral tissue by using a combination of multiple-wavelength near-infrared light and pulsed ultrasound.[66] The technology has unique theoretic advantages in that the ultrasound produces vibration of the red cells, and this vibration is transmitted to the optical signal when the light interacts with the erythrocytes (opticoacoustic coupling). Gating the optical signal to only the portion recovered after a specific time delay following an ultrasound pulse allows for determination of the tissue depth at which the optical signal originated. Relative blood flow can also be determined by this device. Device performance in monitoring patients with traumatic brain injury has been described,[67] but the technology is too new to be adequately evaluated in the cardiac surgical population.

The clinical performance of cerebral oximetry systems appears to be device specific.[53] Supporting evidence for one device does not necessarily apply to competing products. Objective comparison of these devices remains difficult because of the lack of a universally accepted direct reference standard measure of regional brain microcirculatory oxygen saturation.[51]

Technologic Limitations

The technical limitations of cerebral oximetry primarily involve factors influencing photon migration. Cranial and perispinal sensor placement is currently limited to glabrous skin because hair may compromise the measurement as a result of environmental light piping. Convenient forehead placement prevents monitoring the critical posterior watershed at the juncture of the anterior, middle, and posterior cerebral arteries (see Fig. 18.23). Mutoh and colleagues[68] overcame this limitation with a parietotemporal optode placement in head-shaved neurosurgical patients to monitor vasospasm treatment successfully. Weak signals may also result from hematoma or sensor placement over a venous sinus.[69] In either case, the large hemoglobin volume acts as a photon sink. Conversely, recording failures may arise from excessively large signals, such as those produced by a skull defect.[70] Issues can also occur when the optode is placed over a sinus because transmission through (or around) an air-filled sinus is quite different from transmission through aqueous or bony tissue.

Very significant differences exist between pediatric and adult cranial anatomy, and they dramatically favor the transmission of optical signal in the pediatric population. As a result, extrapolation of conclusions from studies in the pediatric population to adults should be undertaken with great care.

Validation

The rSO_2 value has been validated from arterial and jugular bulb oxygen saturation measurements in adults and children.[71,72] Hypoxemia involving cerebral tissue proximate to the cranial optodes was consistently detected. Except during ischemia and CPB, $SjvO_2$ and rSO_2 generally correlate in the midrange saturation, although discrepancies may appear at the extremes.[73] The validity of rSO_2 also has been assessed by comparison with direct microprobe measurement of brain tissue oxygen partial pressure. The two measures appear to be directly and significantly related; however, the invasive monitoring of tissue oxygenation would be appropriate in few cardiac surgical situations.[74]

Normative Values

Kishi and associates[75] examined surgical patients' demographic influences on rSO_2. The measure appeared to be independent of weight, height, head size, or sex, although it was negatively correlated with age and positively correlated with hemoglobin concentration. Values were also affected as the sensor was moved laterally from the recommended position above the eye. The normative INVOS rSO_2 value of 71 ± 6% reported for healthy adults[71] is significantly higher than that obtained from cardiac surgical patients.[76] An even larger difference is observed between healthy infants[77] and infants with congenital heart disease.[59] Because of the previously discussed technical differences among competing oximeters, clinicians should appreciate that *rSO_2 normative values are device dependent and not interchangeable.*[78]

Multimodality Neuromonitoring

Because each monitoring modality may evaluate only a portion of the CNS, multimodal monitoring would appear to be desirable to monitor neurologic wellness more completely (Table 18.4). The variety of techniques for neuromonitoring and the plethora of display formats provide visually confusing information for the anesthesiologist trying to understand the data in the context of the anesthetic regimen and the surgical procedure. The anesthesia record is fundamentally a time-based record (time on the y-axis), having a display rate of several hours per page. Cerebral oximetry and BIS are (potentially) displayed similarly, whereas a raw electroencephalogram has a horizontal time base but a display rate of only seconds per page. Processed electroencephalograms, TCD ultrasound findings, and evoked potentials are commonly displayed with time on the y-axis, but to emphasize symmetry (or asymmetry), processed electroencephalogram and TCD ultrasound findings are commonly displayed with the frequency axes in opposite directions for data from left and right hemispheres. Considerable improvement is needed in ergonomics or the development of alternative display technologies for effective and facile intraoperative use by the cardiac anesthesiologist.

General Procedural Considerations

The list of possible neurologic injuries during cardiac operations is long, and many injuries can be detected by more than one monitoring modality. Because the actual incidence of these injuries is generally low, it is common for studies of surrogate events to provide efficacy data in support of the use of commercial monitoring equipment. For example, changes in regional oxygen saturation are commonly used as a surrogate for cerebral ischemia in assessing the functionality of NIRS systems. Unfortunately, the use of such surrogates overestimates the potential value of these devices, especially when they lack tight physiologic thresholds.

Surgery on the Aorta

Repair or replacement of the ascending and transverse aorta to treat aneurysms and dissections has become more common in recent years.

TABLE 18.4 Multimodality Neuromonitoring for Cardiac Surgical Procedures

Modality	*Function*
Electroencephalography	Cortical synaptic activity
Brainstem auditory-evoked potentials	Cochlear, auditory nerve, and brainstem auditory pathway function
Middle latency auditory-evoked potentials	Subcortical-cortical afferent auditory pathway function
Somatosensory-evoked potentials	Peripheral nerve, spinal cord, and brain somatosensory afferent pathway function
Transcranial motor-evoked potentials	Cortical, subcortical, spinal cord, and peripheral nerve efferent motor pathway function
Transcranial Doppler ultrasonography	Cerebral blood flow change and emboli detection
Tissue oximetry	Regional tissue oxygen balance

Because the operation invariably involves modification of the normal cerebral perfusion up to and including circulatory arrest, the use of various modalities to monitor the CNS is common. The particular modality may vary depending on surgical approach and clinical preference (see Chapter 23).

Circulatory Arrest

When the planned technique includes circulatory arrest, with or without retrograde cerebral perfusion, the first imperative is to ensure that the brain is adequately cooled to withstand the necessary period of cerebral ischemia. Optimal protection of cerebral cortical tissue by cooling occurs when electrical silence has occurred on the electroencephalogram because more than 60% of the brain's metabolic effort is expended in the generation of electrical signals. Cooling slows the electroencephalogram in a dose-dependent fashion (Fig. 18.25),[79] with recovery following a similar pattern but not necessarily following the same curve or returning completely to baseline. The actual temperature at which electrical silence occurs can vary from 11 to 18°C,[80] and therefore reliance on temperature alone may prolong cooling (and therefore rewarming and bypass) unnecessarily.

The BIS monitor is not a particularly useful tool in establishing electrical silence. This discordance occurs because the intrinsic algorithm considers EEG activity to be suppressed when the amplitude is less than 5 μV,[81] whereas voltages lower than 2 μV are generally considered isoelectric.[80]

Cooling prolongs SSEP peak and interpeak latencies and suppresses amplitude of the cortical response predominantly (see Fig. 18.15B). Consequently, SSEP responses can also be used to assess cooling.[82] However, because subcortical SSEP responses involve far fewer synapses than the electroencephalogram, these responses often persist when cortical neuronal activity is totally cold suppressed. Thus detection of cerebral ischemia by SSEPs can be achieved during EEG quiescence (Fig. 18.26). Because clinical results with EEG guidance of cooling are quite good,[80] it is not clear that SSEP monitoring offers any advantage.

A subset of patients undergoing circulatory arrest has aortic dissections, and in this population, evidence indicates that TCD monitoring may be beneficial. One prospective investigation demonstrated that TCD monitoring during acute aortic dissection repair reduced the incidence of transient neurologic deficit from 52% to 15%, although no significant change was observed in the incidence of stroke or in-hospital or 30-day mortality rates. This reduction was achieved in part through TCD-directed changes in perfusion cannula placement and adjustments in the management of retrograde cerebral perfusion,[83] and it may be related to specifics of surgical techniques used in this particular observational single-institution study.

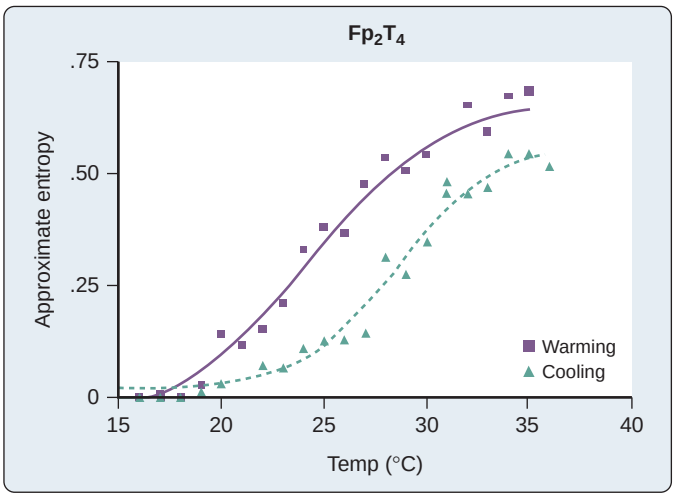


Fig. 18.25 Cooling and rewarming in circulatory arrest. The approximate entropy was calculated from a single channel of the electroencephalogram during cooling to 18°C for circulatory arrest and subsequent rewarming. The delay in the resumption of electroencephalographic activity as a function of nasal temperature is clearly evident. *(From Levy WJ, Pantin E, Mehta S, et al. Hypothermia and the approximate entropy of the electroencephalogram.* Anesthesiology. *2003;98:53–57, with permission of the publisher.)*

Antegrade Cerebral Perfusion

Management of aortic surgical procedures using antegrade cerebral perfusion through the right subclavian artery typically involves only moderate hypothermia. However, the potential for cerebral ischemia secondary to an incomplete circle of Willis emphasizes the need for the early detection of ischemia with some form of neuromonitoring. The circle of Willis is completely normal in only a small fraction (25%) of patients, although many of the anomalies consist of hypoplasia (not absence) of a single segment and may not predispose patients to ischemia. Papantchev and colleagues[84] examined circle of Willis variations in cadavers and found that 42.4% of specimens exhibited variations that could lead to hemodynamically significant alteration in flow during unilateral selective cerebral perfusion. Theoretic arguments favor a multichannel EEG montage because the region of malperfusion cannot be predicted with certainty. In practice, TCD, NIRS, and BIS all appear capable of demonstrating asymmetry in the presence of such malperfusion should it occur in the region monitored. The acute occurrence of asymmetry in any monitored modality coincident with initiation of perfusion through the right subclavian artery would suggest a need to change surgical technique. Clearly, NIRS and BIS have benefits in ease of use compared with both multichannel EEG and TCD techniques. Numerous case reports and case series have identified such rSO_2 assymetry.[85–89] Comparative studies to demonstrate a practical value of the more complex monitoring techniques remain to be done and may be impossible because of the need for a large sample size.

The use of only moderate hypothermia with antegrade cerebral perfusion potentially predisposes patients to another neurologic complication: spinal cord ischemia. Because the brain is perfused but the body is not, a theoretic concern exists about the integrity of the spinal neurons that could justify SSEP monitoring. Clinical reports of spinal cord complications following aortic repair using antegrade cerebral perfusion are infrequent, a finding suggesting that this complication is more theoretic than real. Minatoya and associates[90] compared three groups of patients (N = 229) who underwent aortic arch operations using bilateral selective cerebral perfusion and circulatory arrest temperatures of 20°, 25°, and 28°C, respectively. Stroke and TND rates were not significantly different in the three groups, and no postoperative paraplegia occurred in any group.

Descending Aorta Surgery

Surgical procedures on the descending thoracic aorta may involve partial (left atrial-to-left femoral) bypass, complete circulatory arrest, or entirely endovascular techniques. If circulatory arrest is used because proximal cross-clamping is not possible, the issues already discussed regarding circulatory arrest remain considerations. In addition, and regardless of the management of bypass, operations on the descending aorta imposes significant risk of spinal cord ischemia and warrant consideration of neurologic monitoring for early diagnosis and treatment. Three modalities have the potential to provide this information—SSEPs, MEPs, and tissue oxygenation, although the last is currently viewed as highly experimental. As described earlier, SSEP monitoring documents sensory function through the peripheral nerves and posterior columns of the spinal cord, whereas MEP monitoring documents motor function through the structures of the anterior spinal cord. Anatomic considerations of the vascular supply to the spinal cord suggest that the anterior structures, perfused by radicular arteries from the aorta, are at greater risk than are the posterior columns, whose perfusion is derived as an extension of the vertebral artery. These considerations would suggest that MEP monitoring would be the preferred technology. However, in the period when the

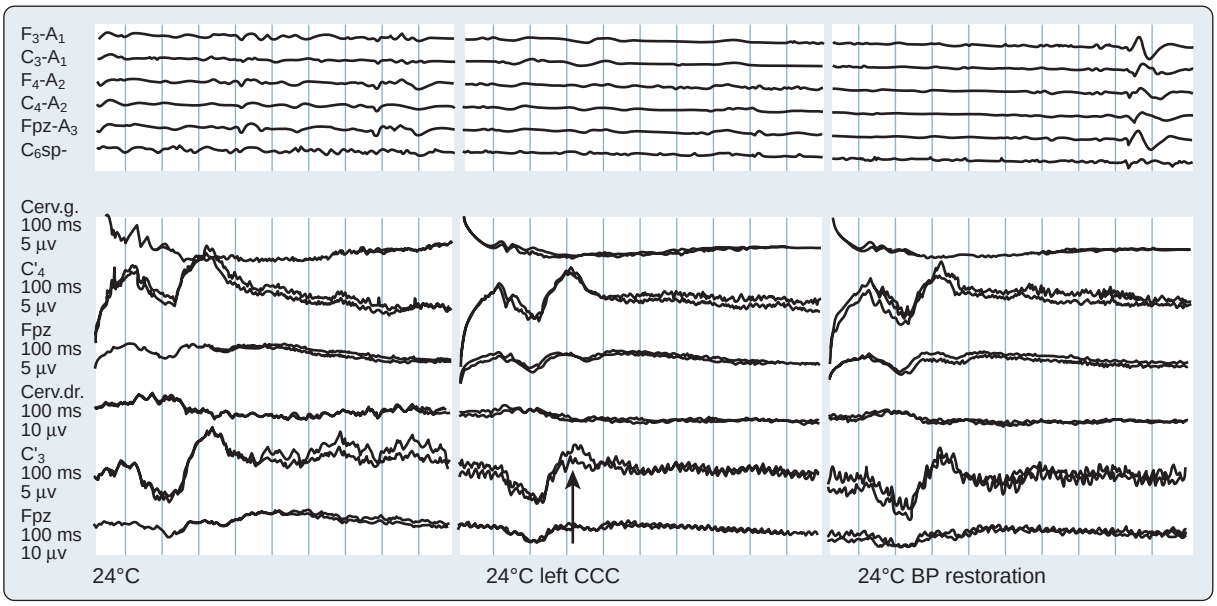


Fig. 18.26 Comparison of electroencephalographic (EEG) and somatosensory-evoked potential (SSEP) changes to regional cerebral hypoperfusion. The upper traces represent bihemispheric cold-suppressed EEG activity derived from scalp (Fpz, F_3, F_4, C_3, and C_4), cervical spine (C_6sp), and earlobe (A_1, A_2, and linked A_3) recorded at 24°C. The lower traces represent contemporaneous bihemispheric upper limb SSEP responses. The *arrow* points to left hemispheric N_{20} suppression accompanying left common carotid artery clamping *(CCC)*. Blood pressure *(BP)* increase restored the N_{20} amplitude. This regional cerebral hypoperfusion was not apparent in the hypothermia-suppressed EEG recording. *Cerv.dr.,* Cervical droite (right median nerve stimulation); *Cerv.g.,* cervical gauche (left median nerve stimulation). *(Modified from Guérit JM. Intraoperative monitoring during cardiac surgery. In: Nuwer MR, ed.* Handbook of Clinical Neurophysiology. *Vol. 8.* Intraoperative Monitoring of Neural Function. *New York: Elsevier; 2008:835.)*

technology to monitor MEPs did not exist, SSEP monitoring was used to identify spinal cord ischemia and guide therapy. Studies using this approach have shown significant association between permanent loss of SSEPs and poor outcome.[91] Comparative studies of MEP and SSEP monitoring have shown very high predictive values for ischemia if the changes are permanent. If the change is transient, SSEPs have a lower incidence of false-positive predictions of neurologic injury than MEPs, thus further suggesting that SSEPs are as useful as MEPs. Other studies support the use of MEPs preferentially to guide sacrifice or reimplantation of intercostal arteries.[92] An added advantage of SSEP monitoring is its relative resistance to potent agents and muscle relaxants, thereby allowing intraoperative use. By comparison, exclusion of these common techniques greatly complicates the anesthetic management of patients when MEP monitoring is planned.

A custom-built NIRS optode and an indocyanine green tracer technique were used to validate translaminar perispinal oxygen saturation (SsO_2). The neuromonitoring technique demonstrated both local blood flow autoregulation and carbon dioxide reactivity.[93] SsO_2 monitoring has been achieved by placing optodes designed for adult transcranial tissue oximetry over the lower thoracic and upper lumbar spine. Case reports and series involving both open and endovascular techniques have suggested possible roles for optical technologies.[94–97] Conversely, these approaches have no possibility of distinguishing anterior from posterior spinal cord ischemia, and the experience with them is too limited to define thresholds for therapeutic intervention or to recommend such an "off-label" application.

Routine Coronary Artery Bypass Graft and Valve Procedures

For purposes of discussing the application of neuromonitoring in routine CPB procedures, a distinction must be made between techniques that can be managed by the anesthesiologist without technical assistance and those that require the presence and assistance of at least a neuromonitoring technician, if not a neurologist or neurophysiologist, skilled in the interpretation of intraoperative changes. Processed electroencephalography and NIRS fall into the former group, whereas multichannel electroencephalograms, evoked potentials, and TCD ultrasound would generally fall into the latter category. These latter choices, because of their increased cost and complexity, must demonstrate clear superiority in patient-related outcomes; in general, such data are lacking. For NIRS and processed electroencephalography, however, technical issues pose no significant constraint, and the costs are modest, potentially leading to a more favorable balance.

NIRS monitoring has been the most thoroughly studied of the neuromonitoring techniques in recent years. The profusion of interest comes both from the (apparent) simplicity of the device and the stimulus of commercial enterprises to justify their use. As mentioned earlier, different devices use different proprietary techniques to extract the signal, and they may result in different values of rSO_2 under identical clinical conditions. This renders the determination of the threshold for treatment somewhat arbitrary and results in the assessment of value on the basis of improvement in surrogate measures (eg, improvement in rSO_2) and not on the prevention of complications. A detailed cardiac surgical intervention algorithm based on this criterion was proposed by Deschamps and colleagues.[98] The value of such an approach remains to be demonstrated by prospective randomized studies.

Carotid Endarterectomy in Combination With Coronary Artery Bypass Graft and Valve Procedures

Patients undergoing combined CEA and CABG or valve operations comprise another group warranting discussion (see Chapter 24). Unfortunately, data regarding monitoring in this specific population

is not extensive. The largest review of the published literature of combined CEA and CABG did not even consider the use or type of neurophysiologic monitoring in its comparison of combined surgical approaches.[99] Even in the literature describing cases of CEA only, robust data are in short supply. A Cochrane review found only 6 randomized or quasirandomized trials including only 1270 patients comparing routine with selective shunting, and the decision to shunt was determined using a variety of neuromonitoring modalities.[100] No outcome preference was demonstrated, and no particular form of neuromonitoring could be recommended. A similar result was found in a retrospective analysis using data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database.[101]

If robust data supporting selective shunting are not available, it is hardly surprising that such data in support of a particular form of neurologic monitoring are even more limited. Comparisons have been published for the following: cerebral oximetry and BIS[102]; SSEPs, MEPs, and electroencephalography[103]; cerebral oximetry and 16-channel electroencephalography[104]; and cerebral oximetry and TCD ultrasound.[105] An extensive review of the literature for comparisons of cerebral oximetry and other modalities (TCD, electroencephalography, stump pressure, and SSEPs) suggested value for cerebral oximetry but could not even define what the thresholds for intervention should be.[106] Studies evaluating BIS in patients undergoing awake CEA also support[107,108] and refute[109] the usefulness of BIS monitoring during CEA. Despite the general acceptance of multichannel electroencephalography as the gold standard of monitoring for CEA, the body of evidence would suggest that any neuromonitoring technique, properly applied, can be justified.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is becoming more common for the support of patients with failing cardiac or pulmonary function (see Chapter 33). The magnitude of the support can encompass complete bypass of the native cardiopulmonary function; however, some cardiac ejection commonly occurs even though ECMO flows are providing essentially all systemic needs. This small cardiac output consists of blood that has gone through the lungs and may be inadequately oxygenated if the patient has respiratory failure. This blood preferentially perfuses the innominate artery, and thus the right side of the brain may be receiving hypoxic blood even though arterial blood gas measurements (obtained from an indwelling catheter in the groin or left radial artery) appear normal. Although application of pulse oximeters to fingers of both hands may detect such right-sided desaturation, the pulse waveform during ECMO is often inadequate for detection of the saturation by pulse oximetry. Cerebral oximetry is well suited for assessing the development of unilateral desaturation in these patients who may need to be monitored continuously for days or weeks.

Depth of Anesthesia

For assessment of anesthetic depth, BIS or other processed EEG methods are the most commonly used technologies. These hypnotic indices appear to provide clinically useful information. However, their *fundamental differences may result in monitor-specific performance, so agreement among these measures during surgical procedures should not be expected.* Consequently, it may be inappropriate to apply clinical outcome evidence obtained with one proprietary index to competing indices.[110–115] Reported rates of intraoperative awareness during cardiac operations range from 0.2% to 2%, a 10-fold increase in risk compared with the general surgical population.[116–119] Three randomized clinical trials of the impact of BIS monitoring on awareness included a relatively large number of patients undergoing cardiac surgical procedures (27%, 49%, and 36%) or lung transplantation, or both.[116,118,119] Based on data, the American Society of Anesthesiologists Practice Advisory on Awareness and Brain Monitoring made the recommendation that the decision to use a brain monitor, including a BIS monitor, should be made on case-by-case basis and should not be considered standard of care.[120]

Summary

Cardiac surgical procedures vary significantly in their associated risk of neurologic injury, the portion of the nervous system at risk, and the options for treatment if injury is identified. Aggressive treatment of clinically insignificant or ambiguous changes may carry unrecognized risks that effectively counter the expected benefit of treatment. An understanding of the methodologies, the underlying physiology, and the therapeutic options is necessary for appropriate application of these technologies during cardiac surgical procedures.

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19

Coagulation Monitoring

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KEY POINTS

1. Monitoring the effect of heparin is done using the activated coagulation time (ACT), a functional test of heparin anticoagulation. The ACT is susceptible to prolongation because of hypothermia and hemodilution and to reduction because of platelet activation or thrombocytopathy.
2. Heparin resistance can be congenital or acquired. Pretreatment heparin exposure predisposes a patient to altered heparin responsiveness because of antithrombin III depletion, platelet activation, or activation of extrinsic coagulation.
3. Heparin-induced thrombocytopenia is a prothrombotic disorder caused by an abnormal immunologic response to the heparin–platelet factor 4 complex and is sometimes associated with overt thrombosis.
4. Protamine neutralization of heparin can be associated with "protamine reactions," which include vasodilatory hypotension, anaphylactoid reactions, and pulmonary hypertensive crises (types 1, 2, and 3, respectively).
5. Before considering a transfusion of plasma, it is important to document that the effect of heparin has been neutralized. This can be done using a heparinase-neutralized test or a protamine-neutralized test.
6. Point-of-care tests are available for use in transfusion algorithms that can measure coagulation factor activity (normalized ratio, activated partial thromboplastin time) and platelet function.
7. Fibrinolysis is common after cardiopulmonary bypass when antifibrinolytic therapy is not used.
8. Newer thrombin inhibitor drugs are available for anticoagulation in patients who cannot receive heparin. These can be monitored using the ecarin clotting time or a modified ACT. Bivalirudin and hirudin are the two direct thrombin inhibitors that have been used most often in cardiac surgical procedures.
9. Platelet dysfunction is the most common reason for bleeding after cardiopulmonary bypass. Point-of-care tests can be used to measure specific aspects of platelet function.
10. The degree of platelet inhibition as measured by standard or point-of-care instruments has been shown to correlate with decreased ischemic outcomes after coronary intervention. However, cardiac surgical patients who are receiving antiplatelet medication are at increased risk for postoperative bleeding.

Cardiac surgery is an area in which coagulation monitoring has vital applications. Cardiopulmonary bypass (CPB) procedures could not be performed without an effective method of preventing blood from clotting in the extracorporeal circuit. In the early part of the 20th century, heparin was discovered to have anticoagulant properties; it remains the anticoagulant most commonly used during CPB. Reversal of heparin effect is most frequently performed using protamine, although several different pharmacologic agents and reversal techniques can be used.

CPB itself induces a "whole-body inflammatory response" because of contact of blood and cellular elements with the extracorporeal circuit. The resultant alterations include leukocyte activation, release of inflammatory mediators, free radical formation, complement activation, kallikrein release, platelet activation, and stimulation of the coagulation and fibrinolytic cascades. This complex interplay of systems induces coagulopathy characterized by microvascular coagulation, platelet dysfunction, and enhanced fibrinolysis.[1,2] The hemostatic perturbations incurred during CPB are major causes of the postbypass coagulopathy that is seen even after the effects of heparin are reversed with protamine.

The need to monitor anticoagulation during and after surgical procedures is the reason that the cardiac surgical setting has evolved into a major area for the evaluation and use of hemostasis monitors. The rapid and accurate identification of abnormal hemostasis has been the major impetus toward the development of point-of-care (POC) tests that can be performed at the bedside or in the operating room. The detection and treatment of specific coagulation disorders in a timely and cost-efficient manner are major goals in hemostasis monitoring for the cardiac surgical patient. This chapter discusses the mechanisms of normal coagulation and how they are affected by CPB. It then discusses the laboratory and POC tests available for monitoring the coagulation system. A comprehensive overview of hemostasis, transfusion medicine, and the management of coagulopathy and bleeding disorders after CPB is provided in Chapters 34 and 35.

Hemostasis

Hemostasis is the body's normal response to vascular injury, and it involves a complex interplay of systems within the body that helps to

seal the endovascular defect and prevent exsanguination. The three major components of hemostasis are as follows: (1) the vascular endothelium; (2) the platelets, which constitute primary hemostasis; and (3) the coagulation cascade glycoproteins, which constitute secondary hemostasis. Fibrinolysis, the normal physiologic response to clot formation, ensures that coagulation remains localized to the area of vascular injury (see Chapter 35).

Anticoagulation for Cardiopulmonary Bypass

CPB could not be accomplished safely without anticoagulation of blood in preparation for its contact with the extracorporeal circuit. An ideal anticoagulant agent should be easy to administer, rapid in onset, titratable, predictable, measurable in a timely fashion, and reversible. Heparin use during CPB has continued until the present time, most likely because of the drug's rapid onset, ease of measurement, and ease of reversibility.

Heparin acts as an antithrombin III (AT III) agonist and accelerates AT III binding to thrombin.[3–5] In the absence of AT III, heparin is clinically ineffective as an anticoagulant agent; adequate AT III activity is necessary in patients about to undergo heparinization for cardiac surgical procedures.[6–9]

Monitoring Heparin Effect

Cardiac surgical procedures had been performed for decades with empiric heparin dosing in the form of a bolus and subsequent interval dosing. Empiric dosing continued because of the lack of an easily applicable bedside test to monitor the anticoagulant effects of heparin. However, many assays are currently available to measure the response to the heparin dose given to institute extracorporeal circulation. These assays are functional tests of anticoagulation or quantitative measures of the level of circulating heparin.

The first clotting time used to measure heparin effect was the whole-blood clotting time (WBCT) or the Lee-White WBCT.[10] This test simply requires whole blood to be placed in a glass tube, maintained at 37°C, and manually tilted until blood fluidity is no longer detected. This test fell out of favor for monitoring cardiac surgical patients because it was so labor intensive and required the undivided attention of the person performing the test for up to 30 minutes. Although the glass surface of the test tube acts as an activator of factor XII, the heparin doses used for cardiac surgical procedures prolong the WBCT to such a profound degree that the test is impractical as a monitor of the effect of heparin during cardiac operations.[11] To speed the clotting time so that the test was appropriate for clinical use, activators were added to the test tubes, and the activated coagulation time (ACT) was introduced into practice.[12]

Activated Coagulation Time

The ACT was first introduced by Hattersley in 1966 and is still the most widely used monitor of heparin effect during cardiac surgical procedures.[13] Whole blood is added to a test tube containing an activator, either diatomaceous earth (celite) or kaolin. The presence of activator augments the contact activation phase of coagulation, which stimulates the intrinsic coagulation pathway. The ACT can be performed manually, whereby the operator measures the time interval from when blood is injected into the test tube to when clot is seen along the sides of the tube. More commonly, the ACT is automated, as it is in the Hemochron (International Technidyne Corp., Edison, NJ) and ACT Plus (Medtronic Perfusion Services, Minneapolis, MN) systems. In the automated systems, the test tube is placed in a device that warms the sample to 37°C. The Hemochron device rotates the test tube, which contains celite activator and a small iron cylinder, to which 2 mL of whole blood is added. Before clot forms, the cylinder rolls along the bottom of the rotating test tube. When clot forms, the cylinder is pulled away from a magnetic detector, interrupts a magnetic field, and signals the end of the clotting time. Normal ACT values range from 80 to 120 seconds. The Hemochron ACT also can be performed using kaolin as the activator in a similar manner (Fig. 19.1).

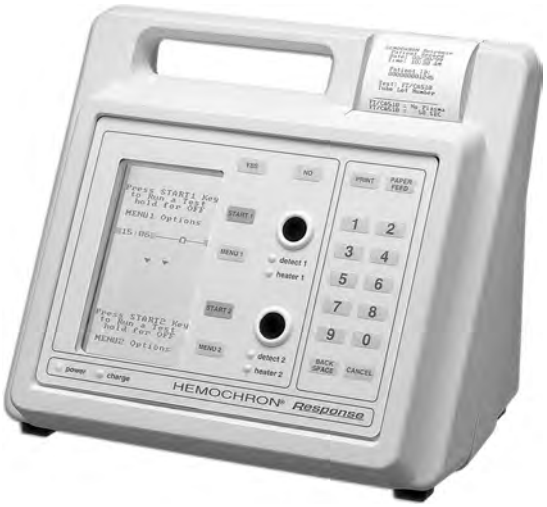


Fig. 19.1 The Hemochron Response (Accriva Diagnostics/International Technidyne Corp., Edison, NJ) is a dual-chamber point-of-care coagulation monitor that can measure clotting times that are compatible with Hemochron technology. This system has software capability for calculation, data management, and storage of results. *(Courtesy International Technidyne, Edison, NJ.)*

The ACT Plus (formerly Hemotec ACT) device is a cartridge with two chambers that contain kaolin activator and is housed in a heat block. Blood (0.4 mL) is placed into each chamber, and a daisy-shaped plunger is raised and passively falls into the chamber. The formation of clot slows the rate of descent of the plunger. This decrease in velocity of the plunger is detected by a photo-optical system that signals the end of the ACT test. The Hemochron and Hemotec ACT tests have been compared in several investigations and have been found to differ significantly at low heparin concentrations.[14] However, differences in heparin concentration, activator concentration, and the measurement technique make comparison of these tests difficult and have led to the realization that the results of the Hemochron and Hemotec ACT tests are not interchangeable. In adult patients given 300 IU/kg of heparin for CPB, the Hemochron and Hemotec (Hepcon) ACTs were both therapeutic at all time points, although the Hemochron ACT was statistically longer at two time points[15] (Fig. 19.2).

This difference was even more pronounced in pediatric patients, who have greater heparin consumption rates (Fig. 19.3). The apparent "overestimation" of ACT by the Hemochron device during hypothermic CPB may result from the different volumes of blood that each assay warms to 37°C.[15]

In another study of heparin monitoring and ACT threshold values, investigators noted that the two most commonly used ACT devices correlated with each other, yet one of the instruments had significant bias.[16] Another observational study showed that many ACT tests correlated poorly with heparin level as assessed by anti–factor Xa plasma activity.[17] Patteril and colleagues[18] demonstrated that after switching their cohort population to a newer ACT device, the new instrument yielded a lower mean ACT value compared with temporal controls (557 vs 618 seconds) despite a higher dose of heparin needed to achieve a minimum ACT of 480 seconds.

The ACT test can be modified by the addition of heparinase. With this modification, the coagulation status of the patient can be monitored during CPB while the anticoagulant effects of heparin are eliminated. Because this test is a side-by-side comparison of the untreated ACT with the heparinase ACT, it also has the advantage of being a rapid test for assessment of a circulating heparin-like substance or for residual heparinization after CPB.[19]

With the introduction of ACT monitoring into cardiac surgical practice, clinicians have been able to titrate heparin and protamine

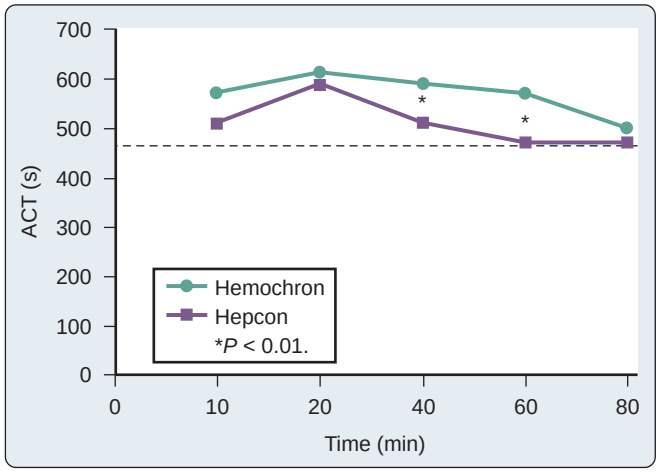


Fig. 19.2 The Hemochron (International Technidyne Corp., Edison, NJ; *circles*) and Hemotec (Hepcon, Medtronic Perfusion Services, Minneapolis, MN; *squares*) activated coagulation time *(ACT)* values in 20 adults at 5 time points during cardiopulmonary bypass (CPB). At 40 and 80 minutes on CPB, the Hemochron ACT was significantly greater. *(From Horkay F, Martin P, Rajah SM, Walker DR. Response to heparinization in adults and children undergoing cardiac operations.* Ann Thorac Surg. *1992;53:822–826, by permission of The Society of Thoracic Surgeons.)*

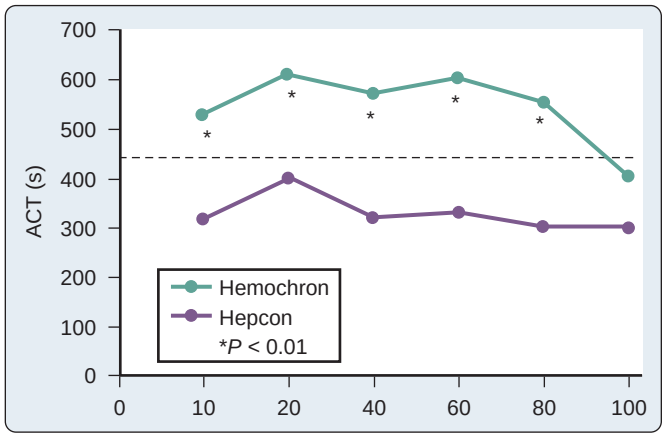


Fig. 19.3 The Hemochron (International Technidyne Corp., Edison, NJ; *green circles)* and Hemotec (Hepcon, Medtronic Perfusion Services, Minneapolis, MN; *purple circles*) activated coagulation time *(ACT)* values in 22 pediatric patients at six time points during cardiopulmonary bypass. Hemochron ACT was significantly greater than Hemotec ACT at five time points. *(From Horkay F, Martin P, Rajah SM, Walker DR. Response to heparinization in adults and children undergoing cardiac operations.* Ann Thorac Surg. *1992;53:822–826, by permission of The Society of Thoracic Surgeons.)*

dosages more accurately.[12,20] As a result, many investigators report reductions in blood loss and transfusion requirements, although many of these studies used retrospective analyses.[21] The improvements in postoperative hemostasis documented with ACT monitoring are potentially attributable to better intraoperative suppression of microvascular coagulation and improved monitoring of heparin reversal with protamine.[22]

ACT monitoring of heparinization is not without pitfalls, and its use has been criticized because of the extreme variability of the ACT and the absence of a correlation with plasma heparin levels (Fig. 19.4). Many factors have been suggested to alter the ACT, and these factors are prevalent during cardiac surgical procedures. When the extracorporeal circuit prime is added to the patient's blood volume, hemodilution occurs and may theoretically increase the ACT. Evidence suggests

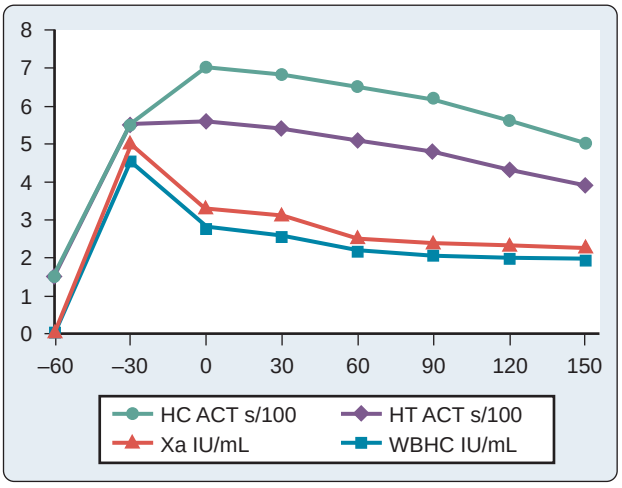


Fig. 19.4 Anticoagulation measured at baseline (–60 minutes), at heparinization (–30 minutes), and six time points after institution of cardiopulmonary bypass. Note the close correlation between the anti–factor Xa *(Xa; triangles)* activity and whole-blood heparin concentration *(WBHC; squares),* which does not parallel the change in Hemochron (International Technidyne Corp., Edison, NJ) activated coagulation time (ACT) *(HC ACT; circles)* or Hemotec (Medtronic Perfusion Services, Minneapolis, MN) ACT *(HT ACT; diamonds). (Modified from Despotis GJ, Summerfield AL, Joist JH. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations.* J Thorac Cardiovasc Surg. *1994;108:1076–1082.)*

that this degree of hemodilution alone is not enough to alter the ACT. Hypothermia increases the ACT in a "dose-related" fashion. Culliford and associates[23] showed that, although hemodilution and hypothermia significantly increase the ACT of a heparinized blood sample, similar increases do not occur in the absence of added heparin. The effects of platelet alterations are more problematic. At mild-to-moderate degrees of thrombocytopenia, the baseline and heparinized ACTs are not affected. It is not until platelet counts are reduced to less than 30,000 to 50,000/μL that the ACT may be prolonged.[24] Patients treated with platelet inhibitors such as prostacyclin, aspirin, or platelet membrane receptor antagonists have a prolonged heparinized ACT compared with patients not treated with platelet inhibitors.[25] This ACT prolongation is not related exclusively to decreased levels of platelet factor 4 (PF4) (PF4 is a heparin-neutralizing substance) because it also occurs when blood is anticoagulated with substances that are not neutralized by PF4. Platelet lysis, however, significantly shortens the ACT because of the release of PF4 and other platelet membrane components, which may have heparin-neutralizing activities.[26] Gravlee and colleagues[27] showed that anesthesia and operation decrease the ACT and create a hypercoagulable state, possibly by creating a thromboplastic response or through activation of platelets.

During CPB, heparin decay varies substantially, and its measurement is problematic because hemodilution and hypothermia alter the metabolism of heparin. In a CPB study, Mabry and associates[28] found that the consumption of heparin varied from 0.01 to 3.86 IU/kg/min, and no correlation was noted between the initial sensitivity to heparin and the rate of heparin decay.[28] In the pediatric population, the consumption of heparin is increased to more than that of adult levels. The heparin administration protocol for pediatric patients undergoing CPB should account for a large volume of distribution, increased consumption, and a shorter elimination half-life. In monitoring the effects of heparin in pediatric patients, the minimum acceptable ACT value should be increased or an additional monitor should be used. The discrepancy between the Hemochron ACT and the Hemotec ACT that is demonstrated in Fig. 19.2 is even more pronounced in pediatric patients (see Fig. 19.3). Some investigators recommend maintaining heparin concentrations in addition to the ACT during operations for

pediatric congenital heart conditions to ensure that optimal anticoagulation is being achieved.[29,30]

Cascade Point-of-Care System

A completely different technology for measuring the effect of heparin is used by the Cascade POC analyzer (Helena, Beaumont, Tex; formerly Rapid Point Coagulation Analyzer Bayer Diagnostics, Tarrytown, NY). This test system contains disposable cards with celite activator for the measurement of heparin activity. This variation of the ACT is called the heparin management test (HMT). The card contains paramagnetic iron oxide particles that move in response to an oscillating magnetic field within the device. When clot formation occurs, movement of the iron oxide particles is decreased, and the end of the test is signaled. This system is capable of measuring prothrombin time (PT) and activated partial thromboplastin time (aPTT), discussed later. The suitability of this platform for ACT monitoring during cardiac surgical procedures has been demonstrated in clinical studies.[31,32] Suitability for monitoring heparinization in the interventional cardiology laboratory also has been reported. The HMT correlates well with anti–factor Xa heparin activity in patients undergoing CPB and is less variable than standard ACT measures. In a comparison with ACT, the coefficients of variation were similar between the tests at baseline, but these values were three times greater for the ACT during heparinization. This degree of agreement with plasma anti–factor Xa measurements has not been demonstrated universally when studying blood from patients undergoing CPB.[33]

Heparin Resistance

Heparin resistance is documented by an inability to increase the ACT of blood to expected levels despite an adequate dose and plasma concentration of heparin. In many clinical situations, especially when heparin desensitization or a heparin inhibitor is suspected, heparin resistance can be treated by administering increased doses of heparin in a competitive fashion. If an adequately prolonged clotting time is ultimately achieved using greater than expected doses of heparin, a better term than heparin resistance would be heparin tachyphylaxis or "altered heparin responsiveness." During cardiac surgical procedures, the belief that a safe minimum ACT value of 300 to 400 seconds is required for CPB is based on a few clinical studies and a relative paucity of scientific data. However, an inability to attain this degree of anticoagulation in the heparin-resistant patient engenders the fear among cardiac surgical providers that the patient will experience microvascular consumptive coagulopathy or that clots will form in the extracorporeal circuit. This potential for fibrin formation in the extracorporeal circuit was reported by Young and associates,[34] who found increased production of fibrin monomer and consumption of fibrinogen and platelets in six of nine rhesus monkeys when the ACT declined to less than 400 seconds. However, Metz and Keats[35] reported no adverse effects of thrombosis or excessive bleeding in 51 patients undergoing CPB whose ACT was less than 400 seconds. In a porcine model, the group whose ACT was maintained between 250 and 300 seconds did not have excessive consumption of coagulation factors, increases in fibrin monomer formation, or changes in oxygenator performance compared with the group whose ACT was maintained at greater than 450 seconds.[36]

Many clinical conditions are associated with heparin resistance.[37] Sepsis, liver disease, and pharmacologic agents represent just a few[38,39] (Table 19.1). Many investigators have documented decreased levels of AT III secondary to heparin pretreatment,[40] whereas others have not found decreased AT III levels.[41] Esposito and colleagues[42] measured coagulation factor levels in patients receiving preoperative heparin infusions and found that a lower baseline ACT was the only risk factor for predicting heparin resistance compared with patients not receiving preoperative heparin.

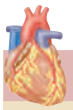
Patients receiving preoperative heparin therapy traditionally require larger heparin doses to achieve a given level of anticoagulation when that anticoagulation is measured by the ACT. Presumably, this "heparin resistance" is the result of deficiencies in the level or activity of AT III.[39,42–45] Other possible causes include enhanced factor VIII activity and platelet dysfunction leading to a decrease in ACT response to heparin. Levy and associates[45] showed that the in vitro addition of AT III enhances the ACT response to heparin. Lemmer and Despotis[44] demonstrated that this heparin resistance, as measured by the ACT, does not correlate with preoperative AT III levels. It is unclear that these patients have increased heparin requirements during CPB because the ideal ACT and monitoring techniques have yet to be elucidated. Nicholson and colleagues[46] demonstrated that the temporal courses of ACT and AT III concentration do not parallel each other, thus further suggesting that AT III depletion is not the sole cause of heparin resistance during CPB. Lower ACTs (<480 seconds) were tolerated in this study with no adverse outcome.

AT III concentrate is available as a heat-treated human product or in recombinant form, and its use is a reasonable method of treating patients with documented AT III deficiency (Box 19.1). Heparin responsiveness in the form of increased ACT levels is documented both in vitro and in vivo when heparin-resistant patients are treated with AT III. In a multicenter, randomized, placebo-controlled trial using 75 IU/kg of recombinant AT III, patients treated with AT III received less fresh frozen plasma to augment ACT levels and also had evidence of less hemostatic activation while undergoing CPB.[47] The trend was toward increased blood loss in the AT III group, which is potentially a dose effect that requires further investigation.[48,49]

TABLE 19.1 Disease States Associated With Heparin Resistance

Disease State or Condition	*Comment*
Newborn status	Decreased AT III levels until 6 months of age
Venous thromboembolism	May have increased factor VIII level Accelerated clearance of heparin
Pulmonary embolism	Accelerated clearance of heparin
Congenital AT III deficiency	40–60% of normal AT III concentration
Type I	Reduced synthesis of normal/abnormal AT III
Type II	Molecular defect within the AT III molecule
Acquired AT III deficiency	<25% of normal AT III concentration
Preeclampsia	Levels unchanged in normal pregnancy
Cirrhosis	Decreased protein synthesis
Nephrotic syndrome	Increased urinary excretion of AT III
DIC	Increased consumption of AT III
Heparin pretreatment	85% of normal AT III concentration because of accelerated clearance
Estrogen therapy	Decreased postheparin triglyceride hydrolase activity
Cytotoxic drug therapy (L-Asparaginase)	Decreased protein synthesis

AT III, Antithrombin III; *DIC,* disseminated intravascular coagulation.



BOX 19.1 HEPARIN RESISTANCE

- It is primarily caused by antithrombin III deficiency in pediatric patients.
- It is multifactorial in adult cardiac surgical patients.
- The critical activated coagulation time value necessary in patients who demonstrate acquired heparin resistance is not yet determined.
- Heparin resistance also can be a sign of heparin-induced thrombocytopenia.

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening disorder that occurs in patients receiving unfractionated heparin (UFH) and, less commonly, low-molecular-weight heparin (LMWH). The incidence is between 0.2% and 5% in patients exposed

TABLE 19.2 Pretest Scoring System for Heparin-Induced Thrombocytopenia: the 4 Ts

4 Ts	*2 Points*	*1 Point*	*0 Points*
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20%[a]	Platelet count fall 30–50% or platelet nadir 10–19%	Platelet count fall <30% and platelet nadir <10%
Timing of platelet count fall	Clear onset between days 5–10 or platelet fall ≤1 day (previous heparin exposure within 30 days)[b]	Consistent with days 5–10 fall, but not clear (eg, missing platelet counts); onset after day 10[c]; or fall ≤1 day (previous heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis[d]; acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis[e]; non-necrotizing erythematous) skin lesions[d]; suspected thrombosis (not proven)[f]	None
Thrombocytopenia of other causes	None apparent	Possible[c]	Definite[c]

[a]Greifswald, Germany (GW): platelet count fall >50% or nadir 20–100%; Hamilton, Canada (but not GW): platelet count fall >50% directly resulting from surgical procedure counts as 1 point, rather than 2 points.
[b]GW: onset from days 5–14 (rather than days 5–10); platelet fall within 1 day (heparin exposure within 100 days).
[c]GW: onset after day 14.
[d]Skin lesions at heparin injection sites.
[e]Progression refers to objectively documented increase in thrombus size (usually, extension of deep vein thrombosis by ultrasonography); recurrence refers to newly formed thromboembolus in previously affected region (usually, new perfusion defects in a patient with previous pulmonary embolism).
[f]In GW, suspected thrombosis (not proven) was not included as a criterion. Determination of whether the presence of another apparent cause of thrombocytopenia was possible or definite was at the discretion of the investigator.

to heparin, with reports of incidence as high as 15% to 20% in patients undergoing cardiac surgical procedures. HIT most often occurs 5 to 14 days after heparin administration and is mediated by antibodies binding to the complex formed between heparin and PF4. This complex binds to platelets, thereby causing platelet activation and subsequently thrombocytopenia. Associated immune-mediated endothelial injury and complement activation cause platelets to adhere, aggregate, and form platelet clots, or "white clots." Among patients in whom HIT develops, the incidence of thrombotic complications approximates 20%. These complications, in turn, may carry a mortality rate as high as 40%.

Diagnosis of HIT requires both clinical evidence (thrombocytopenia and thrombosis) and laboratory findings. Laboratory tests include a functional assay or antibody-based assay. Examples of functional assays are the serotonin release assay (SRA) and the heparin-induced platelet activation (HIPA) assay. These tests detect heparin-dependent antibodies by using platelets from normal donors incubating with the patient's sera. The main advantage of the SRA is its high sensitivity and specificity; however, it is technically demanding and not widely available. The HIPA assay is highly specific but not as sensitive. The most commonly used antibody-based assay is the enzyme-linked immunosorbent assay, which measures immunoglobulin G (IgG), IgM, or IgA antibodies that bind to the heparin-PF4 complex. This test is readily available, although it is less specific than the SRA. Hybrid assays are being developed that can overcome some of the limitations of these tests. Aiding in the diagnosis of HIT is a scoring system called the "4 Ts" as described by Warkentin and Heddle.[50] This systematic method estimates the probability of HIT based on clinical presentation and has the following criteria: thrombocytopenia, timing of platelet count decline, thrombosis, and possible other causes of thrombocytopenia. When combined with a laboratory test, this scoring system provides the highest predictivity for HIT[50,51](Table 19.2).

The risks and appropriate courses of action in patients with HIT are unclear because the antibodies associated with HIT often become undetectable several weeks after discontinuing heparin. Moreover, the clinical syndrome does not always recur on repeat exposure to heparin and sometimes resolves despite continued drug therapy. Many patients never have thrombosis and disseminated intravascular coagulation despite positive laboratory testing. HIT possibly should be considered in the differential diagnosis of intraoperative heparin resistance in patients receiving preoperative heparin therapy.

The options for treating these patients are few. If the clinician has the luxury of being able to discontinue heparin for a few weeks, often the antibody disappears and allows a brief period of heparinization for CPB without complication.[52–55] Changing the tissue source of heparin was an option when bovine heparin was predominantly in use. Some types of LMWH have been administered to patients with HIT, but reactivity of the particular LMWH with the patient's platelets should be confirmed in vitro. Supplementing heparin administration with pharmacologic platelet inhibition using prostacyclin, iloprost, aspirin, or aspirin and dipyridamole have been reported, all with favorable outcomes. Tirofiban with UFH has been used in this clinical circumstance. Plasmapheresis may be used to reduce antibody levels. The use of heparin could be avoided altogether through anticoagulation with direct thrombin inhibitors such as argatroban or bivalirudin. These thrombin inhibitors have become the standard of care in the management of the patient with HIT (Box 19.2). Bivalirudin has been studied in multicenter trials in patients with HIT who must undergo CPB.[56] The use of this drug in patients with acute or subacute HIT requiring urgent cardiac operation has been supported in evidence-based guidelines published by the American College of Chest Physicians.[55] Monitoring the direct thrombin inhibitors during CPB is discussed later in this chapter.

BOX 19.2 HEPARIN-INDUCED THROMBOCYTOPENIA

- The immunologic form is mediated by an antibody to the heparin–platelet factor 4 complex.
- This disease has variable penetrance even in the same patient.
- It has an associated 30% risk for thrombosis.
- Thrombosis carries a 50% mortality rate.

Measurement of Heparin Sensitivity

Even in the absence of heparin resistance, patients' responses to an intravenous bolus of heparin are extremely variable.[57] The variability stems from different concentrations of various endogenous heparin-binding proteins such as vitronectin and PF4. This variability exists whether measuring heparin concentration or the ACT; however, variability seems to be greater when measuring the ACT. Because of the large interpatient variation in heparin responsiveness and the potential for heparin resistance, it is critical that a functional monitor of heparin anticoagulation (with or without a measure of heparin concentration) be used in the cardiac surgical patient. Bull and associates[58] documented a threefold range of ACT response to a 200 IU/kg heparin dose and similar discrepancy in heparin decay rates and thus recommended the use of individual patient dose-response curves to determine the optimal heparin dose. This is the concept on which POC individual heparin dose-response (HDR) tests are based.

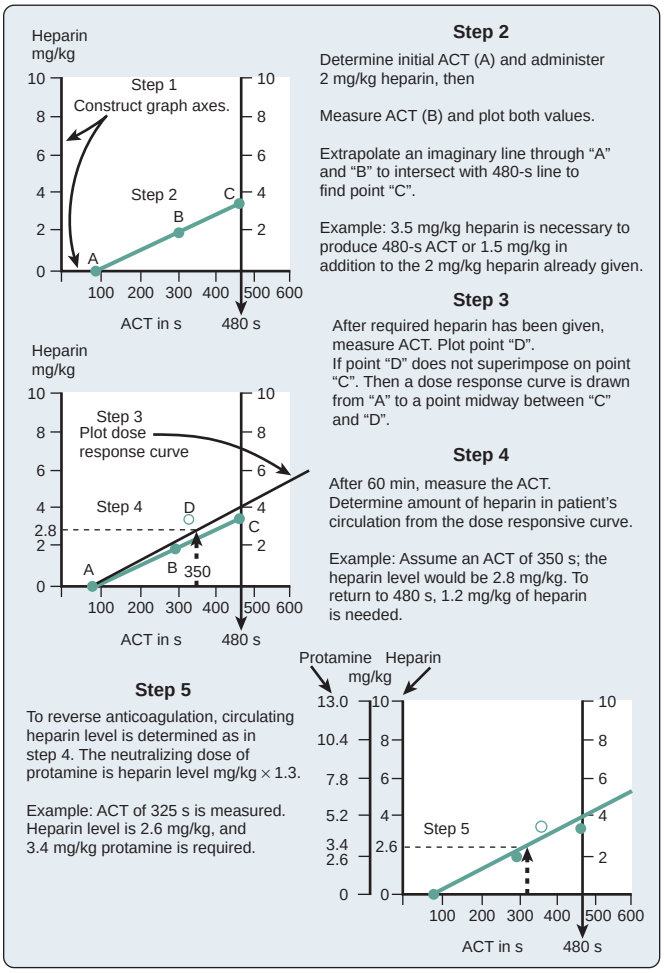


Fig. 19.5 Construction of a dose-response curve for heparin. *ACT,* Activated coagulation time. *(From Bull BS, Huse WM, Brauer FS, et al. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage.* J Thorac Cardiovasc Surg. *1975;69:685–689.)*

An HDR curve can be generated manually by using the baseline ACT and the ACT response to an in vivo or in vitro dose of heparin. Extrapolation to the desired ACT provides the additional heparin dose required for that ACT. Once the actual ACT response to the heparin dose is plotted, further dose-response calculations are made based on the average of the target ACT and the actual ACT (Fig. 19.5). This method was first described by Bull and associates[58] and forms the scientific basis for the automated dose-response systems in the proprietary Hemochron and Hemotec devices. The Hemochron RxDx (International Technidyne Corp., Edison, NJ) system uses the heparin-response test, which is an ACT with a known quantity of in vitro heparin (3 IU/mL). A dose-response curve is generated that enables calculation of the heparin dose required to attain the target ACT by using an algorithm that incorporates the patient's baseline ACT, estimated blood volume, and heparin-response test. The patient's heparin sensitivity can be calculated in seconds per international units per milliliter (s/IU/mL) by dividing the heparin-response test by 3 IU/mL.

The Hemochron RxDx system also provides an individualized protamine dose based on the protamine-response test (PRT). This is an ACT with one of two specific quantities of protamine, depending on the amount of circulating heparin suspected (2 or 3 IU/mL). The protamine dose needed to return the ACT to baseline can be calculated on the basis of a protamine-response curve using the patient's heparinized ACT, the PRT, and an estimate of the patient's blood volume. Jobes and colleagues[59] reported that the heparin dose directed by the

Fig. 19.6 The HMS heparin management system (Medtronic Perfusion Services, Minneapolis, MN) has an automated dispenser that places the appropriate volume of whole blood into each chamber of the test cartridge. A variety of assays can be performed in this instrument, depending on the cartridge used. *(Courtesy Medtronic Perfusion Services, Minneapolis, MN.)*

Hemochron RxDx system resulted in ACT values far greater than the target ACT. In their patients, in vivo heparin sensitivity was higher than in vitro sensitivity. Hemochron RxDx also resulted in lower protamine doses, lower postoperative mediastinal tube losses, and reduced transfusion requirements compared with a ratio-based system of heparin and protamine administration. In a larger study that standardized the treatment of heparin rebound, the reduced protamine dose was confirmed; however, the reductions in bleeding were not substantiated.[60] The use of a protamine dose-response curve has successfully reduced the protamine dose in vascular surgical procedures compared with standard weight-based protamine dosing.[61]

The Hepcon HMS (Medtronic Perfusion Services, Minneapolis, MN) system uses the HDR cartridge in the Hepcon instrument (Fig. 19.6). Each cartridge houses six chambers. Chambers 1 and 2 contain heparin at a concentration of 2.5 IU/mL, chambers 3 and 4 contain heparin at a concentration of 1.5 IU/mL, and chambers 5 and 6 do not contain heparin. Once information regarding a patient's weight, height, and CPB prime volume is entered, the information that can be obtained from this test includes the baseline ACT (chambers 5 and 6) and an HDR slope. The dose-response slope, which is the increase in ACT from 1.5 to 2.5 IU/mL heparin, is extrapolated to the desired target ACT or target heparin concentration, and the heparin dose is calculated.[37,62]

Heparin Concentration

Proponents of ACT measurement to guide anticoagulation for CPB argue that a functional assessment of the anticoagulant effect of heparin is mandatory and that the variability in ACT represents a true variability in the coagulation status of the patient. Opponents argue that during CPB, the sensitivity of the ACT to heparin is altered, and ACT does not correlate with heparin concentration or with anti–factor Xa activity measurement. Heparin concentration can be measured using the Hepcon HMS system, which uses an automated protamine titration technique. With a cartridge with four or six chambers containing tissue thromboplastin and a series of known protamine concentrations, 0.2 mL of whole blood is automatically dispensed into the chambers. The first channel to clot is the channel in which the protamine concentration most accurately neutralizes the heparin without a heparin or a protamine excess. Because protamine neutralizes heparin in the

ratio of 1 mg protamine per 100 IU heparin, the concentration of heparin in the blood sample can be calculated. A cartridge that monitors heparin concentration over a wide range can be used first, followed by another cartridge that can measure heparin concentrations within a more narrow range. The maintenance of a stable heparin concentration rather than a specific ACT level usually results in administration of larger doses of heparin because the hemodilution and hypothermia during CPB increase the sensitivity of the ACT to heparin. The measure of heparin concentration has been shown to correlate more closely with anti–factor Xa activity measurements than the ACT during CPB[63] (Fig. 19.7), although the precision and bias of the test may not prove to be acceptable for exclusive use clinically (Fig. 19.8).

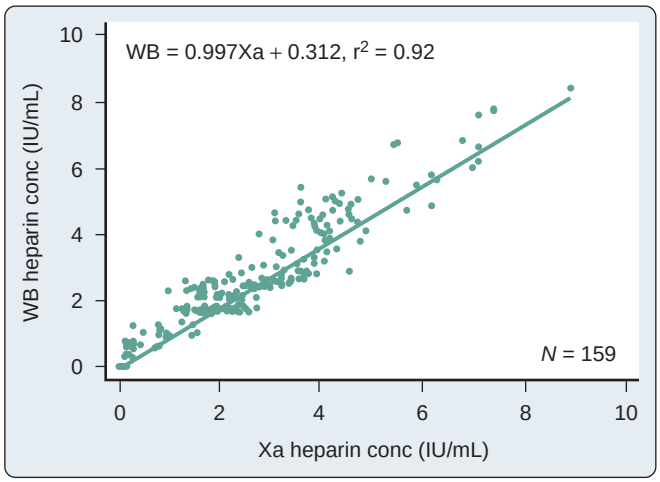


Fig. 19.7 A strong linear relationship exists between whole-blood heparin *([Hep])* concentration *(WB heparin conc)* and the anti–factor Xa plasma heparin concentration *(Xa heparin conc)*. WB heparin conc was measured using the Hepcon (Medtronic Perfusion Services, Minneapolis, MN) protamine titration assay and was corrected for hematocrit value. The Xa heparin conc was measured in plasma by using a substrate assay. *(From Despotis GJ, Summerfield AL, Joist JH. Comparison of activated coagulation time and whole blood heparin measurements with laboratory plasma anti-Xa heparin concentration in patients having cardiac operations.* J Thorac Cardiovasc Surg. *1994;108:1076–1082.)*

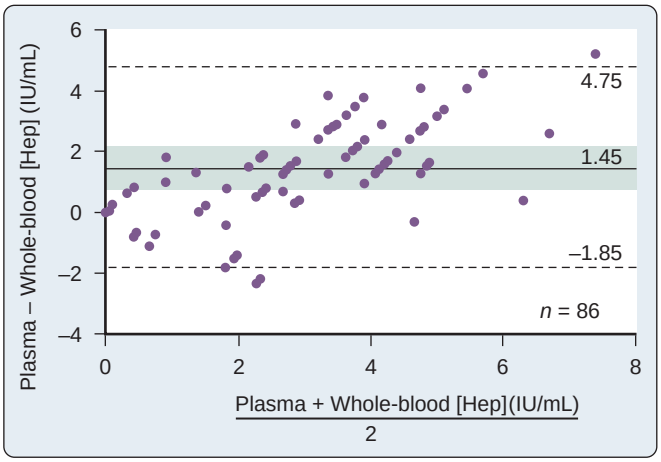


Fig. 19.8 A Bland-Altman plot analyzing the limits of agreement between the whole-blood heparin concentration and the plasma anti–factor Xa heparin concentration. The bias (1.45) and two standard deviations are determined to be the limits of agreement. The limits of agreement do not lie within the predetermined acceptable difference between the tests. *(From Hardy JF, Belisle S, Robitaille D, et al. Measurement of heparin concentration in whole blood with the Hepcon/HMS device does not agree with laboratory determination of plasma heparin concentration using a chromogenic substrate for activated factor X.* J Thorac Cardiovasc Surg. *1996;112:154–161.)*

In a small, prospective, randomized study comparing ACT and heparin concentration monitoring, Gravlee and associates[64] demonstrated increased mediastinal tube drainage postoperatively in the heparin concentration group, a finding that was initially attributed to greater total heparin doses. However, heparin rebound was not systematically assessed. In a follow-up study, these investigators found a greater incidence of heparin rebound in the heparin concentration group that, after treatment, resulted in no difference in bleeding between the ACT and heparin concentration groups.[65] In a prospective, randomized trial, Despotis and colleagues[66] demonstrated that by using a transfusion algorithm in association with Hepcon-based heparin management, chest tube drainage was minimally reduced and transfusion of non–red blood cell products could be significantly reduced relative to a group of patients who had ACT-based heparin management. These investigators attributed their results to better preservation of the coagulation system by high heparin doses because the doses of heparin administered in the Hepcon group were nearly twice the doses used in the ACT management group. However, Gravlee and associates[64] were unable to confirm suppression of ongoing coagulation using Hepcon CPB management. With the exception of during cold CPB, fibrinopeptide A levels in patients who had heparin concentration monitoring were virtually indistinguishable from those in patients who had ACT monitoring (Fig. 19.9). Hepcon, however, remains one of the more sensitive tests for detecting residual heparinization after protamine reversal because the heparin concentration can be measured by protamine titration to levels as low as 0.4 IU/mL (see later).

Other tests that have been used to measure the heparin concentration include polybrene titration (functions similarly to protamine titration) and factor Xa inhibition. The factor Xa inhibition test requires plasma separation and is not practical for intraoperative monitoring. A modification of the thrombin time (TT) can be useful in monitoring heparin levels. One application would be an assay in which a known quantity of thrombin is added to a patient's blood or plasma. When mixed with a fibrin product, cleavage of the fibrin product can be measured fluorometrically. Only thrombin not bound by the heparin–AT III complex is available to cleave fibrin, thus yielding an indirect measure of heparin concentration.

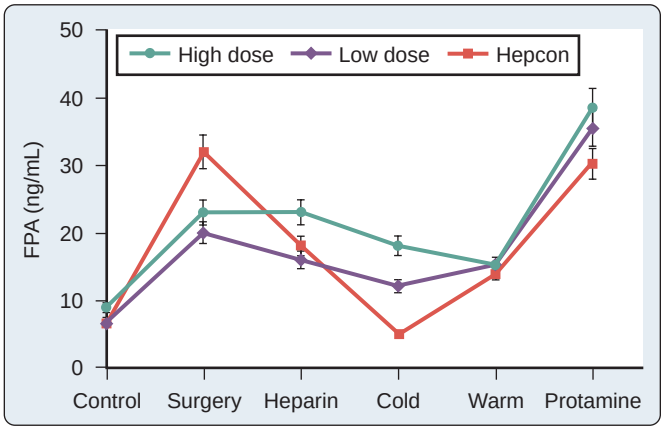


Fig. 19.9 Fibrinopeptide A *(FPA)* levels during cardiopulmonary bypass (CPB) were measured in three groups of patients before anesthetic induction *(Control)*, after heparin administration *(Heparin)*, at lowest temperature on CPB *(Cold)*, at esophageal temperature higher than 36°C *(Warm)*, and 5 minutes after completion of the protamine dose *(Protamine)*. Group 1, patients receiving heparin 300 IU/kg with activated coagulation time (ACT) heparin management; group 2, patients receiving heparin 250 IU/kg with ACT management; group 3, patients receiving 350 to 400 IU/kg with Hepcon (Medtronic Perfusion Services, Minneapolis, MN) heparin management. No differences were noted in FPA levels among groups except during cold CPB group 3 versus group 1; $P < 0.05$. *(From Gravlee GP, Haddon WS, Rothberger HK, et al. Heparin dosing and monitoring for cardiopulmonary bypass: a comparison of techniques with measurement of subclinical plasma coagulation.* J Thorac Cardiovasc Surg. *1990;99:518–527.)*

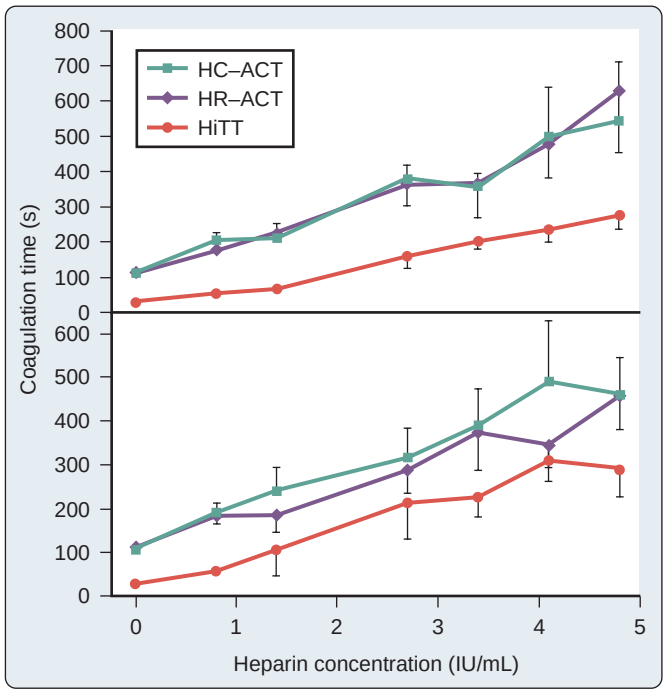


Fig. 19.10 Hemochron (International Technidyne Corp., Edison, NJ) activated coagulation time (ACT) *(HC-ACT; squares),* Hepcon (Medtronic Perfusion Services, Minneapolis, MN) *ACT (HR-ACT; diamonds),* and high-dose thrombin time *(HiTT; circles)* at different in vitro heparin concentrations. The relationship is linear in each group. *(From Wang JS, Lin CY, Karp RB. Comparison of high-dose thrombin time with activated clotting time for monitoring of anticoagulant effects of heparin in cardiac surgical patients.* Anesth Analg. *1994;79: 9–13.)*

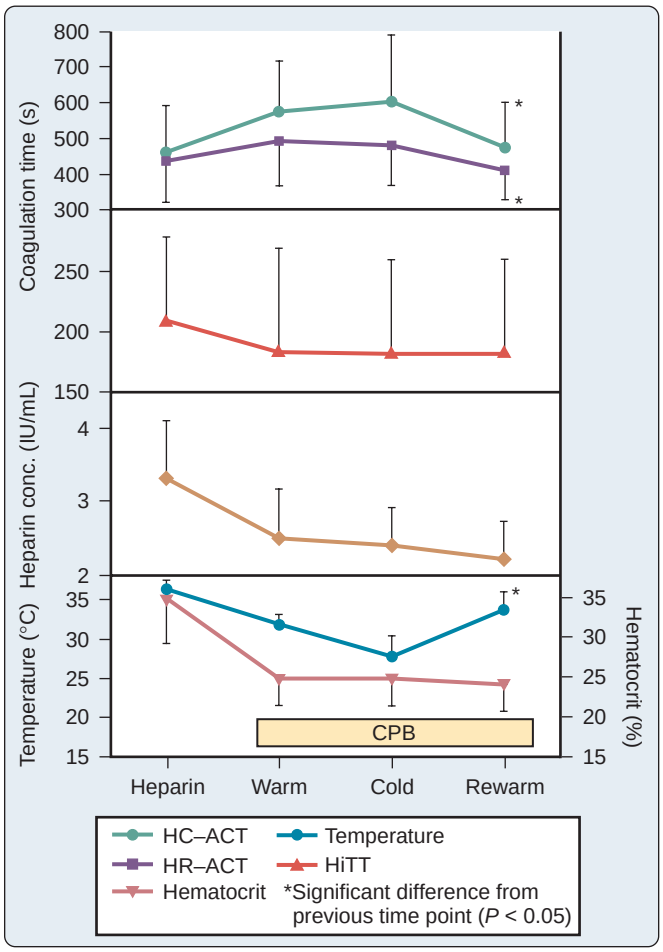


Fig. 19.11 Changes over time in the Hemochron (International Technidyne Corp., Edison, NJ) activated coagulation time (ACT) *(HC-ACT; green circles),* Hepcon (Medtronic Perfusion Services, Minneapolis, MN) ACT *(HR-ACT; squares),* and high-dose thrombin time *(HiTT; upward triangles)* in cardiac surgical patients. HiTT is unaffected by the changes in temperature *(blue circles)* and hematocrit *(downward triangles)* during cardiopulmonary bypass *(CPB).* The HC-ACT and HR-ACT increase with the initiation of CPB, and the heparin concentration *(Heparin conc.)* and HiTT decrease. *(From Wang JS, Lin CY, Karp RB. Comparison of high-dose thrombin time with activated clotting time for monitoring of anticoagulant effects of heparin in cardiac surgical patients.* Anesth Analg. *1994;79: 9–13.)*

High-Dose Thrombin Time

A functional test of heparin-induced anticoagulation that correlates well with heparin levels is the high-dose thrombin time (HiTT; International Technidyne Corp., Edison, NJ). The TT is a clotting time that measures the conversion of fibrinogen to fibrin by thrombin. The TT is prolonged by the presence of heparin and by hypofibrinogenemias or dysfibrinogenemias. Because the TT is sensitive to very low levels of heparin, a high dose of thrombin is necessary in the TT to assay the high doses of heparin used for CPB accurately. The HiTT is performed by adding whole blood to a prewarmed, prehydrated test tube that contains a lyophilized thrombin preparation. After the addition of 1.5 mL of blood, the tube is inserted into a Hemochron well, and the time to clot formation is measured. In vitro assays indicate that the HiTT is equivalent to the ACT in evaluation of the anticoagulant effects of heparin at heparin concentrations in the range of 0 to 4.8 IU/mL (Fig. 19.10). Unlike the ACT, the HiTT is not altered by hemodilution and hypothermia and has been shown to correlate better with heparin concentration than the ACT during CPB.[67] During CPB, heparin concentration and the HiTT decrease, whereas the Hemochron and the Hepcon ACTs increase (Fig. 19.11).

Another potential advantage of HiTT monitoring is for patients receiving aprotinin therapy. In the presence of heparin, aprotinin augments the celite ACT,[68] possibly because its kallikrein-inhibiting capacity prolongs activation of the intrinsic coagulation pathway by factor XIIa. This finding should not be interpreted to represent enhanced anticoagulation. The kaolin ACT is less affected by aprotinin therapy than the celite ACT, perhaps because kaolin, unlike celite, activates the intrinsic pathway by stimulation of factor XI directly.[69] Other investigators have suggested that kaolin binds to aprotinin and reduces the anticoagulant effect of aprotinin in vitro. However, the heparinized kaolin ACT is still somewhat prolonged in the presence of aprotinin. The HiTT is not affected by aprotinin therapy and can be used as a measure of heparinization for patients receiving aprotinin therapy during CPB.[68] The high-dose thromboplastin time is another measure of anticoagulation that is not affected by aprotinin therapy.[70] The high-dose thromboplastin time is a WBCT in which celite is replaced by 0.3 mL of rabbit brain thromboplastin to which 1.2 mL of blood is added. This test measures the time to coagulation by activation of the extrinsic pathway. This pathway of coagulation is also stimulated during pericardiotomy because of the rich thromboplastin environment of the pericardial cavity.

Heparin Neutralization

Protamine Effects on Coagulation Monitoring

Reversal of heparin-induced anticoagulation is most frequently performed with protamine. Biologically, protamine binds to positively charged groups such as phosphate groups and may have important properties in angiogenesis and immune function. Different successful dosing plans have been proposed.[71,72] The recommended dose of

protamine for heparin reversal is 1 to 1.3 mg protamine per 100 IU heparin; however, this dose often results in a protamine excess.

Protamine injection causes adverse hemodynamic effects.[73] Protamine reactions have been classified into three types.[74] The most common is the type I reaction, characterized by hypotension. Type II (immunologic) reactions are categorized as IIA (anaphylaxis), IIB (anaphylactoid), and IIC (noncardiogenic pulmonary edema). Type III reactions are heralded by hypotension and catastrophic pulmonary hypertension leading to right-sided heart failure.[38,61,75]

In addition to hemodynamic sequelae, protamine has adverse effects on coagulation.[76] Large doses prolong the WBCT and the ACT, possibly by thrombin inhibition.[77] In animals and in humans, protamine has been associated with thrombocytopenia, likely because of activation of the complement cascade.[73] The anticoagulant effect of protamine also may be caused by inhibition of platelet aggregation, alteration in the platelet surface membrane, or depression of the platelet response to various agonists.[77–79] These alterations in platelet function result from the presence of the heparin-protamine complex, not protamine alone. Protamine-heparin complexes activate AT III in vitro and result in complement activation. The anticoagulant effects of free protamine occur when protamine is given in doses in excess of those used clinically; however, the risk that free protamine causes a hemostatic defect is small, given the rapid clearance of protamine relative to heparin.

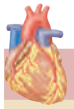
Monitoring for Heparin Rebound

The phenomenon referred to as heparin rebound describes the re-establishment of a heparinized state after heparin has been neutralized with protamine. Various explanations for heparin rebound have been proposed.[9,65,80,81] The most commonly postulated explanation is that rapid distribution and clearance of protamine occur shortly after protamine administration, thus leaving unbound heparin remaining after protamine clearance. Furthermore, endogenous heparin antagonists have an even shorter life span than protamine and are eliminated rapidly, resulting in free heparin concentrations. Also possible is the release of heparin from tissues considered heparin storage sites (endothelium, connective tissues). Endothelial cells bind and depolymerize heparin through PF4. Uptake into the cells of the reticuloendothelial system, vascular smooth muscle, and extracellular fluid may account for the storage of heparin that contributes to the reactivation of heparin anticoagulation referred to as heparin rebound.[9]

Residual low levels of heparin can be detected by sensitive heparin concentration monitoring in the first hour after protamine reversal and can be present for up to 6 hours postoperatively. The study by Gravlee and colleagues[65] suggested that without careful monitoring for heparin rebound in the postoperative period, increased bleeding as a result of heparin rebound may occur, specifically when larger doses of heparin have been administered. Monitoring for heparin rebound can be accomplished using tests that are sensitive to low levels of circulating heparin.[61,66,82,83] These tests are also useful monitors for confirmation of heparin neutralization at the conclusion of CPB (see later).

Heparin Neutralization Monitors

To administer the appropriate dose of protamine at the conclusion of CPB, it would be ideal to measure the concentration of heparin present and give the dose of protamine necessary to neutralize only the circulating heparin. As a result of heparin metabolism and elimination, which vary considerably among individual patients, the dose of protamine required to reverse a given dose of heparin decreases over time. Furthermore, protamine antagonizes the anti–factor IIa effects of heparin more effectively than the anti–factor Xa effects and thus varies in its potency depending on the source of heparin and its anti–factor IIa properties. Administration of a large fixed dose of protamine or a dose based on the total heparin dose given is no longer the standard of care and may result in an increased incidence of protamine-related adverse effects. An optimal dose of protamine is desired because unneutralized heparin results in clinical bleeding, and an excess of protamine may produce undesired coagulopathy. The use of individualized protamine dose-response curves uniformly results in a reduced protamine dose and has been shown to reduce postoperative bleeding.[58,82] One such dose-response test, the Hemochron PRT test, is an ACT performed on a heparinized blood sample that contains a known quantity of protamine. With knowledge of the ACT, PRT, and the estimated blood volume of the patient, the protamine dose needed to neutralize the existing heparin level can be extrapolated. The Hepcon instrument also has a PRT, which is the protamine titration assay. The chamber that clots first contains the dose of protamine that most closely approximates the circulating dose of heparin. The protamine dose required for heparin neutralization is calculated on the basis of a specified heparin/protamine dose ratio by measuring the circulating heparin level.



BOX 19.3 HEPARIN NEUTRALIZATION

- The most benign form of bleeding after cardiac surgical procedures results from residual heparinization.
- Treatment is with either protamine or another heparin-neutralizing product.
- Transfusion of allogeneic blood products is rarely indicated.
- Residual heparin can be measured by using the following:
  - A protamine titration assay
  - A heparin neutralized thrombin time assay
  - A heparinase activated coagulation time (ACT) compared with ACT
  - Any other heparinase test that compares itself with the test without heparinase added

At the levels of heparinization needed for cardiac surgical procedures, tests that are sensitive to heparin become unclottable. The ACT is relatively insensitive to heparin and is ideal for monitoring anticoagulation at high heparin levels, but it is too insensitive to detect incomplete heparin neutralization accurately. Reiner and associates[84] showed that the ACT had a high predictive value for adequate anticoagulation (confirmed by laboratory aPTT) when the ACT was longer than 225 seconds but was poorly predictive for inadequate anticoagulation when the ACT was shorter than 225 seconds. The low levels of heparin present when heparin is incompletely neutralized are best measured by other, more sensitive tests of heparin-induced anticoagulation, such as heparin concentration, aPTT, and TT. Thus, after CPB, confirmation of return to the unanticoagulated state should be performed with a sensitive test for heparin anticoagulation[85–88] (Box 19.3).

Thrombin Time

The TT is the time it takes for the conversion of fibrinogen to fibrin clot when blood or plasma is exposed to thrombin. Fibrin strands form in seconds. Detection of fibrin formation with standard laboratory equipment involves incubation of the blood or plasma sample within the chamber in which an optical or electrical probe sits. A detector senses either movement of the probe or the creation of an electrical field (electrical detection) because of fibrin formation and hence signals the end of the test. International Technidyne manufactures a Hemochron POC TT test that uses a lyophilized preparation of thrombin in a Hemochron test tube to which 1 mL of blood is added. Identification of fibrin formation in a Hemochron machine uses the standard Hemochron technology described previously with the ACT. The manufacturer suggests that the normal TT is 39 to 53 seconds for whole blood and 43 to 68 seconds for citrated blood. Because the TT specifically measures the activity of thrombin, it is very sensitive to heparin-induced enhancement of AT III activity. It is a useful test in the post-CPB period for differentiating the cause of bleeding when both the PT and the aPTT are prolonged because it excludes the intrinsic and extrinsic coagulation pathway limbs and evaluates the conversion of factor I to factor Ia. The TT is increased in the presence of heparin,

hypofibrinogenemia, dysfibrinogenemia, amyloidosis, or antibodies to thrombin.[89] The TT is also increased in the presence of fibrin degradation products if the systemic fibrinogen concentration is low.

The TT is an appropriate laboratory test for monitoring the degree of fibrinolytic activity in patients receiving thrombolytic therapy. Measurements of the quantity of fibrinogen, plasminogen, or plasma proteins generated during fibrinolysis are difficult to interpret and yield no prognostic information for dose adjustments. Thrombolytic agents activate the fibrinolytic system to generate plasmin, which then causes clot dissolution and decreases the quantities of fibrinogen and fibrin. This effect can be monitored using the TT. The TT should be measured at baseline (before institution of fibrinolytic therapy) and 3 to 4 hours after therapy is initiated. If the TT is prolonged by 1.5 to 5 times the baseline value, therapy should be considered effective. If the TT is prolonged by greater than seven times the baseline value, an increased risk for bleeding is incurred; if the TT is not prolonged at all, therapy has failed to activate fibrinolysis.

Bedside Tests of Heparin Neutralization

The HMS Plus Hemostasis Management System (Medtronic Perfusion Services, Minneapolis, MN) measures heparin concentration by a protamine titration assay. Cartridges with varying ranges of protamine concentration are available for use. The cartridge with the lower concentration of protamine in the titration is useful for the detection of residual circulating heparin and is sensitive to levels of heparin as low as 0.2 IU/mL. Whole-blood PT and aPTT assays are sensitive to deficiencies in coagulation factors and overly sensitive to low levels of heparin (aPTT); they lack specificity in assessing residual heparinization. The heparin-neutralized thrombin time (HNTT) is a TT assay with a small dose of protamine sufficient to neutralize 1.5 IU/mL of heparin. Because the TT is increased in the presence of heparin, hypofibrinogenemia, or dysfibrinogenemia, HNTT and TT should be performed together to discriminate among these three causes. A normal HNTT in the presence of an increased TT virtually confirms residual heparin effect and indicates the need for protamine administration. If the HNTT is prolonged as well as the TT, the cause of bleeding may be attributed either to a fibrinogen problem or to a concentration of heparin greater than that which could be neutralized by the HNTT. In a study comparing bedside monitors of anticoagulation, the TT-HNTT difference bore a significant correlation with the aPTT increase. Using the line of best fit, an aPTT elevation of 1.5 times the control corresponded to a 31-second difference in the TT and HNTT, thus indicating a convenient threshold value of TT-HNTT for the administration of protamine.[89]

Platelet Factor 4

A component of the α granule of platelets, PF4 binds to and inactivates heparin. The physiologic role of PF4 is that at the site of vascular injury, PF4 is released from platelets, binds heparin (or heparin-like compounds), and promotes thrombin and clot formation. PF4 adequately neutralizes heparin inhibition of factors Xa and IIa and may be superior to protamine in neutralizing anti–factor Xa effects. Animal data suggest that PF4 is devoid of the adverse hemodynamic effects seen with protamine and that it may be able to be infused more rapidly.[90,91] Heparin reversal has been documented by WBCT, ACT, and heparin concentration at a PF4 concentration of 40 IU/mL, approximately twice the reversal dose of protamine.[83] Levy and colleagues[92] subsequently found the reversal dose of PF4 to be approximately 60 IU/mL and documented similar ACT and viscoelastic measurements of clot formation compared with protamine.

Heparinase

Heparinase (Neutralase I) is an enzyme that specifically degrades heparin by catalyzing cleavage of the saccharide bonds found in the heparin molecule. As demonstrated by the ACT, heparinase in a dose of 5 mg/kg has been shown to neutralize heparin effects successfully in healthy volunteers and in patients who have undergone CPB. A dose of 7 mg/kg has been demonstrated to be even more efficacious in returning ACT to baseline values. Doses sufficient to neutralize a dose of 300 IU/kg of heparin had no significant hemodynamic effects in a canine model.[93] Investigators have not found any platelet-depressive effects of heparinase, in contrast to the well-documented platelet dysfunction associated with protamine therapy.[78] Return to the unanticoagulated state after the use of heparinase has been confirmed using ACT monitoring or heparin concentration monitoring.

Tests of Coagulation

Standard tests of coagulation, the PT and the aPTT, are performed on plasma to which the anticoagulant citrate has been added. Because these tests are performed on plasma, they require centrifugation of blood and generally are not feasible for use at the bedside. The aPTT tests the integrity of the intrinsic and the final coagulation pathways and is more sensitive to low levels of heparin than the ACT. Factors IX and X are most sensitive to heparin effects, and thus the aPTT is prolonged even at very low heparin levels. The test uses a phospholipid substance to simulate the interaction of the platelet membrane in activating factor XII. (Thromboplastin is a tissue extract containing tissue factor and phospholipid. The term *partial thromboplastin* refers to the use of the phospholipid portion only.) The aPTT is prolonged in the presence of the following deficiencies: factors XII, XI, IX, and VIII; HMWK (high-molecular-weight kininogen); and kallikrein. The aPTT reaction is considerably slower than the PT, and an activator such as celite or kaolin is added to the assay to speed activation of factor XII. After incubation of citrated plasma with phospholipid and activator, calcium is added, and the time to clot formation is measured. Normal aPTT is 28 to 32 seconds, which often is expressed as a ratio with a control plasma sample from the same laboratory. This is important because partial thromboplastin reagents have different sensitivities to heparin, and many have nonlinear responses to heparin in various concentration ranges.

The PT measures the integrity of the extrinsic and common coagulation pathways. The PT is prolonged in the presence of factor VII deficiency, warfarin sodium (Coumadin) therapy, or vitamin K deficiency. Large doses of heparin also prolong the PT because of factor II inactivation. The addition of thromboplastin to citrated plasma results in activation of extrinsic coagulation. After a 3-minute incubation and recalcification, the time to clot formation is measured and is recorded as the PT. Normal PT is 12 to 14 seconds; however, because of differences in the quality and lot of the thromboplastin used, absolute PT values are not standardized and are difficult to compare across different testing centers. The international normalized ratio (INR) has been adopted as the standard for coagulation monitoring. The INR is an internationally standardized laboratory value that is the ratio of the patient's PT to the result that would have been obtained if the International Reference Preparation had been used instead of the laboratory reagents. Each laboratory uses reagents with a specific sensitivity (International Sensitivity Index [ISI]) relative to the International Reference Preparation. The ISI of a particular set of reagents is provided by each manufacturer so that the INR can be reported.

Bedside Tests of Coagulation

The PT and aPTT tests performed on whole blood are available for use in the operating room or at the bedside. The Hemochron PT test tube contains acetone-dried rabbit brain thromboplastin to which 2 mL of whole blood is added, and the tube is inserted into a standard Hemochron machine. Normal values range from 50 to 72 seconds and are automatically converted by a computer to the plasma-equivalent PT and INR. The Hemochron aPTT contains kaolin activator and a platelet factor substitute and is performed similarly to the PT. The aPTT is sensitive to heparin concentrations as low as 0.2 IU/mL and displays a linear relationship with heparin concentration up to 1.5 IU/mL.

The former Thrombolytic Assessment System (TAS; Pharmanetics, Raleigh, NC), now the Cascade POC (Helena, Beaumont, TX), previously discussed for its ability to measure heparin by the HMT, also measures the PT and aPTT. The sample is added to a cartridge containing paramagnetic iron oxide particles, which oscillate in a magnetic field. Specific activating reagents are used for each test. The analytes used include rabbit brain thromboplastin for the PT, aluminum magnesium silicate for the aPTT, and celite for the HMT. The blood moves by capillary action and mixes with paramagnetic iron oxide particles and reagent within the testing chamber. The decreased movement of the particles is detected optically as the sample clots, and the resultant time is displayed in seconds and as INRs for the PT.

The CoaguChekProDM (Roche Diagnostics, Mannheim, Germany; former CoaguChek-plus, and formerly Ciba Corning Biotrack 512) coagulation monitor for evaluating the bedside PT and aPTT, uses 0.1 mL of whole blood placed into a disposable plastic cartridge for either the PT or aPTT. The sample is drawn by capillary action into a heated chamber where exposure to reagents occurs. The PT uses rabbit brain thromboplastin. The aPTT uses soybean phosphatide as the platelet substitute and bovine brain sulfatide as the activator. From the reaction chamber, blood traverses a reaction path where clot formation is detected by a laser optical system. The resulting time to clot formation is converted to a ratio of the control value by a microprocessor that has control values encoded.

Many investigators studied the former Ciba Corning Biotrack system for monitoring anticoagulation in different clinical situations. For patients receiving oral anticoagulant therapy, the Biotrack 512 monitor was found to be suitable for monitoring the PT and INR. Reiner and associates[84] compared the bedside Biotrack aPTT with the laboratory aPTT and heparin level in patients receiving therapeutic heparinization after interventional cardiac catheterization. These investigators found a strong correlation ($r = 0.89$) between the Biotrack aPTT and the aPTT from the hospital laboratory. The correlation between Biotrack aPTT and heparin level was not strong, probably because of the many other factors such as heparin neutralization and clearance that affect the heparin concentration in vivo.[94] Another study in patients receiving heparin compared the Ciba Corning Biotrack aPTT assay with the standard laboratory aPTT and documented that Biotrack was less sensitive to heparin than the laboratory aPTT; however, the correlation coefficient of these two tests was $r = 0.82$.[95] In patients receiving warfarin therapy, the Biotrack aPTT was more sensitive than the laboratory aPTT and yielded consistently greater results for aPTT value. In another study in patients undergoing anticoagulation for nonsurgical applications, the bedside aPTT was similar to the standard aPTT in its prediction of treatment in simple therapeutic algorithms. However, in more complex clinical situations, less agreement was noted between the bedside aPTT and the laboratory aPTT.[96]

In a comparison of bedside coagulation monitors after cardiac surgical procedures, Reich and associates[89] documented acceptable accuracy and precision levels for the Hemochron and Ciba Corning Biotrack PTs in comparison with the standard laboratory plasma PT, thus making them potentially valuable for use in the perioperative period. Neither the Hemochron aPTT nor the Ciba Corning aPTT reached this level of clinical competence compared with standard laboratory tests. Other investigators documented that this monitor seems to be more precise for the PT than for the aPTT.[97] Because of rapid turnaround times, these POC coagulation monitors may be useful in predicting which patients will bleed after cardiac surgical procedures,[98] and they have also been used successfully in transfusion algorithms to decrease the number of allogeneic blood products given to cardiac surgical patients.[99,100]

Measures of Fibrin Formation

The "Tenase complex" is the group of factors and cofactors that includes factor Xa, platelet-bound factor Va, platelet factor 3, and calcium. All adhere on the platelet surface and catalyze the cleavage of prothrombin (factor II) to thrombin (factor IIa). Thrombin then catalyzes the cleavage of fibrinogen to form fibrin monomer and fibrinopeptide A and fibrinopeptide B. These end products of fibrinogen cleavage are commonly measured serum markers that help quantify the degree of coagulation that occurs in certain experimental or clinical situations.

One such experimental situation is the use of heparin-bonded extracorporeal circuits during CPB with the expectation that thrombin activation and fibrin formation will be minimized. Coating of the extracorporeal circuit with the heparin ligand makes the circuit more biocompatible such that the inflammatory response elicited is diminished or nonexistent. Heparin-bonded circuits have been extensively studied and considered advantageous because of their ability to reduce the inflammatory response to CPB. Human studies reveal decreases in enzymes that mark leukocyte activation, thus showing a reduction in the whole-body inflammatory response similar to that seen with leukocyte-depletion techniques (see Chapters 31–33).[101–103]

Further enhancements in biocompatibility include less leukocyte activation and preserved platelet function. Reductions in thrombin generation have been difficult to document.[104] The increases in the fibrinogen fragment F1.2 and in D-dimer levels when heparin-coated circuits are used are similar to those seen when uncoated circuits are used.[105,106] Human studies have documented less bleeding and reduced transfusion requirements with the use of a heparin-coated extracorporeal circulation when these circuits are used in conjunction with a reduced systemic heparin dose.[107,108] In this circumstance, markers of thrombin generation are increased even greater than those in patients treated with full-dose heparin and uncoated circuits. In fact, increases are seen in fibrinopeptide A, prothrombin fragment F1.2, thrombin–AT III complexes, D-dimers, and plasminogen activators during CPB and after protamine administration regardless of whether heparin-coated circuits are used and regardless of heparin dose.[109] Despite this finding, the use of reduced heparin doses and coated circuitry has resulted in diminished transfusion requirements and reduced chest tube drainage volumes without evidence of complications.[106,110] Because microvascular coagulation is not fully inhibited, the use of a reduced dose of heparin cannot be systematically advocated and should be implemented with caution.

Fibrinogen Level

Fibrinogen concentration is traditionally measured using clottable protein methods, end-point detection techniques, or immunochemical tests. Of the clottable protein methods, the most commonly used fibrinogen assay relies on the method of Clauss. This method involves a 10-fold dilution of plasma, which ensures that fibrinogen is the rate-limiting step in clot formation. Subsequently, an excess of thrombin is added to the sample, and the time to clot formation is measured. The clotting time is inversely related to the fibrinogen concentration. Because this assay relies on detection of actual clot, it can be affected by fibrin degradation products, polymerization inhibitors, or other inhibitors of fibrin formation. Given the thrombin excess, small clinical concentrations of heparin do not affect fibrinogen determination according to the Clauss technique.

A whole-blood POC fibrinogen assay is available using the Hemochron system. The specific test tube contains a lyophilized preparation of human thrombin, snake venom extract, protamine, buffers, and calcium stabilizers. The test tube is incubated with 1.5 mL of distilled water and is heated in the Hemochron instrument for 3 minutes. Whole blood is placed into a diluent vial, where it is 50% diluted, and from this vial, 0.5 mL of diluted whole blood is placed into the specific fibrinogen test tube. The clotting time is measured using standard Hemochron technology, as described previously. The fibrinogen concentration is determined by comparison with a standard curve for this test. Normal fibrinogen concentration of 180 to 220 mg/dL correlates with a clotting time of 54 ± 2.5 seconds. Fibrinogen deficiency of 50 to 75 mg/dL correlates with a clotting time of 150 ± 9.0 seconds.

Unlike the method of Clauss, the end-point detection assays rely on the detection of changes in turbidity of plasma when clot is formed.

This technique does not require the maintenance of a stable cross-linked fibrin product (is not functional) and therefore does not report underestimated fibrinogen measurements in the presence of inhibitors. Immunochemical measures of fibrinogen concentration comprise a direct and accurate measurement technique; however, they are expensive and time consuming and require specialized laboratory facilities. Coagulation assays and fibrinogen assays can also be performed using viscoelastic testing, as discussed later.

Monitoring Fibrinolysis

Fibrinolysis, the dissolution of fibrin, is the normal modifier of hemostasis that ensures that coagulation does not proceed unchecked. It occurs in the vicinity of a clot and dissolves clot when local endothelial healing occurs. Fibrinolysis is mediated by the serine protease plasmin, which is the product of the cleavage of plasminogen by tissue plasminogen activator (tPA). Fibrinolysis is a normal phenomenon in response to clot formation; when it occurs systemically, it represents a pathologic condition.

Fibrinolysis can be primary or secondary. Primary fibrinolysis occurs when fibrinolytic activators are released or produced in excess and does not represent a response to the coagulation process. Examples of primary fibrinolysis include the release of plasminogen activators during liver transplantation operations and the exogenous administration of fibrinolytic agents such as streptokinase. During primary fibrinolysis, plasmin cleaves fibrinogen, to yield fibrinogen degradation products. These end products can be measured using immunologic techniques.

When fibrinolysis is a result of enhanced activation of the coagulation system, secondary fibrinolysis ensues. A well-known extreme form of secondary fibrinolysis is seen during disseminated intravascular coagulation, in which both systemic coagulation and fibrinolysis occur in excess. During CPB, fibrinolysis is most likely secondary to the microvascular coagulation that is occurring despite attempts at suppression using high doses of heparin.[111,112]

Fibrinolysis can be identified through either direct measurement of the clot lysis time (manual or viscoelastic tests) or measurement of the end products of fibrin degradation. The manual clot lysis time simply involves the placement of whole blood into a test tube. This blood clots in a matter of minutes. Visual inspection determines the end point for observation of clot lysis, and this time period is the clot lysis time. This technique is time consuming and requires constant observation by the person performing the test.

Viscoelastic Tests

Viscoelastic tests measure the unique properties of the clot as it is forming, organizing, strengthening, and lysing. As a result, fibrinolysis determination by this method requires that time elapse during which clot formation is occurring. Clot lysis parameters can be measured subsequent to clot formation and platelet-fibrin linkages. For this reason, viscoelastic tests often require longer than 1 hour to detect the initiation of fibrinolysis; however, if fibrinolysis is enhanced, results often can be obtained in 30 minutes.

End Products of Fibrin Degradation

Other methods for quantifying fibrinolysis include measurement of the end products of fibrin degradation. Fibrin degradation products are the result of the cleavage of fibrin monomers and polymers and can be measured using a latex agglutination assay. When plasmin cleaves cross-linked fibrin, dimeric units are formed that comprise one D-domain from each of two adjacent fibrin units. These "D-dimers" are frequently measured by researchers in clinical and laboratory investigations. They are measured by either enzyme-linked immunosorbent assays or latex agglutination techniques and thus are not available for on-site use. Controversy still exists regarding whether D-dimer levels or fibrin degradation products are the most sensitive test for detecting fibrinolysis, but most investigators agree that the presence of D-dimers is the most specific test for cross-linked fibrin degradation.[113]

Monitoring the Thrombin Inhibitors

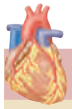
A newer class of drugs, the selective thrombin inhibitors, provides a viable alternative to heparin anticoagulation for CPB. These agents include hirudin, argatroban, bivalirudin, and experimental agents. A major advantage of these agents over heparin is that they can effectively inhibit clot-bound thrombin in an AT III–independent fashion.[114] The platelet thrombin receptor is believed to be the focus of thrombin's procoagulant effects in states of thrombosis such as after coronary artery angioplasty. Because surface-bound thrombin is more effectively suppressed, thrombin generation can be reduced at lower levels of systemic anticoagulation than are achieved during anticoagulation by the heparin–AT III complex. This translates into less bleeding despite the lack of a clinically useful antidote for the thrombin antagonists.[115,116] Thrombin antagonists are also not susceptible to neutralization by PF4 and thus are not neutralized at endothelial sites where activated platelets reside. They are also useful in patients with HIT, in whom the administration of heparin and subsequent antibody-induced platelet aggregation would be dangerous.[117] The lack of a potent antidote (eg, protamine) and a prolonged duration of action are the major reasons that hirudin and other thrombin inhibitors have not found widespread clinical acceptance for use in CPB procedures (see Chapter 35).

Hirudin

Hirudin, a coagulation inhibitor isolated from the salivary glands of the medicinal leech *(Hirudo medicinalis)*, is a potent inhibitor of thrombin that, unlike heparin, acts independently of AT III and inhibits clot-bound thrombin, as well as fluid-phase thrombin. Hirudin does not require a cofactor and is not susceptible to neutralization by PF4. This would seem to be beneficial in patients in whom platelet activation and thrombosis are potential problems. Recombinant hirudin was administered as a 0.25 mg/kg bolus and an infusion to maintain the hirudin concentration at 2.5 μg/mL, as determined by the ecarin clotting time in studies by Koster and colleagues.[118–126] The ecarin clotting time, modified for use in the Cascade POC analyzer, has been used in large series of patients with HIT.[118–123] Compared with standard treatment with heparin or LMWHs, recombinant hirudin–treated patients maintained platelet counts and hemoglobin levels, and had few bleeding complications, when renal function was normal.[124,125] Hirudin is a small molecule (molecular weight, 7 kDa) that is eliminated by the kidneys and is easily hemofiltered at the end of CPB.[126] In patients with abnormal renal function, bivalirudin is preferable to hirudin. An alternative treatment in this setting would be administration of UFH with a platelet antagonist, such as tirofiban, to prevent the hyperaggregability of platelets that occurs in patients with HIT.[125]

Bivalirudin

Bivalirudin is a small, 20–amino acid molecule with a plasma half-life of 24 minutes. It is a synthetic derivative of hirudin and thus acts as a direct thrombin inhibitor. Bivalirudin binds to both the catalytic binding site and the anion-binding exosite on fluid-phase and clot-bound thrombin. The part of the molecule that binds to thrombin is actually cleaved by thrombin itself, so the elimination of bivalirudin activity is independent of specific organ metabolism. Bivalirudin has been used successfully as an anticoagulant agent in interventional cardiology procedures as a replacement for heparin therapy. In fact, in interventional cardiology, bivalirudin has been associated with less bleeding and equivalent ischemic outcomes compared with heparin in combination with a platelet inhibitor.[127] The reason for these effects may be that bivalirudin is both an antithrombin anticoagulant and an antithrombin at the level of the platelet. Merry and associates[128] showed equivalence with regard to bleeding outcomes and an improvement in graft flow after off-pump coronary artery bypass operations



BOX 19.4 THROMBIN INHIBITORS

- These anticoagulant drugs are superior to heparin.
- They inhibit both clot-bound and soluble thrombin.
- They do not require a cofactor, activate platelets, or cause immunogenicity.
- These drugs include hirudin, argatroban, and bivalirudin.
- Heparin remains an attractive drug because of its long history of safe use and the presence of a specific drug antidote, protamine.

when bivalirudin was used (0.75 mg/kg bolus, 1.75 mg/kg/h infusion). Case reports confirm the safety of bivalirudin use during CPB.[129–131]

Multicenter clinical trials comparing bivalirudin with heparin anticoagulation in off-pump coronary artery bypass operations[132] and in CPB[133] demonstrated "noninferiority" of bivalirudin. Efficacy of anticoagulation and markers of blood loss were similar in the two groups, a finding suggesting that bivalirudin can be a safe and effective anticoagulant agent in CPB. These multicenter trials used the ACT as the monitor of anticoagulant activity intraoperatively, but ideal monitoring is performed using the ecarin clotting time, as seen with hirudin.[134] The ecarin clotting time has a closer correlation with anti–factor IIa activity and plasma drug levels than does the ACT. For this reason, standard ACT monitoring during antithrombin therapy is not preferred if ecarin clotting time can be measured. A plasma-modified ACT can be used to assay the anticoagulant effects of the thrombin inhibitor drugs more accurately than ACT. This test requires the addition of exogenous plasma and thus is not readily available as a POC assay.[135]

The anticoagulant effects of the thrombin antagonists can be monitored using the ACT, aPTT, or TT. The bleeding time (BT) also may be prolonged. In a canine CPB model, dogs receiving a synthetic thrombin inhibitor had less postoperative blood loss and greater platelet counts than those receiving heparin; however, those who received a large dose of the thrombin inhibitor still had ACT increases at 2 hours after CPB.[136] No differences in hemodynamics were noted in the groups.

Bivalirudin has been compared favorably with heparin in patients undergoing coronary angioplasty for unstable angina.[137] The half-life of aPTT prolongation is approximately 40 minutes, and reductions in formation of fibrinopeptide A are evidence of thrombin inhibition and fibrinogen preservation. Careful monitoring should be used because of a possible rebound prothrombotic state after cessation of therapy that could lead to recurrence of anginal symptoms (Box 19.4).

Evaluation of Prolonged Activated Partial Thromboplastin Time

The first step in evaluation of a prolonged aPTT is the elimination of heparin contamination as a cause of the elevation. Other potential causes of an elevated aPTT are the presence of factor deficiencies or inhibitors of coagulation. Factor deficiencies can be ruled out by mixing studies in which patient plasma is mixed with an equal volume of plasma derived from healthy volunteers. The test results should return to normal if a deficiency is present because mixing with normal plasma yields greater than the required concentrations of coagulation proteins for adequate clotting. If an inhibitor is present, mixing studies will not return the aPTT to normal values.

Inhibitors of factors VIII and IX and the "lupus anticoagulants" are the most common inhibitors encountered. The lupus anticoagulants are antiphospholipid antibodies that react with the phospholipid surfaces required for coagulation, hence the prolongation of the clotting time. In patients who do not have systemic lupus erythematosus, this syndrome is referred to as primary antiphospholipid syndrome. Testing for this inhibitor has been performed using the aPTT or a dilute viper venom time. The dilute viper venom time consists of activation of factor X by venom and measurement of the clotting time, which will be prolonged if an inhibitor is present. Immunologic assays for anticardiolipin antibodies also are available. Patient serum is incubated with solid-phase cardiolipin, and bound immunoglobulin is measured.

Monitoring Platelet Function

Circulating platelets adhere to the endothelium by platelet surface receptors that bind exposed collagen and become activated. This process initiates platelet activation because collagen is a potent platelet activator. The unstimulated platelet, which is discoid, undergoes a conformational change when activated. The activated platelet is spheric, extrudes pseudopodia, and expresses an increased number of activated surface receptors that can be measured to quantify the degree of platelet reactivity. The intensity of this platelet activation occurs in proportion to the quantity and nature of the platelet stimulus and increases in a graded fashion with increasing concentrations of agonists. The glycoprotein IIb/IIIa (GpIIb/IIIa) receptor is the primary receptor responsible for fibrinogen binding and the formation of the platelet plug.

Platelet Count

Numerous events during cardiac surgical procedures predispose patients to platelet-related hemostasis defects. The two major categories are thrombocytopenia and qualitative platelet defects. Thrombocytopenia commonly occurs during cardiac surgical procedures as a result of hemodilution, sequestration, and destruction by nonendothelial surfaces. Platelet counts commonly decline to 100,000/μL or less; however, the final platelet count greatly depends on the starting value and the duration of platelet-destructive interventions (ie, CPB).[138] Between 10,000 and 100,000/μL, the BT decreases directly; however, at platelet counts greater than 50,000/μL, neither the BT nor the platelet count has any correlation with postoperative bleeding in cardiac surgical patients. In contrast, platelet size or mean platelet volume does have some correlation with hemostatic function. Larger, younger platelets are more hemostatically active than smaller ones.[139] Mean platelet volume multiplied by the platelet count gives an estimation of overall platelet mass and is referred to as the "plateletcrit." It is important to appreciate the inverse relationship between platelet volume and platelet count when using a measure such as the plateletcrit to assess the viability of the existing platelet population. Because the mean platelet volume depends on the method of specimen collection, the anticoagulant used, and temperature of the storage conditions, its reproducibility depends on standardized laboratory procedures.

Qualitative platelet defects occur more commonly than thrombocytopenia during CPB. The range of possible causes of platelet dysfunction includes traumatic extracorporeal techniques, pharmacologic therapy, hypothermia, and fibrinolysis; the hemostatic insult increases with the duration of CPB.[140] The use of bubble oxygenators (although infrequent), noncoated extracorporeal circulation, and cardiotomy suctioning causes various degrees of platelet activation, initiates the release reaction, and partly depletes platelets of the contents of their α granules. Many of these changes are only transiently associated with CPB. Khuri and colleagues[141] characterized the hematologic changes associated with CPB in a group of 85 patients. Whereas the platelet count declined and reached a plateau at 2 hours after CPB, mean platelet volume reached its nadir at 2 hours after CPB and then began to increase during the ensuing 72 hours[141] (Figs. 19.12 and 19.13). The relative thrombocytopenia seen up to 72 hours after cardiac surgical procedures is not consistently associated with a bleeding diathesis. Similarly, the clotting proteins fibrinogen, factor VIII–von Willebrand factor, and factor VIII-C also increase to levels greater than baseline in the 2 to 72 hours after CPB (Fig. 19.14).

Large doses of heparin have been shown to reduce the ability of the platelets to aggregate and to reduce clot strength.[77] This effect is not reversed when protamine is administered; however, it may be

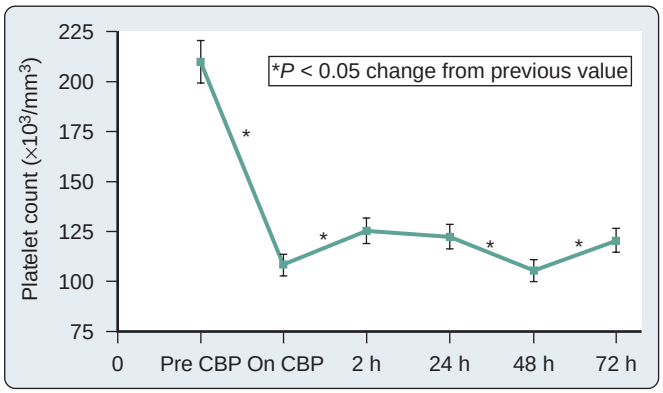


Fig. 19.12 Platelet count changes in patients undergoing cardiopulmonary bypass *(CPB)*. Significant decrease in platelet count occurs on initiation of CPB and remains until at least 72 hours postoperatively. *(From Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss.* J Thorac Cardiovasc Surg. *1992;104:94–107.)*

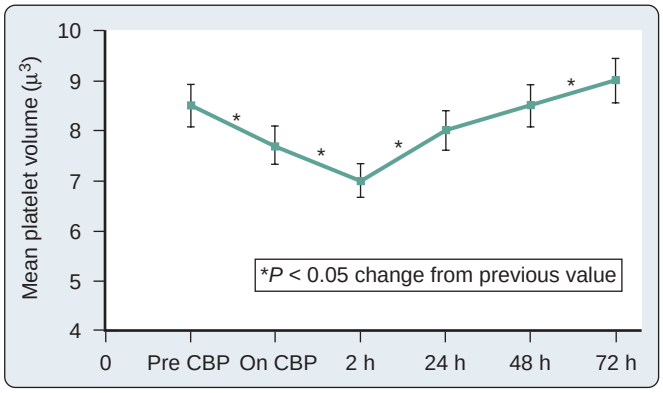


Fig. 19.13 Changes in mean platelet volume (MPV) in patients undergoing cardiopulmonary bypass *(CPB)*. The decrease in MPV that occurs during CPB returns to and exceeds baseline values at 24 hours postoperatively. *(From Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss.* J Thorac Cardiovasc Surg. *1992;104:94–107.)*

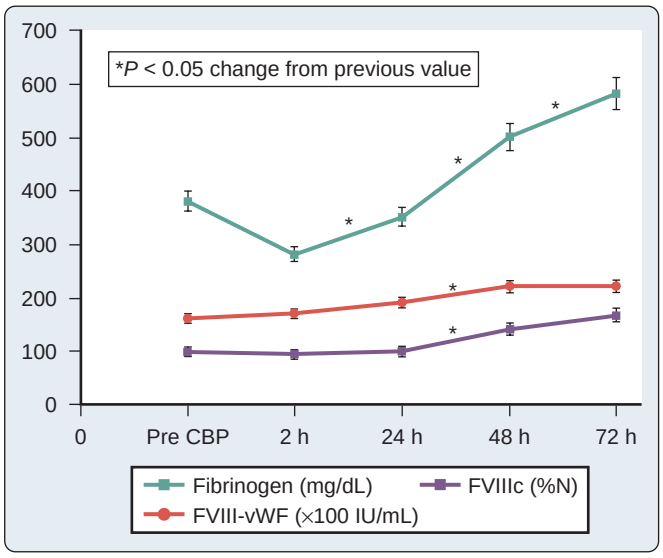
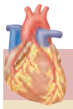


Fig. 19.14 Fibrinogen values *(green squares)* decrease during cardiopulmonary bypass *(CPB)*. All three clotting proteins increase to more than baseline levels in the 24 to 72 hours after CPB. FVIIIc, factor VIIIc *(purple squares)*; FVIII-vWF, factor VIII–von Willebrand factor *(circles)*. *(From Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss.* J Thorac Cardiovasc Surg. *1992;104:94–107.)*



BOX 19.5 PLATELET FUNCTION

- The platelet count does not correlate with bleeding after cardiac surgical procedures.
- Patients frequently have extreme degrees of thrombocytopenia but do not bleed because they have adequate platelet function.
- The measure of platelet function correlates temporally with the bleeding course seen after cardiac surgical procedures.
- The thromboelastogram maximal amplitude, mean platelet volume, and other functional platelet tests are useful in transfusion algorithms.

mitigated by the prophylactic administration of aprotinin or other platelet-protective drugs.[142] The adverse effects of heparin on platelet function may result from the ability of heparin to inhibit the formation of thrombin, the most potent in vivo platelet activator.[143] However, heparin also activates the fibrinolytic system, a system that, through plasmin and other activators, can depress platelet function through other mechanisms. In an extracorporeal baboon model, intravenous heparin administration resulted in increases in plasmin activity, in the quantity of immunoreactive plasmin light chain, and in immunoreactive fibrinogen fragment E.[144] In addition, various degrees of fibrinolysis occur after CPB. Circulating plasmin causes dissolution of the GpIb platelet receptor and decreases the adhesiveness of platelets. Because fibrinolysis is partly responsible for the platelet dysfunction seen after heparin administration and CPB, the efficacy of antifibrinolytic agents as hemostatic drugs can be better appreciated. In addition to reducing platelet adhesiveness to von Willebrand factor, the fibrin degradation products formed depress platelet responsiveness to agonists.[145,146]

Protamine-heparin complexes and protamine alone also contribute to platelet depression after CPB. Mild-to-moderate degrees of hypothermia are associated with reversible degrees of platelet activation and platelet dysfunction.[147] Overall, the potential coagulation benefits of normothermic CPB compared with hypothermic CPB require further study in well-conducted randomized trials (Box 19.5).

Bleeding Time

The BT test is performed by creating a skin incision and measuring the time to clot formation by the platelet plug. The Ivy BT is performed on the volar surface of the forearm, above which a cuff is inflated to 40 mm Hg (above venous pressure). Two parallel incisions are made using a template, and the incisions are blotted with filter paper every 30 seconds until no further bleeding occurs. The time from incision to cessation of blood seepage is the template BT. The Duke BT is performed on the earlobe and has advantages for cardiac surgical procedures because the earlobe is more accessible and less likely to be subjected to the peripheral vasoconstriction seen after hypothermia. However, because neither the width or depth of the incision nor the venous pressure can be controlled in the Duke BT, the Ivy BT is considered the superior test. Normal BT is 4 to 10 minutes.

Numerous prospective blinded investigations confirmed that the BT has little or no value in predicting excessive hemorrhage after cardiac surgical procedures.[148] Even in patients receiving therapeutic doses of aspirin, an increase in the BT does not necessarily translate to an increase in mediastinal tube drainage or transfusions if reinfusion and blood conservation techniques are used aggressively. Substantial evidence indicates that platelet-directed therapy in the form of platelet transfusions or desmopressin acetate shortens a prolonged BT in

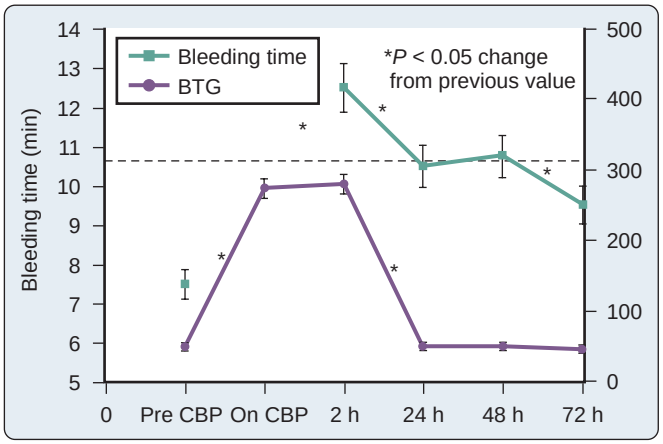


Fig. 19.15 Bleeding time *(squares)* increases on cardiopulmonary bypass *(CPB)* and remains increased until at least 72 hours postoperatively. However, platelet activation is maximal during CPB. The increase in β-thromboglobulin *(BTG; circles)*, indicating platelet activation, occurs on initiation of CPB and returns to baseline by 24 hours afterward. *(From Khuri SF, Wolfe JA, Josa M, et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss.* J Thorac Cardiovasc Surg. *1992;104:94–107.)*

patients with clinical hemorrhage.[149] In a study of 85 patients undergoing CPB, Khuri and associates[141] demonstrated that the BT becomes abnormal during CPB and does not return to baseline even by 72 hours postoperatively, whereas markers of platelet activation return to baseline by 24 hours postoperatively (Fig. 19.15). Although this type of data on the BT exists, the BT is considered by most investigators to be an antiquated test and is rarely used clinically.

Aggregometry

Activated platelets undergo aggregation, which is initially a reversible process. Activation also induces the release of substances from α and dense platelet granules and platelet lysosomes. Because platelet granules contain many platelet agonists, the release of granular contents further stimulates platelet activation and is responsible for the secondary phase of platelet aggregation. This secondary phase of platelet aggregation depends on the release of thromboxane and other substances from the platelet granules, is an energy-consuming process, and is irreversible.

Aggregometry is a useful research tool for measuring platelet responsiveness to a variety of different agonists. The end result, platelet aggregation, is an objective measure of platelet activation. Platelet aggregometry uses a photo-optical instrument to measure light transmittance through a sample during whole-blood or platelet-rich plasma. Platelet-rich plasma undergoes a decrease in light transmittance on the early phase of platelet activation because of the change in platelet shape from discoid to spheric. When exposed to a platelet agonist such as thrombin, adenosine diphosphate (ADP), epinephrine, collagen, or ristocetin, the initial reversible aggregation phase results in increased light transmittance because of the platelet aggregates that decrease the turbidity of the sample. Known major platelet activators are listed in Table 19.3. The larger the platelet aggregates, the greater is the transmittance of light. In the absence of further activation, disaggregation occurs, and the plasma sample becomes turbid. However, when the platelet release reaction occurs, thromboxane and other activators are released from the platelet α granules and the phase of secondary, or irreversible, aggregation occurs. This results in a further increase in light transmittance.

Defects in platelet aggregation can be seen in patients with storage pool deficiency, Bernard-Soulier syndrome, or Glanzmann thrombasthenia, as well as in patients taking salicylates. Impaired platelet aggregation has been demonstrated to occur after CPB, but investigators

TABLE 19.3 Major Platelet Activators Involved in Clot Formation

Reagents	*Receptors and Key Actions*
Collagen	GpVI and the integrin $\alpha_2\beta_1$ Critical for stable platelet adhesion to site of injury
vWF	GpIb Initial adhesion to collagen and slowing down rolling of platelets
Thrombin	GpIb, PAR 1, and PAR 4 Platelet activation for aggregation and clot formation
AA	Thromboxane A_2 receptor Activation and aggregation of platelets Aspirin inhibits COX 1 enzyme of thromboxane A_2 synthesis
ADP	GPCR receptors ($P2Y_1/P2Y_{12}$) Activation and aggregation of platelets Clopidigrel binds and irreversibly inhibits $P2Y_{12}$ receptor
Epinephrine	Epinephrine receptor on platelet membrane Weak activation and aggregation signaling
Fibrinogen	GpIIb/IIIa receptors Bridging between platelets during aggregation Abciximab or eptifibatide blocks the receptor and platelet aggregation

AA, Arachidonic acid; *ADP,* adenosine diphosphate; *COX,* cyclooxygenase; *Gp,* glycoprotein; *GPCR,* G-protein–coupled seven transmembrane receptor; *PAR,* protease-activated receptor; *vWF,* von Willebrand factor.

Reproduced with permission from Stafford M, Weitzel N. Point of care testing in cardiac surgery: diagnostic modalities to assess coagulation and platelet function. *Drug Dev Res.* 2013;74:418–427.

have had difficulty showing a correlation between impaired aggregation and clinical bleeding.[150,151] One ex vivo study demonstrated a significant correlation between platelet aggregation and 3-hour postoperative bleeding; however, correlations were greatest when preoperative aggregometry was performed using whole-blood samples and when postoperative measurements were performed using platelet-rich plasma.[151] The assessment of the platelet defect induced by aspirin consumption is more sensitive when whole-blood aggregometry is performed. The extreme sensitivity of this assay to minor defects in platelet function has resulted in a high negative predictive value, but a low positive predictive value, for bleeding. The inability of this test to be performed easily in the clinical setting has restricted platelet aggregometry to use as a research tool with occasional clinical applications.

Platelet-Mediated Force Transduction

An instrument that measures the force developed by platelets during clot retraction has been shown to be directly related to platelet concentration and function.[152,153] This instrument is called the Hemostasis Analysis System (Hemodyne Inc., Bethesda, MD). The apparatus consists of a cup and a parallel upper plate. The cup is filled with blood or the platelet-containing solution, and the upper plate is lowered onto the clotting solution. Clot forms and adheres to the outer edges of the cup and to the plate above it. A thin layer of oil is deposited onto the surfaces that are exposed to air. The upper plate is coupled to a displacement transducer that translates displacement caused by platelet retraction into a force. Normal values for platelet force development have been suggested by the investigators.[152] The antiplatelet effects of heparin have been evaluated using this force retractometer. Using this instrument, investigators have shown that high heparin concentrations completely abolish platelet force generation.[77] Furthermore, the concentration of protamine required to reverse the anticoagulant effects of heparin is not sufficient to reverse these antiplatelet effects. The antiplatelet effects of protamine alone also have been evaluated using this monitor.

Fluorescence Flow Cytometry

The introduction of fluorescence flow cytometry into the clinical laboratory provided a sensitive and specific means for assessing causes of

TABLE 19.4 Platelet Adhesion and Aggregation

Ligand	*Receptor*	*Properties*
Collagen	GpIa/IIa, GpIIb/IIIa, GpIV	Adhesion, aggregation, secretion
Thrombospondin	GpIV, $\alpha_v\beta_3$	Adhesion, antiadhesion
vWF	GpIb/IX, GpIIb/IIIa	Adhesion
Fibrinogen	GpIIb/IIIa	Aggregation
Laminin	GpIc/IIa	Attachment
Vitronectin	$\alpha_v\beta_3$, GpIIb/IIIa	$\alpha_v\beta_3$ = vitronectin receptor
Fibronectin	GpIc/IIa, GpIIb/IIIa	Attachment, spreading

Gp, Glycoprotein; *vWF,* von Willebrand factor.

platelet dysfunction. The disadvantages of the in vitro assays, such as shear-induced stress and clot retraction measurements, are that they represent nonspecific markers of platelet defects. The measure of specific serum markers of platelet activation, such as β-thromboglobulin and PF4, can be performed; however, plasma collection techniques for these tests are cumbersome, and the assays are often affected by other metabolic functions. Aggregometry is only a semiquantitative process and requires a high concentration of platelets for its optimal performance.

Flow cytometry is ideal for the detection of low concentrations of specific proteins within a large population of cells. These proteins either may be static portions of the platelet surface or dynamic products of platelet activation. The platelet release reaction enables specific integrin proteins, which are a part of the platelet α-granule membrane, to incorporate themselves into the platelet surface membrane through a mechanism analogous to exocytosis. A portion of the GpIIb/IIIa receptor is also a protein of the α-granule membrane that becomes exposed on the surface membrane of the platelet in response to platelet activation. Flow cytometry allows for the detection and quantification of many of these surface membrane constituents as a result of immunofluorescent innovations.

Flow cytometry techniques were enhanced by the development of specific monoclonal antibodies, which recognize antigens on the platelet (or white blood cell) surface. The ligands present on the surface of platelets are responsible for initiating and propagating the activities of adhesion and aggregation when they are bound by the appropriate agonist (Table 19.4). Antibodies developed are so specific that different ligand binding sites can be measured on the same GpIIb/IIIa molecule that characterizes different phases of receptor activation. Some of the epitopes for which monoclonal antibodies have been developed include the following: platelet activation–dependent granule–external membrane (PADGEM) and platelet α-granule membrane protein-140 (GMP-140), markers of platelet activation; the activated GpIIb/IIIa complex; and the GpIb receptor.[154–156] Many monoclonal antibodies are available for identification of specific platelet ligand-binding sites (Table 19.5). Antibodies that bind specifically to activated platelets but minimally to unstimulated platelets are referred to as "activation dependent." In using activation-dependent monoclonal antibodies, flow cytometry measures the platelet reactivity or response to the addition of platelet agonists. The technique of flow cytometry can be performed using whole blood or platelet-rich plasma. The fluorescent-labeled monoclonal antibody directed against a specific platelet membrane protein is quantified by the flow cytometer, which is an instrument equipped with a laser or a light source of a specific excitation wavelength. Light scatter data are collected that help to differentiate platelets from other cellular particles. Fluorescent antibody detection is expressed as percentage of the total number of particles or as fluorescence intensity.

The ability to identify platelet defects specifically by fluorescence flow cytometry has greatly aided in the characterization of hematologic disease states such as the Bernard-Soulier syndrome and Glanzmann thrombasthenia.[157,158] In the cardiac surgical setting, flow cytometry has aided in diagnosis of platelet function disorders induced by CPB and protamine administration.[159,160] Kestin and colleagues[143] used

TABLE 19.5 Monoclonal Antibodies to Platelet Antigens

Antibody Binding Site (Other Name)	*Antibodies Available*	*Requirement for Binding/ Functional Activity*
GpIb (CD42b)	AP-1; 6D1	von Willebrand receptor; platelet adhesion
GpIX	FMC25	Platelet adhesion to endothelium
GpIIb/IIIa complex ($\alpha IIB\beta_3$, CD41)	7E3; 10E5; 4F10; A2A9	Fibrinogen receptor; platelet aggregation
GpIIb/IIIa ($\alpha IIB\beta_3$, CD41a)	PAC1	Active conformation of GpIIb/IIIa only
Fibrinogen	2G5; 9F9	Receptor-induced changes because of bound fibrinogen
GpIIb heavy chain of GpIIb/IIIa	P2; PMI-1	Ligand-induced changes in GpIIb
IIIa portion of GpIIb/IIIa (CD61)	AP6; Ab15; Y2/51	Receptor bound by fibrinogen
GMP140 (CD62P, P-selectin)	S12; KC4; VH10	αGranule membrane protein, mediator of platelet–leukocyte interactions
LAMP-1 (CD63)	CLB-gran/12; H5G11	Lysosome membrane protein, expressed after platelet secretion
40-kDa protein	D495	Dense granule membrane protein
Thrombospondin	P8	Bound thrombospondin
Factor VIIIa light chain	1B3	Present on a procoagulant surface
Factor Va light chain	V237	Present on a procoagulant surface

GMP, Granule membrane protein; *Gp,* glycoprotein; *LAMP,* lysosme membrane protein.

flow cytometry techniques to study the effects of CPB on the in vivo time-dependent up-regulation of P-selectin in blood emerging from a bleeding wound. These investigators showed that P-selectin expression was depressed after heparinization and during CPB and recovered at approximately 2 hours after the conclusion of CPB. In contrast, in vitro activation of CPB blood with the platelet agonist phorbol myristate acetate did not reveal this depression of P-selectin expression at any time point. Using another platelet activator (thrombin-receptor agonist peptide) and flow cytometry, other investigators did not demonstrate depression of P-selectin expression early in CPB, but they did so after 90 minutes of CPB and after protamine administration.[161]

Uncertainty still exists regarding GpIb receptor modulation in response to CPB. Using flow cytometry, George and associates[162] found a modest reduction in platelet surface GpIb during CPB. However, a subsequent study by van Oeveren and colleagues,[163] confirming a reduction in GpIb, subjected the platelets to centrifugation and processing techniques that may have induced in vitro artifactual platelet activation. Kestin and associates[143] used monoclonal antibodies to many epitopes expressed on GpIb and concluded that expression of this receptor is not reduced during CPB.

As a result of the many monoclonal antibodies directed at specific epitopes on the GpIIb/IIIa receptor, investigations into the dynamics of this receptor during CPB have yielded variable results. Some studies confirmed modest reductions in the expression of GpIIb/IIIa, although not all used whole-blood techniques. Rinder and associates,[159] used a whole-blood technique and demonstrated a small decrease in GpIIb/IIIa expression. Monoclonal antibodies are available that bind to the GpIIb/IIIa fibrinogen binding site, and others recognize receptor-bound fibrinogen. Flow cytometry techniques also have helped to characterize the mechanisms of action of several pharmacologic agents that have shown hemostatic potential in the perioperative period.

Bedside Coagulation and Platelet Function Testing

Viscoelastic Tests: Thromboelastography, Thromboelastometry, and Sonoclot

In the late 19th century, investigators first began to explore the possibility that viscoelastic tests of blood could yield information on

TABLE 19.6 Mechanisms of Point-of-Care Platelet Function Monitors

Instrument	*Mechanism*	*Platelet Agonist*	*Clinical Utility*
Thrombelastograph (Haemonetics, Braintree, MA)[168]	Viscoelastic	Thrombin (native), ADP, arachidonic acid	Post CPB, liver transplant, pediatrics, obstetrics, drug efficacy
Sonoclot (Sienco, Arvada, CO)[287]	Viscoelastic	Thrombin (native)	Post CPB, liver transplant
ROTEM (TEM Systems, Durham, NC)[169]	Viscoelastic	Thrombin (native)	Post CPB, transfusion algorithm
HemoSTATUS (Medtronic Perfusion Services, Minneapolis, MN)[149]	ACT reduction	PAF	Post CPB, DDAVP, transfusion algorithm
Plateletworks (Helena Laboratories, Beaumont, TX)[269]	Platelet count ratio	ADP, collagen	Post CPB, drug therapy
PFA-100 (Siemens Medical Solutions USA, Malvern, PA)[288]	In vitro bleeding time	ADP, epinephrine	vWD, congenital disorder, aspirin therapy, post CPB
VerifyNow (Accriva Diagnostics, Accumetrics, San Diego, CA)[289]	Agglutination	TRAP, ADP	GpIIb/IIIa receptor blockade therapy, drug therapy, post-CPB
Clot Signature Analyzer (Xylum, Scarsdale, NY)[290]	Shear-induced in vitro bleeding time	Collagen (one channel only)	Post CPB, drug effects
Whole-blood aggregometry[151]	Electrical impedance	Multiple	Post CPB
Impact Cone and Plate(let) Analyzer (Matis Medical, Beersel, Belgium)[291]	Shear-induced platelet function	None	Post CPB, congenital disorder, drug effects
Multiplate Analyzer (Roche Diagnostics, Indianapolis, IN)[292]	Electrical impedance	ADP, arachidonic acid, collagen, ristocetin, TRAP-6	Drug therapy, congenital disorder, post CPB

ACT, Activated clotting time; *ADP,* adenosine diphosphate; *CPB,* cardiopulmonary bypass; *DDAVP,* desmopressin; *Gp,* glycoprotein; *PAF,* platelet-activating factor; *ROTEM,* rotational thrombelastometry; *TRAP,* thrombin receptor agonist peptide; *vWD,* von Willebrand disease.

coagulation status. The changes that occur in the viscosity of blood as it clots could be studied and measured, and this information would reflect certain aspects of coagulation function. During the early part of the 20th century, many primitive viscometers were developed that used the basic mechanisms and principles on which modern viscoelastic tests are based. Bedside coagulation tests based on these principles demonstrate utility in real-time diagnostic decision making (ie, treating coagulopathy following CPB), and they also show promise in risk stratification and bleeding risk prediction. Viscoelastic testing has been increasingly studied, yet the technique is plagued by questions of reliability and reproducibility. In 2011, the TEG-ROTEM International Working Group published results of an effort to standardize and compare reproducibility in the two devices using platelet rich plasma and factor VIII–deficient plasma from nine different laboratories.[164] Overall coefficient of variance exceeded 10% for both devices in all parameters, with some values as high as 40%. This difference in values from location to location is a major obstacle in the acceptance and reliability of these types of devices.

Thromboelastography

The coaguloviscometers developed in the 1920s formed the basis of viscoelastic coagulation testing that is now known as thromboelastography. Thromboelastography in its current form was developed by Hartert[165] in 1948 and has been used in many different clinical situations to diagnose coagulation abnormalities. Although not truly portable, the Thrombelastograph (TEG, Haemonetics, Braintree, MA) can be used on site either in the operating room or in a laboratory and provides rapid whole-blood analysis that yields information about clot formation and clot dissolution (Table 19.6 and Fig. 19.16). Within minutes, information on the integrity of the coagulation cascade, platelet function, platelet-fibrin interactions, and fibrinolysis is obtained. The principle is as follows: whole blood (0.36 mL) is placed into a plastic cuvette into which a plastic pin is suspended; this plastic pin is attached to a torsion wire that is coupled to an amplifier and recorded; the cuvette then oscillates through an arc of 4 degrees, 45 minutes at 37°C. When the blood is liquid, movement of the cuvette does not affect the pin. However, as clot begins to form, the pin becomes coupled to the motion of the cuvette, and the torsion wire generates a signal that is recorded. The recorded tracing can be stored by computer, and the parameters of interest are calculated using a simple software package. Alternatively, the tracing can be generated online with a recording speed of 2 mm/min. The tracing generated has a characteristic conformation that is the signature of the TEG (Fig. 19.17). The most current commercially available Thrombelastograph incorporates this viscoelastic measurement into a cartridge-based

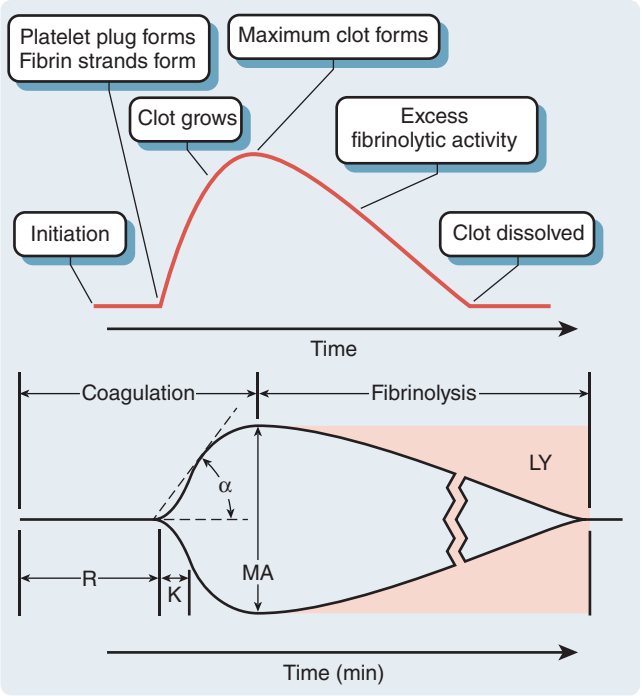


Fig. 19.16 Normal Thrombelastograph (TEG, Haemonetics, Braintree, MA) tracing with standard parameters. *R* is the reaction time or the latency time from placing blood in the cup until the clot begins to form and the tracing opens to 2 mm (typically relates to function or amount of coagulation factors). *K* is a parameter arbitrarily assigned as the time between the TEG trace reaching 2 mm and going up to 20 mm (thought to reflect fibrinogen levels). α is the angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing (predictive of maximal amplitude). *MA* is maximal amplitude (largest measured width on the TEG tracing) is considered to represent maximal thrombin-induced platelet activity and clot formation (total clot strength representing platelet function and clot interactions); LY is lysis index, which is the percent of lysis, typically measured as LY30 or 30 minutes after achieving MA.

hemostasis test, thus eliminating the need for blood pipetting and reducing the instrument sensitivity to motion.

The specific parameters measured by TEG include the reaction time (R value), coagulation time (K value), "α" angle, maximal amplitude (MA), amplitude 60 minutes after the maximal amplitude (A60), and clot lysis indices at 30 and 60 minutes after MA (LY30 and LY60,

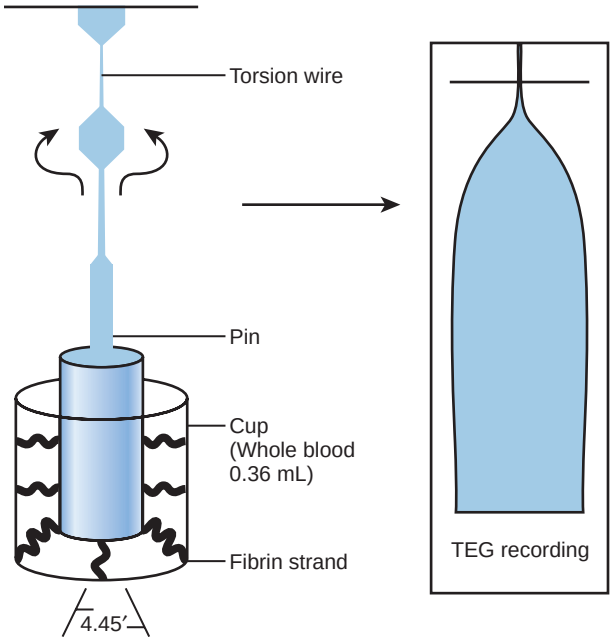


Fig. 19.17 Schematic diagram of Thrombelastograph (*TEG;* Haemonetics, Braintree, MA) instrumentation *(left)* and a sample tracing *(right).* A whole-blood sample is placed into the cup into which a plastic pin is suspended. This plastic pin is attached to a torsion wire that is coupled to an amplifier and recorder. *(From Mallett SV, Cox DJ. Thromboelastography.* Br J Anaesth. *1992;69:307–313.)*

respectively) (Fig. 19.18). The R value represents the time for initial fibrin formation and measures the intrinsic coagulation pathway, the extrinsic coagulation pathway, and the final common pathway. R is measured from the start of the bioassay until fibrin begins to form, and the amplitude of the tracing is 2 mm. Normal values vary by activator, but they range from 7 to 14 minutes using celite activator, or in the rapid TEG from 1 to 3 minutes using tissue factor activator. The K value is a measure of the speed of clot formation and is measured from the end of the R time to the time the amplitude reaches 20 mm. Normal values (3–6 minutes) also vary with the type of activators used. The α angle, another index of speed of clot formation, is the angle formed between the horizontal axis of the tracing and the tangent to the tracing at 20-mm amplitude. The α values normally range from 45 to 55 degrees. Because both the K value and the α angle are measures of the speed of clot strengthening, each is improved by high levels of functional fibrinogen. MA (normal is 50–60 mm) is an index of clot strength as determined by platelet function, the cross-linkage of fibrin, and the interactions of platelets with polymerizing fibrin. The peak strength of the clot, or the shear elastic modulus "G," has a curvilinear relation with MA and is defined as follows: G = (5000 MA) / (96 – MA). The percentage reduction in MA after 30 minutes reflects the fibrinolytic activity present and normally is not more than 7.5%.

Characteristic TEG tracings can be recognized to indicate particular coagulation defects. A prolonged R value indicates a deficiency in coagulation factor activity or level and is seen typically in patients with liver disease and in patients receiving anticoagulant agents such as warfarin (Coumadin) or heparin. MA and the α angle are reduced in states associated with platelet dysfunction or thrombocytopenia and are reduced even further in the presence of a fibrinogen defect. LY30, or the lysis index at 30 minutes after MA, is increased in conjunction with fibrinolysis. These particular signature tracings are depicted in Fig. 19.19.

TEG is a useful tool for diagnosing and treating perioperative coagulopathy in patients undergoing cardiac surgical procedures because of a variety of potential coagulation defects that may exist.[166,167] Within 15 to 30 minutes, on-site information is available regarding the integrity of the coagulation system, the platelet function, fibrinogen function, and fibrinolysis.[168,169] With the addition of heparinase, TEG can be performed during CPB and can provide valuable and timely information regarding coagulation status.[170] Because TEG is a viscoelastic test and evaluates whole-blood hemostasis interactions, proponents suggest that TEG is a more accurate predictor of postoperative hemorrhage than are routine coagulation tests.[168,170,171] Detractors of POC testing point to variance in the results with the earlier instruments and to some evidence that standard parameters have better correlation with bleeding.[163,172] Central laboratory testing certainly has its drawbacks in the surgical setting. In a prospective study of 16-hour postoperative blood loss, Gravlee and associates[173] reported on 897 cardiac surgical patients in whom routine coagulation tests were measured immediately on heparin reversal in the operating room. The weak correlations and poor predictive values of these tests confirmed that these tests perform poorly as predictors of bleeding. TEG was not studied in this trial. Currently the greatest area of benefit with viscoelastic coagulation testing is its use in goal-directed transfusion therapy.

Thromboelastography Modifications

Thromboelastography was originally performed using recalcified citrated whole blood or celite activator. More recent modifications of the original TEG reaction include the Rapid TEG, Functional Fibrinogen, and PlateletMapping (Haemonetics, Braintree, MA). Rapid TEG uses recombinant human tissue factor as an activator to accelerate the rate of thrombin formation and thus the formation of fibrin and stable clot.[174] Rapid TEG has been used to a great degree in trauma settings because the added tissue factor activator shortens the R time to less than 1 minute, and the time to obtain the MA is usually 20 minutes. Disadvantages include loss of some sensitivity to the coagulation factor component of the standard R time. Studies in trauma indicate the utility of TEG in diagnosing trauma-induced coagulopathy, as well as accelerated fibrinolysis, which has been used in a risk prediction model with correlations with mortality rates in trauma.[174–178]

A new application of thromboelastography in the clinical setting is its use in monitoring platelet receptor blockade in patients treated with specific antiplatelet agents.[179,180] In a platelet-rich plasma research model, TEG with tissue factor acceleration and the addition of large concentrations of GpIIb/IIIa-receptor blockers yields an MA value that is reduced from baseline by a degree relative to the platelet inhibition.[179] These TEG MA values correlate strongly with thrombin receptor agonist peptide (TRAP)–activated aggregation studies.

Because the MA is a function of the platelet-fibrinogen interaction, a reduction in the MA can be accomplished by the addition of potent GpIIb/IIIa-receptor blockade to the assay. The resultant MA reflects the fibrinogen concentration and the strength of fibrin alone. This value correlates with plasma fibrinogen concentration and is marketed as the functional fibrinogen test. Functional fibrinogen testing has been validated for use in the TEG system and allows for rapid evaluation of functional levels of fibrinogen.[181] Publications on this test have been limited, and some more recent studies have questioned the correlation of functional fibrinogen levels in clinical applications such as cardiac surgical procedures or in general surgical patients.[182,183]

The thienopyridine ADP receptor blockers clopidogrel, prasugrel, and ticagrelor are widely used in cardiovascular medicine (see Chapter 35).[184] The ability to measure the platelet defect induced by these drugs is difficult unless sophisticated laboratory techniques such as ADP aggregometry are used. Routine TEG analysis does not measure the thienopyridine-induced platelet defect because the formation of thrombin in the assay has an overwhelming effect on the development of the MA. PlateletMapping is a modification of TEG that assesses platelet function by comparing the MA tracing induced by activation with arachidonic acid (AA) or ADP receptors (MA_{pi}) to the MA achieved with no platelet activity (MA_{f}), and with maximal platelet activation (MA_{kh}). For PlateletMapping, the reaction is carried out in the setting of heparinized blood, thus inhibiting thrombin platelet activation. The MA produced in this setting, when reptilase and

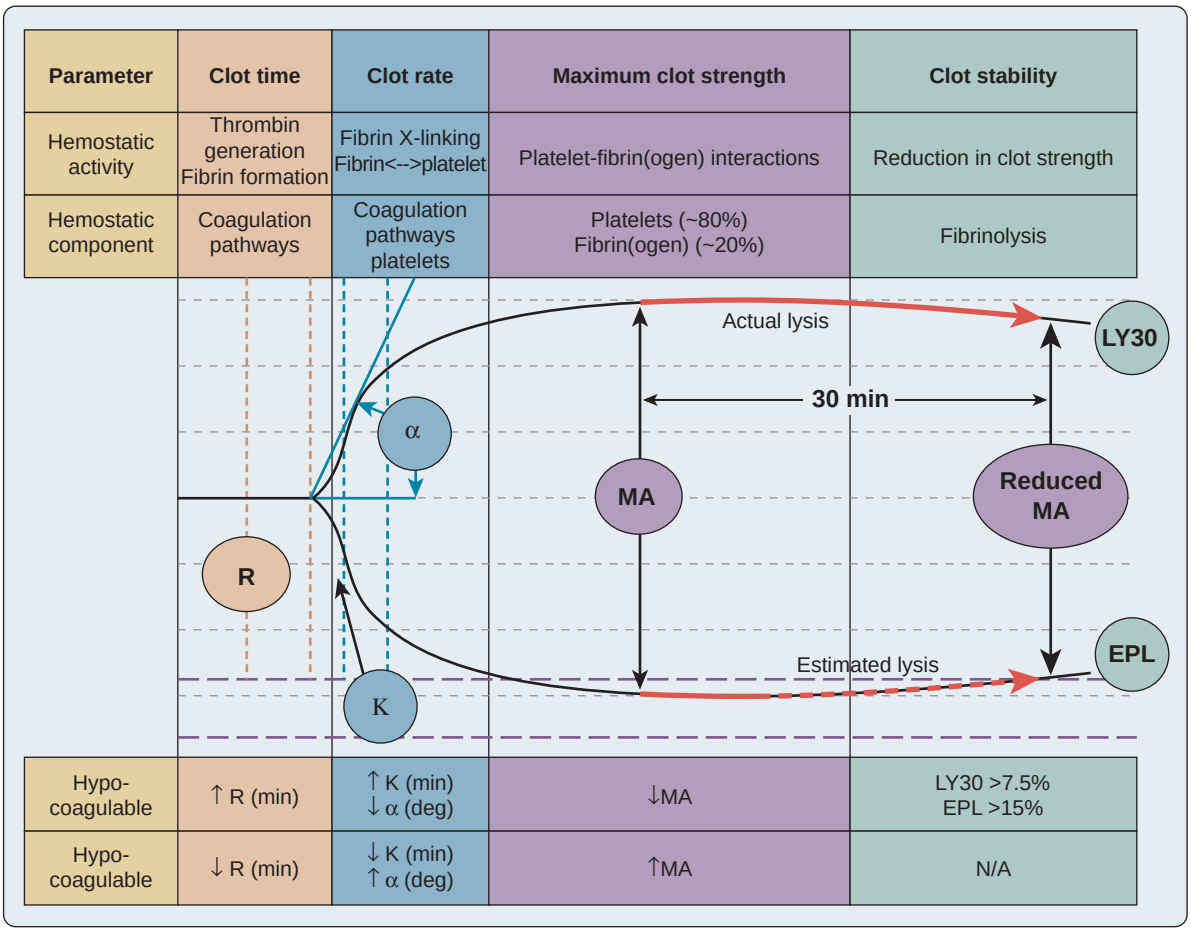


Fig. 19.18 Normal Thrombelastograph (TEG, Haemonetics, Braintree, Mass) tracing with standard parameters. α, An angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing (predictive of maximal amplitude); *K*,A parameter arbitrarily assigned as the time between the TEG trace reaching 2 mm and going up to 20 mm (may represent fibrinogen levels); *LY*, lysis index; *MA*, maximal amplitude, considered to represent maximal thrombin-induced platelet activity and clot formation (total clot strength representing platelet function and clot interactions); *R*, reaction time or the latency time from placing blood in the cup until the clot begins to form, reaching a TEG tracing amplitude of 2 mm (typically relates to function or amount of coagulation factors).

factor XIII are used to form the clot, is the MA with "no platelet activity," or MA_f (fibrin). The MA_{pi} is the maximal activation of platelets and fibrin and is the largest-amplitude that can be achieved with the specific platelet activators (ADP or AA). MA_{pi} (platelet inhibitor) tracings are compared with the MA_f. In addition, a standard kaolin-heparinase–activated TEG tracing is created to demonstrate maximal platelet activation that occurs when thrombin is present (MA_{kh}) (Fig. 19.20). The following formula calculates the percentage reduction in platelet activity using this assay:

$$\%\,\text{inhibition} = 100 - [(MA_{pi} - MA_f)/(MAkh - MA_f) \times 100]$$

PlateletMapping has demonstrated consistent correlation with optical platelet aggregation assays.[185–187]

PlateletMapping has implications in clinical models, and numerous publications now exist. Studies demonstrate sensitivity in detecting aspirin resistance,[188] as well as updated timeframes on when platelet function returns following cessation of clopidogrel therapy.[189] The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) study published by Mahla and colleagues[190] in 2012 investigated the utility of PlateletMapping in stratifying the waiting period for patients needing coronary artery bypass grafting (CABG) who were taking clopidogrel. Results indicated not only that PlateletMapping could be used to individualize this waiting period based on platelet activity, but also that a 50% reduction in these wait times occurred without any increased bleeding complications.[190] PlateletMapping has been shown to be useful in prediction of post-CPB bleeding in multiple small-scale studies, mostly in patients receiving antiplatelet medications.[191–193] The percentage of inhibition, as well as the MA_{ADP} was shown to predict postoperative chest tube output, which was the strategy used in the TARGET-CABG trial.[190,191,193] Finally, TEG reports on the overall clot strength (G), which has been shown to be related to mortality rates in trauma,[194] and a specific ADP-activated platelet clot strength model was proposed that was associated with poststenting ischemic events.

Sonoclot

Another test of viscoelastic properties of blood is the Sonoclot. In 1975, von Kaulla introduced the Sonoclot Analyzer (Sienco, Arvada, CO), which is a coagulation analyzer that measures the changing impedance on an ultrasonic probe immersed in a coagulating blood sample.[195] A tubular probe oscillates up and down at an amplitude of 1 μm and a frequency of 200-Hz within the disposable cuvette containing the blood sample. As fibrin formation occurs, the sample exerts viscous drag, or resistance, on the probe that does not allow the probe to vibrate freely. This resistance is electronically converted into an

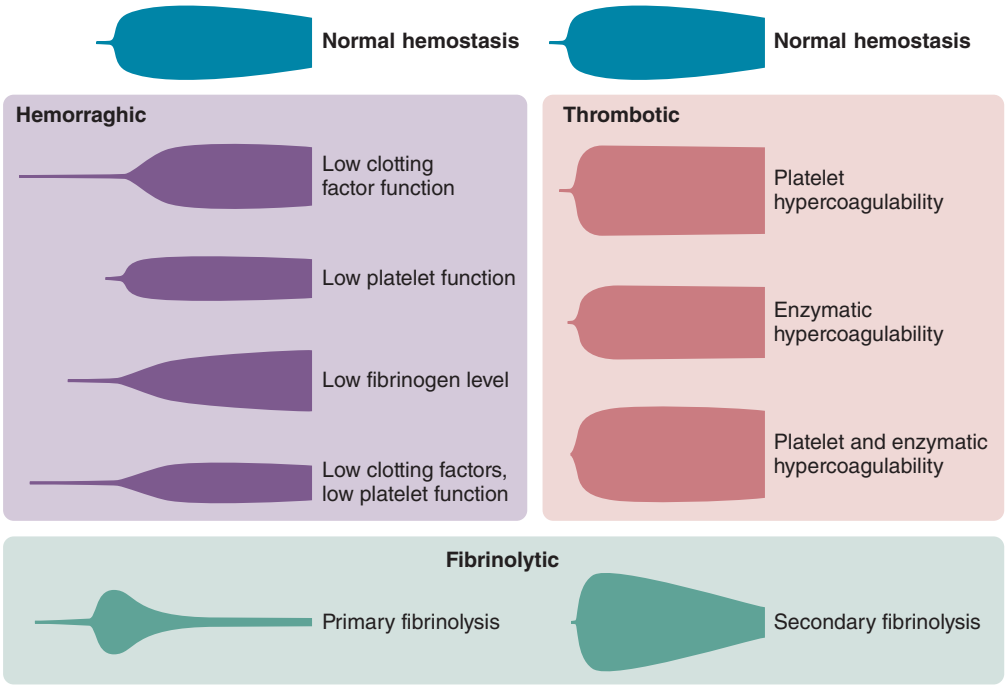


Fig. 19.19 Thrombelastograph (TEG, Haemonetics, Braintree, MA) tracings in various coagulation states.

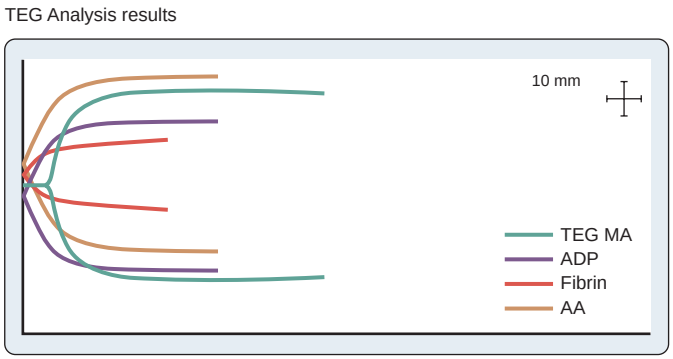


Fig. 19.20 Multitracing displaying standard four reactions involved in the PlateletMapping modification of the Thrombelastograph (TEG, Haemonetics, Braintree, MA). The percentage of inhibition (% inhibition) of platelets is calculated according to the following equation: % inhibition = 100 – [(MApi – MAf) / (TEG MA – MAf) × 100] where MAf is maximum amplitude of fibrin-activated curve, MApi is maximum amplitude by specific platelet activators (either adenosine diphosphate *[ADP]* or arachidonic acid *[AA]*, and *TEG MA* is maximum amplitude of kaolin-activated TEG.

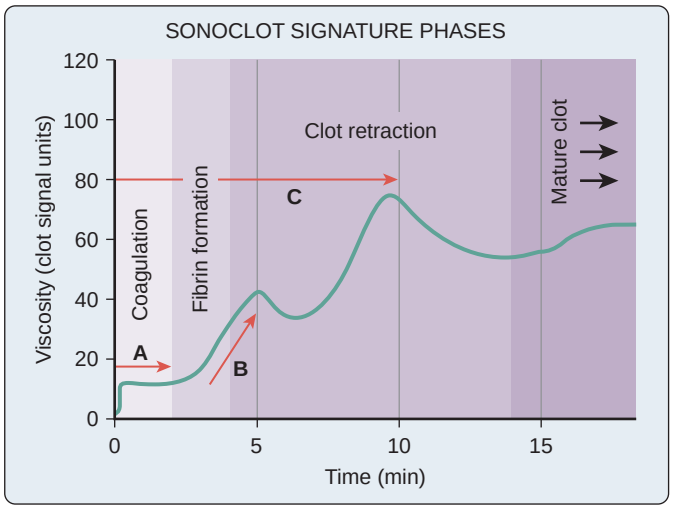


Fig. 19.21 Sonoclot (Sienco, Arvada, CO) Signature phases. *A*, Onset time or activated clotting time; *B*, clot rate; and *C*, time to peak, also known as platelet function time.

output signal, called the Sonoclot Signature (Fig. 19.21). The Sonoclot Signature reflects coagulation in real time, from the start of fibrin formation, to fibrin cross-linkage, platelet-mediated clot strengthening, and, eventually, to clot retraction and fibrinolysis.

The Sonoclot Signature is defined by three distinct parameters: the Onset or ACT, the Clot Rate (CR), and the Time to Peak (TP), which is also referred to as Platelet Function. The ACT is the time for initial fibrin formation and is defined as the time taken to reach an amplitude of 1 mm represented by point A in Fig. 19.21. This is measured in seconds, corresponds to the Hemocron method for ACT, and is typically shorter than the R time in the TEG because the TEG R time reflects a more developed stage of fibrin clot development.[187] The CR phase encompasses two peaks on the Signature trace, and the CR represents the maximal slope based on the rate of fibrin formation. The rate of rise of the first peak represented by point B is expressed as the percentage of the peak amplitude per unit time (normal values, 18–45%). Typically, a shoulder or a dip occurs before the second rise in amplitude and subsequent peak that results from the action of platelets and fibrin in producing clot retraction. As the clot retracts from the walls of the cuvette, the impedance to vibration briefly decreases. As fibrinogen converts to fibrin and fibrin polymerizes, the speed of clot formation and the platelet-fibrin interactions are represented by the TP, which is represented by point C. In the presence of greater concentrations of fibrinogen, a larger clot mass is represented by a greater amplitude of the second peak because of a greater impedance to vibration. The amplitude of this peak is therefore related to the concentration of normal functional fibrinogen. The subsequent downward slope that occurs results from platelet-mediated clot retraction that causes plasma expulsion and clot size diminution and thus reduced impedance. The magnitude of the clot retraction reflects platelet number and

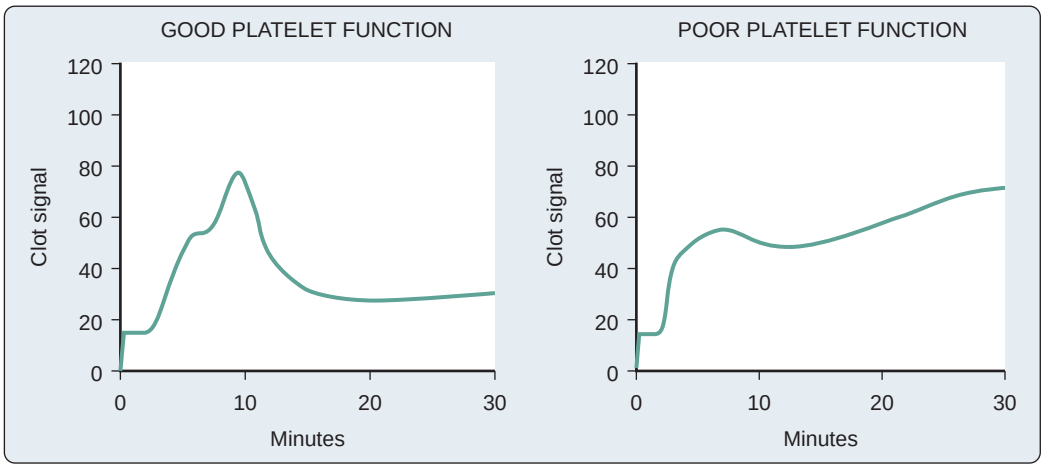


Fig. 19.22 Comparison of a normal Sonoclot (Sienco, Arvada, CO) tracing with a tracing in the setting of poor platelet function. Notice the lack of clot retraction and the slow uptrending curve on the right tracing.

function. Fig. 19.22 demonstrates a tracing with normal and abnormal platelet function.

Sonoclot has been studied and used in both the clinical setting and the research laboratory. As with other POC devices, frequent applications are in the perioperative setting, the catheterization laboratory, intensive care unit, and specialty clinics.[196–199] Early studies along with TEG demonstrated an accuracy of 74% using Sonoclot and an accuracy of 88% using TEG to predict bleeding after cardiac surgical procedures.[170] The reason that viscoelastic tests have been able to predict bleeding so successfully probably relates to their ability to measure platelet function, a major determinant of postoperative hemostasis.[200] Significant correlations have been documented between specific Sonoclot parameters and platelet count and coagulation factor assays. This reproducibility has allowed the use of Sonoclot also to predict and successfully treat coagulation abnormalities in patients undergoing liver transplantation.[201] Published studies indicate Sonoclot's utility in the setting of coagulopathy from CPB,[199] monitoring the use of recombinant factor VIIa,[202] and coagulation changes associated with the use of colloid starches.[197] A novel application is to evaluate hypercoagulabilty associated with oral contraceptive use in women.[196] In addition, Sonoclot was used in combination with HIT to study the clotting reaction to heparin, and it may result in an improved screening tool for HIT.[203]

ROTEM (Rotational Thrombelastometry)

Rotational Thrombelastometry (ROTEM, TEM Systems, Durham, NC) gives a viscoelastic measurement of clot strength in whole blood. A small amount of blood and coagulation activators is added to a disposable cuvette that is then placed in a heated cuvette holder. A disposable pin (sensor) that is fixed on the tip of a rotating shaft is lowered into the whole-blood sample. The loss of elasticity on clotting of the sample leads to changes in the rotation of the shaft that is detected by the reflection of light on a small mirror attached to the shaft. A detector records the axis rotation over time, and this rotation is translated into a graph or thromboelastogram. ROTEM functions to measure changes in viscoelastic properties of clot formation in a fashion similar to that of TEG, but with some key differences.

The main descriptive parameters associated with the standard ROTEM tracing (Fig. 19.23) are the following:

- CT (clotting time): corresponding to the time in seconds from the beginning of the reaction to an increase in amplitude of the tracing of 2 mm. It represents the initiation of clotting, thrombin formation, and start of clot polymerization.
- CFT (clotting formation time): the time in seconds of an increase in amplitude from 2 to 20 mm. This identifies the fibrin polymerization and stabilization of the clot with platelets and factor XIII.
- Alpha (α) angle: the tangent to the clotting curve through the 2-mm point. It reflects the kinetics of clotting. Therefore, a larger α angle reflects the rapid clot formation mediated by thrombin-activated platelets, fibrin, and activated factor XIIIfactor XIIIa); CFT becomes shorter as the alpha angle becomes larger, and the two parameters are closely linked.
- A10 (amplitude obtained at 10 minutes): this directly relates to maximum clot firmness and can be used to predict MCF and platelet function.
- MCF (maximum clot firmness): the maximum amplitude in millimeters reached in the tracing that correlates with platelet count, platelet function, and with the concentration of fibrinogen
- LI30 (lysis index % at 30 minutes): a parameter representing fibrinolysis at a determined time point (typically 30 minutes). It correlates to the MCF (clot % remaining).
- ML (maximum lysis): this is the ratio of the lowest amplitude after reaching the maximum clot firmness to the maximum clot firmness. Like the LI30, this parameter can evaluate for hyperfibrinolysis.

ROTEM has been used extensively in Europe and increasingly in the United States after receiving approval from the US Food and Drug Administration (FDA) in 2011. ROTEM tests coagulation by using various reagents (Table 19.7), and the most common tests include INTEM (intrinsic system), EXTEM (extrinsic system), HEPTEM (intrinsic system in presence of heparin), FIBTEM (measures fibrinogen activity), and APTEM (tissue factor activation + tranexamic acid or aprotinin). Standard ROTEM reactions are conducted on the ROTEM Delta platform (Fig. 19.24). Fig. 19.25 provides an example of a series of ROTEM reactions for a hematologically normal patient, compared with a patient with platelet dysfunction.

In 2015, ROTEM released a module (see Fig. 19.24) that attaches to the standard Delta platform that adds the capability to monitor platelet aggregation function in response to three platelet agonists (ADP, AA, and TRAP) called the ADPTEM, ARATEM, and TRAPTEM, respectively. This system functions using the same concept as standard whole-blood aggregometry and is similar to the Multiplate aggregometer (described in detail later). Differences between ROTEM and TEG include the method for detection of viscoelastic changes and the sensitivity to movement. Investigators have suggested that the variance for ROTEM may be lower than for TEG.[204] Significant numbers of published studies of adult and pediatric patients support the use of ROTEM to evaluate various aspects of coagulation abnormalities.[169,205–219]

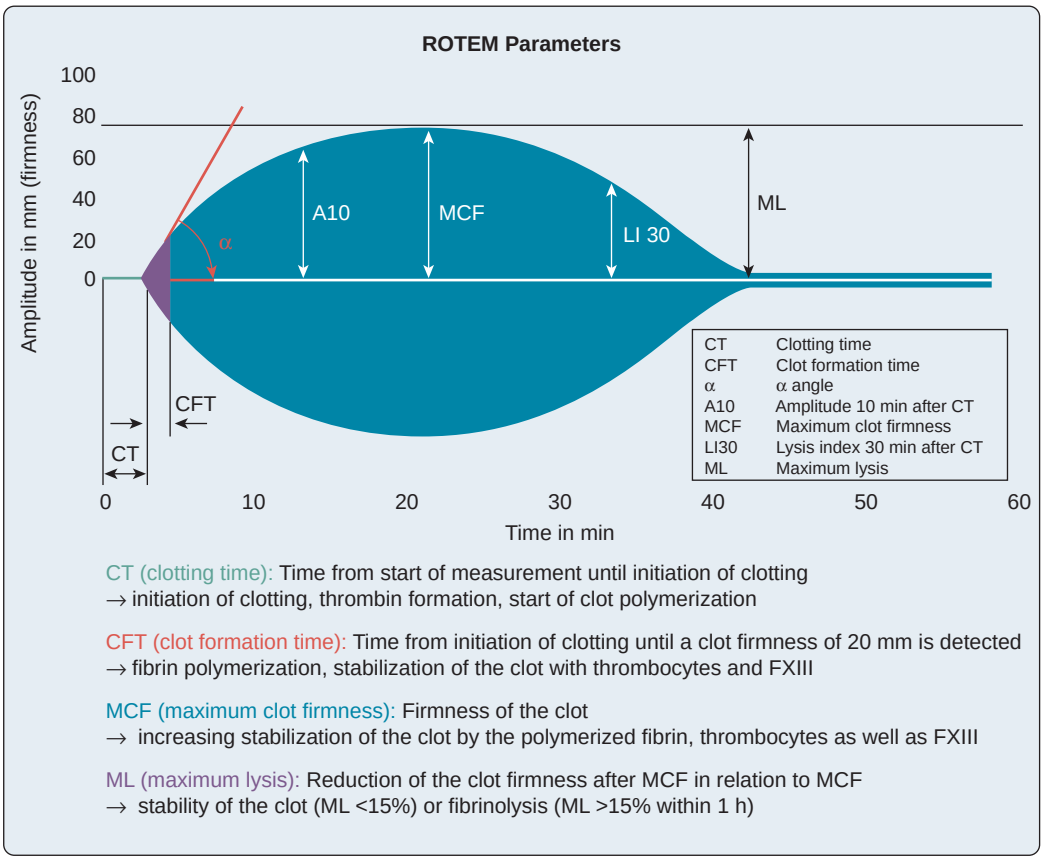


Fig. 19.23 Rotational thrombelastometry (ROTEM, TEM Systems, Durham, NC) parameters.

TABLE 19.7 Standard Rotational Thrombelastometry Reagents and Assessment Pattern

EXTEM	Tissue factor activation; factors VII, X, V, II, I, platelets, and fibrinolysis
INTEM	Contact phase activation; factors XII, XI, IX, VIII, II, I, platelets, and fibrinolysis
FIBTEM	EXTEM + cytochalasin D (platelet blocking); assessment of fibrinogen
APTEM	EXTEM plus aprotinin; useful to rule out fibrinolysis when compared to EXTEM
HEPTEM	INTEM plus heparinase; useful to detect residual heparin

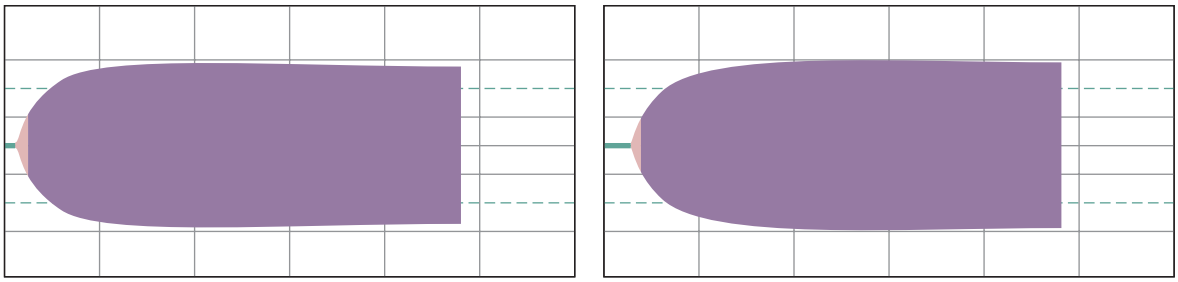
APTEM, Tissue factor activation + tranexamic acid/aprotinin; *EXTEM,* extrinsic system; *FIBTEM,* measure of fibrinogen activity; *HEPTEM,* intrinsic system in presence of heparin; *INTEM,* intrinsic system.

Transfusion Algorithms, Bleeding Prediction, and Comparisons of Viscoelastic Testing

Espinosa and associates[218] reported a comparison of TEG, ROTEM, and Sonoclot in 35 patients undergoing elective CABG with sample collection for all three tests before bypass, 1 hour postoperatively, and at 24 hours. All the TEG parameters measured, the ROTEM parameters (CT/CFM), and the ACT value for Sonoclot showed differences after bypass and could be used to track changes in hemostasis during surgical procedures. Plasma fibrinogen level correlated well with TEG, ROTEM, and Sonoclot assays at all time points. Correlations with standard laboratory tests were difficult to interpret and underscore the difference in using POC whole-blood testing versus plasma-based tests. INR did not correlate with TEG R time, ROTEM CT, or Sonoclot ACT.

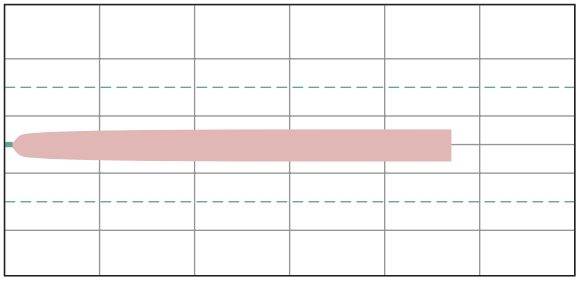
The largest impact of POC testing, however, has been in the development of goal-directed transfusion algorithms based on POC results. Initial research in the 1990s, including a retrospective evaluation in more than 1000 patients by Spiess and colleagues,[219] found that the institution of a transfusion algorithm using TEG resulted in a significant reduction in the incidence of mediastinal exploration and in the rate of transfusion of allogeneic blood products. This study was followed by a prospective trial by Shore-Lesserson and associates[220] in 105 patients assigned to algorithm-based transfusion decisions versus clinical judgment. Results demonstrated reductions in transfused

Fig. 19.24 The rotational thrombelastometry ROTEM (TEM Systems, Durham, NC) platelet module for platelet aggregation. *(Courtesy TEM Systems USA, Durham, NC/Tem Innovations GmbH, Munich, Germany.)*

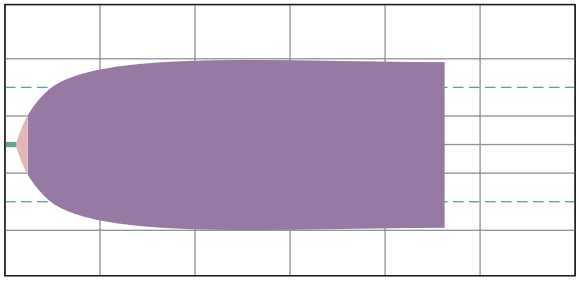


EXTEM					
CT:	67 s	CFT:	87 s	α:	73°
CFR:	54 mm	MCF:	57 mm	ML:	-%

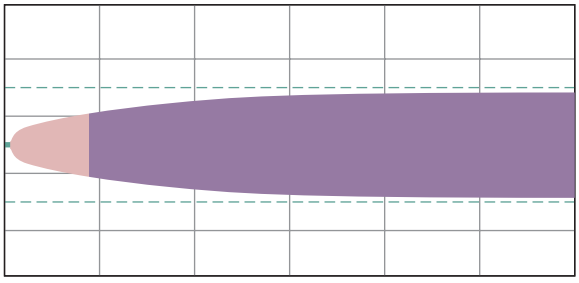
INTEM					
CT:	200 s	CFT:	67 s	α:	77°
CFR:	54 mm	MCF:	61 mm	ML:	-%



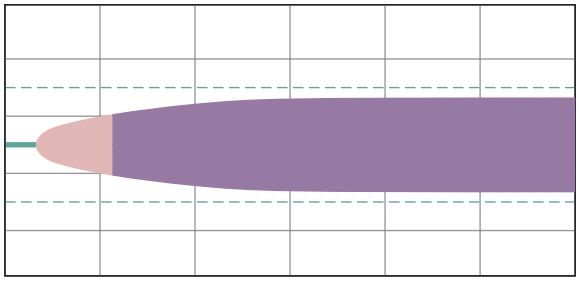
FIBTEM					
CT:	66 s	CFT:	-s	α:	57°
CFR:	9 mm	MCF:	10 mm	ML:	-%



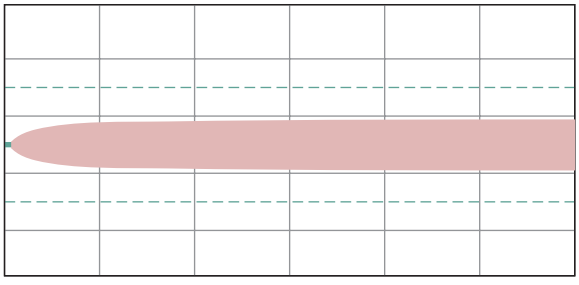
APTEM					
CT:	74 s	CFT:	89 s	α:	72°
CFR:	53 mm	MCF:	61 mm	ML:	-%



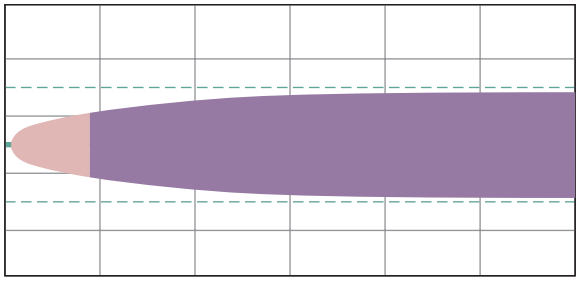
EXTEM					
CT:	57 s	CFT:	444 s	α:	80°
A10:	23 mm	MCF:	35 mm	ML:	-%



INTEM					
CT:	200 s	CFT:	449 s	α:	72°
A10:	23 mm	MCF:	32 mm	ML:	-%



FIBTEM					
CT:	67 s	CFT:	-s	α:	-°
A10:	15 mm	MCF:	16 mm	ML:	-%



APTEM					
CT:	52 s	CFT:	398 s	α:	80°
A10:	25 mm	MCF:	35 mm	ML:	-%

Fig. 19.25 *Left,* Normal tracings for the four standard parameters in the rotational thrombelastometry (ROTEM, TEM Systems, Durham, NC) system. *Right,* Platelet dysfunction, which is demonstrated by the prolonged clot formation time *(CFT),* as well as a decreased maximum clot firmness *(MCF)* in both the extrinsic system *(EXTEM)* and the intrinsic system *(INTEM)* tests. *A10,* amplitude 10 min after CT; *APTEM,* tissue factor activation + tranexamic acid/aprotinin; *CFR,* clot formation rate; *CT,* clotting time; *FIBTEM,* measure of fibrinogen activity.

products in the POC testing group and set the stage for future studies looking into algorithm-based approaches to transfusion.[220] Numerous studies now support this concept using TEG, ROTEM, and platelet function testing such as Multiplate Aggregometry (MEA) (see later).

A review by Gorlinger and colleagues[221] in 2013 quantified 16 studies including both retrospective and prospective trials totaling 8507 patients. The authors reported benefits including consistent reductions in transfusion products using POC-guided algorithms, with the greatest effect in patients with more complex coagulopathy, reduced re-exploration for bleeding, reduced massive transfusion, and overall hospital costs.[169,217,219,220,222–234] Four of these studies demonstrated improvements in patient-related outcomes including reductions in intensive care unit stay, thrombotic events, pulmonary dysfunction, ventilator time, and 6-month mortality rates.[217,224,225,234] A Cochrane review in 2011 that did not include many of these studies indicated fewer transfusions and fewer bleeding complications.[235] More recently, Mishra and associates[236] published a small observational trial in patients undergoing CABG and receiving antiplatelet medications and tested standard TEG along with MEA. These investigators reported that increased bleeding complications in patients receiving antiplatelet agents were best predicted by abnormal test results with MEA. This finding was not surprising because standard TEG does not specifically test platelet function in a comparable manner.[236] Karkouti and colleagues[237] published a retrospective comparison study after institution of a new algorithm using both ROTEM and platelet function testing with Plateletworks in 1170 patients, compared with 1311 cases "pre-algorithm." Results were in line with those of previous studies, indicating reduced transfusion requirements for all products (packed red blood cells, fresh frozen plasma, and platelets).

An interesting innovation with the concept of transfusion algorithms was published by Welsh and associates in 2014.[238] This clinical pathology group established a central laboratory–based rapid testing algorithm for high-risk bleeding cases such as cardiac surgical procedures to guide transfusions. These investigators were able to achieve rapid turnaround of standard clinical laboratory tests such as fibrinogen, PT/PTT/INR, and TEG and VerifyNow results. Initial results suggested their ability to return these test results in as little as 15 to 30 minutes, and preliminary outcomes indicated reductions in blood product transfusions.[238] The utility of POC-guided transfusion algorithms is not isolated to cardiac surgical procedures because these algorithms have also shown promise in trauma settings.[239] Tapia and colleagues[239] reported that a TEG-based transfusion algorithm may improve trauma mortality rates compared with the 1:1:1 massive transfusion protocol, and in some situations higher ratios of plasma or platelets may be advantageous. In conclusion, POC is likely to have the greatest clinical impact in patients with complex coagulopathy and in guiding transfusion practices. Important considerations beyond the use of algorithms include the content of the algorithm itself. In addition to allogeneic blood products, various pharmacologic hemostatic agents and recombinant agents, such as fibrinogen concentrate, prothrombin complex concentrate, and factor VIIa, are being introduced into algorithms guided by POC testing (Fig. 19.26).

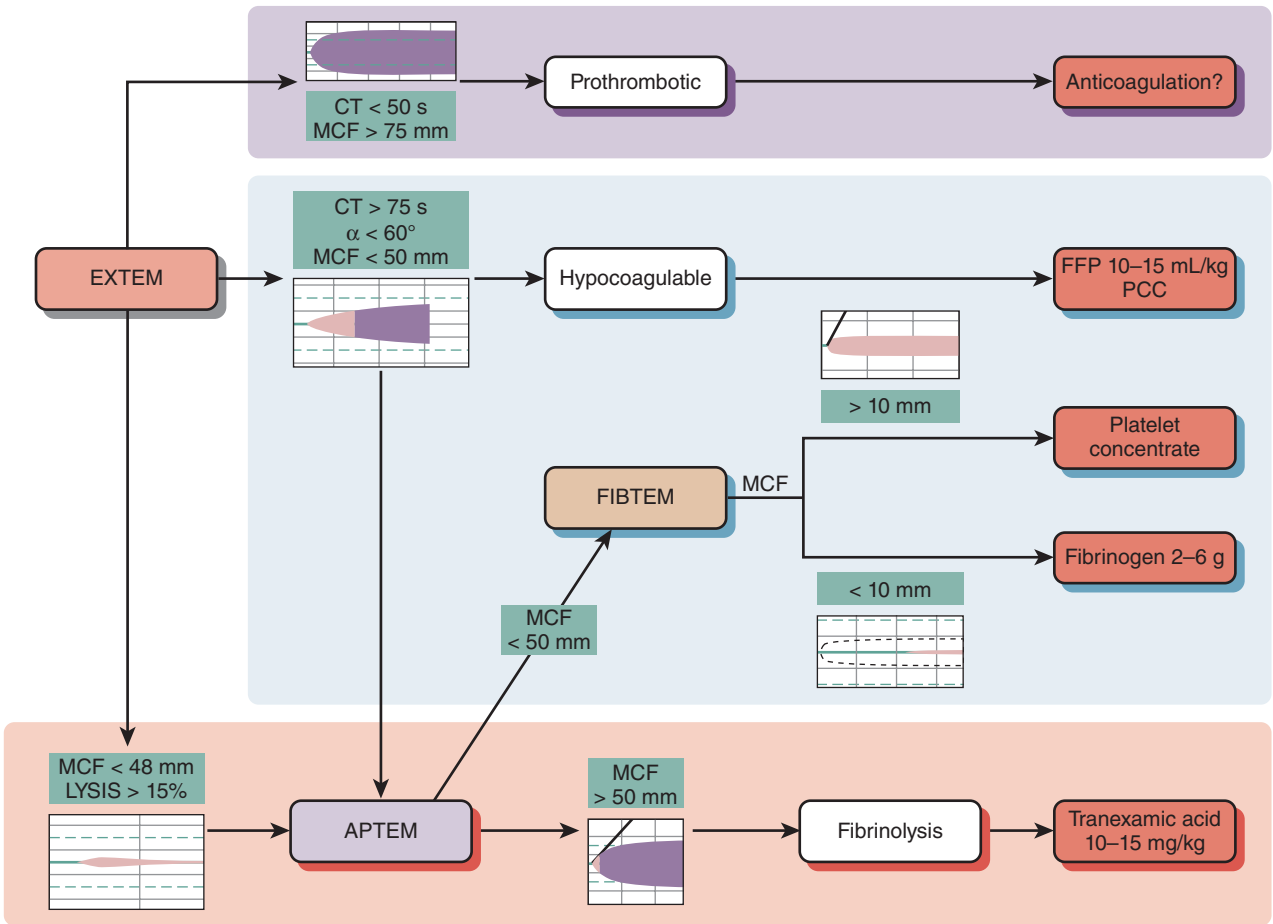


Fig. 19.26 Coagulation management algorithm guided by rotational thrombelastometry (ROTEM, TEM Systems, Durham, NC). *α, α* Angle; *APTEM,* tissue factor activation + tranexamic acid/aprotinin; *CT,* clotting time; *EXTEM,* extrinsic system; *FFP,* fresh frozen plasma; *FIBTEM,* measure of fibrinogen activity; *MCF,* maximum clot firmness; *PCC,* prothrombin complex concentrate.

Point-of-Care Tests of Platelet Response to Agonists

In contrast to viscoelastic testing, various platforms are now available as POC devices that allow for platelet function testing in response to agonists. Each system uses unique concepts, although most have been well validated with laboratory-based light transmission aggregometry (LTA), and some have been validated with the previously described viscoelastic tests. Some methods described here are included for historical purposes only, given that they are not readily available, whereas others are in use clinically.

HemoSTATUS

HemoSTATUS (Medtronic Perfusion Systems, Minneapolis, MN) was a POC platelet function assay that used the Hepcon HMS monitoring system to measure platelet reactivity. A six-channel cartridge measured the heparinized kaolin–activated ACT without platelet activator (channels 1 and 2) and with incrementally increasing doses of platelet-activating factor (PAF; channels 3 to 6). The respective doses of PAF in channels 3 through 6 were 1.25, 6.25, 12.5, and 150 nmol/L. For each channel 3 through 6, the degree of shortening of the ACT as a ratio to the ACT without PAF was the "clot ratio" and was calculated as $1 - (ACT_{activated} / ACT_{control})$. A comparison of the patient's clot ratio with the maximal clot ratio (derived from normal volunteers) yielded a comparative measure of platelet function, termed the "percentage of maximal platelet function." Several studies looked into this test in the late 1990s, but this POC platelet function assay is no longer available.[161,240–243]

VerifyNow

VerifyNow (Accumetrics, San Diego, CA) is a POC monitor (previously called Ultegra) initially designed to measure the platelet response to a TRAP and is approved by the FDA for use as a platelet function assay. In whole blood, it measures TRAP activation–induced platelet agglutination of fibrinogen-coated beads by using an optical detection system. After anticoagulated whole blood is added to the mixing chamber, the platelets become activated if they are responsive to the agonist. The activated GpIIb/IIIa receptors on the platelets bind to adjacent platelets through the fibrinogen on the beads and cause agglutination of the blood and the beads. Light transmittance through the chamber is measured and increases as agglutination increases, much as in standard aggregometry. Antithrombotic drug effects cause diminished agglutination (measured by light transmittance); the degree of platelet inhibition can thus be quantified. VerifyNow has agonists to examine the antiplatelet activity of GpIIb/IIIa inhibitors, aspirin, and clopidogrel and can report and quantify the degree of platelet inhibition with good correlation with LTA.[244–246] However, the system may be less sensitive than PlateletMapping for assessment of aspirin resistance.[188] VerifyNow has been used as part of a novel pathology-based transfusion algorithm service with this algorithm as a preoperative platelet function assessment tool.[238] The platelet function testing ability of VerifyNow has been used extensively to study the response to antiplatelet medications. Ample evidence suggests increased major cardiac adverse events in nonresponders to antiplatelet therapy both in the setting of cardiac surgical procedures and in coronary stenting.[247–250]

Clot Signature Analyzer

The Clot Signature Analyzer (CSA; Xylum, Scarsdale, NY) is a global hemostasis screen that assesses both platelet function and fibrin clot formation.[251] The test has three components: platelet hemostasis time (PHT), clot time (CT), and collagen-induced thrombus formation (CITF). Whole blood is placed under a constant driving pressure of 60 mm Hg as it is forced out into a synthetic vessel. The pressure distally in the vessel is monitored. The tubing of this synthetic vessel is perforated, and the distal pressure decline is measured. The time to restoration of this distal pressure is a function of the development of a platelet plug (PHT). Thus the PHT is a measure of platelet function. A subsequent time is measured, and that is the time to complete pressure loss caused by complete vessel occlusion (CT). This clot is the result of coagulation and clot formation, and the time to the second pressure decline reflects coagulation function. Another chamber of this device contains a collagen-coated fibril on which platelets adhere and form a plug. A similar pressure measurement technique indicates the formation of a platelet thrombus and yields the CITF. In cardiac surgical patients, preoperative platelet reactivity did not have predictive accuracy for bleeding.[252] Data evaluating the CSA in the postoperative period to predict bleeding are lacking.

Platelet Function Analyzer

The Platelet Function Analyzer (PFA-100; Siemens Medical Solutions USA, Malvern, PA) is a monitor of platelet adhesive capacity that is currently approved by the FDA and is valuable in its diagnostic abilities to identify drug-induced platelet abnormalities, platelet dysfunction of von Willebrand disease, and other acquired and congenital platelet defects.[253,254] The test is conducted as a modified in vitro BT. Whole blood is drawn through a chamber by vacuum and is perfused across an aperture in a collagen membrane coated with an agonist (epinephrine or ADP). Platelet adhesion and formation of aggregates seal the aperture, thus indicating the "closure time" measured by the PFA-100.[253,255] In cardiac surgical patients, the preoperative PFA-100 closure time significantly correlated with postoperative blood loss ($r = 0.41$; $P = 0.022$).[256] However, a follow-up study was unable to demonstrate the ability of PFA-100 to differentiate low-bleeding from high-bleeding patients.[257] PFA-100 has demonstrated shear stress–induced platelet dysfunction in patients undergoing heart valve operations,[258,259] and it was used to guide therapy with desmopressin in one study.[260] PFA-100 may be used as a screening test for type II von Willebrand disease, although it does not reliably detect type I von Willebrand disease.[261,262] The PFA-100, like other platelet function tests, seems to have the greatest impact for measuring aspirin resistance in patients with coronary artery disease and coronary stents and after cardiac surgical procedures.[263–265] PFA was demonstrated to have antiplatelet sensitivity similar to that of the Multiplate analyzer, but lower sensitivity than VerifyNow.[246] Test results are more susceptible to inaccuracies as a result of collection, transfer, and transport.[266–268]

Plateletworks

Plateletworks (Helena Laboratories, Beaumont, TX) is a test that uses the principle of the platelet count ratio to assess platelet reactivity. The instrument is a Coulter counter that measures the platelet count in a standard tube containing ethylenediaminetetraacetic acid and compares this with the response to the available agonists: collagen, ADP, and AA. Addition of blood to these agonist tubes causes platelets to activate, adhere to the tube, and effectively be eliminated from the platelet count. The ratio of the activated platelet count to the nonactivated platelet count is a function of the reactivity of the platelets. Results are obtainable in less than 5 minutes. Early investigation in cardiac surgical patients indicated that this assay was useful in providing a platelet count and that it could measure platelet dysfunction that accompanies CPB[269] (Box 19.6).

Plateletworks correlates well with LTA, although results are less sensitive than with PlateletMapping for detection of the effects of aspirin and nonsteroidal antiinflammatory drugs.[186,270] Plateletworks showed utility for preoperative testing and for predicting post-CPB chest tube output, and it correlated with post-CABG transfusion requirements.[271,272] Plateletworks has also been used to monitor response to desmopressin (DDAVP) therapy for platelet dysfunction.[273] The Do Platelet Function Assays Predict Clinical Outcomes in Clopidogrel-Pretreated Patients Undergoing Elective Percutaneous Coronary Intervention (POPULAR) study published results of different POC platelet function tests in detecting resistance to clopidogrel in patients with coronary stent and found that all the assays tested differentiated responders from nonresponders. LTA, VerifyNow, Plateletworks, and PFA-100 were also associated with the composite end points of all-cause death, nonfatal acute myocardial infarction, stent thrombosis, and ischemic stroke.[274,275] In 2014, Orlov and associates[276] reported on

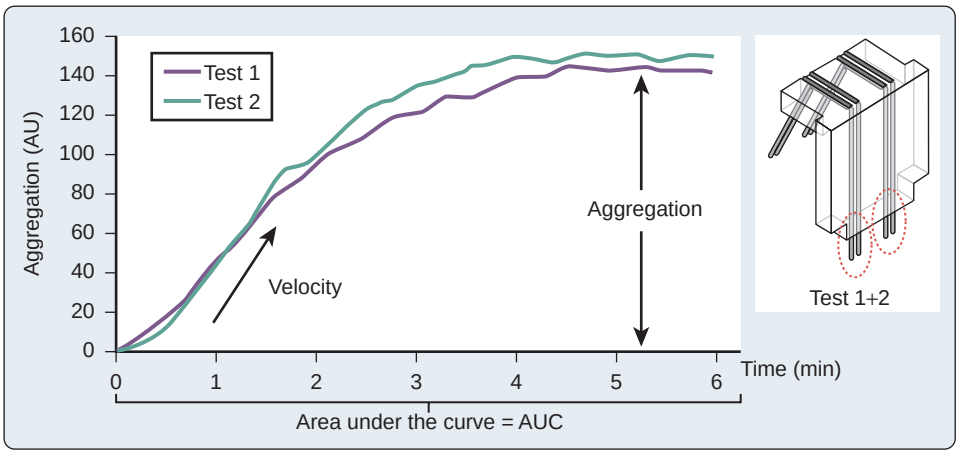
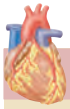


Fig. 19.27 Multiplate Analyzer (Helena Laboratories, Beaumont, TX) tracing. The attachment of platelets onto the Multiplate sensors generates an increase in impedance that is transformed into arbitrary aggregation units *(AU)* and plotted against time. During a measurement period of 6 minutes, the parameters calculated by the software are the mean values of the two curves. *(From* http://www.multiplate.net.*)*



BOX 19.6 PLATELET FUNCTION TESTS

- The appropriate test to measure platelet function depends on the suspected platelet defect.
- The Thrombelastograph (TEG, Haemonetics, Braintree, MA), Rotational Thromboelastometry (ROTEM TEM Systems, Durham, NC), and thromboelastometry, and possibly other viscoelastic tests, are useful to measure platelet defects after cardiopulmonary bypass. VerifyNow (Accumetrics, San Diego, CA) and Multiplate (Helena Laboratories, Beaumont, TX) are useful to measure the effects of glycoprotein IIb/IIIa and adenosine diphosphate receptor-blocker therapy and aspirin therapy.
- The PFA-100 test (Siemens Medical Solutions USA, Malvern, PA) is useful to measure the effects of aspirin on platelet adhesion.
- It is important to understand the platelet defect being sought to use the proper test accurately.

outcomes from a prospective trial in 100 patients undergoing CPB and found that low collagen reactivity during rewarming and after protamine was predictive of excessive bleeding. This observation was in line with findings using collagen agonists in the PlateletMapping assay, in which low collagen activation was found to be predictive of bleeding.[192]

Impact Cone and Plate(let) Analyzer

In the Impact Cone and Plate(let) Analyzer (Matis Medical, Beersel, Belgium), whole blood is exposed to uniform shear by the spinning of a cone in a standardized cup. This allows for platelet function testing under conditions that mimic physiologic blood flow, thus achieving the most accurate pattern of platelet function. After automated staining, platelet adhesion to the cup is evaluated by image analysis software. The test yields two parameters: average size and surface coverage, which determine platelet function in terms of adhesion and aggregation. These values constitute a general platelet function parameter. This device identifies both congenital and acquired platelet defects, as well as the effects of antiplatelet drugs including GpIIb/IIIa antagonists, aspirin, and clopidogrel.[277] Studies suggest that the Impact Cone and Plate(let) Analyzer appears to be a useful tool for testing perioperative platelet function and may help in predicting postoperative blood loss.[278] Experience and clinical publications remain limited with this device, but a few reports focus on detection of responders and nonresponders to antiplatelet medications.[279]

Multiplate Analyzer

The Multiplate Analyzer (Roche Diagnostics, Indianapolis, IN) is a test of platelet function in whole blood that uses impedance aggregometry.[280,281] First introduced in 2005, it is one of the most widely applied platelet aggregometers in Europe today. The analysis is performed in a single-use test cell, which incorporates a magnetic stirrer, as well as two independent impedance sensors. Activated platelets adhere and aggregate on the electrodes and thus enhance the electrical resistance between them. Sample wells are available in "standard" (600 µL) test cells or "mini" test cells (360 µL). Either cell provides reliable results, but results among cell sizes are not intercomparable.[282] The resistance change is transformed to arbitrary aggregation units (AUs) and is plotted against time. The area under the aggregation curve is used to quantify the aggregation response and is expressed in units (1 unit corresponds to 10 AU/min). The mean values of the two independent determinations are expressed as the area under the curve of the aggregation tracing (Fig. 19.27). Multiple channels (or tests) can run simultaneously to evaluate pathways of platelet inhibition. Several specific test reagents are available to detect changes induced by drugs, as well as by acquired or hereditary platelet disorders. These include TRAPtest (thrombin), ASPItest (aspirin), COL test (collagen), ADPtest (clopidogrel), and RISTOtest (ristocetin factor). These reagents allow testing for platelet dysfunction associated with many of the most commonly used platelet antagonist drugs.[187]

The system has a high sensitivity for antiplatelet drugs (aspirin, clopidogrel, prasugrel, GpIIb/IIIa antagonists),[266] and it can predict thromboembolism in stent recipients who are nonresponsive to platelet inhibitors.[283] Many studies now show that Multiplate predicts transfusion requirements in cardiac surgical procedures.[236,280,281,284–286] MEA is available and used widely in Europe, but it is used only for research purposes in the United States and Canada at this time.

Summary

It is essential to understand the complex array of hemostatic insults that result from extracorporeal circulation before selecting an appropriate coagulation or hemostasis monitor during cardiac surgical procedures. Preoperative, intraoperative, and postoperative testing may be mandated for patients in whom a coagulation defect may predispose to serious degrees of postoperative coagulopathy. Even in hemostatically normal patients, CPB induces a heparin effect, platelet dysfunction,

fibrinolysis, and coagulation factor defects for which many clinical laboratory tests are available for accurate diagnoses. With the increase in prescriptions for antithrombotic platelet inhibitors, the hemostatic defect after CPB is even more pronounced. This chapter has introduced the basic principles of hemostasis and the utility of many commonly used monitors for detecting disorders of the coagulation cascade, platelet function, and fibrinolysis. In addition, an increased emphasis on health care economics has created a milieu in which patients have a rapid transit time through the cardiac operating room with minimal exposure to allogeneic blood products. Prophylactic measures such as heparin-bonded circuitry and antifibrinolytic agents have reduced the actual incidence of microvascular bleeding in this population. However, when microvascular bleeding does occur, rapid diagnosis and therapeutic intervention are made possible by POC hemostasis testing, which can take place directly in the operating room. If on-site testing is not available or does not provide sufficient timely information regarding the patient's coagulation defect, transfusion therapy for cardiac surgical patients will remain indiscriminate and empiric at best.

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20

Anesthesia for Myocardial Revascularization

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KEY POINTS

1. Guideline updates emphasize the efficacy of surgical approaches to myocardial revascularization in patients with multivessel coronary artery disease.
2. Perioperative risk reduction includes careful consideration of all of the patient's relevant antihypertensive, antiplatelet, and antianginal medications.
3. Significant valvular abnormalities in patients scheduled for coronary revascularization should be evaluated and considered in surgical planning.
4. Off-pump coronary artery bypass surgery is an established alternative to on-pump myocardial revascularization (ie, coronary artery bypass grafting [CABG]). The choice and outcomes of either approach are highly surgeon dependent. Despite apparent advantages of avoiding cardiopulmonary bypass (CPB), evidence from large prospective trials enrolling mostly low-risk patients has not shown clear reductions in mortality with an off-pump approach.
5. Mitral valve repair for ischemic mitral regurgitation (MR) at the time of coronary revascularization is still controversial; however, it should probably be considered in patients who have a dilated annulus and at least moderate ischemic MR.
6. Possible indications for pulmonary artery catheter use in CABG surgery include patients with pulmonary hypertension, right-sided heart failure, or severely impaired ventricular function, particularly those who require postoperative cardiac output monitoring.
7. Fast-tracking, including early extubation and mobilization, has been almost universally adopted for patients undergoing myocardial revascularization.
8. Anesthetic drugs, especially inhaled anesthetic agents, may help to ameliorate myocardial injury associated with CPB and aortic cross-clamping by their preconditioning and postconditioning effects. However, the magnitude of these effects on outcome remains controversial.

The role of the cardiac anesthesiologist in the perioperative care of patients undergoing myocardial revascularization continues to evolve. Achievements of the past 2 decades include providing safe anesthesia that allows rapid recovery and optimizing monitoring that includes the establishment of transesophageal echocardiography (TEE) as a standard of care in the cardiac operating room. More recent developments in patient care include the introduction of a perioperative surgical home, which affects the management of patients undergoing myocardial revascularization.

The anesthesiologist is vitally important in the multidisciplinary approach to patient care. Optimal perioperative care requires close collaboration and coordination between the various specialties involved on the heart team.[1,2] The process begins with the decision to proceed to surgery and continues with preoperative optimization, state-of-the art perioperative and postoperative care, and rehabilitation after hospital discharge.[3–5]

Epidemiology

According to the American Heart Association Heart Disease and Stroke Statistics, most recently updated in 2014,[6] epidemiologic data relevant to cardiovascular disease can be summarized as follows. Overall rates of death attributable to cardiovascular disease have declined 31%; for CAD, including a 39.2% decrease from 2000 to 2010. This was partially attributed to improvements in acute treatment of patients with acute coronary syndromes (ACSs), secondary preventive therapies after myocardial infarction (MI), treatment of acute heart failure (HF), revascularization of chronic CAD, and other preventive therapies. However, the prevalence remains high, with cardiovascular disease accounting for 31.9% of all deaths in the United States. Based on current estimates, by 2030, 43.9% of the US population will have some form of cardiovascular disease. Similarly, 15.4 million individuals had CAD in 2010; and ischemic heart disease causes approximately 1 of every 6 deaths in the United States. In 2010, 379,559 Americans died of CAD, and statistically, every 34 seconds one person in the United States has a coronary event.

Between 2000 and 2010, the total number of inpatient cardiovascular procedures in the United States increased by 28%, with a total of 7,588,000 cardiovascular procedures performed in 2010. In 2010, an estimated 219,000 patients underwent 397,000 CABG procedures (Fig. 20.1). The in-hospital mortality rate for CABG declined by 50% despite an increase in the comorbidity index. CAD alone resulted in more than $44 billion in expenses, making it the most expensive condition treated. The total direct and indirect cost of cardiovascular disease and stroke was estimated to be $315.4 billion in 2010, more than for any other diagnostic group.

Pathophysiology of Coronary Artery Disease

Anatomy

The anesthesiologist should be familiar with coronary anatomy if only to interpret the significance of angiographic findings. An extensive review of cardiac anatomy can be found in cardiology or cardiac

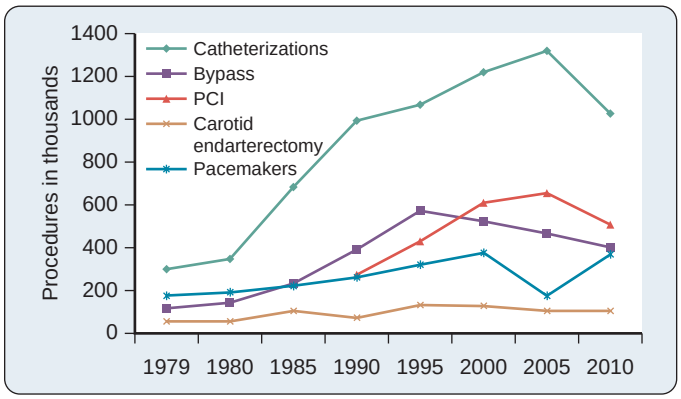


Fig. 20.1 Trends in cardiovascular operations and procedures from 1979 to 2010 for inpatient procedures only. *PCI*, Percutaneous coronary intervention. *(From Mozaffarian D, Benjamin EJ, Go AS, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics: 2015 update. A report from the American Heart Association.* Circulation. *2015;131:e29.)*

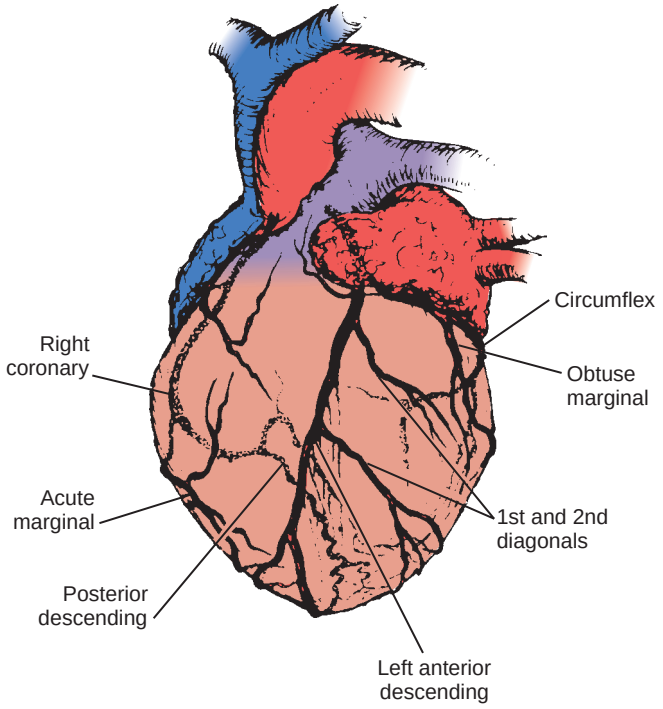


Fig. 20.2 Thirty-degree left anterior oblique angiographic view of the heart, which best shows the right coronary artery. *Lines* indicate common sites of distal vein graft anastomoses. *(From Stiles QR, Tucker BL, Lindesmith GG, et al.* Myocardial Revascularization: A Surgical Atlas. *Boston, Little, Brown; 1976.)*

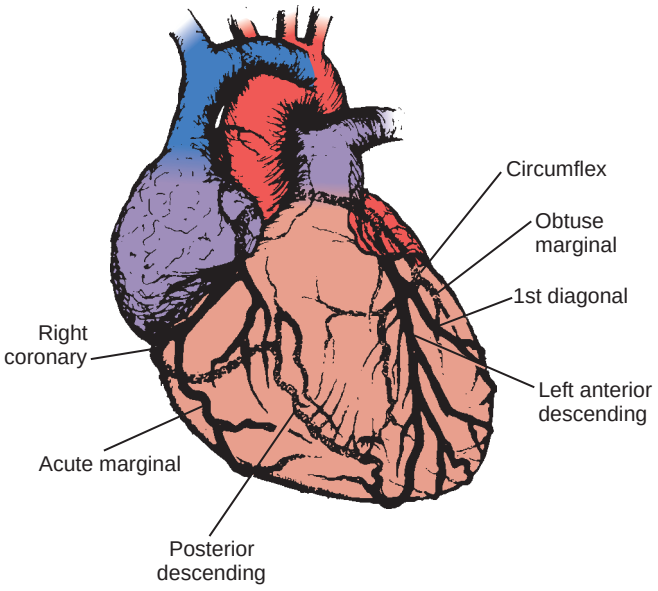


Fig. 20.3 Ten-degree right anterior oblique angiographic view of the heart, which best shows the left main coronary artery dividing into the circumflex and left anterior descending arteries. *Lines* indicate common sites of distal vein graft anastomoses. *(Modified from Stiles QR, Tucker BL, Lindesmith GG, et al.* Myocardial Revascularization: A Surgical Atlas. *Boston: Little, Brown; 1976.)*

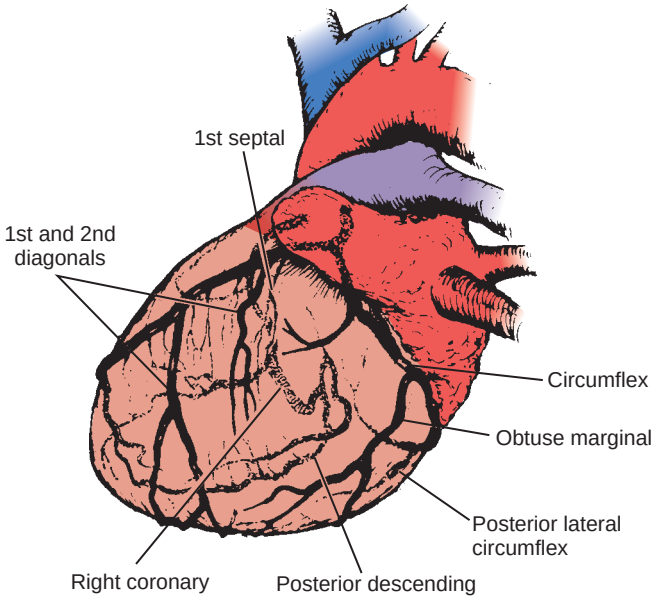


Fig. 20.4 Seventy-five degree left anterior oblique angiographic view of the heart, which best shows branches of the left anterior descending and circumflex coronary arteries. *Lines* indicate common sites of distal vein graft anastomoses. *(Modified from Stiles QR, Tucker BL, Lindesmith GG, et al.* Myocardial Revascularization: A Surgical Atlas. *Boston: Little, Brown; 1976.)*

surgery texts or journals.[7,8] The following is an abbreviated description of the epicardial coronary anatomy. The coronary circulation and common sites for placement of distal anastomoses during CABG are shown in Figs. 20.2 through 20.4.

The right coronary artery (RCA) arises from the right sinus of Valsalva and is best seen in the left anterior oblique view on coronary cine angiography (see Fig. 20.2). It passes anteriorly for the first few millimeters and then follows the right atrioventricular (AV) groove and curves posteriorly within the groove to reach the crux of the heart, the area where the interventricular septum (IVS) meets the AV groove. In 84% of cases, it terminates as the posterior descending artery (PDA), which is its most important branch because it is the sole supply to the posterosuperior IVS. Other important branches are those to the sinus node in 60% of patients and the AV node in approximately 85% of patients. Anatomists consider the RCA to be dominant when it crosses the crux of the heart and continues in the AV groove regardless of the origin of the PDA. Angiographers, however, ascribe dominance to the artery—right coronary or left coronary (ie, circumflex)—that gives rise to the PDA.

The vertical and superior orientation of the RCA ostium allows easy passage of air bubbles during aortic cannulation, cardiopulmonary bypass (CPB), or open valve surgery. In sufficient volume, myocardial

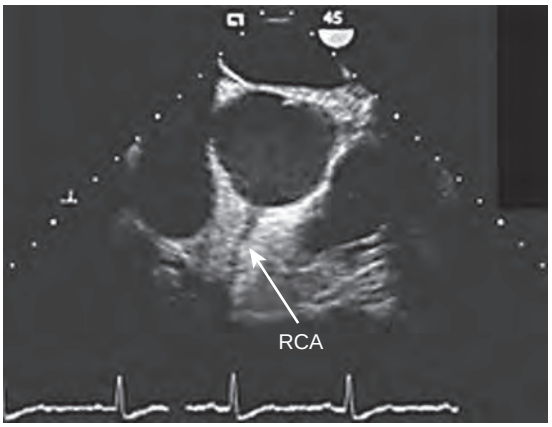


Fig. 20.5 The vertical and superior orientation of the right coronary artery *(RCA)* arising from the aortic root is identified by transesophageal echocardiography (TEE). The TEE transducer in the esophagus is at the top of the screen, and the patient's chest wall is at the bottom. Retained air preferentially enters the RCA, which may cause inferior ischemia, depending on the amount of air and the coronary perfusion pressure. Elevation of perfusion pressure using phenylephrine is often used to treat coronary air embolus. The left main coronary artery (not visible) arises at approximately 3 o'clock on this image. *(Courtesy Martin J. London, MD, University of California, San Francisco, CA [www.ucsf.edu/teeecho].)*

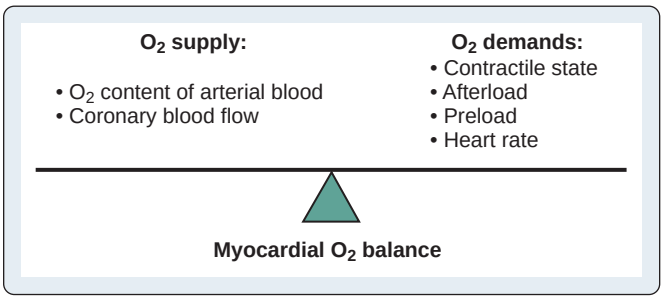


Fig. 20.6 Factors determining myocardial oxygen supply and demand.

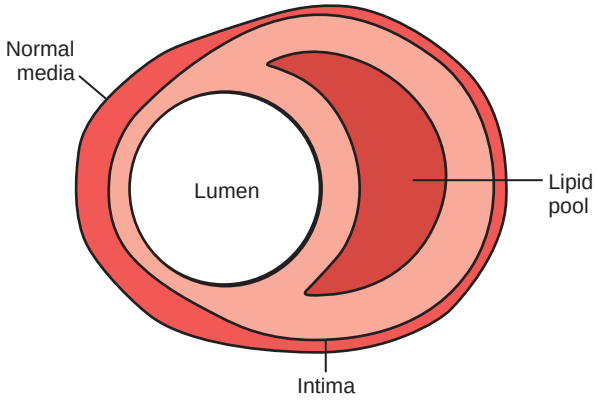


Fig. 20.7 Lipoid plaque lesion of a coronary artery. *(From Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease.* Circulation *82(3 suppl):II38, 1990.)*

ischemia involving the inferior left ventricular (LV) wall segments and the right ventricle may occur (Fig. 20.5). In contrast, the near-perpendicular orientation of the left main coronary ostium makes air embolization much less common.

The left coronary artery arises from the left sinus of Valsalva as the left main coronary artery. It is best seen in a shallow right anterior oblique projection (see Fig. 20.3). The left main coronary artery courses anteriorly and to the left, where it divides in a space between the aorta and pulmonary artery. Its branches are the left anterior descending (LAD) artery and circumflex artery. The LAD passes along the anterior interventricular groove. It may reach only two-thirds of the distance to the apex or extend around the apex to the diaphragmatic portion of the left ventricle. Major branches of the LAD are the diagonal branches, which supply the free wall of the left ventricle; and septal branches, which course posteriorly to supply the major portion of the IVS. Although there may be many diagonal and septal branches, the first diagonal and first septal branches serve as important landmarks in the descriptions of lesions of the LAD (see Fig. 20.4).

The circumflex artery arises at a sharp angle from the left main coronary artery and courses toward the crux of the heart in the AV groove. When the circumflex artery gives rise to the PDA, the circulation is left dominant, and the left coronary circulation supplies the entire IVS and the AV node. In approximately 40% of patients, the circumflex artery supplies the branch to the sinoatrial node. Up to four obtuse marginal (OM) arteries arise from the circumflex artery and supply the lateral wall of the left ventricle (see Fig. 20.4).

All of the previously described epicardial branches give rise to small vessels that supply the outer third of the myocardium and penetrating vessels that anastomose with the subendocardial plexus. The capillary plexus is unique in that it functions as an end-arterial system. Each epicardial arteriole supplies a capillary plexus that forms an end loop rather than anastomosing with an adjacent capillary from another epicardial artery.[9] Significant collateral circulation does not exist at the microcirculatory level.

The capillary anatomy explains the distinct areas of myocardial ischemia or infarction that can be related to disease in a discrete epicardial artery. CAD most commonly affects the epicardial muscular arteries with rare intramyocardial lesions (with the exception of the transplanted heart). However, severe disorders of the microcirculation and primary impairment of coronary vascular reserve in normal coronary arteries have been described, especially in diabetics, females, and those with variant angina.[10–12] Atherosclerosis in all organs is most common at the outer edges of vessel bifurcations because blood flow in these regions is slower and changes direction during the cardiac cycle, resulting in less net shear stress (ie, frictional force per unit area) than in other regions with more steady blood flow and higher shear stress.[13] Low shear stress stimulates the atherogenic phenotype in the endothelium.

Epicardial lesions can be single but are more often multiple. A combined lesion of the RCA and both branches of the left coronary artery is referred to as *triple-vessel disease*.

Venous drainage of the myocardium primarily occurs through the coronary sinus, which enters the right atrium between the inferior vena cava and the tricuspid valve. A small fraction enters the cardiac chambers directly through the Thebesian veins.[14]

Myocardial Ischemia and Infarction

In patients with CAD, myocardial ischemia usually results from increases in myocardial oxygen demand exceeding the capacity of the stenosed coronary arteries to increase oxygen supply (Fig. 20.6). The mechanisms of coronary blood flow (CBF) in health and coronary disease are reviewed in Chapter 7.

In atherosclerotic heart disease, the fundamental lesion is an intimal lipid plaque in the epicardial portion of a coronary artery that causes chronic stenosis and episodic thrombosis and sudden plaque rupture that results in almost complete occlusion (Figs. 20.7 and 20.8). Characteristics of the vulnerable plaque include a high lipid content, a thin fibrous cap, a reduced number of smooth muscle cells, and increased macrophage activity.[15] Chronic inflammation and acute processes such as a plaque rupture result in the release of vasoactive substances from platelets and leukocytes producing endothelial dysfunction and vasoconstriction and further reducing CBF.[15,16] A larger plaque disruption and prolonged thrombosis produce a Q-wave infarction with transmural myocardial necrosis.

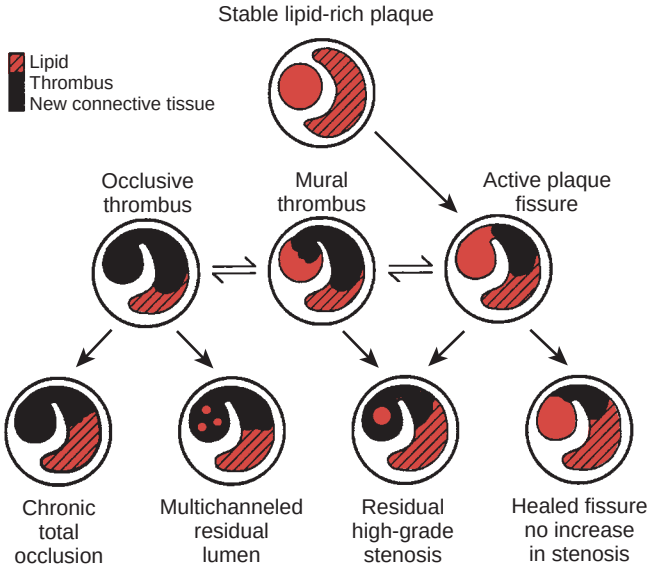


Fig. 20.8 Possible outcomes of intimal plaque rupture. *(From Davies MJ. A macro and micro view of coronary vascular insult in ischemic heart disease. Circulation 82[3 suppl]:II38, 1990.)*

Several studies have found that the coronary artery responsible for an acute infarction is only moderately obstructed chronically.[17,18] The extent of plaque rupture and thrombosis determines the size and extent of an infarction rather than the degree of stenosis. Patients with severely obstructed coronary arteries often have extensive collateral circulations that protect them from infarction. Similar findings have been reported for patients developing postoperative MI after noncardiac surgery.[19–21]

An atherosclerotic lesion produces a pressure gradient and decreases distal coronary perfusion pressure (CPP) that depends on the severity and length of the coronary lesion. Perfusion distal to the lesion depends on the distensibility of the affected coronary artery[22] and flow across the lesion. An increase in blood flow velocity across a stenotic lesion results in a decrease in pressure; whereas a decrease in velocity increases the pressure (see Chapter 21). An increase in flow velocity caused by an atherosclerotic plaque increases the pressure drop and further decreases distal perfusion.[23] Compensatory mechanisms with intact autoregulation include distal vasodilation; however, in the setting of a high-grade stenosis, the microvasculature distal to it may already be maximally dilated, even at rest, further increasing the risk for ischemia.

Collateral vessels exist in normal hearts, but in the setting of CAD, they are increased in size and number.[24] Collaterals may develop between the ischemic zone and an adjacent nonischemic area supplied by a different vessel. Although beneficial at rest, during exercise or periods of increased oxygen demand, CBF may be shunted away from the ischemic myocardium to areas with intact autoregulation able to vasodilate; this is referred to as a *coronary steal*.[25] In experimental models, a partial lesion of the epicardial artery supplying the collateral vessel is required to produce a coronary steal.[26] This anatomic configuration, called *steal-prone anatomy*, occurred in 23% of patients with symptomatic CAD in one large registry of coronary angiograms.[27]

Risk Assessment in Patients Scheduled for Coronary Artery Bypass Grafting

Preoperative risk assessment for patients undergoing CABG has evolved dramatically over the past 3 decades. The institution of federally mandated accounting of surgical outcomes for cardiac surgery in the Department of Veterans Affairs in the 1970s led to the establishment of what is considered the first large-scale, multicenter surgical outcomes database, which applies rigorous statistical methodology for comparing outcomes between centers.[28,29] The applied methodology allows adjustment for different severities of illness between patients (ie, risk adjustment) by using multiple preoperative and perioperative variables thought to be of intrinsic value (usually by expert consensus) that easily can be captured and have high consistency of definition. Statistical models are then used to calculate an expected outcome (eg, mortality). By simple comparison of the observed (O) to expected (E) outcome of a certain procedure such as CABG, hospitals in a particular system can be ranked from best (ie, low O/E ratio) to worst (ie, high O/E ratio).[30]

Although statistical models can be used to compare outcomes and drive performance improvement measures (eg, surgical site infection prevention), experts have cautioned that gaming of the system by exploiting variables with imprecise definitions is an inherent problem.[31] Nonetheless, this methodology and its variants have been adopted widely by many organizations as a measure of quality of care.[29,32] For example The Society of Thoracic Surgeons (STS) instituted a voluntary clinical database system with this approach in the early 1990s, which has continued to grow rapidly as cardiac surgical groups have become increasingly interested in benchmarking their practices against others.[33–36] The STS National Cardiac Database includes more than 98% of all cases performed annually in the United States. New York and many other states maintain risk-adjusted mandatory reporting systems for hospital and individual surgeon performance.[37–39]

Perioperative outcomes can be assessed by a multitude of clinical and nonclinical parameters. The most important outcome measure for surgical risk assessment is operative mortality, defined in the STS database as all deaths, regardless of cause, that occur during hospitalization for the operation or within 30 days after surgery if hospital discharge has already occurred.[40] Mortality rates vary widely with patient risk, acuity, additional procedures (eg, CABG, valve replacement), and previous cardiac surgery. The 1990s saw a notable decline in mortality rates despite increases in patient risk (Fig. 20.9).[41] Risk-adjusted mortality rates for isolated CABG have been consistently between 1.5% and 2% for patients included in the STS database in the past few years.[42] The short-term mortality rate has become a relatively insensitive marker of further improvements[43] and long-term mortality rates,[44] and other outcome measures such as hospital readmission are increasingly investigated.[45,46]

Perioperative or long-term mortality rates seem to be of limited use for the cardiac anesthesiologist. Predicting patients who are difficult to wean from CPB or who develop acute HF requiring pharmacologic or mechanical circulatory support, rhythm abnormalities, or prolonged mechanical ventilation are often considered of greater interest to the anesthesiologist. An analysis of 1009 patients undergoing CABG at Duke University, all of whom were monitored with TEE, found six independent predictors of inotrope support, which was required for 39% of the cohort during weaning from CPB (Fig. 20.10; Table 20.1).[47] However, because many of the factors associated with acute complications frequently encountered in the operating room or intensive care unit (ICU) are also found in the risk assessment scores that predict CABG mortality, the scores are of value and relevant to cardiac anesthesiologists even in the immediate perioperative care setting[48,49] (Box 20.1).

The two risk score models most commonly used to predict outcomes for CABG are the STS score mostly used in North America and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) in Europe. Both assessments are available free of charge online, and a risk score can be automatically calculated.[50,51] Many studies have compared the STS and EuroSCORE regarding their ability to accurately predict perioperative mortality for CABG patients.[52–54] Both models reliably predict mortality associated with cardiac surgery. However, the matter is complicated by a growing variety of surgical procedures used for myocardial revascularization. In addition to on-pump CABG, off-pump coronary artery bypass (OPCAB) surgery, minimally invasive

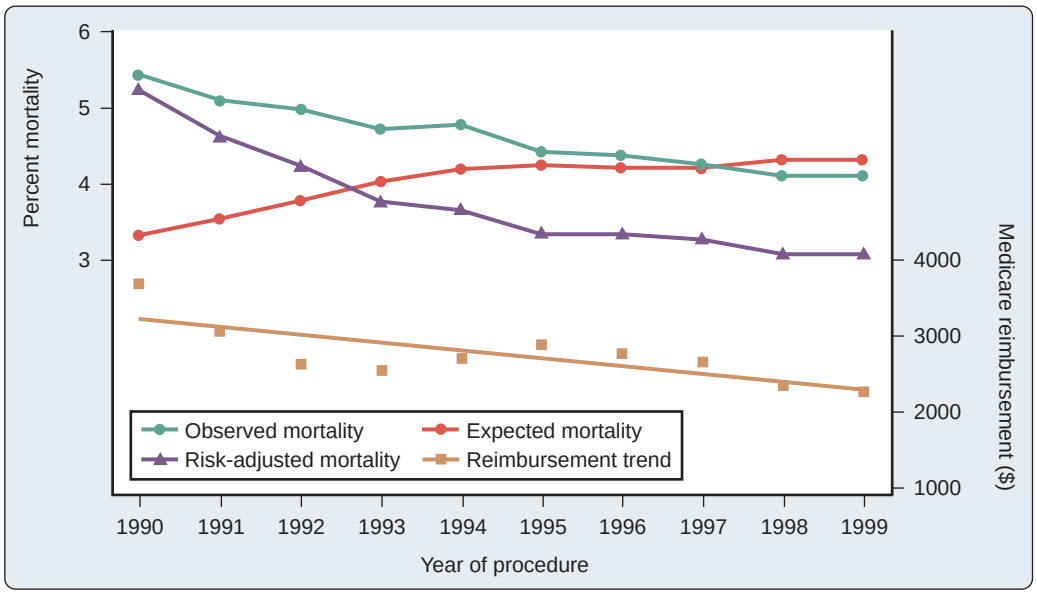


Fig. 20.9 Composite figure demonstrates an increase in the risk profile with declining mortality rates and part B Medicare reimbursement for patients undergoing coronary artery bypass grafting between 1990 and 1999. *(From Ferguson TB Jr, Hammill BG, Peterson ED, et al. A decade of change—risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990–1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons.* Ann Thorac Surg. *2002;73:480.)*

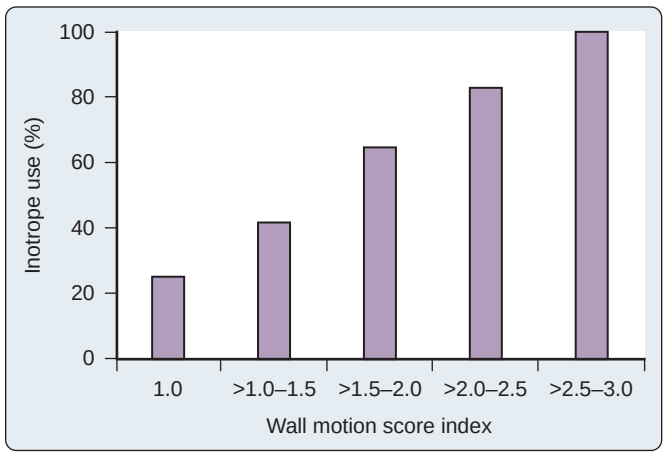


Fig. 20.10 Correlation of degree of wall motion abnormalities before cardiopulmonary bypass (CPB) as reflected by an increasing wall motion score index associated with a greater use of inotropes during weaning from CPB. *(From McKinlay KH, Schinderle DB, Swaminathan M, et al. Predictors of inotrope use during separation from cardiopulmonary bypass.* J Cardiothorac Vasc Anesth. *2004;18:404.)*

TABLE 20.1 Multivariate Predictors of Inotrope Use

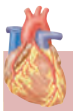
Variable	*Parameter Estimate*	*Odds Ratio (95% CI)*	*P Value*
Intercept	−3.2827		
Cross-clamp time (min)	0.0133	1.013 (1.008–1.019)	<.001
WMSI	1.4389	4.216 (2.438–7.292)	<.001
Reoperation	0.8562	2.375 (1.083–5.212)	<.001
CABG + MVRR	1.2829	3.607 (1.376–9.456)	.009
Moderate/severe MR	0.4144	2.277 (1.169–4.435)	.016
LVEF <35%	0.8654	2.376 (1.303–4.332)	.005

CABG, Coronary artery bypass grafting; *CI*, confidence interval; *LVEF*, left ventricular ejection fraction; *MR*, mitral regurgitation; *MVRR*, mitral valve repair or replacement; *WMSI*, wall motion score index.

From McKinlay KH, Schinderle DB, Swaminathan M, et al. Predictors of inotrope use during separation from cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2004;18:404.

procedures, and hybrid revascularization strategies are increasingly used, which complicate the use and comparability of available outcome models.[55,56]

Morbidity and mortality also are influenced by events in the operating room, including time on CPB and aortic cross-clamping, adequacy of revascularization, and complications such as cardiovascular decompensation or bleeding. Several investigators have attempted to delineate the association of perioperative events and hemodynamic data with outcomes for larger cohorts of patients. For example, Reich and coworkers[57] merged computerized anesthesia record data from 2149 CABG patients (with CPB) at two New York Hospitals from 1993 to 1995 with outcome data from the state's mandatory reporting database. Four independent predictors of mortality were identified: high



BOX 20.1 PREOPERATIVE HIGH-RISK CARDIAC CHARACTERISTICS

1. Acute unstable angina, acute myocardial infarction, uncompensated congestive heart failure, cardiogenic shock
2. Left main lesion, proximal left anterior descending artery lesions
3. Ejection fraction <30% (normal >55%)
4. Concurrent significant valvular disease
5. Advanced age (>70 years)
6. Electrocardiographic signs of acute or ongoing ischemia
7. Aortic calcification (ie, inability to cross-clamp aorta)
8. High-grade occlusive carotid artery disease
9. Preexisting neurologic deficits

mean pulmonary arterial pressure (PAP) before CPB (>30 mm Hg; odds ratio [OR] = 2.1), low mean arterial pressure (MAP) during CPB (40 to 49 mm Hg; OR = 1.3), tachycardia (HR >120 beats/min; OR = 3.1), and high diastolic pulmonary arterial pressure (>20 mm Hg; OR = 1.2) after CPB.

Newer monitoring technologies such as cerebral oximetry have been used to predict outcomes in cardiac surgery. de Tournay-Jetté and colleagues, for example, showed that intraoperative cerebral desaturation is associated with cognitive dysfunction after CABG.[58]

Many of the immediate complications related to CABG manifest after CPB and in the cardiac ICU. Specific scores have been developed for predicting the risk of death of critically ill patients, and some scores have been assessed in the cardiac surgery setting.[59–63] However, the performance of general critical care scoring systems is often inadequate and of limited value for cardiac surgery patients. For example, Doerr and associates[64] compared the performance of four intensive care outcome prediction scoring systems (ie, Acute Physiology and Chronic Health Evaluation II [APACHE II], Simplified Acute Physiology Score II [SAPS II], Sequential Organ Failure Assessment [SOFA], and Cardiac Surgery Score [CASUS]) for patients after cardiac surgery. Two of the critical care scores (ie, APACHE II and SAPS) failed to reliably stratify risks for cardiac surgery patients.

Effective resource management is becoming increasingly important, and predicting ICU length of stay (LOS) is critical for this purpose. Existing predictive models have been tested and new ones developed to predict resource use and particularly LOS. For example, the Surgical Procedure Assessment (SPA) score was compared with four other critical care scores in predicting ICU LOS for cardiac surgical patients.[65] The preoperative assessment using the SPA score is mostly based on procedure complexity, and it reliably predicted ICU LOS and was better than other scores tested. In another study, the Parsonnet Score reliably predicted ICU LOS and postoperative complications for cardiac surgery patients.[66]

Because of the increasing popularity and almost universal use of the STS and EuroSCORE, many of the other critical care risk scores have almost been abandoned in the cardiac surgery ICU setting. Several studies have shown that the EuroSCORE and STS score are suitable for capturing the risk associated with cardiac surgery. A comparison of six commonly used risk scores found the EuroSCORE to yield the highest predictive value for 30-day mortality for cardiac surgery patients (STS score was not included).[67] In another study, the EuroSCORE was compared with the Cardiac Anesthesia Risk Evaluation (CARE) score, which was developed in the mid-1990s.[68] Both scoring systems performed well in predicting cardiac surgical mortality. Ettema and coworkers[69] tested 20 risk score models for their ability to predict ICU LOS for more than 11,000 cardiac surgery patients. The Parsonnet score and the EuroSCORE were superior in identifying patients with longer ICU stays. However, the commonly used risk calculators do not consider some important physical comorbidities (eg, hepatic dysfunction) and psychosocial factors (eg, mental strength, attitude, family support system) that powerfully impact patient outcomes and LOS.

Percutaneous coronary interventions (PCI) and modern coronary stent technology continue to advance. The past few decades have seen shifts in treatment paradigms, and guidelines for surgical versus percutaneous intervention in patients with CAD are updated on a regular basis, reflecting data from the most recent clinical trials.[70]

The SYNergy between percutaneous coronary intervention with TAXus drug-eluting stent and cardiac surgery (SYNTAX) trial, a prospective, randomized, multicenter trial, originally was designed to evaluate current practice patterns and optimal revascularization strategies in patients with three-vessel disease and left main CAD in Europe and the United States.[71] For the purpose of risk stratification in this trial, the SYNTAX score was developed, characterizing the complexity of coronary pathology. The SYNTAX score is based on existing classifications and takes the number, location, complexity, and functional impact of the coronary lesions into consideration.[72] Patients with more complex disease and potentially worse prognosis have higher SYNTAX scores. The initial analysis showed that there was no difference in outcomes (ie, major adverse cardiovascular and cerebrovascular events [MACCEs]) among patients randomized to surgery between those who had low, intermediate, or high scores (MACCE of 14.4%, 11.7%, 10.7%, respectively).[73]

In patients randomized to PCI, however, the SYNTAX score was able to predict adverse outcomes for the described risk groups at 12 months (13.5%, 16.6%, 23.3%, respectively). Comparing outcomes between patients randomized to surgery versus PCI, those with low SYNTAX scores (<22) had similar outcomes irrespective of treatment assignment. Those with more complex CAD (intermediate SYNTAX score of 23 to 32 or high SYNTAX score >32) had better survival and MACCE-free survival with surgery. Longer-term follow-up of the SYNTAX trial through 5 postoperative years confirms the survival advantage of surgery over PCI for patients with CAD of intermediate or high complexity, and this survival advantage increases with increasing duration of follow-up.

Anesthesia for Coronary Artery Bypass Grafting

The practitioner providing anesthesia care for patients undergoing coronary revascularization has to implement an anesthetic plan that takes patient- and surgery-specific factors into consideration, but it should also include the most recent recommendations and guidelines regarding the perioperative care of patients with CAD.

In the earlier days of cardiac surgery, the focus on anesthesia management for patients undergoing CABG was mainly on maintaining hemodynamic stability and preventing ischemia. This reflected the lack of anesthetic agents with minimal hemodynamic effects. Later reports supported a lack of effect of the technique, suggesting that hemodynamic control was more important (ie, it is not what you use, but how you use it).[74,75]

With the introduction of modern anesthetic agents, the focus shifted to investigating how the various regimens and techniques could help to improve outcomes of patients undergoing myocardial revascularization. For example, considerable data demonstrate the beneficial effects of using potent inhalation agents[76,77] or sympathetic blockade[78] on markers of myocardial ischemia and postoperative MI, such as improved recovery and shorter LOS. However, many data are derived from in vitro studies. In vivo investigations mostly suffer from inadequate statistical power and reporting single-center experiences, and they have problems with standardization of definitions and reporting of surrogate outcomes. Clinically recognizable advantages appear to be modest and demonstration of overt reductions in serious morbidity or mortality rates in large-scale, multicenter cohorts have not been reported.[79,80]

Premedication

The concept of premedication has been evolving beyond the traditional ordering of sedative-hypnotics or related agents to reduce patient anxiety and promote amnesia. The cardiac anesthesiologist must be familiar with the potential benefits of administering or hazards of not administering a variety of medications, including antianginal, β-blocker, and antiplatelet drugs.

Anxiolysis, Amnesia, and Analgesia

The purposes of premedication are to pharmacologically reduce apprehension and fear, to provide analgesia for potentially painful events before induction (eg, vascular cannulation), and to produce some degree of amnesia. In patients with CAD, premedication may help prevent preoperative anginal episodes that are relatively commonly observed and may be elicited by tachycardia due to anxiety or painful stimuli. Short-acting benzodiazepines are the mainstay of drugs administered for this purpose. When given intravenously in the preoperative holding area to patients with CAD, supplemental oxygen should be administered and the patients monitored by pulse

oximetry, an electrocardiogram (ECG), and noninvasive blood pressure methods.

The sedative and anesthetic-sparing actions of α_2-adrenergic agonists (eg, clonidine, dexmedetomidine) were evaluated for their efficacy in several older studies of CABG patients alone or in combination with a benzodiazepine.[81–85] However, some of the side effects, such as decreased HR, MAP, cardiac output (CO), and contractility and transiently increased systemic vascular resistance [SVR]), warrant caution for patients with CAD who are prone to myocardial ischemia. Currently, α_2-adrenergic agonists play only a minor role in premedication for patients undergoing myocardial revascularization.

Management of Preoperative Medications

Patients undergoing myocardial revascularization routinely take medications aiming to prevent acute coronary events, worsening of ischemia, or HF symptoms. Many of these drugs have implications for anesthesia management, and the anesthesiologist should be familiar with the current guidelines and recommendations outlining their use in the perioperative setting (Box 20.2) (see Chapters 1 and 11).

β-Blocking Agents

β-Blocking agents are routinely administered to many patients with CAD. As early as the mid-1970s, Kaplan suggested that it was safe to continue β-blockade in patients with ischemic heart disease undergoing cardiac or noncardiac surgery, even those with poor ventricular function.[86,87] This was confirmed in many prospective, randomized trials that established the safety of continuing β-blockade in the perioperative period. Slogoff and colleagues,[88] for example, performed a randomized trial evaluating the safety of propranolol administration within 12 hours of surgery. Based on a significantly greater increase in the incidence of pre-CPB ischemia in patients withdrawn from propranolol, they recommended continuation of therapy until the time of surgery. Further work in the 1980s documented the efficacy of β-blocker continuation through CABG surgery for reducing pre-CPB ischemia and the superior efficacy over the then increasingly popular calcium channel blockers.[89–93]

Although early work established safety of use and harm of discontinuing β-blockers in the perioperative setting, the past 2 decades have seen a few landmark prospective, randomized, controlled trials demonstrating the benefits of β-blockade for patients at risk for adverse cardiac events. For example, Mangano and associates[94] compared the use of atenolol with placebo in high-risk patients undergoing noncardiac surgery. Atenolol reduced mortality rates and the incidence of cardiovascular complications. Several observational studies documented associations of β-blocker therapy with reduction in perioperative mortality rates for CABG patients.[95,96] Ferguson and coworkers[97] considered 629,877 patients in the STS database (1996–1999) for whom a modest but statistically significant reduction in the 30-day risk-adjusted mortality rate was reported. This treatment effect was observed in many high-risk subgroups, although a trend toward increased mortality rates was seen for patients with an ejection fraction (EF) of less than 30%.

In a metaanalysis, Wiesbauer and associates[98] found that perioperative β-blockers reduced perioperative arrhythmias after cardiac surgery, but they were unable to show an effect on MI or mortality. Based on the existing evidence from a few randomized, controlled trials, retrospective studies, and metaanalyses, β-blocker use was recommended by many specialty societies for patients undergoing CABG or those at risk for adverse cardiac events who were undergoing noncardiac surgery. Considerable efforts were being expended by major organizations such as the STS and American College of Cardiology (ACC) in increasing compliance with these guidelines and recommending the use of β-blockers at the time of hospital discharge, along with the use of aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors.[99–101]

The role of β-blockers gained renewed interest with the disclosure of flawed research data that contributed significantly to the recommendations regarding β-blocker use in the perioperative setting.[102] Conclusions drawn from the POISE trial[103] raised questions about the suggested benefits of high-dose β-blockade in patients undergoing surgical procedures and suggested potential harm of this practice.

Due to the adoption of preoperative β-blocker therapy as a national quality standard, most patients who undergo CABG are prescribed β-blockers before surgery. There is no doubt that the acute discontinuation of β-blockers is associated with rebound tachycardia, arterial hypertension, and worsening of HF, which are particularly unwarranted in patients at risk for myocardial ischemia. However, the routine use of β-blockers even in low-risk CABG patients has been questioned. Brinkman and associates[104] retrospectively analyzed 505,110 adult patients listed in the STS database who underwent elective CABG between 2008 and 2012. After risk adjustment, there was no significant difference in major outcomes, including operative mortality, stroke, prolonged mechanical ventilation, renal failure, sternal wound

BOX 20.2 PREOPERATIVE MEDICATION MANAGEMENT

1. β-Adrenergic blockers
   - Should be administered for at least 24 hours before coronary artery bypass grafting (CABG) to all patients without contraindications (eg, hypotension, third-degree heart block, bronchospasm).
   - After CABG surgery, should be reinstituted as soon as possible in all patients without contraindications.
2. Statins: All patients undergoing CABG should receive them unless contraindications apply.
3. Calcium channel blockers: Patients already on calcium channel blockers should continue them perioperatively.
4. Angiotensin-converting enzyme inhibitor:
   - Preoperative discontinuation is controversial (ie, increased risk of hypotension and vasoplegic syndrome).
   - Postoperatively, should be initiated and continued indefinitely in CABG patients who are stable unless contraindications apply.
5. Diuretics: No firm recommendations, but ensure adequate serum potassium levels.
6. Aspirin: Should be administered preoperatively. The decision about whether and when to discontinue aspirin before surgery depends on patient-specific factors such as individual risk for bleeding and presence of an acute coronary syndrome. Postoperatively, aspirin should be started as early as possible (ie, within 6 to 24 hours after surgery).
7. Antiplatelet agents such as oral inhibitors of purinergic receptor P2Y12: Because they are associated with an increased risk of bleeding, recommendations call for withholding for a few days before surgery. However, in high-risk patients and/or after placement of drug-eluting stents, recommendations may change, and intravenous glycoprotein IIb/IIIa inhibitors or cangralor may be continued perioperatively despite increased risk of bleeding.
8. Heparin: Regimen often depends on the surgeon. Usually discontinued 4 hours preoperatively for stable patients, continued up to and through pre–cardiopulmonary bypass period for critical left main disease or acutely unstable angina patients.
9. Oral hypoglycemic agents: No firm recommendations; consider withholding administration. However, glucose control must be ensured.
10. Antibiotic prophylaxis: Optimal timing and weight adjustment (especially important with antibiotics that have slow tissue penetration such as vancomycin). Typically, a second-generation cephalosporin such as cephazolin (2 g IV) or cefuroxime (1.5 g IV) administered 20 to 60 minutes before incision; vancomycin (15 mg/kg) administered as a slow infusion to avoid hypotension and flushing (due to slow tissue penetration, infusion should be completed 20 to 30 minutes before skin incision).

infection, and reoperation, between patients who received β-blockers and those who did not. Patients who received β-blockers within 24 hours of surgery had a higher incidence of new-onset atrial fibrillation (AF).

LaPar and colleagues[105] looked at 43,747 patients listed in the STS database who had isolated CABG between 2001 and 2011. Most (80%) patients used β-blockers preoperatively. Even though the β-blocker group had a lower predicted mortality score compared with the non–β-blocker group, there was no observed benefit in mortality, morbidity, LOS, or hospital readmission associated with its use. The investigators concluded that based on their findings, the routine use of β-blockers for CABG should not be used as a quality outcome measure.

The 2011 American College of Cardiology Foundation and American Heart Association (ACCF/AHA) guideline for CABG surgery[106] recommended that β-blockers should be administered for at least 24 hours before CABG to all patients without contraindications to reduce the incidence or clinical sequelae of postoperative AF. The guidelines state that β-blockers in CABG patients with an EF greater than 30% can be effective in reducing the risk of in-hospital mortality and the incidence of perioperative myocardial ischemia. In patients with severely depressed LV function (EF <30%), the effectiveness of preoperative β-blockers in reducing the in-hospital mortality rate is uncertain. After CABG, β-blockers should be reinstituted as soon as possible for all patients without contraindications.

In 2015, the AHA published a scientific statement complementing the existing guidelines that focused on secondary prevention measures after CABG.[107] The expert statement supports the recommendation to give β-blockers starting before surgery, including administering them to patients with prior MI unless contraindicated (eg, bradycardia, severe reactive airway disease). In patients with previous MI, β-blockers are specifically recommended for patients with HF symptoms and an EF below 40%.

There remains little doubt that β-blockers are beneficial for many patients undergoing surgery who are at risk for myocardial ischemia and adverse cardiac events. However, defining and refining indications, exact end points (ie, HR), exclusion criteria, and specific drug formulas requires further investigations.[108]

Antiplatelet Drugs

In accordance with current guidelines, most patients undergoing CABG are treated with platelet inhibitors. Aspirin is a well-recognized component of primary and secondary prevention strategies for all patients with ischemic heart disease.[109,110] Clopidogrel administration is established practice after coronary artery stent placement, and it is recommended in combination with aspirin for patients with ACS.[111–113] Studies in the 1980s showed benefits of antiplatelet therapy, including prevention of early graft thrombosis in patients after CABG.[114] Additional benefits of antiplatelet therapy also were recognized. For example, in a large observational analysis, Mangano and coworkers[115] reported a substantial reduction in the overall mortality rate (1.3% vs 4.0%) and ischemic complications of the heart, brain, kidneys, and gastrointestinal tract in 5065 patients at 70 hospitals when aspirin was administered within 48 hours after surgery.

The combination of aspirin and potent inhibitors of platelet function such as clopidogrel are even more effective than single agents in treating patients with ACS and preventing early graft thrombosis after CABG.[116] However, controversy exists regarding timing and specifically when to discontinue preoperative antiplatelet therapy.

The risk of hemorrhagic complications should be weighed against the potential benefits of antiplatelet therapy. Several metaanalyses have documented risks of potent antiplatelet agents in patients undergoing CABG. Sun and colleagues found that patients receiving aspirin immediately before surgery had more mediastinal bleeding and received more blood products.[117] In another metaanalysis, late discontinuation of adenosine diphosphate (ADP) receptor antagonists (2–7 days preceding CABG) was associated with an increased risk of death and reoperation for bleeding.[118] Another metaanalysis acknowledged the role of antiplatelet agents in patients with ACS but also recommended discontinuing clopidogrel at least 5 days before CABG to account for an adequate washout period.[119] Biancari and associates found that recent exposure to clopidogrel before CABG was associated with an increased risk of postoperative death, reoperation for bleeding, blood loss, and the need for blood transfusions.[120] Several retrospective and observational studies have reported that CABG in patients receiving clopidogrel is associated with increased bleeding and transfusion requirements.[121,122] Filsoufi and coworkers reported longer ICU and hospital LOS and increased all-cause morbidity and mortality rates for patients who were administered clopidogrel preoperatively.[123] In a multicenter retrospective study, Berger and associates[124] reported that clopidogrel-treated patients were at increased risk for reoperation, major bleeding, and increased LOS.

Guidelines summarizing the current evidence regarding antiplatelet drugs in patients undergoing surgery have been published by various specialty societies and are updated regularly. The most recent update of the STS guidelines on the use of antiplatelet drugs in patients undergoing CABG was published in 2012.[125] The highest level of evidence (class I recommendation, level A evidence) was found for aspirin administration within 6 to 24 hours after surgery in nonbleeding patients to optimize vein graft patency and for dual antiplatelet therapy for patients undergoing CABG after ACS as soon as the bleeding risk is diminished to decrease adverse cardiovascular outcomes. The class I recommendation with level B evidence advised discontinuing inhibitors of the purinergic receptor P2Y12 (ie, chemoreceptor for ADP) for a few days before surgery to reduce the risk of bleeding and need for blood transfusion.

In 2012, the task force acknowledged that there was insufficient data to make definitive statements regarding the exact interval required between drug discontinuation and surgery and that it should be adjusted depending on many factors, including individual drug responsiveness and thrombotic risk. There is a class IIa recommendation with level B evidence that aspirin can be safely discontinued a few days before surgery in patients at high risk for bleeding and patients without ACS. For patients on dual antiplatelet therapy, surgery should be delayed for a day or two if possible to decrease the risk of bleeding.

The 2011 ACCF/AHA guideline for CABG surgery[106] recommended that aspirin should be administered to CABG patients preoperatively. For elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days to limit the need for blood transfusions. For urgent surgery, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications. Postoperatively, aspirin should be started within 6 hours after surgery. For those allergic to aspirin, clopidogrel should be used instead. Low-dose aspirin should be continued indefinitely. The 2015 AHA scientific statement on secondary prevention measures after CABG confirmed these recommendations and recommended dual antiplatelet therapy with aspirin and clopidogrel for 1 year.[107]

HMG CoA Reductase Inhibitors

Potent antiinflammatory and antithrombotic effects and beneficial effects on endothelial function and angiogenesis have been reported for 3-hydroxy-3-methyl-glutaryl–coenzyme A (HMG CoA) reductase inhibitors (ie, statins).[126–129] Administered acutely during PCI,[130–132] statins have direct effects on platelet aggregation and plasminogen activator inhibitors (eg, tPA).[133,134] Improved outcomes also have been described for patients undergoing CABG.[135–138] This includes attenuation of myocardial reperfusion injury after CPB,[139] reducing short- and long-term mortality rates, and decreasing early graft occlusion in CABG patients.[140–145]

From a large metaanalysis evaluating the impact of preoperative statin use on adverse clinical outcomes after cardiac surgery, Liakopoulos and colleagues[146] reported that preoperative statin use significantly reduced all-cause mortality rates. Retrospective analysis of 14, 834 patients undergoing myocardial revascularization (ie, PCI or CABG) showed that statin therapy was associated with a significant risk reduction for major adverse cardiovascular events in the

follow-up period.[147] Statins also decrease the need for postoperative renal replacement therapy, although results regarding a reduction in acute renal dysfunction were conflicting.[142,148] Statins have decreased the incidence of AF after cardiac surgery.[149] Postoperative withdrawal of statin treatment is independently associated with increased hospital mortality rates after CABG.[143]

Based on the accumulating evidence for the beneficial effects of statin therapy in patients undergoing myocardial revascularization, guidelines have been adjusted. The 2011 ACCF/AHA guideline for CABG surgery[106] recommended that unless contraindications apply, all patients undergoing CABG should receive statin therapy with the goal of lowering low-density lipoprotein (LDL) cholesterol by at least 30% or to less than 100 mg/dL. Even lower targets may be advisable (<70 mg/dL) for very-high-risk patients. The most recent AHA scientific statement on secondary prevention measures after CABG confirmed these recommendations, and recommended statin therapy starting preoperatively and continued after surgery,[107,150]

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are widely considered to be vasculoprotective, particularly with regard to ventricular remodeling after acute MI, and they appear to reduce damage after ischemic reperfusion.[151] The role of ACE inhibitors in improving major outcomes for patients with ischemic heart disease and those undergoing myocardial revascularization has been investigated.[151,152] The QUinapril on Vascular Ace and Determinants of Ischemia (QUO VADIS) study[153] showed a significant reduction in ischemic events in patients on ACE inhibitors before CABG.

Although patients with ischemic heart disease and HF may benefit from ACE inhibitor therapy, the effect on many other CABG-relevant outcome parameters is less clear. Although, some studies found an association with ACE inhibitor therapy before CABG and a reduced risk of acute kidney injury[154] and prevention of new-onset AF,[155] preoperative ACE inhibitor therapy is also associated with hypotension during induction or even profound degrees of vasodilation (ie, vasoplegic syndrome) during CPB and weaning due to their vasodilatory effects.[156–163] Hypotension and vasoplegia may counteract some of the potential beneficial properties and increase the risk of adverse events. For example in a large, retrospective, observational study of more than 10,000 patients undergoing CABG, preoperative ACE inhibitor therapy was associated with an increased incidence of perioperative hypotension, and ACE inhibitor therapy was found to be an independent predictor of mortality, need for inotropic support, postoperative renal dysfunction, and new-onset postoperative AF.[164]

In a later retrospective analysis, Shi and coworkers compared 1239 patients who received renin-angiotensin system inhibitors with a control group.[165] The patients in the study group had a significantly lower risk of acute kidney injury, operative mortality, and sepsis. A metaanalysis (ie, 13 studies including a total of 31,390 patients) found preoperative ACE inhibitor administration to be associated with hypotension, postoperative MI, and renal dysfunction; no effect on mortality rates was found.[166]

Miceli and colleagues found that preoperative ACE inhibitor use doubled the risk of death and was independently associated with the use of inotropic drugs.[164] Bandeali and associates[167] retrospectively analyzed 8889 patients undergoing CABG; 3983 used ACE inhibitors preoperatively. Patients who received ACE inhibitors had a higher risk of major adverse events; most significantly renal dysfunction and AF. Drenger and coworkers also investigated ACE inhibitor use in 4224 patients undergoing CABG.[168] ACE inhibitors administered preoperatively and continued after surgery and ACE inhibitors started after surgery were associated with improved in-hospital outcomes. Discontinuation of ACE inhibitors was associated with nonfatal in-hospital ischemic events, but no difference in mortality was found.

The 2011 ACCF/AHA guideline for CABG surgery[106] recommended that preoperative use of ACE inhibitors and angiotension II receptor blockers (ARBs) should prompt reinstitution postoperatively after the patient is stable unless contraindicated. Independent of preoperative use, ACE inhibitors and ARBs should be initiated postoperatively and continued indefinitely in CABG patients who are stable unless contraindications apply. The task force also acknowledges that the safety of the preoperative ACE inhibitors or ARBs in patients on chronic therapy is uncertain. The most recent AHA scientific statement on secondary prevention measures after CABG confirmed these recommendations and recommended administering ACE inhibitors or ARB therapy after CABG to all patients with LV dysfunction.[107,150]

Calcium Channel Antagonists

Early observational studies suggested that calcium channel antagonists were ineffective in the treatment and prevention of myocardial ischemia, particularly when compared with β-blockers.[89,90] There was even less enthusiasm for their use because of concerns in the mid-1990s about excess mortality with shorter-acting preparations, particularly nifedipine, which was thought to cause reflex adrenergic activation due to abrupt vasodilation with each dose.[169]

The two metaanalyses published in 2003 evaluating their efficacy in noncardiac surgery produced conflicting information.[170,171] However, one metaanalysis and a large observational cohort study with propensity-matching adjustment suggested there might be a role for calcium antagonists in reducing mortality rates for CABG patients.[172,173] For patients chronically taking calcium channel antagonists, they should probably be continued perioperatively. However, drug interactions must be considered. Data suggest that calcium channel blockers decrease clopidogrel-mediated platelet inhibition, which plays a crucial role in the management of CAD.[174]

Monitoring

Electrocardiogram

On arrival in the operating room, the patient undergoing CABG should have routine monitors placed, including pulse oximetry, noninvasive BP, and the ECG. A five-lead system is standard for patients undergoing cardiac surgery. Monitoring leads V_5 and II allows detection of 90% of ischemic episodes and assessment of the rhythm to diagnose various atrial and ventricular arrhythmias. Electrocardiographic detection of myocardial ischemia is reviewed in Chapter 12 (Box 20.3).

Arterial Pressure Monitoring

The radial artery usually is cannulated for BP monitoring during CABG. Choosing the best site for radial artery cannulation depends on surgery-specific considerations and institutional and practitioner preferences. Procedures such as previous transradial artery catheterization (TRAC), radial artery harvesting, or axillary CPB cannulation may influence the site chosen for invasive arterial pressure monitoring. The newer TRAC sheaths can be problematic for monitoring during emergency CABG, and they have been associated with many complications.[175] The radial artery on the side of a previous TRAC procedure probably should not be used for monitoring purposes.

With modern sternal retractors, blunting of the arterial pressure tracing on the ipsilateral site of internal mammary artery (IMA) dissection is not typically seen. Some practitioners use bilateral arterial cannulation or choose a more central artery, such as the axillary or femoral artery, to ensure accurate pressure readings after CPB. Radial arterial pressures have proved to be inaccurate immediately after hypothermic CPB. Substantial reductions in radial arterial pressure compared with aortic pressure have been reported in several clinical investigations and often require 20 to 60 minutes after CPB to resolve.[176–180] Decreased forearm vascular resistance is thought to be responsible for this common phenomenon. This problem can be overcome by temporarily transducing the arterial pressure directly from the aorta by a needle or a cardioplegia cannula.

Central Venous Cannulation

Placement of a central venous pressure (CVP) catheter routinely is performed in cardiac anesthesia for right atrial pressure measurement and for infusing vasoactive drugs. Some centers routinely place two

BOX 20.3 INTRAOPERATIVE MONITORING FOR MYOCARDIAL REVASCULARIZATION

1. ECG: V_5 most sensitive for myocardial ischemia; inferior lead II for rhythm monitoring and inferior wall ischemia.
2. Arterial blood pressure: Continuous invasive arterial blood pressure monitoring and blood gas sampling by indwelling arterial catheter. (Consider site of radial artery harvesting, reoperation, bilateral radial artery monitoring for axillary CPB cannulation, femoral artery cannulation for emergency IABP insertion, and more central arterial cannulation (eg, axillary, femoral) for more accurate readings after discontinuation of CPB).
3. PAC: No evidence of improved outcome with PAC use. However, commonly used for treatment guidance in conjunction with TEE monitoring and for postoperative care in the ICU, particularly in patients with severely reduced ventricular function and those with pulmonary hypertension.
4. TEE: Recommended for all cardiac operations. TEE can assist in pre-CPB evaluation of cardiac function, associated valvular lesions (including functional mitral regurgitation), evaluation of atheromatous plaques in the aorta (ie, site of cannulation and aortic cross-clamping, possible no-touch technique), detection of patent foramen ovale, or persistent left superior vena cava (ie, retrograde cardioplegia problem), CPB cannulation (including retrograde cardioplegia cannula positioning, aortic cannula positioning and associated complications such as iatrogenic aortic dissection and venous cannula positioning), volume status, ventricular function and response to inotropic agents, de-airing after release of aortic cross-clamp and during weaning off CPB.
5. Neurophysiologic monitoring: Increasing reports that cerebral oximetry aids in detecting catastrophic events; pending data from large prospective studies regarding outcome.
6. Temperature monitoring: Bladder or esophageal (ie, core temperature) and nasopharyngeal or tympanic (ie, brain temperature) are recommended for all CPB cases to minimize temperature gradients and cerebral hyperthermia during rewarming. For OPCABs, bladder temperature only is sufficient.
7. Foley placement for all patients.

CPB, Cardiopulmonary bypass; *ECG*, electrocardiogram; *IABP*, intraaortic balloon pump; *ICU*, intensive care unit; *OPCAB*, off-pump coronary artery bypass; *PAC*, pulmonary artery catheter; *TEE*, transesophageal echocardiography.

catheters (ie, large introducer and smaller CVP catheter) in the central circulation to facilitate volume infusion and vasoactive or inotropic drug administration. Central venous catheter placement and monitoring is extensively covered in Chapter 13.

Pulmonary Artery Catheterization

The use of a pulmonary artery catheter (PAC) in medical and surgical settings has declined steadily, mostly due to the increasing amount of data from large, randomized studies showing that major clinical outcomes (particularly death) are not changed by PAC use and that the adverse effects of PAC monitoring should be considered. During surgery for myocardial revascularization and in the ICU setting, patient outcomes are independent of PAC use despite the substantial amount of physiologic information obtained.

In a prospective observational study, Tuman and associates,[181] examined the effect of PAC use on the outcomes of 1094 patients undergoing CABG surgery. Although no direct data on LV function were provided, there was no difference in the incidence of LV dysfunction between the group treated with a CVP catheter and the group treated with a PAC. In this study, the investigators could not demonstrate that a PAC had any effect on outcome; however, 7% of the patients initially assigned to CVP monitoring subsequently required a PAC for management.

Several other reports have focused exclusively on PAC use in CABG surgery. Stewart and colleagues[182] reported a retrospective analysis of 312 patients undergoing CABG in 1996 who were thought to be low risk and suitable for CVP monitoring alone. Of these, 32% had a PAC placed and received greater volumes of fluid, gained more weight, and had longer times to extubation. Ramsey and coworkers[183] retrospectively analyzed a commercial health care outcomes-benchmarking database with 13,907 patients who underwent nonemergent CABG in 56 hospitals (Fig. 20.11). Patients (58%) who had a PAC placed for perioperative monitoring had a higher risk of death after risk adjustment (relative risk = 2.1), longer LOS, and higher total costs, particularly in the hospitals with low rates of PAC use.

Schwann and colleagues[184] retrospectively analyzed 2685 consecutive CABG patients at a single private center (1994–1998) in which PAC use was highly selective (ie, used in only 9% based on consideration of multiple cardiac risk factors). Of these instances of PAC use, 6.6% were planned, with the remainder placed postoperatively in response to adverse intraoperative events. Multivariate analysis revealed EF, STS risk score, use of intraaortic balloon pump (IABP), HF, reoperation, and New York Heart Association (NYHA) class IV to be independent predictors of PAC use.

In another multicenter, prospective, observational study, 5065 patients undergoing CABG between 1996 and 2000 were enrolled.[185] Propensity score matching was applied to adjust for differences in patient characteristics that might have led to PAC insertion. In this patient cohort, PAC during CABG was associated with an increased mortality rate (3.5% vs 1.7%) and higher risk of severe end-organ complications.

London and associates[186] documented a high rate of PAC use based on analysis of 3256 CABG patients included in a large, multicenter, observational study of patients undergoing cardiac surgery in the Department of Veterans Affairs (1994–1996). More than 95% of cases were monitored with a PAC, and 49% of these cases used the more expensive mixed venous oxygen saturation catheter. Use of the catheter was center specific, and with the exception of a small reduction in number of postoperative arterial blood gas and thermodilution cardiac output measurements, it was not associated with improvement in outcome over the routine PAC. In a retrospective study, Resano and coworkers[187] did not find significant differences in mortality, conversion to on-pump procedures, or inotropic drug use between the group treated with a CVP catheter and the group treated with a PAC.

Judge and colleagues[188] surveyed the members of the Society of Cardiovascular Anesthesiologists to assess current PAC use. The use of a PAC for myocardial revascularization was practice dependent, with anesthesiologists in private practices using PACs for hemodynamic monitoring the most, followed by those in academic and government practice settings. OPCAB and minimally invasive CABG procedures were more likely to be monitored with a PAC.

Based on the existing literature, it is not possible to give precise criteria for PAC use during CABG. PAC use during CABG depends on institutional and practitioner preference, and most patients undergoing myocardial revascularization can be safely managed without a PAC. Patient risk factors that may warrant PAC placement include significant impairment of ventricular function, known pulmonary hypertension, and right-sided HF. Some physicians have advocated a wait-and-see approach. In a prospective, observational study, Djaiani and associates[189] showed the safety and usefulness of delaying the insertion of a PAC until the clinical need arises in the operating room or in the ICU after CABG.

The 2011 ACCF/ACC guideline for CABG surgery[106] suggested that PAC placement can be useful in patients in cardiogenic shock or hemodynamically unstable patients. PAC use is reviewed in Chapter 13.

Transesophageal Echocardiography

The earliest signs of myocardial ischemia include diastolic dysfunction followed by systolic regional wall motion abnormalities (RWMAs),

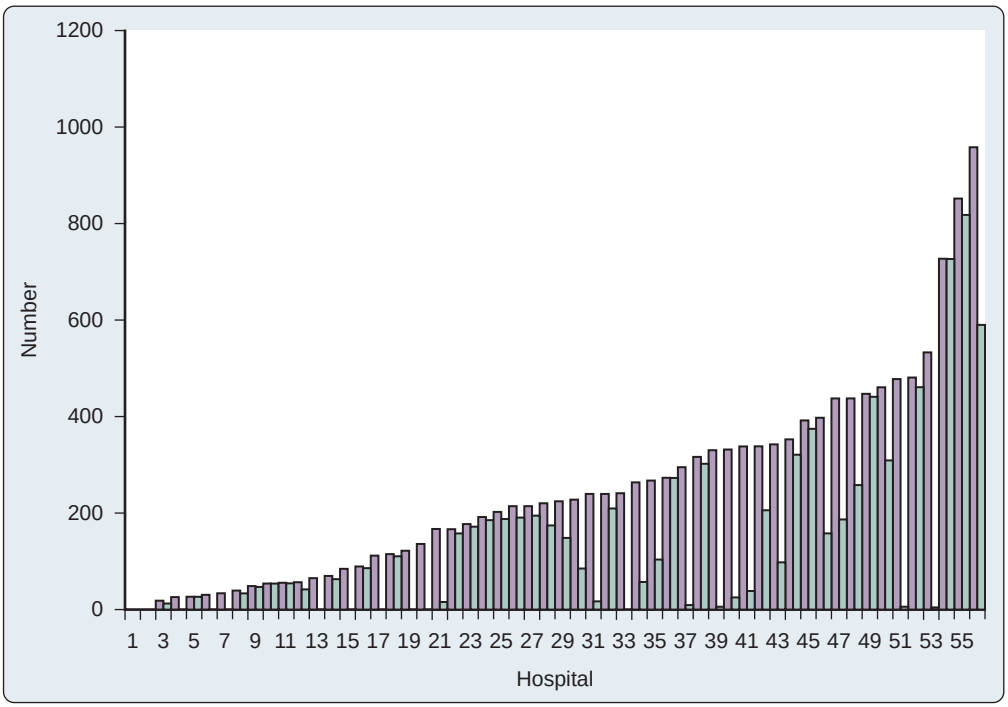


Fig. 20.11 Variation in the use of pulmonary artery catheterization (PAC) for elective coronary artery bypass grafting (CABG) in 13,907 patients at 56 community-based hospitals in 26 states in 1997, with data obtained from an administrative health outcomes benchmarking database. PAC was used in 58% and was associated with greater risk of in-hospital mortality, particularly in hospitals with the lowest use of PAC, hospital length of stay, and costs. *Purple bars* indicate the total number of CABG cases; *green bars* indicate the number of patients with PAC. *(From Ramsay SD, Saint S, Sullivan SD, et al. Clinical and economic effects of pulmonary artery catheterization in nonemergent coronary artery bypass graft surgery.* J Cardiothorac Vasc Anesth. *2000;14:113.)*

which occur within seconds of acute coronary occlusion. Worsening of RWMAs after CABG is associated with an increased risk of long-term adverse cardiac morbidity and has been suggested as a prognostic indicator of adverse cardiovascular outcome.[190] New RWMAs detected in the intraoperative period frequently may result from nonischemic or ischemic causes such as changes in loading conditions, alteration in electrical conduction in the heart, post-CPB pacing, myocardial stunning due to ischemia before or during weaning from CPB, or poor myocardial preservation. TEE is highly sensitive but lacks specificity for myocardial ischemia monitoring.[191,192] Additional limitations apply because not all wall segments can be monitored continuously in real time and compared with preoperative findings.

Despite these limitations, TEE use in patients undergoing CABG can provide invaluable information beyond ischemia detection. TEE can assist in the pre-CPB evaluation of cardiac function, assessment and quantification of associated valvular lesions that may impact the surgical plan (eg, concomitant functional mitral regurgitation [MR], aortic stenosis), or CPB management (eg, aortic regurgitation).

In the setting of valvular heart disease at the time of CABG, the 2011 ACCF/AHA guideline for CABG surgery[106] recommended adding the following surgical procedures. A class I recommendation with level of evidence (LOE) B applies to aortic valve replacement for moderate aortic stenosis, and mitral valve repair or replacement should be undertaken for severe MR. A class IIa recommendation and LOE B applies to mitral valve repair or replacement for moderate MR. However, the value or risk of adding mitral valve repair that requires open heart surgery at the time of CABG remains controversial, and a prospective, randomized trial did not find improved 1-year outcomes.[193] Recommendations will likely be adjusted as more long-term evidence emerges.

The aorta can be assessed for the presence and severity of atheromatous plaques, and TEE can help to locate appropriate cannulation and cross-clamp sites or avoid the manipulation of the aorta altogether (ie, no-touch techniques). Cannulation techniques, including retrograde cardioplegia cannula positioning, a persistent left superior vena cava cannula (ie, retrograde cardioplegia problem), venous cannula positioning allowing unobstructed venous drainage, and an aortic cannula position in the aortic arch, can be assisted by TEE guidance. TEE can detect complications such as iatrogenic aortic dissection and can evaluate de-airing after release of the aortic cross-clamp. TEE monitoring can guide hemodynamic management after CPB, including the assessment of ventricular function, volume status, and the choice of and response to inotropic support.

The American Society of Anesthesiologists (ASA) and the Society of Cardiovascular Anesthesiologists (SCA) developed practice guidelines in 1996 for the perioperative use of TEE.[194] The guidelines were updated in 2010,[195] and the routine use of TEE was recommended for all cardiac or thoracic aortic surgery, including all CABG or OPCAB procedures. The ASA Task Force thereby acknowledged that TEE information could impact perioperative anesthesia, surgical management, and patient outcomes. A comprehensive TEE examination is recommended by the ASE/SCA Task Force before and after CPB or after completion of revascularization in OPCAB surgery.[196,197]

Despite existing guidelines recommending TEE for all patients undergoing cardiac surgery, many centers still do not use TEE for elective CABG. Morewood and coworkers[198] obtained more than 1800 survey responses from members of the SCA in 2000. Of approximately 1500 clinicians involved in CABG, 11% reported never using TEE, and more than 30% used it frequently or always. The number using TEE is probably much higher today because of its widespread availability and ongoing popularity of the technology. Proper education and certification are critical, and guidelines on training requirements and certification have been published[199,200] (see Chapter 17). Adequate training is essential to minimize the rare but potentially serious complications of

this minimally invasive technique.[201–206] Perioperative TEE is reviewed in Chapters 14 though 17.

Neuromonitoring

Stroke and neurocognitive dysfunction are feared complications associated with CABG, whether or not CPB is used, and they occur at a high enough rate that further improvements are needed.[207–209] Intraoperative awareness is frequently reported by cardiac surgery patients. Cerebral oximetry and processed electroencephalography are monitoring modalities that have become more widespread. They play an important role in patient management and detecting adverse events.

Although monitoring alone cannot change outcomes, early recognition of potentially harmful events and interventions with an associated outcome benefit may be useful. There is no consensus about which neuromonitoring modality should be selected. However, specialty societies have increasingly recommended neuromonitoring in an effort to decrease the incidence of poor neurologic outcomes associated with cardiac surgery, including CABG and OPCAB. The 2011 ACCF/AHA guideline for CABG surgery,[106] recommended central nervous system monitoring for patients undergoing myocardial revascularization (class IIb recommendation). However, they also recognized that more evidence demonstrating clear benefits was needed and that the effectiveness of detecting cerebral hypoperfusion based on the available data is uncertain. The 2013 American Society of Extracorporeal Technology (AmSECT) standards and guidelines for perfusion practice also recommend the use of neuromonitoring.[210]

Cerebral Oximetry

The technologic background of near-infrared spectroscopy–based cerebral oximetry monitoring is reviewed in Chapter 18.[211–213] The use of cerebral oximetry has been suggested for cardiac surgical patients for several reasons. It is unique in its ability to continuously monitor regional tissue oxygenation, even during periods of low-CO nonpulsatile flow during CPB and with nonpulsatile ventricular assist devices. Many case reports have demonstrated that cerebral oximetry can provide early warning signs for detecting catastrophic events not detected by other monitoring devices such as pulse oximetry.[214–216] The cerebral cortex can be seen as an index organ. Although autoregulatory mechanisms have to be considered, cerebral tissue oxygenation correlates with measures of systemic oxygen delivery and consumption.[217]

Data from large, randomized, controlled studies with clearly defined treatment protocols and outcome measures are needed to demonstrate that interventions based on cerebral oximetry can improve neurologic outcomes for CABG patients. Two prospective trials of CABG patients have been published. Slater and colleagues[218] randomized 265 CABG patients to a blinded control group or an unblinded intervention group. There were no statistically significant differences in cognitive decline and major postoperative complications (eg, cerebrovascular accident, MI, renal insufficiency, reoperation for bleeding) between the two study groups, a result the investigators attributed to poor compliance with the treatment protocol. In the multivariate analysis, prolonged regional cerebral oxygen desaturation was an independent risk factor for postoperative cognitive decline regardless of the assigned study group.

In a similar study, Murkin and associates[219] demonstrated that treatment of cerebral oxygen desaturation improved outcomes of patients undergoing CABG. They randomized 200 patients undergoing CABG to an intervention group, in which cerebral tissue desaturation was linked to a treatment intervention protocol attempting to return the readings to baseline values, or to a control group, in which cerebral oximetry readings were blinded to the practitioner. The hypothesis was that most of the interventions to optimize cerebral oxygen saturation would also influence systemic perfusion. There was no difference in the overall incidence of adverse complications, but significantly more patients in the control group had major organ morbidity or outcomes such as death, ventilation for more than 48 hours, stroke, MI, and reoperation for exploration.

Further studies are needed to determine whether postoperative cognitive dysfunction can be reduced by treatment of intraoperative cerebral oxygen desaturation. A clear threshold below which the risk of postoperative cognitive dysfunction is increased needs to be defined.

Processed Electroencephalography Monitoring

Processed electroencephalography monitoring is based on fast Fourier transformation analysis and bispectral analysis of one-channel electroencephalographic (EEG) data obtained from electrodes on the patient's forehead (see Chapter 18). Several devices have been approved by the US Food and Drug Administration (FDA).[220–223] Processed EEG monitoring is frequently associated with anesthesia depth monitoring in an attempt to decrease intraoperative awareness. *Recall* is defined as postoperative memory for intraoperative events, an infrequent but well-recognized phenomenon during general anesthesia.[224,225] *Awareness*, a conscious subjective experience (ie, implicit memory), may be much more common than conscious recall (ie, explicit memory) of intraoperative events.[226–228]

Patients undergoing cardiac surgery always have been considered to be at increased risk of intraoperative awareness, with older reports of an incidence up to 23%.[229] This situation resulted from anesthetic regimens intentionally devoid of high doses of inhalation anesthetics (ie, era of high-dose, opioid-based anesthetics), frequent periods of light anesthesia in the setting of hemodynamic instability caused by surgical manipulation of the heart and great vessels, depressed contractility after CPB, or bleeding. However, the frequent use of inhalation agents and short-acting benzodiazepines in modern anesthetic regimens has reduced the risk of intraoperative awareness for this type of surgery.[230] Ranta and coworkers[231] found definite intraoperative awareness with recall in 0.5% of patients undergoing cardiac surgery, and Dowd and colleagues[232] reported a low incidence (0.3%) of intraoperative awareness, attributing it to the continuous administration of volatile anesthetics or propofol.

The role of processed EEG monitoring (eg, bispectral index [BIS]) in preventing intraoperative awareness by patients undergoing cardiac surgery is not clear. Myles and associates[233] studied 2463 patients considered to be at high risk for awareness in a prospective, randomized, double-blinded, multicenter trial with 45% of patients undergoing high-risk cardiac surgery or OPCAB. Among those surgical patients, three possible awareness events occurred. Possible awareness events occurred irrespective of the use of BIS monitoring. Similarly, Barr and coworkers[234] found no correlation between bispectral EEG analysis of anesthesia depth and conscious recall in a small series of patients undergoing cardiac surgery.

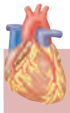
Besides monitoring anesthetic depth, there may be a role for processed EEG monitoring in titration of intravenous anesthetic agents to their effective dose, and this may be associated with improved satisfaction of patients undergoing CABG.[235,236] The raw EEG data also can help to ensure adequacy of burst suppression for hypothermic circulatory arrest.

Induction and Maintenance of General Anesthesia

The main considerations in choosing an induction technique for patients undergoing CABG are LV function and coronary pathology. No single approach to anesthesia for CABG is suitable for all patients. Most hypnotics, opioids, and volatile agents have been used in different combinations for the induction and maintenance of anesthesia, with good results in the hands of experienced clinicians. Limiting the amount of opioids or use of short-acting drugs is encouraged for patients eligible for fast-tracking and early extubation. With modern cardioplegia techniques and assuming an uneventful intraoperative course, cardiac function typically is well preserved, and the goal should be to extubate the patient within 6 hours postoperatively (Box 20.4).

Anesthetic Agents

The cardiac effects of commonly used induction agents have been investigated over many years, sometimes with conflicting results (see



BOX 20.4 CONSIDERATIONS FOR ANESTHESIA INDUCTION AND MAINTENANCE DURING MYOCARDIAL REVASCULARIZATION

1. Anesthetic induction with tight control of hemodynamic parameters (ie, avoid tachycardia, hypotension), particularly in patients with left main or proximal LAD disease.
2. Fast-track anesthetic protocols aiming for early extubation are favored for most patients.
3. Given the increasing evidence for preconditioning effects, a potent volatile agent should be part of the anesthetic regimen. Avoid nitrous oxide because of the possibility of expanding gaseous emboli.
4. Maintain CPP without increasing myocardial oxygen demand (eg, phenylephrine, nitroglycerin, avoid tachycardia).
5. Antifibrinolytic therapy (ie, ε-aminocaproic acid or tranexamic acid) except in OPCAB patients. Aprotinin is no longer available in the United States.
6. Consider low tidal volume mechanical ventilation and no PEEP during LIMA dissection.
7. Heparin usually is administered before clamping the LIMA pedicle to avoid thrombosis. Papaverine, if injected retrograde into the LIMA by the surgeon, is frequently associated with hypotension.
8. Heparin administration (300–400 IU/kg) or as calculated by heparin titration (Hepcon) in CABG patients with CPB. ACT >480 seconds and/or heparin level >2.5 U/mL is required for institution of CPB.

ACT, Activated coagulation time; *CABG*, coronary artery bypass grafting; *CPP*, coronary perfusion pressure; *LAD*, left anterior descending coronary artery; *LIMA*, left internal mammary artery; *OPCAB*, off-pump coronary artery bypass; *PEEP*, positive end-expiratory pressure.

Chapter 10). Unraveling the direct or indirect effects of a particular drug on the heart and circulation is complex because overall effects are based on contractility, vascular tone, and response of the autonomic nervous system and baroreceptors. Additional concerns are the details of the animal preparation (eg, species, acute vs chronic preparation, open vs closed chest) or clinical setting (eg, type and speed of induction). One drug is usually not used exclusively (ie, balanced anesthesia), and all drugs must be titrated to effect with the overall goal of avoiding hypotension, excessive hypertension, tachycardia, and myocardial depression.

Thiopental had been used for decades for induction in patients undergoing CABG. It is rarely used today, and in the United States, thiopental is no longer available. Its predominant hemodynamic effects include reductions in MAP and CO accompanied by a modest increase in HR. These effects are thought to result from a combination of direct myocardial depression, venodilation, and a decrease in central sympathetic outflow. Thiopental is reported to have greater negative inotropic effects than propofol.[237–240] However, opposite findings also have been reported[241] and may be related to the greater degree of vasodilation seen with propofol, which maintains overall cardiac output.[242,243] Adverse effects on airway resistance, a greater propensity to elicit bronchospasm, and a greater association with postoperative nausea and vomiting are other factors accounting for its decreased use.

Etomidate is often the preferred induction agent in patients with depressed cardiac function because it has minimal or no direct negative inotropic or sympathomimetic effects.[237,240] In an isolated rabbit heart preparation, Komai and colleagues[244] demonstrated that etomidate at very high concentrations inhibited the influx of extracellular calcium but had no effect on availability of intracellular calcium required for excitation-contraction coupling. Despite the observed hemodynamic stability, unwanted side effects are common. Significant pain during injection, particularly in a small superficial vein, is unpleasant for the patient and causes tachycardia and hypertension, both of which increase myocardial oxygen demand. Unless combined with adequate amount of opioids, blunting of the adrenergic response to intubation is poor and may result in hypertension and tachycardia. Even a single dose of etomidate can inhibit adrenal mitochondrial hydroxylase activity, resulting in reduced steroidogenesis[245,246]; however, outcome differences in cardiac surgery patients have not been documented consistently.[247,248] Myoclonic jerking can be observed in the absence of muscle relaxation, and a greater association with postoperative nausea and vomiting are adverse effects seen with etomidate administration.

Propofol is commonly used as an induction agent in patients undergoing CABG, for anesthesia maintenance, and for sedation postoperatively in the ICU.[249–251] Its isolated effects on contractility are controversial, with conflicting findings depending on the research model used. A sophisticated analysis of its effects in CABG patients using TEE assessment of preload-adjusted maximal power, a load-independent measure of contractility, at four different plasma concentrations (0.6–2.6 mg/mL) found no direct effect on contractility, although it lowered preload and afterload.[252] It previously was evaluated in numerous clinical studies for induction and maintenance with an opioid, and it was compared with a volatile-opioid combination for CABG in patients with normal or depressed EF. These studies reported minimal differences in hemodynamics or the incidence of myocardial ischemia.[253–258] However, more sophisticated and larger contemporary studies closely evaluating ventricular function on weaning from CPB and perioperative release of biomarkers of ischemia consistently reported better myocardial protective properties with the use of volatile agents over a total intravenous anesthesia (TIVA) technique with propofol. This effect is thought to be related to the anesthetic preconditioning and postconditioning effects of volatile agents (see Chapter 10).

Although there seem to be well-documented advantages for using inhalation anesthetics in patients at risk for myocardial injury, benefits of propofol also have been reported. Propofol has strong free radical–scavenging properties that in one CABG study appeared to attenuate myocardial lipid peroxidation in atrial tissue biopsies.[259] In a multicenter, prospective study comparing an inhalation-based anesthetic with TIVA in patients undergoing combined valvular and CABG surgery, no observed beneficial effect of sevoflurane on the composite end point of mortality, prolonged ICU stay, and troponin levels was found.[260] A large metaanalysis that included 133 studies and 14,516 cardiac and noncardiac surgery patients found no difference in mortality when propofol was used.[261] In a prospective, randomized controlled trial, patients were assigned to an inhalation or propofol-based anesthetic.[262] Patients in the inhalation group had a shorter time to extubation and a higher prevalence of hypotension requiring vasoconstrictive support; mortality rates, ICU LOS, and hospital LOS did not differ. Dexmedetomidine is an alternative drug available for sedation in the ICU, and both drugs have been compared in clinical trials with mixed findings.[263,264]

Ketamine is rarely used in CABG patients. In patients with severely decreased LV function, etomidate is usually the preferred drug. Administration of ketamine is associated with increases in HR and MAP through indirect central and peripheral sympathetic stimulation (eg, inhibition of neuronal reuptake of catecholamines). In states associated with depletion of catecholamines and in isolated preparations, ketamine has direct negative inotropic and vasodilating effects,[265] and it may have a negative lusitropic effect, decreasing diastolic compliance.[266] In a double-blind, randomized, controlled trial, Zilberstein and associates[267] documented a potent antiinflammatory effect (ie, suppression of increases in superoxide anion production after CPB) with a very small dose of ketamine (0.25 mg/kg) that persisted for several days postoperatively.

Benzodiazepines are commonly used in CABG patients for preoperative sedation and in combination with a narcotic to induce anesthesia. Historically, diazepam was added to high-dose morphine or fentanyl as the main anesthetic for patients undergoing CABG.[268–270] With the introduction of short-acting benzodiazepines, particularly midazolam, diazepam has almost become obsolete for induction and maintenance in cardiac surgery.[271–282]

Midazolam is very well tolerated, with minimal hemodynamic effects even in patients with severe cardiac dysfunction. There has been relatively little research on midazolam's direct cardiac effects, which are difficult to evaluate in the clinical setting because it is typically administered with other drugs. For example, Messina and coworkers[283] reported a clinical study of 40 CABG patients in whom 0.1 mg/kg of midazolam was administered after induction and intubation with thiopental, fentanyl, and pancuronium. Contractility was mildly depressed, although afterload was reduced simultaneously, resulting in no net change in the cardiac index.

High-dose opioid anesthesia was introduced into cardiac surgery by Lowenstein and coworkers[284] in 1969, in an attempt to provide safe anesthesia without myocardial depression in patients with severe valvular heart disease and compromised cardiac function. Although this revolutionized anesthesia for patients with cardiac dysfunction, it was apparent that morphine had several disadvantages: vasodilation from histamine release, increased requirements for fluids and vasoconstrictors, and prolonged respiratory depression. Even when morphine was given to patients with normal LV function, dramatic hemodynamic responses occurred with surgical stress, amnesia could not be guaranteed, and the anesthesia often was inadequate. In modern practice, a high-dose morphine anesthetic has become obsolete.

In the late 1970s, Stanley and collaborators first reported the use of high doses of fentanyl for CABG, with and without supplemental benzodiazepines.[269,270,285] Clinicians worldwide perceived the lack of histamine release to be a very favorable property and rapidly adopted fentanyl into their clinical practice.[286–292] However, it was recognized early on that recall still could be a problem.[293] Reports on the use of the more potent sufentanil appeared at the same time as fentanyl, although most studies were not reported until the late 1980s.[272,279,280,294–300] It was also widely adopted, although there was concern about its very potent bradycardic effects at high doses, particularly when administered with nonvagolytic muscle relaxants.[301,302] Sufentanil's substantially higher costs compared with fentanyl also have limited its use. Most evidence suggests that despite documented associations of sufentanil use with shorter times to extubation, overall costs and hospital LOS have been unaffected relative to fentanyl.[79,303,304]

In the mid-1990s, remifentanil was introduced, and fueled by intense interest in fast-tracking (promoted in the same time frame), it was intensively investigated.[305–314] Careful planning with regard to when it is terminated and adequate continuation of pain control is required. Combination with neuraxial anesthetics also has been advocated.[315]

The previously described opioids are pure opioid agonists, and none provides complete anesthesia as defined by predictable dose-response relationships for suppression of the stress response and release of endogenous catecholamines (particularly norepinephrine), even with high serum concentrations.[316–318] Hypertension and tachycardia commonly have been reported in response to induction or intubation and surgical stimuli (particularly with sternotomy) in older studies of high-dose opioid anesthesia with fentanyl or sufentanil.[292,319] Figs. 20.12 and 20.13 demonstrate this lack of association of serum levels with hemodynamic responses.

Philbin and colleagues[320] investigated the relationship between opioid dose and hemodynamic effect with fentanyl or sufentanil in a randomized study of CABG patients. Forty patients were allocated to receive fentanyl or sufentanil boluses, and an additional 40 patients were randomized to sufentanil bolus dosing followed by continuous infusion. Plasma opioid and catecholamine concentrations were obtained after intubation and after sternotomy. A hemodynamic response was defined as a 15% or greater increase in systolic blood pressure (HRs were not reported), and a hormonal response was a 50% or greater increase from control. In the bolus-only group, the frequency of hemodynamic responders was unrelated to drug and dose administration. Similarly, in the sufentanil-infusion group, the frequency of response was unrelated to plasma sufentanil levels. Although the study had design flaws (eg, small sample sizes, lack of reporting of hemodynamics), it provided some evidence that even high-dose opioids alone could provide incomplete anesthesia.

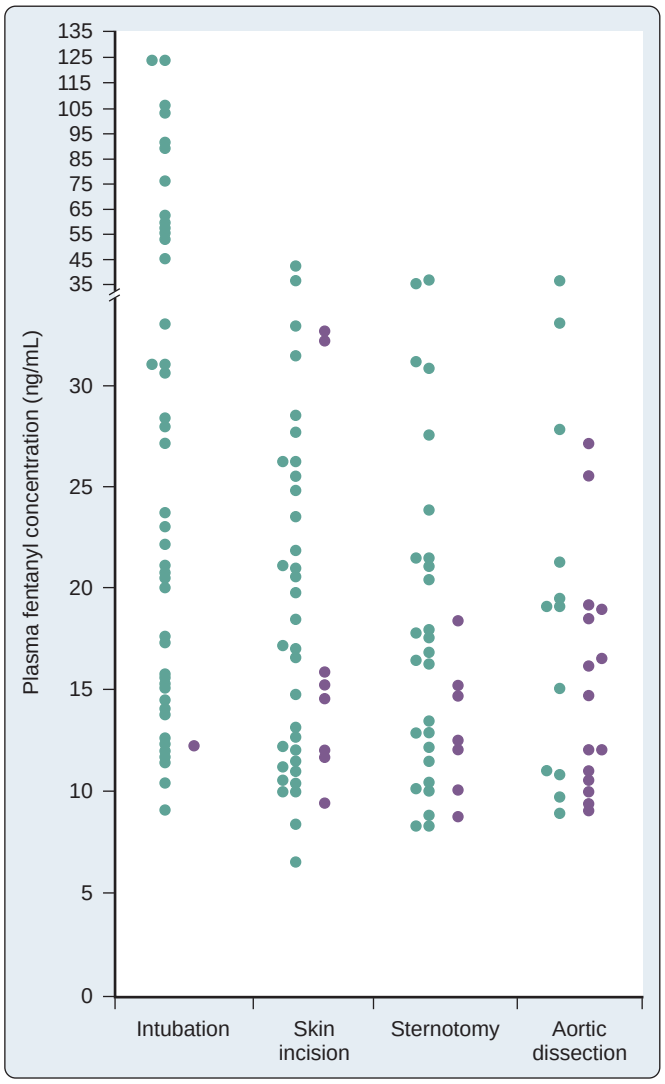


Fig. 20.12 The plasma fentanyl concentration and number of patients with a hypertensive response at each event studied. *Purple circles* indicate hypertensive status; *green circles* indicate normotensive status. *(From Wynands JE, Townsend GE, Wong P, et al. Blood pressure response and plasma fentanyl concentrations during high and very high-dose fentanyl anesthesia for coronary artery surgery.* Anesth Analg. *1983;62:661.)*

In current practice, anesthesia using only a high-dose opioid is rarely practiced. To provide complete anesthesia, the usual practice is to supplement opioids with inhaled or other intravenous agents. This permits a reduction in the total dose of opioid and, particularly with volatile agents, more rapid return of respiratory drive, facilitating early extubation. Thomson and associates[321] incorporated this approach and extended the concepts investigated by Philbin and coworkers[322] in a small but sophisticated study of CABG patients. Specific effect-related concentrations of fentanyl or sufentanil were targeted by using a computer-assisted infusion pump. Three targeted concentrations for each opioid were evaluated (sufentanil at 0.4, 0.8, and 1.2 ng/mL; fentanyl at 5, 10, and 15 ng/mL), and the end-tidal concentration of isoflurane required to control MAP and HR in the pre-CPB period by predetermined criteria was monitored. The sufentanil subgroups required 1.9, 3.1, and 4.9 μg/kg, and fentanyl subgroups received 18.8, 33.9, and 50.4 μg/kg in this period. The average end-tidal concentration of isoflurane was significantly greater between the low- and medium- or high-concentration groups, with no difference found

between the medium- and high-concentration groups. Most of the responses were increases in MAP.

Regression analysis of the study results revealed significant correlations between serum opioid concentrations and isoflurane concentrations at most of the time points sampled in the pre-CPB period. By inspecting plots of the data pairs, the investigators were able to ascertain the inflection point at which the isoflurane concentration began to rise rapidly, indicating poor control of hemodynamics by the respective opioid. For sufentanil, this was 0.71 ± 0.13 ng/mL, and for fentanyl, it was 7.3 ± 1.1 ng/mL. Given the use for fast-tracking of approximate levels of 20 µg/kg for fentanyl and 3 µg/kg for sufentanil for the entire procedure, it is unlikely these concentrations can be obtained. However, the perioperative use of β-blockers, α_2-agonists, and other drugs such as benzodiazepines provide additional hemodynamic control.

Neuromuscular blocking agents have been used to produce adequate intubating conditions and muscle relaxation during CABG (Table 20.2). Traditionally, pancuronium was advocated for use with high-dose narcotic techniques because it offset opioid-induced bradycardia. Despite the availability of newer short-acting neuromuscular blocking agents (NMBAs), pancuronium remained popular among practicing cardiac anesthesiologists for patients undergoing on-pump and off-pump cardiac surgical procedures 10 to 15 years ago.[323] However, it has long been recognized that clinically significant tachycardia resulting in myocardial ischemia could occur during induction of anesthesia with high-dose fentanyl and pancuronium.[324]

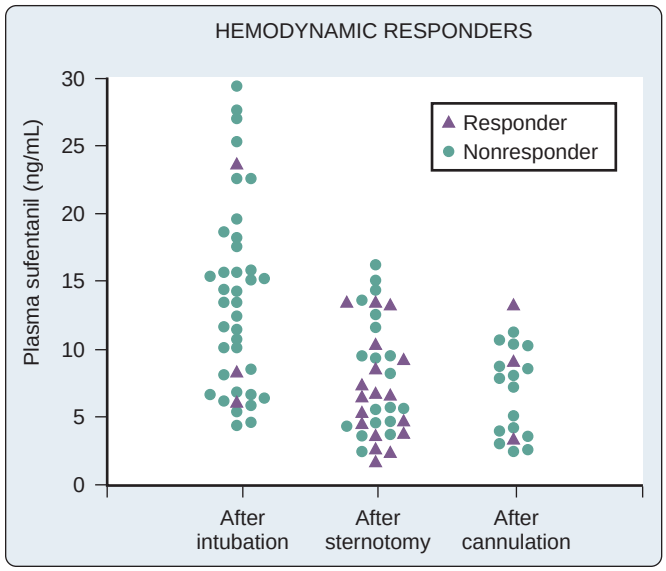


Fig. 20.13 The graph plots patients with a hemodynamic response and the plasma sufentanil concentration at that time, as well as the sufentanil concentrations for the nonresponders. Therapy was initiated at the time of the initial response, and no further data points were included for those patients. *(From Philbin DM, Rosow CE, Schneider RC, et al. Fentanyl and sufentanil anesthesia revisited: how much is enough?* Anesthesiology. *73:5, 1990.)*

Several studies have compared the durations of action of pancuronium with modern, shorter-acting NMBAs such as rocuronium.[325–327] Whether used as a single intubating dose or a continuous infusion, pancuronium use resulted in significantly longer neuromuscular blockade and delayed time to extubation.[328–330] Especially in fast-track cardiac surgery, shorter-acting NMBAs have completely replaced pancuronium, allowing earlier extubation and ICU discharge.[331]

Additional considerations are warranted for patients with underlying comorbidities such as chronic renal failure, which may alter pharmacokinetics. When magnesium is administered to cardiac surgical patients for prophylaxis of perioperative arrhythmias, blockade from nondepolarizing NMBAs may be significantly prolonged.[332] The question remains about whether continuous neuromuscular blockade for cardiac surgery is necessary at all. Gueret and colleagues[333] showed that a single intubating dose of atracurium or cisatracurium provided adequate paralysis and surgical conditions, leading to quicker neuromuscular blockade recovery for cardiac surgical patients. Advocates of this technique also point to potential advantages with regard to prevention of recall (as indicated by patient movement). However, potential disadvantages include the possibility of greater oxygen demand and consumption and movement during surgery.

α2-Agonists can help to prevent hypertension and tachycardia during intubation, surgical stimulation, and emergence from anesthesia and can decrease plasma catecholamine levels.[334–338] Zhang and associates summarized the role of dexmedetomidine in patients undergoing cardiac surgery.[334] Currently, α_2-agonists are rarely administered preoperatively, but they play a larger role in sedation and transitioning to the postoperative ICU.

Jalonen and coworkers, in a randomized, double-blind study, administered dexmedetomidine or placebo to CABG patients starting 30 minutes before induction and continued until the end of surgery.[83] Patients receiving dexmedetomidine had significantly lower plasma norepinephrine levels and more stable hemodynamics (ie, less increase in MAP and HR during induction, less intraoperative variability of systolic arterial pressure). Dexmedetomidine administration was associated with decreased incidences of intraoperative and postoperative tachycardia (5% vs 32% and 4% vs 40%, respectively) compared with placebo. Patients who received dexmedetomidine also were less likely to receive β-blocker therapy for tachycardia. However, a higher incidence of hypotension (MAP <30 mm Hg) was seen during CPB (22% vs 0% of patients for dexmedetomidine vs placebo). These data demonstrate that dexmedetomidine can be effective in attenuating sympathetic stress responses, although the same effect may predispose patients to hypotension.

Inhalation Anesthetics and Myocardial Protection

Inhalation anesthetics are routinely used in patients undergoing CABG due to the shift from using a high-opioid anesthetic to fast-tracking and because of mounting evidence that potent inhalation anesthetics protect the myocardium against ischemia by eliciting protective cellular responses similar to those seen with ischemic preconditioning.[76,77,339–348]

Murry and colleagues[349] first showed that brief periods of ischemia before a prolonged period of coronary artery occlusion significantly reduced infarction size after myocardial reperfusion. This concept is referred to as *ischemic preconditioning*. Brief periods of ischemia initiate signaling pathways that render the myocardium resistant to

TABLE 20.2 Nondepolarizing Neuromuscular Blocking Agents Used in Cardiac Anesthesia

Relaxant	*Intubating Dose (mg/kg)*	*Maintenance Dose*	*Clinical Duration (min)*	*Hemodynamic Effects*	*Special Considerations*
Pancuronium	0.08–0.12	0.01 mg/kg q20–60min	60–120	Strong vagolytic effects at clinical doses, releases norepinephrine	Reduce dose or avoid in renal insufficiency
Vecuronium	0.08–0.2	0.8–2 µg/kg/h	45–90	Insignificant	Accumulation of active metabolite with long-term use
Cisatracurium	0.15–0.2	1–2 µg/kg/min	40–75	Insignificant	Hoffman elimination
Rocuronium	0.4–1.0	0.01 mg/kg/min	35–75	Mildly vagolytic (high dosage)	No active metabolites

subsequent prolonged periods of ischemia (ie, memory effect).[350] There is a clear evolutionary advantage to self-defense by adjusting to repeated stressors. After a short ischemic period (ie, preconditioning signal), the myocardium is rendered more resistant to prolonged ischemia when the subsequent ischemic event occurs within a certain time window. Research has identified two distinct phases, also referred to as *early preconditioning* (about 2 hours) and *delayed or late preconditioning* (24 to 72 hours).

Although multiple approaches are used to protect the heart during CPB (eg, blood cardioplegia, topical hypothermia, pharmacologic additives), aortic cross-clamping defines a period of myocardial ischemia that often results in transient or prolonged dysfunction after reperfusion.[351,352] Clinical research of patients undergoing CABG appears to support the concept of ischemic preconditioning. Brief periods of aortic cross-clamping with consequent reperfusion intervals before a period of ventricular fibrillation have been shown to preserve ATP content, decrease markers of ischemia such as troponin I, and improve cardiac function in patients undergoing CABG.[353–356] However, ischemic preconditioning is not practical in clinical practice because controlled periods of myocardial ischemia are difficult to achieve, cumbersome, and potentially dangerous.[357] Repeatedly cross-clamping an atherosclerotic aorta may result in embolism formation and endothelial damage, increasing mortality.[358] Some degree of myocardial protection may be conferred when brief periods of ischemia are applied to organs or tissues remote from the heart, also referred to as *remote preconditioning*, improving the applicability of ischemic preconditioning.[359–363]

There is evidence that pharmacologic agents such as potent inhalation anesthetics and opioids mimic the effects seen with ischemic preconditioning, a concept called *pharmacologic or anesthetic preconditioning*.[364,365] Not all anesthetic drugs have preconditioning effects. For example, the commonly used induction agents etomidate and ketamine do not have cardioprotective properties.[366,367]

The pathways associated with myocardial preconditioning involve a variety of triggering stimuli, mediators, receptors, and effectors.[368] It is thought that activation of sarcolemmal and mitochondrial ATP-sensitive K^+ (K^+_{ATP}) channels play a pivotal role in the preconditioning process.[369] Channel opening protects the myocardium by preventing cytosolic and mitochondrial Ca^{2+} overload. The exact mechanisms of preconditioning are much more complex and continue to be investigated.

After the administration of a preconditioning signal such as ischemia or certain pharmacologic agents, membrane-bound receptors (eg, A_1 adenosine, adrenergic, bradykinin, muscarinic, δ_1-opioid) coupled to inhibitory G-proteins are activated.[370–375] Consequently, products of intracellular transduction pathways (eg, protein kinase C [PKC], tyrosine kinases, MAP kinases) mediate the opening and stabilization of mitochondrial K^+_{ATP} channels, the effectors thought to be mainly responsible for the preconditioning phenomenon.[376,377] Increased formation of nitric oxide (NO),[378–380] free oxygen radicals,[368] and enzymes such as cyclooxygenase 2[381] are also involved in the preconditioning process.

The delayed phase of myocardial protection, which may last well beyond the documented 24 to 72 hours, probably is based on transcriptional changes of protective proteins,[382,383] which may explain the time gap between early and late preconditioning.[384] Inhalation anesthetics also preserve cardiac function after reperfusion and decrease ischemia-induced intracoronary adhesion of polymorphonuclear neutrophils and platelets.[385–389]

Whether early results from in vitro studies and PCIs could be generalized to cardiac surgery has been investigated in multiple clinical studies. For example, Belhomme and associates[344] exposed patients to 5 minutes of preconditioning with a 2.5 minimum alveolar concentration (MAC) of isoflurane after the onset of CPB but before aortic cross-clamping. Troponin I and creatinine kinase MB subtype (CK-MB) levels were not significantly different from those of the control group. Nevertheless, patients who were exposed to isoflurane had increased activity of 5-nucleotidase, a marker for PKC activation, which is early evidence of preconditioning pathway activation similar to the in vitro findings.

Julier and coworkers,[342] in a double-blind, placebo-controlled, multicenter study, reported the effect of sevoflurane preconditioning on biochemical markers for myocardial and renal dysfunction in patients undergoing CABG. Patients who had sevoflurane preconditioning during the first 10 minutes of CPB had lower levels of biochemical markers of myocardial and renal impairment. Brain natriuretic peptide level as an indicator of myocardial dysfunction was significantly decreased in the sevoflurane group.

Conzen and colleagues[341] studied randomized patients undergoing OPCAB surgery with a propofol infusion or a continuous inhalation-based anesthetic technique with sevoflurane. Patients in the sevoflurane group had significantly lower troponin I levels and better LV function. Nader and associates[346] added vaporized sevoflurane (2%) versus oxygen alone to a cold blood cardioplegia solution in a small, randomized trial of patients undergoing CABG. Markers of the inflammatory response (ie, neutrophil β-integrins, tumor necrosis factor-α, and interleukin-6) were lower, and cardiac function (ie, stroke work index and wall motion analysis) was better preserved in the sevoflurane group (Fig. 20.14).

Whether the biochemical markers of improved cardiac outcome translate into reduced mortality rates or improved long-term outcomes is unclear. Garcia and coworkers[343] reported the results of a prospective, randomized study of the effect of sevoflurane preconditioning (10 minutes before aortic cross-clamping) on late cardiac events. Coronary artery reocclusion, HF, and cardiac death were assessed at 6 and 12 months postoperatively, and preconditioning with sevoflurane appeared to significantly reduce the incidence of late cardiac events. In a prospective, randomized, nonblinded study, De Hert and colleagues[77] compared the inhalation anesthetics desflurane and sevoflurane with intravenous anesthesia using a continuous propofol infusion in high-risk patients undergoing CABG. In the volatile anesthetic group, myocardial function was better preserved, troponin I levels were lower, and ICU and hospital LOS was shorter compared with propofol or

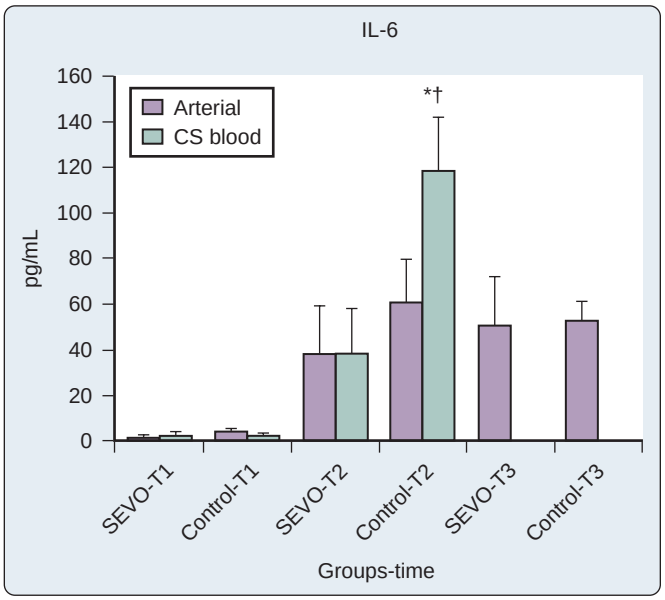


Fig. 20.14 Blunting of elevation of interleukin-6 (IL-6) levels in response to cardiopulmonary bypass (CPB) in patients receiving 2% sevoflurane *(SEVO)* added to the cardioplegia solution (1.4 ± 1.2 to 38.2 ± 21.6 pg/mL vs 4.1 ± 1.4 to 118.2 ± 23.5 pg/mL, $P < .05$). Levels were similar by 6 hours after CPB. *CS,* Coronary sinus; *T1,* baseline; *T2,* after separation from CPB; *T3,* 6 hours after separation from CPB. *(From Nader ND, Li CM, Khadra WZ, et al. Anesthetic myocardial protection with sevoflurane.* J Cardiothorac Vasc Anesth. *2004;18:269.)*

midazolam-based anesthesia regimens in this setting.[76] Guarrancino and associates[390] showed that desflurane-based anesthesia resulted in reduced troponin I release, inotropic drug use, and number of patients requiring prolonged hospitalization compared with a propofol-based technique in OPCAB procedures.

Several metaanalyses looked at preconditioning and mortality rates or long-term outcomes for patients undergoing cardiac surgery. In a metaanalysis that included only studies with sevoflurane and desflurane, Landoni and coworkers showed a reduction in mortality rates and the incidence of MI after cardiac surgery.[391] In two other meta-analyses that also included isoflurane, no such benefit was seen.[392,393]

Landoni and colleagues later published another metaanalysis applying Bayesian methodology, allowing them to investigate the various inhalation anesthetics compared with each other and ranking them in order of efficacy. Standard metaanalysis confirmed that the use of volatile anesthetics was associated with a reduction in mortality rates compared with TIVA, and the Bayesian analysis showed that sevoflurane and desflurane conferred the greatest benefits among the inhalation agents.[394]

Data from a Danish database used in a retrospective, multicenter analysis that included 10,535 patients did not show a difference in overall postoperative mortality or MI rates between propofol- and sevoflurane-based anesthesia.[395] To further investigate these controversial findings, Bignami and associates[396] conducted a longitudinal survey of 64 Italian cardiac surgical centers to study the correlation between the use of volatile anesthetics and 30-day mortality rates for CABG. The results showed that risk-adjusted 30-day mortality rate was significantly reduced when volatile agents were used during cardiac surgery, especially when there was prolonged use of these agents. The most consistent results were found when isoflurane was used. In a multicenter trial comparing desflurane or sevoflurane with propofol-based anesthesia, De Hert and coworkers[397] were unable to find a difference in troponin release, but they did show that the use of inhalation anesthetics reduced hospital LOS and that patients in the inhalation anesthetic group had a lower 1-year mortality rate.

The optimal timing and duration of inhalation anesthetic administration are uncertain.[398–401] Whereas some of the studies use brief periods of anesthetic preconditioning before aortic cross-clamping, others have reported the use of volatile anesthetics throughout the operative period. The older studies using brief periods of preconditioning showed improved cardiac function, although levels of markers of myocardial injury such as CK-MB or troponin I often were not significantly different from those of the control group. De Hert and colleagues[340] showed that the best results for myocardial protection were achieved when sevoflurane was administered throughout the intraoperative period rather than immediately before the planned myocardial ischemic event.

Most similarly designed studies have confirmed De Hert's findings. However, Bein and associates[401] found that levels of myocardial cell damage and dysfunction were lower in patients who received sevoflurane in an interrupted manner. Frassdorf and coworkers[400] also demonstrated that preconditioning-related myocardial protection was superior with multiple periods of sevoflurane administration applied rather than one short period. When sevoflurane was added to the anesthesia regimen after the coronary anastomoses were completed (ie, postconditioning), myocardial recovery was faster compared with propofol-based anesthesia. Nevertheless, patients who received sevoflurane during the entire procedure had the lowest troponin I levels, and the stroke volume changed the least compared with baseline levels. Most available data suggest not limiting the use of inhalation anesthetics to brief periods but rather using prolonged administration.

Research on pharmacologic preconditioning is not restricted to inhalation anesthetics only. There is increasing evidence that a variety of drugs that are commonly administered perioperatively have cardioprotective properties involving preconditioning pathways. Besides inhalation anesthetics, opioids (ie, δ-opioid receptor), adenosine (ie, adenosine A_1 receptor), and bradykinin have been investigated for their preconditioning effects, with various results.[364,365,402,403]

During cardiac surgery, several of the known preconditioning triggering agents may be used and appear to have additive or synergistic effects. Toller and colleagues[404] reported that the administration of sevoflurane and mechanical ischemic preconditioning reduced infarction size significantly compared with either stimulus alone. Ludwig and associates[364] demonstrated the additive effect of isoflurane and morphine on the reduction of infarction size.

There are insufficient data on how the potential beneficial effects of potent inhalation anesthetics differ between OPCAB and on-pump CABG patients. Some data show that OPCAB patients may benefit more.[405]

Several clinical factors appear to impair the protective effects of preconditioning. Diabetics and female patients appear to have attenuated responses to mechanical preconditioning signals during PCI.[406] Intraoperative hyperglycemia blocks the preconditioning effect, although this effect may be reversed by *N*-acetylcysteine, an oxygen radical scavenger.[366,407–410]

The role of postconditioning has also been investigated.[411,412] Short periods of flow followed by ischemia at the onset of myocardial reperfusion, referred to as *postconditioning*, elicit cellular mechanisms that help reduce MI size. Mitochondrial K^+_{ATP} channels, NO, and PKC also are thought to play important roles in postconditioning.[384,413–415] The beneficial effects of ischemic postconditioning have been shown in humans during coronary angioplasty for acute MI.[416,417] As in preconditioning, postconditioning has been found to work when applied remotely.[418] Postconditioning has improved contractile function[419] and attenuated postischemic arrhythmias.[420] However, similar to preconditioning, it is unlikely that repeated cross-clamping of the aorta during reperfusion would be achievable in clinical practice without risking major embolic strokes.

Inhalation anesthetics mimic some of the postconditioning effects and can blunt the deleterious effects of postischemic reperfusion injury and the inflammatory response syndrome after cardiac surgery.[421,422] The data suggest that the protective properties of potent inhalation anesthetics may not be restricted to the myocardium but also extend to other organ systems.[423–426]

The 2011 ACCF/AHA guideline for CABG surgery[106] provided level A evidence for using volatile-based anesthesia for patients undergoing myocardial revascularization to reduce the risk of perioperative myocardial ischemia and infarction. In the 2014 ACC/AHA guidelines on the management of patients undergoing noncardiac surgery, there was no preference given to a volatile or intravenous anesthetic (class of recommendation IIa, LOE A).[427] This is consistent with the lack of data demonstrating the protective effects during noncardiac surgery.

In summary, there is increasing evidence suggesting that potent inhalation anesthetics should be part of the anesthetic regimen for patients undergoing cardiac surgery, particularly patients undergoing CABG or OPCAB procedures.[428]

Role of Central Neuraxial Blockade

A balanced general anesthetic is still the most commonly used technique for patients undergoing CABG. However, there are many publications on the use of neuraxial techniques, particularly from Europe and Asia, for patients undergoing cardiac surgery.[429–431] It has been long appreciated that thoracic sympathectomy has favorable effects on the heart and coronary circulation.[432] The coronary vasodilating effects from thoracic epidural anesthesia (TEA) have been well documented, and the use of chronically implanted patient-controlled catheters has been reported.[433–438]

In the United States, medicolegal concerns about the rare but real danger of a devastating neurologic injury, the substantial logistic issues regarding placement of the catheter the night before surgery (most patients undergoing nonemergent CABG in the United States are admitted on the morning of surgery), and the potential for cancellation of a procedure in the event of a bloody tap during epidural catheter placement. The ubiquitous use of potent antiplatelet drugs in patients with CAD and the insufficient data regarding when to safely

discontinue those drugs before TEA and before catheter removal postoperatively are major concerns. The advent of fast-tracking may be a driving force (ie, ability to extubate faster and have a more comfortable patient with TEA), although most evidence suggests that a wide variety of techniques can be used effectively to facilitate early extubation. The cardioprotective effects of volatile agents may be as effective as the beneficial effects of thoracic sympathectomy.

High TEA for conscious OPCAB surgery has been reported mostly from centers outside the United States.[439–446] Karagoz and coworkers[447] described 137 patients, of whom 97% were successfully managed under awake TEA. In the reported series, most grafts were single-vessel left internal mammary artery (LIMA)–to–LAD grafts, although two-vessel and a small number of three-vessel procedures were performed successfully. In most series, 2% to 3% of catheters were unable to be placed in potential candidates, and 2% to 3% of procedures had to be converted to general anesthesia. Patients were fast-tracked, an ICU stay was not used, and some were discharged from the hospital the day of surgery. The rate of patient acceptance appeared to be quite high. In these small series, no TEA-related complications were observed. This is an area of growing interest and one that has potential advantages, particularly for countries with different health care systems, resource constraints, and cultural variations.

Although feasibility of using TEA has been demonstrated, outcome benefits associated with neuraxial blockade in patients undergoing OPCAB surgery need to be measured. Study designs are inherently flawed because it is impossible to perform a double-blind study, and operator bias and practitioner preference influence reported findings. In most studies, no significant difference in major outcome parameters, such as perioperative mortality and major morbidity rates, were found when neuraxial techniques were compared with general anesthesia alone or as a combined technique.[74,75,448,449] However, differences in minor outcome findings, such as quality of analgesia and time to extubation, are frequently reported.[450,451] Priestley and colleagues[452] conducted a prospective randomized study and did not find improved pulmonary or cardiac function with TEA or decreased LOS, despite improved analgesia and earlier extubation.

In 2006, Hansdottir and associates[453] randomized patients who had general anesthesia for cardiac surgery to TEA (given before surgery) or intravenous morphine for postoperative analgesia. Although time to extubation was shorter in the TEA group, none of the other examined outcome parameters was significantly different between the two groups. The investigators concluded that TEA combined with general anesthesia offered no major advantage compared with general anesthesia alone.

Bracco and coworkers[454] found fewer postoperative complications such as delirium, pneumonia, acute renal failure, and myocardial dysfunction in patients undergoing cardiac surgery who had TEA in addition to general anesthesia compared with general anesthesia alone. Based on shorter ICU LOS and mechanical ventilator times for patients with TEA, they calculated $8800 cost savings per person if TEA was used. Another trial enrolling obese patients (BMI >30 kg/m^2) undergoing OPCAB surgery showed better analgesia, improved lung function tests, and shorter time to extubation and ICU LOS for patients who had TEA in addition to general anesthesia.[455]

Liu and colleagues[456] reported a metaanalysis of 15 randomized trials of TEA with 1178 cardiac patients. In contrast to an earlier mixed metaanalysis (ie, cardiac and noncardiac surgery, observational and randomized),[457] there were no effects on postoperative MI or mortality rates. However, significant favorable effects were observed for arrhythmias, pulmonary complications, time to extubation, and reduction in visual analog pain scales. In a later study, Stenger and colleagues matched patients undergoing elective cardiac surgery to TEA or control groups (508 patients in each group) using EuroSCORE criteria.[458] Patients in the epidural group had a lower 6-month mortality rate and a lower incidence of MI, and TEA was associated with a reduced risk of postoperative dialysis (OR = 0.22 [0.06–0.74]).

The potential advantages of TEA on cardiac function were investigated in several studies. Berendes and coworkers[78] reported improved regional LV function by wall motion score index and lower troponin I and atrial and brain natriuretic peptide levels. However, the control for this study was a TIVA technique, and it is unclear whether a volatile anesthetic would have similar effects.

In a prospective, controlled study, Barrington and colleagues[459] randomized 120 patients to general anesthesia with or without high TEA. Although postoperative analgesia was improved in the TEA group and led to earlier extubation, there were no significant differences found in troponin levels in the two groups. Crescenzi and associates[460] evaluated the effect of TEA on N-terminal pro–brain natriuretic peptide (NT-proBNP) levels in elderly patients undergoing CABG. TEA in addition to general anesthesia significantly attenuated NT-proBNP release.

Lee and coworkers[461] addressed a slightly different question using total spinal sympathectomy (37.5 mg of bupivacaine) before induction of general anesthesia. Patients randomized to bupivacaine had less β-receptor dysfunction in response to CPB of more than 1 hour, lower catecholamine levels, a higher cardiac index, and lower pulmonary vascular resistance index in the post-CPB period. In another study, Bektas and colleagues[462] randomized 34 patients to intravenous morphine patient-controlled analgesia and high TEA with continuous levobupivacaine infusion after anesthesia induction. General anesthesia was maintained in both groups with a TIVA technique. TEA was associated with lower troponin I and CK-MB levels and a higher cardiac index after CABG.

Safety concerns are a major consideration in the use of neuraxial techniques in patients undergoing cardiac surgery because of chronic use of antiplatelet agents, systemic anticoagulation during surgery, and potential coagulopathy induced by CPB. The true incidence of serious complications (particularly epidural hematoma) is unknown.[463,464] A widely quoted estimation of the risk of epidural hematoma with TEA for patients undergoing cardiac surgery is 1 in 12,000 with a 95% confidence interval (CI) of 1 in 2100 to 1 in:68,000 and 1 in 1000 with 99% confidence.[465] A later risk assessment of neuraxial anesthesia in cardiac surgery estimates the risk of a catheter-related epidural hematoma in patients undergoing cardiac surgery to be 1 in 5493 with a 95% CI of 1 in 970 to 1 in 31,114.

Large, retrospective studies attempting to explore safety concerns with neuraxial manipulation in patients undergoing cardiac surgery have been published. Chakravarthy and associates[466] presented an audit of 2113 cardiac operations using TEA over a 13-year period with no permanent neurologic deficits, a 0.9% dural puncture rate, and 0.2% rate of transient neurologic deficits. Jack and coworkers published their experience of thoracic epidural catheter placement in 2837 patients undergoing cardiac surgery.[467] No epidural hematoma was seen in this series. Similar results were reported by Royse and colleagues,[468] who reviewed 874 cardiac surgery cases involving epidural anesthesia over a 7-year period with no complications attributable to epidural catheter use. Pastor and associates[469] reported 714 uneventful cases over a 7-year period, emphasizing their use of safety guidelines mandating discontinuing antiplatelet drugs 7 days before surgery, and routine coagulation tests and neurologic examinations were performed postoperatively. Even with these studies, the major concerns about adding a neuraxial technique are the subsequent heparin administration and the not infrequent coagulopathy associated with cardiac surgery. There are isolated reports of spontaneous spinal hematomas after cardiac surgery without neuraxial manipulation, which further complicates this issue.[470,471]

Planning a neuraxial technique for cardiac surgery patients requires careful attention to the most recent guidelines on neuraxial anesthesia in the setting of evolving anticoagulant and antiplatelet agents. The American Society of Regional Anesthesia and Pain Medicine published the Consensus Statements on Neuraxial Anesthesia and Anticoagulation.[472] They include recommendations for appropriate withdrawal of anticoagulant and antiplatelet therapy before neuraxial anesthesia and can be found at https://www.asra.com.

In summary, although neuraxial techniques can be performed for patients undergoing myocardial revascularization, outcome parameters

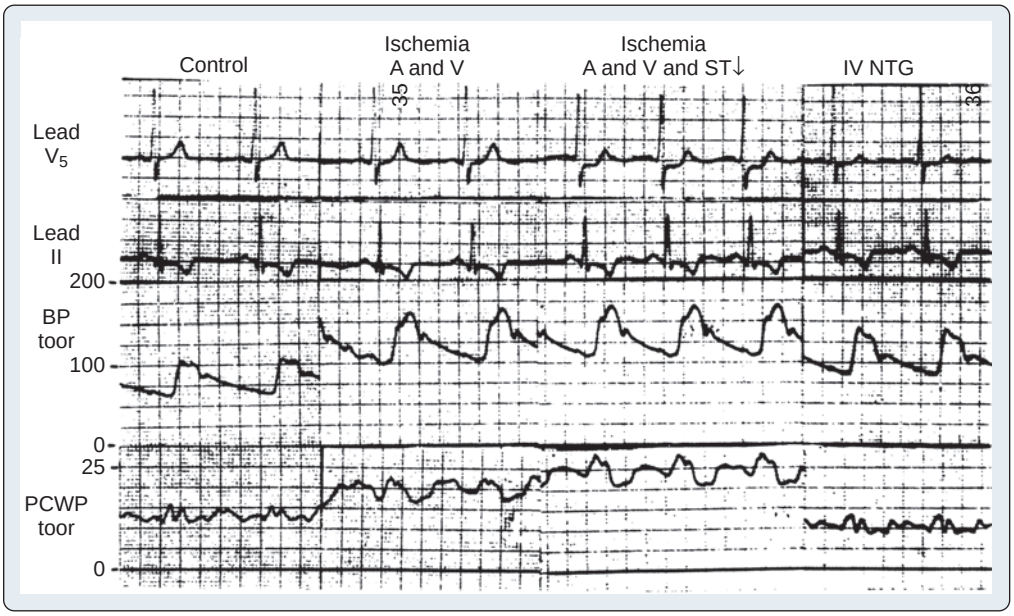


Fig. 20.15 Nitroglycerin *(NTG)* relieved postintubation intraoperative myocardial ischemia, as evidenced by large V waves in the pulmonary capillary wedge pressure *(PCWP)* tracing and then by ST-segment depression. *BP,* Blood pressure. *(From Kaplan JA, Wells PH: Early diagnosis of myocardial ischemia using the pulmonary arterial catheter.* Anesth Analg. *1981;60:789.)*

such as major morbidity and mortality rates are minimally affected by the anesthetic technique and probably depend more on patient-related factors and the quality of surgical intervention. This makes the risk-benefit ratio for TEA very questionable.

Myocardial Ischemia in Patients Undergoing Revascularization Surgery

In addition to providing anesthesia, a major concern of the anesthesiologist is the prevention and treatment of myocardial ischemia. The 2011 ACCF/AHA guideline for CABG surgery[106] recommended that determinants in coronary perfusion (ie, HR, diastolic pressure or MAP, and right ventricular [RV] or LV end-diastolic pressure [LVEDP]) should be monitored to reduce the risk of perioperative ischemia. Monitoring relevant hemodynamic parameters, detecting myocardial ischemia, and prompt treatment are of paramount importance for patients undergoing myocardial revascularization.

Diastolic dysfunction detected with TEE or a PAC is one of the earliest changes associated with myocardial ischemia, and it may precede the development of abnormal systolic function. RWMAs also have been described as early signs of ischemia. They occur within seconds of inadequate blood flow or oxygen supply. RWMAs detected by TEE provide a more sensitive indicator of myocardial ischemia compared with ST-segment changes.[191] However, a major limitation is that multiple TEE views monitored simultaneously are required to detect subtle changes in RWMAs. Fig. 20.15 demonstrates how hypertension (ie, increase in wall stress), even in the absence of tachycardia, as a response to surgical stress (eg, skin incision) can be associated with pulmonary hypertension, elevated pulmonary capillary wedge pressure (PCWP), and prominent A and V waves on the PCWP waveform. Signs of myocardial ischemia (ie, ischemic MR) often resolve with administration of a nitroglycerin (NTG) infusion (see Chapters 11 through 16).[473]

Intraoperative Treatment of Myocardial Ischemia

The main hemodynamic goals are to ensure an adequate CPP (ie, diastolic blood pressure minus LVEDP) and HR control; HR is the single most important treatable determinant of myocardial oxygen consumption. Table 20.3 summarizes the treatment of acute perioperative myocardial ischemia. Some of the routinely used pharmacologic interventions for intraoperative myocardial ischemia are discussed in the following section (see Chapter 11).

Intravenous Nitroglycerin

Since the introduction in 1976 by Kaplan and coworkers of the V_5 lead to diagnose myocardial ischemia[474] and intravenous NTG to treat it,[475] the drug has been one of the mainstays for treating perioperative myocardial ischemia. Intravenous NTG acts immediately to reduce LV preload and wall tension, primarily by decreasing venous tone at lower doses, and at larger doses, it decreases arterial and epicardial coronary arterial resistance.[476–478] It is most effective in treating acute myocardial ischemia with ventricular dysfunction accompanied by sudden elevations in left ventricular end-diastolic volume, LVEDP, and PAP. The elevations in LV preload and wall tension further exacerbate perfusion deficits in the ischemic subendocardium and usually respond immediately to NTG (Fig. 20.16).

Preoperatively, NTG often is used to treat patients with unstable angina or ischemic MR.[479,480] In the pre-CPB period and during OPCAB, NTG is used to treat signs of ischemia such as ST-segment depression, hypertension uncontrolled by the anesthetic technique, ventricular dysfunction, and coronary artery spasm (Box 20.5). During CPB, NTG can be used to control the MAP,[481] but only about 60% of patients are responders because of alterations of the pharmacokinetics and pharmacodynamics of the drug with CPB. Factors contributing to the reduction of its effectiveness include adsorption to the plastic in the CPB system, alterations in regional blood flow, hemodilution, and hypothermia. Booth and colleagues[482] showed that different oxygenators and filters sequester up to 90% of circulating NTG during CPB. After revascularization, NTG is used to treat residual ischemia or coronary artery spasm, reduce preload and afterload, and it may be combined with vasopressors (eg, phenylephrine) to increase the CPP when treating coronary air embolism (Box 20.6).

Studies of the prophylactic role of NTG in preventing perioperative myocardial ischemia have had mixed results, with most studies showing no effects of NTG infusions on the incidence of perioperative myocardial ischemic events.[483–485] In a prospective, double-blind, placebo-controlled study, Zvara and associates[486] randomized patients undergoing CABG using a fast-track anesthesia technique to 2 μg/kg per minute of NTG or placebo starting before induction

TABLE 20.3 Acute Treatments for Suspected Intraoperative Myocardial Ischemia[a]

Associated Hemodynamic Finding	*Therapy*	*Dosage*
Hypertension, tachycardia[b]	Deepen anesthesia	
	Intravenous (IV) β-blockade	Esmolol, 20–100 mg ±50–200 μg/kg/min prn Metoprolol, 0.5–2.5 mg Labetalol, 2.5–10 mg
	IV nitroglycerin	Nitroglycerin, 10–500 μg/min[c]
Normotension, tachycardia[b]	Ensure adequate anesthesia, change anesthetic regimen	
	IV β-blockade	β-Blockade, as above
Hypertension, normal heart rate	Deepen anesthesia	
	IV nitroglycerin or nicardipine	Nicardipine, 1–5 mg ±1–10 μg/kg/min Nitroglycerin, 10–500 μg/min[c]
Hypotension, tachycardia[b]	IV α-agonist	Phenylephrine, 25–100 μg Norepinephrine, 2–4 μg
	Alter anesthetic regimen (eg, lighten)	
	IV nitroglycerin when normotensive	Nitroglycerin, 10–500 μg/min[c]
Hypotension, bradycardia	Lighten anesthesia	
	IV ephedrine	Ephedrine, 5–10 mg
	IV epinephrine	Epinephrine, 4–8 μg
	IV atropine	Atropine, 0.3–0.6 mg
	IV nitroglycerin when normotensive	Nitroglycerin, 10–500 μg/min[c]
Hypotension, normal heart rate	IV α-agonist/ephedrine	α-Agonist, as above
	IV epinephrine	Epinephrine, 4–8 μg
	Alter anesthesia (eg, lighten)	
	IV nitroglycerin when normotensive	Nitroglycerin, 10–500 μg/min[c]
No abnormality	IV nitroglycerin IV nicardipine	Nitroglycerin, 10–500 μg/min[c] Nicardipine, 1–5 mg ±1–10 μg/kg/min

[a]Ensure adequacy of oxygenation, ventilation, and intravascular volume status and consider surgical factors, such as manipulation of heart of coronary grafts.
[b]Tachyarrhythmias (eg, paroxysmal atrial tachycardia, atrial fibrillation) should be treated directly with synchronized cardioversion or specific pharmacologic agents.
[c]Bolus doses (25–50 μg) and a high infusion rate may be required initially.

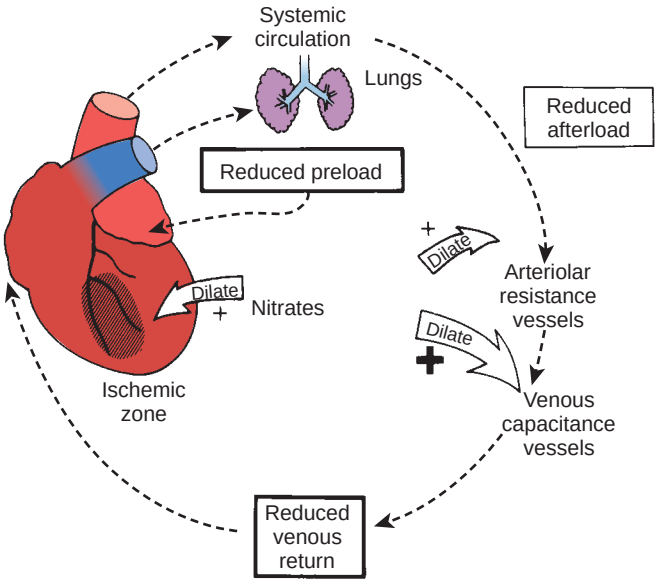


Fig. 20.16 The effects of nitrates on the circulation include prominent venodilation and reduction of preload. Afterload is decreased because of mild arteriolar dilatation. Coronary dilation also occurs and benefits the ischemic myocardium. *(From Opie LH: Drugs and the heart: II. Nitrates.* Lancet. *1980;1:750.)*

BOX 20.6 USES OF INTRAVENOUS NITROGLYCERIN ON TERMINATION OF CARDIOPULMONARY BYPASS

- Myocardial ischemia or stunning
- Diastolic dysfunction
- Elevated pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, pulmonary vascular resistance, systemic vascular resistance
- Increase coronary perfusion pressure along with a vasopressor
- Prevention of arterial graft spasm (ie, radial artery graft)
- Coronary artery spasm
- Reinfusion of oxygenator volume

BOX 20.5 INTRAOPERATIVE USE OF INTRAVENOUS NITROGLYCERIN

Hypertension
Elevated pulmonary artery pressure
New-onset AC and V waves (ischemic mitral regurgitation)
Acute ischemia (ST changes >1 mm)
New regional wall motion abnormalities on transesophageal echocardiography
Diastolic dysfunction
Systolic dysfunction (with adequate coronary perfusion pressure)
Coronary artery spasm

and continuing until 6 hours after extubation in the ICU. They found a similar incidence, severity, and duration of myocardial ischemia whether the patients received NTG or placebo (37% vs 35%, respectively). Although there were more patients in the placebo group with positive enzyme and electrocardiographic signs of MI, the findings were not statistically significant. Similarly, in a prospective, randomized, controlled study, 0.5 to 1 μg/kg per minute of NTG administered after aortic cross-clamp release in patients undergoing CABG did not decrease the incidence of postoperative myocardial ischemia.[487]

Intravenous NTG has been compared with other vasodilators such as nitroprusside and calcium channel blockers. Kaplan and Jones[476] first demonstrated that NTG was preferable to nitroprusside during CABG. Both drugs controlled intraoperative hypertension and decreased myocardial oxygen consumption, but NTG improved ischemic changes on the ECG, whereas nitroprusside did not. Nitroprusside decreased CPP or produced an intracoronary steal in about one third of patients with myocardial ischemia.

Calcium Channel Antagonists

The calcium antagonists are a structurally diverse group of drugs that inhibit the passage of calcium through the slow channels of the cell membrane. These agents collectively relax arterial smooth muscle, with little effect on most venous beds. Despite areas of commonality, the calcium antagonists have different actions and hemodynamic effects. For example, nifedipine acts primarily on vascular smooth muscle and has little effect on the AV node. In contrast, verapamil acts mainly on

the cardiac conduction system and has less effect on vascular smooth muscle. Diltiazem and verapamil do not significantly increase CBF or consistently decrease coronary vascular resistance. Both drugs produce significant hemodynamic changes with myocardial depression and conduction disturbances during anesthesia.[488,489] This limits their use in the treatment of perioperative myocardial ischemia.

Nicardipine is a short-acting dihydropyridine calcium antagonist similar to nifedipine, but it possesses a tertiary amine structure in the ester side chain. Nicardipine is stable as a parenteral solution and therefore can be administered intravenously.[490] It has highly specific modes of action, which include coronary antispasmodic and vasodilatory effects and systemic vasodilation. Among the calcium antagonists, nicardipine is unique in its consistent augmentation of CBF and its ability to induce potent vasodilator responses in the coronary bed. Nicardipine produces minimal myocardial depression and significantly improves diastolic function in patients with ischemic heart disease.[491,492] Despite these beneficial properties, nicardipine is typically not the primary choice in treating myocardial ischemia during CABG. However, its relatively rapid onset and cessation of action make it an attractive drug for the perioperative management of hypertension.[493–498]

Van Wezel and coworkers[499] used a 3 to 12 μg/kg per minute infusion of nicardipine and compared it with a 1 to 3 μg/kg/min infusion of nitroprusside. Both drugs were equally effective in controlling BP, but there was a 24% incidence of ST-segment depression in the nitroprusside group versus 9% in the nicardipine group. Van Wezel and colleagues[500] also compared intravenous NTG with intravenous administration of verapamil or nifedipine in patients undergoing CABG. Nitroglycerin was found to be the drug of choice because it controlled BP while not producing as much tachycardia (as nifedipine) or myocardial depression and conduction blockade (seen with verapamil).

Apostolidou and associates[487] randomized patients undergoing CABG with CPB to nicardipine (0.7 to 1.4 μg/kg per minute), NTG (0.5 to 1 μg/kg per minute), or placebo. Immediately after coronary revascularization (after aortic cross-clamp release until end of surgery), there were significantly fewer episodes of myocardial ischemia in the nicardipine group (0% vs 10% vs 24%, respectively). During the postoperative period, there was no difference in myocardial ischemia among the drug groups.

Clevidipine was introduced for the treatment of perioperative hypertension.[501] Clevidipine is an ultrashort-acting, intravenously administered, dihydropyridine calcium channel blocker that acts as an arterial-selective vasodilator, and its action is rapidly terminated by blood and tissue esterases. In a randomized, double-blind, placebo-controlled, multicenter trial of the drug in patients undergoing cardiac surgery, clevidipine effectively reduced arterial blood pressure.[502] The Evaluation of Clevidipine In the Perioperative Treatment of Hypertension (ECLIPSE) trial compared clevidipine with NTG, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients.[503] Clevidipine effectively maintained the arterial blood pressure within a prespecified range. Compared with nitroprusside, clevidipine-treated patients had a significantly reduced mortality rate ($P = .04$).

β-Blockers

Hypertension, tachycardia, arrhythmias, and myocardial ischemia from sympathetic stimulation are common occurrences in the perioperative period. Despite the benefits of early use of β-blockers in the treatment of myocardial ischemia, the relatively long half-life and prolonged duration of action of previously available β-blockers had significantly limited their use during surgery and the immediate postoperative period.[504] However, with the introduction of esmolol in the late 1980s, an ultrashort-acting cardioselective β_1-blocker with a half-life of 9 minutes became available. Esmolol was soon adopted by many clinicians for the prevention and treatment of myocardial ischemia. A mean esmolol dose of 17 ± 16 mg/min, with a range of 8 to 24 mg/min, was found to be effective in alleviating chest pain while increasing CO in patients with unstable angina.[505]

Kirshenbaum and coworkers[506] showed that esmolol was effective in treating acute myocardial ischemia, even in patients with poor LV function (ie, increased PCWP of 15–25 mm Hg). Esmolol was infused in these patients in doses up to 300 μg/kg per minute and produced decreases in HR, BP, and cardiac index. However, the PCWP was not significantly altered by the drug infusion. The results suggested that even in the setting of moderate LV dysfunction, esmolol could safely reduce BP and HR in patients with acute myocardial ischemia.

Because of the favorable pharmacologic properties and encouraging clinical findings, esmolol was soon used frequently during CABG to treat hypertension and tachycardia and to prevent myocardial ischemia.[507–509] Before the introduction of newer mechanical stabilizing devices, it had also been used to slow the HR to facilitate OPCAB procedures.

Weaning Patients From Cardiopulmonary Bypass After Coronary Revascularization

Chapter 36 discusses the predictors and techniques of weaning a patient successfully from CPB. Some factors and concerns are specific to patients undergoing myocardial revascularization. Good surgical technique that provides high-quality anastomoses and preserves the heart during aortic cross-clamping is key to cardiac function immediately after separation from CPB. Because administration of cardioplegia can be problematic in patients with CAD, various techniques are used, including a combination of hypothermia and antegrade and retrograde cardioplegia, by some surgeons.

In patients with normal preoperative function, minimal or no inotropic support is usually required. In patients with impaired ventricular function, TEE evaluation immediately before weaning off CPB can provide invaluable information for choosing an inotrope, vasodilator, or vasoconstrictor. In patients who arrive in the operating room with an IABP inserted, support typically is continued into the postoperative period. In patients with very poor ventricular function, the insertion of an IABP to support ventricular function during weaning from CPB can be helpful.[510,511] In a metaanalysis, preoperative IABP insertion in patients undergoing CABG was associated with a significant reduction in 30-day mortality rates (3.5% vs 11%).[512]

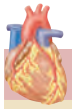
The Immediate Postoperative Period

Sedation

Patients usually are sedated to facilitate transport to the ICU and during the immediate postoperative period until extubation criteria are fulfilled (see Chapter 37). Dexmedetomidine, propofol, and midazolam are intravenously administered agents with favorable properties in this setting.

α_2-Adrenergic receptor agonists have unique properties (Box 20.7) that explain their increasing use in some cardiac surgery centers. Although the FDA approved clonidine in 1974, it was available only as an oral formulation in the United States, limiting its widespread use. In 1999, the FDA approved dexmedetomidine for continuous (up to 24 hours) intravenous sedation in the ICU. It is a more selective α_2-adrenoceptor agonist than clonidine, and exhibits central sympatholytic and peripheral vasoconstrictive effects. Intravenous bolus administration causes a transient increase in MAP and SVR due to stimulation of peripheral α- and β_2-adrenergic receptors in vascular smooth muscle. A continuous infusion (0.2–0.8 μg/kg per hour) has dose-dependent hemodynamic effects; most consistently decreases in HR, plasma catecholamine levels, and MAP.[513,514] Higher doses of dexmedetomidine result in more profound sedation with some analgesia sparing effects, and large doses may be associated with increases in MAP, SVR, and PAP.[515]

There are limited data from animal studies demonstrating potential coronary vasoconstrictive and cardiodepressant effects for dexmedetomidine.[83,516–518] Coronary vasoconstriction was seen mainly with bolus doses of 10 μg/kg and higher. At the recommended loading (0.5–2 μg/kg) and maintenance (0.2–0.7 μg/kg per hour) doses,



BOX 20.7 α_2-AGONIST PROPERTIES

- Sedation
- Anxiolysis
- Analgesia
- Hemodynamic stability
- Central sympatholytic effect
- Decreased blood pressure and heart rate
- Decreased perioperative oxygen consumption
- Decreased plasma catecholamine levels
- Decreased incidence of tachyarrhythmias
- Prevention of histamine-induced bronchoconstriction
- Treatment and prevention of postoperative shivering
- Sedation in patients with postoperative delirium
- Blunting of withdrawal symptoms in drug and alcohol addicts
- Possible inhibition of inflammatory response

dexmedetomidine most likely has a favorable effect on myocardial perfusion.[519] Roekaerts and colleagues[520,521] showed an increase in the endocardial-to-epicardial blood flow ratio in the postischemic myocardium, with an overall reduction of myocardial oxygen demand after experimentally induced myocardial ischemia in dogs. The greatest reduction in oxygen demand was seen when baseline HR and arterial BP were increased.

Dexmedetomidine may be a useful agent in the early postoperative period because its sedative properties are associated with minimal respiratory depression and appear to mimic natural sleep patterns.[522] When administered continuously in postoperative patients, it caused no changes in respiratory rate, oxygen saturation, arterial pH, and arterial carbon dioxide (CO_2) tension compared with placebo.[523] These patients usually were effectively sedated but still arousable and cooperative in response to verbal stimulation.[524] Due to its analgesic properties, it significantly reduced additional opioid analgesia requirements in mechanically ventilated patients in the ICU.[525–527]

The α_2-agonists have been used successfully in patients with postoperative delirium,[528] administered for withdrawal symptoms in alcohol or drug addicts, and are associated with a low rate of shivering.[529,530] A study of 724 patients undergoing CABG showed a lower risk of delirium and higher 30-day and 1-year survival rates when dexmedetomidine was administered after CPB and continued in the ICU.[531] Increasing data show that dexmedetomidine administration is associated with a decreased risk of tachyarrhythmias after cardiac surgery,[264,532] but the incidence of bradycardia is increased.

Propofol has been used extensively intraoperatively and for sedation in the ICU. Several studies compared propofol and dexmedetomidine in the postoperative period after surgery.[533,534] Venn and associates[524] randomized a small number of patients to propofol or dexmedetomidine sedation in the immediate postoperative period. Dexmedetomidine reduced the requirement for opioid analgesia, but for patients after myocardial revascularization, it reduced HR more than propofol, whereas the arterial blood pressure did not differ between the two groups.

In a multicenter, randomized study, Herr and coworkers[263] compared a dexmedetomidine-based sedation regimen with propofol sedation after CABG in the ICU. Although there were no differences in time to extubation, the investigators found a significantly reduced need for additional analgesics (ie, propofol-sedated patients required four times the mean dose of morphine), antiemetics, and diuretics and they had fewer episodes of tachyarrhythmias requiring β-blockade (ie, ventricular tachycardia in 5% of the propofol-sedated group vs none in the dexmedetomidine group). However, hypotension was more common in the dexmedetomidine group compared with the propofol-sedated patients (24% vs 16%) (Fig. 20.17). Approximately 25% of the dexmedetomidine-associated hypotension occurred in the first hour of the study, particularly during or within 10 minutes after the loading infusion of 1 μg/kg. To avoid hypotension seen with a large loading dose of dexmedetomidine, loading doses are infrequently administered in clinical practice, but a continuous maintenance dose is started earlier to achieve appropriate plasma levels at the time of patient transfer from the operating room.

With regard to patient satisfaction, there are insufficient data to clearly favor one of the agents. Corbett and colleagues[535] randomized 89 adult patients after CABG to dexmedetomidine or propofol. Patients were interviewed regarding awareness, recall, generalized comfort, level of pain, ability to interact with health care providers and family, feelings of agitation and anxiety, ability to sleep and rest, and overall satisfaction with their ICU stay. The level of awareness and additional morphine and midazolam requirements did not differ between the groups. Patients favored propofol for sleep and rest, there was more patient discomfort and pain in the dexmedetomidine group, and the investigators concluded that dexmedetomidine did not offer any advantages over propofol for short-term sedation after CABG. The increased incidence of pain in the dexmedetomidine group was surprising because most studies have shown reduced opioid requirements with α_2-adrenoceptor agonists.

Barletta and associates[536] compared propofol and dexmedetomidine after CABG or valve surgery, or both, in a fast-track recovery room setting. Patients ($N = 100$) were matched according to surgery type and LV function. Dexmedetomidine resulted in lower opioid requirements, but this did not result in shorter duration of mechanical ventilation, improved quality of sedation, or rate of adverse events.

In summary, although there are theoretic advantages to using dexmedetomidine for sedation after CABG, no clear benefits have been documented for either drug. Sedation-related costs are higher with dexmedetomidine administration.

Coronary Artery and Arterial Conduit Spasm

Since 1981, when Buxton and coworkers[537] first reported coronary artery spasm immediately after CABG, there have been numerous descriptions of this complication. Spasm usually has been associated with profound ST-segment elevation on the ECG, hypotension, severe dysfunction of the ventricles, and myocardial irritability. Many hypotheses have been put forward to explain the origin of coronary artery spasm (Fig. 20.18).[538] The underlying mechanism may be similar to the coronary spasm seen with Prinzmetal variant angina.

Therapy is usually effective with a wide range of vasodilators such as NTG, calcium channel blockers, milrinone, or combinations of NTG and calcium channel blockers in both situations. Arterial grafts with a vessel such as the LIMA and particularly radial artery grafts are prone to spasm after revascularization, and prevention and recognition are crucial to prevent serious complications.[539]

He and colleagues[540] tested the reactivity of ring segments of human IMAs in organ baths to various constrictor and dilator agents. Thromboxane was the most potent IMA constrictor, followed by norepinephrine, serotonin, phenylephrine, and potassium chloride. NTG, nitric oxide, papaverine, milrinone, and the calcium channel blockers nifedipine, verapamil, and diltiazem produced relaxation. In a similar study, Mussa and associates[541] observed the vasodilating properties of topically applied phenoxybenzamine. It prevented vasoconstriction with a long-lasting effect (>5 hours) in response to various vasoconstrictors, followed by verapamil/NTG (5 hours), and papaverine (1 hour). In vivo, for prophylaxis of IMA spasm, the calcium antagonists, especially diltiazem, were thought to be as useful as NTG.[542–544]

Prevention and treatment of arterial conduit spasm with diltiazem may cause serious side effects such as low CO or conduction abnormalities. Diltiazem is also a more expensive drug compared with NTG. Shapira and coworkers[545] showed in vitro (ie, radial artery, IMA, and saphenous vein) and in vivo (ie, radial artery) that NTG was a superior vasodilator compared with diltiazem. The same investigators monitored patients undergoing CABG using radial artery grafts who were randomized to receive NTG or diltiazem intravenously after induction of anesthesia followed by a NTG patch or oral diltiazem postoperatively for 6 months. There was no significant difference in outcome (ie, morbidity, MI, and CK-MB) between the two groups. The

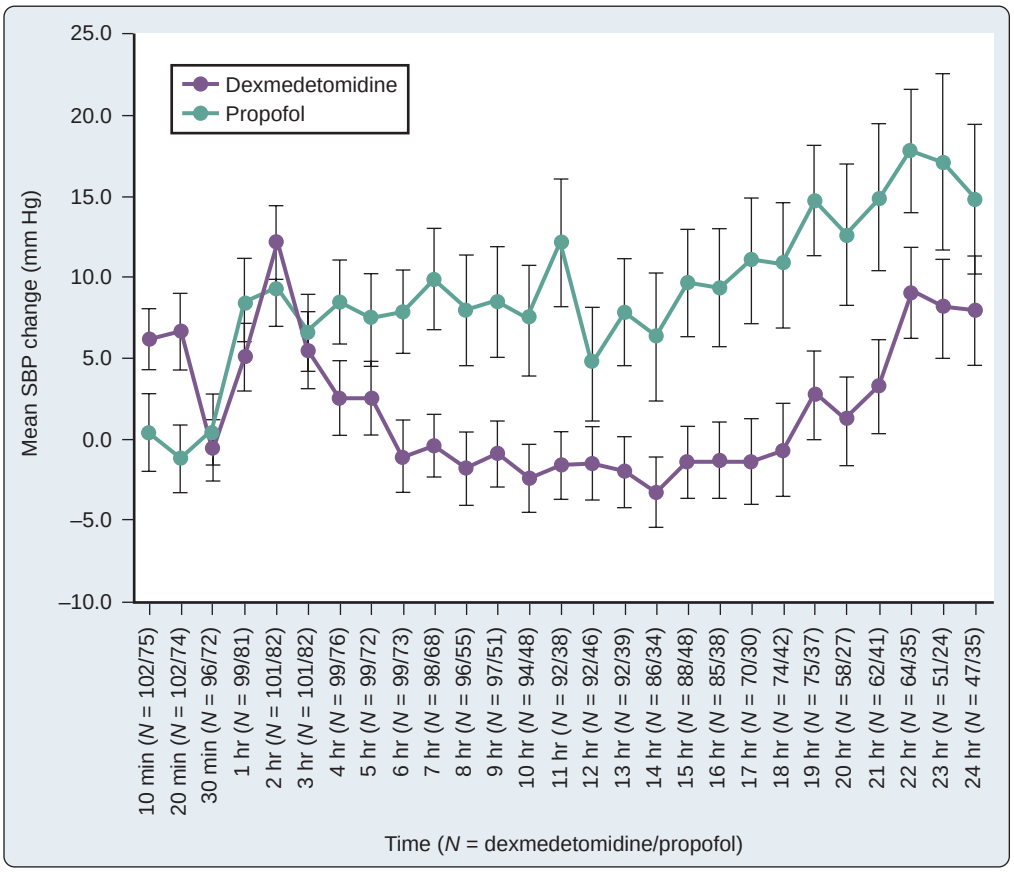


Fig. 20.17 Changes from baseline in systolic blood pressure *(SPB)* between coronary artery bypass grafting patients sedated with dexmedetomidine or propofol. The baseline is the mean SPB for each treatment group just before sternal closure. Numbers of patients receiving each drug (x-axis) declines progressively as they are extubated postoperatively. *(From Herr DL, Sum-Ping ST, England M: ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens.* J Cardiothorac Vasc Anesth. *2003;17:576.)*

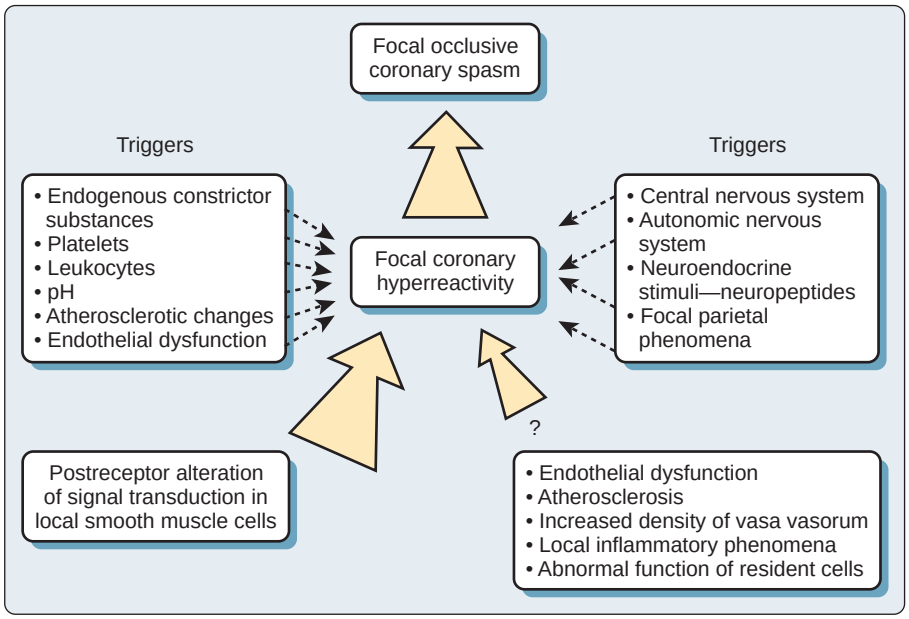


Fig. 20.18 Schematic representation of the pathogenesis of coronary artery spasm.

6-month diltiazem treatment was associated with 16-fold higher costs and significantly more patients requiring cardiac pacing compared with NTG (28% vs 13%, respectively).[546]

In a double-blind, randomized study, Mollhoff and colleagues[547] compared milrinone (0.375 μg/kg per minute) to nifedipine (0.2 μg/kg per minute) in patients with impaired LV function undergoing CABG. ST changes after revascularization (including use of the IMA graft) indicative of myocardial ischemia occurred in 33.3% of the milrinone group compared with 86.6% of the nifedipine group. Levels of biochemical markers of myocardial damage (ie, CK-MB and troponin I) after 24 hours were significantly higher in the nifedipine group.

Fast-Track Management for Coronary Artery Bypass Grafting

Fast-tracking was introduced into patient management when costs started to play a more significant role in patient care in the late 1970s and early 1980s. Diagnosis-related groups (DRGs) had been introduced about the same time in an effort to reduce Medicare reimbursements to hospitals. With this reimbursement model, less resource use, mostly driven by shorter ICU and hospital LOSs, became linked to financial benefits for the hospitals.

In 1990, Krohn and associates[548] reported a study of 240 patients undergoing CABG at a private southern California hospital between 1984 and 1986. They described a clinical pathway emphasizing early extubation, rapid mobilization, intraoperative fluid restriction, and steroid administration. This management strategy was associated with a median postoperative LOS of 4 days and in-hospital mortality rate of only 2%. The strategy was forged from intense economic competition with the first major incursion of managed care into this area's competitive market.

In 1994, the term *fast-track* in cardiac anesthesia was introduced by Engelman and colleagues in their article "Fast-Track Recovery of the Coronary Bypass Patient." It included a complete care plan, which was associated with a reduced hospital LOS.[549] In a similar time frame, reports appeared from the financially constrained UK health care system, in which formal ICU care was bypassed based primarily on rapid early extubation (with apparent success).[550,551]

The publicity associated with these reports contributed to Medicare's interest in cost reduction, leading to the Medicare Participating Heart Bypass Center Demonstration conducted between 1991 and 1996 in which seven participating hospitals agreed to a single, sharply discounted rate for CABG in return for preferential market share.[552] Over the 5-year period, it was estimated that $50.3 million dollars were saved. In their summary report, reduction of cost and LOS by retooling processes of care was emphasized, and reducing time to extubation was considered a key factor. In the participating centers, LOS and mortality rates declined annually despite increased severity of the case mix.

Although the fast-track clinical pathway encompasses a variety of perioperative and after-discharge management strategies, early extubation is the one that has received the greatest attention (Box 20.8).[553,554] Early extubation is acknowledged as a key component of the fast-track clinical pathway and one that was considered the most radical change in practice during the peak of scrutiny of the fast-track pathway in the middle to late 1990s (Box 20.9).

Reports of prolonged ventilatory management after cardiac surgery first appeared in the late 1950s (for valve surgery because CABG was not yet performed), and those from the 1960s (including the first reports of CABG patients) strongly advocated its routine use.[555] This was further emphasized with the adoption of high-dose morphine and with fentanyl and sufentanil at the end of that decade.[269,284]

As early as 1974, the first reports advocating early extubation, primarily by greater reliance on volatile anesthesia, appeared.[556] In 1980, Quasha and coworkers[557] reported the first small, randomized, controlled trial enrolling CABG patients ($N = 38$), in which 89% were extubated in less than 8 hours. Ramsay and colleagues[558] reported a small, randomized, controlled trial ($N = 20$) in which opioid reversal with nalbuphine was used. However, this resulted in an unacceptable increase in postoperative pain. The larger and more rigorous, randomized, controlled trial reported by Cheng and associates[559] in 1996 ($N = 100$), in which mean time to extubation was 4.1 hours, is recognized as the most influential of the contemporary studies of early extubation. Reports of successful use of fast-tracking in a variety of patient populations have been reported since, including academic,[79,560] private,[309,561–564] elderly,[565–567] rural settings, and Veterans Affairs patients[80,568] from the United States and many other countries. It is used as a quality improvement marker in many health care systems.[79,560,569] In some of these systems, alterations of the traditional models of ICU care have been adopted,[570] although many use routine ICU models with shorter stays (see Chapter 37).

The first metaanalyses of early extubation reported were based on accumulated data from randomized, controlled trials. Myles and coworkers[553] reviewed studies in which fast-tracking was defined as use of reduced opioid dosing (ie, fentanyl ≤20 μg/kg) with stated intention to attempt extubation in less than 10 hours postoperatively. They identified 10 trials ($N = 1800$) with most involving CABG patients from 1989 to 2002. The fast-track groups had shorter times to extubation (by 8.1 hours), with no significant differences in major morbidity or mortality rates and only one instance of reintubation. ICU LOS was reduced by 5.4 hours, although hospital LOS was not shortened.

Hawkes and colleagues[571] reported a metaanalysis from the UK-based Cochrane Collaboration. The investigators considered only randomized, controlled trials that defined time to extubation as within 8 hours and that specifically evaluated mortality rates (ie, in ICU, at 30 days, and up to 1 year), incidence of postoperative myocardial ischemia (eg, biomarkers, ECG), and pulmonary outcomes (eg, reintubation, respiratory dysfunction). Secondary outcomes of ICU and hospital LOS were analyzed. Given their more stringent requirements and

BOX 20.8 PERIOPERATIVE GOALS OF FAST-TRACK MANAGEMENT

- Preoperative education
- Same-day admission whenever possible
- Anesthetic technique tailored to early extubation
- Effective postoperative analgesia
- Flexibility in the use of recovery areas (eg, postanesthesia care unit instead of intensive care unit)
- Protocol-driven care
- Early mobilization
- Early intensive care unit and hospital discharge
- Follow-up (eg, telephone, office visits) after hospital discharge
- Interdisciplinary continuous quality improvement strategies

BOX 20.9 SUGGESTED CRITERIA FOR EARLY EXTUBATION

- Body temperature >35°C
- Normal acid-base status
- Stable hemodynamics on minimal inotropic support
- Adequate hemostasis with decreasing or stable mediastinal drainage
- Stable cardiac rhythm
- Spontaneous respiratory rate and adequate tidal volumes and inspiratory force
- Chest radiograph without major abnormalities (eg, minimal atelectasis)
- Adequate urine output
- Adequate reversal of neuromuscular blockade
- Awake, alert, cooperative, and moving all extremities

predetermined hypotheses for testing, they found only six studies ($N = 871$) meeting the criteria, and almost one-half of the patients were from a single study (Reyes and associates).[557,559,572–575]

The study by Reyes and coworkers[574] is unusual because both treatment groups received high-dose fentanyl, in contrast to all other studies of fast-tracking in which opioid doses were deliberately lower. However, exclusion of this study did not alter the findings. Overall, there was no difference in ICU and 30-day mortality rates; the 1-year mortality rate was assessed in only one study, which showed difference between groups. All other outcome parameters, including postoperative myocardial ischemia, incidence of early reintubation within 24 hours (1.6%), late reintubation (>24 hours), and atelectasis, did not vary significantly between groups. The ICU LOS was significantly reduced by 7 hours, and hospital LOS was reduced by 1.1 days.

Some centers have adopted an even more aggressive form of fast-tracking. Walji and colleagues[564] coined the term *ultrafast-tracking* to describe their practice and reported a 56% hospital discharge rate by postoperative day 4 and 23% discharge rate by postoperative day 2, although the readmission rate was 3.9%, but there was no early mortality. Ovrum and associates[576] from Norway reported a cohort of 5658 CABG patients, 99% of whom were extubated by 5 hours (median, 1.5 hours), with a 1.1% reintubation rate. More than 99% of patients were transferred to the ward the next morning.

Although postoperative pain management is detailed in Chapter 42, it should be mentioned that nonopioid analgesics are frequently administered to patients who are fast-tracked. The use of nonsteroidal antiinflammatory drugs (NSAIDs) after CABG is controversial; particularly after the FDA issued a black box warning in 2005 recommending against their use after cardiac surgery. However, recent data seem to support the safety of NSAIDs in the cardiac surgery setting.[577–579] More data are required to make conclusive recommendations.

Coronary Artery Bypass Grafting Without Cardiopulmonary Bypass

Introduction and Surgical Considerations

Although OPCAB gained increasing popularity in the late 1990s, surgery on the beating heart had already been performed in the 1950s and early 1960s, preceding the widespread use of on-pump CABG. Limitations included a lack of adequate equipment and CPB techniques in the early days of cardiac surgery. After CPB could be safely accomplished, many surgeons lost interest in OPCAB surgery, preferring a nonbeating heart for coronary anastomoses. However, the inherent risks of CPB and aortic cross-clamping continued to be a major factor in CABG morbidity and mortality. Avoiding CPB altogether seemed to offer a solution, but technical limitations with the then available surgical equipment were significant. It was not until the middle to late 1990s, when surgical researchers developed efficient mechanical stabilizer devices that minimized motion around the anastomotic site, that OPCAB surgery regained more widespread interest.

The pace and tempo of OPCAB surgery differs substantially from that of conventional CABG.[580] Surgical manipulations involve a variety of geometric distortions of the cardiac anatomy, with resulting hemodynamic effects. Communication between all members of the surgical team and anticipation of these changes are vitally important to minimize resulting adverse hemodynamic effects on the heart and other organs. Significant hemodynamic changes that cannot be reversed may necessitate emergent conversion to CPB at any time during OPCAB surgery.

Cardiovascular Effects of Off-Pump Coronary Artery Bypass Grafting

Hemodynamic changes encountered during OPCAB involve the two independent variables of distortion of the right or left atria and ventricles by stabilizer and suspension devices and the effects of myocardial ischemia during anastomosis. The ability to expose the posterior surface of the heart to access the posterior descending and the circumflex vessels using suction devices placed on the apex or anterolateral wall of the heart, pericardial retraction sutures, slings, or other techniques without producing major hemodynamic compromise is critical for multivessel application of OPCAB surgery. Lifting of the heart to work on the posterior vessels commonly is referred to as *verticalization*, in contrast to *displacement* for the LAD and diagonal anastomoses (Figs. 20.19 through 20.21).

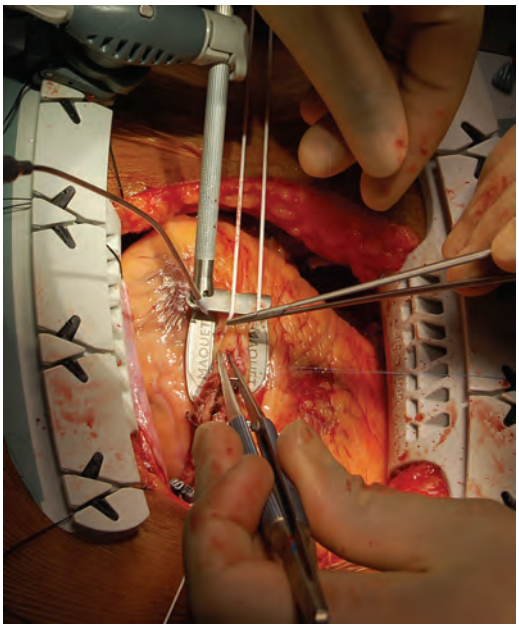


Fig. 20.19 Image depicting left anterior descending (LAD) artery anastomosis during off-pump coronary artery bypass grafting using a left internal mammary artery (LIMA) graft. The view is from the head of the patient. The Maquet mechanical stabilizer (Maquet, Wayne, NJ) is in place along with vascular snare sutures used to transiently occlude the artery. The LIMA is being anastomosed to the LAD, assisted by use of pressurized and heavily humidified carbon dioxide ("mister blower" metal cannula) to facilitate visualization of the vessel lumen. *(Courtesy Alexander Mittnacht, MD, Mount Sinai School of Medicine, New York, NY.)*

The effects of positional maneuvers, including verticalization of the heart, have been investigated in humans and animal models. Grundeman and coworkers[581] have investigated hemodynamics, CBF, and echocardiographic changes with the use of the suction cup Octopus stabilizer systems (Medtronic, Minneapolis, MN) during verticalization to 90 degrees and anterior displacement of the posterior wall (as used to access circumflex vessels during OPCAB) in an anesthetized and β-blocked pig model. With the stabilizer alone, they found significant reductions in SV (44% reduction), CO (32%), MAP (26%), and HR (26%) that were corrected with a 20% head-down tilt.

They also evaluated CBF in the three major coronary distributions using flow probes.[582] With a 42% decrease in CO, coronary flow was reduced in all three distributions, with the greatest decline in the circumflex distribution (50%). However, with the Trendelenburg position, the changes largely were ameliorated. Placement of a TEE probe demonstrated substantial compression of the right ventricle, with a decrease in diastolic cross-sectional area of 62%, but the LV area declined only by 20% (Fig. 20.22). No valvular incompetence was observed, and institution of right-heart CPB restored all hemodynamic parameters; LV bypass had only marginal effects. This work documents the importance of compression of the thin-walled, low-pressure right ventricle in hemodynamic compromise during OPCAB.

The investigators also reported the use of a different stabilizer system, the Starfish apical suction device (Medtronic, Minneapolis, MN) using the pig model.[581,583] They observed substantially fewer hemodynamic changes, with only a 6% reduction in SV and 5%

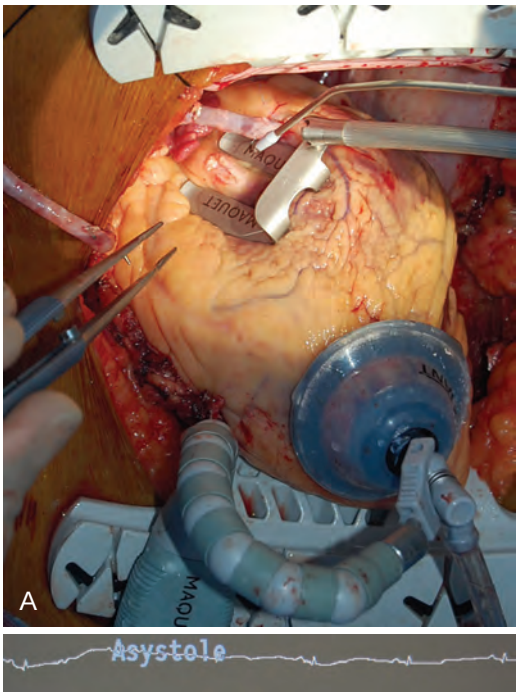


Fig. 20.20 (A) Posterior descending artery (PDA) anastomosis during off-pump coronary artery bypass grafting (CABG) uses a saphenous vein graft. The view is from the head of the patient. The Maquet access device (Maquet, Wayne, NJ) uses suction to position the heart (ie, verticalization) for easy access to the inferior surface of the left ventricle. The stabilizer is in place, and the anastomosis to the PDA is being performed. (B) Characteristic electrocardiographic (ECG) tracing during verticalization of the heart facilitates exposure of the PDA for anastomosis during off-pump CABG. Heart manipulations modify the positional relationship between the heart and surface electrodes. The shape of the tracing is altered, and the amplitude is reduced. The low-voltage electrocardiogram is interpreted by the device as asystole, an audible alarm sounds, and the practitioner is alerted with *Asystole* next to the ECG tracing. *(Courtesy Alexander Mittnacht, MD, Mount Sinai School of Medicine, New York, NY.)*

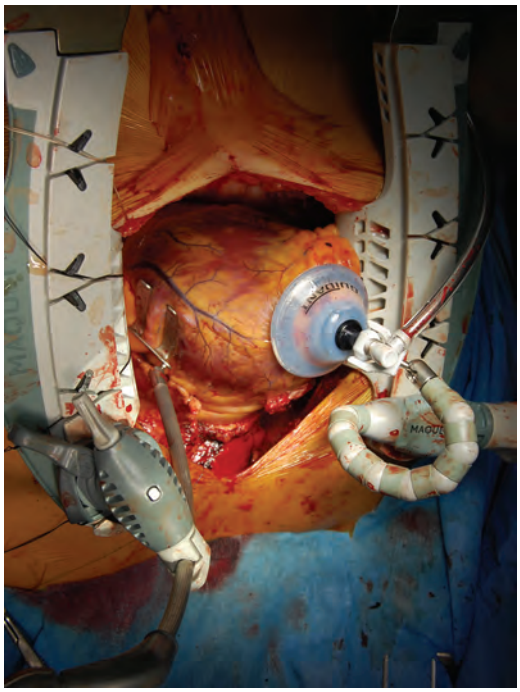


Fig. 20.21 First obtuse marginal anastomosis during off-pump coronary artery bypass grafting using a saphenous vein graft. The view is from the head of the patient. The previously completed left internal mammary artery to left anterior descending anastomosis is seen. The Maquet access device (Maquet, Wayne, NJ) uses suction to position the heart (ie, verticalization) for easy access to the circumflex coronary artery system. *(Courtesy Alexander Mittnacht, MD, Mount Sinai School of Medicine, New York, NY.)*

reduction in MAP, no reduction in coronary flows, and approximately 30% increases in RV end-diastolic pressure (RVEDP) and LVEDP. With institution of a Trendelenburg position, mild overshoot occurred in SV and MAP, with greater increases in RVEDP and LVEDP, suggesting that the maneuver is not required.

Using a sheep model, Porat and colleagues[584] demonstrated significant hemodynamic benefits using a right-heart internal cannula system that expels blood from the right atrium into the pulmonary artery, bypassing the compressed right ventricle and increasing CO and MAP, with a reduction in CVP of 49%.

Hemodynamic effects have also been reported from human clinical series.[585,586] Most data have been obtained from patients with normal or only mildly depressed ventricular function without significant valvular disease. Mathison and associates[587] evaluated the effects of displacement with the Octopus stabilizer in the Trendelenburg position. RVEDP increased in each position, with the greatest increase occurring with exposure of the circumflex vessels (Fig. 20.23). This position was associated with the greatest deterioration of SV (approximately 29% vs 22% for PDA and vs 18% for LAD). When comparing patients with EFs of more than or less than 40%, there were nonsignificant trends toward greater reductions in MAP and CO with lower EF. TEE, used in 31 patients, revealed moderate or severe biventricular compression with circumflex artery and PDA positioning.

Nierich and coworkers[588] reported use of the Octopus stabilizer in 150 patients, including 54 patients with anterolateral thoracotomy exposure undergoing LAD or diagonal anastomosis only. Stroke volume decreased 6% with LAD, 14% with RCA, and 21% with OM anastomoses. The Trendelenburg position was required in only 50% of LAD anastomoses, increasing to 100% with OM anastomosis. Dopamine was used in only 5% of LAD anastomoses, increasing to 30% with OM anastomoses (Fig. 20.24).

Mishra and colleagues[589] have reported large-scale, prospective observational data on patients undergoing OPCAB surgery. TEE and PAC were used in all patients, and approximately 40% were considered high risk. Verticalization for exposure of the posterior wall was associated with a reduction in MAP of 18%, an increase in CVP of 66%, and a reduction in SV of 36% and cardiac index of 45%. New RWMAs were common (60%), and global function decreased in a similar proportion. Their practice involved the use of inotropes during this period (79% vs 22% for the anterior wall). However, only 11% required IABP, and 0.7% required CPB. On multivariate analysis, an EF less than 25%, MI within the prior month, HF, and preoperative hemodynamic instability (which was only marginally significant) were identified as independent predictors of conversion to CPB.

Specific Anesthetic Considerations in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting

The anesthesia technique used for patients undergoing OPCAB surgery does not differ much from on-pump CABG (Box 20.10). The anesthesia technique should be tailored to the individual patient, and among other factors, it depends on the indication for OPCAB surgery. Fast-tracking, including early ICU and hospital discharge, is frequently a goal associated with OPCAB surgery,[590,591] particularly for patients with adequate LV function.

Patients with advanced age, significant ascending aortic disease, poor LV function, and multiple comorbidities may be scheduled for OPCAB surgery to avoid aortic cross-clamping, and a single

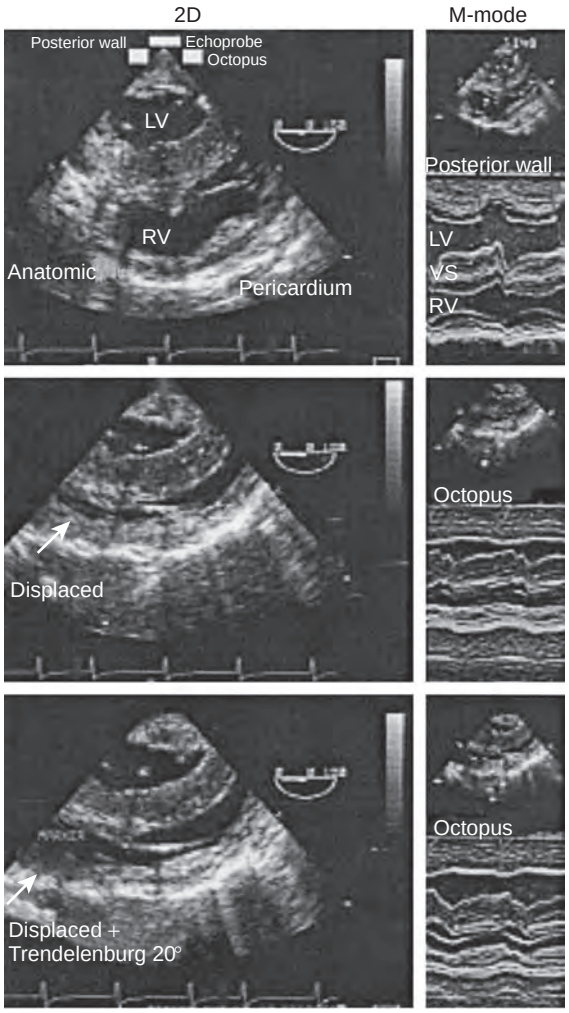
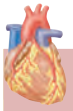


Fig. 20.22 Alteration in right ventricular and left ventricular chamber sizes with verticalization of the heart and subsequent Trendelenburg positioning in a porcine open chest model obtained from a transesophageal echocardiographic probe placed between the two arms of a stabilizer device on the posterior wall. Two-dimensional *(left)* and M-mode images *(right)* are displayed. *LV,* Left ventricle; *RV,* right ventricle; *VS,* ventricular septum. *(From Grunderman PF, Borst C, Verlaan CW, et al. Exposure of circumflex branches in the tilted, beating porcine heart: echocardiographic evidence of right ventricular deformation and the effect of right or left heart bypass.* J Thorac Cardiovasc Surg. *1999;118:316.)*

LIMA-to-LAD anastomosis is sometimes performed. These patients may not be ideal for ultrafast-track anesthesia. A neuraxial technique may be considered for postoperative analgesia or as the primary anesthesia technique. However, significant limitations (eg, preoperative antiplatelet agents) and concerns regarding the safety of neuraxial manipulation with subsequent heparinization remain.

A challenge during OPCAB surgery can be the hemodynamic changes encountered during positioning of the heart. PAP, PCWP, and CVP typically are increased during this phase; the occurrence of large v waves should alert the practitioner to acute ischemia or MR. Wall motion abnormalities and acute, significant MR frequently are seen on TEE. Exacerbation or new onset of MR may be related to structural changes from positioning the heart (eg, annular distortion), stabilizer application, or ischemia.[592,593]

Hemodynamic compromise during OPCAB surgery can be managed with Trendelenburg positioning, volume administration, and temporary vasoconstrictor administration to maintain CPP during distal anastomosis. Opening of the right pleural space may accommodate



BOX 20.10 ANESTHETIC CONSIDERATIONS FOR OFF-PUMP CORONARY ARTERY BYPASS SURGERY

1. Use standard monitoring, including invasive arterial blood pressure monitoring and central venous access.
2. A PAC should be considered in patients with poor LV function or significant mitral regurgitation.
3. TEE is recommended for all patients undergoing OPCAB surgery, unless contraindicated.
4. Use warming devices to maintain normothermia.
5. Dose of heparin according to institutional or surgeon's preference.
6. Fast-tracking, including early extubation, is often a goal in OPCAB surgery.
7. A neuraxial anesthesia technique may be used for postoperative analgesia or as the primary anesthetic technique. The patient must be carefully evaluated for absolute contraindications (eg, potent antiplatelet regimens).
8. Hemodynamic compromise may occur with positioning of the heart or stabilizer application. Positional maneuvers, volume administration, and vasoactive medications are used to maintain hemodynamic stability. CPB always should be immediately available.

CPB, Cardiopulmonary bypass; *LV*, left ventricular; *OPCAB*, off-pump coronary artery bypass grafting; *PAC*, pulmonary artery catheter; *TEE*, transesophageal echocardiography.

the right ventricle, relieving the compression and improving hemodynamics. The right limb of the sternal retractor should be routinely elevated on a rolled towel to create space and avoid compressing of the right atrium or right ventricle against the right sternal border. Similarly, the right-sided pericardial traction sutures must be loosened when the heart is rotated to the right to avoid compression of the hemodynamically vulnerable right atrium and right ventricle against the right pericardial edge. Maintaining the CPP is critical during distal coronary anastomosis, and MAP is typically kept above 80 mm Hg during this phase.

Depending on the severity of the lesion and the degree of collateralization, ischemia and RWMAs can be seen. In poorly collateralized vessels, severe hemodynamic compromise may result from clamping the target vessel. It is important for the surgeon to graft and reperfuse collateralized vessels early in the operative sequence and to graft collateralizing vessels only after the vessels to which they provide collateral flow have been bypassed. This avoids the dangerous scenario in which the myocardium subtended by the collateralizing and the collateralized vessels is rendered ischemic during temporary occlusion of the collateralizing vessel to construct its distal graft anastomosis.

Vasoconstrictor and volume therapy are preferred with inotrope use only in cases of severe hemodynamic compromise. In the setting of ongoing ischemia, the greater increase in oxygen demand with inotropes may place the patient at substantial risk for myocardial injury. In the setting of significant MR not responsive to antiischemic treatment, further increasing the afterload may worsen the clinical picture. Positive inotropic medications are then temporarily indicated if the surgeon cannot correct the position of the heart during critical phases of surgical anastomosis. The surgeon may or may not place temporary intracoronary shunts to allow distal coronary perfusion. There are controversial data and opinions about whether shunts have a clinical benefit in providing myocardial protection or instead cause endothelial damage.[594–596]

CPB should always be immediately available during OPCAB surgery in case the hemodynamic situation cannot be managed pharmacologically. A lower arterial blood pressure typically is preferred during the proximal (aortic) anastomosis to avoid complications seen with partial aortic clamping (ie, aortic side-clamp). Automated suture devices and techniques that eliminate aortic cross-clamping are being

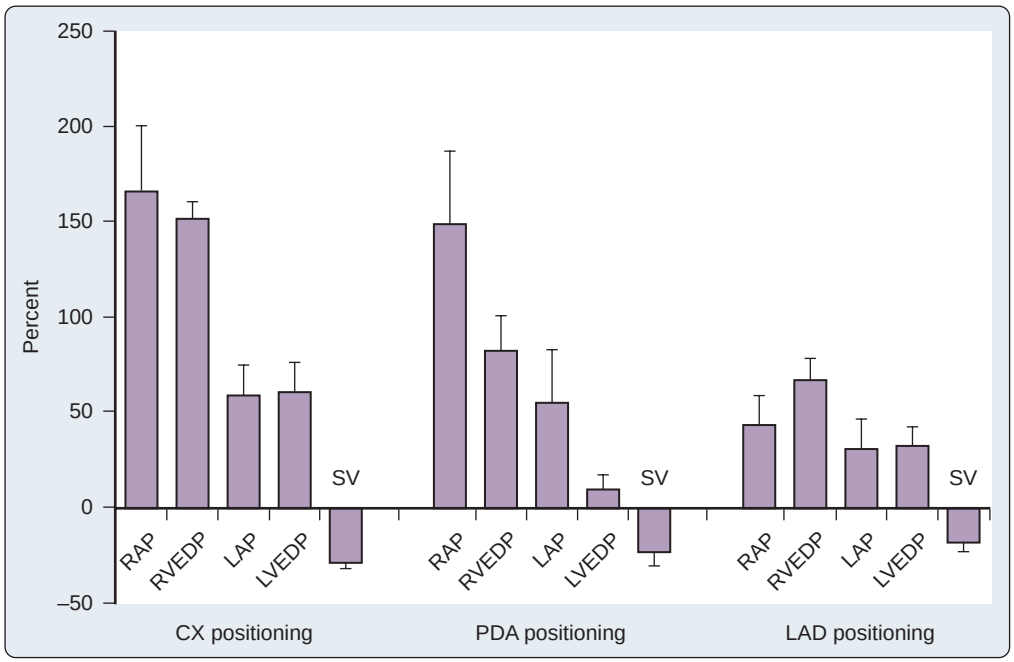


Fig. 20.23 Hemodynamic changes (mean ± standard error) with off-pump coronary artery bypass (OPCAB) grafting cardiac positioning with application of the stabilizer in 44 patients. *CX*, Circumflex artery; *LAD*, left anterior descending artery; *LAP*, left atrial pressure; *LVEDP*, left ventricular end-diastolic pressure; *PDA*, posterior descending artery; *RAP*, right atrial pressure; *RVEDP*, right ventricular end-diastolic pressure; *SV*, stroke volume. *(From Mathison M, Edgerton JR, Horswell JL, et al. Analysis of hemodynamic changes during beating heart surgical procedures.* Ann Thorac Surg. *2000;70:1355.)*

used.[597–599] Avoidance of aortic partial clamping has been associated with a striking reduction in cerebral emboli and neurologic events during OPCAB. Regardless of the specific technique or device used, the MAP should be kept around 60 mm Hg during manipulation of the aorta and proximal anastomosis. Vasodilators such as NTG are frequently administered and titrated to achieve this goal.

Because CPB with a heat exchanger is not available for maintaining a target temperature, patients are at increased risk for hypothermia during OPCAB surgery. This is particularly problematic if fast-tracking with early extubation is the goal. The room temperature should be adjusted accordingly, and patient-warming devices should be applied.

Anticoagulation in patients undergoing OPCAB surgery is an area of controversy, and the topic always should be discussed with the surgeon before anesthesia induction. Some surgeons prefer low-dose heparinization (eg, 100–200 U/kg of heparin) with a target activated coagulation time (ACT) of 250 to 300 seconds, whereas others may choose full heparinization (eg, 300 U/kg) during the procedure. The ACT is measured every 30 minutes, and heparin is administered accordingly to maintain the target ACT.

Patients who are immobilized, undergoing major surgery, and hypercoagulable are at increased risk for thrombotic events. A potential concern in OPCAB surgery is early graft occlusion with potentially catastrophic consequences, including sudden cardiac death after revascularization. Some surgeons continue antiplatelet medications until the day of surgery, and potent antiplatelet drugs such as clopidogrel may be reinstituted immediately after the procedure. When planning the anesthesia, it is important to follow current recommendations for neuraxial catheter placement in patients on anticoagulant medications. A neuraxial technique may not be feasible or may be contraindicated.

Outcomes for Off-Pump Coronary Artery Bypass Grafting

Although the literature base is increasing, the final word about differences in outcomes and which patients may benefit from OPCAB has not been written.[600–602] This is not surprising given the technical challenges of OPCAB surgery and highly operator-dependent outcomes, which are difficult to account for even in large, prospective, randomized trials.[602,603]

Raja and Dreyfus reviewed observational and randomized trials and scored the efficacy of OPCAB by levels of literature evidence for outcomes related to various organ systems and processes of care.[601] Although the grading must be considered informal because of a lack of a formal consensus panel of experts, it mirrors results obtained from a metaanalysis of randomized trials by Cheng and associates.[600] These investigators analyzed 37 randomized trials of 3369 patients with comparable treatment groups, with the exception of a marginal difference in the average number of grafts performed (2.6 OPCAB vs 2.8 CABG). All but one of the studies specifically excluded high-risk patients. Although various definitions were used, most excluded patients with low EF, repeat procedures, and renal failure, and several studies excluded patients with diseased circumflex vessels. The investigators found no significant differences in 30-day or 1- to 2-year mortality rates, MI, stroke (at 30 days and 1 to 2 years), renal dysfunction, need for IABP, wound infection, or reoperation for bleeding or reintervention (for ischemia).

OPCAB was associated with significant reductions in AF (OR = 0.58), numbers of patients transfused (OR = 0.43), respiratory infections (OR = 0.41), need for inotropes (OR = 0.48), duration of ventilation (weighted mean difference [WMD] of 3.4 hours), ICU LOS (WMD of 0.3 day), and hospital LOS (WMD of 1.0 days). Changes in neurocognitive dysfunction were not different in the immediate postoperative period; they were significantly improved at 2 to 6 months (OR = 0.57), but there were no differences seen at 12 months.

The critical issue of graft patency was addressed in only four studies, which varied substantially with regard to when assessment occurred (ie, 3 months in two and 12 months in two studies). Only one study reported a difference (ie, reduction in circumflex patency with OPCAB). Because of the small numbers of patients, the overall data for this category were considered inadequate for metaanalysis.

Four randomized, controlled trials have analyzed quality of life. Various methods precluded inclusion in the metaanalysis, but it

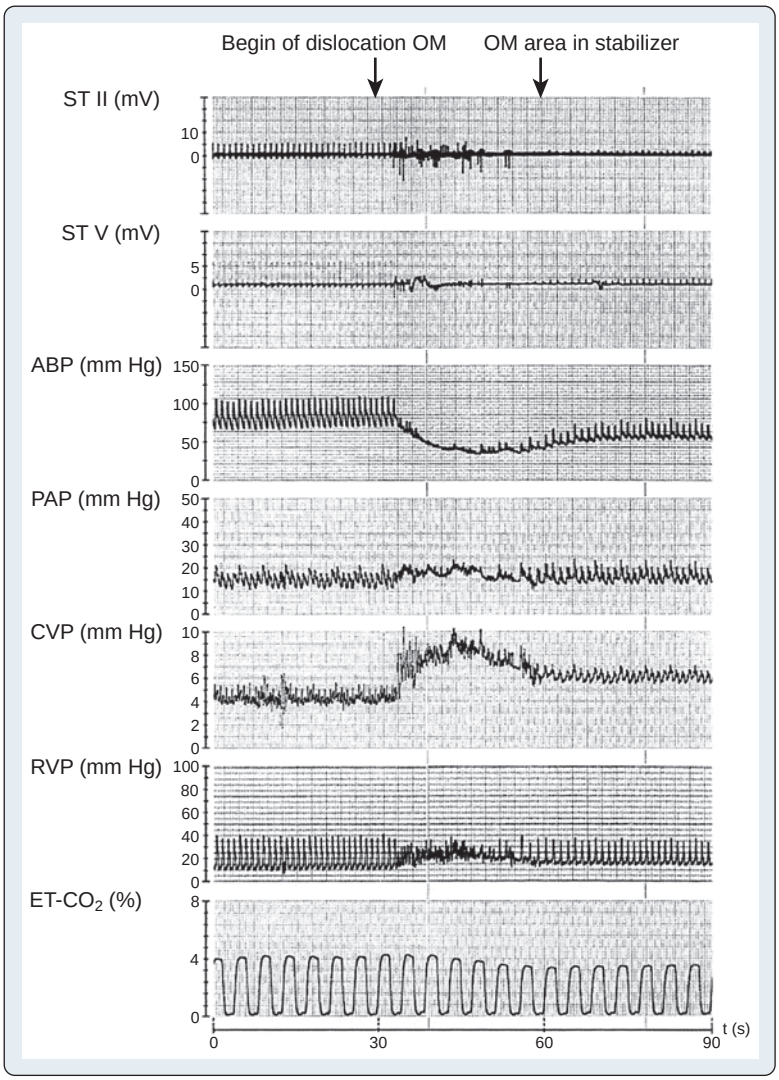


Fig. 20.24 Acute hemodynamic alterations during verticalization and placement of a stabilizer in a patient, demonstrating reduction in electrocardiographic voltage *(mV)*, wedging of the pulmonary artery catheter, decrease of end-tidal carbon dioxide *(ET-CO_2)*, and increase in central venous pressure *(CVP)*. Changes partially resolve after stabilizer placement. *ABP*, Arterial blood pressure; *OM*, obtuse marginal arteries; *RVP*, right ventricular pressure. *(From Nierich AP, Diephuis J, Jansen EW, et al. Heart displacement during off-pump CABG: how well is it tolerated?* Ann Thorac Surg. *2000;70:466.)*

appears there is little difference between operations. Of the 20 trials reporting conversion rates, 8% of OPCAB patients required conversion to on-pump CABG. The conversion rate for OPCAB in these low- to medium-risk patients is substantial and is expected to be even higher in higher-risk patients with greater disease burdens, more complex lesions, or impaired ventricular function, in whom tolerance of stabilization and verticalization may be less. The comprehensive analysis suggested that for every 1000 patients undergoing OPCAB, 91 fewer patients would develop AF, 143 fewer would require transfusion, 83 fewer would require inotropes, 53 fewer would develop respiratory infections, 100 fewer would have cognitive dysfunction at 2 to 6 months postoperatively, and there would be 300 fewer ICU days and 1000 fewer hospital days. The neutral findings regarding stroke, renal failure, MI, and mortality are surprising, but they may be found to be different for higher-risk patients after additional trial data are analyzed.

A working group of the AHA Council on Cardiovascular Surgery and Anesthesia analyzed the then current literature and several small metaanalyses, although not the same ones as Cheng and coworkers (discussed earlier). In an informal manner, they concluded that OPCAB probably was associated with less bleeding, less renal dysfunction, less short-term neurocognitive dysfunction (especially in patients with calcified aortas), and shorter hospital LOS. However, they also observed that it is more technically demanding, has a greater learning curve, and may be associated with lower rates of long-term graft patency.[602] Perhaps related to the greater technical demands, surgeons appear to place fewer grafts compared with on-pump CABG, and incomplete revascularization may influence long-term outcomes. The investigators emphasized the ongoing need for large-scale, randomized study data.

The fact that OPCAB surgery is technically more demanding and requires a significant learning curve was highlighted by Shroyer and colleagues,[605] who published the results of their prospective, randomized study of on-pump versus off-pump CABG. The investigators reported worse composite outcomes and poorer graft patency in the off-pump group. The study was criticized, however, for inadequate surgeon experience with the off-pump technique (a minimum of 20 cases' experience was required for study participation), a conversion rate to on-pump of 12.4% (<1% with experienced surgeons[606])

with associated higher mortality rates,[607] and a higher rate of incomplete revascularization in the OPCAB group. The 2203 patients were almost exclusively male (female patients are higher-risk patients who can benefit from OPCAB[608]). When patients who were converted to on-pump CABG were excluded from the analysis, there was no significant difference in the 1-year primary end point.

Puskas and colleagues[609] reviewed 12,812 CABG patients (1997–2006) and compared in-hospital major adverse events and long-term survival after OPCAB versus on-pump CABG. Long-term (10-year follow-up) outcomes did not differ significantly between on-pump and off-pump patients. OPCAB was associated with significant reductions in short-term outcomes such as operative mortality, stroke, and major adverse cardiac events. Further data analysis showed that short-term outcome (ie, operative mortality rate) did not differ between the two groups for patients at low risk (ie, STS predicted risk of death), whereas lower mortality rates were found for OPCAB surgery in high-risk patients.[610] Female gender was associated with higher rates of death, stroke, MI, and other major adverse cardiac events. Women undergoing OPCAB surgery had a lower mortality rates compared with those for on-pump CABG.

Bakaeen and coworkers conducted a large, multicenter, observational study comparing OPCAB to on-pump CABG surgical outcomes for 65,097 patients undergoing myocardial revascularization at VA hospitals between 1997 and 2011.[611] In the propensity score–matched patients, 30-day or in-hospital mortality rates were not significantly different between OPCAB and on-pump CABG. In a previous analysis from the same group and same patient population looking at long-term outcomes, adjusted mortality rates after 5 years and 10 years were higher for the OPCAB group.[612]

OPCAB presents the possibility of minimizing or avoiding aortic manipulation (ie, anaortic OPCAB). With the knowledge that aortic atheroembolism is an important source of adverse neurologic events during cardiac surgery performed on CPB, an off-pump approach that avoids aortic partial clamping should be associated with a reduced risk of perioperative stroke, transient ischemic attack, and neurocognitive dysfunction. Daniel and colleagues[613] reported that the odds ratio for stroke after CABG among 10,054 consecutive patients was 2.6 for on-pump double-clamp (ie, cross-clamp plus partial-clamp) versus a single-clamp technique. Similarly, patients who had OPCAB with a partial clamp had an odds ratio of 1.46 for stroke compared with OPCAB patients whose proximal anastomoses were performed with a clampless facilitating device.

Edelman and associates[614] performed a metaanalysis of stroke after anaortic OPCAB versus partial-clamped OPCAB and anaortic OPCAB versus conventional CABG on CPB. They reported that in each comparison, the risk of perioperative stroke was significantly reduced when aortic manipulation was reduced or avoided altogether. Emmert and coworkers[615] compared the incidence of stroke or MACCE after OPCAB performed with a partial clamp versus a Heartstring clampless facilitating device. They reported a striking reduction in adverse neurologic events in the clampless group.

In summary, increasing data show that OPCAB surgery can be performed safely and may benefit certain patient populations. Remaining concerns are incomplete revascularization, especially in patients with poor targets, and the significant learning curve and surgeon experience required. Patient selection is critical in obtaining good results. With ongoing technologic advances, it is likely that the number of patients who are candidates and the surgical complexity of procedures will continue to expand.

Minimally Invasive Coronary Artery Surgery

First reported in 1967, minimally invasive direct coronary artery bypass (MIDCAB) was performed with a limited left thoracotomy and LIMA-to-LAD graft on a beating heart.[616] In the subsequent 5 decades, coronary artery surgery through a midline sternotomy has become the most commonly used approach. In the earlier years of cardiac surgery, this involved a large midline incision with associated complications such as wound infection and brachial plexus injury. Less invasive techniques were sought and developed with the goals of avoiding these complications, faster patient recovery, earlier hospital discharge, and improved patient satisfaction (eg, cosmetically more appealing incision). The following terminology is a sample of what is being used to describe the various surgical approaches.

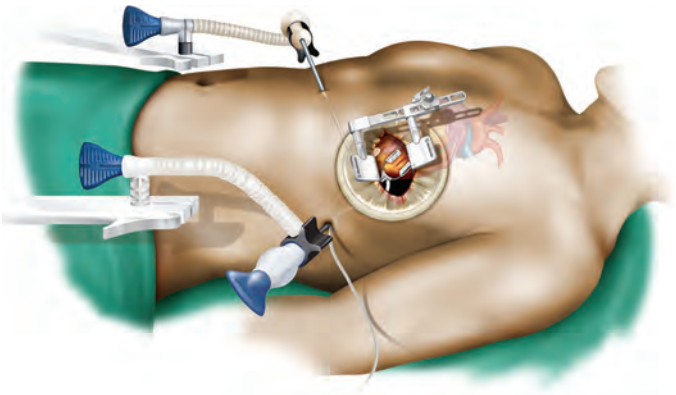


Fig. 20.25 Stabilization of the left anterior descending artery with a commercialized retractor during multivessel small thoracotomy revascularization using nonsternotomy surgical solutions such as the Octopus NS Tissue Stabilizer and Starfish NS Heart Positioner (Medtronic, Minneapolis, MN.)

The original term *MIDCAB* refers to LIMA takedown and anastomosis to the LAD through a small anterior thoracotomy (Fig. 20.25).[617–619] It can be performed off-pump or on-pump with femoral cannulation. Thoracoscopic and robotic techniques have been developed to avoid chest wall retraction and associated complications.[620–622] Experience with robotically assisted CABG is limited, and clear outcome benefits have not been reported.[623] Because of limited access to the coronary artery system using this approach, the procedure is often combined with percutaneous revascularization using coronary stents (ie, hybrid coronary revascularization [HCR]).[624] The hybrid approach is gaining popularity for selected patients with complex proximal-ostial LAD stenosis and typically one other lesion in a non-LAD vessel that can be easily stented.

Totally endoscopic coronary revascularization (TECAB) describes complete surgical revascularization through small chest wall incisions using thoracoscopic instruments and a robot to access coronary lesions that are not close to the chest wall incision (Fig. 20.26).[625] The procedure can be performed with or without CPB; the latter is called *beating-heart TECAB*.[626] Endoscopically assisted CABG (EndoACAB) was developed to avoid the high costs associated with robotic use.[627] In place of expensive robotic equipment, EndoACAB uses thoracoscopic and nondisposable instruments to harvest the LIMA. The coronary anastomosis is performed on a beating heart.

The advantages and problems encountered with the minimally invasive techniques goes beyond the scope of this text and have been published extensively elsewhere. Proper patient selection and experience of the surgeon are crucial in obtaining good results.[628] The following paragraphs describe specific anesthesia considerations for patients undergoing minimally invasive coronary artery surgery.

Most minimally invasive coronary artery surgical techniques are technically demanding and require close cooperation by the multidisciplinary surgical team to plan the exact approach, including the type and location of surgical incision; on-pump versus off-pump, patient access during surgery (especially in robotic surgery); and goals of fast-tracking, including early extubation and adequate pain relief. Although a fast-track anesthesia technique often is preferred, anesthesia induction and maintenance do not differ from the approach used in a midline sternotomy (Box 20.11).

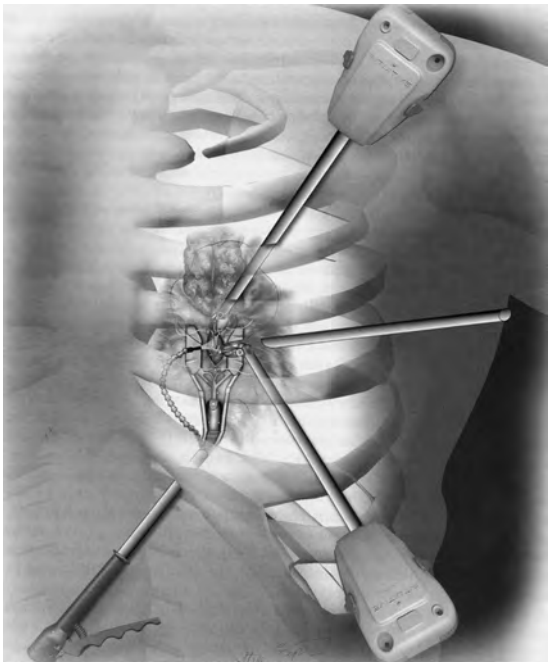
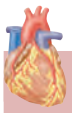


Fig. 20.26 Totally endoscopic coronary artery revascularization on the beating heart: The stabilizer is inserted through a subxiphoid incision.



BOX 20.11 ANESTHETIC CONSIDERATIONS FOR MINIMALLY INVASIVE CORONARY ARTERY SURGERY

1. Apply fast-track anesthesia techniques, including adequate postoperative pain management.
2. Intraoperative monitoring should include central venous access, invasive arterial pressure monitoring, and transesophageal echocardiography. In complex multivessel coronary artery revascularization, the benefits of pulmonary artery catheter monitoring may outweigh the risks.
3. Defibrillator pads are mandatory and need to be placed with regard to the exact location of surgical incisions.
4. Lung separation may be required for off-pump procedures.
5. Intrathoracic carbon dioxide insufflation can cause hemodynamic changes.
6. In prolonged procedures, measurements of adequate body perfusion and oxygen balance should be performed frequently.
7. Emergency conversion to an on-pump procedure and/or emergency sternotomy may be required.

An important difference is the requirement for lung deflation on the side of the surgical incision during a beating-heart minimal thoracotomy or thoracoscopy approach. Lung separation techniques, including a double-lumen tube and bronchial blockers with a standard endotracheal tube, have been described.[629–631] Alternatively, jet ventilation has been reported to facilitate surgical access.[632] Additional challenges compared with thoracic surgery with one-lung ventilation are thoracic insufflation of CO_2, which is required for intrathoracic surgical instrument manipulation and access to surgical anastomosis on the heart, and its hemodynamic consequences. Insufflation pressures are typically kept below 10 to 15 mm Hg; nevertheless, significant increases in CVP and PAP typically occur.[633–635]

RWMAs have been described with thoracic insufflation,[636] as has decreased CO at higher insufflation pressures.[637] Fluid administration and vasoconstrictor or inotropic support are frequently used to maintain hemodynamic stability. Urine output, plasma lactate, and SvO_2 should be monitored frequently, especially during long procedures.

If hemodynamic stability cannot be maintained or is acutely compromised (including uncontrolled surgical bleeding), the use of femoral-femoral cannulation and prompt initiation of CPB can be lifesaving. Any otherwise unexplained rise in end-tidal CO_2 should alert the practitioner to increased CO_2 absorption from the positive-pressure thoracic insufflation. Sudden decreases in end-tidal CO_2 have been described with positive-pressure CO_2 insufflation in different settings, and if encountered, they should alert the practitioner to possible massive CO_2 embolization.[638,639]

Due to the hemodynamic changes associated with thoracic inflation and prolonged one-lung ventilation in long surgical cases, adequate monitoring of hemodynamic and oxygenation parameters is considered prudent.[640] TEE is recommended, and although outcome data are lacking, a PAC catheter is frequently inserted, especially if more than a single- vessel LIMA anastomosis is planned.

Access to the heart is limited, and defibrillator pads have to be placed before the patient is positioned and draped. This is further complicated by interference with surgical instruments and left chest wall incisions, and the defibrillator pad position may have to be modified accordingly. Because of the frequently cited advantages of early patient mobilization and hospital discharge, fast-track anesthesia is often part of the perioperative management strategy. A midline sternotomy is less painful for most patients compared with a small thoracoscopic incision with chest wall retraction. Adequate pain management is therefore mandatory in achieving fast-tracking goals for these patients. Long-acting intercostal nerve or other types of nerve blocks, administered before skin incision and redosed at the end of the surgical procedure, can facilitate overall anesthesia and pain management.[641]

Conclusions

Anesthesia for myocardial revascularization continues to evolve, with advances in surgical approach and technique, anesthetic pharmacology, monitoring technologies, and basic science, clinical, and epidemiologic research. As part of a multidisciplinary team, anesthesiologists are increasingly involved in the management of these patients.

Considerable health care resources are consumed by revascularization procedures, and there is an urgent need to better control costs. Adjusting anesthesia techniques to better meet the needs of the current health care environment, such as facilitating fast-tracking and reducing LOS, is important in this process. Ensuring that quality of care measures are met allows anesthesiologists to take more responsibility in the care of CAD patients.

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21

Valvular Heart Disease: Replacement and Repair

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KEY POINTS

1. Although various valvular lesions generate different physiologic changes, all valvular heart disease is characterized by abnormalities of ventricular loading.
2. The left ventricle normally compensates for increases in afterload by increases in preload. This increase in end-diastolic fiber stretch or radius further increases wall tension in accordance with Laplace's law, resulting in a reciprocal decline in myocardial fiber shortening. The stroke volume is maintained because the contractile force is augmented at the higher preload level.
3. Factors that influence heart function include afterload stress, preload reserve, ventricular compliance, contractility, and the existence of pathology such as valve lesions and hypertrophy.
4. Treatment modalities for hypertrophic obstructive cardiomyopathy, a relatively common genetic malformation of the heart, include β-adrenoceptor antagonists, calcium channel blockers, and myectomy of the septum. Newer approaches include dual-chamber pacing and septal reduction (ie, ablation) therapy with ethanol.
5. The severity and duration of symptoms of aortic regurgitation may correlate poorly with the degree of hemodynamic and contractile impairment, delaying surgical treatment while patients are undergoing progressive deterioration.
6. Mitral regurgitation causes left ventricular volume overload. Treatment depends on the underlying mechanism and includes early reperfusion therapy, angiotensin-converting enzyme inhibitors, and surgical repair or replacement of the mitral valve.
7. Rheumatic disease and congenital abnormalities of the mitral valve are the main causes of mitral stenosis, a slowly progressive disease. Surgical treatment options include closed and open commissurotomy and percutaneous mitral commissurotomy.
8. Most tricuspid surgery occurs in the context of significant aortic or mitral disease, and anesthesia management primarily is determined by the left-sided valve lesion.
9. Innovations in surgical valve repair include aortic valve repair and closed- and open-chamber procedures for mitral regurgitation.

In many ways, surgery for coronary artery disease (CAD) has matured, and although there continue to be incremental advances such as off-pump surgery, anastomotic connectors, and endoscopic vein harvest, coronary artery surgery may have seen its best days, in no small part because of advances in interventional cardiology. The same has not been true of valve surgery. At institutions where valve surgery is well represented, surgical volumes remain stable. This reflects the aging of the population and the lesser impact of cardiac interventions on the valvular heart disease (VHD) process.

From the standpoint of anesthesia care, valve surgery is usually very different from coronary artery bypass grafting (CABG). Over the natural history of VHD, the physiology changes markedly. In the operating room, physiologic conditions and hemodynamics are quite dynamic and are readily influenced by anesthesia. For some types of valve lesions, it can be relatively difficult to predict before surgery how the heart will respond to the altered loading conditions associated with valve repair or replacement.

It is essential to understand the natural history of adult acquired valve defects and how the pathophysiology evolves. Clinicians must also understand surgical decision making for valve repair or replacement. A valve operated on at the appropriate stage of its natural history has a good and more predictable outcome compared with a heart operated on at a later stage, for which the perioperative result can be poor. The dynamic physiology and natural history of each valve defect govern the anesthesia plan, which must include the requirements for preload, pacing rate, and rhythm; use of inotropes or negative inotropes; and use of vasodilators or vasoconstrictors to alter loading conditions.

Although valvular lesions impose different physiologic changes, a unifying concept is that all VHD is characterized by abnormalities of ventricular loading. The status of the ventricle changes over time because ventricular function and the valvular defect itself are influenced by the progression of volume or pressure overload. The clinical status of patients with VHD can be complex and dynamic. It is possible to have clinical decompensation in the context of normal ventricular contractility or have ventricular decompensation and performance with normal ejection indices. The altered loading conditions characteristic of VHD may result in a divergence between the function of the heart as a systolic pump and the intrinsic inotropic state of the myocardium. The divergence between cardiac performance and inotropy results from compensatory physiologic mechanisms that are specific to each of the ventricular loading abnormalities.

In analyzing the physiologic response of the left ventricle (LV) to a variety of abnormal loading conditions, it is useful to consider the concepts of *afterload mismatch* and *preload reserve*.[1] They frame discussions about the pathophysiology of individual valvular lesions. Other concepts essential to understanding VHD and its evolution are *pressure-volume loops* and the linear *end-systolic pressure-volume*

relationships (ESPVRs). The former provides a graphic analysis of ventricular pressure-volume relationships in a single beat, and the latter is a method for quantifying the intrinsic contractility of the myocardium over multiple contractions and is relatively independent of changes in loading conditions (see Chapters 6 and 13 through 16).

Pathophysiology

Pressure-Volume Loops

The pressure and volume changes that occur during a normal cardiac cycle are depicted in Fig. 21.1. A pressure-volume loop is generated when ventricular volumes are plotted against simultaneously occurring ventricular pressures for a single contraction (Fig. 21.2).

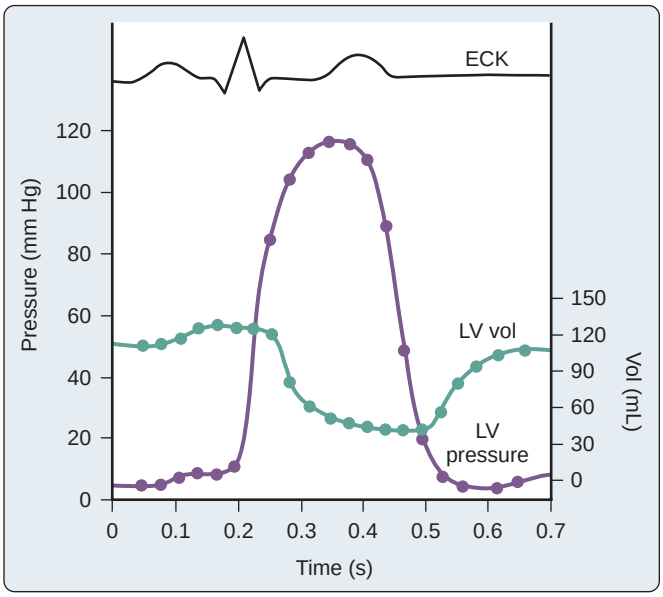


Fig. 21.1 Simultaneous left ventricular *(LV)* volume and pressure during one cardiac cycle. *ECG*, Electrocardiogram. *(From Barash PG, Kopriva DJ. Cardiac pump function and how to monitor it. In: Thomas SJ, ed.* Manual of Cardiac Anesthesia. *New York: Churchill Livingstone; 1984:1.)*

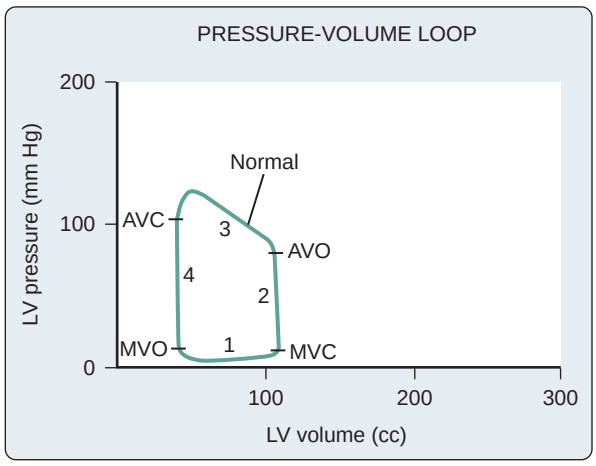


Fig. 21.2 An idealized pressure-volume loop for a single cardiac cycle. *AVC*, Aortic valve closure; *AVO*, aortic valve opening; *LV*, left ventricular; *MVC*, mitral valve closure; *MVO*, mitral valve opening; *1–4*, phases of the cardiac cycle. *(From Jackson JM, Thomas SJ, Lowenstein E. Anesthetic management of patients with valvular heart disease.* Semin Anesth. *1982;1:239.)*

Familiarity with this graphic analysis of cardiac function, the normal pressure-volume loop of the LV, provides a basis for appreciating a load-insensitive index of contractility, the ESPVR.

Phase 1 in Fig. 21.2 shows ventricular filling and represents loading of the heart before contraction (ie, preload). During early and middle diastole, filling of the ventricle is rapid, depending on the pressure gradient between the left atrium and the LV. In late diastole, the left atrium contracts (ie, *a* wave), which results in the final left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP). Atrial contraction in the normal heart accounts for 15% to 20% of ventricular filling. The normal ventricle accommodates large changes in ventricular volume with only a small change in ventricular diastolic pressure.

Ventricular systole occurs in the isovolumic and ejection phases. During isovolumic (isometric) systole (ie, phase 2 of the cardiac cycle), intraventricular pressure increases dramatically. However, there is little or no concurrent decrease in ventricular volume because the aortic valve is still closed. Phase 3 is the systolic ejection period. When intraventricular pressure exceeds aortic pressure, the aortic valve opens, and ejection begins. At the end of phase 3, the aortic valve closes. This point is the end-systolic pressure-volume coordinate, which may uniquely reflect the cardiac inotropic state.

Afterload Stress and Preload Reserve

Fig. 21.3 shows the response of the LV to changes in afterload (with preload held constant) in the context of the pressure-volume loops from single contractions. These curves are constructed experimentally by infusing a pure α-adrenergic agonist while simultaneously measuring the corresponding end-systolic volumes (ESVs). The resultant curves describe the diastolic pressure-volume relationship (ie,

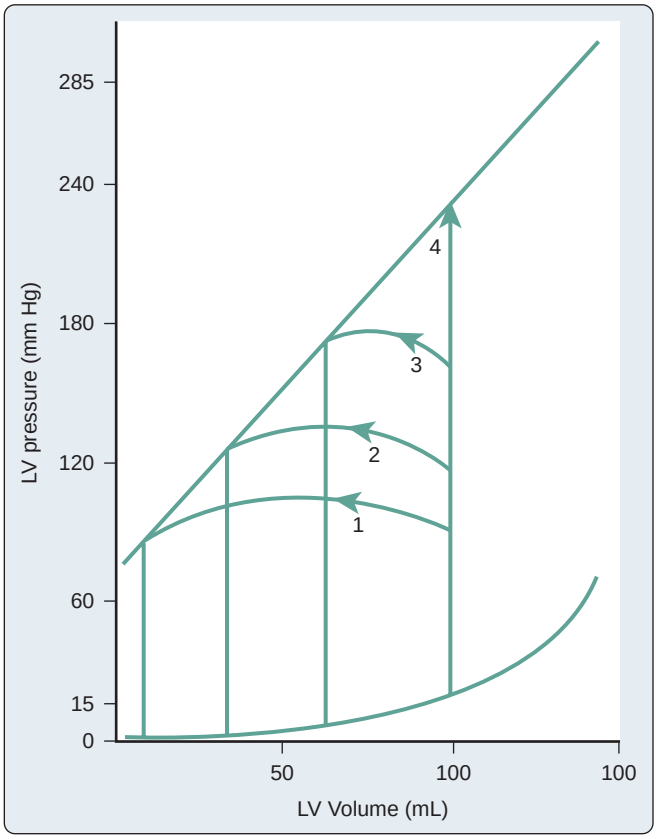


Fig. 21.3 Pressure-volume loops show the left ventricular *(LV)* response to progressive increases in afterload *(1–4)* when the preload is artificially held constant. *(From Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy.* J Am Coll Cardiol. *1985;5:811.)*

ventricular compliance) and the linear ESPVR at a given level of myocardial contractility.

Each counterclockwise loop represents a cardiac cycle. The stroke volume (SV) progressively decreases as the impedance to ejection increases from beats 1 to 3. This pattern continues until beat 4, when the peak ventricular systolic pressure fails to open the aortic valve and only isovolumic contraction ensues.[1] This inverse relationship between afterload and SV (ie, inverse force-velocity relation) also was documented experimentally in a canine preparation in which the LVEDV was held constant (Fig. 21.4).[2]

In the intact heart, afterload is a function of ventricular size and arterial pressure.[3] Its pivotal role in cardiovascular regulation is summarized in Fig. 21.5. *Afterload* is as the tension, or force per unit of cross-sectional area, in the ventricular wall during ejection.[4] Laplace's law provides a mathematical expression for the wall tension[5] (in which P is the intraventricular pressure) developed in a spherical chamber of radius, R, and wall thickness, h:

$$\text{Wall tension} = P \times R/2h$$

This means that ventricular afterload, a function of the constantly changing intraventricular pressure and radius, varies continuously during systole. It is difficult to precisely quantify afterload in the clinical setting, and commonly used approximations such as blood pressure or systemic vascular resistance (SVR) are inherently misleading because they fail to reflect instantaneous pressure-volume variations.

Left ventricular size or preload is a determinant of the SV and afterload.[6] Normally, the LV compensates for increases in afterload by increases in preload. The increase in end-diastolic fiber stretch or radius further increases wall tension in accordance with Laplace's law, resulting in a reciprocal decline in myocardial fiber shortening (ie, inverse force-velocity relationship). Despite the relative decline in fiber shortening, the SV is maintained because contractile force is augmented at the higher preload (ie, Starling or length-active tension effect). The increased contractility at higher LVEDVs may be mediated by an increased sensitivity to the inotropic effects of extracellular calcium at longer muscle lengths.[7–9]

Use of this preload reserve allows the LV to maintain its SV in the face of an afterload stress,[1] as shown in Fig. 21.6.[1] The increase in afterload (ie, beat 2) elicits a compensatory increase in end-diastolic volume (EDV) (ie, beat 3), preserving SV at the higher afterload. However, when the ventricle reaches the limit of its preload reserve, it overdistends, and preload behaves as if it were fixed. SV then decreases with further increases in the systolic pressure (ie, afterload mismatch; beat 4), a clinical corollary of the inverse force-velocity relation.

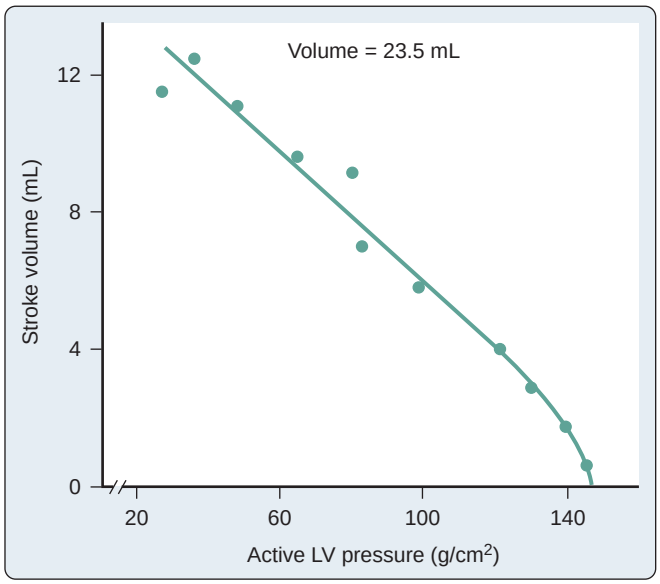


Fig. 21.4 Plot of left ventricular *(LV)* stroke volume versus LV systolic pressure when the ventricle's end-diastolic volume is held constant (ie, inverse force-velocity relationship). *(From Burns JW, Covell JW, Ross J Jr. Mechanics of isotonic left ventricular contractions.* Am J Physiol. *1973;224:725.)*

Ventricular Compliance

Translating the physiologic analysis to the clinical setting is complicated by several practical constraints. One of the most important is the inconstant relationship between LVEDV and LVEDP. The diastolic pressure-volume relationship for the normal mammalian LV is a curvilinear function (Fig. 21.7).[3,10] The slope of this curve (ie, ratio of change in volume to change in pressure during diastole) is the *ventricular compliance* (dV/dP). Although the normal ventricle is extremely compliant in the physiologic range, the instantaneous compliance decreases with increments in diastolic filling. This progressively increasing slope of the pressure-volume curve becomes evident at the extremes of ventricular volume, in which succeeding increments in volume result in exponentially greater increases in end-diastolic pressure (EDP). Patients with acute aortic regurgitation (AR) experience the hemodynamic consequences of this phenomenon. The catastrophic increases in ventricular filling pressure reflect the absolute magnitude of the volume overload and are a corollary of a precipitously declining compliance relationship.

The hemodynamic manifestations of acute shifts up and down a single compliance curve must be distinguished from chronic, pathologic alterations in ventricular compliance, which produce shifts of the entire curve relating diastolic pressure and volume. For example, in animal models of chronic volume overload, the entire pressure-volume curve is shifted to the right, and substantial increases in ventricular volume are tolerated with relatively little change in EDP (Fig. 21.8).[11] The slope of the new pressure-volume curve (ie, compliance) is decreased. Similarly, time-dependent, rightward shifts of the entire pressure-volume relationship occur in patients with severe ventricular volume overload resulting from chronic AR.[12] In these examples, the

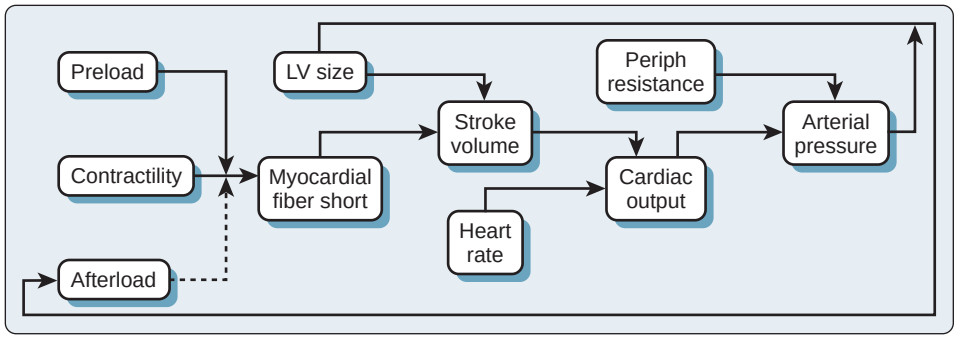


Fig. 21.5 Role of afterload in cardiac regulation. *LV*, Left ventricular; *Periph*, peripheral. *(From Braunwald E. Regulation of the circulation.* N Engl J Med. *1974;290:1124.)*

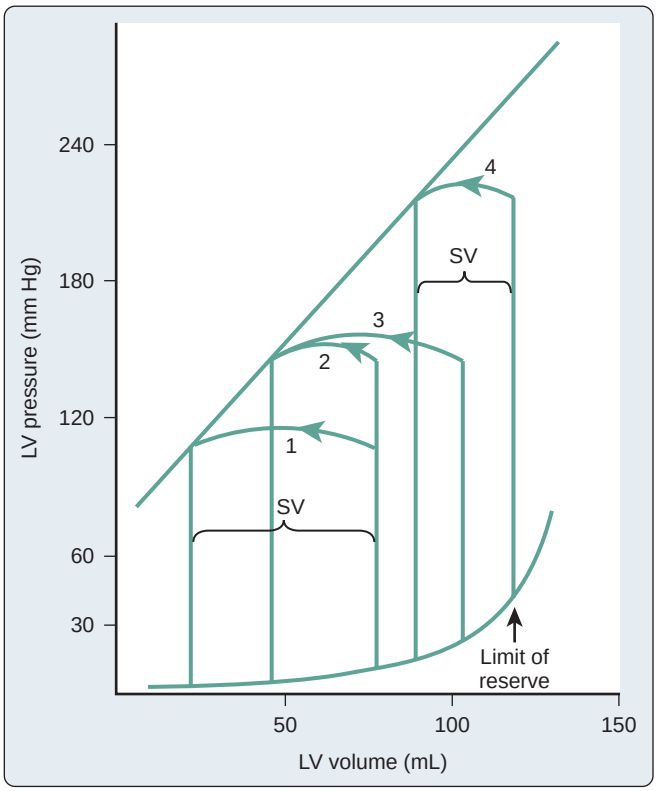


Fig. 21.6 Pressure-volume loops illustrating the concept of preload reserve. Increases in afterload (1–4) elicit compensatory increases in left ventricular *(LV)* end-diastolic volume such that stroke volume *(SV)* is maintained at the higher afterload. *(From Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy.* J Am Coll Cardiol. *1985;5:811.)*

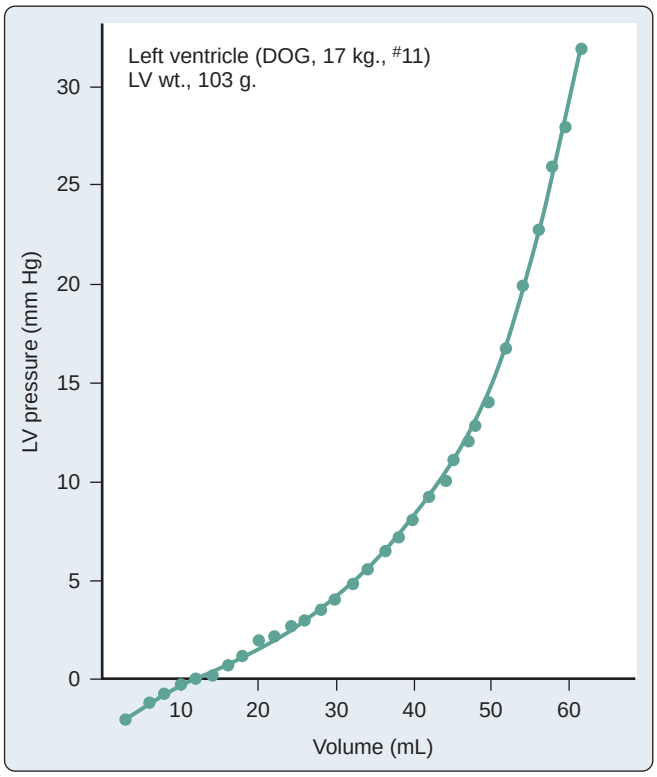


Fig. 21.7 The normal diastolic pressure-volume relationship. *LV,* Left ventricular. *(From Spotnitz HM, Sonnenblick EH, Spiro D. Relation of ultrastructure to function in the intact heart: sarcomere structure relative to pressure-volume curves of the intact left ventricles of dog and cat.* Circ Res. *1966;18:49.)*

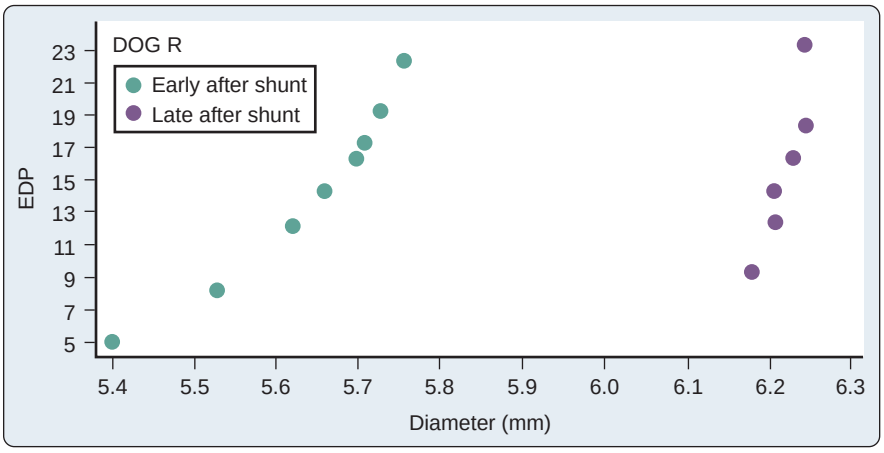


Fig. 21.8 Relationships between left ventricular *(LV)* end-diastolic pressure *(EDP)* and volume *(diameter)* in an animal studied early *(green circles)* and late *(purple circles)* after the production of chronic volume overloading (ie, arteriovenous fistula). *(From McCullagh WH, Covell JW, Ross J Jr. Left ventricular dilation and diastolic compliance changes during chronic volume overloading.* Circulation. *1972;45:943.)*

development of a new relationship between pressure and volume may reflect the physiologic process of *creep*, the time-dependent change in the size or dimension of tissue maintained at a constant level of stress.[4]

Myocardial wall thickness is an important determinant of diastolic compliance. In clinical settings of chronic pressure overload (eg, aortic stenosis [AS], chronic hypertension), diastolic compliance and ventricular wall thickness are linearly and inversely related (Fig. 21.9).[13] This may explain why the normal, thinner-walled right ventricle (RV) is more compliant than the normal LV, although the ventricles share similar qualities of intrinsic myocardial stiffness.[3,14] The association between pathologic hypertrophy of the ventricle and deterioration in its diastolic compliance is a well-documented but poorly understood phenomenon.

It has become customary to characterize diastolic function in certain disease states as normal or abnormal (eg, diastolic dysfunction, diastolic failure).[15,16] Diastolic failure is a distinct pathophysiologic entity that results from increased resistance to ventricular filling and leads to an inappropriate upward shift of the diastolic pressure-volume

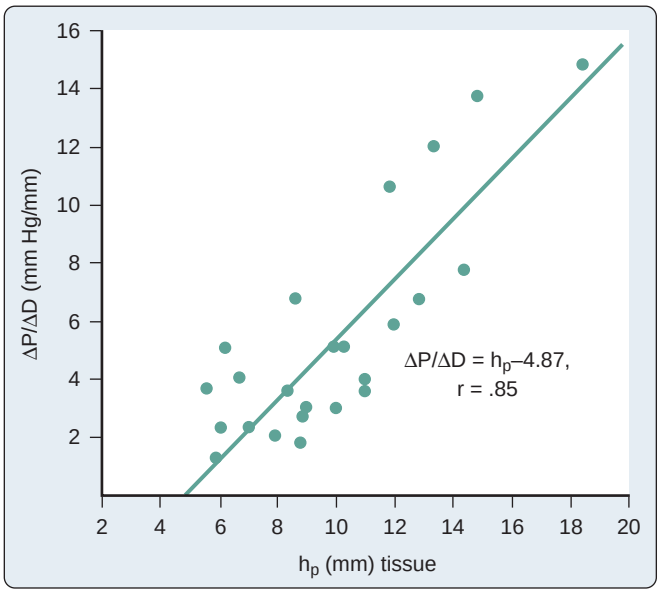


Fig. 21.9 Relationship between chamber stiffness (*ΔP/ΔD*), which is the inverse of compliance) and ventricular wall thickness (h_p). *(From Grossman W, McLaurin P, Moos SP, et al. Wall thickness and diastolic properties of the left ventricle.* Circulation. *1974;49:129.)*

relationship.[17] For example, diastolic dysfunction is seen in ischemic cardiomyopathy, particularly when combined with pressure-overload hypertrophy.[18]

In certain diseases, primary derangements of diastolic function may predominate over abnormalities of diastolic function associated with ventricular hypertrophy. For example, in hypertrophic cardiomyopathy (HCM), the impaired ventricular relaxation inherent in the myopathic process appears to play the greater role in the observed abnormalities of diastolic filling because the diastolic dysfunction is often disproportionate to the degree of ventricular hypertrophy.[19,20] The effects of pathologic hypertrophy on diastolic compliance and ventricular relaxation are complex and are considered in more detail later in the "Aortic Stenosis" and "Hypertrophic Cardiomyopathy" sections.

Filling of one ventricle or changes in its configuration or compliance properties can significantly alter the diastolic pressure-volume characteristics of the other ventricle.[21,22] Progressive increases in right ventricular filling shift the left ventricular compliance curve up and to the left. This effect is greatest at high right ventricular filling pressures and is accentuated by the pericardium.[23] With severe right ventricular distention, the interventricular septum encroaches on the LV, which reduces the size of the LV and alters its geometric configuration such that its compliance declines.[21] As a result, left ventricular filling pressures may fail to reflect directional changes in left ventricular size.[24]

Contractility

Myocardial contractility is the ability of the heart to generate force at a given preload.[25] Although most clinicians and researchers seem to be comfortable with their intuitive notions of the cardiac inotropic state, a consensus on a quantitative yardstick of ventricular inotropy has proved to be elusive. Its accurate and reproducible measurement is of more than theoretic interest because the contractile function of the heart is a key determinant of prognosis for most cardiac diseases, and it is especially important in critical decisions regarding the timing of surgical correction in patients with VHD.

Historically, methods of assessing myocardial contractility have been divided into two groups based on analysis of the isovolumetric or the ejection phase of cardiac contraction.[4] Details of their clinical determination and relative reproducibility are beyond the scope of this discussion, but more information can be found in several excellent reviews[4,26,27] and in Chapters 6 and 13. Isovolumetric indices include measurements such as maximal velocity of myocardial fiber shortening (V_{max}), peak pressure development (dP/dt), and peak dP/dt measured at an instantaneous pressure (dP/dt/P). Although relatively insensitive to loading conditions, these tests poorly reflect basal levels of contractility and are unreliable for comparing contractility among patients or assessing directional changes in contractility in an individual patient over time.[26]

Ejection phase indices, such as the ejection fraction (EF), are determined in part by the intrinsic inotropic state and can be used to define basal levels of contractility.[26] The measurements are extremely useful for evaluating ventricular function in patients with CAD or other conditions that do not significantly alter ventricular loading conditions.[28] Ejection phase indices are understandably popular because they are readily available, and they are the most widely used clinical measures of left ventricular function. However, these indices are directly proportional to preload, vary inversely with ventricular afterload, and are unreliable for assessing contractile performance in patients with most forms of VHD.

The use of the pressure-volume diagram and analysis of the ESPVR allow a more precise appreciation of left ventricular contractility, which is independent of preload.[29] The extent of myocardial shortening and therefore of end-systolic fiber length is a direct function of afterload (ie, inverse force-velocity relationship), and myocardial contractility can be evaluated by making use of this fundamental property. In most instances, end-systolic pressure (ESP) can be substituted for afterload. Only with pathologic degrees of ventricular hypertrophy is there a major divergence between ESP and afterload. This means that for any level of contractility, the ESV to which a ventricle contracts is a linearly increasing function of ESP. A stronger ventricle contracts to a smaller ESV (ie, empties more completely) at any given level of ventricular afterload.

Changes in the inotropic state also can be viewed in the context of the idealized pressure-volume loop. Positive inotropic interventions shift the curve up and to the left, increasing the work that can be performed at any given EDV (ie, preload). Conversely, negative inotropic interventions shift the curve down and to the right[30] (Fig. 21.10; see Chapters 6 and 13). Load-independent indices of contractility are largely research tools, but in the future, it may be possible to construct pressure-volume loops and quantify ESPVRs in real time with echocardiographic equipment featuring automated border detection[31] (see Chapters 14 and 15).

Clinical studies of patients with relatively normal loading conditions have shown that variations in the ESV reliably correlate with changes in ejection phase indices (Fig. 21.11).[32] The ESPVR represents an index of contractility that depends on systolic ventricular pressure (ie, afterload) but is independent of end-diastolic length (ie, preload).[28,33,34] Pressure-volume loops also provide a framework for considering the interactions between systolic (ie, inotropic) and diastolic (ie, lusitropic) function. Although the preload (ie, EDV) is an independent determinant of SV, because of the circular nature of blood flow, the SV ultimately determines venous return and the resultant preload for the next cardiac cycle.[30]

The inotropically determined ESV is the other element besides the venous return that contributes to the EDV. Just as the ESPVR uniquely describes systolic function, the end-diastolic pressure-volume relationship is a manifestation of the intrinsic relaxation (ie, lusitropic) properties of the ventricle. Positive lusitropic interventions facilitate ventricular filling and shift the end-diastolic pressure-volume relationship down and to the right, and a negative lusitropic intervention shifts it up and to the left (Fig. 21.12).

Aortic Stenosis

Clinical Features and Natural History

Aortic stenosis (AS) is the most common cardiac valve lesion in the United States. Approximately 1% to 2% of people are born with a

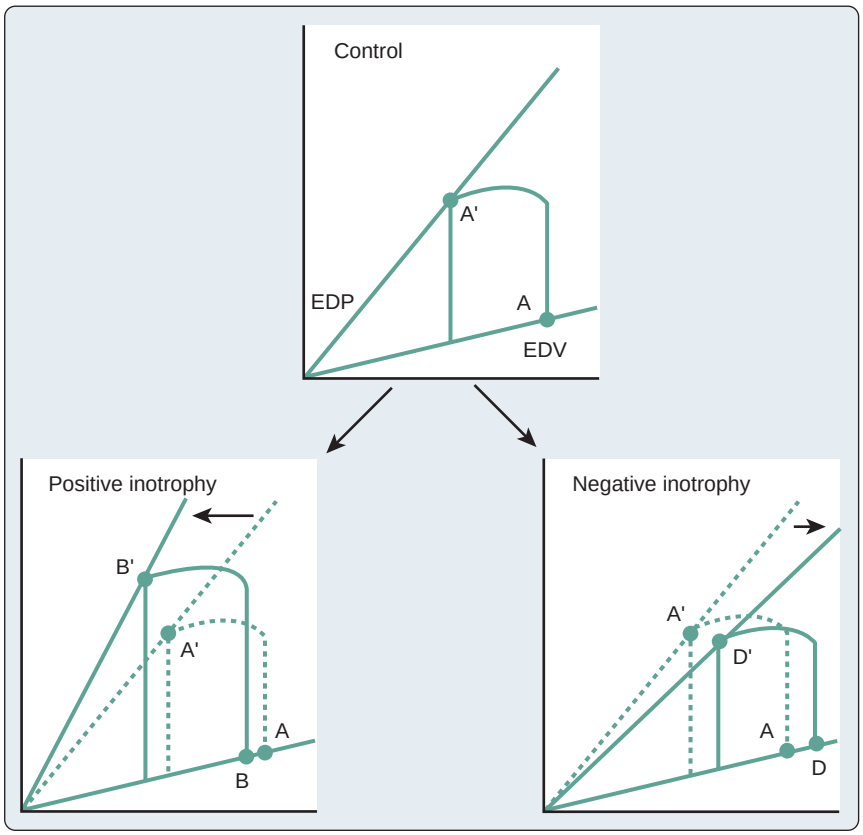


Fig. 21.10 A positive inotropic intervention increases the heart's ability to do work at a given end-diastolic volume *(EDV)* and end-diastolic pressure *(EDP)*. As illustrated, increased inotropy need not imply an increased stroke volume *(SV)*; however, SV is maintained despite a greater peak systolic pressure, producing the upward and leftward shift of the end-systolic pressure-volume point. Negative inotropy shifts the end-systolic pressure-volume point down and to the right. The SV is unchanged, but the EDV and end-systolic volume are increased, and the peak systolic pressure achieved is reduced. *(From Katz AM. Influence of altered inotropy and lusitropy on ventricular pressure-volume loops.* J Am Coll Cardiol. *1988;11:438.)*

bicuspid aortic valve, which is prone to stenosis with aging, and the population is aging. Clinically significant aortic valve stenosis occurs in 2% of unselected individuals older than 65 years and in 5.5% of those older than 85 years.[35] Incipient aortic valve stenosis with calcification and stiffening is observed in 50% of people between the ages of 75 and 80 years and in up to 75% in those older than 85 years.

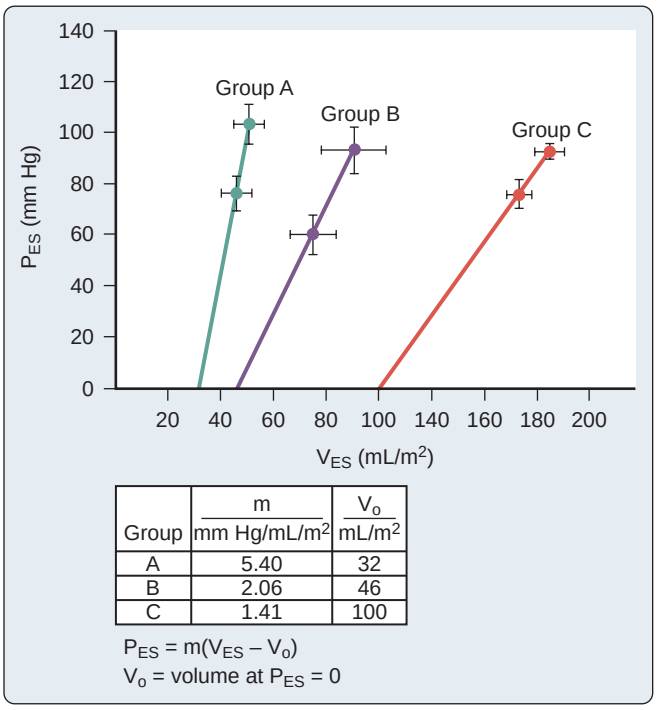
Bicuspid aortic valve is a common congenital cardiac abnormality, occurring in approximately 1% of the population.[36] The heritability coefficient is estimated at 89%, suggesting that the bicuspid aortic valve is almost entirely genetic in nature.[37] It is a risk factor for premature AS and ascending aortic aneurysms. The ascending aorta in bicuspid valvular disease has the same histopathologic features as Marfan syndrome, such as medial degeneration, decreased fibrillin 1 levels, and enhanced matrix metalloproteinase activity in the aortic wall.

Data from the International Registry of Acute Aortic Dissection show that patients with bicuspid aortic valve have a 6.14% lifetime risk of aortic dissection (ie, nine times that of the general population), compared with 40% for patients with Marfan syndrome. Bicuspid aortic valvular disease is a hundred times more common than Marfan syndrome and is therefore responsible for a larger number of aortic dissections.[36]

Calcific AS has several features in common with CAD. Both conditions are more common in men, older people, and patients with hypercholesterolemia, and both result in part from an active inflammatory process. Clinical evidence indicates an atherosclerotic process is the cellular mechanism of aortic valve stenosis. There is a clear association between clinical risk factors for atherosclerosis and the development of AS: increased lipoprotein levels, increased low-density lipoprotein (LDL) cholesterol, cigarette smoking, hypertension, diabetes mellitus, increased serum calcium and creatinine levels, and male sex.[38] Homozygous familial hypercholesterolemia produces a severe form of AS in children.[39] The early lesion of aortic valve sclerosis may be associated with CAD and vascular atherosclerosis. The extent of aortic valve calcification is an important predictor of poor outcomes for patients with AS.[40] Studies suggest that aortic valve calcification is an inflammatory process promoted by atherosclerotic risk factors.

The early lesion of AS resembles that of the initial plaque of CAD, and there is a close correlation between calcification found in coronary arteries and the amount of calcification found in the aortic valve. Pathologic studies of aortic valves revealed the presence of LDL, suggesting a common cellular mechanism for the genesis of valvular and vascular atherosclerotic disease.[38] Degenerative lesions on aortic valves contain an inflammatory infiltrate of nonfoam cells and foam cell macrophages, T lymphocytes, and other inflammatory cells. Lipid is accumulated in the fibrosa immediately below the endothelium layer on the aortic side of the valve. LDL- and apolipoprotein E–containing lipoproteins also exist.

Little is known about the synthesis of bone matrix proteins in calcific aortic valve stenosis. The calcifications are composed of hydroxyapatite on a matrix of collagen, osteopontin, and other bone matrix proteins. A potential mechanism for cellular inflammation involves the combination of macrophages, LDL, and secretion by macrophages of transforming growth factor-β and platelet-derived growth factor



Group	m mm Hg/mL/m²	V_o mL/m²
A	5.40	32
B	2.06	46
C	1.41	100

Fig. 21.11 Average values of end-systolic pressure (P_{ES}) versus end-systolic volume (V_{ES}) at two levels of afterload plotted for groups *A, B,* and *C* with different contractile performance as evaluated by ejection fraction (A >0.6; B = 0.41–0.59; C <0.4). The V_{ES} point correlates inversely with contractility. *(From Grossman W, Braunwald E, Mann T, et al. Contractile state of the left ventricle in man as evaluated from end-systolic pressure-volume relations.* Circulation. *1977;56:845.)*

to stimulate the conversion of valvular fibroblast cells into osteoblasts that produce bone proteins.[38]

The 3-hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors (ie, statins) can retard progression of CAD and AS.[41,42] The odds ratio of AS progression was 0.46 for 38 treated patients compared with 118 untreated patients.[43] Other studies have shown similar results, and it is possible that therapy with statins or other drugs may be used to block or slow the progression of valve lesions in the future.[38,44]

In addition to recruitment of inflammatory cells and lipid accumulation into valves, calcification is a prominent feature that contributes to leaflet thickness and rigidity. Early development of aortic valve calcification may be related to vitamin D–receptor genotypes or mutations in the *NOTCH* gene.[35] Calcification is an active process that includes osteopontin, osteonectin, osteocalcin, and other bone morphogenic proteins that regulate calcification and ossification. Active osteoblastic bone formation and osteoclastic bone resorption occur in stenotic valves. Increased fibroblasts produce collagen, leading to fibrosis. Concomitant elastin degradation also contributes to valve stiffening. Whereas normal valves are avascular, microvessels form in thickened stenotic valves, ensuring the continued supply of inflammatory cells and lipids.

Advances in genetic epidemiology have demonstrated the strong heritability of a bicuspid aortic valve. The three loci on chromosomes 18q, 5q, and 13q likely contain genes responsible for a bicuspid aortic valve.[37] The mode of inheritance of other valvular diseases is unclear. No heritability or inheritance studies have been reported for calcific aortic valve disease. In smaller genetic studies, a few candidate genes such as *VDR, APOE, APOB, IL10,* and *ESR1* have been identified as possibly playing a role in aortic valve disease.

A breakthrough in the genetics of aortic valve disease was identification of the *NOTCH1* signaling pathway. It is involved in embryonic patterning and is highly expressed within the developing embryonic aortic valve. The NOTCH1 protein is a repressor of the transcription factor RUNX2, which regulates osteoblast development. This finding supports the concept that a developmental program may be reactivated in disease processes.[37]

The average rate of progression is a decrease in aortic valve area (AVA) of 0.1 cm^2/year, and the peak instantaneous gradient increases by 10 mm Hg/year.[45] The rate of progression of AS in men older than 60 is faster than in women, and it is faster in women older than 75 than in women 60 to 74 years old.[46] Treatment with hemodialysis, the use of calcium supplements, and increased serum creatinine levels correlated with rapid progression of AS.[47] Plasma brain natriuretic peptide, produced to a large extent by the ventricles, and the N-terminal–brain natriuretic peptide (NT-proBNP) may serve as early markers of left ventricular hypertrophy (LVH), whereas atrial natriuretic peptide and NT-proBNP reflect an atrial pressure increase.[48] Repeated measurements of this marker may provide information on the stage of AS and its hemodynamic impact.[49]

Angina, syncope, and congestive heart failure (CHF) are the classic symptoms of the disease, and their appearance is of serious prognostic significance because postmortem studies indicate that symptomatic AS is associated with a life expectancy of only 2 to 5 years.[50–52] The early natural history studies were completed before the availability of cardiac catheterization studies, and some patients, although symptomatic, might have had objectively less severe degrees of stenosis. The "hemodynamically insignificant murmur of AS" seen often in cardiologic consultations does not portend such dire consequences, although it is sometimes difficult to correlate AS severity with clinical symptoms. There is evidence that patients with moderate AS (ie, valve areas of 0.7 to 1.2 cm^2) are also at increased risk for the complications, with the appearance of symptoms further increasing their risk.[53]

According to the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, a peak velocity greater than 4 m/s, a mean gradient greater than 40 mm Hg, and a valve area less than 1.0 cm^2 constitute hemodynamically severe AS.[54] Aortic valve surgery should be performed promptly for symptomatic patients. In asymptomatic patients, a high aortic valve calcium content and a positive exercise test result are features that suggest a benefit from early aortic valve replacement (AVR).

The question of whether the natural history of AS has changed significantly over time is prompted by two trends.[55] In North America, the first is related to the steadily diminishing number of patients with rheumatic disease. Today, AS is essentially the bicuspid, calcific, or senile variety. The second trend is that people are living longer, particularly those with heart disease. The typical patient with AS is older and much more likely to have other significant medical problems, including major coexisting cardiac disease, most often CAD.

Angina is a frequent and classic symptom of the disease, occurring in approximately two-thirds of patients with critical AS and about one-half of symptomatic patients have anatomically significant CAD.[56–58] However, controversy persists about the incidence of CAD among patients with AS who do not have angina, and the controversy probably reflects the underlying sense of change in the natural history of the disease. Some studies report that the absence of angina virtually excludes the possibility of atherosclerotic heart disease.[59,60] In contrast, a 25% incidence rate of angiographically significant (>70% obstruction) coronary occlusions was described for angina-free patients, most of whom had single-vessel disease.[61] However, a much larger study found that 14% of patients with triple-vessel or left main CAD and AS had no angina.[62] Underscoring the continued lack of a consensus on this topic is the finding of a review that the reported incidence rates of significant CAD for asymptomatic patients range from 0% to 33%.[63]

Identification of asymptomatic patients is important because although coexistent, untreated (ie, unbypassed) CAD has a detrimental effect on early and late survival rates after AVR; concomitant CABG with AVR does not increase perioperative mortality rates.[64–67] It appears that a substantial number of patients with coexisting CAD may have symptoms other than chest pain.[68] However, there do not appear to be other significant differences in the clinical or hemodynamic

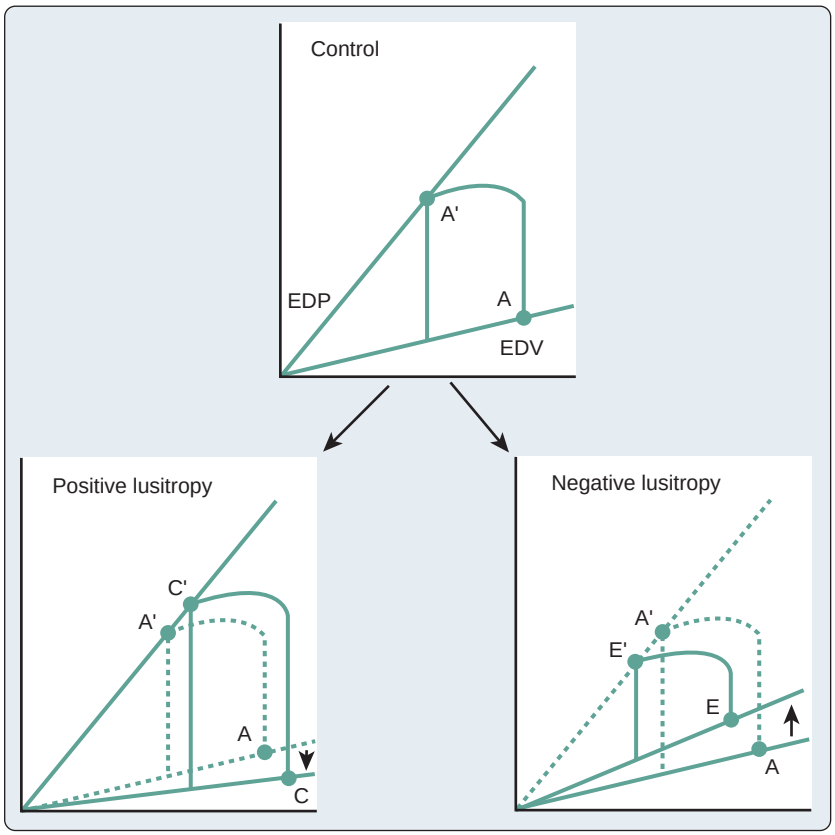


Fig. 21.12 Positive lusitropic interventions enhance diastolic filling, shifting the end-diastolic pressure-volume point down and to the right. A negative lusitropic intervention shifts the end-diastolic pressure-volume point up and to the left. *EDP,* End-diastolic pressure; *EDV,* end-diastolic volume. *(From Katz AM. Influence of altered inotropy and lusitropy on ventricular pressure-volume loops.* J Am Coll Cardiol. *1988;11:438.)*

findings between patients with normal coronary arteries and those with coexistent coronary stenoses.

If the traditional natural history of AS is perhaps more ominous in the elderly patient with likely coexistent CAD, is there any rationale for prophylactic AVR? With steady improvement in surgical results, this question has been raised, although rigorous studies still suggest that asymptomatic patients with hemodynamically significant disease face a very low risk of sudden death before the onset of symptoms.[69–71] In an attempt to settle this question, an editorial by Braunwald[72] stated that there was no role for prophylactic AVR and that "operative treatment is the most common cause of sudden death in asymptomatic patients with AS." These patients warrant careful follow-up, and the case against prophylactic surgical intervention is further supported by studies showing that ventricular function is preserved and myocardial hypertrophy regresses after successful valve replacement.[73–75]

It is probably never too late to operate on patients with symptomatic AS.[76,77] Unlike AR patients, most symptomatic patients undergo valve replacement when left ventricular function is still normal. Even when impaired left ventricular function develops in AS, the relief of pressure overload almost always restores normal function or produces considerable improvement. Morbidity rates, mortality rates, and clinical results are favorable even for the oldest surgical candidates.[78,79] Advances in operative techniques and perioperative management have contributed to excellent results after AVR in patients 80 years of age or older, with minimal incremental postoperative morbidity.[80] The principal postoperative complication is respiratory failure.

Preoperative assessment of AS with Doppler echocardiography includes measurement of the AVA and the transvalvular pressure gradient.[81,82] The latter is calculated from the Doppler-quantified transvalvular velocity of blood flow, which is increased in the setting of AS. The maximal velocity (v) is then inserted into the modified Bernoulli equation to determine the pressure gradient (PG) between the LV and the aorta (see Fig. 21.2):

$$PG = P(\text{left ventricle}) - P(\text{aorta}) = 4(v^2)$$

The *pressure gradient* is the maximal difference between the LV and aortic pressures that occurs during ventricular systole.[83,84] The maximal instantaneous gradient is not the same as the peak-to-peak gradient determined by cardiac catheterization. The peak-to-peak gradient is determined by separate measurements of events that are not synchronous in real time. Of more practical interest is the fact that the best estimate of obstruction severity, as determined from pressure data alone, is the mean systolic gradient, which is calculated online by Doppler equipment[85] (see Chapters 3, 6, and 13 through 15).

The Doppler-calculated gradient is subject to the same flow limitation as invasively calculated gradients. Best understood by considering the extreme, this means that a patient with true end-stage AS would exhibit a relatively low calculated gradient because of minimal flow across a critically narrowed valve. In part because of this flow dependency, pressure gradients determined invasively or by Doppler echocardiography correctly classify AS severity in less than 50% of cases compared with estimates of AVA.[86] However, the latter also can be determined by Doppler echocardiographic techniques. The preferred method requires only two Doppler-generated velocities: those proximal or distal to the stenotic valve. These values are inserted into the continuity equation, which relates the respective velocities and cross-sectional areas proximal and distal to a stenotic area (see Fig. 21.3):

$$V_{max} \times AVA = \text{area(LVOT)} \times V(\text{LVOT})$$

In the equation, AVA is the aortic valve area, V is the volume, and LVOT is the left ventricular outflow tract. Several studies have demonstrated the reliability of these Doppler-determined valve areas.[83–86]

Although advances in Doppler technology allow completely noninvasive evaluation of a large number of patients, coronary angiography is probably indicated for all patients older than 50 years who have significant AS. Angiography and, if indicated, CABG may improve the long-term outlook for patients with CAD who undergo AVR.[62] Angiography also can identify a smaller number of patients whose CAD alone warrants CABG.

Pathophysiology

The normal AVA is 2.6 to 3.5 cm^2, with hemodynamically significant obstruction usually occurring at cross-sectional valve areas of 1 cm^2 or less. Accepted criteria for critical outflow obstruction include a systolic pressure gradient greater than 50 mm Hg, with a normal cardiac output, and an AVA of less than 0.4 cm^2. In view of the ominous natural history of severe AS (AVA <0.7 cm^2),[55,87] symptomatic patients with this degree of AS are usually referred for immediate AVR.[88] The Hakki equation is a simplification of the Gorlin equation to calculate the AVA based on the cardiac output (CO) and the peak pressure gradient (PG) across the valve.

$$\text{AVA} = \text{CO}/\sqrt{(\text{PG})}$$

A corollary of the previously described relationship is that minimal pressure gradients may reflect critical degrees of outflow obstruction when the CO is significantly reduced (ie, generation of a pressure gradient requires some finite amount of flow). Clinicians have long recognized this phenomenon as a paradoxical decline in the intensity of the murmur (ie, minimal transvalvular flow) as the AS worsens.

Stenosis at the level of the aortic valve results in a pressure gradient from the LV to the aorta. The intracavitary systolic pressure generated to overcome this stenosis directly increases myocardial wall tension in accordance with Laplace's law:

$$\text{Wall tension} = \text{P} \times \text{R}/2\text{h}$$

In the equation, P is the intraventricular pressure, R is the inner radius, and h is the wall thickness.

The increase of wall tension is thought to be the direct stimulus for the further parallel replication of sarcomeres, which produces the concentrically hypertrophied ventricle characteristic of chronic pressure overload.[89,90] The consequences of LVH include alterations in diastolic compliance, potential imbalances in the myocardial oxygen supply and demand relationship, and possible deterioration of the intrinsic contractile performance of the myocardium.

Fig. 21.13 shows a typical pressure-volume loop for a patient with AS. Two differences from the normal curve are immediately apparent.

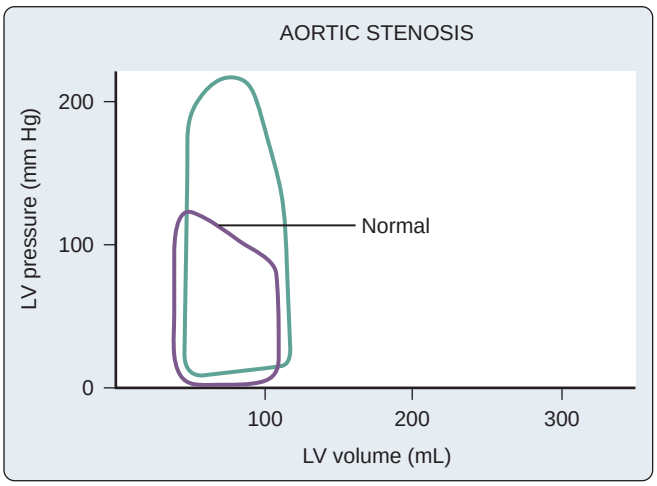


Fig. 21.13 Pressure-volume loop *(green)* in a patient with aortic stenosis and a normal patient *(purple)*. *LV*, Left ventricular. *(From Jackson JM, Thomas SJ, Lowenstein E. Anesthetic management of patients with valvular heart disease.* Semin Anesth. *1982;1:239.)*

First, the peak pressure generated during systole is much greater because of the high transvalvular pressure gradient. Second, the slope of the diastolic limb is steeper, reflecting the reduced left ventricular diastolic compliance that is associated with the increase in chamber thickness.[13] Clinically, small changes in diastolic volume produce relatively large increases in ventricular filling pressure.

Increased chamber stiffness places a premium on the contribution of atrial systole to ventricular filling, which in patients with AS may account for up to 40% of the LVEDV rather than the 15% to 20% characteristic of the normal LV. Echocardiographic and radionuclide studies have documented that diastolic filling and ventricular relaxation are abnormal in patients with hypertrophy from a variety of causes, and significant prolongation of the isovolumic relaxation period is the most characteristic finding.[91–94] This necessarily compromises the duration and amount of filling achieved during the early rapid diastolic filling phase and increases the relative contribution of atrial contraction to overall diastolic filling (Fig. 21.14). A much greater mean left atrial (LA) pressure is necessary to distend the LV in the absence of the sinus mechanism. One treatment of junctional rhythm is volume infusion.

The systolic limb of the pressure-volume loop shows preservation of pump function, as evidenced by maintenance of the SV and EF (see Fig. 21.13). Use of preload reserve and adequate LVH are likely the principal compensatory mechanisms that maintain forward flow. Clinical studies have confirmed that ejection performance is preserved at the expense of myocardial hypertrophy, and the adequacy of the hypertrophic response has been related to the degree to which it achieves normalization of wall stress, in accordance with the Laplace relation.[95–97] LVH can be viewed as a compensatory physiologic response that completes a negative feedback loop (Fig. 21.15). It is possible, however, that severe afterload stress and proportionately massive LVH could decrease subendocardial perfusion and superimpose a component of ischemic contractile dysfunction.

In patients with AS, LVH results from the increase in pressure load. The development of LVH and its regression after therapeutic interventions are accompanied by changes in the cardiac extracellular matrix guided by an increase in *ECM1* gene expression during LVH and complete regression after complete correction.[98]

Systemic hypertension and AS represent an increase in afterload to the LV, and each contributes to left ventricular remodeling and LVH. In a large series of 193 patients with AS, 62 of whom were hypertensive, symptoms manifested with larger AVAs and lower stroke work loss.[99] Patterns of left ventricular remodeling (ie, concentric vs eccentric remodeling and hypertrophy) were not different for hypertensive and normotensive patients. Left ventricular mass decreased by 23% 1 year after AVR, returning to the normal range, in patients with normal preoperative ventricular function; diastolic function improved concomitantly. Improvements in myocardial blood flow and coronary vasodilator reserve after AVRs result from reduced extravascular compression and increased diastolic perfusion time.[100–102]

Ejection phase indices of contractile function are abnormal in many patients with AS.[103,104] However, indices of contractile function, which are exquisitely sensitive to afterload, are inherently unreliable for quantitating the inotropic state in a disease such as AS, in which the essence of the hemodynamic insult is the severely increased ventricular afterload. This in no way excludes the possibility that a subset of patients also may experience some intrinsic depression of myocardial contractility. For example, patients with AS may be particularly at risk for superimposed ischemic ventricular dysfunction, but this possibility can be assessed only by the application of load-insensitive measurements of contractile function.

In most patients, load-insensitive indices of contractility (ie, end-systolic stress-diameter determinations) are virtually identical before and after the development of hypertrophy, suggesting that the increase in chamber thickness compensates for the afterload stress and that myocardial contractility is therefore normal, albeit appropriate for the higher afterload. Fig. 21.16 illustrates the adaptation of the LV to chronic pressure overload. Fig. 21.16A shows the pressure-volume

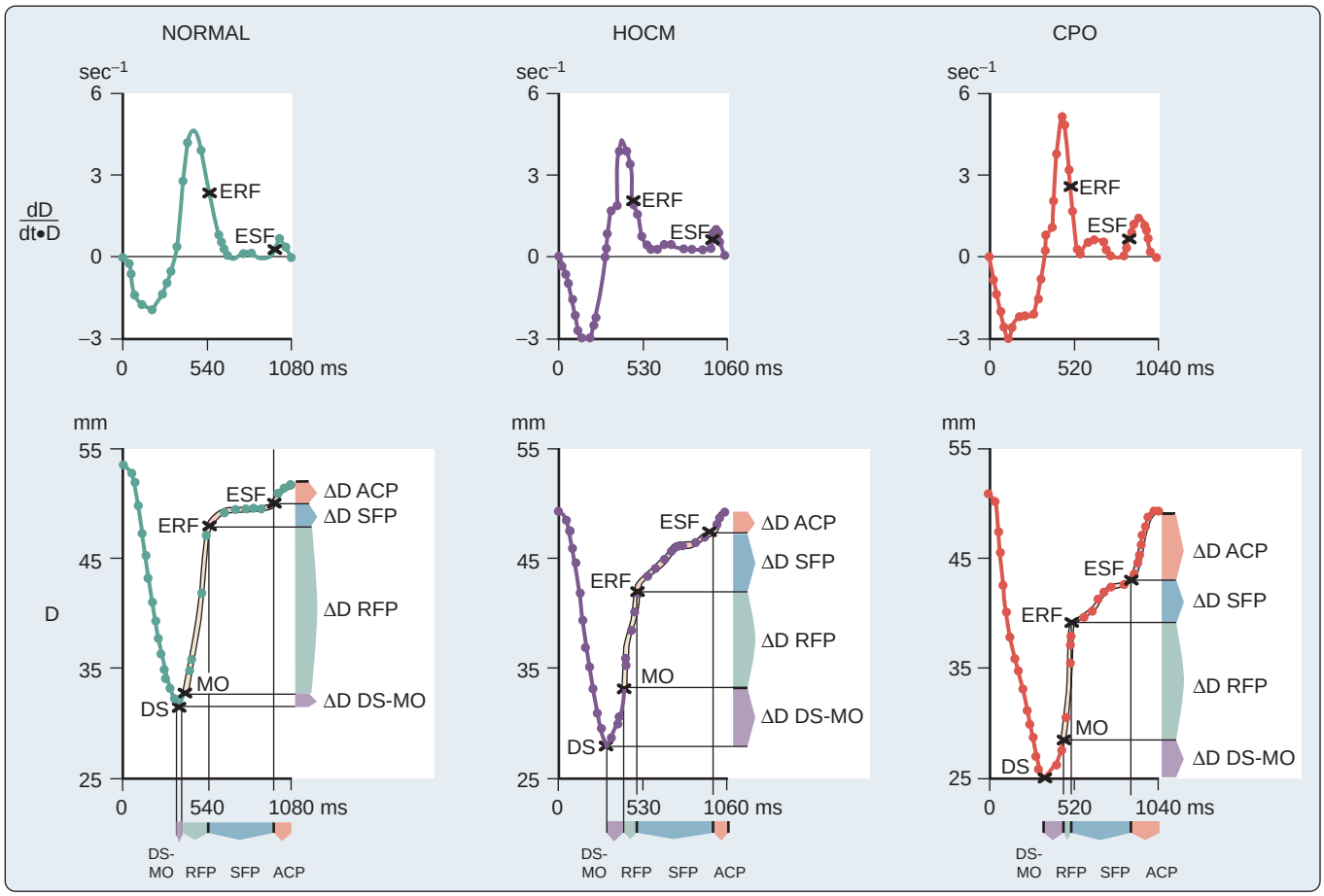


Fig. 21.14 Computer-generated echograms of left ventricular *(LV)* cavity size in healthy subjects and patients with ventricular hypertrophy (ie, hypertrophic obstructive cardiomyopathy *[HOCM]* or chronic pressure overload *[CPO]*). *Top panels* show the rate of ventricular dimensional change. In the *bottom panels*, for patients with both forms of hypertrophy, the mitral valve opening *(MO)* with regard to the end-systolic LV dimension *(DS)* is delayed, and the dimensional change during this interval *(ΔD DS-MO)* is abnormally large. The duration of the rapid-filling phase *(RFP)* and the volume change during this interval *(ΔD RFP)* are correspondingly reduced. This is followed by a large dimensional increase during the atrial contraction phase *(ΔD ACP)* in the patient with chronic pressure overload; *ERF*, End point of rapid filling phase; *ESF*, end point of slow filling phase; *SFP*, slow filling phase. *(From Hanrath P, Mathey DG, Siegert R, et al. Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: an echocardiographic study.* Am J Cardiol. *1980;45:15.)*

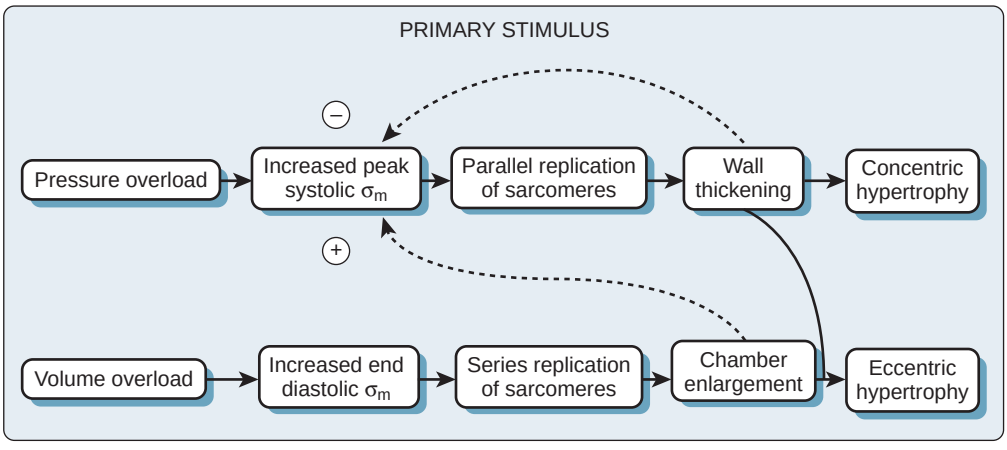


Fig. 21.15 The increased peak systolic wall stress (σ_m) resulting from chronic pressure overload directly stimulates concentric ventricular hypertrophy, which tends to counteract or normalize the increased ventricular wall stress. *(From Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle.* J Clin Invest. *1975;56:56.)*

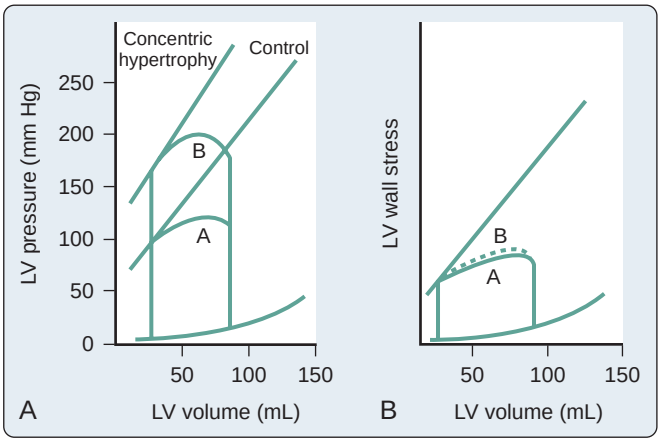


Fig. 21.16 Adaptation to pressure overload. (A) Pressure-volume curves and the linear end-systolic pressure-volume relationship before *(A)* and after *(B)* the development of concentric hypertrophy. After hypertrophy development, the end-systolic pressure-volume relationship is shifted upward and to the left (ie, apparent supranormal contractility). (B) The same relationships are plotted with stress-volume loops. The loops before *(A)* and after *(B)* concentric hypertrophy are essentially the same, reaching the identical end-systolic wall stress–volume point (ie, contractility unchanged). *LV*, Left ventricular. *(From Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy.* J Am Coll Cardiol. *1985;5:811.)*

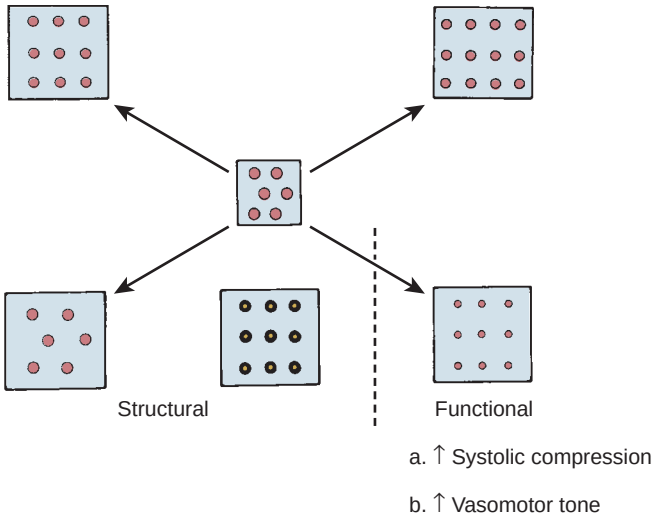


Fig. 21.17 Possible coronary circulatory changes accompanying ventricular hypertrophy. The *box size* indicates myocardial mass, and the *circle area* indicates the cross-sectional area of coronary vasculature. The relationship may be normal, as illustrated by the *top left box*, when growth of the coronary bed has kept pace with ventricular hypertrophy. Experimental data support two possible anatomic derangements: inadequate growth of structurally normal vessels *(bottom left)* or appropriate growth of abnormally thickened resistance vessels whose luminal area is accordingly compromised *(bottom center)*. The *bottom right box* illustrates compression of coronary vascular channels by extra-vascular forces *(a)* and vascular tone *(b)*. *(From Marcus ML. Effects of cardiac hypertrophy on the coronary circulation. In: Marcus ML, ed.* The coronary circulation in health and disease. *New York: McGraw-Hill, 1983.)*

relationship before (ie, loop A) and after (ie, loop B) development of concentric hypertrophy. The linear ESPVR is shifted up and to the left after concentric hypertrophy occur. However, the ESPVR may not be as accurate or load insensitive in assessing contractility at the extremes of afterload. Fig. 21.16B shows normalization of the apparently supranormal contractility, when wall stress (rather than pressure) is used as a more exact measure of ventricular afterload. Concentric hypertrophy normalizes wall stress, and contractility remains unchanged.

A decline in any index of myocardial contractility in patients with AS may represent relatively inadequate hypertrophy for the degree of wall stress, some intrinsic depression of contractility, or a combination of these two factors.[56,105,106] The fact that most patients have normal contractility is the reason for the usually favorable response to AVR.

In AS, signs and symptoms of CHF usually develop when preload reserve is exhausted, not because contractility is intrinsically or permanently impaired. This contrasts with mitral regurgitation (MR) and AR, in which irreversible myocardial dysfunction may develop before the onset of significant symptoms. An important exception is the patient with AS whose symptoms of CHF occur in the setting of associated MR. The latter may accompany hypertrophy-induced left ventricular chamber or mitral annular enlargement. MR in patients with AS is often referred to as *functional* rather than anatomic mitral insufficiency. The implication is that with relief of the high intracavitary systolic pressure, the MR can largely resolve if the mitral valve is anatomically normal. Grade 2 or 3 MR often is significantly reduced after AVR.

Intrinsic contractility is commonly preserved, and the major threat to the hypertrophied ventricle is its exquisite sensitivity to ischemia. Ventricular hypertrophy directly increases basal myocardial oxygen demand ($M\dot{V}O_2$). The other major determinants of overall $M\dot{V}O_2$ are heart rate, contractility, and most important, wall tension. Increases in wall tension occur as a direct consequence of Laplace's law in patients with relatively inadequate hypertrophy. The possibility of ischemic contractile dysfunction in the inadequately hypertrophied ventricle arises from increases in wall tension, which directly parallels the imbalance between the increased peak systolic pressure and the degree of mural hypertrophy. Although there is considerable evidence for supply-side abnormalities in the myocardial supply and demand relationship in patients with AS, clinical data also support increased $M\dot{V}O_2$ as important in the genesis of myocardial ischemia.

On the supply side, the greater LVEDP of the poorly compliant ventricle inevitably narrows the diastolic coronary perfusion pressure (CPP) gradient. With severe outflow obstruction, decreases in SV and resultant systemic hypotension may critically compromise coronary perfusion. A vicious cycle may develop because ischemia-induced abnormalities of diastolic relaxation can aggravate the compliance problem and further narrow the CPP gradient.[107] This sets the stage for ischemic contractile dysfunction, additional decreases in SV, and worsening hypotension.

Cardiac hypertrophy is associated with structural abnormalities of the coronary circulation (Fig. 21.17).[108,109] Animal models have documented that epicardial coronary vessels do not enlarge proportionately when the LV is subjected to a chronic pressure load.[110,111] LVH accompanying chronic hypertension is associated with an increased wall lumen ratio of the coronary arterioles, a change that limits vessel dilation and augments active constriction.[112,113] Animal models of pressure-induced myocardial hypertrophy also have shown a decrease in the capillary density of about 20% to 30%.[108,110,112–116] In LVH caused by pressure overload, a reduction in the coronary vascular reserve may underlie episodes of myocardial ischemia[117,118] (see Chapters 6 and 7).

Echocardiographic and hemodynamic assessments of the myocardial oxygen supply and demand ratio are not significantly different in the presence or absence of angina in patients with AS.[119] However, considerable data indicate that dynamic factors relative to oxygen supply may be crucial to the pathogenesis of angina in these patients.[120] Several clinical studies have documented a decrease in coronary vascular reserve in adult and pediatric patients with significant LVH or right ventricular hypertrophy (RVH).[121–123] It is further postulated that repeated episodes of subendocardial ischemia may contribute to the development of subendocardial fibrosis, a component of ischemic contractile dysfunction.[108]

Myocardial ischemia may underlie the impaired ventricular relaxation that has been documented in patients with myocardial hypertrophy due to a variety of causes.[91,93,94] Prolongation of ventricular relaxation and resultant diastolic dysfunction (ie, poor compliance) are probably universal features of myocardial ischemia in a variety of

TABLE 21.1 Pressure-Overload Hypertrophy

Beneficial Aspects	*Detrimental Aspects*
Increases ventricular work	Decreases ventricular diastolic distensibility
Normalizes wall stress	Impairs ventricular relaxation
Normalizes systolic shortening	Impairs coronary vasodilator reserve, leading to subendocardial ischemia

From Lorell BH, Grossman W. Cardiac hypertrophy: the consequences for diastole. *J Am Coll Cardiol.* 1987;9:1189.

clinical settings.[124–128] Experimental data suggest that ischemia-induced impairment of calcium sequestration by the sarcoplasmic reticulum may underlie the increased diastolic chamber stiffness.[129] Prevention of ischemia-induced myoplasmic calcium overload may be the mechanism by which the calcium channel blockers are able to improve diastolic dysfunction in patients with CAD.[130] These drugs also ameliorate ventricular relaxation and diastolic filling in patients with HCM, although the mechanism of action is controversial.[91,131–133] The absence of diastolic filling abnormalities in patients with physiologic rather than pathologic hypertrophy also may reflect the relative likelihood of ischemia in the two conditions.[134–136]

In summary, the pathophysiologic response to chronic pressure overload is a complex one characterized by interactions among the divergent effects of hypertrophy on systolic and diastolic function. Mural thickening enhances systolic performance, maximizing the mechanical work performed while minimizing its metabolic cost. The price of systolic efficiency is relatively inadequate growth of the coronary microcirculation, which contributes to relaxation abnormalities, diastolic dysfunction, and the potential for superimposition of ischemia-induced abnormalities of systolic dysfunction (Table 21.1).[137] The potentially deleterious effects of LVH cannot be overemphasized. Even in the absence of AS, in which LVH can be viewed as a compensatory and potentially beneficial pathophysiologic response, LVH has been found to have an independent adverse effect on survival.[138,139]

Difficulty of Low-Gradient, Low-Output Aortic Stenosis

A subset of patients with severe AS, left ventricular dysfunction, and low transvalvular gradient suffers a high operative mortality rate and poor prognosis.[140] It is difficult to assess accurately the AVA in low-flow, low-gradient AS because the calculated valve area is proportional to forward SV and because the Gorlin constant varies in low-flow states. Some patients with low-flow, low-gradient AS have a decreased AVA as a result of inadequate forward SV rather than anatomic stenosis. Surgical therapy is unlikely to benefit these patients because the underlying pathology is a weakly contractile myocardium. However, patients with severe anatomic AS may benefit from valve replacement despite the increased operative risk associated with the low-flow, low-gradient hemodynamic state.[140] ACC/AHA guidelines call for a dobutamine echocardiography evaluation to differentiate patients with fixed anatomic AS from those with flow-dependent AS with left ventricular dysfunction.[141] Low-flow, low-gradient AS is defined as a mean gradient of less than 30 mm Hg and a calculated AVA less than 1.0 cm^2.

Dobutamine echocardiography revealed three basic response patterns—fixed AS, relative AS, and absence of contractile reserve—in an initial study by deFilippi and colleagues.[142] In a series of 45 patients with low-flow, low-gradient AS, the 30-day operative mortality rate was 8% for patients with contractile reserve and 50% for those without contractile reserve.[143]

Dobutamine challenges during cardiac catheterization provided unique insights into low-flow, low-gradient AS, and the details are summarized in Fig. 21.18.[144] In Fig. 21.18A, the transvalvular gradient and cardiac output increased, and the valve area did not change. Patients represented in Fig. 21.18B increased their CO with little or no change in gradient, and the calculated valve area increased slightly. This group still benefited from surgery. The third group of patients had no contractile reserve because CO did not increase with dobutamine, and the transvalvular gradient decreased (see Fig. 21.18C). Dobutamine infusion in the cardiac catheterization laboratory appears to be helpful in identifying patients with low-flow, low-gradient AS who have a truly fixed anatomic stenosis that may benefit from valve replacement.

The findings of these studies also emphasize that contractile reserve is an important prognostic indicator for these patients and that dobutamine challenge may help select patients for valve replacement. Those with contractile reserve and fixed AS have a relatively good prognosis with valve replacement. Left ventricular contractile reserve appears to be a critical variable for prognosis. Studies have focused on AS with low transvalvular gradients and normal ventricular EF. The pathophysiology of the low transvalvular gradient has been explained by decreased EDV caused by excessive ventricular hypertrophy accompanied by increased SVR. In a series of patients with severe AS (AVA <0.8 cm^2) with ventricular dysfunction (EF <35%) with or without a low transvalvular gradient (<30 mm Hg), mortality predictors were advanced age, low EF, renal insufficiency, and lack of AR. Regardless of ventricular function, patients who underwent AVR had a significantly better survival rates.[36]

Developments in the Hemodynamic Management of Critical Aortic Stenosis Patients

The use of vasodilators is traditionally contraindicated for patients with severe AS because cardiac output is relatively fixed across a narrowed orifice. Vasodilation reduces SVR without any possibility for a compensatory increase in CO, and severe hypotension typically results. This traditional paradigm was reexamined in patients with fixed, severe AS (area <1.0 cm^2) and left ventricular dysfunction (EF <0.35).[145] Nitroprusside was carefully titrated to maintain a mean arterial pressure of more than 60 mm Hg with concomitant hemodynamic monitoring. The cardiac index increased over 24 hours from a mean of 1.60 to 2.52 L/min/m^2 with no changes in heart rate and mean arterial pressure (Fig. 21.19). The pulmonary capillary wedge pressure (PCWP) and SVR decreased, whereas SV increased.

This treatment can effectively alleviate to some extent the left ventricular dysfunction component of the complete syndrome. Left ventricular dysfunction benefits derived from unloading and careful titration of the nitroprusside most likely allows SVR to decrease without changes in mean arterial pressure. Titrated unloading may benefit patients with severe AS and left ventricular dysfunction, and it may serve as a bridge to AVR or oral vasodilator therapy.[145] It is unclear whether treatment with positive inotropic agents can produce similar effects with fewer risks. Patients with AS, a depressed EF, and a low transvalvular gradient continue to pose a diagnostic and therapeutic challenge.[146] The use of nitroprusside in AS in the absence of ventricular dysfunction may not be as effective and may even be deleterious because of the prompt decrease in preload by nitroprusside.

Timing of Intervention

For asymptomatic patients with AS, it appears to be relatively safe to delay surgery until symptoms develop, but outcomes vary widely. Moderate or severe valvular calcification along with a rapid increase in aortic-jet velocity identify patients with a very poor prognosis. They should be considered for early valve replacement rather than delaying until symptoms develop.[40]

Echocardiography and exercise testing may identify asymptomatic patients who are likely to benefit from surgery.[147] In a study of 58 asymptomatic patients, 21 had symptoms for the first time during exercise testing.[148] Guidelines for AVR in patients with AS are shown in Fig. 21.20.

Functional outcome after AVR for patients older than 80 years is excellent, operative risk is limited, and late survival rates are good.[149] For patients with severe left ventricular dysfunction and a low transvalvular mean gradient, the operative mortality rate was increased, but AVR was associated with improved functional status.[150] Postoperative

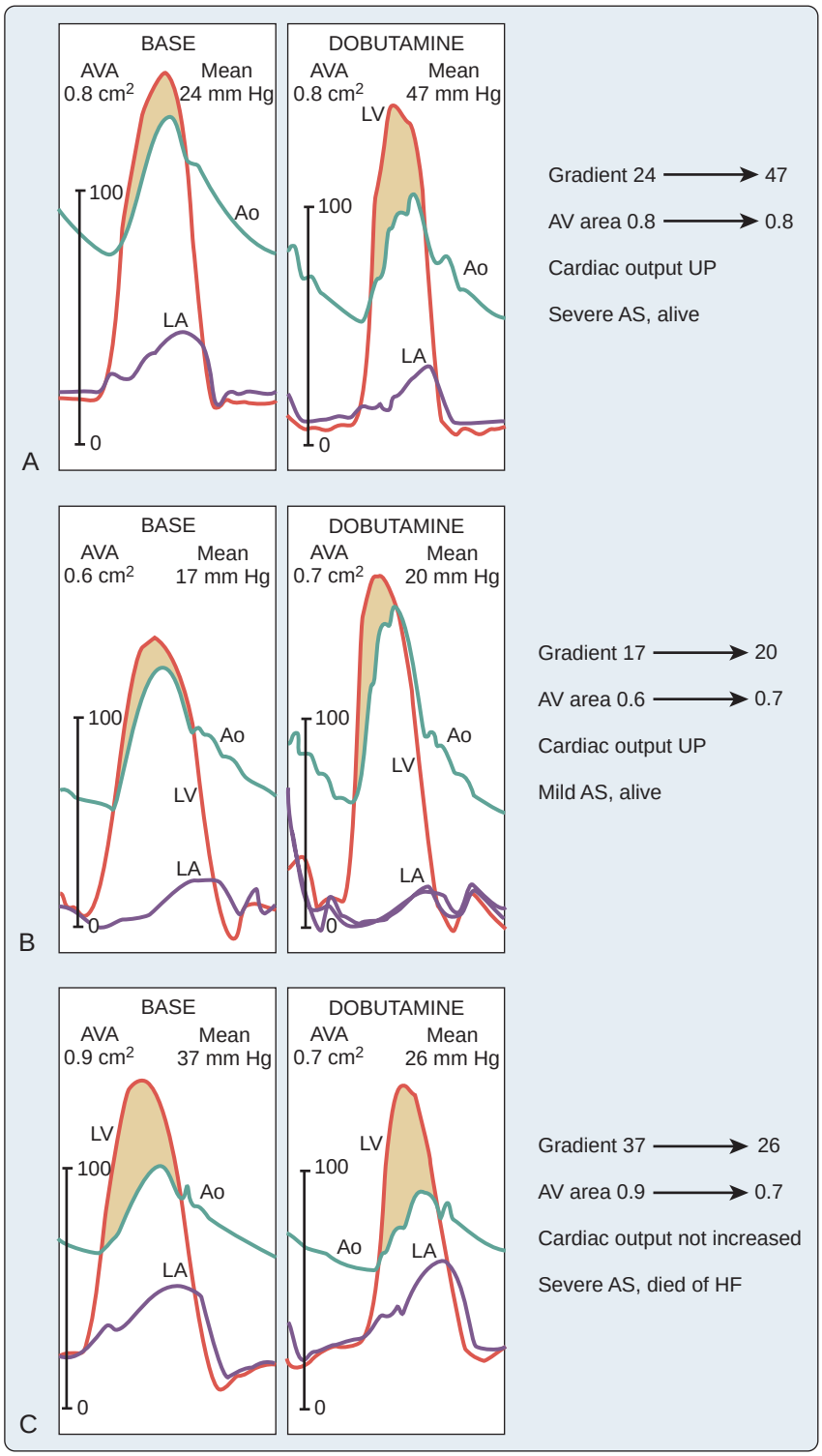


Fig. 21.18 (A–C) Hemodynamic tracings from three patients with different responses to dobutamine. *Ao*, Aorta; *AS*, aortic stenosis; *AV*, aortic valve; *AVA*, aortic valve area; *HF*, heart failure; *LA*, left atrium; *LV*, left ventricle. *(Modified from Nishimura RA, Grantham JA, Connolly HM, et al. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory.* Circulation. *2002;106:809.)*

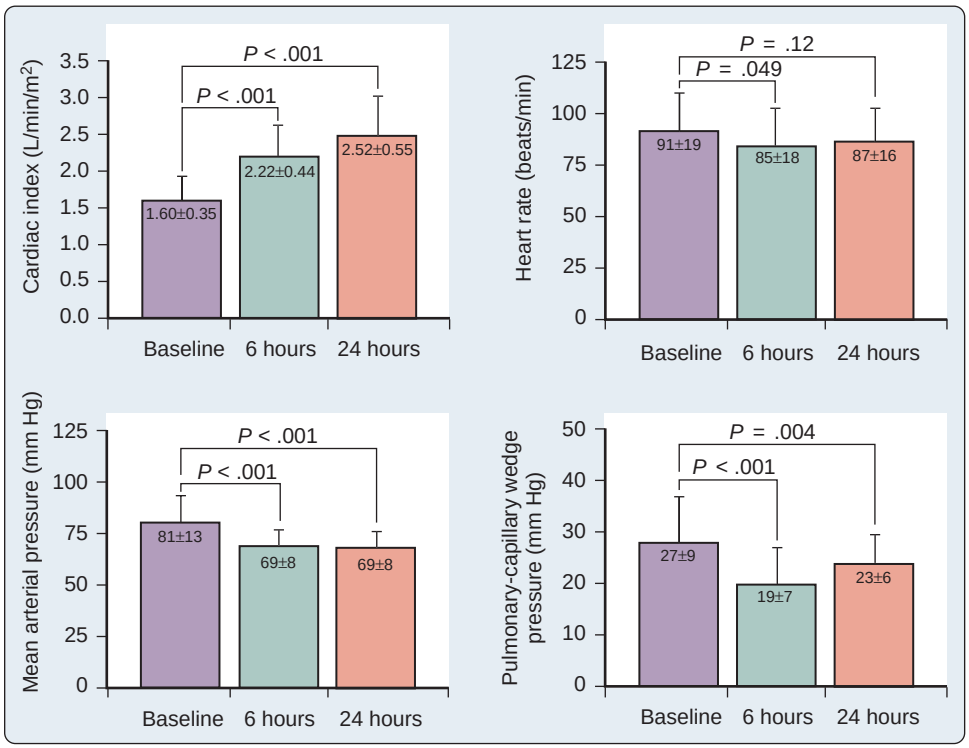
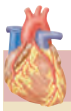


Fig. 21.19 Changes in cardiac index, heart rate, mean arterial pressure, and pulmonary-capillary wedge pressure during titration with nitroprusside over 24 hours in patients with severe aortic stenosis and left ventricular dysfunction. *(Modified from Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis.* N Engl J Med. *2003;348:1756.)*



BOX 21.1 AORTIC STENOSIS

- Maintain preload and diastolic filling.
- Maintain sinus rhythm.
- Maintain or increase afterload.
- Avoid myocardial depression.
- Avoid tachycardia, hypotension, and increased myocardial oxygen demand situations.

survival rates were best for younger patients and those with larger prosthetic valves, whereas medium-term survival rates were correlated with improved postoperative functional class.[150]

Anesthesia Considerations

The described pathophysiologic principles dictate anesthesia management based on avoidance of systemic hypotension, maintenance of sinus rhythm and an adequate intravascular volume, and awareness of the potential for myocardial ischemia (Box 21.1). In the absence of CHF, adequate premedication may reduce the likelihood of undue preoperative excitement, tachycardia, and exacerbation of myocardial ischemia and the transvalvular pressure gradient. In patients with critical outflow tract obstruction, however, heavy premedication with an exaggerated venodilatory response can reduce the appropriately increased LVEDV (and LVEDP) needed to overcome the systolic pressure gradient. In these patients, the additional precaution of administering supplementary oxygen may obviate the possibility of a similarly pronounced response to the sedative effects of the premedicant.

Intraoperative monitoring should include a standard five-lead electrocardiographic (ECG) system, including a V_5 lead, because of the LV's vulnerability to ischemia. A practical constraint in terms of interpretation is that these patients usually exhibit ECG changes because of preoperative LVH. The associated ST-segment abnormalities (ie, strain pattern) may be indistinguishable from or very similar to those of myocardial ischemia, making the intraoperative interpretation difficult. Lead II and possibly an esophageal electrocardiogram should be readily obtainable because for assessing the P-wave changes in the event of supraventricular arrhythmias (see Chapter 12).

Hemodynamic monitoring is controversial, and few prospective data are available on which to base an enlightened clinical decision. The central venous pressure (CVP) is a particularly poor estimate of left ventricular filling when left ventricular compliance is reduced. A normal CVP can significantly underestimate the LVEDP or PCWP. The principal risks, although minimal, of using a pulmonary artery catheter (PAC) in the patient with AS are arrhythmia-induced hypotension and ischemia. Loss of synchronous atrial contraction or a supraventricular tachyarrhythmia can compromise diastolic filling of the poorly compliant LV, resulting in hypotension and the potential for rapid hemodynamic deterioration. The threat of catheter-induced arrhythmias is significant for the patient with AS. However, accepting a low-normal CVP as evidence of good ventricular function can lead to similarly catastrophic underfilling of the LV on the basis of insufficient replenishment of surgical blood loss. To some extent, even the PCWP can underestimate the LVEDP (and LVEDV) when ventricular compliance is markedly reduced. Placement of a PAC also allows measurement of CO, derived hemodynamic parameters, mixed venous oxygen saturation (Svo_2), and possible transvenous pacing (see Chapter 13).

Intraoperative fluid management should be aimed at maintaining appropriately increased left-sided filling pressures. This is one reason why many clinicians think that the PAC is worth its small arrhythmogenic risk. Keeping up with intravascular volume losses is particularly important in noncardiac surgery, in which the shorter duration of the operation may make inhalation or potentially vasodilating regional anesthesia preferable to a narcotic technique.

Patients with symptomatic AS are usually encountered only in the setting of cardiovascular surgery because of their ominous prognosis without AVR. Few studies have specifically addressed the response of

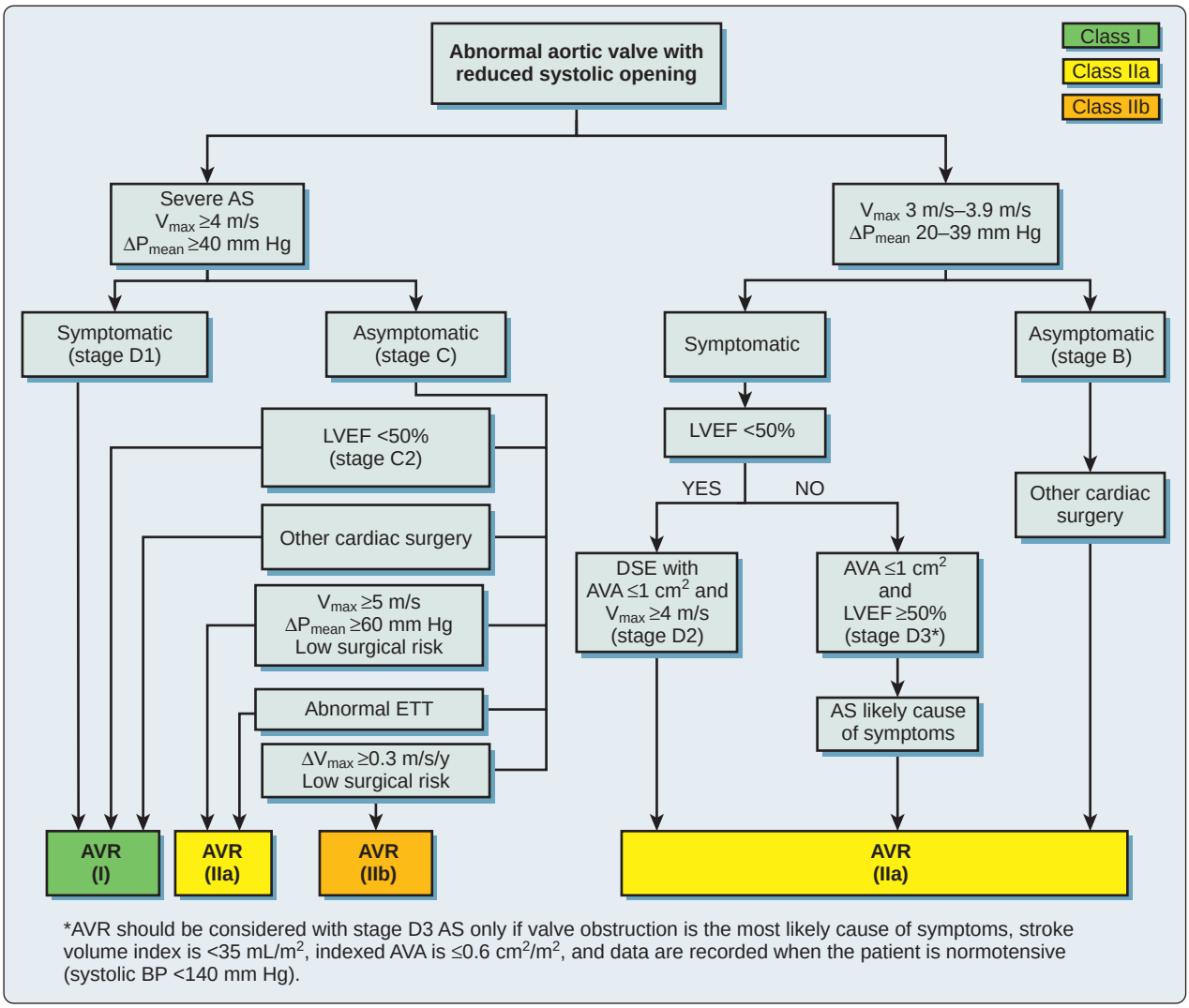


Fig. 21.20 Indications for aortic valve replacement (AVR) in patients with aortic stenosis (AS). *Arrows* show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradient AS (stage D2 or D3) who do not meet the criteria for intervention. *AVA,* Aortic valve area; *AVR,* aortic valve replacement by either surgical or transcatheter approach; *BP,* blood pressure; *DSE,* dobutamine stress echocardiography; *ETT,* exercise treadmill test; *LVEF,* left ventricular ejection fraction; ΔP_{mean}, mean pressure gradient; V_{max}, maximum velocity. *(From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63[22]:2438–2488.)*

these patients to the standard intravenous and inhalation induction agents; however, the responses to narcotic[151,152] and nonnarcotic[153,154] intravenous agents are apparently not dissimilar from those of patients with other forms of VHD. The principal benefit of a narcotic induction is assurance of an adequate depth of anesthesia during intubation, which reliably blunts potentially deleterious reflex sympathetic responses capable of precipitating tachycardia and ischemia.

Many clinicians also prefer a pure narcotic technique for maintenance. The negative inotropy of inhalation anesthetics is a theoretical disadvantage for a myocardium faced with the challenge of overcoming outflow tract obstruction. A more clinically relevant drawback may be the increased risk for arrhythmia-induced hypotension, particularly that associated with nodal rhythm and resultant loss of the atrium's critical contribution to filling of the hypertrophied ventricle[155,156] (see Chapter 10).

Occasionally, surgical stimulation elicits a hypertensive response despite the impedance posed by the stenotic valve and a seemingly adequate depth of narcotic anesthesia. In these patients, a judicious trial of low concentrations of an inhalation agent, used purely for control of hypertension, may prove efficacious. The ability to concurrently monitor CO is useful in this situation. The temptation to control intraoperative hypertension with vasodilators should be resisted in most cases. Given the risk for ischemia, nitroglycerin seems to be a particularly attractive drug. Its effectiveness in relieving subendocardial ischemia in patients with AS is controversial[157,158]; however, there is always the risk for transient episodes of overshoot. The hypertrophied ventricle's critical dependence on an adequate CPP may be unforgiving of even a momentary dip in the systemic arterial pressure.

Intraoperative hypotension, regardless of the primary cause, should be treated immediately and aggressively with a direct α-adrenergic agonist such as phenylephrine.[159] The goal should be to immediately restore the CPP and then to address the underlying problem (eg, hypovolemia, arrhythmia). After the arterial pressure responds, treatment of the precipitating event should be equally aggressive, but

rapid transfusion or cardioversion should not delay the administration of a direct-acting vasoconstrictor. Patients with severe AS in whom objective signs of myocardial ischemia persist despite restoration of the blood pressure should be treated extremely aggressively. This may mean the immediate use of an inotropic agent or accelerating the institution of cardiopulmonary bypass (CPB).

Intraoperative myocardial ischemic injury in the patient with AS has been appreciated for some time, and there are several theories regarding its pathogenesis. The potential vulnerability of the hypertrophied myocardium to ischemic damage was initially speculated on by cardiac surgeons who described the phenomenon of irreversible ischemic contracture—what they called the *stone heart*—occurring after AVR in a group of patients with severe LVH.[160] The anatomic and hemodynamic bases for an unfavorable myocardial oxygen supply and demand relation have already been considered, but the possibility that these patients may be experiencing prebypass ischemic injury remains a plausible, although unproven, hypothesis.

Most attention has been focused on the potential for irreversible cellular damage occurring during the period of ischemic cardiac arrest. Although there is a consensus that improved myocardial preservation has been crucial in reducing the mortality rate after CABG, there is evidence that current cardioplegic techniques may provide suboptimal protection for patients with VHD.[161,162] Ultrastructural evidence (ie, intracellular or mitochondrial edema) suggests that the hypertrophied myocardium is uniquely susceptible to ischemic damage during the aortic cross-clamp interval despite the presumed protection. Although these changes are observed in patients whose clinical course is seemingly unremarkable, ischemic cellular damage also may underlie the frequent occurrence of postoperative low-output syndromes and the greater mortality rates associated with valvular operations.[163]

Although a detailed consideration of myocardial preservation is beyond the scope of this chapter (see C), certain aspects are peculiar to the operative management of patients with AS, and improved cardioplegic techniques likely will play an important role in reducing operative morbidity and mortality rates. Because the operation requires an ascending aortotomy, many surgeons routinely use direct coronary ostial cannulation for the delivery of the cardioplegic solution. Problems associated with this approach are uncommon but include the inherent hazard of injury to the coronary ostia and cannula-induced late stenosis of the left main coronary artery.[164] Coronary ostial delivery requires interrupting the surgical procedure for subsequent reinfusions of the cardioplegic solution. These problems are obviated by the use of cardioplegia delivery through the coronary sinus. The retrograde technique commonly is used in conjunction with an initial dose of antegrade cardioplegia; the latter provides for a more immediate electromechanical arrest.[165–167]

Noncardiac Surgery in the Patient With Aortic Stenosis

Patients with AS who undergo noncardiac surgery were identified by Goldman and coworkers[148] as being at increased risk for cardiac complications, including myocardial infarction, CHF, and supraventricular tachyarrhythmias. Likewise, the ACC Task Force on perioperative evaluation of the cardiac patient identified patients with severe or symptomatic AS as being at increased risk for serious perioperative cardiac morbidity.[168] It stated that symptomatic stenotic lesions are associated with the risk of perioperative severe CHF or shock and often require percutaneous valvotomy or valve replacement before noncardiac surgery to reduce cardiac risk.

Due to the aging of the surgical population and a peak incidence of significant AS in the fifth and sixth decades, these patients likely will be encountered with increasing frequency in the setting of noncardiac surgery. Because of the natural history of the disease and the conservative ACC guidelines cited previously, one approach is to recommend immediate elective AVR to all AS patients before noncardiac procedures. Although there is a rationale for this shotgun solution, a variety of ethical, practical, and economic constraints argue for a more selective approach.

A common clinical problem is the elderly, asymptomatic patient with a harsh systolic ejection murmur who is scheduled for noncardiac surgery. Risk assessment for the asymptomatic patient is challenging because the prognosis in the absence of AVR may be quite benign. However, symptoms correlate poorly with AS severity, which may by itself portend a more ominous natural history. For these patients, a two-dimensional Doppler echocardiographic examination allows a noninvasive assessment of the severity of stenosis[57] and some quantification of contractile function (see Chapters 14 and 15). Patients with moderate AS have a greater short-term incidence of cardiovascular complications, and this risk is further increased by symptoms or objective evidence of contractile impairment.[53]

Armed with the echocardiographic evaluation (eg, stenosis severity, contractile state), the clinician can make an initial assessment of relative risk. Depending on the overall clinical picture, some patients may warrant immediate elective AVR by a surgical or transcutaneous approach, whereas for others, it may be more appropriate to proceed with the noncardiac operation along with hemodynamic monitoring as dictated by the echocardiographic data and the nature of the operation. In the clinical setting, the overall picture often dictates that the anesthesiologist proceed with the originally planned operation, albeit at increased risk for perioperative cardiac morbidity (see Chapter 27).

Hypertrophic Cardiomyopathy

Hypertrophic Obstructive Cardiomyopathy

Obstructive hypertrophic cardiomyopathy (HCM) is a relatively common genetic malformation of the heart with a prevalence of approximately 1 case in 500 births (see Chapter 24). The hypertrophy initially develops in the septum and extends to the free walls, often giving a picture of concentric hypertrophy. Asymmetric septal hypertrophy leads to a variable pressure gradient between the apical left ventricular chamber and the LVOT. The LVOT obstruction leads to increases in left ventricular pressure, which fuels a vicious cycle of further hypertrophy and increased LVOT obstruction.[169]

Treatment modalities include β-adrenoceptor antagonists, calcium channel blockers, and surgical myectomy of the septum. For more than 40 years, the standard treatment has been the ventricular septal myotomy-myomectomy of Morrow, in which a small amount of muscle from the subaortic septum is resected.[170] Two new treatment modalities have gained popularity in recent years: dual-chamber pacing and septal reduction (ie, ablation) with ethanol.

Dual-chamber DDD pacing is based on the observation that excitation of the septum of the LV contracts it away from the apposing wall, which can reduce the LVOT gradient. The precise mechanism by which dual-chamber pacing decreases LVOT gradient or improves symptoms is uncertain. Possible mechanisms are asynchronous ventricular activation, paradoxical septal wall motion, a negative inotropic effect, an increase in ESV, decreased systolic anterior leaflet motion, altered myocardial perfusion, and regression of LVH.[171] The AV interval must be sufficiently short to guarantee early right ventricular apical activation without conduction through the His-Purkinje system. Although some studies have shown a decrease in the LVOT gradient of 25%, there are still variable results with respect to improvements in exercise capacity and symptoms.[171–174]

Patients with severe, drug-resistant symptoms of CHF, angina, or syncope are considered for nonsurgical septal reduction therapy. In one series, patients with a resting gradient of more than 40 mm Hg or a dobutamine-induced gradient of more than 60 mm Hg were included.[175] After coronary angiography to exclude significant CAD and after placement of temporary pacing wires, the LVOT gradient was measured at rest and during various interventions (eg, Valsalva, postextrasystolic, isoproterenol, amyl nitrite). The coronary septal branches were cannulated with a small balloon-equipped catheter.

The balloon was inflated to prevent overflow or spillage into the left anterior descending coronary artery. Depending on the septal branch size and area of septal hypertrophy, a dose of 2 to 5 mL of ethanol was injected slowly through the balloon catheter lumen. The LVOT gradient decreased immediately in 85% to 90% of patients. Further decreases in gradient were reported after 6 months.[171]

The septal muscle mass was not decreased adequately through alcohol injections at the time of the intervention, but ventricular remodeling continued and led to sustained symptomatic improvement, most dramatically over the first 3 to 6 months.[169] Exercise tolerance also increased, but atrioventricular block, right bundle branch block, and left bundle branch block were frequent adverse consequences. Permanent heart blocks occurred in 5% to 10% of cases.[176]

Clinical Features and Natural History

HCM is a familial disorder in which there is pronounced hypertrophy of histologically abnormal sarcomeres with characteristically disproportionate involvement of the interventricular septum.[177–179] This disease has numerous pathologic and pathophysiologic features, which vary in their relative predominance in individual patients. The cause and exact pattern of inheritance of the disease remain unknown, although it appears to be an autosomal dominant trait expressed with a high degree of penetrance.[179–181]

Many names have been applied to the disorder, including asymmetric septal hypertrophy, muscular sub-AS, and idiopathic, hypertrophic sub-AS. Each emphasizes some aspect of the disease that may or may not be a prominent feature of its manifestation in an individual patient.

The clinical presentation of patients vary widely. Echocardiography has unquestionably increased the number of asymptomatic patients who carry the diagnosis. Most patients with HCM are asymptomatic and have been seen by the echocardiographer because of relatives having clinical disease. Follow-up remains an important problem for cardiologists because sudden death or cardiac arrest may occur as the presenting symptom in slightly more than one-half of previously asymptomatic patients.[182]

Less dramatic presenting complaints include dyspnea, angina, and syncope.[179] The clinical picture is often similar to valvular AS. The symptoms may share a similar pathophysiologic basis (eg, poor diastolic compliance) in the two conditions. The prognostic implications of clinical disease, however, are less certain for patients with HCM. Although cardiac arrest may be an unheralded event, some patients may have a stable pattern of angina or intermittent syncopal episodes for many years.[183] Palpitations are frequently described and may be related to a variety of underlying arrhythmias. Of patients studied with continuous ambulatory monitoring, ventricular arrhythmias occur in more than 75%, supraventricular tachycardias in 25%, and atrial fibrillation (AF) in 5% to 10%.[184–186] The latter often precipitates clinical deterioration because of the dependence of the noncompliant LV on atrial systole for its filling.[187]

The natural history of patients with HCM varies broadly. These patients are at risk for sudden death, although those with a family history of this problem form an especially high-risk group.[188] Unfortunately, younger and previously asymptomatic patients with minimal subaortic gradients also may be at greater risk for sudden death because of their more frequent and vigorous physical activity.[182,189] It is unknown whether vigorous physical activity by patients with HCM is an independent risk factor for sudden death, but HCM is the most frequent autopsy finding in previously healthy competitive athletes who die suddenly.[190]

Although patients referred to diagnostic centers for evaluation of HCM are usually young to middle-aged, a syndrome with similar clinical and echocardiographic findings has been identified in the elderly.[93] Echocardiographically, these patients exhibit a similarly thickened and hypercontractile LV. Their most common symptoms are those of CHF and are thought to reflect severe reductions in ventricular diastolic compliance. As in younger patients with classic HCM, there is marked systolic anterior motion (SAM) of the mitral apparatus. However, in HCM of the elderly, the SAM is caused or accentuated by a severe degree of mitral annular calcification, which results in a particularly small LVOT.[191] Previously asymptomatic, these patients often experience the onset of progressively severe symptoms in the sixth decade of life, and the response to medical therapy, usually calcium channel blockers, has been poor.[191] The lack of improvement with medical therapy may reflect the fact that mitral annular calcification plays a key role in producing a physical (ie, less dynamic) subaortic obstruction. It also would explain the female predominance of the disease because mitral annular calcification is more common in elderly women. It is unclear whether this represents a true variant of classic HCM with late onset or it is etiologically linked to long-standing systemic hypertension, with secondary, unexplained, disproportionate involvement of the interventricular septum.[93]

Pathophysiology

In HCM, the principal pathophysiologic abnormality is myocardial hypertrophy. The hypertrophy is a primary event in these patients and occurs independently of outflow tract obstruction. Unlike in AS, the hypertrophy begets the pressure gradient, not the other way around. Histologically, the hypertrophy consists of myocardial fiber disarray, and anatomically, there is usually disproportionate enlargement of the interventricular septum.[192]

Controversy exists concerning the intrinsic contractile strength of the myocardium in patients with HCM. Several studies have demonstrated normal or supranormal indices of systolic function in patients with this disease.[193–195] Left ventricular ejection is rapid, with 80% of the SV ejected very early during systole.[193,196] This is true regardless of the presence, temporal location during systole, or magnitude of outflow tract obstruction. However, studies have shown that end-systolic stress is significantly reduced in relation to ESV (Fig. 21.21).[197,198] The Laplace formula for wall stress ($P \times R/2h$) shows that the degree of primary hypertrophy (ie, with increased wall thickness [h]) in HCM should minimize instantaneous left ventricular afterload. There is preservation and perhaps elevation of afterload-sensitive indices of systolic function (eg, EF).[199]

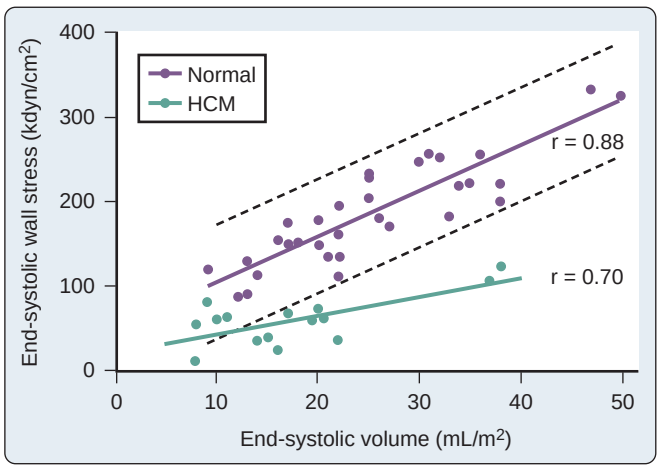


Fig. 21.21 End-systolic stress versus end-systolic volume in healthy subjects *(purple circles)* and in patients with hypertrophic cardiomyopathy *(HCM) (green circles). Dashed lines* indicate the 95% confidence limit. Stress-volume data for most patients with HCM are located downward and to the right of the confidence band (ie, decreased end-systolic stress related to volume), which indicates intrinsically depressed myocardial contractility. *(From Pouleur H, Rousseau MF, van Eyll C, et al. Force-velocity-length relations in hypertrophic cardiomyopathy: evidence of normal or depressed myocardial contractility.* Am J Cardiol. *1983;52:813.)*

Myocardial hypertrophy, particularly to the extent that it accentuates subaortic obstruction, increases the ESPVR, widening the divergence between it and the more accurate (load-insensitive) ratio of end-systolic wall stress to ESV. High peak systolic pressures (ie, subaortic obstruction), elevation of ejection phase indices, and low ESV (ie, minimal afterload) may reflect uncontrolled hypertrophy of an abnormal and perhaps intrinsically depressed myocardium. Whether overall contractility is normal, supranormal, or impaired in a patient, regional differences in a ventricle's contractile function likely correlate with the histologic heterogeneity characteristic of this disease.[200]

HCM is characterized by a broad spectrum of obstruction, which is absent in some patients and varies from mild to severe in others. The most distinctive qualities of obstruction are its dynamic nature (ie, depends on contractile state and loading conditions), its timing (ie, begins early and peaks variably), and its subaortic location.[193,201] Many think that subaortic obstruction arises from the hypertrophied septum's encroachment on the systolic outflow tract, which is bounded anteriorly by the interventricular septum and posteriorly by the anterior leaflet of the mitral valve.

In most patients with obstruction, exaggerated anterior (ie, toward the septum) motion of the anterior mitral valve leaflet during systole accentuates the obstruction.[202] The cause of SAM is unclear. One possibility is that the mitral valve is pulled toward the septum by contraction of the papillary muscles, whose orientation is abnormal because of the hypertrophic process.[203] Another theory is that vigorous contraction of the hypertrophied septum results in rapid acceleration of the blood through a simultaneously narrowed outflow tract. The generated hydraulic forces (consistent with a Venturi effect) can cause the anterior leaflet of the mitral valve to be drawn close to or in contact with the interventricular septum[204] (Fig. 21.22). After the obstruction is triggered, the mitral valve leaflet is forced against the septum by the pressure difference across the orifice. However, the pressure difference further decreases orifice size and further increases the pressure difference in a time-dependent, amplifying feedback loop.[205] This analysis is consistent with observations that the measured gradient directly correlates with the duration of mitral-septal contact. Although still controversial,[206–208] there appears to be good correlation between the degree of SAM and the magnitude of the pressure gradient.[209,210] The SAM-septal contact also underlies the severe subaortic obstruction characteristic of HCM of the elderly, although the narrowing usually is more severe and the contribution of septal movement toward the mitral valve is usually greater.[191]

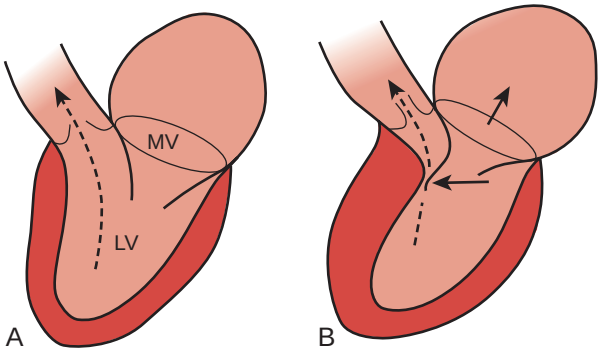


Fig. 21.22 Proposed mechanism of systolic anterior motion in hypertrophic cardiomyopathy. (A) Normally, blood is ejected from the left ventricle *(LV)* through an unimpeded outflow tract. (B) Thickening of the ventricular septum restricts the outflow tract, and the obstruction causes the blood to be ejected at a higher velocity and closer to the area of the anterior mitral valve *(MV)* leaflet. Due to its proximity to the high-velocity fluid path, the anterior MV leaflet is drawn toward the hypertrophied septum by a Venturi effect *(left arrow). (From Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy—a review.* Prog Cardiovasc Dis. *1985;28:1.)*

The timing of SAM-septal contact is important because the magnitude of the subaortic gradient is proportional to the fraction of forward flow ejected in the setting of anatomic obstruction.[211] Large gradients occur as a result of early and prolonged SAM-septal contact, and small gradients arise from delayed and brief SAM-septal contact.[204,209] In studies of patients with various degrees of subaortic obstruction, the proportion of flow ejected in the presence of a gradient was between 30% and 70%.[209,212,213] Patients with evidence of systolic obstruction at rest have the longest intervals of systolic contact between the anterior leaflet of the mitral valve and the septum.[214] However, if SAM-septal contact is restricted to late systole, a pressure gradient may occur on the basis of so-called cavity obliteration in the absence of functional obstruction to blood flow.[215,216] In these patients, 95% of the SV may be ejected by the halfway point in systole, when SAM-septal contact is just beginning.[193,209] Despite its seemingly critical role in producing outflow tract obstruction, SAM of the mitral valve is not a specific finding for HCM, and it may occur in patients with HCM who do not have obstruction.[206,207,214]

In addition to SAM, approximately two-thirds of patients exhibit a constellation of structural malformations of the mitral valve.[217] Malformations include increased leaflet area and elongation of the leaflets or anomalous papillary muscle insertion directly into the anterior mitral valve leaflet. HCM is not a disease process confined to cardiac muscle alone because these anatomic abnormalities of the mitral valve are unlikely to be acquired or caused by mechanical factors.

Three basic mechanisms—increased contractility, decreased afterload, and decreased preload—exacerbate the degree of SAM-septal contact and produce the dynamic obstruction characteristic of patients with HCM. The common pathway is a reduction in ventricular volume (actively by increased contractility directly or reflexively in response to vasodilation or passively by reduced preload), which increases the proximity of the anterior mitral valve leaflet to the hypertrophied septum.[179,183,218] Factors that usually impair contractile performance, such as myocardial depression, systemic vasoconstriction, and ventricular overdistention, characteristically improve systolic function in patients with HCM and outflow tract obstruction.

Diagnostically, the paradoxes are exploited by quantifying the degree of subaortic obstruction after isoproterenol (eg, increased inotropy, tachycardia, decreased volume) and the Valsalva maneuver (eg, decreased venous return, ventricular volume), both of which reliably elicit increases in the pressure gradient. In the operating room, catheter-induced ectopy or premature ventricular contractions resulting from cardiac manipulation may transiently exacerbate the gradient by increased inotropy from postextrasystolic potentiation. Therapeutically, volume loading, myocardial depression, and vasoconstriction can minimize obstruction and augment forward flow.

Patients with HCM demonstrate critical derangements in diastolic function. Although in some ways more subtle than the unique phenomenon of subaortic obstruction, they may contribute equally to the challenge posed.[219–222] Abnormalities include prolongation of the isovolumic relaxation time (ie, aortic valve closure to mitral valve opening) and reduction in the peak velocity of left ventricular filling.[91,195] Diastolic dysfunction exhibits the same heterogeneity as systolic dysfunction, probably because the underlying cause is intrinsic to the primary myopathic process and not merely caused by the associated chamber hypertrophy.[223] Diastolic filling abnormalities in HCM are largely independent of the magnitude of LVH and are seen even in patients with only mild, localized hypertrophy.[20]

Poor diastolic compliance is the most clinically apparent manifestation of the relaxation abnormalities. Left ventricular filling pressures are markedly increased despite enhanced systolic ejection and a normal or subnormal EDV. The reduced ventricular volume emphasizes the pivotal role played by the hypertrophied but intrinsically depressed myocardium. Reductions in afterload, which are mediated by hypertrophy, support the ventricle's systolic performance, resulting in increased emptying and a small diastolic volume. However, hypertrophy also impairs relaxation, resulting in poor diastolic compliance and an increased ventricular filling pressure. The high filling pressure

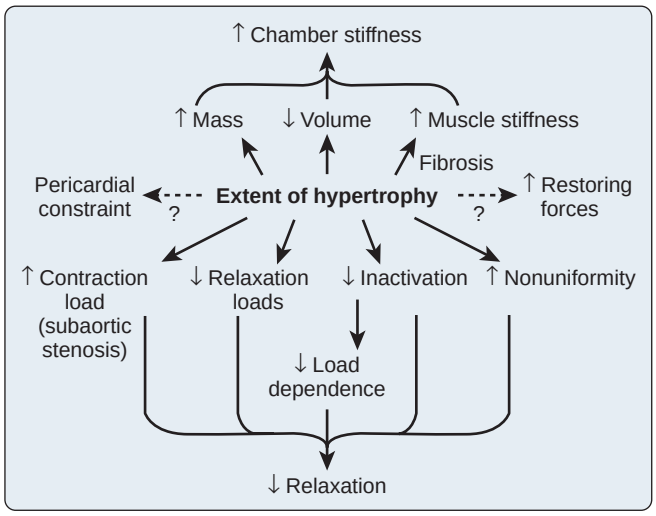


Fig. 21.23 Proposed interactions between myocardial hypertrophy and other related properties of ventricular function. ↑, Increased; ↓, decreased. *(From Wigle ED, Sasson Z, Henderson MA, et al. Hypertrophic cardiomyopathy: the importance of the site and the extent of hypertrophy—a review.* Prog Cardiovasc Dis. *1985;28:1.)*

BOX 21.2 FACTORS AFFECTING LEFT VENTRICULAR DIASTOLIC FILLING IN HYPERTROPHIC CARDIOMYOPATHY

- Chamber stiffness[a]
- Relaxation
  - Loads
    - Contraction load
      - Subaortic stenosis
    - Relaxation loads
      - Late-systolic loading
      - End-systolic deformation (ie, restoring forces)
      - Coronary filling
      - Ventricular filling
  - Inactivation
    - Myoplasmic calcium overload
      - Primary
      - Ischemic
  - Nonuniformity of load and inactivation in space and time[b]
- Pericardial constraints and ventricular interaction
- Effect of extent of hypertrophy on the preceding factors

[a]Chamber stiffness = myocardial mass × myocardial stiffness/ventricular volume.
[b]Nonuniformity of contraction and relaxation.
From Wigel ED, Wilansky S. Diastolic dysfunction in hypertrophic cardiomyopathy. *Heart Fail.* 1987;3:85.

does not reflect distention of a failing ventricle, although stress-volume relationships suggest that contractility is intrinsically depressed (Fig. 21.23 and Box 21.2). This disease is characterized by systolic and diastolic dysfunction.

As in patients with valvular AS, relatively high filling pressures reflect the LVEDV (ie, degree of preload reserve) needed to overcome the outflow obstruction. Intervention with vasodilators is therefore inappropriate. The poor ventricular compliance also means that patients with HCM depend on a large intravascular volume and the maintenance of sinus rhythm for adequate diastolic filling. The atrial contribution to ventricular filling is even more important in HCM than in valvular AS, and it may approach 75% of total SV.[132]

Another similarity between HCM and valvular AS is that the combination of myocardial hypertrophy, with or without LVOT obstruction, may precipitate imbalances in the myocardial oxygen supply and demand relationship. Angina-like discomfort is a classic symptom of patients with HCM, and its pathogenesis has been attributed to increases in $M\dot{V}O_2$, specifically the increased overall muscle mass and the high systolic wall tension generated by the ventricle's ejection against the dynamic subaortic obstruction. However, as in patients with AS, there is evidence of a compromise in myocardial oxygen supply.[224,225]

Patients with HCM suffer from several types of hypertrophy-related abnormalities of the coronary circulation; some are common to other conditions associated with pathologic hypertrophy (eg, AS), and others are unique to this distinctive form of hypertrophy.[226] Reduced capillary density in the hypertrophied myocardium prevents flow from increasing in proportion to the increase in myocardial mass.[227] It is also possible that there are primary HCM-associated abnormalities of the coronary circulation that are unrelated to myocardial hypertrophy.[228] In addition to the coronary circulatory abnormalities, there is evidence of a metabolic derangement in the hypertrophied interventricular septum, whereby there is a decreased use of adequately delivered metabolic substrates.[225]

The reduction in coronary vascular reserve is similar to that observed in patients with valvular AS, in whom $M\dot{V}O_2$ may be presumed to be uniformly increased.[118] However, angina also occurs in patients with HCM in the absence of subaortic obstruction. Although basal $M\dot{V}O_2$ is increased in proportion to the increased muscle mass, clinical studies support a greater pathogenetic role for coronary circulatory abnormalities in producing ischemia in patients with nonobstructive hypertrophy.[229]

Hemodynamic derangements peculiar to the disease may aggravate the ventricle's anatomic vulnerability to ischemia. The increased LVEDP for any LVEDV (ie, poor compliance) inevitably narrows the diastolic CPP gradient. This may precipitate subendocardial ischemia in some patients with HCM, particularly those faced with the increased oxygen demand of overcoming late-systolic obstruction.[219] There is evidence that hypertrophy-induced myocardial ischemia may underlie the diastolic dysfunction characteristic of HCM.[230] As in patients with valvular AS, ischemia-induced abnormalities of diastolic calcium sequestration may further exacerbate relaxation abnormalities, initiating a vicious cycle (Fig. 21.24).[107,122,137,160,161,231]

β-Blockers and calcium channel blockers form the basis of medical therapy for HCM. β-Blockade is most useful for preventing sympathetically mediated increases in the subaortic gradient and for the prevention of tachyarrhythmias, which can exacerbate outflow obstruction. Disopyramide also has been used to reduce contractility and for its antiarrhythmic properties.[232] Calcium channel blockers often prove clinically effective in patients with HCM, regardless of the presence or absence of systolic obstruction.[233] The mechanism of action involves improvement in diastolic relaxation, allowing an increase in LVEDV at a lower LVEDP. The negative inotropy may attenuate the subaortic pressure gradient, but in selected patients, the gradient may worsen because of pronounced and unpredictable degrees of vasodilation.[234,235]

Surgery (ie, septal myotomy or partial myomectomy by the aortic approach) is reserved for patients who remain symptomatic despite maximal pharmacologic therapy. In a long-term retrospective study, the cumulative survival rate was significantly better in surgically than in pharmacologically treated patients.[236] However, it is likely that pharmacologic therapy may be more appropriate for the patient with a dynamic component to their degree of subaortic obstruction.[237] Further improvement in the clinical outcome of surgically treated patients may be achieved with the addition of verapamil, presumably reflecting a two-pronged attack on the systolic (ie, myomectomy) and diastolic (ie, verapamil) components of the disease.

Enthusiasm continues for the therapeutic use of dual-chamber pacing in this disease, with some patients demonstrating reductions in their subaortic gradients.[171–174,238,239] It is not an option for patients with AF.

Myomectomy usually results in significant symptomatic improvement and a reduction in the subaortic gradient.[240] Intraoperative guidance and evaluation of the surgical result by an experienced

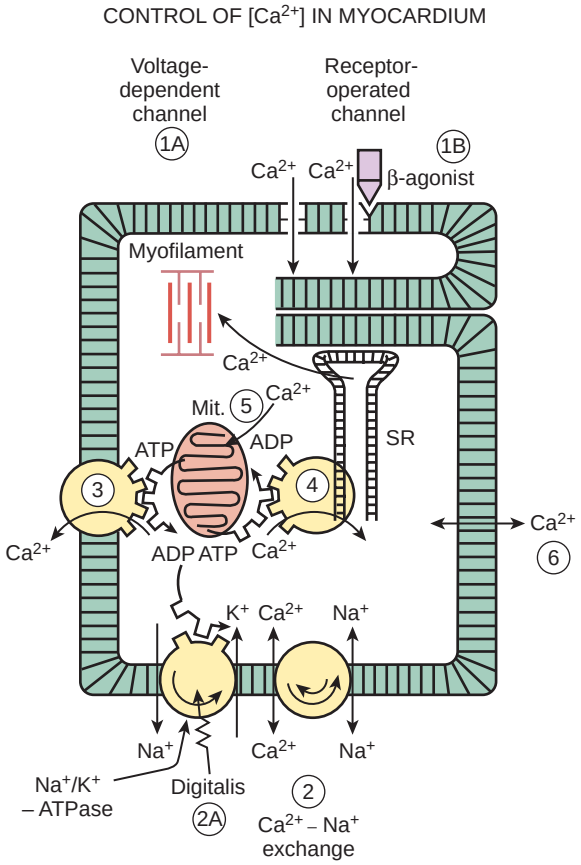


Fig. 21.24 Regulation of cytoplasmic calcium. The diastolic extrusion of calcium *(Ca^{2+})* from the myofilaments occurs at several sites. At two of the most important sites, energy *(ATP)* is required for the active reuptake of calcium by the sarcolemma *(3)* and the SR *(4)*. *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *SR*, sarcoplasmic reticulum. *(From Braunwald E. Mechanisms of action of calcium channel blocking agents.* N Engl J Med. *1982;307:1618.)*

echocardiographer are essential for the success of this procedure.[241–243] In successful cases, the postmyomectomy study shows dramatic septal thinning, widening of the LVOT, and resolution of SAM and the LVOT color mosaic.

As in any disease with diverse diagnostic criteria, it is difficult to compare mortality rates among various series, but perioperative mortality rates for isolated septal myomectomy are less than 2%, although operative risks are greater when combined with other procedures.[244,245] However, clinical studies of predominantly elderly patients reported mortality rates in excess of 15%. Complications other than heart block are uncommon, although more than one-third of patients experience new, clinically insignificant AR.[246] It is unclear whether the new AR poses a long-term risk for these patients from the standpoint of CHF, but it probably warrants the continued use of endocarditis prophylaxis.

Anesthesia Considerations

Priorities in anesthesia management are to avoid aggravating the subaortic obstruction while remaining aware of the derangements in diastolic function that may be somewhat less amenable to direct pharmacologic manipulation (Box 21.3). It is necessary to maintain an appropriate intravascular volume while avoiding direct or reflex increases in contractility or heart rate. The latter goals can be achieved with a deep level of general anesthesia and the associated direct myocardial depression.

Regardless of the specific technique, preservation of an adequate CPP using vasoconstrictors rather than inotropes is necessary to avoid

BOX 21.3 HYPERTROPHIC CARDIOMYOPATHY

- Preload is increased.
- Afterload is increased.
- Goal is myocardial depression.
- Avoid tachycardia, inotropes, and vasodilators.

myocardial ischemia. Heavy premedication is advisable, with a view to avoiding anxiety-induced tachycardia or a reduction in ventricular filling. Chronic β-blockade or calcium channel blockade, or both, should be continued up to and including the day of surgery. These medications should be restarted immediately after surgery, particularly in patients undergoing noncardiac surgery.

Intraoperative monitoring should include an ECG system with the capability of monitoring a V_5 lead and each of the six limb leads. Inspection of lead II may be helpful in the accurate diagnosis of supraventricular and junctional tachyarrhythmias, which may precipitate catastrophic hemodynamic deterioration because of the potential for inadequate ventricular filling resulting from the reduction in diastolic time or loss of the atrial contribution to ventricular filling. The latter may be crucial in patients with significantly reduced diastolic compliance.[132]

Abnormal Q waves have been described on the electrocardiograms of 20% to 50% of patients with HCM.[179] These waves should not raise concern about a previous myocardial infarction; instead, they probably represent accentuation of normal septal depolarization or delay in depolarization of electrophysiologically abnormal cells.[247] Some patients exhibit a short PR interval with initial slurring of the QRS complex, and they may be at increased risk for supraventricular tachyarrhythmias due to preexcitation.[248] Although the specific predisposing factors are unknown, patients with HCM are at increased risk for any type of arrhythmia in the operative setting.[249]

Because of the pronounced abnormalities in left ventricular diastolic compliance, the CVP is likely to be an inaccurate guide to changes in left ventricular volume. However, a CVP catheter is extremely useful for the prompt administration of vasoactive drugs if they become necessary. As in valvular AS, the information provided by insertion of a PAC is worth the small arrhythmogenic risk. The potential for hypovolemia-induced exacerbation of outflow tract obstruction makes it crucial that the clinician have an accurate gauge of intravascular filling. Reduced diastolic compliance means that the PCWP overestimates the patient's true volume status, and a reasonable clinical objective is to maintain the PCWP in the high-normal to elevated range. A PAC with pacing capability is ideal because atrial overdrive pacing can effect immediate hemodynamic improvement in the event of episodes of junctional rhythm (see Chapter 13). The absolute requirement of these patients for an adequate preload cannot be overemphasized because even abrupt positioning changes have resulted in acute hemodynamic deterioration, including acute pulmonary edema.[250]

Intraoperative arrhythmias require aggressive therapy. During cardiac surgery, insertion of venous cannulas may precipitate atrial arrhythmias. Because the resultant hypotension may be severe, the surgeon should cannulate the aorta before atrial manipulation. Supraventricular or junctional tachyarrhythmias may require immediate cardioversion if they precipitate catastrophic degrees of hypotension. Although verapamil is one drug of choice for paroxysmal atrial and junctional tachycardia, it can disastrously worsen the LVOT obstruction if it elicits excessive vasodilation or it is used in the setting of severe hypotension.[235] Cardioversion is preferable when the mean arterial pressure is already very low. The concurrent administration of phenylephrine also is advisable. This drug is typically a low-risk, high-yield choice for the hypotensive patient with HCM. It augments perfusion, may ameliorate the pressure gradient, and often elicits a potentially beneficial vagal reflex when used to treat tachyarrhythmia-induced hypotension.

The inhalation anesthetics commonly are used for patients with HCM. Their dose-dependent myocardial depression is ideal because negative inotropy reduces the degree of SAM-septal contact, which reduces LVOT obstruction. Hypotension is usually the result of underlying hypovolemia, which is potentially exacerbated by anesthetic-induced vasodilation. Inotropes, β-adrenergic agonists, and calcium are contraindicated because they worsen the systolic obstruction and perpetuate the hypotension. In most cases, a beneficial response can be obtained with aggressive replenishment of intravascular volume and concurrent infusion of phenylephrine.

Several investigators have suggested that regional anesthesia, with its potential for accentuating peripheral vasodilation, may be relatively contraindicated in the management of patients with HCM.[251,252] The theoretic constraints are similar to those for patients with valvular AS, and the same clinical caveats apply. If the vascular system is kept appropriately full and "tight" with vasopressors, it is reasonable to consider these techniques in the light of other clinical advantages they can offer the patient. Catheter techniques (eg, continuous spinals, epidurals) may be preferable to the bolus administration of local anesthetics to achieve a finer degree of control of the anesthesia level.[253] There unquestionably is the potential for a cascade of iatrogenic complications if sympatholytic hypotension is treated in a knee-jerk fashion with ephedrine, epinephrine, or a variety of other equally contraindicated β-adrenergic agonists.

Although echocardiography has undoubtedly contributed to an increased frequency of diagnosis of this disease, an occasional patient escapes detection by ultrasound examination in the course of the preoperative workup. When other objective data, including the physical examination, ECG results, and chest radiograph, show only nonspecific abnormalities, it is easy to disregard vague or atypical complaints of chest pain, presyncope, and dyspnea. This is particularly true when the symptoms may reasonably be attributed to the primary condition that brought the patient to surgery (eg, CABG).[254] Other identifiable populations are said to be at high risk for occult HCM. HCM of the elderly has been discussed, and probably only a fraction of these patients arrive in the operating room with a formal diagnosis. However, it is not uncommon for the anesthesiologist to encounter an elderly patient with long-standing systemic hypertension and unexplained episodes of pulmonary congestion for whom the primary physician has prescribed a digitalis preparation.

Anesthesiologists occasionally may be presented with the opportunity to diagnose unsuspected HCM or one of its variants. Intraoperative events that can provoke or accentuate physiologic manifestations of the disease include hypovolemia, tachycardia, spontaneous or manipulative ectopy, and paradoxical responses to vasoactive drugs (eg, inotropes, vasodilators, vasoconstrictors) or anesthetic agents.[254,255] Clues such as these allow the experienced and astute clinician to recognize the phenomenon of dynamic subaortic obstruction when it occurs in less obvious clinical settings.

Aortic Regurgitation

Clinical Features and Natural History

AR may result from an abnormality of the valve itself, bicuspid anatomy, a rheumatic or infectious origin, or in association with any condition producing dilation of the aortic root and leaflet separation. Nonrheumatic valvular diseases commonly resulting in AR include infective endocarditis, trauma, and connective tissue disorders such as Marfan syndrome or cystic medial necrosis of the aortic valve.[56] Aortic dissection from trauma, hypertension, or chronic degenerative processes also can result in dilation of the root and functional incompetence (see Chapter 23).

The natural history of chronic AR is that of a long asymptomatic interval during which the valvular incompetence and secondary ventricular enlargement become progressively more severe.[3,141] When symptoms do appear, they are usually those of CHF, and chest pain, if it occurs, is often nonexertional in origin. The life expectancy for patients with significant disease has historically been about 9 years, and in contrast with AS, the onset of symptoms because of AR does not portend an immediately ominous prognosis.[256,257] In the absence of surgery, early recognition of AR and chronic use of vasodilators prolong the life span for this patient population.[141,258]

A relatively unique and problematic feature of chronic AR is that the severity of symptoms and their duration may correlate poorly with the degree of hemodynamic and contractile impairment.[141,259] The issue in surgical decision making is that many patients can remain asymptomatic, during which time they are undergoing progressive deterioration in myocardial contractility. Noninvasive diagnostic studies (ie, radionuclide cine angiography and two-dimensional and Doppler echocardiographic assessment of response to pharmacologic afterload stress) may facilitate the detection of early derangements in contractile function in relatively asymptomatic patients.[260–262] These findings are important to the cardiologist when considering surgical referral (see Chapters 1 through 3) because patients with depressed preoperative LV function have greater perioperative mortality rates and are at increased risk for persistent postoperative heart failure (HF).[96,263,264]

As in acute MR, the physiology of acute AR is quite different from chronic AR. Common causes include endocarditis, trauma, and acute aortic dissection. Because of a lack of chronic compensation, these patients usually have pulmonary edema and heart failure refractory to optimal medical therapy. Patients are often hypotensive and clinically appear to be on the verge of cardiovascular collapse.

Pathophysiology

Left ventricular volume overload is the pathognomonic feature of chronic AR. The degree of volume overload is determined by the magnitude of the regurgitant flow, which is related to the size of the regurgitant orifice, the aorta-ventricular pressure gradient, and the diastolic time. It has been suggested that the size of the regurgitant aortic orifice is constant and independent of changes in loading conditions.[265] However, in other valvular lesions (eg, AS, MR), the orifice size is not constant and depends on the hemodynamic state. An experimental model of acute AR showed that the regurgitant orifice area could change with increases or decreases in the transvalvular pressure gradient.[266] When AR occurs in the absence of valvular fibrosis or calcification (ie, valve elasticity is preserved), reduction of regurgitant area may be a beneficial effect of afterload reduction.

The hemodynamic effects of changes in heart rate are less straightforward than may be assumed.[267] Theoretically, tachycardia should maximize net forward flow by shortening the regurgitant diastolic time interval. This hypothesis, first offered by Corrigan in 1832, may be the pathophysiologic basis for the seemingly paradoxical observation that patients with AR may tolerate exercise despite having symptoms of pulmonary congestion at rest. Sympathetically mediated vasodilation, increased inotropy, and tachycardia may contribute to the increased CO achieved during isometric exercise in patients with AR.[268] Chronically, similar reflex-induced hemodynamic changes may contribute to the beneficial effects of arteriolar dilators.[269] The peripheral vasculature directly affects regurgitant volume through reflex changes in heart rate, and it can alter volume loading by effects on the diastolic time. It plays a key role in the overall pathophysiology of AR[270,271] (Fig. 21.25).

Despite these observations, the beneficial effects of shortened diastolic time alone may be less clear-cut. Angiographic study of subjects with chronic AR has shown that pacing-induced tachycardia can decrease the SV, LVEDV, and LVEDP and can increase cardiac output,[272] but the ratio of the regurgitant volume to the total SV may remain unchanged. This occurs because tachycardia shortens the diastolic period per stroke but increases the number of strokes per minute, leaving the net diastolic time per minute relatively unchanged. A similar observation has been made in radionuclide studies that demonstrated that tachycardia can increase CO and decrease LVEDV; however, pulmonary arterial pressure (PAP) and PCWP may not change with increasing heart rate.[273] The divergence between the effects of tachycardia on left ventricular volume (ie, decreased) and filling

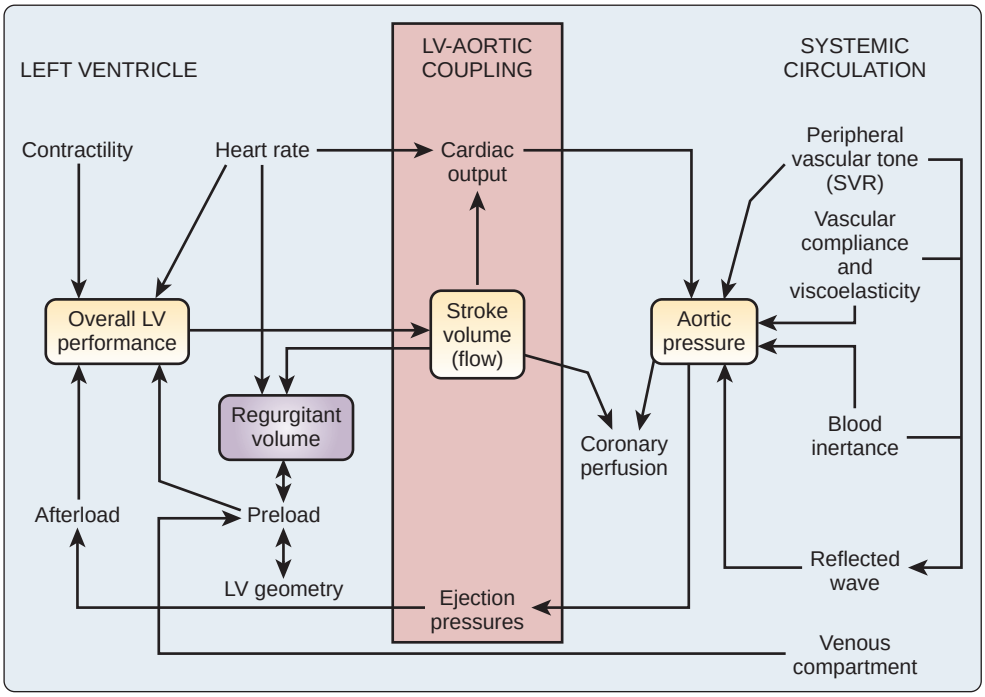


Fig. 21.25 The peripheral circulation plays a pivotal role in supporting left ventricular *(LV)* performance in the face of chronic volume overloading. *SVR*, Systemic vascular resistance. *(From Borow KM, Marcus RH. Aortic regurgitation: the need for an integrated physiologic approach.* J Am Coll Cardiol. *1991;17:898.)*

pressures (ie, unchanged) may reflect the pronounced rightward shift of the left ventricular pressure-volume loop that is characteristic of long-standing AR.

Chronically, AR results in a state of left ventricular volume and pressure overload. Progressive volume overloading from AR increases end-diastolic wall tension (ie, ventricular afterload) and stimulates the serial replication of sarcomeres, producing a pattern of eccentric ventricular hypertrophy.[97,264] In accordance with Laplace's law, dilation of the ventricle increases the systolic wall tension, stimulating some concentric hypertrophy. The result is normalization of the ratio of ventricular wall thickness to cavitary radius.[97] This process of eccentric hypertrophy results in the greatest absolute degrees of cardiomegaly seen in valve disease. EDV may be three to four times normal, and very high COs can be sustained.[274]

Fig. 21.26 shows the pressure-volume loops for acute and chronic AR. In the chronic form, the diastolic pressure-volume curve is shifted far to the right. This permits a tremendous increase in LVEDV with minimal change in filling pressure, a property frequently described as high diastolic compliance.[274] However, animal models of chronic left ventricular volume overloading instead suggest that the entire diastolic pressure-volume curve is shifted to the right (see Fig. 21.8).[11] This accounts for the apparent paradox of high ventricular volumes at relatively low filling pressures.

The parallel shifts of the entire curve relating diastolic pressure and volume are a manifestation of the physiologic process known as *creep*.[4] It refers to the time-dependent increase in dimension that occurs as a result of an applied stress, which in this case is volume overload. Because of the chronic adaptation, left ventricular filling pressures are in the low to normal range and are relatively insensitive to changes in intravascular volume. This is not true of greater filling pressures, for which increases are a reliable guide to volume overload and ventricular distention.

Because the increase in preload is compensated for by ventricular hypertrophy, CO is maintained by the Frank-Starling mechanism, and cardiac failure is not seen despite probable decreases in contractility.[258] There is virtually no isovolumic diastolic phase because the ventricle is filling throughout diastole. The isovolumic phase of systole also is brief

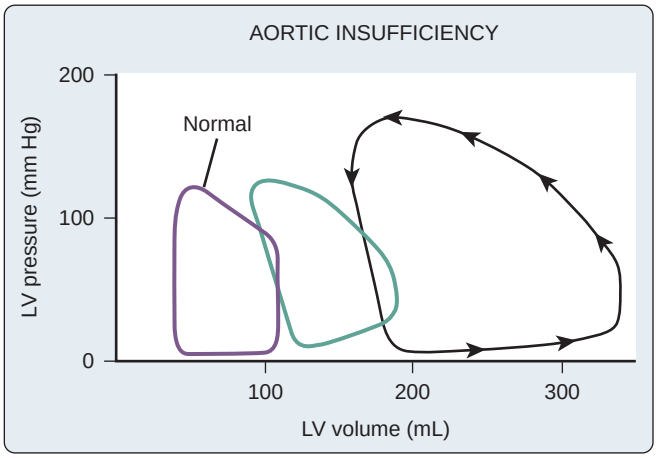


Fig. 21.26 Pressure-volume loop in aortic regurgitation (AR). Acute AR *(green loop)*; chronic AR *(black loop)*. *LV*, Left ventricular. *(Modified from Jackson JM, Thomas SJ, Lowenstein E. Anesthetic management of patients with valvular heart disease.* Semin Anesth. *1982;1:239.)*

because of the low aortic diastolic pressure. Minimal impedance to the forward ejection of a large SV allows performance of maximal myocardial work at a minimum of oxygen consumption. Eventually, however, progressive volume overload increases ventricular EDV to the point that compensatory hypertrophy is no longer sufficient to compensate, and a decline in systolic function occurs. As systolic function declines, the end-systolic dimension increases further, left ventricular wall stress increases, and left ventricular function is further compromised by the excessive ventricular afterload. At this point, the decline of ventricular function is progressive and can be quite rapid. As is shown in Fig. 21.27A, in the patient with compensated AR, the eccentrically dilated ventricle maintains its SV and EF by using preload reserve; wall stress is only slightly increased. In Fig. 21.27B, the limit of preload reserve has been reached and ventricular dysfunction has shifted the end-systolic wall stress relationship to the right. As a result of the higher

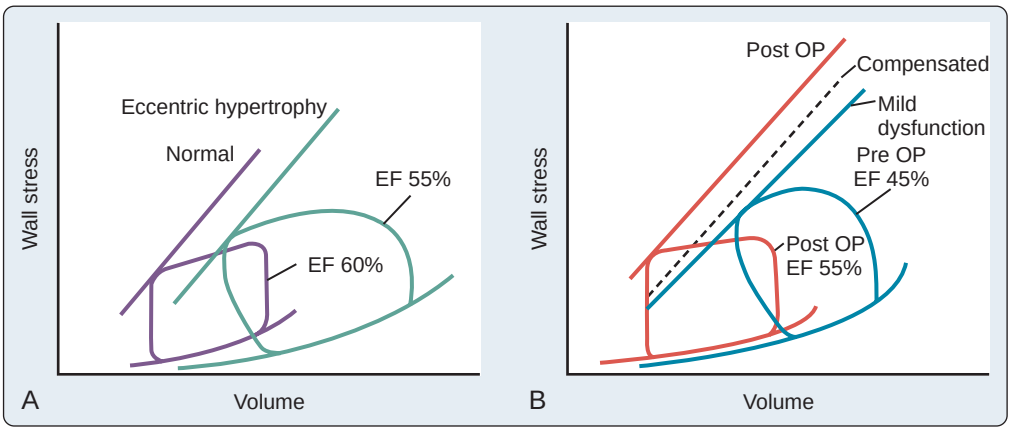


Fig. 21.27 Adaptation to volume overload. (A) Stress-volume curves and the linear end-systolic stress-volume relationship are shifted to the right in compensated aortic regurgitation compared with normal values. The stroke volume and ejection fraction *(EF)* are maintained despite slightly increased systolic wall stress. B, The same associations in a hypothetical patient with mild left ventricular dysfunction as evidenced by rightward shift of the end-systolic wall stress–volume relationship. Exhaustion of preload reserve causes wall stress to increase, resulting in reciprocal declines in the stroke volume and the EF. Valve replacement corrects afterload mismatch, allowing the end-diastolic and end-systolic volume relationships to shift to the left. Lower wall stress allows the EF to return to normal. *Post OP*, Postoperative; *Pre OP*, preoperative. *(From Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy.* J Am Coll Cardiol. *1985;5:811.)*

wall stress, the SV and EF inevitably decline. In patients in whom the EF has become less than 25% or the end-systolic diameter larger than 60 mm, irreversible myocardial changes are likely to have occurred.[141]

The primary determinants of $M\dot{V}O_2$ (ie, contractility and wall tension) usually are not significantly increased with chronic AR, although calculated myocardial work may be twice normal. The $M\dot{V}O_2$ may be only minimally increased because the greater proportion of myocardial work is spent in the energy-efficient process of fiber shortening, with little increase occurring in oxygen-consuming tension development.[275]

Despite the relatively normal $M\dot{V}O_2$, angina can occur in one third of patients with severe AR, even in the absence of CAD.[276] Patients with chronic AR may be at risk for myocardial ischemia caused by hypertrophy-induced abnormalities of the coronary circulation. The increase in total myocardial mass can increase baseline $M\dot{V}O_2$, and there is evidence that total coronary blood flow, although increased, fails to keep pace with the increase in myocardial mass. Evidence suggests that the insidious development of contractile dysfunction may in part have an ischemic basis.[277]

Despite these rather favorable considerations in terms of myocardial energetics, an increase in $M\dot{V}O_2$ may pose a threat to the patient with chronic AR because of decreased coronary vascular reserve.[278] Although this phenomenon has been more thoroughly documented in patients with chronic pressure-induced hypertrophy, some studies indicate that the coronary vascular reserve is similarly compromised in patients with left ventricular volume overload.[279,280] The process of hypertrophy may be a double-edged sword from the standpoint of myocardial oxygen balance. Hypertrophy minimizes oxygen consumption as measured by wall stress, but increases basal $M\dot{V}O_2$ and may elicit derangements in the quality or quantity of the coronary vasculature.

Intraoperatively, patients with chronic AR may be at risk for acute ischemia with episodes of significant bradycardia. As bradycardia prolongs diastolic time, it increases regurgitant flow, and left ventricular diastolic pressure and wall tension increase rapidly. Simultaneously, the CPP is decreased as aortic runoff occurs during diastole and diastolic ventricular pressure is increased.[281] Under these conditions, myocardial perfusion pressure may be insufficient. Clinically, very rapid decompensation can occur. The ischemic ventricle can dilate rapidly such that progressively increased end-systolic dimensions are seen, and ischemia and ventricular failure become a positive feedback loop.

Surgical Decision Making

An accurate assessment of contractility is crucial to surgical decision making, because the clinical history of chronic AR may be an unreliable index of ventricular function. Asymptomatic patients may have ventricular dysfunction, whereas symptomatic patients may be free of myocardial depression. A variety of prognostic indicators have been used to identify early ventricular dysfunction as a trigger for surgical intervention. Clinical status, such as exercise capacity and New York Heart Association (NYHA) class, and noninvasive and invasive laboratory tests have been used. Hemodynamic parameters such as the end-systolic stress-volume relationship and estimates of the left ventricular contractile state have been evaluated as predictors of worsening left ventricular function.

Although ejection phase indices (eg, EF) are most familiar to anesthesiologists, they are inherently unreliable for quantifying ventricular function in the setting of chronic volume overloading, because the Starling mechanism continues to support increases in the SV long after the onset of intrinsic myocardial depression. Left ventricular dilation, compensatory hypertrophy, and minimal afterload may normalize the EF, even though contractility is significantly depressed.[258] Preload can be exquisitely sensitive to changes in heart rate and systemic vascular tone. Ventricular performance therefore may not be adequately reflected by the EF.[282,283] The often-reported regurgitant volume and regurgitant fraction are similarly rate and load dependent, and they may correlate poorly with the underlying inotropic state.[284]

A variety of end-systolic indices have been examined in chronic AR, and they provide a more load-independent assessment of the inotropic state. Although the left ventricular end-systolic volume (LVESV) is preload independent, it does vary with myocardial contractility and afterload. An increased ESV may reflect a depressed inotropic state, or it may increase because of an increased left ventricular afterload resulting from increased chamber size or pressure.[282] There also is evidence that the relative load independence of the LVESV is limited when ventricular hypertrophy is primarily eccentric.[25] However, with long-standing volume overload, virtually all studies have found that an increased end-systolic dimension correlates with a poor prognosis and a significantly depressed contractile state.[261,285]

When valve surgery is performed after ventricular decompensation has occurred, the immediate and long-term results are marginal. Much of the increased mortality rate is a function of postoperative deaths

from heart failure.[264,286] When valve surgery occurs before significant ventricular decompensation, ventricular recovery is remarkable, with remodeling and a reduction in left ventricular size beginning as early as 2 weeks after surgery.[141,264] Because delays in surgical intervention can be catastrophic and the response to surgery is so good, there is evidence of a shift toward earlier valve replacement, and surgery in relatively asymptomatic patients has been advocated.[264]

Based on a review of the published literature, the ACC and AHA have provided practice guidelines for surgical intervention in chronic AR.[141] Valve surgery is recommended for asymptomatic patients with left ventricular systolic dysfunction. Surgery also should be considered if ventricular dilation has occurred in the asymptomatic patient, even if the EF is normal. In patients who are symptomatic but have normal ventricular function, the ACC and AHA recommend further evaluation for an unrelated cause and observation. In these cases, serial echocardiographic assessment is appropriate. Symptomatic patients with left ventricular dysfunction should undergo surgery.[13]

Acute Aortic Regurgitation

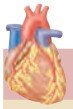
In acute AR, sudden diastolic volume overload of a nonadapted LV results in a precipitous increase in the EDP because the ventricle is operating on the steepest portion of the diastolic pressure-volume curve (see Fig. 21.26).[287] In severe acute AR, the LVEDP can equilibrate with aortic diastolic pressure and exceed the left atrial pressure in late diastole. This may be sufficient to cause closure of the mitral valve before atrial systole.[288] This is an important echocardiographic finding indicative of severe AR.[289] Although this phenomenon initially shields the pulmonary capillaries from the full force of the dramatically increased LVEDP, the protection may be short lived.[290] Severe left ventricular distention often follows and produces mitral annular enlargement and functional MR.

The inevitable decline in SV in acute decompensating AR elicits a reflex sympathetic response, making tachycardia and a high SVR common. Moderate tachycardia beneficially shortens the regurgitant time without reducing the transmitral filling volume.[291] Vasoconstriction, however, preserves CPP at the expense of increasing the aortic-ventricular gradient and regurgitation.

Patients with acute AR may be at greater risk for myocardial ischemia. As with chronic AR and bradycardia, coronary perfusion may be compromised by the combination of a low diastolic arterial pressure and the precipitously increased LVEDP. Narrowing of CPP may be so severe that the phasic epicardial blood flow may change to a predominantly systolic pattern with severe acute AR.[292] Dissection of the coronary ostia is rare but frequently causes the death of patients with acute AR. In addition to the structural impediment to myocardial oxygen delivery, catastrophic hypotension and high LVEDP combine to cause accentuated ischemia and ventricular dilation. Immediate surgical correction is the only hope for salvaging these patients, who often prove refractory to inotropes and vasodilators. Attempts at stabilizing the ischemic component of their injury with an intraaortic balloon are usually contraindicated because augmenting the diastolic pressure worsens regurgitation.

Acute AR most commonly results from infective endocarditis or aortic dissection, and intraoperative transesophageal echocardiography (TEE) has assumed increasing importance in the diagnosis of acute AR and in decisions regarding its surgical management.[293] Transesophageal echocardiographic studies are highly sensitive and specific for the diagnosis of infective endocarditis and are significantly more sensitive than transthoracic echocardiography.[294] TEE is particularly useful in the diagnosis of abscesses associated with endocarditis[295] and may detect previously unsuspected abnormalities.

Although an area of active investigation, there is currently no completely satisfactory noninvasive method for quantifying the severity of AR. Premature closure of the mitral valve, determination of the pressure half-time of AR, and color-flow estimation of the regurgitant jet's width and its size in relation to the LVOT are commonly described techniques.[296–298] (see Chapters 14, 15, and 23)



BOX 21.4 AORTIC REGURGITATION

- Preload is increased.
- Afterload is decreased.
- Goal is augmentation of forward flow.
- Avoid bradycardia.

Anesthesia Considerations

Intraoperative monitoring should include an ECG system for monitoring a lateral precordial lead because ischemia is a potential hazard (Box 21.4). For most valvular procedures, a PAC provides useful information. A PAC allows determination of basal filling pressures and CO, which is particularly useful in chronic AR given the potential unreliability of the clinical history and EF.

Equally important is the ability to accurately monitor ventricular preload and CO response to pharmacologic interventions. The aggressive use of vasodilators often is appropriate therapy perioperatively for the failing ventricle, but their use can compromise the preload to which the ventricle has chronically adjusted. Concurrent preload augmentation, guided by the diastolic PAP or PCWP, may be crucial to optimize CO when afterload is pharmacologically manipulated[299–301] (see Chapters 11, 13, 36, and 38).

The other requirement for a PAC is to allow for pacing when it is anticipated. The deleterious effects of significant bradycardia in AR have been described. In patients who arrive in the operating room with heart rates less than 70 beats per minute or patients for whom rapid epicardial pacing may be difficult to establish (eg, reoperations), placement of a pacing wire probably is indicated. Typically, only a ventricular wire is appropriate. It is more reliable than atrial pacing, and in AR, the atrial contribution to ventricular diastolic volume usually is not essential. Capturing the ventricle with a PAC-based, transvenous wire can be difficult because of the very large ventricular cavity size in patients with chronic AR.

Because patients with AR may have widely different degrees of myocardial dysfunction, anesthesia management must be appropriately individualized. For cardiac or noncardiac surgery, the hemodynamic goals are a mild tachycardia, positive inotropic state, and controlled reduction in SVR. For cardiac surgery, dopamine or dobutamine, pancuronium, ketamine, and nitroprusside infusions are excellent choices. For the patient with acute AR, the goals are the same, but urgency must be stressed. It is essential to rapidly reduce end-diastolic and end-systolic ventricular volumes with the very aggressive use of inotropes (eg, epinephrine) and vasodilators. There is sometimes concern that inotropes may exacerbate the root dissection in acute AR by increasing the shear force on the aortic wall. Despite this theoretic concern, positive inotropes should not be withheld from the patient who deteriorates in the operating room because they may provide the precious additional minutes of hemodynamic stability needed to get on CPB.

In acute and chronic forms of AR, serial measurements of CO can indicate that ventricular size and CO have been optimized, regardless of the systemic pressure. TEE is useful to look at ventricular size, but probably maximizing CO under these conditions gets closer to the therapeutic goal than looking at ventricular size alone. With acute AR and premature closure of the mitral valve, PAPs may grossly underestimate the LVEDP, which continues to increase under the influence of the diastolic regurgitant jet from the aorta. For noncardiac surgery in the patient with AR, there are advantages to epidural or other regional techniques when appropriate. Epidural anesthesia usually is preferable to spinal techniques, in which more precipitous declines in SVR can occur.

Predicting the response of the patient with AR to anesthesia can be difficult if the contractile state of the ventricle is unknown. Although reductions in functional status or EF are broad indicators of poorer outcomes, examining the medical history for *serial* measurements of

EF or ventricular ESVs may be most useful. Because patients with chronic AR are subject to a rapid, self-perpetuating decline in ventricular performance, demonstration of recent decreases in EF or increases in ventricular size may be the best indication of a challenging intraoperative course.

A few other practical points in AR surgery bear comment. The early and late phases of CPB can be a problem, particularly in reoperations. Before cross-clamp placement, the ventricle is at risk for distention if it is not ejecting or being vented. If the ventricle dilates with AR during CPB, the intraventricular pressures may equilibrate with the aortic root pressures. Under these conditions, there is no coronary perfusion, and the ventricle may dilate rapidly and become profoundly ischemic. This can occur before cross-clamp placement with bradycardia, ventricular fibrillation, or tachycardia or with a rapid supraventricular rhythm that compromises organized mechanical activity. Correcting the rhythm, pacing, cross-clamping the aorta, or venting the ventricle addresses the problem.

The problem also can occur in cardiac surgery for conditions other than AR. In patients with unknown or uncorrected AR, removal of the cross-clamp causes the same ventricular dilation and ischemia if the rhythm and ejection are not rapidly established. Ventricular venting or pacing may be essential until an organized, mechanically efficient rhythm is established. This problem must be considered in patients referred for CABG alone, in those with mild or moderate AR not having AVR, and in patients for whom intraoperative TEE is not used.

Mitral Regurgitation

Clinical Features and Natural History

Unlike mitral stenosis (MS), which is usually the result of rheumatic valve disease, MR may result from a variety of disease processes that affect the valve leaflets, chordae tendineae, papillary muscles, valve annulus, or LV. MR can be classified as organic or functional. Organic MR describes diseases that result in distortion, disruption, or destruction of the mitral leaflets or chordal structures. In Western countries, degenerative processes that lead to leaflet prolapse with or without chordal rupture are the most common cause of MR.[300] Other causes of organic MR include infective endocarditis, mitral annular calcification, rheumatic valve disease, and connective tissue disorders such as Marfan or Ehlers-Danlos syndrome. Much less common causes of organic MR include congenital mitral valve clefts, diet-drug or ergotamine toxicity, and carcinoid valve disease with metabolically active pulmonary tumors or right-to-left intracardiac shunting.[302]

Mitral valve prolapse (MVP) is a common (2.4%) disorder with a strong hereditary component. Several genes play a pivotal role in heart valve formation, including those for the calcineurin catalytic and regulatory subunits, WNT/beta-catenin signaling pathways, fibroblast growth factor 4 *(FGF4)*, a homeobox gene *(SOX4)*, and the downstream modulator of transforming growth factor-β superfamily signaling *(SMAD6)*. Genotypic linkage was found to chromosomes 11, 13, and 16. The finding of a mutation in familial MVP not related to connective tissue syndromes, an X-linked filament A mutation, suggests that MVP may be the final common outcome of multiple genetic defects.

The term *functional MR* describes MR that occurs despite structurally normal leaflets and chordae tendineae. Resulting from altered function or geometry of the LV or mitral annulus, functional MR often occurs in the setting of ischemic heart disease, and the term *ischemic MR* is sometimes used interchangeably with *functional MR*. However, the functional form can occur in patients without demonstrable CAD, such as those with idiopathic dilated cardiomyopathy and mitral annular dilation. The term *ischemic MR* probably best applies to functional cases with a known ischemic cause. Rupture of a papillary muscle with acute, severe MR is somewhat more difficult to classify. Although usually a sequela of acute myocardial infarction (AMI) with normal leaflets and chordae, there is an obvious anatomic disruption of the mitral apparatus.

The natural history of MR varies because it can be caused by a wide variety of disease processes.[302] Even among patients with acute-onset disease, the clinical course depends on the mechanism of regurgitation and the response to treatment. For instance, patients with acute, severe MR caused by a ruptured papillary muscle have a dismal outcome without surgery.[302] However, the clinical course of acute MR caused by endocarditis can be favorable if the patient responds well to antibiotic therapy.[302] Although those with chronic MR usually enter an initial, often asymptomatic, compensated phase, the time course for progression to left ventricular dysfunction and symptomatic heart failure is unpredictable.[302] The literature reflects the wide variation in the natural history of MR, with 5-year survival rates for patients with MR of 27% to 97%.[303] Selection bias, small study populations, and poorly defined degrees of MR likely explain these discrepancies.[304]

Later studies better define the clinical course of certain subgroups of patients with MR. For instance, Ling and associates[305] examined the natural history of patients with MR because of flail leaflets. Among this group, the investigators observed an annual mortality rate of 6.3%, with a combined rate of death or surgery of 90% within a 10-year period.[305] Patients with flail mitral valve leaflets also are at increased risk for sudden death.[306] Grigioni and colleagues[306] reported a 1.8% per year rate of sudden death among patients with flail mitral leaflets who were being treated medically. The rate of sudden death diminished after surgical intervention in this population.[306]

The application of quantitative Doppler echocardiography to the prospective study of MR has allowed researchers to document the progressive nature of the condition. Enriquez-Sarano and coworkers[307] found that on average, the regurgitant volume increased 7.5 mL and the effective regurgitant orifice increased 5.9 mm^2 each year. However, there was significant variation in the rate of progression among patients. Rapid progression of severity occurred among patients who developed flail leaflets, but MR regressed in 11% of those studied.[307]

Pathophysiology

MR causes left ventricular volume overload. The regurgitant volume combines with the normal left atrial volume and returns to the LV during each diastolic period. The increased preload leads to increased sarcomere stretch and, in the initial phases of the disease process, augmentation of LV ejection performance by the Frank-Starling mechanism. Systolic ejection into the relatively low-pressure left atrium (LA) further enhances the contractile appearance of the LV.

The clinical presentation of patients with MR depends on the pathophysiology of the specific condition, including the mechanism, severity, and acuity of the disease. In cases of acute, severe MR, such as in patients with a ruptured papillary muscle after AMI, the sudden increase in preload enhances left ventricular contractility by the Frank-Starling mechanism. Despite the increased preload, the size of the LV is initially normal. Normal left ventricular size combined with the ability to eject into a low-pressure circuit (ie, the LA) results in decreased afterload in the acute setting. The measured LVEF in cases of sudden, severe MR may approach 75%, although forward SV is reduced.[302] However, because the LA has not yet dilated in response to the large regurgitant volume, left atrial pressure increases acutely and may lead to pulmonary vascular congestion, pulmonary edema, and dyspnea.[302]

Many patients with MR, particularly those whose valvular incompetence develops more slowly, may enter a chronic, compensated phase. In this phase, chronic volume overload triggers left ventricular cavity enlargement by promoting eccentric hypertrophy (see Fig. 21.15). Increased preload continues to augment left ventricular systolic performance. At the same time, the LA dilates in response to the ongoing regurgitant volume. Although left atrial dilation maintains a low-pressure circuit that facilitates left ventricular systolic ejection, the increased radius of the left ventricular cavity leads to increased wall tension according to Laplace's law.

Unlike the case of sudden, acute MR, which is characterized by normal left ventricular size and reduced afterload, the afterload remains in the normal range in the chronic, compensated phase of

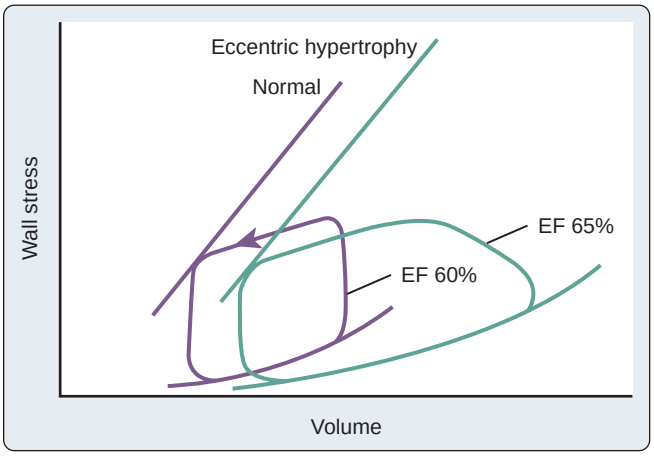


Fig. 21.28 Volume overload with mitral regurgitation (MR). As in volume overloading from aortic regurgitation, wall stress–volume loops of the eccentrically hypertrophied left ventricle are shifted to the right. However, in chronic MR, retrograde ejection into the low-pressure left atrium minimizes ventricular wall stress, supporting the ejection fraction *(EF). (From Ross J Jr. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy.* J Am Coll Cardiol. *1985;5:811.)*

MR.[308] The changes seen in chronic, compensated MR are represented graphically in Fig. 21.28. The isovolumic contraction phase is shortened as the blood is ejected into the low-pressure LA early in the cycle of ventricular systole. Because the dilated, compliant LV accepts increased diastolic volumes at low or normal filling pressures, some physicians think that left ventricular diastolic function is enhanced in patients with chronic MR.[308] Whereas dilation of the left heart chambers permits left ventricular filling at low or normal pressures, chamber enlargement progressively dilates the mitral annulus, potentially increasing the effective regurgitant orifice and regurgitant volume over time. Patients may tolerate the phase of chronic, compensated MR for many years because increased preload maintains left ventricular ejection performance. If symptoms develop during this time, they often are related to diminished forward CO because the regurgitant fraction may exceed 50%. Instead of dyspnea or signs of pulmonary congestion, fatigue and weakness predominate.

With the eventual decline in left ventricular systolic function, patients enter a decompensated phase. Progressive left ventricular dilation increases wall stress and afterload, causing further deterioration in left ventricular performance,[302] mitral annular dilation, and worsening of the MR. Left ventricular end-systolic pressure increases. The increased left ventricular filling pressures result in increased left atrial pressures and, given time, pulmonary vascular congestion, pulmonary hypertension, and right ventricular dysfunction. In addition to fatigue and weakness, patients with decompensated, chronic MR also may report dyspnea and orthopnea. It is difficult to predict when a patient with MR is likely to decompensate clinically. Progression of disease in any patient depends on the underlying cause of MR, its severity, the response of the LV to volume overload, and possibly the effect of medical management.[302,309]

Assessment of left ventricular function in patients with MR is controversial but critically important for clinical decision making.[303] As in AR, the altered loading conditions that characterize MR confound traditional, load-dependent measures of left ventricular systolic function such as EF. Although numerous methods of assessing left ventricular function have been proposed, no consensus exists.[303] Despite its limitations, EF remains the most studied variable of left ventricular function in patients with MR and the most predictive of clinical outcome. For instance, preoperative EF is the most important prognostic factor for long-term survival after surgery for MR.[310] Preoperative EF also predicts postoperative EF and the occurrence of CHF after the surgical correction of MR.[311,312]

Because of the combination of increased preload and the ability to eject into the low-pressure LA, a normally functioning LV should display an increased EF in the setting of significant MR. Conversely, an EF considered normal in a patient with competent valves may represent diminished left ventricular function in the setting of MR. In patients with severe MR, an EF in the range of 50% to 60% likely represents significant left ventricular dysfunction and is an indication for surgery.[141] Enriquez-Sarano and colleagues[310] reported that the postoperative survival rate after mitral repair or replacement declines after the preoperative EF decreases to less than 60%.

Several studies provide insight into the origin of left ventricular dysfunction in the setting of MR. In animal models of the disease, myocardial mass accumulates mainly by a decrease in the natural degradation of cellular elements, rather than by an increased rate of protein synthesis.[313–315] In contrast, myocardial protein synthesis increases within hours of the creation of simulated AS and left ventricular pressure overload.[316] Histologic preparations from animals with experimental MR and left ventricular dysfunction show a 35% reduction in contractile elements within individual myocytes.[317]

Examination of pressure-volume loops from patients with AS and MR is insightful (see Figs. 21.13 and 21.27). If the area contained within each loop is examined, it can be seen that this area, or stroke work, is similar for the two disease states. However, patients with AS usually display a greater degree of myocardial hypertrophy compared with patients with MR. Stroke work per gram of myocardium is greater in patients with MR, a finding that also may explain left ventricular dysfunction in this patient population.[308]

Ischemic Mitral Regurgitation

Ischemic MR represents MR occurring in the setting of ischemic heart disease in patients without significant abnormalities of the valve leaflets or chordal structures. Although some clinicians use the terms *ischemic MR* and *functional MR* interchangeably, ischemic MR more accurately describes cases of functional MR that occur in the setting of CAD. Papillary muscle rupture, which is almost always a sequela of AMI, also may be classified as ischemic MR, although a clear organic defect of the mitral apparatus exists.

Clinicians are increasingly recognizing the importance of ischemic MR because it is common. The incidence rate of MR after AMI as detected by echocardiography ranges from 39% to 73%.[309] Echocardiographic studies also demonstrate that in 13% to 29% of cases, the ischemic MR is at least moderate in severity.[309] Ischemic MR also portends a worse clinical outcome. For instance, patients with ischemic MR after AMI have a twofold to sixfold increase in cardiovascular mortality rates in the first year after the ischemic event.[318] Patients with severe ischemic MR have a 1-year mortality rate that approaches 50%.[319]

In evaluating patients with MR presumed to be of ischemic origin, clinicians should attempt to identify the severity of the regurgitation, the time of onset, and the likely mechanism of valvular incompetence because these factors influence prognosis and treatment. For instance, patients with mild ischemic MR in the early phase of an AMI rarely experience hemodynamic sequelae from mitral leakage, whereas those with ischemic rupture of a papillary muscle often have acute CHF and have a poor prognosis without surgical intervention.

Investigators have identified patient characteristics associated with an increased incidence of ischemic MR. Patients with advanced age, inferior or posterior AMI, spherical left ventricular geometry, and multivessel CAD tend to have greater rates of ischemic MR.[309,320] Other factors associated with increased rates of ischemic MR include left atrial enlargement, mitral annular dilatation, and decreased EF.[309] Frank rupture of a papillary muscle, which occurs in 1% of AMI cases, usually involves the posteromedial papillary muscle because its blood supply is derived from a single coronary artery.

Understanding of the pathophysiologic basis of ischemic MR continues to evolve. Early investigators proposed ischemic papillary muscle dysfunction as a primary cause of ischemic MR.[321–323] Later studies

indicated that isolated ischemia of one or both papillary muscles did not cause significant MR.[324–327] Instead, ischemia of the papillary muscle and the adjacent myocardium is necessary to produce ischemic MR.[309,324,326,327] Myocardial ischemia may result in focal or global left ventricular bulging and, with time, ventricular remodeling to a more spherical shape. Geometric changes cause outward migration of the papillary muscles. The finding most strongly correlated with chronic ischemic MR is outward papillary muscle displacement.[309,328] When the papillary muscles are displaced outward, the point of mitral leaflet coaptation moves apically and away from the mitral annulus, resulting in the appearance of valve tenting.

Besides outward bulging of the LV, scarring and retraction of the papillary muscles may produce mitral leaflet tethering, with the net effect of incomplete leaflet coaptation and valvular incompetence. Some investigators think that papillary muscle dysfunction may reduce the degree of ischemic MR in certain patients.[329,330] Komeda and associates[330] suggested that reduced contractility of the papillary muscles might counteract the tethering effect of ischemic myocardium, allowing leaflet coaptation to occur closer to the mitral annulus.

An additional potential mechanism of ischemic MR is decreased contractility of the posterior mitral annulus. During systole, annular contraction reduces the mitral orifice area by 25%.[331–333] Because the anterior portion of the mitral annulus is more fibrous, posterior annular contraction plays a greater role in reducing the size of the mitral orifice. Loss of posterior annular contraction may contribute to MR in the setting of myocardial ischemia.

The clinical approach to ischemic MR depends on its underlying mechanism. Timely surgical intervention often is warranted in cases of papillary muscle rupture. For patients with an intact mitral apparatus who have ischemic MR in the setting of AMI, early reperfusion therapy improves regional and global left ventricular function, reduces ventricular dilation, and decreases the likelihood of adverse remodeling and associated papillary muscle displacement.[329,334–337] The resultant improvements in ventricular function and geometry combine to reduce the incidence of ischemic MR.

Clinicians often prescribe angiotensin-converting enzyme inhibitors to patients with ischemic heart disease. Chronic angiotensin-converting enzyme inhibitor therapy may decrease the incidence and severity of ischemic MR by preventing left ventricular remodeling, although data to support this theory are lacking.[329]

Assessment of Mitral Regurgitation

Clinicians may suspect MR on the basis of current symptoms, medical history, or findings on physical examination. Echocardiography with the capability of two-dimensional and Doppler (including color-flow) imaging is the diagnostic modality of choice for assessment of MR. Transthoracic echocardiography (TTE) is readily available in most areas, is noninvasive, and provides detailed information about the mechanism of MR, its severity, and its impact on cardiac chamber size and function. Additional information available from TTE includes calculation of right ventricular systolic pressure based on the peak velocity of the tricuspid regurgitant signal and an estimate of right atrial pressure. Whenever possible, echocardiographers should attempt to provide a quantitative assessment of MR severity.

Techniques that allow the determination of effective regurgitant orifice, regurgitant volume, or regurgitant fraction include the proximal isovelocity surface area (PISA) method and the continuity equation. Echocardiographic findings such as pulmonary vein systolic flow reversals suggest severe MR, and they should be reported. Assessment of the size of the regurgitant jet in the LA may provide a gross estimation of MR severity, but is limited by factors such as left atrial size and pressure, machine settings such as color-flow gain and aliasing velocity, and the orientation of the regurgitant jet itself. Eccentric regurgitant jets propagating along the wall of the LA often appear smaller than a centrally directed jet of equal severity.

When TTE is suboptimal, patients may be referred for TEE. Because of the proximity of the transducer to the mitral valve, TEE often produces superior images of the mitral valve. When performing intraoperative TEE examinations, anesthesiologists should recall that altered loading conditions, such as anesthesia-induced decreases in SVR, may favor forward CO and diminish the observed amount of MR. The echocardiographic evaluation of the mitral valve is discussed in Chapters 1 and 14 through 16.

Cardiac catheterization with left ventriculography may also be used to evaluate MR. This invasive procedure often is reserved for cases in which the echocardiographic data are suboptimal, conflicting, or discordant with the clinical findings.[302] Assessment of severity by ventriculography requires analysis of the amount of contrast material that enters the LA after injection into the LV. However, the amount of contrast material appearing in the LA depends on the severity of MR, the left atrial volume, the catheter position, and the rate of contrast injection.[302] Right-heart catheterization may or may not demonstrate v waves in patients with significant MR. A high degree of left atrial compliance makes the appearance of prominent v waves less likely (see Chapter 3).

Other diagnostic tests commonly obtained for patients with MR include an electrocardiogram and chest radiograph. ECG findings such as AF, left atrial enlargement, and ST-segment abnormalities may be observed in patients with MR, but they are not specific.[301] Similarly, chest radiographs may identify enlargement of the left heart chambers and pulmonary vascular congestion, but the findings are not specific for MR.

Surgical Decision Making

The surgical approach to MR has evolved as its pathophysiology has been clarified. High operative mortality rates associated with the surgical correction of MR in the 1980s led many clinicians to treat patients conservatively.[303,304,338] Because favorable loading conditions and high left atrial compliance allow patients with significant MR to remain asymptomatic for long periods, it is likely that many patients did not undergo surgery until the onset of disabling symptoms. More severe preoperative symptoms are associated with a lower EF and a greater incidence of postoperative CHF.[304,311,312] Historically, poor outcomes after surgery for MR might have occurred because clinicians did not appreciate the true degree of left ventricular dysfunction at the time of surgery in symptomatic patients. An EF of less than 60% in the setting of severe MR represents significant left ventricular dysfunction and predicts a worse outcome with surgery or medical management.[305,310]

Surgical techniques common in the 1980s probably also contributed to unfavorable postoperative outcomes. For instance, although the mechanisms are incompletely understood, resection of the subvalvular apparatus contributes to decreased left ventricular systolic performance after mitral valve replacement.[339] In part because of improved surgical techniques, the operative mortality rate for patients with organic MR who are younger than 75 years is about 1% in some centers.[310] Besides preservation of the subvalvular apparatus, valve repair is another surgical technique associated with improved postoperative outcome.[304,340] Although not applicable to all patients, such as those with advanced rheumatic disease, the popularity of valve repairs continues to grow.

Studies indicate numerous benefits associated with mitral repair. For instance, after accounting for baseline characteristics, patients who undergo mitral repair instead of replacement have lower operative mortality rates and longer survival times, largely because of improved postoperative left ventricular function.[304,340] The survival benefit that accompanies valve repair also is observed among patients undergoing combined valve and CABG surgery.[340]

Valve repair does not increase the likelihood of reoperation compared with replacement.[340] Although originally used most often for posterior leaflet disease, surgeons now routinely repair anterior mitral leaflets with good success.[341] When repairing anterior leaflet prolapse, surgeons may insert artificial chordae.[342,343] The approach to flail or prolapsing posterior mitral leaflet segments often involves resection of a portion of the leaflet.[343] In addition to resecting a portion of the

leaflet and plicating the redundant tissue, an annuloplasty ring often is placed to reduce mitral orifice size and return the annulus to a more anatomic shape.[343] Some surgeons favor a flexible, partial, posterior annuloplasty band, which may allow improved systolic contraction of the posterior annulus and better postoperative left ventricular function.[332,343,344]

Timely and appropriate surgical referral helps improve the perioperative outcome of patients with MR. To appropriately refer patients for surgery, clinicians should have an understanding of the factors that influence surgical risk in this population.[303] Those that correlate best with increased operative risk in patients with significant MR include age older than 75 years, severe preoperative symptoms of CHF, and concomitant CAD.[310,345,346] Although they represent a high-risk group, patients with severe MR and symptoms of heart failure should be referred for surgery because valve repair or replacement offers a survival advantage compared with medical management.[303,305] Similarly, although perioperative risk remains increased, patients with evidence of left ventricular dysfunction, such as an EF less than 60% or an end-systolic left ventricular diameter greater than 45 mm, should be referred for surgery to prevent further, possibly irreversible deterioration in ventricular performance.[141,303] Asymptomatic patients without evidence of left ventricular dysfunction also should be considered for surgery if conditions such as AF, ventricular tachycardia, or pulmonary hypertension are identified or the effective regurgitant orifice is greater than 40 mm.[2,141,303] Institutional experience, particularly with techniques such as valve repair, is an important consideration for clinicians contemplating early surgical referral.[303]

Minimally Invasive Mitral Valve Surgery

Beginning in the mid-1990s, several groups adopted a minimally invasive approach to mitral valve repair.[347,348] Initially performed through lower ministernotomies or right parasternal incisions, aortic cannulation for CPB was accomplished through the chest. The venous cannula was placed in the femoral vein[347] or the right atrium.[348] Standard surgical repair techniques were used.

For a series of 707 minimally invasive mitral valve repairs, McClure and coworkers[347] reported an operative mortality rate of 0.4% and an incidence rate of stroke of 2%. Failed repair necessitating reoperation occurred in 4.8% of cases, with long-term follow-up demonstrating an 83% survival rate beyond 11 years. Compared with conventional sternotomy for mitral repair, these investigators also identified reductions in hospital length of stay, aortic cross-clamp time, and total CPB time in the minimally invasive cases.[347,349]

Additional benefits of minimally invasive approaches were reported by Svensson and associates.[348] From a cohort of patients who underwent minimally invasive mitral repair between 1995 and 2004, the study authors selected 590 cases that were matched using propensity scores with 590 patients who received mitral repair by conventional sternotomy. The study demonstrated improved pain scores and forced expiratory volume in 1 second (FEV_1) values, together with reductions in perioperative bleeding and transfusion requirements in the minimally invasive group. Procedural success was not reduced by the adoption of a minimally invasive approach, and there was a trend toward fewer patients with 3+ or 4+ residual MR at 1- and 5-year follow-up assessments for this cohort.

The trend toward even less invasive mitral repair continued in the late 1990s with the advent of thoracoscopic and robotically assisted procedures. In 1996, Carpentier[350] and colleagues performed the first video-assisted mitral valve repair by means of a minithoracotomy with fibrillatory arrest. The era of robotically assisted mitral repair began the following year, when Mohr and coworkers[351] used a voice-controlled robotic arm (ie, automated endoscopic system for optimal positioning [AESOP]) to provide thoracoscopic visualization of the mitral valve during a repair that was accomplished through a 4-cm right thoracotomy.

In 1998, Carpentier used a prototype robotic system (da Vinci, Intuitive Surgical, Mountain View, CA) to perform a mitral repair.[352]

Fig. 21.29 Close-up view of the chest incisions for a robotically assisted mitral valve repair. The surgeon has inserted his left index finger into the 4-cm primary incision located in the fourth intercostal space.

Although approved 2 years earlier for general laparoscopic surgery, the da Vinci system was given US Food and Drug Administration (FDA) approval for mitral valve surgery in the United States in 2002.[353] A review of The Society of Thoracic Surgeons Adult Cardiac Surgical Database (STS ACSD) from 2004 to 2008 showed use of minimally invasive mitral valve techniques (direct or robotic) increased from 12% to 35%[354] Within a 6-year period, more than 200 articles on robotically assisted cardiac surgery were published, including 60 from a single researcher.[355] Several centers have published series of more than 100 robotic cases.[356–358]

The concept of minimally invasive mitral surgery usually refers to valve repairs accomplished through a 3- or 4-cm right inframammary incision in the fourth or fifth intercostal space (Fig. 21.29). Several additional 1-cm incisions around the primary incision facilitate placement of robotic arms or other thoracoscopic instruments. The arterial cannula for CPB may be inserted directly or by a chimney graft into the femoral artery (Fig. 21.30) or into the ascending aorta through a thoracic incision under direct visualization.

Venous drainage is accomplished by the femoral route using TEE guidance with a multiple side hole peripheral access cannula (Fig. 21.31). Supplementary venous drainage is used in some centers by inserting either a 15- to 17-Fr right internal jugular vein cannula or specialized PAC with multiple end holes that drains to the venous reservoir during CPB.

Cardioplegia may be given antegrade into the aortic root or retrograde through the coronary sinus. Surgeons typically administer antegrade cardioplegia by one of two methods. The first involves the placement of a catheter tip into the ascending aorta through a right parasternal stab incision under thoracoscopic vision. This method is similar to standard antegrade cardioplegia administration in median sternotomy cases. A long-shafted aortic cross-clamp placed through a stab incision in the right lateral chest wall is used to occlude the aorta distal to the cardioplegia cannula. The second method of antegrade cardioplegia administration uses a specialized endoaortic cannula inserted into the femoral artery. A balloon near the distal end of this cannula is positioned in the ascending aorta using TEE guidance. Inflation of the balloon occludes the ascending aorta while antegrade cardioplegia delivery commences at the distal tip of the device.

Although the choice of antegrade cardioplegia system varies between surgeons and institutions, use of the endoaortic clamp and cardioplegia delivery system has been associated with increased morbidity, cost, cross-clamp times, and risk of aortic dissection.[359,360] Retrograde cardioplegia may be given by means of a coronary sinus catheter that has been percutaneously placed into the right internal jugular vein (see Chapters 13 and 15). When using a right minithoracotomy approach, the repair may be performed using long-handled thoracoscopic instruments (Fig. 21.32) or robotic assistance.

Although referred to as *robotic*, systems such as the da Vinci are probably more appropriately described as telemanipulators. These

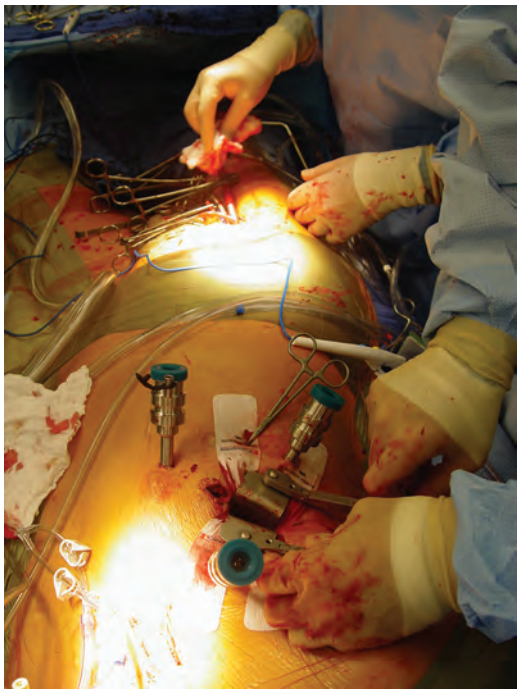


Fig. 21.30 Intraoperative photograph taken from near the patient's head before robotically assisted mitral valve repair. Femoral cannulation for cardiopulmonary bypass has been completed *(top)*. The primary surgical incision and working ports are also shown *(bottom)*.

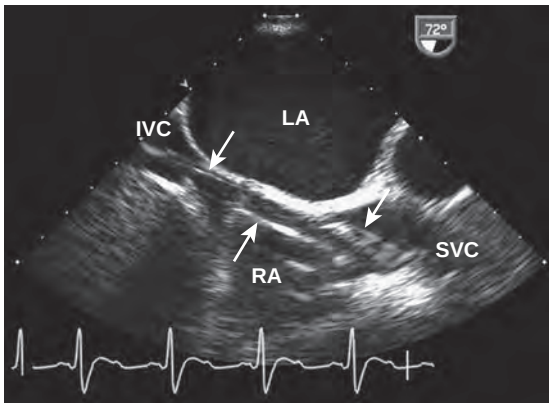


Fig. 21.31 Midesophageal, bicaval, transesophageal echocardiogram demonstrates the venous cannula *(arrows)*, which has been passed through the inferior vena cava *(IVC)*, across the right atrium *(RA)*, and into the superior vena cava *(SVC)*. The left atrium *(LA)* is visualized at the top of the image.

devices receive direct input from the hands and feet of the surgeon who is seated at a remote console that translates these motions to end-effectors within the chest of the patient (Fig. 21.33). Proponents of robotically assisted mitral repair cite several advantages of this approach compared with minimally invasive thoracoscopic surgery.[353] When seated at the remote console of a robotic device, the surgeon has near-stereoscopic vision compared with viewing a two-dimensional image on a television screen. Robotic devices provide motion scaling and tremor filtration to smooth movements. Because the robotic arms have articulating "wrists" at their distal ends, the surgeon can achieve 7 degrees of freedom of movement within the chest, similar to open surgery. By comparison, long-handled thoracoscopic instruments, which are often oriented almost parallel to one another, afford only 4 degrees of freedom.

Both thoracoscopic and robotically assisted approaches use the same operative techniques as standard open repairs. Techniques such

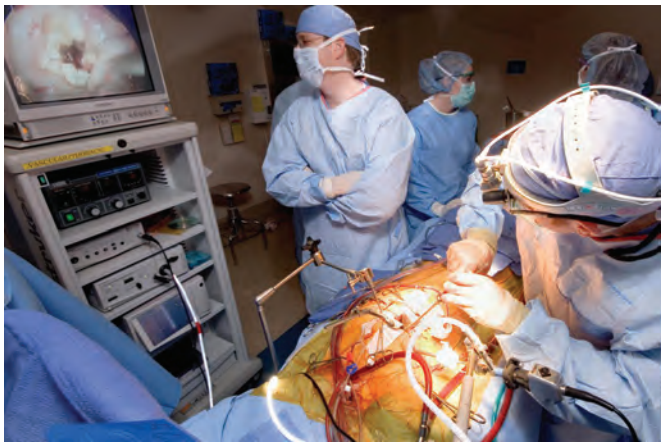


Fig. 21.32 Minimally invasive thoracoscopic mitral valve repair. The surgeon *(right)* is repairing the mitral valve through a right minithoracotomy using long-shafted instruments. A thoracoscopic view of the mitral valve can be seen on the television monitor *(left)*.

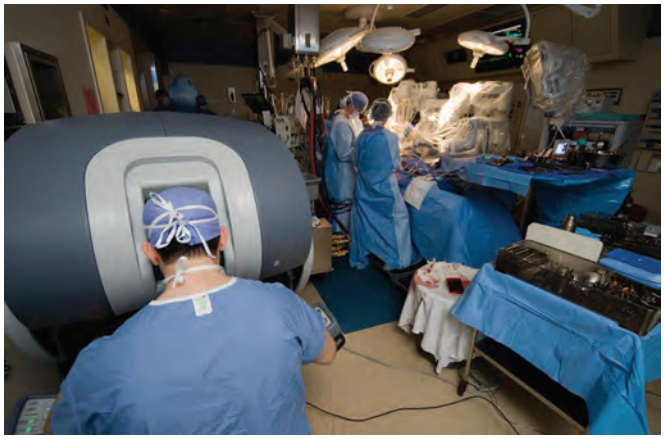


Fig. 21.33 Robotically assisted mitral valve repair. The surgeon *(lower left)* controls the robotic arms while seated at a console remote from the patient.

as leaflet resection, chordal insertion or transfer, sliding plasties, edge-to-edge repair, and annuloplasty band insertion may be used by experienced surgeons. Adoption of robotic approaches can be hindered by longer procedure times, increased cost per case, and a significant time commitment for training all members of the surgical team.

The procedural success and operative mortality rates of robot-assisted mitral repair in larger series appear comparable with traditional surgical approaches. For their first 300 robotically assisted mitral repairs, Chitwood and associates[356] reported a 30-day mortality rate of 0.7% and a stroke rate of 0.7%. Mean CPB time was 159 minutes, with a mean aortic cross-clamp time of 122 minutes. Eighty-nine concomitant procedures such as the Maze procedure and closure of atrial level shunts were performed. At a mean follow-up of 815 days, 93% of patients had residual MR that ranged from none to mild. Technical failure, such as annuloplasty band dehiscence, led to reoperation in 3.3% of cases. Hospital length of stay averaged 5.2 days.

Cheng and collaborators[357] described the outcomes of their first 120 robot-assisted mitral repair cases. Similar to Chitwood and colleagues,[356] Cheng's group[357] reported a 30-day mortality rate of less than 1%. Mean CPB time was 157 minutes, with a mean aortic cross-clamp time of 117 minutes. Fifty-three concomitant procedures were performed in these patients. Failed repair necessitating reoperation was encountered in 5% of cases. Citing a procedural learning curve, the investigators found that all failed repairs occurred in the first 74 cases. Average hospital length of stay was 6.3 days.

Another niche for the use of minimally invasive mitral valve repair techniques is in patients who have previously undergone cardiac surgery by a median sternotomy. Repeat sternotomies have a list of life-threatening intraoperative adverse events, including injuries to bypass grafts, right-sided cardiac chambers, and great vessels. Roselli and associates[361] reviewed 1847 patients undergoing reoperative cardiac surgery and found a 7% occurrence of these events, which were associated with poor patient outcomes and increased costs.

The ability to complete mitral valve surgery and avoid the potential risks of a repeat sternotomy is desirable and has been reported by several investigators. Arciddi and colleagues[362] described 167 patients over 14 years who underwent mitral valve repair or replacement in the setting of a previous CABG or valvular procedure. The mortality rate at 30 days was 3% (ie, five patients total), with a 3% reoperation rate for bleeding. There was a trend toward lower mortality with each successive interval of experience, culminating at a 0% 30-day mortality rate during the interval between 2006 and 2010, which also had the highest (51%) surgical volume. The mean CPB and cross-clamp times were 167 and 113 minutes, respectively.

Murzi and collaborators[363] reported reoperations involving the mitral valve (ie, repair or replacement) in 173 patients with a previous sternotomy. Two patients required a conversion to sternotomy, and the overall 30-day mortality rate was 4.1%, with reoperation for bleeding occurring in 6.3% of patients. Mean CPB time was 160 minutes, with a mean cross-clamp time of 82 minutes. During the postoperative follow-up period, of the 53 patients who underwent repair, 7 had moderate MR by echocardiography, and the remainder had trivial or no MR.

Just as catheter-based techniques have been developed to treat valvular AS, efforts are underway to develop percutaneous interventions for MR (see Chapters 3 and 27). Several devices that use different approaches to correct the underlying mechanism are being investigated. A classification system proposed by Chiam and Ruiz[364] groups interventions based on anatomic targets and device action:

1. Leaflets: percutaneous plication, leaflet coaptation or leaflet ablation
2. Annulus: indirect annuloplasty through the coronary sinus or direct annuloplasty, including percutaneous and hybrid approaches
3. Chordae: percutaneous or transapical chordal insertion
4. LV: remodeling with application of external devices

The device with the largest clinical experience is the MitraClip system (Abbott Laboratories, Abbott Park, IL) (see Chapter 27). Leaflet plication is based on the open mitral repair technique reported by Alfieri and colleagues.[365] It entails the creation of a double-orifice mitral valve by suturing the free edges of the leaflets at the site of regurgitation together to improve leaflet coaptation and reduce MR. MitraClip uses a percutaneous femoral venous transseptal delivery system to deploy a cobalt-chromium clip to secure the mitral leaflets under fluoroscopic and echocardiographic guidance.

The system was evaluated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST).[366] In this safety and feasibility study, 107 patients with 3+ or greater MR with symptoms or asymptomatic patients with compromised left ventricular function (EF <60%), regurgitant jet origin of A2 to P2, and a leaflet anatomy amenable to application of the clip underwent the procedure with application of up to two clips. Acute procedural success (APS) defined as grade 2+ or less severe MR occurred in 79 patients (74%), and at 12 months, 66% of patients continued to have the severity of MR graded at 2+ or less. The in-hospital mortality rate was less than 1%, with 10 patients (9.1%) experiencing a major adverse event at 30 days, including complications from the transseptal approach, prolonged mechanical ventilation, and bleeding requiring transfusion. At the median follow-up of 680 days, 75 (70%) of patients remained surgery free. Over the follow-up period, 32 patients of the total cohort had open mitral valve surgery, 23 of whom had a clip placed previously.

EVEREST II,[367] reported in 2011, was a randomized, controlled trial that compared MitraClip treatment with conventional mitral valve surgery plus CPB in patients with severe MR. Patients were followed for major adverse events at 30 days and clinical success at 1 year. At 30 days, investigators analyzed the composite end point of major adverse events, including death, AMI, reoperation of the mitral valve, stroke, renal failure, deep wound infection, permanent AF, mechanical ventilation for more than 48 hours, and blood transfusion of more than 2 units of blood. The rates of major adverse events were 15% in the percutaneous repair group and 48% in the conventional surgery group. If transfusion was excluded, the occurrence of adverse events narrowed to 5% in the MitraClip group and 10% in the conventional surgery group. At 1 year, of patients randomized to the MitraClip, 28 (20%) had severe MR and 37 (20%) underwent surgery for mitral valve dysfunction, compared with 3 (4%) and 2 (2%) patients, respectively, who underwent reoperation in the conventional surgery group.

The mitral annulus plays an important role in the function of the mitral valve, and pathologic dilation of the annulus leads to poor leaflet coaptation and MR. Conventionally, the mitral annulus is divided into two components: the anterior fibrous portion and the posterior muscular portion. The anterior portion is relatively fixed, whereas the posterior portion is in continuity with the atrial and ventricular muscle and affected by dilation of the ventricle. Functional MR occurs as a result of altered function or geometry of the LV or mitral annulus. Most surgical procedures for functional MR are directed at reducing this portion of the annulus by placement of an annuloplasty ring to support the annulus.

Percutaneous techniques attempt to correct annular pathology by indirectly pushing the posterior annulus anteriorly[364] using devices that exploit the anatomic relationship of the coronary sinus and mitral annulus. One device is the Carillon Mitral Contour System (Fig. 21.34). It consists of self-expandable nitinol (ie, nickel-titanium alloy) proximal and distal anchors connected by a nitinol bridge. The application of tension on the system pulls the posterior mitral annulus anteriorly, reducing septal–lateral annular diameter.

The prospective, nonrandomized, multicenter TITAN trial[368] included 53 patients with dilated or nonischemic cardiomyopathy (EF <40%) and at least moderate (2+) MR. Of these patients, 36 underwent permanent implantation, whereas 17 had the device acutely recaptured for clinical reasons (eg, transient coronary compromise, <1 grade MR reduction) and served as the comparison group. Overall, the major adverse event rate for the implanted group at 30 days was 0%, with statistically significant improvement in echocardiographic assessment of MR severity and exercise performance at 12 months. Device-related limitations include coronary artery compromise due to the proximity of the circumflex artery to the CS,[369] slipping of the distal anchor, and device fracture.

Several percutaneous transcatheter mitral valve replacement devices are in preclinical and early clinical evaluation.[370] The two primary percutaneous techniques involve edge-to-edge repair and annuloplasty band insertion.[371] Edge-to-edge repair, popularized in open mitral operations by Alfieri and colleagues.[365] uses a percutaneously delivered clip to secure the anterior leaflet to the posterior leaflet, creating a double-orifice mitral valve. Although several proprietary devices are under development by different manufacturers, the MitraClip (Evalve, Menlo Park, CA) received FDA approval for use in patients deemed too high risk for surgical treatment in 2013 after completing the phase II multicenter EVEREST II trial.[372]

One-year follow-up results for this high-risk patient population continue to be reasonable, with low mortality rates and low rates of adverse events.[373,374] However, the 4-year follow-up results of the EVEREST II trial demonstrated a significantly greater requirement for late open surgical intervention in patients treated with percutaneous versus surgical repair.[375]

Anesthesia Considerations

Patients with MR may have significantly different risk factors for surgery, including duration of disease, symptoms, hemodynamic stability, ventricular function, and involvement of the right heart and pulmonary circulation (Box 21.5). For instance, a patient with severe MR caused by acute papillary muscle rupture may enter the operating

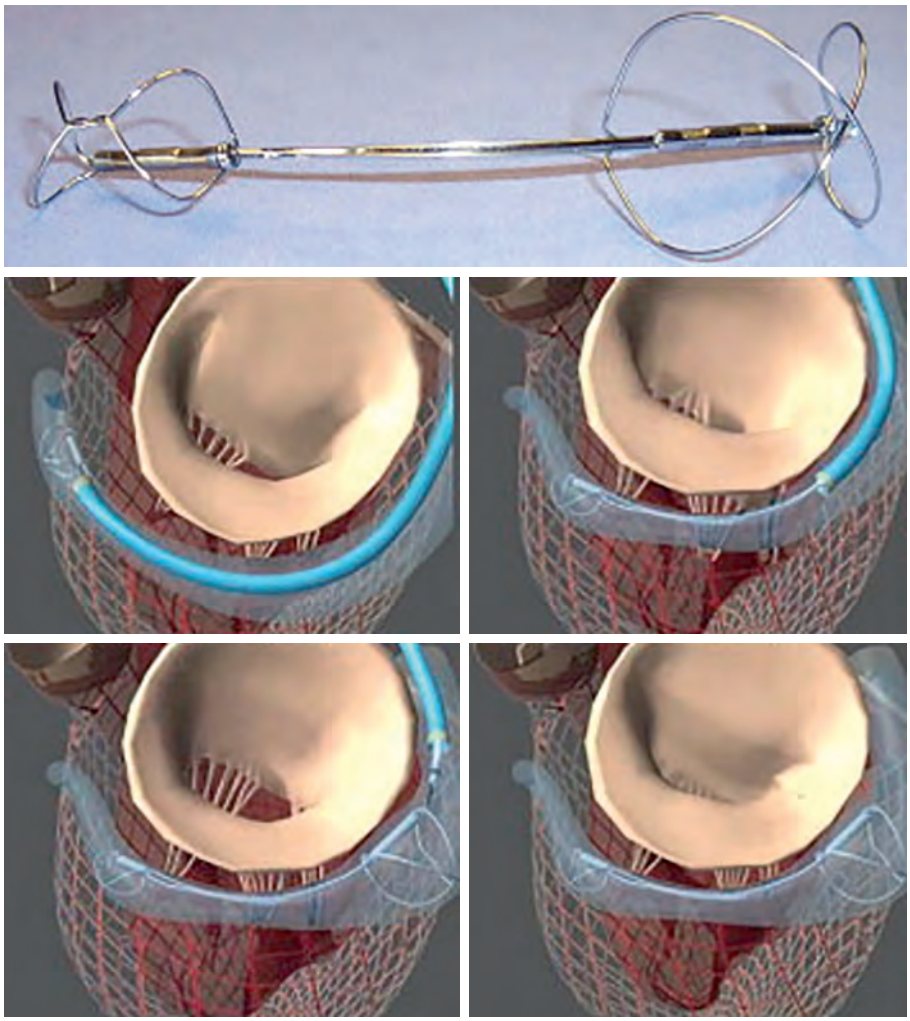
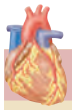


Fig. 21.34 The Carillon Mitral Contour System *(top panel)* at various steps in its deployment *(bottom panels). (From Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology.* JACC Cardiovasc Intv. *2011;4:1–13.)*



BOX 21.5 MITRAL REGURGITATION

- Preload is increased.
- Afterload isdecreased.
- Goal is mild tachycardia, vasodilation.
- Avoid myocardial depression.

room in cardiogenic shock with pulmonary congestion requiring intraaortic balloon pump augmentation. Another patient with a newly diagnosed flail posterior mitral leaflet may enter the surgical suite with relatively preserved left ventricular function and no symptoms; the compliance of the LA might have prevented pulmonary vascular congestion, pulmonary hypertension, and right ventricular dysfunction.

Despite differences in presentation, the general management goals remain similar and include maintenance of forward CO and reduction in the mitral regurgitant fraction. The anesthesiologist must optimize right ventricular function, in part by avoiding increases in pulmonary vascular congestion and pulmonary hypertension. Depending on the clinical presentation, various degrees of intervention are needed to achieve these hemodynamic management goals.

Information obtained during the preoperative interview and examination provides the anesthesiologist with important insight into the patient's degree of hemodynamic compromise. For example, a patient who reports dyspnea at rest or with minimal activity may have significant pulmonary vascular congestion and possibly compromised right ventricular function. Combined with the estimated pulmonary artery systolic pressure derived from the preoperative TTE report, this information helps the anesthesiologist prepare for potential right-heart dysfunction intraoperatively. For the patient, it is best to avoid heavy premedication with its attendant risk for obtundation, hypoventilation, and increased PAP. Auscultation of the heart may reveal rhythm disturbances such as AF and the systolic murmur of MR. However, in cases of acute, severe MR, a significant increase in left atrial pressure decreases the systolic pressure gradient between the left heart chambers, and the murmur of MR may be diminished or absent.[302]

Invasive hemodynamic monitoring provides a wealth of important information. Arterial catheters are essential for monitoring beat-to-beat changes in blood pressure that occur in response to a variety of surgical and anesthesia manipulations. PACs facilitate many aspects of intraoperative patient management. Intraoperative use of a PAC allows careful optimization of left-sided filling pressures. Although the PCWP and diastolic PAP depend on left atrial and left ventricular compliance and filling, examination of intraoperative trends in these variables helps the anesthesiologist to provide appropriate levels of preload while avoiding volume overload. Periodic determination of CO allows a more objective assessment of the patient's response to interventions such as fluid administration or inotropic infusion. The

presence or size of a v wave on a PCWP tracing does not reliably correlate with the severity of MR because this finding depends on left atrial compliance.

As in the management of patients with AR, a benefit of PAC insertion is the ability to introduce a ventricular pacing wire to rapidly counteract hemodynamically significant bradycardia. In patients with right ventricular compromise, monitoring trends in the CVP recording may be helpful. Tricuspid regurgitation (TR) detected through analysis of the CVP tracing may suggest right ventricular dilation, which may be caused by pulmonary hypertension.[376]

Intraoperative TEE provides invaluable information during the surgical correction of MR. It reliably identifies the mechanism of MR, thereby guiding the surgical approach,[377] and it objectively demonstrates the size and function of the cardiac chambers. TEE can identify the cause of hemodynamic derangements, facilitating proper intervention. For instance, the appearance of SAM of the mitral apparatus immediately after valve repair allows the anesthesiologist to intervene with volume infusion and medications such as esmolol or phenylephrine as appropriate. In rare circumstances, when hemodynamically significant SAM persists despite these interventions, the surgeon may elect to further repair or replace the mitral valve. TEE also identifies concomitant pathology that may warrant surgical attention, such as atrial-level shunts and additional valve disease (see Chapters 14 through 16).

Intraoperative TEE is essential during minimally invasive and robotically assisted mitral valve surgery. The use of a right minithoracotomy for these procedures precludes bypass cannulation in the chest. Instead, femoral arterial and venous cannulation with or without supplementary venous drainage from the superior vena cava or pulmonary artery is used. Real-time TEE imaging typically guides cannulation for CPB. If an endoaortic balloon clamp is used, the echocardiographer ensures that the balloon is correctly positioned in the ascending aorta. If a transthoracic aortic cross-clamp is chosen, the aortic cannula inserted into the femoral artery usually is not visualized with TEE. However, confirmation of guidewire placement in the descending aorta may be requested to exclude accidental passage into the contralateral iliac artery. The desired position of the tip of the femoral venous cannula varies; some prefer the tip within the superior vena cava, whereas others select the right atrium or inferior vena cava–right atrial junction.

For all positions of the venous cannula, TEE imaging can identify a malpositioned cannula or guidewire (Fig. 21.35). Tamponade after perforation of the left atrial appendage by a guidewire that was placed across a patent foramen ovale has been reported.[378] TEE also is invaluable during the percutaneous placement of coronary sinus catheters for retrograde cardioplegia delivery (Fig. 21.36A and B). Patients who may benefit from retrograde cardioplegia, such as those with significant AR, may be identified by TEE.

In addition to TEE considerations related to cannulation procedures, the selection of a minimally invasive or robotically assisted approach to mitral repair necessitates other changes in anesthesia management. Although not universally used, one-lung ventilation is preferred in many centers. This may be achieved by the usual methods, such as a double-lumen endotracheal tube or bronchial blocker. Impaired oxygenation can occur when one-lung ventilation is used during the termination of CPB during these procedures.[379]

The delivery of cardioplegia requires special attention by the surgical and anesthesia teams. If an endoaortic balloon clamp system is used, one or more methods should be used to verify its position. In addition to TEE, some centers place arterial catheters in the right and left radial arteries; dampening of the right radial arterial waveform can signify balloon migration toward the innominate artery. If retrograde cardioplegia is administered through a percutaneously placed catheter, its position should be well documented by TEE with or without fluoroscopy. Coronary sinus pressure should be monitored at baseline, during balloon inflation, and during cardioplegia administration. External patches for defibrillation are usually applied before patient positioning. A multimodal approach to analgesia may facilitate

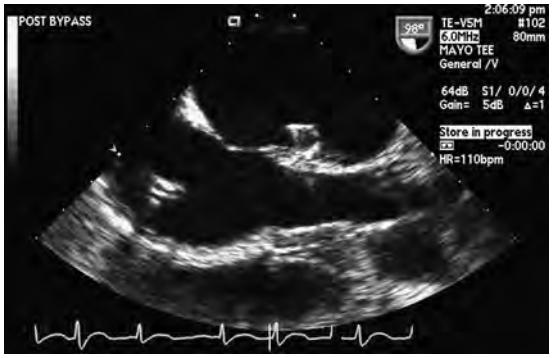


Fig. 21.35 Midesophageal, bicaval, transesophageal echocardiogram demonstrates the J-tipped guidewire for the femoral venous cannula crossing a patent foramen ovale.

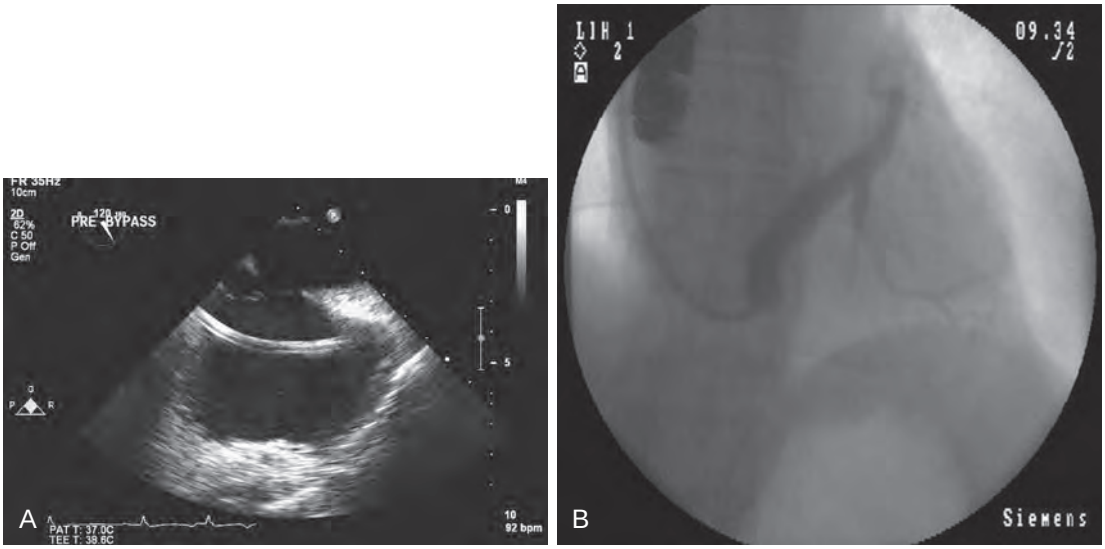


Fig. 21.36 (A) Modified midesophageal, bicaval, transesophageal echocardiogram demonstrates a percutaneously placed coronary sinus catheter entering the coronary sinus *(left side)*. (B) Intraoperative fluoroscopic image was taken after contrast injection into the distal tip of a correctly placed coronary sinus catheter.

early extubation of these patients. Some centers include a regional technique such as intrathecal opioids or paravertebral blocks as part of the anesthesia plan.

Intraoperative care of patients with MR before the institution of CPB focuses on optimizing forward CO, minimizing the mitral regurgitant volume, and preventing deleterious increases in PAPs. Maintaining adequate left ventricular preload is essential. An enlarged LV that operates on a higher portion of the Frank-Starling curve requires adequate filling. At the same time, excessive volume administration should be avoided because it may cause unwanted dilatation of the mitral annulus and worsening of the MR. Excessive fluid administration may precipitate right ventricular failure in patients with pulmonary vascular congestion and pulmonary hypertension. Optimization of preload is aided by analysis of data obtained from PAC measurements and TEE images.

Because significant left ventricular dysfunction is seen in many patients with MR, specific induction and maintenance regimens are selected to avoid further depressing left ventricular function. Large doses of narcotics have been popular in the past.[151,152] Other researchers have shown that smaller doses of narcotics combined with vasodilating inhalation anesthetics produce acceptable intraoperative hemodynamics.[380,381] By reducing the amount of narcotics administered, the addition of a vasodilating inhalation agent to the anesthetic regimen may allow for faster extubation of the trachea after surgery. With the current trend toward early referral of asymptomatic patients for mitral repair, anesthetic regimens that reduce the duration of postoperative mechanical ventilation may be advantageous.

In patients with severe left ventricular dysfunction, infusions of inotropic medications such as dopamine, dobutamine, or epinephrine may be required to maintain an adequate cardiac output. Phosphodiesterase inhibitors such as milrinone also may augment systolic ventricular performance and reduce pulmonary and peripheral vascular resistances. By reducing pulmonary and peripheral vascular resistance, forward CO is facilitated. Nitroglycerin and sodium nitroprusside represent two additional options for reducing the impedance to ventricular ejection. If patients prove refractory to inotropic and vasodilator therapy, insertion of an intraaortic balloon pump should be strongly considered (see Chapters 11, 13 through 16, 28, 36, and 38).

Manipulation of the heart rate may be necessary in some patients to optimize hemodynamics. Bradycardia usually should be avoided because slower heart rates allow larger filling volumes, potentially resulting in left ventricular distention and mitral annular dilation. Regurgitant volumes may increase at slower heart rates. Slightly increased heart rates, especially when combined with increased left ventricular contractility, favor a smaller mitral annular area and may decrease the regurgitant fraction. Sinus rhythm and preserved atrial contraction are less important in patients with MR than in patients with stenotic valves. Mitral annular dilation accompanies most cases of long-standing MR. Patients with pure MR usually have no impedance to left ventricular filling, and AF usually is better tolerated than in patients with stenotic lesions.

Because severe MR may result in pulmonary hypertension and right ventricular dysfunction, intraoperative management strategies should avoid hypercapnia, hypoxia, and acidosis. Mild hyperventilation may be beneficial in some patients. The effect of nitrous oxide on pulmonary vascular resistance (PVR) and pulmonary hypertension is controversial. Some studies show no change in PVR when nitrous oxide is administered to anesthetized patients with CAD or VHD.[382–384] Other studies of patients with MS demonstrate an increase in PVR after nitrous oxide administration, and in vitro evidence suggests that nitrous oxide increases norepinephrine release from the pulmonary artery.[385–387]

Patients with severe right ventricular dysfunction after CPB can prove exceptionally difficult to treat. Besides avoiding the factors known to increase PVR, only a few options exist for these patients. Inotropic agents with vasodilating properties such as dobutamine, isoproterenol, and milrinone augment right ventricular systolic performance and decrease PVR, but their use often is confounded by systemic hypotension. Prostaglandin E_1 (PGE_1) reliably reduces PVR and undergoes extensive first-pass metabolism in the pulmonary circulation.[388,389] Although PGE_1 reduces PAPs after CPB, systemic hypotension requiring infusions of vasoconstrictors through a left atrial catheter has occurred.[390–393]

Inhaled nitric oxide is an alternative for the treatment of right ventricular failure in the setting of pulmonary hypertension. Nitric oxide reliably relaxes the pulmonary vasculature and is then immediately bound to hemoglobin and inactivated. Studies indicate that systemic hypotension during nitric oxide therapy is unlikely[394,395] (see Chapters 11, 26, and 39).

Left ventricular dysfunction may contribute to post-CPB hemodynamic instability. With mitral competence restored, the low-pressure outlet for left ventricular ejection is removed. The enlarged LV must then eject entirely into the aorta. Because left ventricular enlargement leads to increased wall stress, a condition of increased afterload often exists after CPB. At the same time, the preload augmentation inherent to MR is removed. The systolic performance of the LV often declines after surgical correction of MR. Treatment options in the immediate post-CPB period include inotropic and vasodilator therapy and, if necessary, intraaortic balloon pump augmentation (see Chapters 26 and 39).

Mitral Stenosis

Clinical Features and Natural History

Clinically significant MS in adult patients usually is a result of rheumatic disease. Congenital abnormalities of the mitral valve are a rare cause of MS in younger patients. Other uncommon conditions that do not directly involve the mitral valve apparatus but may limit left ventricular inflow and simulate the clinical findings of MS include cor triatriatum, large left atrial neoplasms, and pulmonary vein obstruction.[396]

A decades-long asymptomatic period characterizes the initial phase of rheumatic MS. Symptoms rarely appear until the normal mitral valve area (MVA) of 4 to 6 cm^2 (Fig. 21.37) has been reduced to 2.5 cm^2 or less.[397] When the MVA reaches 1.5 to 2.5 cm^2, symptoms usually occur only in association with exercise or conditions such as fever, pregnancy, or AF that lead to increases in heart rate or cardiac output.[398,399] After the MVA decreases to less than 1.5 cm^2, symptoms may develop at rest. Some patients are able to remain asymptomatic for long periods by gradually reducing their level of activity.[396]

Patients with MS commonly report dyspnea as their initial symptom, a finding reflective of increased left atrial pressure and pulmonary congestion. In addition to dyspnea, patients may report palpitations that signal the onset of AF. Systemic thromboembolization occurs in 10% to 20% of patients with MS and does not appear to be correlated with the MVA or left atrial size.[398] Chest pain that simulates angina occurs in a small number of patients with MS and may result from RVH rather than CAD.[398]

There has been a change in the typical age at which patients are diagnosed with MS.[398] Previously, patients, often women, with MS were identified while in their 20s and 30s.[398,400,401] Since the early 1990s, perhaps because of more slowly progressive disease in the United States, patients have been diagnosed in their 40s and 50s.[398,402,403]

After symptoms develop, MS remains a slow, progressive disease. Patients often live 10 to 20 years with mild symptoms, such as dyspnea with exercise, before disabling NYHA class III and IV symptoms develop. The symptomatic state of the patient predicts the clinical outcome. For instance, the 10-year survival rate of patients with mild symptoms approaches 80%, but the 10-year survival rate of patients with disabling symptoms is only 15% without surgery.[398,403–405]

Pathophysiology

Rheumatic MS results in valve leaflet thickening and fusion of the commissures. Later in the disease process, leaflet calcification and

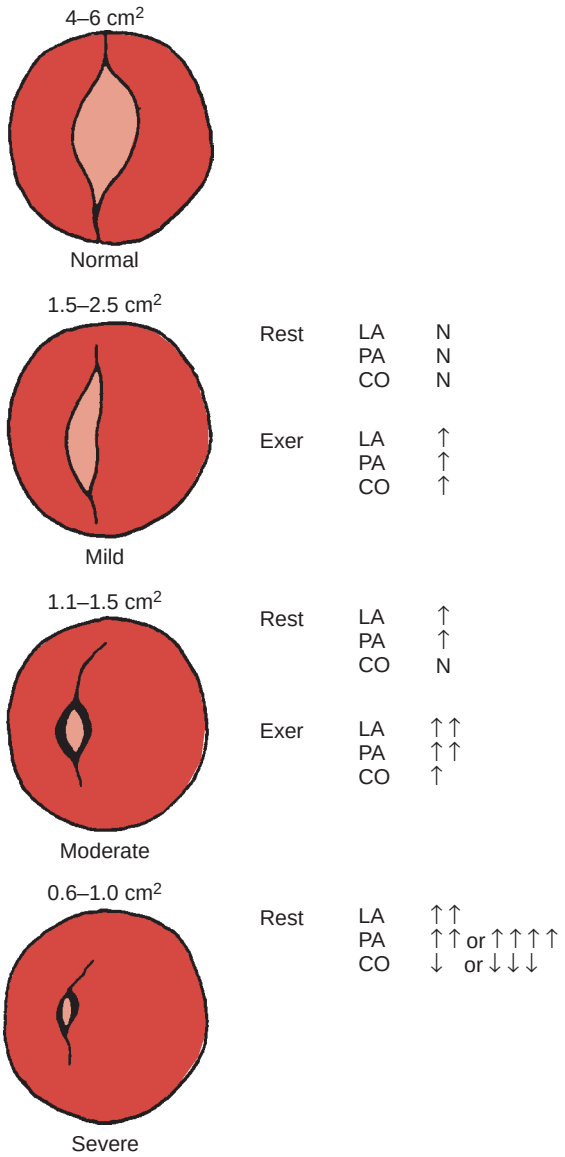


Fig. 21.37 Hemodynamic changes with progressive narrowing of the mitral valve. *CO*, Cardiac output; *Exer*, exercise; *LA*, left atrium; *N*, normal; *PA*, pulmonary artery; ↑, increased; ↓, decreased . *(From Rapaport E. Natural history of aortic and mitral valve disease.* Am J Cardiol. *1971;35:221.)*

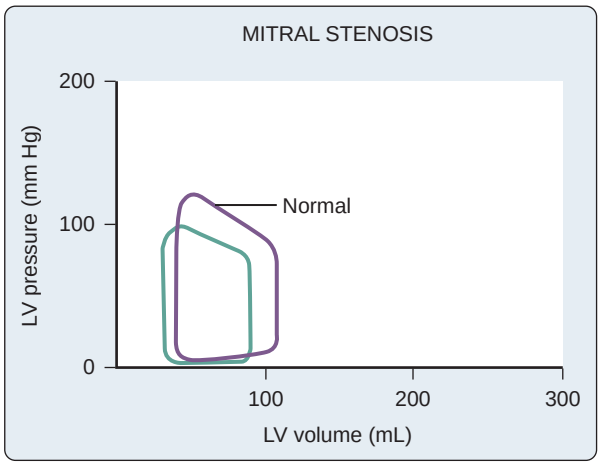


Fig. 21.38 Pressure-volume loop *(green)* for mitral stenosis. *LV*, Left ventricular. *(From Jackson JM, Thomas SJ, Lowenstein E. Anesthetic management of patients with valvular heart disease.* Semin Anesth. *1982;1:239.)*

subvalvular chordal fusion may occur.[398] These changes combine to reduce the effective MVA and limit diastolic flow into the LV. As a result of the fixed obstruction to left ventricular inflow, left atrial pressures increase. Elevated left atrial pressures limit pulmonary venous drainage and result in increased PAPs.[310] Over time, pulmonary arteriolar hypertrophy develops in response to chronically increased pulmonary vascular pressures.[311] Pulmonary hypertension may trigger increases in right ventricular end-diastolic volume (RVEDV) and pressure (RVEDP), and some patients may have signs of right ventricular failure such as ascites or peripheral edema.[400,401] Left atrial enlargement is an almost universal finding in patients with established MS and is a risk factor for AF.

Patients with MS tolerate tachycardia particularly poorly. Left ventricular inflow, already limited by a mechanically abnormal valve, is further compromised by the disproportionate decline in the diastolic period that accompanies tachycardia. The flow rate across the stenotic valve must increase to maintain left ventricular filling in a shorter diastolic period. Because the valve area remains constant, the pressure gradient between the LA and LV increases by the square of the increase in the flow rate, according to the Gorlin formula, in which PG is the transvalvular pressure gradient:

$$\text{Valve area} = \text{Transvalvular flow rate}/\text{Constant} \times \sqrt{\text{PG}}$$

Tachycardia necessitates a significant increase in the transvalvular pressure gradient and may precipitate feelings of breathlessness in awake patients. In patients with AF, it is the increased ventricular rate that is most deleterious, rather than the loss of atrial contraction.[312] Although coordinated atrial activity is always preferable, the primary goal in treating patients with MS and AF should be control of the ventricular rate.

MS results in diminished left ventricular preload reserve. As seen in the pressure-volume loop in Fig. 21.38, LVEDV and LVEDP are reduced with an accompanying decline in SV. Controversy exists regarding the contractile state of the LV in these patients. Gash and colleagues[406] reported that almost one-third of their study population of patients with MS had an EF less than 50%. Limited preload may contribute to a reduced EF in some of these patients. However, the observation that left ventricular contractile impairment persists after surgery in some patients suggests that other causes of left ventricular dysfunction may exist. Rheumatic myocarditis has been reported, although its role in producing left ventricular contractile dysfunction is uncertain.[406] Other investigators have described posterobasal regional wall motion abnormalities, perhaps a consequence of thickening and calcification of the mitral apparatus.[314,315] Vasoconstriction occurring in response to diminished CO also may impair left ventricular ejection.[407] Afterload may be increased because of inadequate myocardial wall thickness.[406] The lack of adequate wall thickness leads to elevations in wall stress in accordance with Laplace's law.

In addition to abnormalities in systolic function, patients with MS may have impaired diastolic function. MS impairs left ventricular diastolic filling. The intrinsic compliance of the LV also may be reduced by the rheumatic disease process. Using conductance catheter and micromanometer techniques, Liu and associates[408] discovered decreased left ventricular compliance in a group of patients with MS scheduled for mitral balloon valvuloplasty. On repeat measurements taken immediately after valvuloplasty, the investigators observed a significant increase in left ventricular compliance. Because the increase in compliance occurred immediately after valvuloplasty, the physicians hypothesized that the changes associated with rheumatic MS created an internal constraint that limited left ventricular compliance.

Assessment of Mitral Stenosis

As for patients with MR, echocardiography represents the diagnostic modality of choice for patients with suspected MS.[396,409,410] Two-dimensional and Doppler echocardiographic techniques can accurately and noninvasively measure the transvalvular pressure gradient and MVA. Because the pressure gradient varies with the flow rate and diastolic period, the assessment of MS severity ideally should be based on the measured or calculated MVA.[396] Echocardiographic methods used to obtain MVA include the pressure half-time technique, the continuity equation, planimetry of the valve orifice, and PISA analysis. Other invaluable information obtained during an echocardiographic study includes the size and function of the ventricle and an estimation of the PAP.

Exercise echocardiography can be used when the patient's symptoms and the resting echocardiographic data are discordant.[409] In these cases, echocardiography may be performed while the patient exercises on a supine bicycle. If during exercise the transmitral gradient or PAP increases significantly, MS is the likely cause of the patient's symptoms.[409]

With the accuracy and widespread use of echocardiography, cardiac catheterization and invasive measurements of hemodynamics are rarely necessary.[398,410] Even patients referred for preoperative coronary angiography need not undergo invasive hemodynamic studies at the time of catheterization if adequate echocardiographic data already have been obtained.[410] Catheter-based hemodynamic assessments are reserved for situations in which echocardiographic studies are suboptimal or conflict with the clinical picture because invasive mitral valve hemodynamic studies are complex and limited.[398] For instance, a transseptal puncture is required to measure the left atrial–to–left ventricular pressure gradient directly and entails risks such as tamponade, aortic injury, and heart block.[398] If the PCWP is used in place of direct left atrial pressure measurements, the gradient derived is less accurate than that obtained with Doppler echocardiography.[319]

Similar to patients with MR, nonspecific findings commonly are seen on electrocardiograms and chest radiographs for patients with MS. Potential ECG findings include AF and left atrial enlargement. Radiographs may also reveal left atrial enlargement and pulmonary vascular congestion.

Surgical Decision Making

Appropriate referral of patients for surgical intervention requires integration of clinical and echocardiographic data. Patients with severe symptoms (ie, NYHA class III and IV) should be immediately referred for surgery because the outcome is poor if treated medically.[313,398] Patients with only mild MS and few or no symptoms may be treated conservatively with periodic evaluation. Patients who are asymptomatic but have moderate MS (ie, MVA between 1.0 and 1.5 cm^2) require careful assessment. If significant pulmonary hypertension (ie, pulmonary artery systolic pressure >50 mm Hg) is identified, surgical intervention should be considered.[313] Intervention also may be indicated if a patient becomes symptomatic or PAPs increase significantly during exercise testing.[398]

The surgical options for treating MS continue to evolve. Closed commissurotomy, in which the surgeon fractures fused mitral commissures, was first performed in the 1920s. It became popular in the 1940s and still is used to treat MS in developing countries.[409] With the advent of CPB in the 1950s, techniques of open commissurotomy developed, allowing the surgeon to directly inspect the valve before splitting the commissures.[409] The common goals of closed and open mitral commissurotomy include increasing the effective MVA and decreasing the left atrial to left ventricular pressure gradient, with a resultant relief in the patient's symptoms.

Percutaneous mitral commissurotomy (PMC) allows a less invasive, catheter-based approach to MS. It was first reported by Inoue and coworkers in 1984,[411] and clinicians worldwide perform PMC more than 10,000 times each year.[412] The technique of PMC involves directing a balloon-tipped catheter across the stenotic mitral valve. Specifically designed balloons allow sequential inflation of the distal and proximal portions of the balloon, ensuring correct positioning across the mitral valve before the middle portion of the device is inflated to split the fused commissures.[413]

Patient selection for PMC requires careful echocardiographic evaluation. Echocardiographic grading scales have been developed to evaluate mitral leaflet mobility, thickness, calcification, and subvalvular fusion.[414] Patients who score favorably on echocardiographic assessments (eg, adequate leaflet mobility with little calcification) may be referred for PMC. Success rates for PMC are similar to those achieved with surgical commissurotomy, and most patients experience a doubling in the effective MVA.[409] An increase in the amount of MR represents the most common complication associated with PMC.[409]

Not all patients are candidates for surgical commissurotomy or PMC. Those with heavily calcified valves or significant MR are likely to experience suboptimal results after commissurotomy. Mitral valve anatomy unsuitable for PMC is more commonly encountered in Western countries, where patients with MS typically are diagnosed at an older average age.[412] Mitral valve replacement commonly is recommended for these patients. The risk for mitral valve replacement depends on patient characteristics such as age, functional status, and other comorbid conditions.[409] Surgical risk in younger patients with few coexisting medical problems usually is less than 5%. Conversely, surgical risk in elderly patients with severe symptoms related to MS and multiple comorbidities may be 10% to 20%.[409]

Anesthesia Considerations

Several important goals should guide the anesthesia management of patients with significant MS. First, the anesthesiologist should prevent tachycardia or treat it promptly in the perioperative period (Box 21.6). Second, left ventricular preload should be maintained without exacerbation of pulmonary vascular congestion. Third, anesthesiologists should avoid factors that aggravate pulmonary hypertension and impair right ventricular function.

Prevention and treatment of tachycardia are central to perioperative management. Tachycardia shortens the diastolic filling period. An elevation in transvalvular flow rate is required with a resultant increase in the left atrial–to–left ventricular pressure gradient to maintain left ventricular preload with a shortened diastolic period. Avoidance of tachycardia begins in the preoperative period. Anxiety-induced tachycardia may be treated with small doses of narcotics or benzodiazepines. However, excessive sedation is counterproductive because sedative-induced hypoventilation can result in hypoxemia or hypercarbia, potentially aggravating a patient's underlying pulmonary hypertension and because large doses of premedication can jeopardize the patient's already limited left ventricular preload. Appropriate monitoring and supplemental oxygen therapy should be considered for patients receiving preoperative narcotics or benzodiazepines.

Medications taken by the patient before surgery to control heart rate, such as digitalis, β-blockers, calcium receptor antagonists, or amiodarone, should be continued in the perioperative period. Additional doses of β-blockers and calcium-receptor antagonists may be required intraoperatively, particularly to control the ventricular rate in patients with AF. Control of the ventricular rate remains the

BOX 21.6 MITRAL STENOSIS

- Preload is normal or increased.
- Afterload is normal.
- Goal is controlled ventricular response.
- Avoid tachycardia, pulmonary vasoconstriction

primary goal in managing patients with AF, although cardioversion should not be withheld from patients with atrial tachyarrhythmias who become hemodynamically unstable. Narcotic-based anesthetics often are helpful in avoiding intraoperative tachycardia. However, clinicians should realize these patients may be receiving other vagotonic drugs and that profound bradycardia is possible in response to large doses of narcotics.[326,327] The selection of a muscle relaxant such as pancuronium may help prevent the unwanted bradycardia associated with high-dose narcotics.

Maintenance of preload is an important goal for treating patients who have a fixed obstruction to left ventricular filling. Appropriate replacement of blood loss and prevention of excessive anesthetic-induced venodilation help preserve hemodynamic stability intraoperatively. Invasive hemodynamic monitoring allows the anesthesiologist to maintain adequate preload while avoiding excessive fluid administration that can aggravate pulmonary vascular congestion. Placement of an arterial catheter facilitates timely recognition of hemodynamic derangements. PACs can be invaluable in treating patients with significant MS. Although the PCWP overestimates left ventricular filling and the pulmonary artery diastolic pressure may not accurately reflect left-heart volume in patients with pulmonary hypertension, trends and responses to intervention can be more readily assessed. Tachycardia increases the pressure gradient between the LA and LV. Increased heart rates widen the discrepancy between the PCWP and the true LVEDP. Despite these limitations, the PAC remains a useful monitoring tool, providing information on CO and PAPs.

Many patients with MS have pulmonary hypertension. Anesthesia techniques that avoid increases in PVR are likely to benefit these patients and prevent additional right ventricular embarrassment. Meticulous attention to arterial blood gas results allows appropriate adjustment of ventilatory parameters. Vasodilator therapy for patients with pulmonary hypertension usually is ineffective because the venodilation produced further limits left ventricular filling and does not improve cardiac output. The only MS patients who may benefit from vasodilator therapy are those with concomitant MR or those with severe pulmonary hypertension and right ventricular dysfunction in whom pulmonary vasodilation can facilitate transpulmonary blood flow and improve left ventricular filling.[325] The treatment of right ventricular dysfunction was discussed earlier (see Chapters 26 and 38).

Tricuspid Regurgitation

Clinical Features and Natural History

The tricuspid valve is the right-sided atrioventricular valve that under normal conditions separates a low-pressure gradient from the right ventricle to the right atrium. It is possible to have a normal CO without a tricuspid valve if the PAPs and resistances are low, and because most tricuspid disease is clinically silent, it is often referred to as the *forgotten valve*.[415]

Tricuspid disease is caused by a structural defect in the valve apparatus or a functional lesion. Primary disorders of the tricuspid valve apparatus that may lead to more significant degrees of TR include congenital disease (ie, Ebstein anomaly), rheumatic valve disease, prolapse, irradiation, carcinoid syndrome, blunt chest trauma, endomyocardial biopsy–related trauma, and right ventricular pacemaker/defibrillator lead trauma.[416–419] In rheumatic disease, histologic involvement of the tricuspid valve may occur in 46% of patients, but it is rarely clinically severe, and in these cases, the valve usually is also stenotic.[56,420]

Despite numerous potential causes of primary tricuspid disease, they account for only 20% of TR cases. The remainder of TR disease is functional in nature. Left-sided valvular disease, usually MR, most commonly is responsible. Functional tricuspid incompetence also can result from MS, AR, or AS and from isolated pulmonary hypertension. Causes of functional TR include dilation of the annulus or leaflet tethering from right ventricular dilation and remodeling,[416,417] global right ventricular dysfunction from cardiomyopathy and myocarditis or segmental dysfunction due to endomyocardial fibrosis, and CAD with resulting ischemia, infarction, or rupture of the right ventricular papillary muscles.[415,421] When mitral valve disease is severe enough to warrant valve repair or replacement, TR may be identified in 30% to 50% of patients.[422-428]

Symptoms of isolated TR are usually minor in the absence of concurrent pulmonary hypertension. Intravenous drug abusers who develop tricuspid endocarditis are the classic example. In these patients, structural damage to the valve may be quite severe, but because they are free of other cardiac disease, they can tolerate complete excision of the tricuspid valve with few adverse effects.[429] Excision of the tricuspid valve in endocarditis has been common because of the undesirability of placing a valve prosthesis in a region of infection.[419] Surgical annuloplasty may be a better long-term option if the valve is structurally salvageable.

Another factor that broadly favors tricuspid repair rather than replacement is the high incidence of thrombotic complications with a valve in this position. The lower pressure and flow state on the right side of the heart are responsible for this phenomenon. Increasingly, valve replacement in the tricuspid area is relegated to patients who have unreconstructable rheumatic valve disease, totally destroyed tricuspid valves from endocarditis, or rare congenital lesions.[430–436] The literature shows improved longer-term outcomes with valve repair than with replacement.[437]

In chronic TR caused by right ventricular dilation, the clinical scenario often is much different from that of isolated tricuspid disease. The major hemodynamic derangements are usually those associated with mitral or aortic valve disease. The RV dilates in the face of the afterload stress from long-standing pulmonary hypertension, and the resultant increase in end-diastolic fiber stretch (ie, preload reserve) promotes increases in SV mediated by the Starling mechanism. These increases are negated by a concurrently increasing right ventricular afterload because of relatively inadequate RVH.[438] Regurgitation through the tricuspid valve reduces right ventricular wall tension at the price of a decrease in effective forward SV.

An important corollary to right ventricular chamber enlargement is the possibility of a leftward shift of the interventricular septum and encroachment on the left ventricular cavity.[439] This phenomenon can reduce the left ventricular chamber size and the slope of the left ventricular diastolic pressure-volume curve, rendering the LV less compliant.[440–442] Septal encroachment may mask left ventricular underfilling by decreasing left ventricular compliance, artificially increasing LVEDP. A failing RV underloads the left side by reduced effective SV and anatomic (ie, septal shift) mechanisms (see Chapter 26).

Right ventricular failure may be relatively mild early in the course of functional TR, but over time, the regurgitation worsens, with further dilation leading to further right ventricular volume overload and chamber enlargement, which may worsen the TR.[418] As in MR, the incompetent tricuspid valve serves as a pop-off circulation during right ventricular systole, and over time, the capacitance of the RA and vena cavae can increase dramatically. Untreated, this eventually leads to systemic venous congestion, hepatic congestion, severe peripheral edema, and ascites.

Because tricuspid insufficiency in the absence of pulmonary hypertension is rare, it has been difficult to demonstrate that chronic volume overload and ventricular dilation result in right ventricular cardiomyopathy. However, when right ventricular volume overload occurs in the context of pulmonic valve insufficiency, right ventricular failure results from volume overload.[443] Clinical experience also supports the presumption of right ventricular cardiomyopathy in severe TR. In late tricuspid insufficiency, right ventricular function can decline when tricuspid valve repair renders the valve competent.

The AHA/ACC guidelines classify TR in four stages (ie, A, B, C, and D). Each stage is subdivided by four defining features, including valve anatomy, valve hemodynamics, hemodynamic consequences, and symptoms.[444] Stage A patients are at risk for functional TR ad have

mild anatomic changes, including mild prolapse, rheumatic changes, early annular dilation, or an intraannular pacemaker or implantable cardioverter-defibrillator (ICD) lead with no hemodynamic or clinical symptoms. Stage B patients have progressive, asymptomatic TR with early annular dilation, moderate leaflet tethering or prolapse, and mild or moderate TR by echocardiographic parameters. Mild TR is defined as a central jet area less than 5.0 cm^2 and a soft, parabolic, and continuous-wave Doppler envelope with systolic-dominant hepatic vein flow. Moderate TR has a central jet area of 5 to 10 cm^2 with a vena contracta width greater than 0.7 cm, a continuous-wave Doppler profile that is dense, and systolic blunting of hepatic vein flow. Patients with moderate TR may have mild inferior vena cava and right atrial enlargement and normal right atrial pressure, and they are often asymptomatic.

Stages C and D are both defined as severe TR identified by echocardiography, but stage D is associated with clinical symptoms, including fatigue, palpitations, dyspnea, abdominal bloating, anorexia or edema, and reduced right ventricular function in the late phase. The echocardiographic definition of severe TR includes flail or grossly distorted leaflets, severe annular dilation (>40 mm or 21 mm/m^2), and marked leaflet tethering. The central jet area is greater than 10.0 cm^2, the vena contracta width is greater than 0.70 cm, and the dense continuous-wave Doppler signal is triangular with an early peak and systolic flow reversal in the hepatic veins.

Medical therapies for patients with severe TR are limited, and treatment should be focused on the causative lesion in patients with functional TR. However, for patients with severe TR and symptoms associated with right-sided heart failure (ie, stage D), the AHA/ACC guidelines recommend diuretic therapy to help decrease volume overload.[445] Pulmonary hypertension is an independent predictor for progression of TR. For patients with severe functional TR (ie, stages C and D), pulmonary vasodilators should be considered in cases of demonstrated responsiveness during invasive testing.[445]

Surgical Decision Making

In cases of structural tricuspid insufficiency, the decision to repair or replace the valve is straightforward. The same cannot be said of functional TR. Because most functional cases are the consequence of left-sided valve lesions with right ventricular overload, the TR usually improves significantly (typically by at least one grade) after the aortic or mitral valve is repaired or replaced. It can be unclear in the operating room whether addition of a tricuspid procedure to the left-sided valve surgery is indicated. In this situation, intraoperative TEE plays an essential role. If the TR is severe in the pre-CPB assessment, tricuspid valve surgery is usually performed.[422] The evidence is less clear when regurgitation is graded as moderate. Some surgeons choose to repair the tricuspid valve in cases of moderate TR, but others advocate observation.[422,424,446]

In the context of left-sided valve surgery, it is common with moderate or more severe TR to complete the left-sided procedure and then reassess the tricuspid valve with TEE when the heart is full and ejecting.[447,448] If the TR remains more than moderate after the left-sided valve is fixed, many surgeons perform the tricuspid procedure. If regurgitation is moderate or less severe, the appropriate surgical course may remain unclear.

A single-center, retrospective study evaluated the impact of untreated moderate or more severe functional TR on outcomes of patients undergoing mitral valve surgery. They were divided into two groups. Group A had no or mild TR ($n = 102$), and group B had moderate to severe TR ($n = 63$). Before hospital discharge, both groups had improvement in the severity of TR after left-sided valve surgery alone. However, during follow-up, the TR grade for group B returned to the preoperative severity or became worse. Moderate or more severe TR was also associated with a lower 5-year survival rate.[449]

Some patients having left-sided valve procedures must return to the operating room for tricuspid surgery, and data from the Mayo Clinic suggest that this problem may be increasing.[450] Their morbidity and mortality rates are probably significantly higher than those for patients undergoing tricuspid valve repair at the time of the aortic or mitral valve procedure.

The evidence regarding tricuspid intervention for mild to moderate functional TR at the time of left-sided heart valve surgery has been extensively developed over the past 15 to 20 years and supports the AHA/ACC guidelines.[425] The reported trials base their intraoperative decision making on TEE findings of severity of TR by Doppler analysis or tricuspid annular diameter, or both. For example, a prospective, single-center, observational trial evaluated the effect of tricuspid annuloplasty in patients undergoing surgery for severe MR.[425] Patients with a tricuspid annular diameter greater than 70 mm (ie, more than two times normal) measured by the surgeon also underwent tricuspid annuloplasty, regardless of the grade of regurgitation. Of the total 311 patients, 148 received mitral valve repair and tricuspid annuloplasty. The patients who underwent the combined procedure had significant improvement in postoperative TR and NYHA functional class. There was no significant difference between the two groups in terms of hospital mortality or 10-year actuarial survival.[425,451]

A second single-center trial evaluated the effect of tricuspid annuloplasty in patients with at least moderate MR with or without a systolic tricuspid annular diameter greater than 24 mm who underwent mitral valve surgery. Of the167 patients who had tricuspid annuloplasty ($N = 298$), 108 had moderate or more severe TR, and 59 cases were based on a systolic tricuspid annular diameter greater than 24 mm. Due to surgeon preference, tricuspid annuloplasty was not performed for 81 patients with a systolic tricuspid annular diameter greater than 24 with mild TR. Postoperatively, reduction of the severity of TR in the treated group lasted for the 1 year of follow-up. In the patients without tricuspid intervention, regression analysis demonstrated that a systolic tricuspid annular diameter greater than 24 was a risk factor for greater TR severity during follow-up.[452]

Several other trials of tricuspid intervention demonstrate a significant improvement in right ventricular remodeling,[453,454] risk of CHF,[30] 6-minute walk test,[29] and a reduction of TR severity postoperatively and for up to 3 to 5 years.[455–458] With all of these outcomes, there is still no reproducible improvement in long-term morbidity and mortality rates.[459]

Functional TR is common and clinically important for patients undergoing left ventricular assist device (LVAD) implantation. In a single center trial of LVAD implantation, the incidence of moderate or severe functional TR was 49%, which persisted after implantation of the LVAD, and was associated with increased hospital stay and inotropic support.[460] A German single-center trial reported that tricuspid annular dilation greater than 43 mm preoperatively predicted decreased survival after LVAD implantation.[461]

Early results of tricuspid procedures at the time of LVAD implantation seemed promising, with improved right ventricular reverse remodeling and significantly reduced severity of TR.[462] In later clinical trials, tricuspid valve intervention at the time of LVAD implantation had little or no positive effect on clinical outcomes.[460,463–466] One metaanalysis suggested that completion of tricuspid valve surgery prolonged CPB times, with no significant difference found for right ventricular support device (RVAD) placement, acute renal failure, or early mortality.[466] Further trials are required to resolve the question about the best management of TR in LVAD recipients.[425]

Decision making for cases of functional TR is made more complicated by the inability to rigorously quantify the severity of the regurgitation and right ventricular dysfunction.[450] As with MR and the LV, significant TR makes right ventricular function difficult to assess because the regurgitant fraction leads to a falsely increased EF. In the absence of sophisticated echocardiographic assessments, such as determination of the rate of right ventricular pressure increase with pulsed Doppler, it is common to look at enlarged right ventricular chamber size and a decrease in RVEF as indicators of decompensation.[450,467]

Clinical experience suggests that pulmonary hypertension is likely to be a marker for right ventricular failure after tricuspid surgery, but

studies of sufficient size are lacking. Like assessment of right ventricular function, grading of TR severity is at best semiquantitative. Color-flow mapping of the volume of the regurgitant jet in the RA is standard,[437] and this can be supplemented by looking for systolic flow reversal in the portal veins using pulsed-wave Doppler.[468] Although the assessment of residual TR after left-sided valve surgery is important, the tricuspid valve is sometimes difficult to examine with TEE, and the presence of an aortic or mitral mechanical prosthesis makes the assessment more difficult.

Anesthesia Considerations

Because most tricuspid surgery occurs in the context of significant aortic or mitral disease, anesthesia management primarily is determined by the left-sided valve lesion. The exception is when significant pulmonary hypertension and right ventricular failure exist. Under these conditions, the primary impediment to hemodynamic stability after surgery is right ventricular failure rather than the left-sided process.

If right ventricular dysfunction is predicted, it is useful to place a PAC, even if the tricuspid valve will be replaced. If the PAC must be removed because of tricuspid valve replacement, it still can be helpful to obtain CO and PAPs before CPB to get insight into right ventricular function and anticipate the hemodynamic support that may be required. A PAC is of greater use than CVP alone because the CVP is a poor index of intravascular filling and the degree of TR. he RA and vena cavae are highly compliant and accept large regurgitant volumes with relatively little change in pressure.

A PAC also is useful when intraoperative TEE is used. As in AR within the LV, the RV in chronic TR is volume overloaded and dilated and requires a large EDV to maintain forward flow. Because of the unreliability of the CVP as an indicator of filling, it is possible to volume overload patients with TR and right ventricular failure. Cardiac output in right ventricular failure often can be augmented with the use of vasodilators, and although right ventricular dimensions can be followed intraoperatively with TEE, maximizing CO (sometimes at the cost of systemic arterial pressure) is best done with serial CO measurements (as in AR). When there is significant right ventricular distention, the possibility of septal shift and secondary deterioration of left ventricular diastolic compliance should be carefully considered. Echocardiography is uniquely helpful for this assessment.

Post-CPB treatment of the patient undergoing an isolated tricuspid valve procedure is usually straightforward. Patients usually do not have significant right ventricular failure or pulmonary hypertension and typically require only a brief period of CPB without aortic cross-clamping. A larger group of patients, particularly those with TR related to AS, typically come off CPB with little need for support of the RV. These patients often do well because the improvement in left ventricular function after AVR for AS is usually sufficient to reduce PAPs significantly and offload the right heart. When left-sided valve surgery is for mitral disease, the improvement usually is not as marked, and greater degrees of inotropic support of the RV often are indicated. The combination of a phosphodiesterase inhibitor with a vasodilator and a catecholamine infusion is useful. Serial CO measurements to balance systemic pressure and right ventricular output and filling are critical.

A few other practical points on tricuspid valve repair and replacement should be made. First, because right-sided pressures can be chronically increased with TR, it is important to look for a patent foramen ovale and the potential for right-to-left shunting before initiation of CPB. Second, intravascular volume may be quite high in this patient population, and it is often practical to avoid red blood cell transfusion by hemofiltration during bypass. Third, if the patient has significant right ventricular dysfunction or peripheral edema or ascites, there is the potential for a coagulopathy related to liver congestion, and the patient should be treated accordingly. Fourth, central catheters, particularly PACs, should not be entrapped by right atrial suture lines.

Innovations in Valve Repair

Interventional cardiology has had a significant impact on the volume of CABG, and it can be predicted that interventional cardiology will alter surgery for VHD over time. Many less invasive approaches to mitral valve repair are being assessed in animal studies or clinical trials, and tremendous inroads have been made in percutaneous replacement of the aortic valve. Innovations also are being made in surgical valve repair, including aortic valve repair and closed- and open-chamber procedures for MR.

Aortic Valve Repair

During the past several years, there has been a major shift from valve replacement to valve repair in patients with degenerative mitral valve disease. The same has not been true of the aortic because the valve disease is different in most patients and because of the high flow and pressure conditions across the aortic valve that make repair more prone to failure. However, aortic valve repair is being increasingly done as an appropriate patient population is defined.

Although valve repair for AR has found broader use when regurgitation is associated with dissection or dilation of the aortic root,[469,470] isolated valve repair has been less common. A growing body of data suggests that aortic valve repair may offer advantages over valve replacement in younger individuals with AR due to bicuspid valves.[469,471] In contrast with AVR, aortic valve repair eliminates the need for anticoagulation for a mechanical valve and should delay the need for reoperation for a failed tissue valve.

When regurgitation occurs with a bicuspid valve, the insufficiency usually is caused by retraction or prolapse, or both, of the conjoined cusp. Repair consists of a triangular incision to shorten and elevate the cusp to improve apposition. Although very-long-term follow-up results have not been reported, in a large series from the Mayo Clinic with a mean follow-up of 4.2 years, late failure of the repair requiring reoperation occurred in 14 of 160 consecutive patients. Most of the failure was attributed to repairs done in the first decade of the 15-year experience.[469]

As a result of this experience, aortic valve repair is likely to find increasing application in this patient population. For this group, anesthesia management usually is straightforward, although the clinical indications for valve repair in AR are the same as those for valve replacement. The compelling issue for the anesthesiologist in these cases is echocardiographic assessment of the valve for suitability of repair and the adequacy of the repair after the procedure.

Sutureless Valve Replacement

Surgical aortic valve replacement continues to be the gold standard for patients with severe symptomatic aortic valve stenosis. Transcatheter aortic valve replacement (TAVR) reduced the rate of death and cardiac symptoms for patients deemed inoperable compared with medical therapy alone.[472] These procedures have been associated with a decreased mortality rate at 1 year compared with open surgery in high-risk patients.[473] However, these procedures are not without risk. A systematic review of TAVR in high-risk surgical patients reported a 30-day mortality rate between 0% and 25%, with risks of other complications, including bradyarrhythmias requiring permanent pacemaker insertion, cardiac perforation, myocardial infarction, access-related complications, and other valve-related issues such as perivalvular leak and unknown long-term durability[474] (see Chapters 3 and 27).

There is increased interest in the treatment of aortic valvular disease with sutureless AVR in patients who can benefit from a shorter cross-clamp time but are not truly inoperable.[475] In the early 1960s, Magovern and coworkers[476] described implantation of specially made sutureless aortic and mitral valve prostheses (Fig. 21.39). The goal of rapid nonsuture fixation was achieved, decreasing CPB times; however, the technique was subsequently abandoned because of paravalvular leaks and valve-related thromboembolic events.

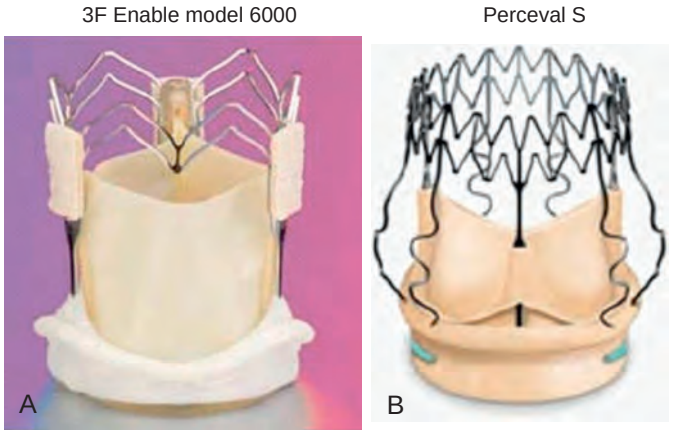


Fig. 21.39 ATS 3f Enable (A) and Perceval S (B) sutureless bioprosthetic aortic valves. *(A, Courtesy ATS Medical, Minneapolis, MN. B, Courtesy of Sorin Biomedica Cardio Srl, Saluggia, Italy.)*

With the rapid technologic progress made in transcatheter valve technology and materials, sutureless AVR has been proposed as an additional therapeutic option for high-risk patients with severe AS. Potential advantages of sutureless AVR include removal of the diseased and often calcific native aortic valve and reduction in aortic cross-clamp and CPB times in the setting of a potentially minimally invasive surgical approach.

The Perceval S (Sorin group, Arvada, CO) and the ATS 3f Enable (ATS Medical, Minneapolis, MN) valves consist of bovine or equine pericardial tissue on a self-expanding nitinol frame. After access to the aortic valve is obtained and the diseased valve excised, the appropriate valve size is selected using dedicated sizers. The 3f Enable valve is deployed by rinsing it with warm saline, and the nitinol frame expands in the annulus.[477] The Perceval S valve uses a balloon inflation to complete deployment of the valve.[478]

Early results of the use of these devices seem promising. Eichstaedt and colleagues[479] reported a retrospective, single-center analysis of 120 patients who underwent isolated AVR or combined AVR with other cardiovascular procedures using the ATS 3f Enable device. In the isolated AVR group, the mean CPB time was 62 ± 18 minutes, and the mean cross-clamp time was 37 ± 11 minutes. The researchers found that in an ideal situation, aortic cross-clamp times of less than 20 minutes were feasible. Reapplication of the aortic cross-clamp was necessary in 10 patients; causes included paravalvular leak (7 patients), acute migration of the prosthesis into the LV (2 patients), and ascending aorta (1 patient). The overall 30-day mortality rate was 6.7% (8 of 120 patients), with a reoperation rate of 4.3% (5 of 120 patients). The long-term durability has not been reported.

Folliguet and coworkers[478] described 208 high-risk patients enrolled in an international, multicenter, prospective, nonrandomized study of the Perceval S prosthesis in patients requiring AVR with or without concomitant procedures. Implantation was successful in 95.6% of patients. In the isolated AVR group, CPB time was 50 ± 22 minutes, with a cross- clamp time of 30 ± 12 minutes. During follow up, 4% (9 patients) developed a paravalvular leak requiring reoperation. Two of these patients developed an intraprosthetic leak, one due to endocarditis and the other due to pannus ingrowth on the stent causing restricted leaflet motion. Although the 30-day mortality rate was not reported, 2.4% (5 patients) died during the hospital stay with no evidence at autopsy of valve-related pathology.

Development of the sutureless aortic valve has found a specific role in the setting of minimally invasive AVR. In a retrospective, observational cohort study, Gilmanov and colleagues[480] compared a total of 515 patients who underwent surgical AVR with a right anterior minithoracotomy with placement of a sutureless ($n = 246$) or conventional ($n = 269$) aortic prosthesis. In patients who underwent sutureless valve implantation, CPB times and cross-clamp times were significantly shorter. A larger prosthesis could be implanted in the sutureless group. There were no significant differences between the groups in conversion to sternotomy, reexploration for bleeding, intensive care unit or hospital length of stay, or overall survival.

New Techniques for Mitral Valve Repair

MR frequently is associated with CHF. In dilated and ischemic cardiomyopathy, enlargement of the mitral annulus results in a failure of coaptation of the mitral leaflets and valve incompetence. Although cardiac surgery is an effective treatment, morbidity can be high. Three approaches have been developed to address MR occurring in the absence of structural mitral pathology. They address the failure of leaflet coaptation at the level of the valve leaflets or valve annulus or by altering the anatomic relationship of the septal and lateral walls of the LV.

Altering Ventricular Anatomy to Reduce Mitral Regurgitation

Valve leaflet and annulus repair techniques are described in earlier sections of this chapter and in Chapters 3 and 27. The approach to closed mitral valve repair consists of altering the geometry of the lateral and septal left ventricular walls to bring the valve leaflets together. The commercial Coapsys device has entered clinical trials. It consists of anterior and posterior epicardial pads connected by a cord. With an open chest, the cord is placed transventricularly in a subvalvular position, and the tension on the cord is adjusted before the opposing epicardial pad is fixed in place.[481] This effectively brings the ventricular walls together and improves leaflet coaptation. TEE is used to optimize cord length and pad positioning.

In contrast to the leaflet-based and annulus-based approaches, the Coapsys approach is surgical, requiring an open chest but not CPB. The position of the epicardial vessels and the relation to the submitral apparatus could pose significant risk, but the device has been used successfully in animal models.

Percutaneous Valve Replacement

Although surgery, particularly for aortic valve disease, has expanded to include a much older population, there remains a subset of patients for whom cardiac surgery may entail unacceptable risks. For them, less invasive techniques such as percutaneous valve replacement are being developed.

The first clinical percutaneous placement of an aortic valve was reported in 2002.[482] Experience and technical refinement have led to the two current strategies for transcatheter AVR: retrograde through the femoral artery and advanced into the aorta and across the aortic valve or antegrade through a limited thoracotomy, in which a valve-loaded catheter punctures the left ventricular apex and the new valve is seated antegrade (see Chapters 3 and 27).

Covello and collaboratrs[483] described management strategies and periprocedural outcomes for 18 patients in whom retrograde, percutaneous AVR was performed through the femoral artery. The treatment of 100 patients who underwent successful transapical antegrade aortic prosthesis placement was reported by Fassl and associates.[484] Although technical aspects of prosthetic valve delivery were different, common themes included the need for rigorous assessment of aortic leaflet, root, and coronary ostial anatomy; a well-coordinated, multidisciplinary approach to patient evaluation and clinical management; the use of rapid ventricular pacing to diminish CO during prosthesis deployment; and the potential for sudden hemodynamic collapse necessitating emergent intervention.

In a report of retrograde transfemoral AVR by Covello and colleagues,[483] general anesthesia was used early; however, with experience, monitored anesthesia care was selected. This contrasts with the practice

of anesthesiologists at other centers, where relatively large numbers of transfemoral, retrograde AVR procedures are performed. The advantages of general anesthesia include patient immobility during rapid ventricular pacing, valvuloplasty, and prosthesis deployment. General anesthesia facilitates surgical repair of the femoral cannulation site, which may be required. The use of general anesthesia allows prolonged TEE imaging and rapid intervention in the event that sternotomy or CPB becomes an emergent necessity (see Chapter 27).

Transapical catheter-based AVR typically is selected because of vasculopathy, small or tortuous femoral and iliac vessels, or severe aortic atheromatous disease. After general anesthesia, typically in a hybrid operating suite, a small left anterior thoracotomy is made, and the ventricular apex is exposed. Balloon aortoplasty is performed, and under a combination of fluoroscopic and echocardiographic guidance, the aortic valve is seated with deployment of a balloon.

The long-term benefits of less invasive interventions are being compared with each other or with traditional surgical approaches. Some investigators are finding use in high-risk patients as temporizing procedures, in place of reoperations, or in conjunction with percutaneous approaches for CAD. These technologies will get better, and there will be further pressure for clinical applications. The most important considerations will be case selection and long-term follow-up of outcomes.

Case Study 1: Transapical Aortic Valve Implantation

Framing

- An 89-year-old man with medical history significant for four-vessel CABG performed 11 years earlier
- Recurrent CAD with recent placement of two bare metal stents in the left internal mammary artery (LIMA) and into the left anterior descending (LAD) artery at a distal anastomosis 1 month earlier
- Dyspnea on exertion with mild chest tightness that goes away with rest
- Severe, symptomatic AS; does not wish to be considered for repeat sternotomy
- Patient's femoral anatomy not conducive to transfemoral transcutaneous aortic valve replacement; consider for transapical approach
- NYHA class II heart failure
- Society of Thoracic Surgeons risk of death is 20.9%

Medical and Surgical History

- Severe AS with a valve area of 0.73; mild to moderate AR with a mean transaortic gradient of 44 mm Hg
- CAD, four-vessel CABG 11 years earlier
- Placement of two bare metal stents 1 month earlier
- Moderate mitral regurgitation
- Atherosclerotic cerebrovascular disease, bilateral carotid endarterectomy 2 years earlier
- Mild pulmonary hypertension
- Type 2 diabetes mellitus
- Hypercholesterolemia
- Hypertension
- Chronic kidney disease
- Peripheral vascular disease
- Sleep apnea

Current Medications

- Furosemide, 40 mg once per day
- Glipizide, 10 mg bid
- Hydralazine, 25 mg tid
- Metoprolol, 25 mg bid
- Nitroglycerin (NitroQuick), 0.4 mg prn
- Rosuvastatin, 20 mg
- Timolol, 0.5% drops
- No known medication allergies

Vital Signs

- Height: 154.80 cm
- Weight: 61 kg
- Body mass index (BMI): 25.5 kg/m^2
- Body surface area (BSA): 1.64 m^2
- Afebrile
- Pulse 58/min
- Blood pressure: 156/61 mm Hg
- Chest radiograph
  - Sternotomy
  - Prominent left nipple shadow
  - Fibrotic strands in the bases
  - Calcified granulomas
  - Surgical clips on left side of the neck
  - Unchanged since previous radiograph
- Electrocardiogram
  - Ventricular rate: 56
  - Sinus bradycardia, left ventricular hypertrophy with secondary ST-T abnormalities
  - Cannot rule out anteroseptal infarct
  - No significant change was found

Laboratory Results

- Hemoglobin: 12.8 g/dL
- Platelets: 164,000/μL
- International normalized ratio (INR): 1.0
- Sodium (Na^+): 138 mmol/L
- Potassium (K^+): 4.0 mmol/L
- Glucose: 109 mg/dL
- Creatinine: 2.2 mg/dL

Data Collection and Interpretation

Computed Tomography Without Contrast of the Chest, Abdomen, and Pelvis

The aortic annulus measured 33 mm. The left main artery–to–aortic valve annulus dimension was 18 mm. The diameter at the sinus of Valsalva was 35 mm. The sinotubular junction was 31 mm. The diameter of the ascending aorta was 34 mm. The diameter of the aortic arch was 24 mm. The diameter of the aorta at the diaphragm was 24 mm. Extensive vascular disease included coronary artery calcifications. There were extensive aortic valve and mitral annular calcifications.

Bilateral renal atrophy was identified. The infrarenal aorta was 10 × 12 mm. The right common iliac artery was 10 × 11 mm. The right external iliac artery was 8 × 8 mm. The right common femoral artery was 5 × 6 mm. The left common iliac artery was 10 × 9 mm. The left external iliac artery was 9 × 9 mm, and the left common femoral artery was 5 × 5 mm.

Cardiac Catheterization and Percutaneous Transluminal Coronary Angioplasty Summary

The patient had a prior four-vessel CABG. Angiography showed patent vein grafts to the first and second obtuse marginal branches and to the diagonal branch. The free LIMA graft to the LAD artery had severe disease. The patient's native right coronary artery had severe disease, but this vessel could not be bypassed earlier when he had CABG surgery. The patient also has chronic renal insufficiency limiting the possibility of multivessel percutaneous coronary intervention because of limitation in contrast load. He had successful percutaneous transluminal coronary angioplasty (PTCA) of the middle LAD artery and

successful PTCA of the distal site of free internal mammary graft to the middle LAD artery.

Description of Operation

The patient underwent general anesthesia in the supine position, and a left inframammary incision was made in the chest entered over the top of the fifth rib. Purse-string sutures were placed just lateral to the apex of the heart. Heparin was given, and the activated coagulation time (ACT) was maintained above 300 seconds. The apex of the heart was punctured with a needle, and the wire was advanced across the aortic valve under fluoroscopic guidance. A wire was advanced up into the proximal ascending aorta, and a 23-cm, 7-Fr sheath was advanced across the aortic valve. The 7-French sheath was removed. The Ascendra sheath was inserted without difficulty. The balloon was advanced across the aortic valve. Rapid ventricular pacing was instituted and the balloon aortic valvuloplasty completed. The balloon was removed, but the patient remained hypotensive with increases in his PAPs refractory to escalating doses of epinephrine. We elected to proceed rapidly with placement of the valve.

Rapid ventricular pacing was instituted, and the valve was positioned perfectly. The balloon was deflated, and rapid ventricular pacing was stopped, but the patient remained hypotensive. The Ascendra sheath and wire were removed, and TEE showed good valvular function with no significant AR. Because there was significant PAP elevation and right-heart function was poor by TEE, the patient was prepared for femoral-femoral bypass.

A percutaneous arterial cannula was placed over a wire, the femoral artery was dilated without apparent difficulty, and a 15-Fr percutaneous arterial inflow cannula was placed. A 22-Fr percutaneous venous cannula was then inserted, and CPB was initiated. During this time, the patient was hypotensive and required initiation of external cardiac massage. The patient had recurrent ventricular fibrillation and was successfully defibrillated to a stable cardiac rhythm.

The PAPs began to decline, and the heart function appeared to improve. However, the CPB circuit volume could not be maintained, and a retrograde arteriogram identified extravasation of contrast at the bifurcation of the right common iliac artery. An attempt was made to place an endograft. A balloon was inflated in the infrarenal aorta to achieve proximal control to come off CPB. The arterial inflow line was transferred to the venous line to continue to give blood. Limited angiography confirmed disruption of the proximal right external iliac artery. Blood pressure could not be supported; the patient deteriorated and arrested. Despite cardiopulmonary resuscitation, the patient died (see Video 21.1).

Discussion

This case illustrates almost every major clinical point about the assessment and care of patients undergoing transapical AVR. There were clinical indications for a catheter-based approach:

1. The patient's desire not to undergo an open-chest approach
2. History of prior multivessel CABG
3. Perioperative risk factors, including advanced age, diffuse vasculopathy, and chronic renal insufficiency

Evaluation for a catheter-based approach demonstrated aortic valvular, sinus, and coronary anatomy suitable for catheter-based placement but severe iliac and femoral vasculopathy that excluded a transarterial approach.

A multidisciplinary approach to evaluation and preoperative optimization included participation of the cardiac surgery, echocardiography, interventional cardiology, anesthesiology, and radiology departments. The patient underwent cardiac catheterization, PTCA, and noncontrast computed tomography, and surgery was scheduled a month later to allow renal recovery.

The case was managed in a hybrid operating room with the presence of specialists in interventional cardiology and cardiovascular surgery, along with CPB standby and one-to-one coverage by a cardiovascular anesthesiologist. The technical approach to surgery was exactly as planned. Femoral vessels were wired in advance, and by a transapical approach, the valve was positioned without difficulty. However, three complications developed that are relatively common with this technique in this population: refractory hypotension after rapid ventricular pacing, difficulty in establishing rapid CPB support because of the small size and calcification of femoral and iliac vessels, and iliac artery disruption.

Although catheter-based AVR is less invasive than the open-chest approach, it probably requires more planning, complex assessment, and coordination than conventional cardiac surgery. Most patients have comorbid conditions that make them poor open surgical candidates, and untoward events during these procedures are life-threatening.

Case Study 2: Robotically Assisted Mitral Valve Repair

Framing

A 46-year-old woman had a 4-month history of decreasing tolerance for strenuous exercise. An advertising executive and amateur triathlete, she reported that increased fatigue prevented her from jogging more than 4 miles in a day. Evaluation by her physician revealed a new systolic murmur, and she was referred for echocardiography.

TTE revealed a flail posterior mitral valve leaflet with an eccentric, anteromedially directed jet of severe MR. Reliable quantification of the regurgitant volume by the PISA method was not possible. However, systolic flow reversals were identified during pulsed-wave Doppler examination of the right superior pulmonary vein. This study also demonstrated normal left ventricular dimensions in systole and diastole and a calculated EF of 67%. The LA was mildly enlarged. The right-heart chambers were of normal size, and the calculated right ventricular systolic pressure was 35 mm Hg.

During an appointment with a cardiologist, surgical consultation for possible mitral valve repair was recommended. The patient was hesitant to pursue surgery for several reasons. She worried about missing work and being unable to drive during a multiweek postoperative convalescence. She was concerned about the cosmetic implications of a median sternotomy, and she was uncertain about her need for surgical intervention at that time because she experienced symptoms only with vigorous exercise.

Data Collection and Interpretation

Although visualization of the mitral valve is superior with TEE compared with TTE, flail mitral leaflets often can be identified during transthoracic examinations. This patient had a flail leaflet that was likely caused by chordal rupture. Although quantification of the mitral regurgitant volume or effective regurgitant orifice by the PISA method was not possible during the TTE examination, the severity of the regurgitation was supported by the finding of systolic flow reversals in the right superior pulmonary vein. The right superior pulmonary vein is often the easiest pulmonary vein to visualize during TTE studies when using an apical four-chamber view. PISA analysis may be difficult in some patients with eccentrically directed regurgitant jets because of the difficulty in aligning the Doppler cursor with a significant portion of the regurgitant jet, with the resultant inability to measure the peak regurgitant velocity and obtain a complete regurgitant velocity-time integral.

In addition to detecting severe, organic MR, other important information was obtained during the TTE examination. For example, there was no evidence of left ventricular enlargement, and the calculated EF was 67%. Mild left atrial enlargement was consistent with the reported 4-month history of symptoms; severe MR of longer duration might be expected to produce a greater degree of left atrial dilation. A calculated right ventricular systolic pressure of 35 mm Hg likely corresponds to a mean PAP of less than 25 mm Hg and does not indicate pulmonary hypertension.

If surgical intervention is anticipated, additional information must be sought. Confirmation of the mechanism of MR and a thorough inspection for anterior leaflet pathology can be obtained by intraoperative TEE. The presence or absence of a patent foramen ovale can be determined by intraoperative TEE. The decision about whether to pursue preoperative coronary angiography in a 46-year-old, athletic woman depends on other risk factors for premature CAD and physician preference. The preoperative electrocardiogram should be examined for evidence of atrial tachyarrhythmias such as AF that may lead to consideration of additional surgical interventions such as the Maze procedure or exclusion of the left atrial appendage.

Decision Making and Reassessment

In deciding whether to proceed with surgery in this patient, several factors must be considered. Her MR was organic in nature, and medical management was unlikely to prevent deleterious structural changes in the heart over time such as left ventricular dilation. Progression of the severity of MR can be expected in the absence of surgical intervention.[307] A flail mitral leaflet is associated with a small but defined increase in the annual risk for sudden cardiac death; the risk can be reduced by surgical repair.[306] The patient's LVEF is currently acceptable. Postponing surgery risks the development of left ventricular systolic dysfunction. A decline in EF to less than 60% is associated with reduced survival after mitral surgery.[310] All these factors combined with a procedural mortality rate of less than 1% in many centers argue for early elective mitral valve repair.

Concerns related to cosmetic outcome and delayed return to work may be addressed by offering the patient a minimally invasive surgical approach with or without robotic assistance. A 4-cm incision in the right inframammary crease provides an excellent cosmetic result for many women. Minimally invasive techniques, including robotically assisted surgery, have been associated with decreased postoperative pain scores, earlier hospital discharge, and earlier return to work.

The patient was referred to a surgeon who was experienced in robotically assisted mitral valve repair. On the day of surgery, the anesthesiologist performed a series of right paravertebral injections before induction of anesthesia. One-lung ventilation was achieved by means of a double-lumen endotracheal tube. The intraoperative TEE confirmed the presence of a flail middle scallop of the posterior mitral leaflet with multiple ruptured chords (see Videos 21.2 and 21.3). No additional valvular pathology was found, and the atrial septum was intact. Cannulation for CPB, which was guided by intraoperative TEE, included femoral arterial and venous lines, as well as a 16-Fr superior vena cava cannula placed percutaneously through the right internal jugular vein. Cardioplegia was given antegrade through a catheter placed into the aorta by means of a right parasternal stab incision. Aortic cross-clamping was accomplished with a long-shafted clamp introducer through a stab incision in the right lateral chest wall. Mitral repair was performed with robotic assistance and consisted of a triangular resection of the middle scallop of the posterior mitral leaflet and insertion of a flexible posterior annuloplasty band.

The patient was weaned from CPB without difficulty and extubated in the operating room at the conclusion of surgery. Her postoperative course was uneventful, and she was discharged on postoperative day 3.

Case Study 3: Mitral Valve Repair With Systolic Anterior Motion After Bypass Needing Additional Repair

A 66-year-old male presented for mitral valve repair. He had a known history of moderate MR followed for 7 years. He had recently developed worsening of his chronic shortness of breath. Echo showed more LV dilatation compared to 6 months ago. His mitral regurgitant volume was 79 mL, his LA was dilated at 63mm. His LV end-diastolic and end-systolic diameters were 58 and 33mm, respectively. EF was preserved at 66%.

Video 21.4 shows a significantly prolapsed P2 segment. On CPB, the leaflets were severely myxomatous with a prolapsed P2 and a long, floppy anterior leaflet. The surgical repair consisted of a quadrangular P2 resection with extended sliding leaflet repair reinforced with a 30-mm partial annuloplasty band placed trigone to trigone. Coming off CPB, the long anterior leaflet and the patient's hyperdynamic conditions created severe MR with systolic anterior motion (SAM) of the mitral valve (see Videos 21.5 and 21.6).

A decision was made to surgically correct this phenomenon. The patient was placed back on full CPB. The heart was rearrested, the LA was reopened, and the surgeon performed a more radical sliding-leaflet resection of the entire posterior leaflet.

The patient was weaned off CPB without inotropes and under better loading conditions (see Videos 21.7 and 21.8). The patient had no residual SAM and had good valve function with no residual MR.

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22

Congenital Heart Disease in Adults

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KEY POINTS

1. Because of successes in treating congenital cardiac lesions, there are currently as many or more adults than children with congenital heart disease (CHD).
2. These patients may require cardiac surgical intervention for primary cardiac repair, repair following prior palliation, revision of repair due to failure or lack of growth of prosthetic material, or conversion of a suboptimal repair to a more modern operation.
3. Noncardiac anesthesiologists will see these patients for a vast array of ailments and injuries requiring surgery.
4. If at all possible, noncardiac surgery on adult patients with moderate-to-complex CHD should be performed at an adult congenital heart center with the consultation of an anesthesiologist experienced with adult CHD.
5. Delegation of one anesthesiologist as the liaison with the cardiology service for preoperative evaluation and triage of adult CHD patients is helpful.
6. All relevant cardiac tests and evaluations should be reviewed in advance.
7. Sketching out the anatomy and path(s) of blood flow is often an easy and enlightening aid in simplifying apparently very complex lesions.

Advances in perioperative care for children with congenital heart disease (CHD) over the past several decades has resulted in an ever-increasing number of these children reaching adulthood with their cardiac lesions palliated or repaired. The first paper on adult CHD, published in 1973,[1] is of increasing interest to the medical community. A brief search for the term "adult congenital heart disease" found 51 papers published from 1995 to 2004 and 433 from 2005 to 2014. The field has grown such that several texts are now devoted to it, and a dedicated specialty society, the International Society for Adult Congenital Heart Disease (http://www.isachd.org), was formed in the 1990s. Each year an estimated 32,000 new cases of CHD occur in the United States and 1.5 million worldwide.[2] More than 85% of infants born with CHD are expected to grow to adulthood. It is estimated that there are more than 1 million adults with CHD in the United States[3] and 1.2 million in Europe,[4] and this population is growing at approximately 5% per year; 55% of these adults remain at moderate-to-high risk, and more than 115,000 in the U.S. have complex disease.[5] The increasing survival of children with complex disease has shifted the spectrum of adults with CHD. Once it was thought that adults represent milder degrees of disease, but this is now changing.[3,6,7] Annual admissions for adults with CHD have increased significantly faster than those for children, and adults now account for 37% of admissions for those with CHD.[7] As many adults as children have congenital cardiac defects considered severe.[6] As an example to support the increased life expectancy of this patient group, the leading cause of mortality in adults with acyanotic CHD in the United States is currently coronary artery disease (arrhythmia remains the leading cause of death for cyanotic patients, as it was for acyanotic patients before 1990).[8] Not surprisingly, mortality in adults with CHD is increased with increased disease severity, and in one large series 77% of deaths in this group were from cardiovascular causes.[9] These patients can be seen by anesthesiologists for primary cardiac repair, repair following a prior palliation, revision of repair due to failure or lack of growth of prosthetic material, or conversion of a suboptimal repair to a more modern operation (Box 22.1). In addition, these adults with CHD will be seen for the other common ailments of aging and trauma that require surgical intervention. Additionally, women of childbearing age with CHD will become pregnant. They must cope with the added physiologic demands of pregnancy and will require analgesia for labor and anesthesia for cesarean delivery. Although it has been suggested that teenagers and adults can have repair of congenital cardiac defects with morbidity and mortality approaching that of surgery done during childhood, these data are limited and may reflect only a relatively young and acyanotic sampling.[10] Other data suggest that, in general, adults over 50 years of age represent an excessive proportion of the early postoperative mortality encountered, and the number of previous operations and cyanosis are both risk factors.[11]

Despite the fact that congenital cardiac disease carries implications for lifelong medical problems, a significant number of patients, even those with lesions deemed severe, will not have continuing cardiology follow-up, despite ongoing general medical care.[12] These patients bring with them anatomic and physiologic complexities of which physicians accustomed to caring for adults may be unaware, as well as medical problems associated with aging or pregnancy that might not be familiar to physicians used to caring for children. This is even more complicated because a significant number of these patients will be unaware of their cardiac diagnosis, and having lived with their disease for many years, these patients will self-limit exercise or think of themselves as asymptomatic, when in fact they are not.[13] This problem has led to the establishment of the growing subspecialty of adult CHD. Two Bethesda conferences have been devoted to the issue, most recently in 2001.[14] The American College of Cardiology reviewed the available evidence and published superb guidelines for the care of these patients in 2008.[15] It is important to note that most of the current recommendations are based on Level C evidence (only consensus opinion or case studies) because prospective studies and large registries of patient outcomes are rare. A major recommendation of both Bethesda Conferences (also recommended by conferences in Canada[16] and Europe[17]) was that adult patients with moderate or complex CHD be cared for in specialized adult congenital heart centers. This recommendation, as logical as it was, was unsupported until recently, when a study from Quebec showed that mortality for adult congenital heart disease (ACHD) patients decreased following the introduction of specialized ACHD centers and that less than half die of cardiovascular diseases.[18] This

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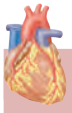


BOX 22.1 INDICATIONS FOR CARDIAC SURGERY IN ADULTS WITH CONGENITAL HEART DISEASE

- Primary repair
- Total correction following palliation
- Revision of total correction
- Conversion of suboptimal obsolescent operation into more modern repair
- Heart transplantation

is in contrast to the findings of the Dutch CONCOR registry, which found that 77% of deaths were cardiovascular in origin: chronic heart failure in 26% (mean age 51 years) and sudden death in 19% (mean age 39 years) were the most common.[9] Another review determined that among adults with CHD and cyanotic lesions, the leading cause of death was arrhythmia followed by heart failure. For patients with acyanotic disease, however, the leading cause of death until 1990 was arrhythmia; after 1990, it was myocardial infarction, consistent with the longer lifespan of these patients.[19]

An informed anesthesiologist is a critical member of the team required to care optimally for these patients. A specific recommendation of the Bethesda conference was that noncardiac surgery on adult patients with moderate-to-complex CHD be done at an adult congenital heart center (regional centers) with the consultation of an anesthesiologist experienced with ACHD.[14,20] In fact, one of the founding fathers of the subspecialty wrote, "A cardiac anesthesiologist with experience in CHD is pivotal … . The cardiac anesthesiologist and the attending cardiologist are more important than the noncardiac surgeon."[2] Despite this recommendation, the majority of adult patients with CHD having ambulatory surgery appear not to be having their surgery at ACHD centers.[21]

TABLE 22.1 Rhythm Disturbances in Adults With Congenital Heart Disease

Rhythm Disturbance	*Associated Lesions*
Tachycardias	
Wolff-Parkinson-White syndrome	Ebstein anomaly Congenitally corrected transposition
Intraatrial reentrant tachycardia (atrial flutter)	Postoperative Mustard Postoperative Senning Postoperative Fontan Tetralogy of Fallot Other
Atrial fibrillation	Mitral valve disease Aortic stenosis Tetralogy of Fallot Palliated single ventricle
Ventricular tachycardia	Tetralogy of Fallot Aortic stenosis Other
Bradycardias	
Sinus node dysfunction	Postoperative Mustard Postoperative Senning Postoperative Fontan Sinus venosus ASD Heterotaxy syndrome
Spontaneous AV block	AV septal defects Congenitally corrected transposition
Surgically induced AV block	Surgical VSD closure Subaortic stenosis relief AV valve replacement Device closure of VSD

ASD, Atrial septal defect; *AV,* atrioventricular; *VSD,* ventricular septal defect.
Reprinted with permission from ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2008;52:e143–e263.

Noncardiac Surgery in Adults With Congenital Heart Disease

A recent study utilizing the National Surgical Quality Improvement Program database confirmed that young adults (aged 18-39 years) with a history of cardiac surgery had increased risk of a series of serious morbidities and mortality following noncardiac surgery.[22] A survey of academic anesthesiology faculty at a leading institution showed that, not unexpectedly, those with pediatric and cardiac fellowship training had better knowledge than other faculty about ACHD, whose knowledge was generally low and who had decreased levels of comfort in caring for these patients.[23] High-risk patients include, but are not limited to, those with Fontan physiology, cyanotic disease, severe pulmonary arterial hypertension, complex disease with residua such as heart failure, valve disease or the need for anticoagulation, or the potential for malignant arrhythmias (Table 22.1). Centers may find it helpful to delegate one attending anesthesiologist to be the liaison with the cardiology service to centralize preoperative evaluations and to delegate the triage of patients to an anesthesiologist with specific expertise in managing patients with CHD, rather than relying on random consultations with generalist anesthesiologists.[23]

Adults with CHD represent approximately 0.1% of admissions represented in the National Inpatient Sample, and this has increased from about 0.07% to 0.18% from 2002 to 2009.[24] The fraction of adult CHD admissions associated with noncardiac surgery also increased over this time period. Most were cared for in nonteaching hospitals. It was shown several years ago that CHD conferred an incremental mortality risk with noncardiac inpatient surgery in children.[25] This has now been confirmed for adults with CHD having inpatient noncardiac surgery. In data from the National Inpatient Sample, mortality was greater in the adult CHD cohort (odds ratio 1.3), as was a composite morbidity endpoint (odds ratio 1.44) compared with a matched cohort without CHD.[24] In both the pediatric and adult studies, mortality was highest with the most complex lesions. Risk factors for noncardiac surgery include heart failure, pulmonary hypertension, and cyanosis.[26]

The classic examination question of onset of anesthesia with right-to-left versus left-to-right shunts and with inhalational versus intravenous inductions pertains here as well. Because the lungs are bypassed by a fraction of the blood in right-to-left shunts, the onset of intravenous agents is faster, because it takes less time to enter the systemic circulation. The opposite is true for left-to-right shunts, because a fraction of an intravenous agent will recirculate from the systemic circulation to the pulmonary. The situation is opposite for inhalation inductions, where the onset is slower in right-to-left shunts. However, with the newer, low-solubility volatile anesthetic, this difference might not be clinically apparent until the degree of right-to-left shunting becomes significant, generally oxygen saturation in the upper 80% range or less. In general, patients with right-to-left shunts will have systemic oxygen saturation increases with the induction of anesthesia. With the decrease in oxygen consumption, the saturation of mixed venous blood—the blood that will be shunted—is increased, so that the "final" systemic arterial saturation will be increased.

General Noncardiac Issues With Longstanding Congenital Heart Disease

A variety of organ systems can be affected by longstanding CHD; these are summarized in Box 22.2 and Box 22.3. Because congenital cardiac disease can be one manifestation of a multiorgan genetic or dysmorphic syndrome, all patients require a full review of systems and examination.

BOX 22.2 POTENTIAL NONCARDIAC ORGAN INVOLVEMENT IN PATIENTS WITH CONGENITAL HEART DISEASE

Potential Respiratory Implications
- Decreased compliance (with increased pulmonary blood flow or impediment to pulmonary venous drainage)
- Compression of airways by large, hypertensive pulmonary arteries
- Compression of bronchioles
- Scoliosis
- Hemoptysis (with end-stage Eisenmenger syndrome)
- Phrenic nerve injury (prior thoracic surgery)
- Recurrent laryngeal nerve injury (prior thoracic surgery; very rarely from encroachment of cardiac structures)
- Blunted ventilatory response to hypoxemia (with cyanosis)
- Underestimation of $PaCO_2$ by capnometry in cyanotic patients

Potential Hematologic Implications
- Symptomatic hyperviscosity
- Bleeding diathesis
- Abnormal von Willebrand factor
- Artifactually elevated prothrombin/partial thromboplastin times with erythrocytic blood
- Artifactual thrombocytopenia with erythrocytic blood
- Gallstones

Potential Renal Implication
- Hyperuricemia and arthralgias (with cyanosis)

Potential Neurologic Implications
- Paradoxical emboli
- Brain abscess (with right-to-left shunts)
- Seizure (from old brain abscess focus)
- Intrathoracic nerve injury (iatrogenic phrenic, recurrent laryngeal, or sympathetic trunk injury)

BOX 22.3 NONCARDIAC ORGAN SYSTEMS WITH POTENTIAL INVOLVEMENT BY LONGSTANDING CONGENITAL HEART DISEASE

- Pulmonary
- Hematologic
- Renal
- Neurologic
- Vasculature
- Genitourinary (pregnancy)
- Psychosocial

Pulmonary

Any lesion that results in either increased pulmonary blood flow or pulmonary venous obstruction can cause increased pulmonary interstitial fluid with decreased pulmonary compliance and increased work of breathing.[27] Patients with cyanotic heart disease have increased minute ventilation and maintain normocarbia.[28] These patients have a normal ventilatory response to hypercapnea but a blunted response to hypoxemia that normalizes after corrective surgery and the establishment of normoxia.[29–31] End-tidal CO_2 underestimates arterial $PaCO_2$ in cyanotic patients with decreased, normal, or even increased pulmonary blood flow.[32]

Although enlarged hypertensive pulmonary arteries or an enlarged left atrium can impinge on bronchi in children, this is rare in adults. Late-stage Eisenmenger syndrome can result in hemoptysis, and patients with Eisenmenger physiology and erythrocytosis can develop thrombosis of upper lobe pulmonary arteries.[33] Prior thoracic surgery could have injured the phrenic nerve with resultant diaphragmatic paresis or paralysis.

Scoliosis can occur in up to 19% of CHD patients, most commonly in cyanotic patients. It can also develop in adolescence, years after surgical resolution of cyanosis.[34] The relative contributions of cyanosis and congenital cardiovascular defects versus early lateral thoracotomy remain unclear—scoliosis occurs more commonly with open surgical versus interventional techniques but is nevertheless increased over the general population in children with coarctation or patent ductus who had percutaneous rather than open interventions.[35] Scoliosis is rarely severe enough to impact respiratory function.

In an attempt to increase pulmonary blood flow, large collateral vessels originating from the aorta may have developed. These are sometimes embolized in the catheterization laboratory before thoracic surgery to prevent excessive intraoperative blood loss.

BOX 22.4 SYMPTOMS OF HYPERVISCOSITY

- Headache
- Faintness, dizziness, light-headedness
- Blurred or double vision
- Fatigue
- Myalgias, muscle weakness
- Paresthesias of fingers, toes, or lips
- Depressed or dissociative mentation

Hematologic

Hematologic manifestations of chronic CHD are primarily a consequence of longstanding cyanosis and incorporate abnormalities of both hemostasis and red cell regulation. Longstanding hypoxemia causes increased erythropoietin production in the kidney and resultant increased red cell mass. Because solely red cell production is affected, these patients are correctly referred to as erythrocytotic rather than polycythemic. There is, however, a fairly poor relationship among oxygen saturation, red cell mass, and 2,3-diphosphoglycerate.[36] The oxygen-hemoglobin dissociation curve is normal or minimally shifted to the right. Most patients have established an equilibrium state at which they have a stable hematocrit and are iron replete. Some patients, however, develop excessive hematocrits and are iron deficient, causing a hyperviscous state. Iron-deficient red cells are less deformable and cause increased viscosity for the same hematocrit.[37] This is a strong independent predictor of thrombosis in the setting of Eisenmenger syndrome. However, recently there is some conflicting evidence.[38] Symptoms of hyperviscosity are uncommon and typically develop only at hematocrits exceeding 65%, provided the patient is iron replete. Iron deficiency also shifts the oxygen-hemoglobin dissociation curve to the right, decreasing oxygen affinity in the lungs.[39] Symptoms of hyperviscosity are listed in Box 22.4. Iron deficiency can be the result of misguided attempts to lower the hematocrit by means of repeated phlebotomies.[40] The red cells in these patients may be hypochromic and microcytic despite the high hematocrit. Assessment of iron status is best done by measures of serum ferritin and transferrin rather than inferences from red cell indices.[40] Treatment with oral iron needs to be undertaken with care, because rapid increases in hematocrit can result.

Symptomatic hyperviscosity is the indication for treatment to temporarily relieve symptoms. It is not indicated to treat otherwise asymptomatic elevated hematocrits (generally hemoglobin >20 and hematocrit >65). Treatment is by means of a partial isovolumic exchange transfusion, and it is assumed that the increased hematocrit is not related to dehydration. Partial isovolumic exchange transfusion usually results in regression of symptoms within 24 hours. It is rare to require exchange of more than 1 unit of blood. Preoperatively, phlebotomized blood can be banked for autologous perioperative

retransfusion if required. Elective preoperative isovolumic exchange transfusion has decreased the incidence of hemorrhagic complications of surgery.[41,42]

Hyperviscosity and erythrocytosis can cause cerebral venous thrombosis in younger children, but it is not a problem in adults, regardless of the hematocrit.[33] Protracted preoperative fasts need to be avoided in erythrocytotic patients, because they can be accompanied by rapid elevations in the hematocrit.

Bleeding dyscrasias have been described in up to 20% of patients. A variety of clotting abnormalities have been described in association with cyanotic CHD, although none uniformly.[43] Bleeding dyscrasias are uncommon until the hematocrit exceeds 65%, although excessive surgical bleeding can occur at lower hematocrits. Generally, higher hematocrits are associated with a greater bleeding diathesis. Abnormalities of a variety of factors in both the intrinsic and extrinsic coagulation pathways have been described inconsistently. Both cyanotic and acyanotic patients have been reported with deficiencies of the largest von Willebrand factor multimers, which have normalized following reparative surgery.[44] Fibrinolytic pathways are normal.[45]

The decreased plasma volume in erythrocytotic blood can result in spuriously elevated measures of the prothrombin and partial thromboplastin times, and the fixed amount of anticoagulant in the collection tube will be excessive because it presumes a normal plasma volume in the blood sample. Erythrocytotic blood has more red cells and less plasma in the same volume. If informed in advance of a patient's hematocrit, the clinical laboratory can provide an appropriate sample tube. Normalizing to a hematocrit of 45%, the amount of citrate added to the tube can be calculated:

$$\text{mL citrate} = (0.1 \times \text{Blood volume collected}) \times [(100 - \text{Patient's hematocrit}) \div 55]$$

Platelet counts are typically normal or occasionally low, but bleeding is not due to thrombocytopenia. Platelets are reported per milliliter of blood, not per milliliter of plasma. When corrected for the decreased plasma fraction in erythrocytotic blood, the total plasma platelet count is closer to normal. That said, abnormalities in platelet function and life span have on occasion been reported.[46,47] Patients with low-pressure conduits (Fontan pathway) or synthetic vascular anastomoses are often maintained on antiplatelet drugs.

Cyanotic erythrocytotic patients have excessive hemoglobin turnover, and adults have an increased incidence of calcium bilirubinate gallstones. Biliary colic can develop years after cyanosis has been resolved by cardiac surgery.[33]

A variety of mechanical factors can also affect excessive surgical bleeding in patients with cyanotic CHD. These factors include increased tissue capillary density, elevated systemic venous pressure, aortopulmonary and transpleural collaterals that have developed to increase pulmonary blood flow, and prior thoracic surgery. Aprotinin and ε-aminocaproic acid improve postoperative hemostasis in patients with cyanotic CHD.[48] The results with tranexamic acid have been mixed.[49]

Renal

Some degree of renal insufficiency is not uncommon in adults with CHD, and the severity is a predictor of mortality. Moderate or severe renal dysfunction (estimated glomerular filtration rate of <60 mL/min/m^2) carries a five-fold increased risk of death at 6-year follow-up compared with patients with normal glomerular filtration rate and a three-fold increase over those with mild elevations in glomerular filtration rate [50] Renal dysfunction is particularly prevalent in cyanotic patients and those with poor cardiac function. Adult patients with cyanotic CHD can develop abnormal renal histology with hypercellular glomeruli and basement membrane thickening, focal interstitial fibrosis, tubular atrophy, and hyalinized afferent and efferent arterioles.[51] Cyanotic CHD is often accompanied by elevations in plasma uric acid levels that are due to inappropriately low fractional uric acid excretion.[52] Decreased urate reabsorption is thought to result from renal hypoperfusion with a high filtration fraction. Despite the elevated uric acid levels, urate stones and urate nephropathy are rare.[53] Although arthralgias are common, true gouty arthritis is less frequent than would be expected from the degree of hyperuricemia.[52] There appears to be an increased incidence of postcardiopulmonary bypass renal dysfunction in adults with longstanding cyanosis.[54]

Neurologic

Adults with persistent or potential intracardiac shunts remain at risk for paradoxical embolism. Paradoxical emboli can occur even through shunts that are predominantly left to right, because during the cardiac cycle there can be small transient reversals of the shunt direction. It has been said that, unlike in children, adults with cyanotic CHD are not at risk for the development of cerebral thrombosis despite the hematocrit.[33,55] However, this assertion has been challenged by Ammash and Warnes,[56] who suggested an association of stroke, not with red cell mass, but with iron deficiency and repeated venesection. Adults do, however, remain at risk for the development of brain abscess. A healed childhood brain abscess can provide the nidus for the development of seizures throughout life.

Prior thoracic surgery can result in permanent peripheral nerve damage. Surgery at the apices of the lungs is particularly associated with the risk of nerve damage. These operations would include Blalock-Taussig shunts, ligation of patent ductus arteriosus (PDA), banding of the pulmonary artery, and repair of aortic coarctation. Nerves that are susceptible to injury include the recurrent laryngeal nerve, the phrenic nerve, and the sympathetic chain. The incidence of migraine headaches is higher in adults with CHD compared with a control group with acquired heart disease (45% vs 11%) and is increased in left-to-right, right-to-left, and no-shunt groups.[57]

Vasculature

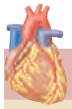
Vessel abnormalities can be congenital or iatrogenic. They can affect the suitability of vessels for cannulation by the anesthesiologist or measurement of correct pressures. These abnormalities are described in Table 22.2.

Pregnancy

The physiologic changes of pregnancy, labor, and delivery can significantly alter the physiologic status of women with CHD, and mortality and morbidity are increased in mothers with CHD.[58] There are several

TABLE 22.2 Potential Vascular Access Issues

Vessel	*Possible Problem*
Femoral vein(s)	May have been ligated if cardiac catheterization was done by cutdown. Large therapeutic catheters in infants often thrombose femoral veins.
Inferior vena cava	Some lesions, particularly when associated with heterotaxy (polysplenia) have discontinuity of the inferior vena cava; Will not be able to pass a catheter from the groin to the right atrium.
Left subclavian and pedal arteries	Distal blood pressure will be low in the presence of coarctation of the aorta or following subclavian flap repair (subclavian artery only), and variably so if postoperative recoarctation; pulses can be absent or palpable with abnormal blood pressure.
Subclavian artery	Blood pressure low with classic Blalock-Taussig shunt on that side, and variably so with modified Blalock-Taussig shunt.
Right subclavian artery	Blood pressure artifactually high with supravalvular aortic stenosis (Coanda effect).
Superior vena cava	Risk of catheter-related thrombosis with Glenn operation.



BOX 22.5 RISK FACTORS FOR PREGNANCY

- Pulmonary hypertension
- Depressed ventricular function
- Marfan syndrome with dilated aortic root
- Cyanosis
- Severe left heart obstructive lesions
- Pressure (vs volume) lesions

texts available that specifically discuss issues of the pregnant woman with CHD in more detail than is possible here.[59–61] Also, a recent review has been completed of generic cardiac surgery in the parturient.[62] Management and clinical outcomes during pregnancy and delivery for several cardiac lesions are included under the later discussions of those lesions.

Although cardiac complications, spontaneous abortions, premature delivery, thrombotic complications, peripartum endocarditis, and poor fetal outcomes can occur,[63] successful pregnancy to term with vaginal delivery is possible for most patients with congenital defects.[64] High-risk factors for mother and fetus are shown in Box 22.5. Eisenmenger physiology is a particular risk factor. Up to 47% of cyanotic women have worsening of functional capacity during pregnancy.[65] Hematocrits greater than 44% are associated with birth weights less than 50th percentile, and fetal death is about 90% or more with hemoglobin levels greater than 18 g/dL or oxygen saturation less than 85%, with most losses in the first trimester. The increases in stroke volume and cardiac output during pregnancy can stress an already pressure-overloaded ventricle. The decrease in systemic vascular resistance that accompanies pregnancy is better tolerated by women with regurgitant lesions and typically offsets the added insult of pregnancy-related hypervolemia. The decrease in systemic vascular resistance can, however, increase right-to-left shunting. Hypervolemia can be problematic in patients with poor ventricular function. Maternal cyanosis is associated with increased incidences of prematurity and intrauterine growth retardation. Profound cyanosis is associated with a high rate of spontaneous abortion.[66] Endocarditis prophylaxis is not currently recommended for vaginal deliveries.[67] The recurrence risk of any congenital cardiac defect in a newborn is 2.3% with one affected older sibling (any defect), 7.3% with two, 6.7% if the mother has a congenital cardiac defect, but only 2.1% if the father is affected.[2] However, it has become apparent that recurrence risk can be specific to the type of maternal defect and the underlying genetic basis. If possible, pregnancies in mothers with CHD should be managed in a high-risk obstetric center with cardiologists experienced with the care of ACHD, and with early consultation with the obstetric anesthesia service. Women on long-term anticoagulation will likely need peripartum modifications, and postpartum thromboembolism is a potential significant problem.

Anesthesiologists will generally encounter pregnant patients well into the last trimester. Most of the major physiologic changes associated with pregnancy occur before the third trimester, and if patients have maintained good functional status to this point, they will have demonstrated themselves to be in a relatively low-risk group. Pregnancy is a stress test, and if they have successfully arrived at the mid-to-late third trimester, it is more likely that they will successfully tolerate delivery. Also, many high-risk women will have been counseled to avoid pregnancy. There is no a priori reason to favor an instrumented or cesarean delivery over a vaginal one. This is an obstetric, not cardiologic, decision. That said, there is a common belief that women with ACHD will not tolerate the "stress" of labor, particularly bearing down in the second stage. However, a well-functioning epidural makes uterine contractions easy to tolerate. Furthermore, avoidance of second-stage pushing is an option as long as progress is being made and can be combined with a maneuver such as low-outlet vacuum or forceps to facilitate delivery. A functioning epidural makes uterine contractions easy to tolerate. Bearing down, associated with the second stage, requires close observation. The third stage can be accompanied by an autotransfusion of placental blood or potentially with hypovolemia with uterine atony and hemorrhage. If oxytocic drugs are required, the hemodynamic effects must be kept in mind. Oxytocin will decrease systemic vascular resistance and increase heart rate and pulmonary vascular resistance (PVR). Methylergonovine will increase systemic vascular resistance. These rapid changes in loading conditions can be poorly tolerated in mothers with fixed cardiac output, and pulmonary edema or heart failure can develop.

Some mothers will be taking medications for their cardiac condition, including antiarrhythmics. In general these are safe for the infant.[68] Exceptions include beta-blockers that can interfere with fetal growth and the response of the fetus to the stress of labor, and amiodarone, which can affect fetal thyroid function. Maternal cardioversion would appear to be safe for the fetus at all stages because of the low intensity of the electrical field at the uterus. However, the fetus should be monitored throughout the procedure. Women with implanted internal defibrillators have carried successfully to term.[69] Should cardiopulmonary bypass (CPB) be required during pregnancy, it carries with it increased fetal risk, particularly if hypothermia is used. Care for the obstetrical patient is presented in more detail in Chapter 50.

Psychosocial

Teenagers with CHD are certainly no different from other teenagers in that issues of denial, a sense of immortality, and risk-taking behavior can affect optimal care for these youngsters. Bodies that carry scars from prior surgery and physical limitations can complicate the body-conscious teenage years. Although most adolescents and adults with CHD function well, adults with CHD are less likely to be married or cohabitating and are more likely to be living with their parents.[70] There are several reports of the psychosocial outcomes of adolescent and adult patients, but there are no well-done controlled studies.[71–78] It has been suggested that depression is common and can exacerbate the clinical consequences of the cardiac defect.

Adolescent CHD patients have higher medical care expenses than the general population, and they can have difficulty in obtaining life and health insurance after they can no longer be covered under their parents' policies.[79–81] Life insurance is somewhat more available to adult CHD patients than in the past; however, policies vary widely among insurers.[82]

The issue of denial or lack of awareness of their cardiac condition is very relevant in teenagers and young adults. While they are children, these patients rely on their parents to ensure regular cardiac appointments are kept and surveillance echocardiograms are done. Unfortunately, young adults with ACHD often do not appreciate their physiologic limitations because they have lived with them their entire life. Many often lack basic knowledge of their cardiac condition. Sadly, this can result in ACHD patients being "lost to follow-up" until they arrive in their local emergency department with an urgent condition requiring surgery.

Cardiac Issues

The basic hemodynamic effects of an anatomic cardiac lesion can be modified by time and by the superimposed effects of chronic cyanosis, pulmonary disease, or the effects of aging. Although surgical cure is the goal, true universal cure, without residua, sequelae, or complications, is uncommon on a population-wide basis. Exceptions include closure of a nonpulmonary hypertensive PDA or atrial septal defect (ASD), probably in childhood. Although there have been reports of series of surgeries on adults with CHD, the wide variety of defects and sequelae from prior surgery make generalizations difficult, if not impossible. Poor myocardial function can be inherent in the CHD but can also be affected by longstanding cyanosis or superimposed surgical injury, including inadequate intraoperative myocardial protection.[82,83] This is particularly true of adults who had their cardiac repair several decades ago when myocardial protection may not have been as good and when

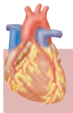
repair was undertaken at an older age. Postoperative arrhythmias are common, particularly when surgery entails long atrial suture lines, and the incidence of atrial arrhythmias increases with time, either as a primary sequela or as an indicator of diminished cardiac function.[84] Thrombi can be found in these atria precluding immediate cardioversion.[85] Bradyarrhythmias can be secondary to surgical injury to the sinus node or conducting tissue or can be a component of the cardiac defect.

The number of cardiac lesions and subtypes, together with the large number of contemporary and obsolescent palliative and corrective surgical procedures, make a complete discussion of all CHD impossible. The reader is referred to one of the current texts on pediatric cardiac anesthesia for more detailed descriptions of these lesions, the available surgical repairs, and the anesthetic implications during primary repair.[86,87] Some general perioperative guidelines to caring for these patients are offered in Box 22.6. This chapter provides a discussion of the more common and physiologically important defects that will be encountered in an adult CHD population. Defining outcome after CHD surgery is like trying to hit a continuously moving target. Both short-term and long-term results from older series can differ significantly from contemporary results.

Aortic Stenosis

Valvar aortic stenosis is the most common congenital heart defect but is often not seen in that light because it typically does not cause problems until adulthood. Most aortic stenosis in adults is due to a congenitally bicuspid valve that does not become problematic until late middle age or beyond, although endocarditis risk is lifelong. Congenital aortic stenosis can on some occasions, however, become severe enough to warrant surgical correction in adolescence or young adulthood, in addition to those severely affected valves that present in infancy. Once symptoms (angina, syncope, near-syncope, heart failure) develop, survival is markedly shortened. Median survival is 5 years after the development of angina, 3 years after syncope, and 2 years after heart failure.[88] Anesthetic management of aortic stenosis does not vary whether the stenosis is congenital (most common) or acquired (see Chapter 21).

Most mothers with aortic stenosis can successfully carry pregnancies to term and have vaginal deliveries. Severe stenosis (valve area <1.0 cm^2) can result in clinical deterioration and maternal and fetal mortality. Hemodynamic monitoring during delivery with maintenance of adequate preload and avoidance of hypotension is critical. When intervention is required during pregnancy, percutaneous balloon valvuloplasty is an attractive option compared with aortic valve replacement. A contraindication to balloon valvuloplasty is significant aortic insufficiency. Additionally, there is a risk of stroke from calcium that embolizes from the valve during balloon dilation. The quoted risk of stroke is usually higher than in surgical valve replacement; however, there is an overall benefit to the fetus in avoiding a procedure requiring CPB.



BOX 22.6 GENERAL APPROACH TO ANESTHESIA FOR PATIENTS WITH CONGENITAL HEART DISEASE

General

- The best care for both cardiac and noncardiac surgery in adult patients with congenital heart disease (CHD) is afforded in a center with a multidisciplinary team experienced in the care of adults with CHD and knowledgeable about both the anatomy and physiology of CHD and the manifestations and considerations specific to adults with CHD.

Preoperative

- Review most recent laboratory data, catheterization, and echocardiogram, and other imaging data. The most recent office letter from the cardiologist is often most helpful. Obtain and review these in advance.
- Drawing a diagram of the heart with saturations, pressures, and direction of blood flow often clarifies complex and superficially unfamiliar anatomy and physiology.
- Avoid prolonged fast if patient is erythrocytotic to avoid hemoconcentration.
- No generalized contraindication to preoperative sedation.

Intraoperative

- Large-bore intravenous access for redo sternotomy and cyanotic patients (see Table 22.2 for vascular access considerations).
- Avoid air bubbles in all intravenous catheters. There can be transient right-to-left shunting even in lesions with predominant left-to-right shunting (filters are available but will severely restrict ability to give volume and blood).
- Apply external defibrillator pads for redo sternotomies and patients with poor cardiac function.
- Appropriate endocarditis prophylaxis (orally or intravenously before skin incision).[53]
- Consider antifibrinolytic therapy, especially for patients with prior sternotomy.
- Transesophageal echocardiography for cardiac operations.
- Modulate pulmonary and systemic vascular resistances as appropriate pharmacologically and by modifications in ventilation.

Postoperative

- Appropriate pain control (cyanotic patients have normal ventilatory response to hypercarbia and narcotics).
- Maintain hematocrit appropriate for arterial saturation.
- Maintain central venous and left atrial pressures appropriate for altered ventricular diastolic compliance or presence of beneficial atrial level shunting.
- PaO_2 may not increase significantly with the application of supplemental oxygen in the face of right-to-left shunting. Similarly, neither will it decrease much with the withdrawal of oxygen (in the absence of lung pathology).

Aortopulmonary Shunts

Depending on their age, adult patients may have had one or more of several aortopulmonary shunts to palliate cyanosis during childhood. These are shown in Fig. 22.1. Although lifesaving, these shunts had considerable shortcomings in the long term. All were inherently inefficient, because some of the oxygenated blood returning through the pulmonary veins to the left atrium and ventricle would then return to the lungs through the shunt, thus volume loading the ventricle. It was difficult to quantify the size of the earlier shunts, such as the Waterston (side-to-side ascending aorta to right pulmonary artery) and Potts (side-to-side descending aorta to left pulmonary artery). If too small, the patient was left excessively cyanotic; if too large, there was pulmonary overcirculation with the risk of developing pulmonary vascular disease. The Waterston, in fact, could on occasion stream blood flow unequally, resulting in a hyperperfused, hypertensive ipsilateral (right) pulmonary artery and a hypoperfused contralateral (left) pulmonary artery. There were also surgical issues when complete repair became possible. Takedown of Waterston shunts often required a pulmonary arterioplasty to correct deformity of the pulmonary artery at the site of the anastomosis, and the posteriorly located Potts anastomoses could not be taken down from a median sternotomy. Patients with a classic Blalock-Taussig shunt almost always lack palpable pulses on the side of the shunt and arm length and strength can be mildly affected.[89] Even if there is a palpable pulse (from collateral flow around the shoulder), blood pressure obtained from that arm will be artifactually low. Even after a modified Blalock-Taussig shunt (using a piece of GORE-TEX tubing instead of an end-to-side anastomosis of the subclavian and pulmonary arteries), there can be a blood pressure disparity between the arms. To ensure a valid measurement, preoperative blood pressure should be measured in both arms (Table 22.3).

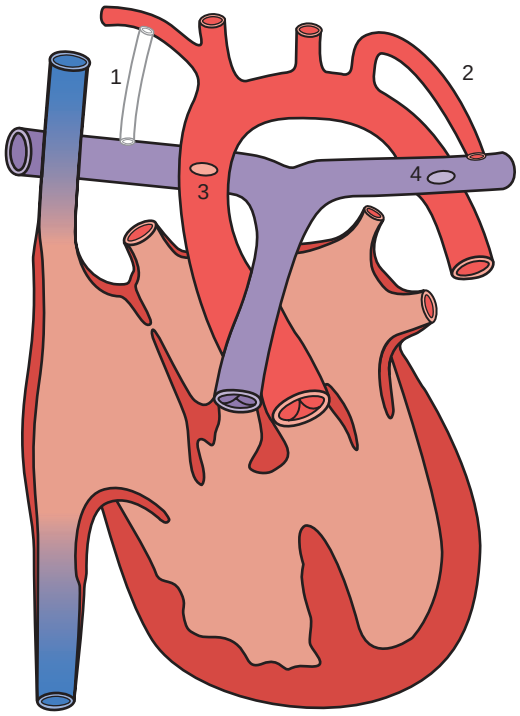


Fig. 22.1 The various aortopulmonary anastomoses. The illustrated heart is one with tetralogy of Fallot. The anastomoses are *(1)*, modified Blalock-Taussig, *(2)* classic Blalock-Taussig, *(3)* Waterston (Waterston-Cooley), and *(4)* Potts. *(Reprinted with permission from Baum VC. The adult with congenital heart disease.* J Cardiothorac Vasc Anesth. *1996;10:261.)*

TABLE 22.3 Aortopulmonary Shunts

Shunt	*Anatomy*	*Current Status*
Waterston	Ascending aorta → right pulmonary artery	No longer done
Potts	Descending aorta → left pulmonary artery	No longer done
Classic Blalock-Taussig	Subclavian artery → ipsilateral pulmonary artery	No longer done
Modified Blalock-Taussig	GORE-TEX tube subclavian artery → ipsilateral pulmonary artery	Current
Central shunt	GORE-TEX tube ascending aorta → main pulmonary artery	Current

Atrial Septal Defect and Partial Anomalous Pulmonary Venous Return

There are several anatomic types of ASD. The most common type—and, if otherwise undefined, the presumptive type—is the secundum type located in the midseptum. The primum type at the lower end of the atrial septum is a component of endocardial cushion defects, the most primitive of which is the common atrioventricular canal (see later). The sinus venosus type, high in the septum near the entry of the superior vena cava, is almost always associated with partial anomalous pulmonary venous return, most frequently drainage of the right upper pulmonary vein to the low superior vena cava. An uncommon atrial septal–type defect occurs when blood passes from the left atrium to the right via an unroofed coronary sinus. For purposes of this section, only secundum defects are considered, although the natural histories of all of the defects are similar (Box 22.7).

Both the natural history and the postoperative outcome of ASDs and the physiologically related partial anomalous venous return are similar.[90–92] Because the symptoms and clinical findings of an ASD can be quite subtle and patients often remain asymptomatic until

BOX 22.7 COMPLICATIONS OF ATRIAL SEPTAL DEFECT IN ADULTHOOD

- Paradoxical emboli
- Effort dyspnea
- Atrial tachyarrhythmias
- Right-sided failure with pregnancy
- Pulmonary hypertension
- ↑ Right-sided failure with ↓ left ventricular compliance with aging
- Mitral insufficiency

adulthood, ASDs represent approximately one-third of all CHD discovered in adults. Although asymptomatic survival to adulthood is common, significant shunts ($\dot{Q}_p/\dot{Q}_s > 1.5:1$) will probably cause symptoms over time, and paradoxical emboli can occur through defects with smaller shunts. Surgical repair of restrictive lesions less than or equal to 5 mm in size does not impact the natural history. Thus surgical closure of small lesions is not indicated in the absence of paradoxical emboli. Effort dyspnea occurs in 30% by the third decade, and atrial flutter or fibrillation in about 10% by age 40.[90] The avoidance of complications developing in adulthood provides the rationale for surgical repair of asymptomatic children. The mortality for a patient with an uncorrected ASD is 6% per year over 40 years of age, and essentially all patients over 60 years of age are symptomatic.[90–92] Large unrepaired defects can cause death from atrial tachyarrhythmias or right ventricular failure in 30- to 40-year-old patients.[93] With the decreased left ventricular diastolic compliance accompanying the systemic hypertension or coronary artery disease that is common with aging, left-to-right shunting increases with age. Pulmonary vascular disease typically does not develop until after the age of 40, unlike ventricular or ductal level shunts, which can lead to it in early childhood. Mitral insufficiency can be found in adult patients and is significant in about 15% of adult patients.[94] Paradoxical emboli remain a lifelong risk.

Late closure of the defect, after 5 years of age, has been associated with incomplete resolution of right ventricular dilation.[95] Left ventricular dysfunction has been reported in some patients having defect closure in adulthood, and closure, particularly in middle age, may not prevent the development of atrial tachyarrhythmias or stroke.[96–99] Survival of patients without pulmonary vascular disease has been reported to be best if operated on before 24 years of age, intermediate if operated on between 25 and 41 years of age, and worst if operated on thereafter.[99] However, more recent series have shown that even at ages over 40, surgical repair provides an overall survival and complication-free benefit compared with medical management,[100] although pulmonary artery pressure can progress even after surgical closure if done late.[101] Surgical morbidity in these patients is primarily atrial fibrillation, atrial flutter, or junctional rhythm.[97] Current practice is to close these defects in adults in the catheterization laboratory via transvascular devices if anatomically practical (Fig. 22.2). For example, there needs to be an adequate rim of septum around the defect to which the device can attach. Device closure is inappropriate if the defect is associated with anomalous pulmonary venous drainage. The indications for closure with a transvascular device are the same as for surgical closure.[102] Surgical closure of ASD also lends itself to a thoracoscopic approach.[103]

An otherwise uncomplicated secundum ASD, unlike most congenital cardiac defects, is not associated with an increased endocarditis risk.[104] Presumably this is because the shunt, although potentially large, is low pressure and unassociated with jet lesions of the endocardium from turbulent flow.

Although some discussion is given to onset times with intravenous or inhalation induction agents, clinical differences are hard to notice with modern low-solubility volatile agents. Thermodilution cardiac output reflects pulmonary blood flow, which will be in excess

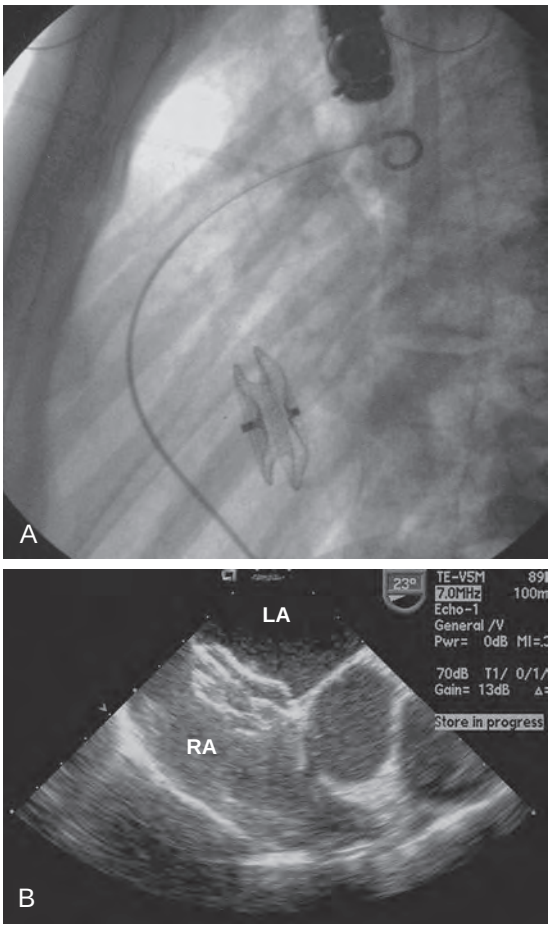


Fig. 22.2 Closure of an atrial septal defect in an adult with use of a transvascular device (the Amplatzer septal occluder). (A) Radiograph. (B) Transesophageal echocardiogram. The device is clearly visualized spanning and occluding the atrial septal defect. *RA,* Right atrium; *LA,* left atrium. *(Courtesy Dr. Scott Lim.)*

of systemic blood flow. Pulmonary arterial catheters are not routinely indicated. Patients generally do tolerate any appropriate anesthetic; however, particular care should be taken in patients with pulmonary arterial hypertension or right-sided failure.

The vast majority of women with an ASD tolerate pregnancy well. However, the normal hypervolemia associated with pregnancy can result in heart failure in women with large defects. Hypovolemia accompanying delivery can result in right-to-left shunting through the defect, and there is a risk of pulmonary thromboembolism or paradoxical embolism.

Coarctation of the Aorta

Unrepaired coarctation of the aorta in the adult brings with it significant morbidity and mortality. Mortality is 25% by age 20, 50% by age 30, 75% by age 50, and 90% by age 60.[93,105–107] Left ventricular aneurysms, rupture of cerebral aneurysms, and dissection of a postcoarctation aneurysm all contribute to the excessive mortality. Left ventricular failure can occur in patients over 40 with unrepaired lesions. If repair is not undertaken early, there is incremental risk for the development of premature coronary atherosclerosis.[108] Even with surgery, coronary artery disease remains the leading cause of death 11 to 25 years after surgery.[109] However, more recent data have questioned that assertion.[110] Coarctation is accompanied by a bicuspid aortic valve in the majority of patients. Although endocarditis of this abnormal valve is a lifelong risk, these valves often do not become stenotic until middle age or later. Coarctation can also be associated with mitral valve abnormalities (Box 22.8).

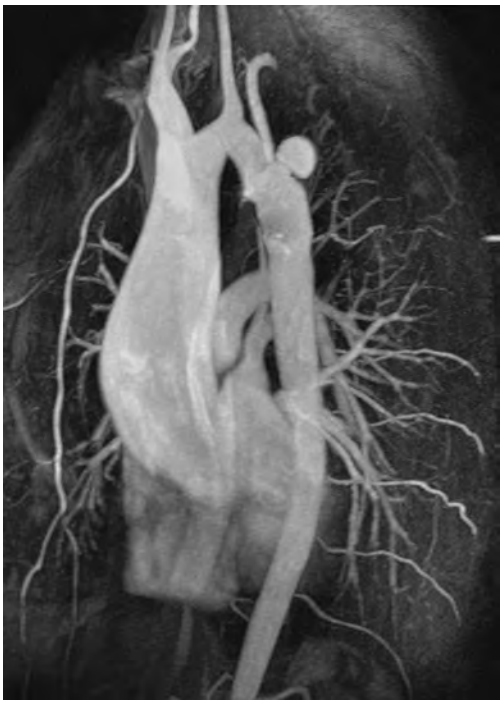


Fig. 22.3 Magnetic resonance image of a 37-year-old man showing descending thoracic aortic pseudoaneurysm at the site of a coarctation that had been repaired years earlier. This patient also has a bicuspid aortic valve and an aneurysm of the ascending aorta that was later repaired. *(Courtesy Dr. Christopher Kramer.)*

BOX 22.8 COMPLICATIONS OF AORTIC COARCTATION IN ADULTHOOD

- Left ventricular failure
- Premature coronary atherosclerosis
- Rupture of cerebral aneurysm
- Aneurysm at site of coarctation repair
- Complications of associated bicuspid aortic valve
- Exacerbation of hypertension during pregnancy

Aneurysms at the site of coarctation repair can develop years later (Fig. 22.3), and restenosis as well can develop in adolescence or adulthood. Repair includes resection of the coarctation and end-to-end anastomosis. Because this sometimes resulted in recoarctation when done in infancy, for many years a common repair was the Waldhausen or subclavian flap operation, in which the left subclavian artery is ligated and the proximal segment opened and rotated as a flap to open the area of the coarctation. Aneurysms in the area of repair are a particular concern in adolescents and adults following coarctectomy. Persistent systemic hypertension is common following coarctation repair.[111] The risk of hypertension parallels the duration of unrepaired coarctation. Adult patients require continued periodic follow-up for hypertension. A pressure gradient of 20 mm Hg or more (less in the presence of extensive collaterals) is an indication for treatment.[112] Recoarctation can be treated surgically or by balloon angioplasty with stenting.[113] Surgical repair of recoarctation or aneurysm in adults is associated with increased mortality and can be associated with significant intraoperative bleeding due to previous scar or extensive collateral vessels. It requires lung isolation for optimal surgical exposure and placement of an arterial catheter in the right arm. Endovascular repair by ballooning/stenting has proven useful for these patients.[114,115]

Half of patients operated on after age 40 have persistent hypertension, and many of the remainder have an abnormal hypertensive response to surgery. Long-term survival is worse for patients having repair later in life. Patients older than 40 undergoing repair have a 15-year survival of only 50%.[109] Pulmonary hypertension can develop secondary to longstanding restrictive left ventricular physiology.[116]

Blood pressure should be obtained in the right arm unless pressures in the left arm or legs are known to be unaffected by residual or recurrent coarctation. Postoperative hypertension is common after repair of coarctation and often requires treatment for some months. Postoperative ileus is also common, and patients should be maintained NPO for about 2 days.

Pregnancy can exacerbate preexisting hypertension in women with unrepaired lesions, increasing the risk of aortic dissection or rupture, heart failure, angina, and rupture of a circle of Willis aneurysm. Adequate blood pressure control during pregnancy is paramount in these women. Most aortic ruptures during pregnancy occur during labor and delivery. Presumably, epidural analgesia would moderate hypertension during delivery.

Congenitally Corrected Transposition of the Great Vessels (L-Transposition, Ventricular Inversion)

"Transposition" in this context refers solely to the fact that the aorta arises anterior to the pulmonary artery. It bears no reference to the origin of blood in the aorta or pulmonary artery or to the ventricle of origin of those vessels. In L-transposition, as a consequence of the embryonic heart tube rotating to the left (levo) rather than to the right, the flow of blood is through normal vena cavae to the right atrium, through a mitral valve to a right-sided morphologic left ventricle, to the pulmonary artery, through the pulmonary circulation, to the left atrium, through a tricuspid valve to a left-sided morphologic right ventricle, and thence to the aorta (Fig. 22.4) The L refers to the fact that the aorta originates anterior and to the left ("levo") of the pulmonary artery. Although anatomically altered, the physiologic flow of blood is appropriate, and there are no associated shunts. L-Transposition of the great vessels (L-TGV) is very frequently associated with other cardiac lesions, most commonly a ventricular septal defect (VSD), subpulmonic stenosis, heart block, or systemic atrioventricular (tricuspid) valve regurgitation. In the absence of any of these associated cardiac defects, L-TGV will usually be asymptomatic through infancy and childhood. When L-transposition is an isolated lesion, most patients maintain normal biventricular function through early adulthood and can attain a normal lifespan. However, the relatively thin-walled morphologic right ventricle is not well suited to eject blood against systemic pressure. Over a lifetime the right ventricle can fail, and the patient will develop heart failure. Over the past few years an alternative surgical approach has been utilized in some centers to avoid a systemic right ventricle. If an associated lesion has allowed for a hypertensive left ventricle, or if the left ventricle has been prepared by pulmonary artery banding, an anatomic repair can be undertaken by means of an atrial switch (Senning operation) + an arterial switch, or a Senning + Rastelli operation, resulting in a systemic morphologic left ventricle. There are as yet no long-term results for this approach. The goal of establishing the morphologic left ventricle as the systemic ventricle comes at the cost of a very complex operation with significant short- and long-term complications. Specifically, the atrial baffles may obstruct resulting in the physiologic equivalent of tricuspid or mitral stenosis. Also, the extensive atrial sutures make the long development of atrial arrhythmias likely.

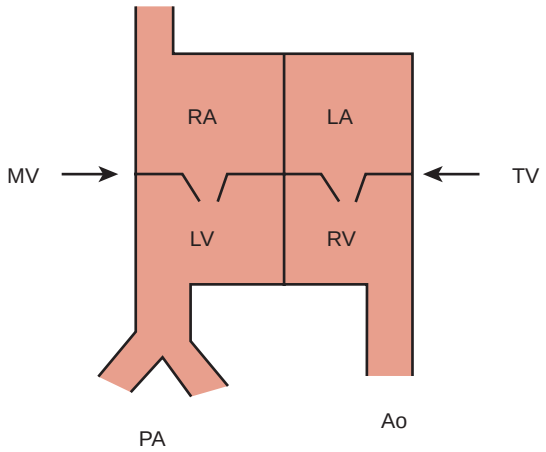


Fig. 22.4 Diagram of the anatomy of L-TGA. Note that the atrioventricular valves are associated with the "usual" ventricle. *Ao,* Aorta; *LA,* left atrium; *LV,* morphologic left ventricle; *MV,* mitral valve; *PA,* pulmonary artery; *RA,* right atrium; *RV,* morphologic right ventricle; *TV,* tricuspid valve.

Systemic atrioventricular (tricuspid) valve insufficiency may not develop until later in life, resulting in approximately 60% of patients being diagnosed as adults.[117] Dysfunction of the right (the systemic) ventricle can develop with aging, and asymptomatic aging is relatively uncommon.[118] By age 45, heart failure will be present in 67% of those patients with associated lesions and 25% of those without.[119] Resynchronization therapy for severe ventricular dysfunction can be problematic because of significant abnormal cardiac venous drainage with variations in coronary sinus anatomy.[120] These patients can be born with congenital heart block, which can progress in degree. Second- or third-degree heart block occurs at a rate of about 2% per year. More than 75% of patients develop some degree of heart block, although the intrinsic pacemaker remains above the His bundle with a narrow QRS complex. Chronic subpulmonary (left) ventricular pacing can be associated with a deterioration in systemic (right) ventricular function.[121] L-Transposition can be associated with an Ebstein-like deformity of the systemic atrioventricular (tricuspid) valve, and there can be a bundle of Kent causing the Wolff-Parkinson-White (WPW) syndrome associated with that abnormal valve. There is a significant incidence of tricuspid valve insufficiency in the systemic ventricle, and this is higher still in patients with an Ebstein deformity of the valve.[122] Anesthetic management depends on the presence of any associated lesions and the adequacy of right (systemic) ventricular function.

Although women generally do well with pregnancy,[123] the physiologic stresses of pregnancy and delivery can result in ventricular or valvar dysfunction, particularly with baseline dysfunction and/or an insufficient systemic atrioventricular valve; however, even if these develop, pregnancy can be successfully managed.[123–126] The decrease in systemic vascular resistance associated with both pregnancy and neuraxial analgesia might be advantageous to women with tricuspid (systemic) valve insufficiency. The acute autotransfusion associated with delivery could potentially cause problems for women with existing diminished systemic ventricle function. A recent study suggested that pregnancy resulted in a sustained deterioration in right (systemic) ventricular function.[127]

Ebstein Anomaly of the Tricuspid Valve

This defect,[128] one of arrested or incomplete delamination of the embryonic tricuspid valve from the right ventricular myocardium, resulting in apically displaced valve tissue, is the most common cause of congenital tricuspid insufficiency. The septal leaflet tends to be the most dysplastic. The anterior leaflet tends to be large and redundant. The defect is associated with a patent foramen ovale or a secundum ASD. There is "atrialization" of part of the right ventricle. The displacement of the tricuspid valve toward the right ventricular apex results in a portion of the right ventricle being above the tricuspid valve and becoming functionally part of the right atrium. Apicalization of the tricuspid valve results in a portion of the heart above the valve having a ventricular intracardiac electrogram (it is ventricular myocardium) but atrial pressures (it lies above the tricuspid valve). The right atrium can be massively enlarged (Fig. 22.5), and the right ventricle,

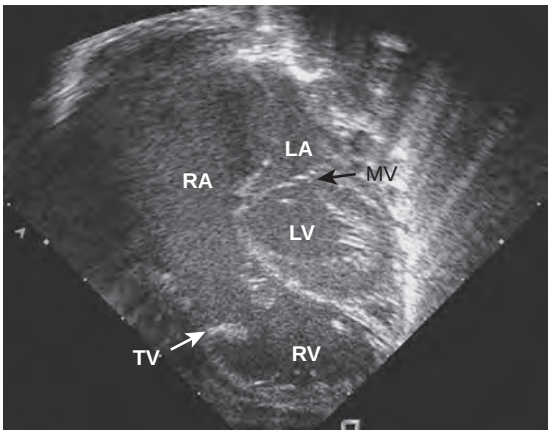


Fig. 22.5 Ebstein anomaly of the tricuspid valve. This echocardiogram shows the apically displaced redundant tricuspid valve tissue and a massively enlarged right atrium with bowing of the atrial septum to the left. *LA,* Left atrium; *LV,* left ventricle; *MV,* mitral valve; *RA,* right atrium, *RV,* right ventricle; *TV,* tricuspid valve. *(Reprinted with permission from Baum VC. Abnormalities of the atrioventricular valves. In: Lake CL, Booker P, eds.* Pediatric Cardiac Anesthesia, *4th ed. Philadelphia: Lippincott Williams and Wilkins; 2004.)*

lacking the inflow portion that is now part of the right atrium, is smaller than usual with varying degrees of pulmonic stenosis. Patients with L-transposition (see earlier) can have an Ebstein or Ebstein-like anomaly of a left-sided tricuspid valve, and Ebstein anomaly is on occasion associated with left ventricular noncompaction.

Symptoms will vary based on the amount of displacement of the valve and the size of the smaller-than-normal right ventricle. Cyanosis from atrial-level right-to-left shunting can be a neonatal phenomenon, resolving with the normal postnatal decrease in PVR, only to recur in adolescence or adulthood. Very mild disease is quite compatible with asymptomatic survival into adulthood, although overall earlier reports suggested a mean age at death of about 20 years with about one-third dying before 10 years of age and only 15% survival by 60 years.[129–131] About one-half develop arrhythmias, typically supraventricular tachyarrhythmias. Once symptoms develop, disability rapidly progresses.

Valve repair is currently the approach of choice, and only uncommonly will tricuspid valve replacement be required.[132] Additional intervention may be required for progressive insufficiency, stenosis, prosthetic valve failure, or valve replacement with growth. Following valve replacement, up to 25% of patients develop high-grade atrioventricular block. Surgery in older patients (>50 years of age) is associated with acceptable but not outstanding long-term survival (65% 20-year survival versus 74% for controls, plus 4% early mortality).[133] Ebstein valves are often associated with a right-sided bypass tract, causing WPW syndrome. This is of concern, because 25% to 30% of patients develop supraventricular tachyarrhythmias. The dilated right atrium is ready substrate for the development of atrial fibrillation. In addition to a decrease in cardiac performance, atrial fibrillation is also potentially very dangerous in patients with underlying WPW because very high atrial rates can be conducted to the ventricle through the bypass tract.

The major concerns when anesthetizing patients who have Ebstein anomaly include decreased cardiac output, right-to-left atrial-level shunting with cyanosis, and the propensity for atrial tachyarrhythmias. The right atria of these patients are very sensitive, and arrhythmias are easily induced by catheters or guidewires passed into the right atrium or during surgical manipulation; arrhythmias remain a concern into the postoperative period. Supraventricular arrhythmias should be treated aggressively. If associated with significant hypotension, the arrhythmia needs to be electrically cardioverted.

In the absence of marked cyanosis, pregnancy and delivery are generally well tolerated.[134] There is, however, an increased incidence of prematurity and fetal loss. Birth weights are lower in infants of cyanotic mothers.[135] and incidence of CHD is increased in offspring.

Eisenmenger Syndrome

Eisenmenger described a particular type of large VSD with dextroposition of the aorta.[136] In a general way, the term *Eisenmenger syndrome* has come to describe the clinical setting in which a large left-to-right cardiac shunt results in the development of pulmonary vascular disease and has been the subject of recent reviews.[137,138] Although early on the pulmonary vasculature remains reactive, with continued insult pulmonary hypertension becomes fixed and does not respond to pulmonary vasodilators. Ultimately, the level of PVR is so high that the shunt reverses and becomes right to left. Clinically, patients who are cyanotic from intracardiac right-to-left shunting are deemed to have Eisenmenger physiology even though their PVR may not yet truly be fixed. This is the intermediate phase of the disease before progression to a truly fixed PVR. That is, at baseline they shunt right to left but may still retain some pulmonary vascular reactivity in the presence of vasodilating agents such as oxygen or nitric oxide. The degree of reactivity can be determined in the catheterization laboratory by measuring the pulmonary blood flow on room air, pure oxygen, and pure oxygen with nitric oxide added. The development of pulmonary vascular disease is dependent on shear rate. Lesions with high shear rates, such as a large VSD or a large PDA, can result in pulmonary hypertension in early childhood. Lesions such as an ASD with high pulmonary blood flow but low pressure may not result in pulmonary vascular disease until late middle age. Pulmonary vascular disease progression is also accelerated in patients living at altitude.

The most common presenting symptom is dyspnea on exertion. Additional symptoms include palpitations, edema, hemoptysis, syncope, hyperpnea, and of course, increasing cyanosis. Hepatic synthetic function can be altered from the elevated central venous pressure. There can be CNS symptoms from increased blood viscosity from the erythrocytosis associated with cyanosis. Right ventricular ischemia is a possibility. Patients may be on chronic therapy with drugs such as intravenous prostacyclin, an oral phosphodiesterase 5 inhibitor such as sildenafil (eg, Revatio), an oral endothelin receptor antagonist such as bosentan (eg, Tracleer), a prostanoid, or a soluble guanylate cyclase stimulator such as riociguat (Adempas). Because of the risk of pulmonary thromboses,[139] patients may be on chronic anticoagulants.

Eisenmenger physiology is compatible with survival into adulthood.[140,141] However, reported rates of survival after diagnosis vary, probably based on the relatively long life expectancy and variability in the time of diagnosis. Cantor and colleagues[142] reported median survival to 53 years but with wide variation. Saha and coworkers[143] reported survival of 80% at 10 years after diagnosis and 42% at 25 years. Oya and others,[144] however, reported survival of 77% at 5 years and 58% at 10 years. A recent study, however reported worse long-term survival and challenged these other data for methodologic reasons.[145] Syncope, increased central venous pressure, and arterial desaturation to less than 85% are all associated with poor short-term outcome.[140] Other factors associated with mortality include syncope, age at presentation, functional status, supraventricular arrhythmias, elevated right atrial pressure, renal insufficiency, severe right ventricular dysfunction, and trisomy 21. Most deaths are sudden cardiac deaths. Other causes of death include heart failure, hemoptysis, brain abscess, thromboembolism, and complications of pregnancy and noncardiac surgery.[146] These patients face potentially significant perioperative risks. Findings of Eisenmenger syndrome are summarized in Box 22.9.

Surgical closure of cardiac defects with fixed pulmonary vascular hypertension is associated with very high mortality. Lung or heart-lung transplantation is a surgical alternative.[147] Although there are several surgical series reporting survival after heart-lung or single- or double-lung transplantation performed for primary pulmonary hypertension, it is unclear if this cohort of patients is similar to patients with Eisenmenger physiology.

BOX 22.9 FINDINGS IN EISENMENGER SYNDROME

- Physical examination: Loud pulmonic component of the second heart sound, single or narrowly split second heart sound, Graham-Steell murmur of pulmonary insufficiency, pulmonic ejection sound ("click")
- Chest radiography: Decreased peripheral pulmonary arterial markings with prominent central pulmonary vessels ("pruning")
- Electrocardiogram: Right ventricular hypertrophy
- Impaired exercise tolerance
- Exertional dyspnea
- Palpitations (often due to atrial fibrillation or flutter)
- Complications from erythrocytosis/hyperviscosity
- Hemoptysis from pulmonary infarction, rupture of pulmonary vessels or aortopulmonary collateral vessels
- Complications from paradoxical embolization
- Syncope from inadequate cardiac output or arrhythmias
- Heart failure (usually end stage)

When noncardiac surgery is deemed essential and time permits, a preoperative cardiac catheterization may be helpful to determine the presence of pulmonary reactivity to oxygen or nitric oxide. Fixed PVR precludes rapid adaptation to perioperative hemodynamic changes. Changes in systemic vascular resistance are mirrored by changes in intracardiac shunting. A decrease in systemic vascular resistance is accompanied by increased right-to-left shunting and a decrease in systemic oxygen saturation. In addition, an acute fall in systemic resistance can impair left ventricular filling with the right ventricular encroachment. Systemic vasodilators, including regional anesthesia, should be used with caution, and close assessment of intravascular volume is important. Epidural analgesia has been used successfully in patients with Eisenmenger physiology, but the local anesthetic must be delivered slowly and incrementally with close observation of blood pressure and oxygen saturation.[148] Postoperative postural hypotension can also increase the degree of right-to-left shunting, and these patients should change position slowly. All intravenous catheters must be maintained free of air bubbles.

Placement of pulmonary artery catheters in these patients is problematic for a variety of reasons, and they are of less utility than might be expected. Pulmonary arterial hypertension is a risk factor for pulmonary artery rupture from a pulmonary artery catheter. Rupture is particularly worrisome in these cyanotic patients, who can also have hemostatic deficits associated with erythrocytosis.[149] Abnormal intracardiac anatomy and right-to-left shunting can make successful passage into the pulmonary artery difficult without fluoroscopy. Relative resistances of the pulmonary and systemic beds are reflected in the systemic oxygen saturation, readily measured by pulse oximetry, so measures of pulmonary artery pressure are not required. In addition, in the presence of right-to-left shunting, thermodilution cardiac outputs do not accurately reflect systemic output. Thus the value of pulmonary artery catheters in these patients is minimal at best, and they essentially are never indicated. The one potential exception is the patient with an ASD who is at risk to develop right ventricular failure if suprasystemic right ventricular pressure develops.[150]

Fixed PVR is by definition unresponsive to pharmacologic or physiologic manipulation, but as previously mentioned, only patients at the true end stage of disease have fixed PVR. Thus the clinician must still avoid factors known to increase PVR, including cold, hypercarbia, acidosis, hypoxia, and α-adrenergic agonists. Although the last of these is commonly listed to be avoided, in the face of pulmonary vascular disease due to intracardiac shunting, the systemic vasoconstrictive effects predominate and systemic oxygen saturation increases.

Nerve blocks offer an attractive alternative to general anesthesia if otherwise appropriate. Although Martin and colleagues in a literature review found that the mortality in nerve block cases was less than that for general anesthesia cases (5% vs 15%), they could not differentiate the relative risk between type of anesthetic and type (complexity) of surgery.[151]

If patients have general anesthesia, consideration should be given to postoperative observation in an intensive or intermediate care unit. Because of the increased perioperative risk, patients should be observed overnight, particularly if they have not had recent surgery or anesthesia, because their responses will be unknown. Ambulatory surgery is possible for patients having uncomplicated minor surgery with sedation or nerve block.

Although the perioperative mortality risk in the past has been estimated as high as 30%,[151,152] estimates of mortality after noncardiac surgery in adulthood from more current series suggest that the mortality risk from noncardiac surgery and/or anesthetics is less than in the past. For example Ammash and colleagues in 1999 reported a mortality rate of 7% (2 of 24)[153] and Bennett and associates in 2014 reported a mortality of 3.8% (2 of 53).[154] However, all of these series suffer from being somewhat small, conducted at single institutions, and including operations and patients of varying complexity. In the series from Bennett and others, 26% of patients developed significant systemic hypotension and 17% oxygen desaturation. Not surprisingly, hypoxemia was preceded by systemic hypotension. The incidence of hypotension was worse with propofol and inhalation inductions, and the authors found that use of a vasopressor during induction was helpful. Worrisomely, the authors reported that the only two deaths in their series occurred following monitored anesthesia care: the first patient developed hypoxic respiratory failure 2 hours after TEE and cardioversion, and the second patient died on postoperative day 6 following TEE, cardioversion, and upper and lower endoscopy.

Pregnancy carries very high risks of mortality and premature delivery. From 20% to 30% of pregnancies result in spontaneous abortions, and premature delivery occurs in about half.[155] At least half of newborns have intrauterine growth retardation. From 30% to 45% of all pregnancies end in maternal death intrapartum or during the first postpartum week, and successful first pregnancy does not preclude maternal death during a subsequent pregnancy.[156] The hemodynamic changes of both pregnancy and delivery increase maternal risk. Pulmonary microembolism and macroembolism have caused peripartum maternal deaths, even days after delivery. Factors influencing mortality include thromboembolism (44%), hypovolemia (26%), and preeclampsia (18%).[155,156] Mortality is similar with cesarean section or vaginal delivery, and both carry significantly higher mortality rates than that for spontaneous abortion. In a literature review Martin and colleagues found a 24% mortality rate for laboring women who received regional anesthesia. Most of these women died several hours after delivery.[151] Of course reporting bias cannot be excluded in a report such as this. Pregnancy should be discouraged in these women. Women who do become pregnant should be closely monitored with arterial catheters during delivery. Epidural analgesia, delivered slowly and incrementally, can moderate many of the deleterious hemodynamic changes of active labor. Pulmonary arterial catheters are of little to no use during delivery. Prompt treatment of blood loss and hypotension during delivery is absolutely required. Postpartum observation should be in an intensive care setting. Pulmonary hypertension in pregnancy was reviewed in detail.[157,158]

Endocardial Cushion Defects (Atrioventricular Canal Defects)

The endocardial cushions are the embryonic cardiac tissues that form the crux of the heart—the primum (lower) atrial septum, the posterior basal part of the ventricular septum, the septal leaflet of the tricuspid valve, and the anterior leaflet of the mitral valve. The endocardial cushion defects then consist of one or more of a primum ASD, inlet VSD, cleft septal leaflet of the tricuspid valve, and/or cleft anterior leaflet of the mitral valve. The most primitive form is the complete atrioventricular canal. In this defect, there is a single large

atrioventricular valve with mitral and tricuspid components with large ASDs and VSDs. This valve is usually "balanced." In the more complex, unbalanced defects, one component of the valve can be predominant, and this large valve is not centered over the ventricular septum, leading to underfilling of one of the ventricles. Three-dimensional echocardiography can be particularly useful in delineating the specific anatomy with these lesions.[159] These defects can occur alone or can be part of more complex cardiac defects such as tetralogy of Fallot or single ventricle. Half of all children with Down syndrome have CHD; one-half of these have an endocardial cushion defect. These lesions are marked by a typical electrocardiogram (ECG) with first-degree block and a superior QRS axis with a counterclockwise QRS loop. Although adults with unrepaired complete atrioventricular canal will likely have developed inoperable pulmonary arterial hypertension, partial canal defects can sometimes be first diagnosed in adults and can be appropriate candidates for surgical repair. The AV node and bundle of His are displaced inferiorly, putting them at risk for surgical injury and the induction of heart block.

Much subtlety is required to construct two separate functional atrioventricular valves without residual stenosis or insufficiency of either component. Postoperative or residual mitral insufficiency is not uncommon, and 10% to 30% require repeat surgery.[160] The strongest predictor of postoperative mitral insufficiency is the degree of preoperative regurgitation of the common atrioventricular valve. Anesthesia for these patients depends on the degree of shunt, valve insufficiency, and pulmonary vascular disease.

Fontan Physiology

In 1968, performing the operation that now bears his name, Fontan and colleagues proved that it was possible to deliver the entire systemic venous return to the lungs without the benefit of a ventricular pump.[161] The Fontan operation was a landmark development in CHD because it established a "normal" series circulation in patients with a single ventricle. The price to be paid for a series circulation is the unique physiologic demand of passive pulmonary blood flow. Complications never envisioned at the time of the original operation have occurred, necessitating significant changes in operative technique. Fontan's original operation (Fig. 22.6) was soon modified to an atriopulmonary connection[162] (Fig. 22.7). The original strict eligibility criteria[163] have been liberalized, but patients meeting as many of the criteria as possible still have the best prognosis for good long-term survival. By the mid-1980s, it became clear that success of Fontan circulation was based on an unobstructed pathway from systemic veins to pulmonary artery, a pulmonary vasculature that was free from anatomic distortion (eg, from previous Blalock-Taussig shunt), low PVR, and good ventricular function without significant atrioventricular valve regurgitation. The incorporation of the atrium in the Fontan pathway proved disappointing. The atrium lost its contractile function, providing no assistance to pulmonary blood flow and causing serious complications. Understanding these complications and how the Fontan operation has evolved is the key to managing these challenging patients whose complex CHD has been palliated, not cured.

Complications (Box 22.10)

The dilated, noncontractile atrium serves as a reservoir of blood and a ready source of thrombus.[164–166] Pulmonary embolization will impair the passive blood flow necessary for successful Fontan circulation. Atrial thrombus could embolize paradoxically through residual right-to-left shunts. Patients are also at risk for arterial thrombosis, secondary to a mild hypercoagulable state.[167,168] Given the morbidity associated with thromboembolism, it seems reasonable to put all Fontan patients on aspirin.[169] Those who display further potential for thrombosis such as low cardiac output state, atrial arrhythmia with significant atrial dilation, or marked venous hypertension may benefit from warfarin (Coumadin).

Fontan patients show a steady increase in atrial tachyarrhythmias with an incidence of over 50% at 20 years.[170] Changes in surgical technique evolved in part to decrease the rate of atrial arrhythmias. Although initial results were promising,[171] unfortunately, much of this benefit is lost with longer-term follow-up.[172] Fontan patients tolerate tachycardia very poorly, and acute episodes usually require urgent treatment using medical therapy to control ventricular rate or cardioversion. Late-onset atrial tachyarrhythmias usually occur between 6 to 10 years post-Fontan completion.[173] The most common tachyarrhythmia

BOX 22.10 COMPLICATIONS OF FONTAN OPERATION

- Atrial thrombus
- Atrial arrhythmia (tachyarrhythmia or bradyarrhythmia)
- Ventricular dysfunction
- Chylothorax
- Protein-losing enteropathy

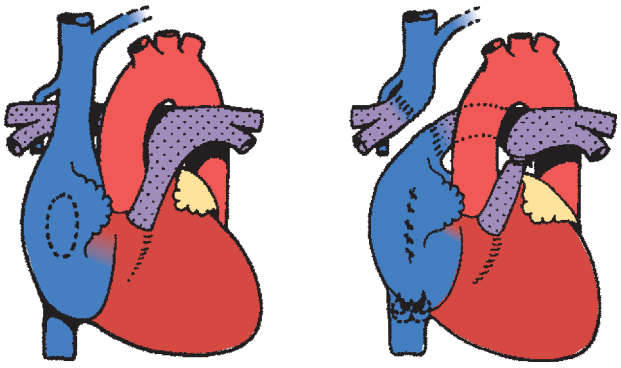


Fig. 22.6 The original Fontan operation. Note the classic Glenn shunt connecting the superior vena cava to the right pulmonary artery and the homografts at the inferior vena cava-right atrial junction and connecting the right atrium to the left pulmonary artery. *(Reprinted with permission from Fontan F, Baudet E. Surgical repair of tricuspid atresia.* Thorax. *1971;26:240.)*

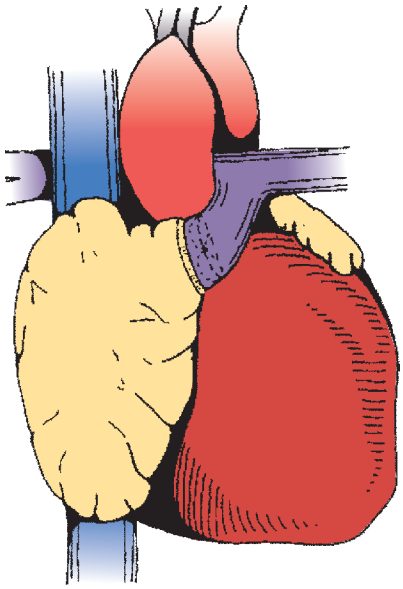


Fig. 22.7 The atriopulmonary modification of the Fontan operation. *(Reprinted with permission from Kreutzer G, Galindez E, Bono H, et al. An operation for the correction of tricuspid atresia.* J Thorac Cardiovasc Surg. *1973;66:613.)*

is right intraatrial reentrant tachycardia. Over time, episodic attacks of tachycardia become more frequent. Frequently, atrial fibrillation occurs, and the loss of atrioventricular synchrony results in decreased effort tolerance. The onset of atrial tachyarrhythmias mandates an evaluation of the Fontan pathway with attention turned to relieving any significant obstructions. In the setting of passive pulmonary blood flow, even small gradients can be very hemodynamically significant.[174] Therapies for chronic atrial arrhythmias consist of medication, catheter ablation, and surgery. Given the complex anatomy, dilated atrium, and atrial scar with suture lines from prior surgeries, it is not surprising that atrial arrhythmias can become refractory to standard treatment in many patients. Catheter ablation typically has high initial success rates that are not maintained.[174]

Bradyarrhythmias, caused by sinus node ischemia, are common. In a large cohort of patients with atriopulmonary connections, the incidence of bradyarrhythmias requiring pacemakers was 13%.[175] Progressive fibrosis and scar around the sinus node, caused by prior surgical dissection, eventually leads to ischemia and clinical sinus node dysfunction. If accompanied by premature atrial contractions, sinus or junctional bradycardia can precipitate an intraatrial reentry tachycardia. Thus sinus node dysfunction also serves as a risk factor for the development of atrial tachyarrhythmias. Clinically significant bradyarrhythmias require pacing. Pacemakers pose special problems in the Fontan patient because the altered anatomy precludes transvenous placement. Thus Fontan patients who require pacing will have epicardial leads placed via repeat sternotomy with all the accompanying risks. Even though atrioventricular synchrony can be achieved with pacing, it is still not as desirable as intrinsic sinus rhythm. The incidence of sinus node dysfunction is less with a cavopulmonary versus an atriopulmonary connection.[176] However, a clear benefit from an extracardiac connection (see later) when compared with the lateral tunnel approach has been difficult to prove.[177–179]

The last major complication of Fontan physiology is protein-losing enteropathy (PLE), a condition as confounding as it is serious. The incidence is quoted as high as 15%, but a large international multicenter study found a rate of 3.7%.[180] Clinically, there is an edematous state with ascites and pleural-pericardial effusions. Serum albumin is low and the diagnosis is confirmed by finding enteric protein loss with elevated levels of stool α1-antitrypsin. Most ominously, PLE is accompanied by 50% mortality 5 years from diagnosis despite treatment. It was believed that PLE constituted a straightforward situation of elevated portal pressures secondary to central venous hypertension. Elevated portal pressures lead to vascular congestion, lymphatic obstruction, and enteric protein loss from the gut. Unfortunately, there is not a good correlation between central venous pressures and PLE.[181] This has led to a broader understanding of PLE as a multifactorial phenomenon due to reduced mesenteric perfusion,[181] chronic inflammation[182] and enterocyte dysfunction.[183] Patients who present with PLE should have a complete hemodynamic evaluation. This is vital because interventions that improve cardiac output have proven successful in PLE. Any Fontan pathway obstruction should be treated and cardiac output optimized with medical therapy, fenestration, or pacing. In the absence of correctable obstructions, PLE portends a poor prognosis, despite surgery or cardiac transplantation.

The Modern Fontan Operation

The atriopulmonary connection proved an inefficient method of pulmonary blood flow. Colliding streams of blood from the superior and inferior vena cavae resulted in energy loss and turbulence within the atrium.[184] The energy required to propel blood forward into the pulmonary vasculature was lost as blood swirled sluggishly in the dilated atrium (Fig. 22.8). The modern Fontan operation is a total cavopulmonary connection (Fig. 22.9). The lateral tunnel Fontan improved pulmonary blood flow, and only the lateral wall of the atrium was exposed to central venous hypertension. There was no dilated atrium to serve as a source of thrombus. The extensive atrial suture lines, however, remained a risk for arrhythmia. The extracardiac Fontan is a further modification of the total cavopulmonary connection. The extracardiac Fontan greatly reduces the number of atrial incisions and hopefully the long-term development of atrial arrhythmias. Has the modern Fontan improved outcomes? Reductions in arrhythmia and improvements in overall survival have been noted.[185] Results for the extracardiac Fontan are even better than those of the lateral tunnel Fontan but are limited by the shorter duration of follow-up. It is not yet certain if the development of long-term complications has been truly reduced or only delayed.

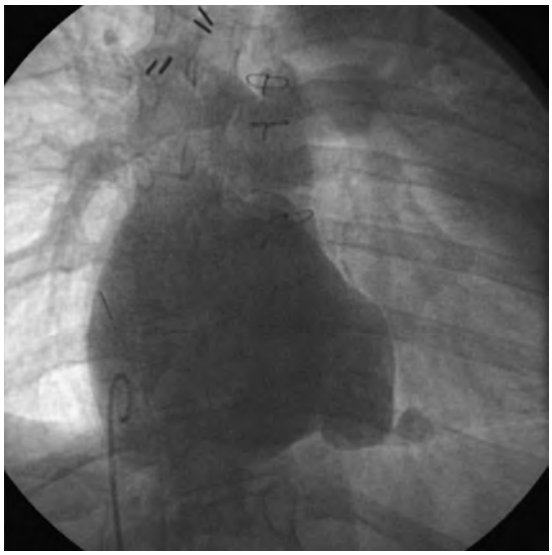


Fig. 22.8 Injection of contrast into the inferior vena cava reveals a markedly dilated right atrium following an atriopulmonary Fontan operation.

Preoperative Assessment

Patients with Fontan physiology are presenting in larger numbers for the entire array of noncardiac surgery, including obstetric procedures. Preoperative assessment begins with a directed history, concentrating on functional status and the presence of major complications. Heightened suspicion is clearly needed for patients with atriopulmonary connections and for those with a systemic right ventricle. Patients with Fontan circulation have a low cardiac output state. This low output state exists despite the presence of good ventricular function, minimal atrioventricular valve regurgitation, and low PVR. A cohort of patients with an atriopulmonary Fontan performed at an older age showed striking reductions in anaerobic threshold (less 50% of controls), $\dot{V}O_2$ max (less than 33% of controls) and systemic ejection fraction both at rest and exercise.[186] Further compounding the issue is that patients' self-assessment grossly overestimates their objective exercise capacity.[187] This places the anesthesiologist in a considerable dilemma when faced with a Fontan patient who rates his or her functional status as "good." The authors believe that transthoracic echocardiography should be the initial preoperative investigation and is mandatory except in cases of very minor surgery. Further testing is guided by the results of the echocardiogram and in consultation with a cardiologist experienced in caring for adults with CHD. Normal ventricular function on echocardiogram would stratify the patient as "low risk" only within the context of patients with Fontan circulation.

A term that should immediately get the attention of the anesthesiologist is *failing Fontan*. Specific reasons for failing may differ, but the common denominator in these patients is a marked limitation of functional status. They will manifest some combination of refractory arrhythmias, PLE, liver dysfunction, hypoxemia, or congestive heart failure. Although PLE always signifies a failing Fontan, the converse is not always true. That is, patients can have severely limited function with elevated central venous pressures and even evidence of cirrhosis on liver biopsy without demonstrating PLE.[188] Patients with a "failing

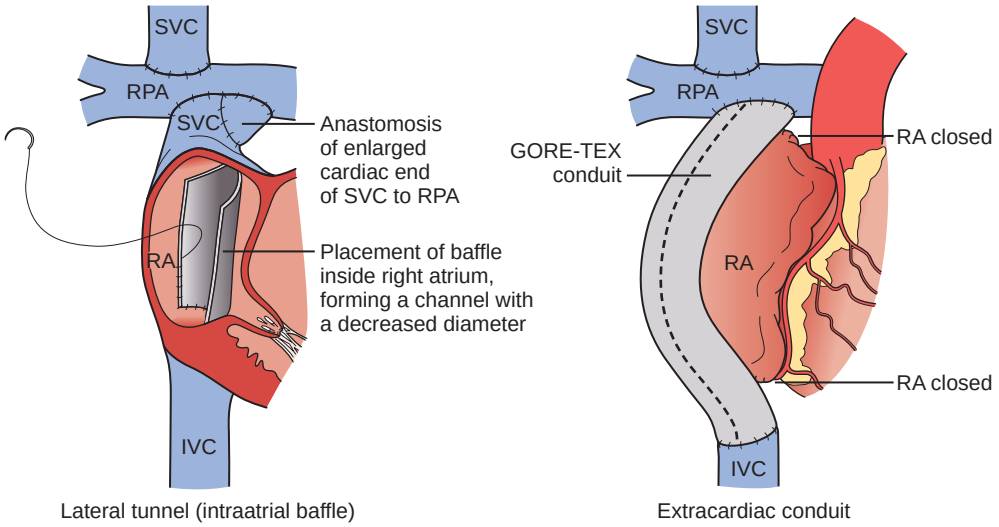


Fig. 22.9 Two variations of the modern Fontan operation, the lateral tunnel and extracardiac operations. *IVC,* Inferior vena cava; *RA,* right atrium; *RPA,* right pulmonary artery; *SVC,* superior vena cava. *(Reprinted with permission from D'Udekem Y, Iyengar AJ, Cochrane AD, et al: The Fontan procedure: contemporary techniques have improved long-term outcomes.* Circulation. *2007;116[11 Suppl]:I157.)*

Fontan" require a search for correctable lesions.[189] First, any obstructions within the Fontan pathway should be treated, preferably with percutaneous techniques of dilation and stenting. Second, loss of sinus rhythm should be treated with pacing. If loss of sinus rhythm is accompanied by severe tachyarrhythmias, Fontan conversion surgery is indicated. Third, some patients develop collateral vessels. Aortopulmonary collaterals result in a progressive volume load on the single ventricle. Collaterals from the venous system to the systemic atrium or ventricle cause hypoxemia. In both cases large collaterals should be coil occluded in the catheterization laboratory. Another option is the creation of a fenestration, which can improve cardiac output and lower central venous pressures but at the expense of a right-to-left shunt. Unfortunately, not all of these therapeutic options are indicated or successful in every patient. At this point, if no realistic hope of further improvement exists, the only option is cardiac transplantation.

The functional state of Fontan patients exists across a spectrum but generally falls into two groups. The first and largest group is made of those who report NYHA I-II level of function but have been shown to possess much less cardiorespiratory reserve than age-matched two-ventricle controls. These patients will tolerate most surgical procedures with an acceptably low risk. The second group is smaller but consists of those patients who have manifested one of more of the "failing Fontan" criteria. Surgery in these patients carries much greater risk and should only be undertaken after careful consultation with physicians experienced in ACHD. When it comes to a discussion of anesthetic technique, the same lessons learned in caring for patients with acquired coronary artery disease apply. That is, there is no right drug for these patients, nor is there a single "best" anesthetic technique. Rather, the critical issue is to gain a clear and comprehensive understanding of the patient's pathophysiology. The key is not which drugs are used, but rather how they are used. Certain principles for patients with Fontan physiology are important and need to be stressed (Box 22.11).

Ventilatory Management

In an effort to minimize PVR, functional residual capacity should be maintained by the application of small amounts of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP), and excessive lung volumes should be avoided. PEEP or CPAP will not significantly impede cardiac output if less than 6 cm H_2O. Spontaneous ventilation has been assumed to be optimal for these patients to minimize intrathoracic pressure and encourage forward flow into the pulmonary circulation; but as discussed by Steven and McGowan,[190] hard evidence for this approach is mostly lacking. Cardiac output should be optimized by limiting mean airway (intrathoracic) pressure: minimizing peak inspiratory pressure, limiting inspiratory time, using low respiratory rates, and applying judicious amounts of PEEP while using higher tidal volumes to maintain normocarbia. The

BOX 22.11 MANAGEMENT PRINCIPLES FOR PATIENTS WITH FONTAN PHYSIOLOGY

1. Maintenance of preload is essential. A prolonged NPO period without intravenous hydration should be avoided.
2. Regional and neuraxial techniques are attractive options, with appropriate attention to volume status. A neuraxial anesthetic is a poor choice if a high level of block is required. A slowly titrated epidural is preferable to a rapid-acting spinal anesthetic.
3. Airway management must be skilled to avoid hypercarbia and elevations in pulmonary vascular resistance (PVR).
4. Adequate levels of anesthesia must be established before stimulating events such as laryngoscopy. A surge of catecholamines may precipitate dangerous tachycardia.
5. Spontaneous ventilation that augments pulmonary blood flow is desirable but must not be pursued at all costs. Spontaneous ventilation under deep levels of anesthesia will result in significant hypercarbia. The benefit of spontaneous ventilation may be negated by the rise in PVR secondary to hypercarbia.
6. A plan must be in place to treat tachyarrhythmias.
7. Patients with pacemakers must have the device interrogated before surgery and a plan developed to avoid potential interference from electrocautery, particularly if the patient is pacemaker dependent.
8. If large volume shifts are anticipated, invasive monitoring with central lines and transesophageal echocardiography is recommended.
9. An appropriate plan for postoperative pain management should be established. The need for anticoagulation in many Fontan patients may preclude the use of epidural analgesia.
10. A cardiologist experienced in caring for patients with congenital heart disease should be involved perioperatively.

benefits of very early postoperative tracheal extubation (in the operating) have been considered particularly useful in these patients.[191]

Pregnancy

It was inevitable that as some of the female Fontan patients reached childbearing age they would become pregnant. Case reports first began appearing in 1989.[192,193] Unfortunately, 20 years later the body of knowledge on this important subject consists primarily of more case reports with no large registry documenting outcomes. The physiologic changes of pregnancy are well known and described in standard texts. Can a Fontan patient cope with the increased cardiovascular demands of pregnancy? The dilemma facing physicians caring for these patients is that Fontan patients are known to have decreased cardiac reserve, even those who report good functional status. Because pregnancy is a "stress test," who will pass this test and who will fail? The literature provides conflicting data. One series of 33 pregnancies found women tolerated pregnancy, labor, and delivery well but there was an increased risk of spontaneous abortion.[50] More recently, a smaller series found live birth pregnancies complicated by high rates of NYHA class deterioration, atrial arrhythmia, prematurity, and intrauterine growth retardation.[63] What can be made of these reports? They suffer from the usual problems of retrospective review and self-reporting. However, they do provide clinicians with some reassuring information. First, pregnancy is usually undertaken only in those patients with relatively good functional status, thereby removing the highest risk patients. Undoubtedly, most adult congenital cardiologists would counsel against pregnancy in any patient with evidence of a failing Fontan circulation. In patients with good functional status, pregnancy can successfully be carried to term, albeit with increased risk of miscarriage and premature delivery. A review of the case reports in the anesthetic literature shows that epidural analgesia is well tolerated and indeed recommended for the first stage of labor. The caesarian section rate approaches 50%.[64] Neuraxial anesthesia for caesarian section, in addition to its usual benefits, preserves spontaneous ventilation, which is desirable in Fontan patients. However, no increased risk from general anesthesia was identified. Perioperative complications are low, and peripartum cardiac decompensation is rare. Obstetric anesthesia care in these women has been reviewed.[194]

Fontan Conversion Surgery

There is now a large cohort of patients with atriopulmonary connections suffering from some degree of thrombosis, arrhythmia, PLE, or ventricular dysfunction. These patients are candidates for Fontan conversion surgery, which is the most commonly performed high-risk operation in the ACHD population. Case reports and small case series began to appear in the literature in the mid-1990s. At this time, interest focused on the best indications for this major surgery, outcome predictors, and optimizing the surgical technique. Nearly 15 years later there are some answers to these important questions. It was believed that conversion of an atriopulmonary Fontan to the improved hemodynamics of the modern Fontan would relieve severe atrial arrhythmias. The profile of the early patient undergoing Fontan conversion surgery was one of refractory atrial arrhythmias and poor functional state.[195] Two general trends have been identified. First, in this very-high-risk group of patients perioperative mortality was low. Second, arrhythmia control was much better in the group that underwent extracardiac connection with arrhythmia surgery. Conversion to extracardiac Fontan without an ablative procedure resulted in a high rate of arrhythmia recurrence. The largest experience came from Mavroudis, whose preferred technique was conversion to an extracardiac Fontan with intraoperative electrophysiologic mapping, arrhythmia ablation, and pacemaker placement.[196] The risk factors for death or transplantation were right or ambiguous ventricular morphology, PLE, atrioventricular valve regurgitation graded moderate or worse, and long CPB time.

These encouraging results give hope to the many patients with atriopulmonary connections and poor functional status. Patients should not have multiple failed attempts at arrhythmia ablation in the catheterization laboratory because of a fear that surgery is associated with an unacceptably high mortality. The ideal patient is one with refractory arrhythmia and poor functional status despite adequate ventricular function. The higher risk groups of patients are those with significant ventricular dysfunction, atrioventricular valve regurgitation, or PLE. Fontan conversion surgery provides myriad challenges to the anesthesiologist. Preoperatively, the important factors are the degree of arrhythmia control and the ventricular function. Most of the patients will be on at least one antiarrhythmic drug. They may be in sinus rhythm, but it is more likely they have an atrial arrhythmia with some degree of ventricular rate control. They retain the ability to become tachycardic very easily. This is almost always associated with prompt hemodynamic deterioration. The underlying ventricular function may be poor due to longstanding arrhythmia, made worse by the negative inotropic effect of antiarrhythmic medications. Transcutaneous patches for cardioversion should be placed before induction. Intravenous induction can be prolonged because blood moves sluggishly through the greatly dilated atrium. Airway management needs to be prompt and skilled, as it does for all Fontan patients. Once safely through induction and intubation, large-bore intravenous access must be established. This is usually not a problem because the central venous hypertension of Fontan patients creates dilated peripheral veins. Small central venous catheters are appropriate for delivering inotropic drugs and monitoring but some centers will prefer to place transthoracic atrial lines and completely avoid central access for fear of thrombosis. Transesophageal echocardiography is routinely used to assess volume status and ventricular function, as well as to exclude intracardiac thrombus. The repeat sternotomy, usually at least the third, can be especially bloody because of the raised central venous pressure. Maintenance of preload and the ability for large-volume transfusion is required. Also, a plan should be worked out with the surgeon and perfusionist for emergency establishment of femoral bypass if necessary. Patients with pacemakers are vulnerable to electromagnetic interference because the repeat sternotomy requires extensive use of electrocautery in close proximity to the heart and pacemaker generator. If the patient is pacemaker dependent, consideration should be given to reprogram the device to an asynchronous mode. The ability to pace using transcutaneous patches is necessary. The pre-bypass period can obviously be one of high stress.

In preparation to separate from CPB, full recruitment of the lungs and modest hyperventilation with 100% oxygen are necessary to keep PVR as low as possible. Other factors that raise PVR, such as acidosis and hypothermia, must be corrected before separation from CPB. Fontan conversion is a lengthy surgery, and the long duration of CPB can precipitate a potent inflammatory response with release of numerous mediators that raise PVR. Milrinone's pulmonary vasodilating properties make it an attractive choice. Despite long CPB times for this type of surgery, aortic cross-clamp time usually is short. Thus ventricular function after CPB is generally good but must be supported as necessary with inotropes to ensure that atrial and pulmonary venous pressures remain low. Finally, aggressive management of coagulation is required, and in this regard there is no substitute for point-of-care testing to guide transfusion products. The anesthetic considerations for Fontan conversion surgery have been reviewed in detail.[197]

Patent Ductus Arteriosus

Beyond the neonatal period, spontaneous closure of a PDA is uncommon. The risk of a longstanding moderate-to-large PDA is volume overloading of the left atrium and left ventricle with the risk of development of pulmonary vascular disease. The progression of pulmonary vascular disease is relatively accelerated when compared with patients with other types of right-to-left shunts with equivalent degrees of shunting. The development of pulmonary vascular disease is dependent on the volume and pressure of the right-to-left shunt. A PDA delivers blood at high shear stress (ie, arterial pressure) to the pulmonary vasculature and flow occurs continuously throughout the cardiac cycle. With time, the ductus can become calcified or aneurysmally dilated with a risk of rupture. Ductal calcification or aneurysm

increases the risk of surgery, which rarely requires CPB.[198] Unrepaired, the natural history is for one-third of patients to die of heart failure, pulmonary hypertension, or endocarditis by 40 years of age and two-thirds by age 60.[199] Although small PDAs are of no hemodynamic consequence, even small PDAs carry relatively high endocarditis risk. Surgical closure should be considered for all adults with PDA[198]; transvascular closure by means of one of several devices is possible and is currently the treatment of choice unless excluded by atypical anatomy. With calcification and friability of the ductus, if device closure is not practicable, it is possible to do a patch closure from inside the aorta or pulmonary artery.

Small PDAs do not carry a hemodynamic risk for pregnancy. The decrease in systemic vascular resistance accompanying pregnancy could lead to right-to-left shunting in a woman with a large PDA.

Pulmonary Valve Stenosis

Long-term asymptomatic survival is typical of patients, with the exception of neonates with critical stenosis.[200] There is a 94% survival rate 20 years after diagnosis, and adults generally do not require surgical intervention.[201] With aging, however, right ventricular fibrosis and failure can develop, and this is the most common cause of death, usually in the fourth decade. Almost all patients who have relief of stenosis either surgically or by balloon valvuloplasty have normal right ventricular function postoperatively, although surgical reintervention may be required in a significant number in the long term.[202] Percutaneous pulmonary valve implantation, done in the catheterization laboratory, is another option. However, abnormal ventricular function may not resolve after late surgical correction. The development of isolated pulmonary valvular stenosis, even of a severe degree, is usually well tolerated during pregnancy, even in the face of the volume overload that accompanies pregnancy.[203]

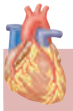
In patients with significant right ventricular hypertension, right ventricular ischemia can occur if systemic hypotension and decreased coronary perfusion occur. This is manifest on the ECG. Coronary ischemia resolves if coronary perfusion pressure is increased, as with use of phenylephrine.

Single Ventricle

See the Fontan Physiology section earlier in this chapter for a detailed discussion.

Tetralogy of Fallot

As with many things in medicine, tetralogy of Fallot was first described by someone else—probably in 1673 by Stenson. The classic description of tetralogy of Fallot includes (1) a large, nonrestrictive malaligned VSD, with (2) an overriding aorta, (3) infundibular pulmonic stenosis, and (4) consequent right ventricular hypertrophy, all derived from an embryonic anterocephalad deviation of the outlet septum. However, there is a spectrum of disease with more severe defects including stenosis of the pulmonary valve, stenosis of the pulmonary valve annulus, or stenosis and hypoplasia of the pulmonary arteries in the most severe cases. Pentalogy of Fallot refers to the addition of an ASD. With advances in genetics, up to one-third or more of cases of tetralogy have been ascribed to one of several genetic abnormalities, including trisomy 21, the 22q11 microdeletion, the genes NKX 2-5, JAG1, GATA4, and others. Tetralogy of Fallot is the most common cyanotic lesion encountered in the adult population. Unrepaired or nonpalliated, approximately 25% of patients survive to adolescence, after which the mortality is 6.6% per year. Only 3% survive to age 40.[204] Unlike children, teenagers and adults with tetralogy do not develop "tet spells." Long-term survival with a good quality of life is expected after repair. The 32- to 36-year survival has been reported to be 85% to 86%, although symptoms, primarily arrhythmias and decreased exercise tolerance, occur in 10% to 15% at 20 years after the primary repair[205–208] (Box 22.12). In the past, most children with tetralogy were managed with a preliminary palliation with an aortopulmonary shunt such as a Blalock-Taussig, followed by complete correction. Essentially all patients would eventually have come for complete repair. Currently, most children are managed with a complete repair in infancy, without preceding palliation.



BOX 22.12 RISK FACTORS FOR SUDDEN DEATH AFTER REPAIR OF TETRALOGY OF FALLOT

- Repair requiring ventriculotomy
- Older age at repair
- Severe left ventricular dysfunction
- Postoperative right ventricular hypertension (residual outflow tract obstruction)
- Wide-open pulmonary insufficiency
- Prolongation of the QRS

It is uncommon to encounter an adolescent or adult with unrepaired tetralogy. However, it can be encountered in immigrants or in patients whose anatomic variation was considered to be inoperable when they were children. In tetralogy, the right ventricle "sees" the obstruction from the pulmonic stenosis. PVR is typically normal to low. Right-to-left shunting is caused by obstruction at the level of the right ventricular outflow tract and is unaffected by attempts at modulating PVR. Shunting is minimized, however, by pharmacologically increasing systemic vascular resistance. Because there is an unrestrictive VSD, in the unrepaired adult systemic hypertension developing in adult life imposes an additional load on both ventricles, not just the left. The increase in systemic vascular resistance decreases right-to-left shunting and diminishes cyanosis but at the expense of right ventricular or biventricular failure. Increases in the inotropic state of the heart increase the dynamic obstruction at the right ventricular infundibulum and worsen right-to-left shunting. β-Blockers are often used to decrease inotropy. Although halothane was the historic anesthetic of choice in children with tetralogy due to its myocardial depressant effects and ability to maintain systemic vascular resistance, current practice is to use sevoflurane, without undue consequence from a reduction in systemic vascular resistance.[209] Anesthetic induction in adults can easily be achieved with any of the available agents, keeping in mind the principles of maintenance of systemic blood pressure, avoidance of hypovolemia, and preventing increases in inotropy.

Patients require closure of the VSD and resolution of the pulmonic stenosis. Although current practice is to repair the VSD through the right atrium in an effort to maintain competence of the pulmonary valve and limit any ventriculotomy, older patients will likely have had repair via a right ventriculotomy. A large right ventriculotomy increases the risks of arrhythmias and sudden death.[210] Patients who have had a right ventriculotomy will have an obligate right bundle-branch block pattern on the ECG. However, unlike the more usual bundle-branch block in adults, this represents disruption of the His-Purkinje system only in the right ventricular outflow, in the area of the right ventricular incision. Because the vast majority of His-Purkinje conduction is intact, it does not carry increased risk for the development of complete heart block. These patients can have an abnormal response to exercise.

Some patients require repair of pulmonic stenosis by placement of a transannular patch, with obligate residual pulmonary insufficiency. Isolated mild-to-moderate pulmonary insufficiency is generally well tolerated, but in the long term, it can contribute to right ventricular dysfunction with a risk of ventricular tachycardia and sudden death. Patients requiring pulmonary valve replacement in their late teens or early 20s after a transannular patch in early childhood are a growing proportion of the adult CHD population. Atrial tachyarrhythmias occur in about one-third of adults late after repair and can contribute to late morbidity.[211,212] The development of atrial flutter or atrial

reentrant tachycardia is often a harbinger of hemodynamic compromise. The substrate is usually an atrial surgical scar and the trigger is atrial dilation, such as from tricuspid insufficiency with right ventricular dysfunction. The mechanism for the development of ventricular arrhythmias is presumably the same, namely, dilation superimposed on surgical scar.

In some cases, the right ventricular outflow tract patch needs to be extended onto the branch pulmonary arteries to relieve obstruction. Patients with abnormal coronary arteries may have required repair using a right ventricle–to–pulmonary artery conduit to avoid doing a right ventriculotomy in the area of the coronary artery. Repair at a younger age (<12 years) results in better postoperative right ventricular function.[213]

Sudden death or ventricular tachycardia requiring treatment can occur in up to 5.5% of postoperative patients over 30 years, often years postoperatively.[206,207,214] The foci for these arrhythmias are typically in the right ventricular outflow tract in the area that has had surgery, and they can be ablated in the catheterization laboratory. Older age at repair, severe left ventricular dysfunction, postoperative right ventricular hypertension from residual or recurrent outflow tract obstruction, wide-open pulmonary insufficiency, and prolongation of the QRS (to >180 milliseconds) are all predictors of sudden death.[210,215] Premature ventricular contractions and even nonsustained ventricular tachycardia are not rare but do not seem to be associated with sudden death, making appropriate treatment options difficult.[216] QRS prolongation to longer than 180 milliseconds, although highly sensitive, has a low positive predictive value.[217] The impact of this risk factor in the current group of younger patients who have not had ventriculotomies is unclear, because their initial postoperative QRS durations are shorter than in patients who had a right ventriculotomy.

Although for many years it was thought that moderate-to-severe pulmonary insufficiency in these patients was well tolerated, it has become apparent from a number of series that right ventricular dysfunction and both atrial and ventricular arrhythmias can be common long-term sequelae. For this reason, patients with symptomatic pulmonary insufficiency from a transannular patch or aneurysm formation at the site of a right ventricular outflow tract patch can require reoperation to replace a widely incompetent pulmonary valve with a bioprosthetic valve with or without a tricuspid annuloplasty.[218] Of interest, the incidence of atrial arrhythmias may not be diminished when adult patients have a pulmonary valve placed, although the incidence of ventricular arrhythmias is decreased. Right ventricular dysfunction improves in a variable number of adults, suggesting that pulmonary valve placement be done sooner rather than later. The development of pulmonary valves that can be delivered via a vascular catheter holds much promise.[219,220]

Additional possible late-term complications include residual VSD, patch dehiscence, progressive aortic insufficiency, left ventricular dysfunction from surgical injury to an anomalous coronary artery or longstanding preoperative cyanosis, and heart block from VSD closure (uncommon today). Because patients who have had repairs using a conduit require multiple sternotomies and the valved conduit tends to lie immediately behind and in close proximity to the sternum, sternotomy carries with it significant potential risk for laceration of the conduit. On occasion, the femoral vessels are cannulated for bypass before sternotomy.

Most adult patients require reoperation to repair the right ventricular outflow tract or to insert or replace a valve in the pulmonic position. Other reasons for reoperation include repair of an outflow tract aneurysm at the site of a patch, repair of a residual VSD, or repair of an incompetent tricuspid valve.[208] These patients often have diminished right ventricular diastolic compliance and require higher-than-normal central venous pressure. Postoperative management includes minimizing PVR and maintaining central venous pressure. Patients often require treatment postbypass with an inotrope and afterload reduction.[221]

Women with good surgical results without residual defects should tolerate pregnancy and delivery well with outcomes approximating those of the general population, although there is a significant rate for CHD in the infant.[222,223] Women with uncorrected tetralogy, particularly those with significant cyanosis, have a high incidence of fetal loss (80% with hematocrit >65%). The fall in systemic vascular resistance that accompanies pregnancy and delivery can worsen cyanosis, and the physiologic volume loading of pregnancy can exaggerate failure of both ventricles.

Transposition of the Great Arteries (D-Transposition)

In D-transposition of the great arteries, there is a discordant connection of the ventricles and the great arteries. The aorta (with the coronary arteries) arises from the right ventricle, and the pulmonary artery arises from the left ventricle. Thus the two circulations are separate. Postnatal survival requires interchange of blood between the two circulations, typically via a patent foramen ovale and/or a PDA or VSD. With a 1-year mortality approximating 100%, all adults with D-transposition have had some type of surgical intervention. Older adults will have had atrial-type repairs (Mustard or Senning), whereas children born after the mid-1980s will have had repair by arterial switch (the Jatene operation). Some will also have had repair of D-transposition with a moderate-to-large VSD by means of a Rastelli operation (see later).

Atrial repairs function by redirecting systemic venous blood to the left ventricle (and thence to the transposed pulmonary artery) and pulmonary venous blood to the right ventricle (and thence to the aorta). The Mustard operation uses an intraatrial conduit of native pericardium (Fig. 22.10), whereas the Senning operation uses native atrial tissue to fashion the conduit. The arterial switch operation transposes transected aorta and pulmonary artery such that they then arise above the appropriate ventricle. This operation also requires transposing the coronary arteries from the aorta to the pulmonary root,

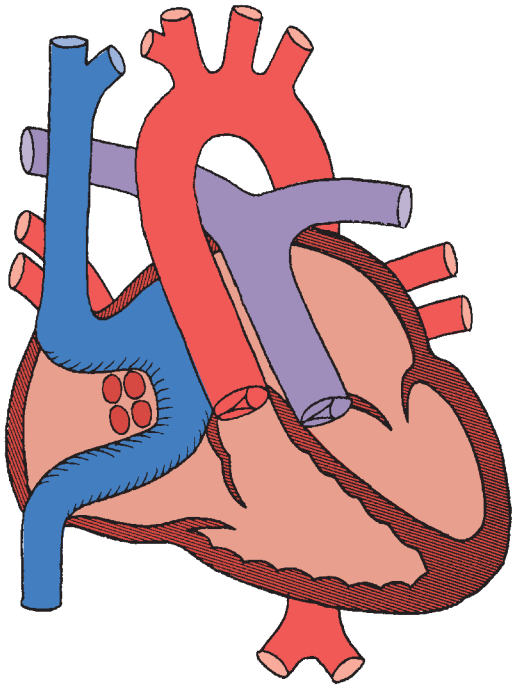


Fig. 22.10 The Mustard operation. An intraatrial baffle has directed vena caval blood across the excised atrial septum to the mitral valve and pulmonary venous blood to the tricuspid valve. The right ventricle remains as the systemic ventricle and the left ventricle as the subpulmonary ventricle. *(Reprinted with permission from Mullins C, Mayer D. Congenital Heart Disease. A Diagrammatic Atlas. New York: Wiley-Liss, Inc.; 1988.)*

which following the procedure, becomes the aortic root. The Rastelli procedure closes the VSD on a bias such that the left ventricle empties into the aorta and connects the right ventricle to the pulmonary artery by means of a valved conduit.

Atrial repairs result in a systemic right ventricle, and these patients consistently have abnormal right ventricular function that can be progressive with a right ventricular ejection fraction of about 40%.[224] Mild tricuspid insufficiency is common, but severe tricuspid insufficiency suggests the development of severe right ventricular dysfunction. There is an 85% to 90% 10-year survival with these operations, but by 20 years, survival is less than 80%.[225–227] Over 25 years, about half develop moderate right ventricular dysfunction and one-third develop severe tricuspid insufficiency.[225,226,228–230] Although function always remains abnormal, it has been suggested that earlier surgery minimizes right ventricular dysfunction.[231] Because of the incidence of right ventricular dysfunction, some patients with atrial repairs have been converted to an arterial switch, following preparation of the left ventricle by a pulmonary artery band to prepare it to tolerate systemic arterial pressure.[232]

Atrial repairs bring an incidence of late electrophysiologic sequelae including sinus node dysfunction (bradycardia), junctional escape rhythms, atrioventricular block, and supraventricular arrhythmias. Atrial flutter occurs in 20% of patients by age 20, with half of them having progressive sinus node dysfunction by that time.[225,229] On occasion these tachyarrhythmias can result in sudden death, presumably from 1:1 conduction producing ventricular fibrillation.[225,233] The loss of sinus rhythm in the face of right ventricular (the systemic ventricle) dysfunction can also contribute to late sudden death. The risk of late death after an atrial repair is almost three times higher if there is an associated VSD. The incidence of tachyarrhythmias does decrease, however, after the tenth postoperative year.

An arterial switch operation can be done after a failed atrial repair in adults, but the outcome is generally poor. It is suggested that younger patients do better.[234] Survival after an arterial switch operation, even early in the experience with this operation, is approximately 90% at 10 years.[235] Very-long-term outcome after the arterial switch procedure is still not known. It does appear that there is essentially no mortality after 5 years postoperatively, and late surgical reintervention is mostly due to supravalvular pulmonic stenosis.[236] Neoaortic root dilation, though only rarely requiring repair, has been noted as a long-term problem.[237] Although many of these children have abnormal resting myocardial perfusion, up to 9% can show evidence of exercise-induced myocardial ischemia.[238] The implication for the development of premature coronary artery disease in adulthood is not known, and there is also some concern about the ultimate function of the neoaortic valve. Patients who have had a Rastelli repair will require episodic reoperation for replacement of the prosthetic conduit valve.

Following an atrial or a Rastelli repair, pregnancy and delivery are generally well tolerated, although right ventricular failure and deterioration in functional capacity can occur. Women with an atrial repair in particular have an increased incidence of complications. There is an increased incidence of prematurity and small-for-date infants in these women.[239]

Truncus Arteriosus

Truncus arteriosus derives from lack of septation of the embryonic truncus arteriosus into aortic and pulmonary artery components, resulting in a single great vessel, the aorta, arising from the heart with a truncal (semilunar) valve. The truncal valve is an amalgamation of the aortic and pulmonary valves and therefore contains between three and six cusps. Additionally, truncal valve insufficiency is a common finding with this morphologically abnormal valve. A large malalignment-type VSD allows filling from both ventricles. The pulmonary arteries arise from the ascending aorta. Although various types have been described depending on the exact anatomy of the pulmonary artery origin, in actual experience, it is more common to see a spectrum of types I through III. Type IV, or pseudotruncus, describes the situation of pulmonary atresia with VSD and supply of the pulmonary arteries from large collaterals originating from the descending aorta. Repair is by closure of the VSD and connection of the right ventricle to the pulmonary artery (or pulmonary arteries) by a conduit containing a homograft valve.

The 1-year survival is less than 10%. Because of the very high risk of congestive heart failure followed by pulmonary vascular disease in childhood from high pulmonary blood flow from the aorta, essentially all patients who survive to adolescence have had surgical repair or will have inoperable pulmonary vascular disease. The rare exception is the patient with stenosis near the origin of the pulmonary arteries from the aorta. Patients with valved conduits placed in infancy and early childhood have requisite reoperations to replace the conduit with patient growth, even in the face of adequate valve function. Conduits placed in later childhood can suffice until adulthood. There can be ongoing problems with incompetence and stenosis of the truncal valve (postoperatively functioning as the aortic valve), and eventual dysfunction from stenosis and/or incompetence of the homograft conduit is routinely encountered, requiring replacement.[240,241] Aortic dilation in adulthood will on occasion require surgical correction, but the criteria for repair remain somewhat undefined. Some use an aortic diameter of greater than 55 mm.[242] Because these patients require multiple sternotomies and the valved conduit tends to lie immediately behind and in close proximity to the sternum, sternotomy carries with it significant potential risk for laceration of the conduit. On occasion the femoral vessels are cannulated for bypass before sternotomy.

Ventricular Septal Defects

The natural history of VSDs has been reviewed in detail.[200] More than 75% of small and moderate VSDs close spontaneously during childhood by a gradual ingrowth of surrounding septum. Of those that close spontaneously, almost all have closed by 10 years of age. Other mechanisms for natural closure include closure by tricuspid valve tissue, closure by prolapsed aortic leaflet, and closure by endocarditis. Some VSDs result in the development of aortic insufficiency in adults from prolapse of the aortic valve into the defect.[243] Although the risk of endocarditis is ongoing, there is no hemodynamic risk of a small VSD in the adult. If pulmonary vascular disease is present, it can progress if closure of a large VSD is delayed.

Although some studies have reported possible ventricular dysfunction years after surgical repair, these are older reports and patients were operated on later than by current standards.[244–246] It does appear, though, that the ventricle successfully remodels from chronic volume overload if surgical correction is done by 5 years of age and perhaps up to 10 to 12 years of age. Iatrogenic heart block is a possible surgical complication, but this was much more common in the earlier days of cardiac surgery. If significant pulmonary hypertension has developed, closure can sometimes be done by means of a unidirectional valve patch, as described by Novick and others.[247] Percutaneous closure devices for use with certain VSDs are available.

Although some discussion is given to onset times with intravenous or inhalation induction agents, clinical differences are hard to notice with modern low-solubility volatile agents. Thermodilution cardiac output reflects pulmonary blood flow, which will be in excess of systemic blood flow. Pulmonary arterial catheters are not routinely indicated. In the patient with a moderate or large left-to-right shunt, low inspired oxygen and moderate hypercarbia avoid intraoperative decreases in PVR with pulmonary overcirculation and left ventricular dilation. However, unlike children, it would be rare to encounter adults with large left-to-right shunts. Adults with unrepaired lesions would either have small shunts or have large shunts that caused Eisenmenger physiology.

Pregnancy is well tolerated in the absence of preexisting heart failure or pulmonary hypertension. Pregnancy with a naturally or surgically closed defect carries with it no additional risk in the absence of additional cardiac problems.

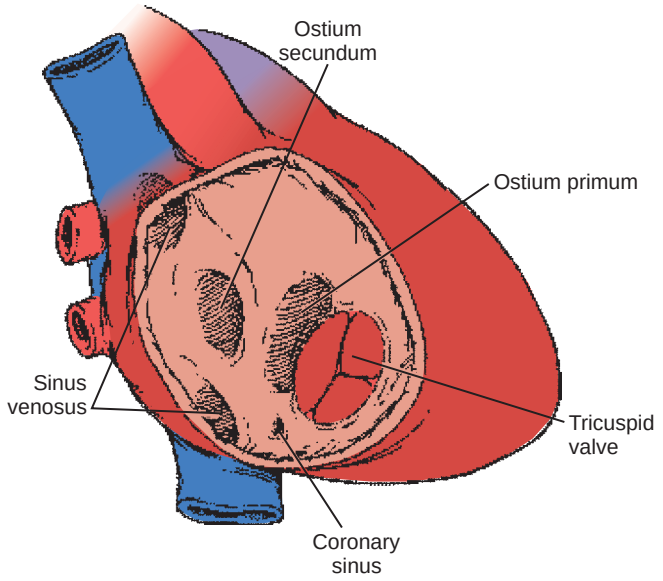


Fig. 22.11 Types of atrial septal defects. *(Reprinted with permission from Nichols DG, Cameron DE, Greeley WG, et al: eds.* Critical Heart Disease in Infants and Children. *St Louis: Mosby; 1995.)*

Case Study 1: Atrial Septal Defect

Framing

The different types of ASDs arise from problems that occur in the various embryologic structures that combine to form the atrial septum (Fig. 22.11). The echocardiographer is required to know the different types of ASD and any associated cardiac defects that accompany each lesion. Secundum ASDs are by far the most common type and are rarely associated with other cardiac defects. Those lesions requiring intervention are usually treated with percutaneous device closure providing there is an adequate rim of surrounding atrial septum for the device to "grab on to." The echocardiographer is vital in helping the interventional cardiologist "see" the atrium in three dimensions and guide placement of the device.

The primum ASD arises from an endocardial cushion defect. When combined with an inlet VSD, it becomes the atrial component of complete atrioventricular canal. As an isolated septal defect, a primum ASD is frequently associated with mitral regurgitation owing to a cleft in the anterior leaflet of the mitral valve. Sinus venosus ASD occurs at the cavoatrial junction, either superiorly or inferiorly. The superior sinus venosus ASD is usually accompanied by anomalous drainage of the right superior pulmonary vein to the superior vena cava (SVC). The inferior sinus venosus ASD is strongly associated with anomalous drainage of the right inferior pulmonary vein to the inferior vena cava (IVC). These associated defects are crucial information for the echocardiographer to incorporate into the transesophageal echocardiographic (TEE) examination.

Data Collection and Interpretation

The intraoperative TEE examination is focused on confirming the presumptive diagnosis of ASD and determining the presence of any other associated defects. The Society of Cardiovascular Anesthesiologists has published guidelines with 20 views that constitute a comprehensive intraoperative TEE examination[248] and this has recently been expanded.[249] When a more detailed examination of a specific cardiac structure is sought, we recommend focusing on the structure by using the zoom feature. The specific structure can then be carefully assessed by using the multiplane function to advance 15 to 30 degrees at a time until the structure has been visualized in multiple views from 0 to 180 degrees. In this example the echocardiographer would focus on the atrial septum in the midesophageal four-chamber view at 0 degrees and then slowly multiplane forward to 180 degrees, providing a comprehensive examination of the structure. The pulmonary veins can be difficult to identify, even for experienced echocardiographers. In the midesophageal four-chamber view with the multiplane angle at 0 degrees, the ultrasound image is focused on the left atrium. The probe is then gently turned to the patient's left to identify the left-sided pulmonary veins and to then to right to identify the right-sided pulmonary veins. Visualizing two separate pulmonary veins from each side is challenging because they arrive at a confluence as they enter the left atrium. The use of color Doppler is often helpful to identify blood flowing within the pulmonary veins.

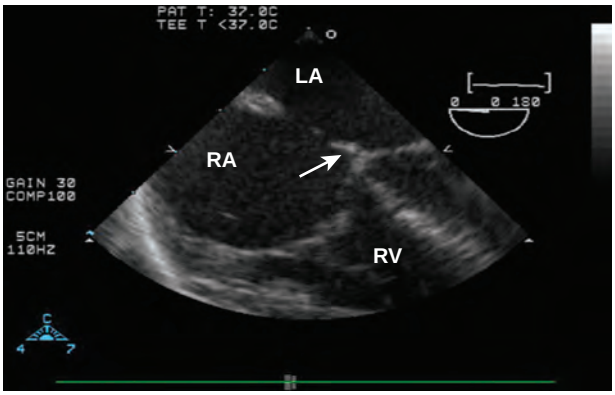


Fig. 22.12 Midesophageal four chamber view at 0 degrees focusing on the atrial septum. There is a large secundum atrial septal defect with only a small rim of inferior atrial septum *(arrow)*. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle.

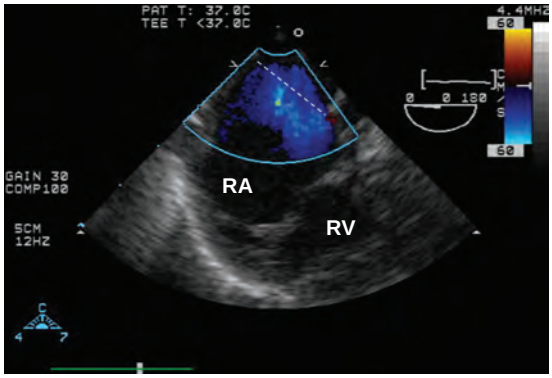


Fig. 22.13 Midesophageal four chamber view at 0 degrees with color flow Doppler. There is a large volume left-to-right shunt *(blue)* across the atrial septal defect (ASD). The *dashed line* represents the approximate location of the ASD. The *uniform blue* color confirms low velocity flow through a large defect. *RA,* Right atrium; *RV,* right ventricle.

Decision Making and Interpretation

A patient was scheduled for surgical resection of an ASD. Preoperative transthoracic echocardiography confirmed a large secundum ASD with inferior extension toward the IVC (Fig. 22.12). The size and inferior extension of the ASD precluded percutaneous device closure. The TEE examination confirmed the preoperative findings and demonstrated four pulmonary veins returning to the left atrium. The volume of left-to-right shunting was large (Fig. 22.13). Right ventricular volume overload was present with significant right ventricular dilation (Fig. 22.14). After closure of the ASD and separation from CPB, a residual ASD was seen at the inferior aspect of the ASD patch (Fig. 22.15). Comparing Figs. 22.13 and 22.15 demonstrates the echocardiographic difference in appearance between a high-volume, low-velocity shunt

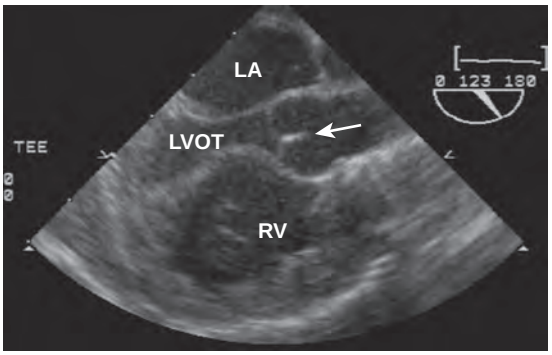


Fig. 22.14 Midesophageal aortic valve long axis view at 123 degrees. The aortic valve *(arrow)* is closed signifying diastole. The atrial septal defect has caused marked volume overload of the right ventricle. During diastolic filling of the right ventricle, the septum bulges into the left ventricle. *LA,* Left atrium; *LVOT,* left ventricular outflow tract; *RV,* right ventricle.

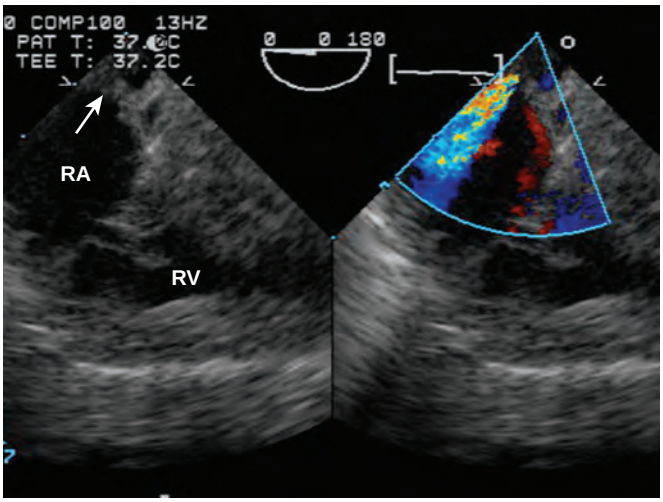


Fig. 22.15 Side-by-side images in 2D *(left image)* and with color flow Doppler *(right image).* In the 2D image there is a possible inferior residual atrial septal defect (ASD; *arrow*). With color flow Doppler the residual ASD is clearly appreciated. The *orange speckling* superimposed on the *blue* color confirms high-velocity flow. *RA,* Right atrium; *RV,* right ventricle.

and a more restrictive, higher-velocity shunt. The configuration of the TEE machine in the color Doppler mode identifies blood flow towards the transducer in red and blood flow away from the transducer in blue. There is also a threshold of velocity set, such that when blood flow exceeds the velocity threshold, speckling occurs. In Fig. 22.13 there is a uniform blue color demonstrating a significant volume shunt. The absence of color speckling confirms low-velocity blood flow. Fig. 22.15, taken after attempted repair of the ASD, shows a smaller blue area with orange speckling. The speckling confirms higher-velocity blood flow, which is to be expected because the residual defect is much smaller than the unrepaired ASD. Velocity increases as blood flows through a narrower orifice.

How is a residual septal defect assessed? The defect can be assessed qualitatively by examining the degree of shunt using color flow Doppler. After attempted surgical repair, it would be unusual to have a large residual septal defect. What other information can guide the surgeon in determining whether to return to CPB and attempt to close what appears to be a small residual defect? The residual defect results in a left-to-right shunt, which allows the measurement of the "oxygen step-up" between the SVC and pulmonary artery. To do this, the patient should be ventilated with room air. High levels of inspired oxygen result in left atrial blood having a high PaO_2, which causes an overestimation of the residual shunt. After a period of 5 minutes to allow equilibration, blood gas samples from the SVC and pulmonary artery were sent. The oxygenation saturation was 58% in the SVC and 72% in the pulmonary artery. Using a simple equation allows for an estimation of the ratio of pulmonary to systemic blood flow ($Q_p:Q_s$). The saturation at four anatomic locations is entered into the following equation. The oxygen saturations from the SVC and pulmonary artery are measured, the oxygen saturation for the aorta is taken from the peripheral pulse oximeter, and the oxygen saturation for the pulmonary vein assumed to be 100%.

$$Q_p:Q_s = \frac{\text{Aorta} - \text{SVC}}{\text{Pulmonary vein} - \text{Pulmonary artery}} = \frac{100-58}{100-72} = 1.5$$

The $Q_p:Q_s$ ratio of 1.5 was high enough that, if unrepaired, it would likely leave the patient symptomatic from excessive pulmonary blood flow. Integrating the echocardiographic images with quantitative data estimating the degree of the shunt provided the surgeon with a sound justification to return to CPB and attempt to close the residual ASD. The echocardiographic images suggested it was very unlikely the residual defect would close spontaneously. The decision to return to CPB and subject the heart to another period of aortic cross-clamp and ischemia must never be made lightly. It was the surgeon's opinion that the residual defect was not amenable to closure with a percutaneous device at some later date and the patient's underlying heart function was good enough to withstand another period of ischemia and aortic cross-clamp.

After the second attempt at repair, the patient separated easily from CPB. The ASD patch appeared intact on TEE examination, but there was an unusual color flow Doppler jet seen originating from the junction of the IVC and right atrium. What are the possible explanations? Could this simply be turbulence in the area of the ASD repair? The echocardiographer must now rely on knowledge of the lesion and the potential surgical complications associated with its repair. Fig. 22.11 clearly demonstrates the very close proximity of an inferior sinus venosus ASD to the IVC. A known, albeit rare, complication of inferior sinus venosus ASD repair is to suture the ASD patch from the IVC to the ASD, thus creating a path from the IVC to left atrium. This suspicion was bolstered by the fact the peripheral pulse oximeter reading varied between 85% and 88%. This was confirmed by arterial blood gas results. The presence of a right-to-left shunt demanded correction. The patient returned to CPB for a third time for takedown of the patch and closure of the ASD. Based on the two previous attempted repairs, the surgeon realized the secundum ASD might extend even farther into the sinus venosus region of the septum than previously imagined. The IVC venous cannula was repositioned more inferiorly, allowing greater exposure of the defect. After repair, the patient once again separated easily from CPB. The TEE examination confirmed the success of the repair with no residual shunting. This case well demonstrates the need for the intraoperative echocardiographer to be more than a "technician" and integrate supporting physiologic information with the TEE images.

Case Study 2: Anomalous Left Main Coronary Artery

Framing

Anomalous coronary arterial lesions comprise a spectrum of defects. In one variant, the left main coronary artery (LMCA) originates from the pulmonary artery. The clinical presentation is heart failure secondary to left ventricular ischemia and generally occurs in the first few months of life. A more insidious but also potentially lethal form of anomalous coronary arterial lesion occurs when both coronary arteries arise from the aorta but from abnormal locations. Most well described

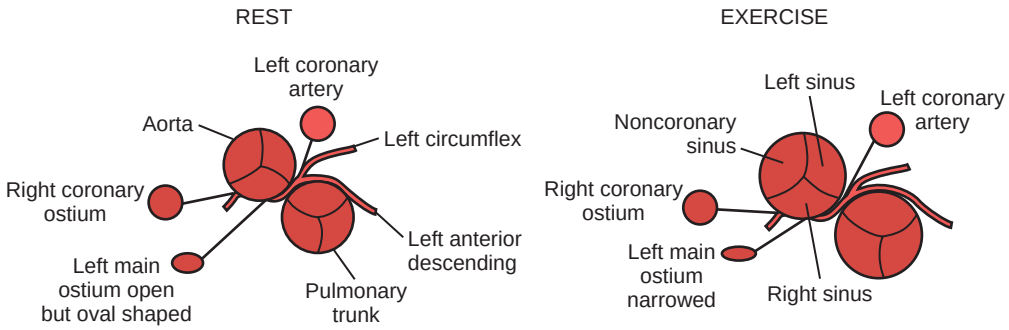


Fig. 22.16 Anomalous left main coronary artery. Compression of the left main coronary artery occurs during exercise. *(Reprinted with permission from Basilico FC. Cardiovascular disease in athletes.* Am J Sports Med. *1999;27:108–121.)*

is an anomalous LMCA that originates from the right coronary sinus. The LMCA may originate from a separate ostium or may share the same ostium as the right coronary artery (RCA) (Fig. 22.16). As the figure demonstrates, the path of the LMCA is abnormal. First, the LMCA travels within the wall of the aorta for a short distance before exiting to the epicardial surface of the heart. This is known as an intramural coronary artery. The path of LMCA then follows a path between the aorta and pulmonary artery. The abnormal path of the anomalous LMCA explains why the clinical presentation is sudden death, most often during exercise. The increased blood flow caused by exercise results in dilation of both the aorta and pulmonary artery. This dilation can compress the LMCA between the aorta and pulmonary artery. Alternatively, if the LMCA is intramural, it can be compressed within the wall of the aorta. Either case leads to ischemia in the entire territory of the LMCA with sudden cardiac death. Tragically, an anomalous LMCA is often a postmortem finding after an unexplained sudden death in an otherwise healthy young person. For reasons that are unclear, patients rarely, if ever, develop exertional chest pain. Also the amount of exertion that precipitates a cardiac event is not predictable. That is, the patient may have vigorously exercised in the past without a problem but then suffers a cardiac event during more modest exertion. For these reasons, if a diagnosis of anomalous LMCA is made, surgery is indicated for the prevention of sudden cardiac death.

Data Collection and Interpretation

The diagnosis of LMCA is most often an incidental finding when echocardiography is done for other indications. Proving the absence of a structure is difficult because it may be present but not well visualized by the particular test being used. Echocardiography, either transthoracic or transesophageal, is not the recommended test for demonstrating the origins of the coronary arteries. Therefore if the ostium of the LMCA is not seen with echocardiography, confirmatory testing is needed. Magnetic resonance imaging or computed tomography is highly specific and sensitive in accurately diagnosing coronary artery anomalies.

The preferred surgical approach is to divide the LMCA from the right coronary sinus and reimplant it in its proper location. This requires mobilization of the LMCA to allow safe reimplantation on the left coronary sinus. An anomalous LMCA does not cause chronic ischemia. The TEE examination should demonstrate normal left ventricular function. The absence of the LMCA ostium may be noted, but even in patients with normal coronary anatomy, the ostia are frequently not well visualized.

Decision Making and Interpretation

During investigations for nonspecific chest pains, an otherwise healthy patient was discovered to have an anomalous LMCA and was scheduled for coronary reimplantation. After induction of anesthesia, the

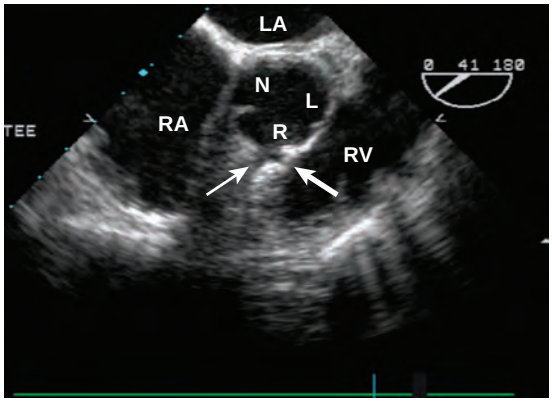


Fig. 22.17 Midesophageal aortic valve short axis view at 41 degrees. The left main coronary artery *(thick arrow)* and right coronary artery *(thin arrow)* both arise from a single ostium in the right coronary sinus. *L,* Left coronary sinus; *LA,* left atrium; *N,* noncoronary sinus; *R,* right coronary sinus; *RA,* right atrium; *RV,* right ventricle.

TEE probe was inserted, which demonstrated normal left ventricular function and the LMCA originating from the right coronary cusp, sharing a common ostium with the RCA (Fig. 22.17). After the aortic cross-clamp was applied and cardioplegia delivered, the heart was slow to arrest. The cardioplegia circuit was checked and found to be working properly. However, throughout the period of aortic cross-clamp the heart frequently recovered electrical and mechanical activity before the next scheduled dose of cardioplegia. At the conclusion of the coronary reimplantation, the surgeon felt the myocardial preservation had been poor and the patient would likely need inotropic support. Upon attempted separation from CPB, the patient was hypotensive with poor myocardial function. What is the differential diagnosis of ventricular dysfunction after CPB? The ECG showed sinus tachycardia with nonspecific S-T changes in both leads II and V5. This was confirmed in other ECG leads. The question to be answered was whether ventricular dysfunction could be due to possible poor myocardial preservation or whether the LMCA reimplantation was unsuccessful. By visual inspection, the right ventricle was contracting well. There was no S-T elevation in lead II to suggest air embolus to the RCA. What is the preferred TEE view to assess ventricular function? The transgastric short axis view at the midpapillary level is used routinely to assess preload, contractility, and regional wall motion abnormalities. Knowing the coronary artery that corresponds to the various left ventricular segments allows the echocardiographer to identify regional wall motions abnormalities caused by ischemia (Fig. 22.18). The transgastric image showed marked left ventricular dilation with akinesis of the septal, anterior, lateral, and posterior walls. There was minimal decrease in left ventricular cavity size during systole (Video 22.1). The reimplanted

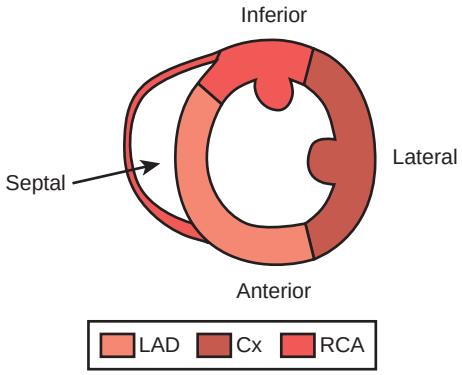


Fig. 22.18 Regional left ventricular anatomy with the corresponding coronary artery distribution. *Cx,* Circumflex artery; *LAD,* left anterior descending artery; *RCA,* right coronary artery. *(Reprinted with permission from Shanewise JS, Cheung AT, Aronson S, et al. ASE/SCA guidelines for performing a comprehensive intraoperative multiplane transesophageal echocardiography examination: recommendations of the American Society of Echocardiography Council for Intraoperative Echocardiography and the Society of Cardiovascular Anesthesiologists Task Force for Certification in Perioperative Transesophageal Echocardiography.* Anesth Analg. *1999;89:870–884.)*

LMCA could not be seen originating from the left coronary sinus. Global ventricular dysfunction secondary to poor myocardial preservation was unlikely because right ventricular function was good. The inferior region of the left ventricle, which is supplied by the RCA, had normal function. The findings of severe regional wall motion abnormalities in the distribution of the LMCA confirmed the suspicion of unsuccessful LMCA reimplantation. The extensive wall motion abnormalities suggested the patient had left dominant coronary circulation. By inspection the reimplanted LMCA appeared to free of tension or kinking. After consultation with the surgeon and a description of the TEE findings, it was decided that a second attempt at LMCA reimplantation was very unlikely to be successful.

A decision was made to perform a left internal mammary artery (LIMA) to proximal left anterior descending (LAD) artery graft. It was hoped that a very proximal anastomosis to the LAD would ensure flow into the circumflex artery as well. The patient separated easily from CPB. The TEE revealed normal left ventricular function with dramatic resolution of the previous regional wall motion abnormalities (Video 22.2). Specifically, the lateral and posterior regions of the left ventricle had good function, which provided strong evidence that the LIMA to proximal LAD graft was also perfusing the circumflex artery. Contrasting the two video images illustrates that the echocardiographic assessment of contractility is based on the degree of ventricular wall thickening during systole. In the first image, the ischemic regions (septal, anterior, lateral, posterior) of the left ventricle do not thicken during systole, but they do move because they are contiguous with the other regions that retain normal function. Although unlikely in this example because the findings are so dramatic, the novice echocardiographer can often confuse ventricular motion with contractility. After the LIMA to LAD graft, the previously akinetic segments increase their wall thickness by more than 50% during systole. The significant reduction in left ventricular cavity size during systole denotes a normal ejection fraction.

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23 Thoracic Aorta

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KEY POINTS

1. Diseases of the thoracic aorta can occasionally be managed with medical treatment and surveillance, whereas others require surgical intervention. Depending on the disease process, some surgeries may be performed electively, whereas others are truly emergency operations.
2. Aortic surgery is complex, and therefore it requires an anesthetic tailored to the specific goals for hemodynamics, neuromonitoring, and cerebral/spinal cord perfusion.
3. Multidisciplinary guidelines for the diagnosis and management of thoracic aortic disease summarize the evidence and expert consensus for this challenging group of important diseases.
4. Thoracic aortic aneurysms can cause compression of the trachea, left mainstem bronchus, right ventricular outflow tract, right pulmonary artery, or esophagus.
5. Deliberate hypothermia is the most important therapeutic intervention to prevent cerebral ischemia during temporary interruption of cerebral perfusion during aortic arch reconstruction.
6. Early detection and interventions to increase spinal cord perfusion pressure are effective for the treatment of delayed-onset spinal cord ischemia after thoracic or thoracoabdominal aortic aneurysm repair.
7. Severe atheromatous disease or thrombus in the thoracic or descending aorta is a risk factor for stroke.
8. Stanford type A dissection, involving the ascending aorta and aortic arch, is a surgical emergency. Stanford type B dissection, confined to the descending thoracic or abdominal aorta, should be managed medically when possible.
9. When adequate preoperative imaging is lacking, intraoperative transesophageal echocardiography can be used to diagnose type A dissection or traumatic aortic injuries that require emergency surgery.
10. Intraoperative transesophageal echocardiography and ultrasound imaging of the carotid arteries are useful for the diagnosis of aortic regurgitation, cardiac tamponade, myocardial ischemia, or cerebral malperfusion, complicating type A aortic dissection.
11. Newer endovascular approaches to the management of thoracic aortic disease continue to have a great impact on both elective and emergent aortic surgery.

Thoracic aortic diseases typically require surgical intervention (Box 23.1). Acute aortic dissections, rupturing aortic aneurysms, and traumatic aortic injuries are surgical emergencies. Subacute aortic dissection and expanding aortic aneurysms require urgent surgical intervention. Stable thoracic or thoracoabdominal aortic aneurysms (TAAAs), aortic coarctation, or atheromatous disease causing embolization may be addressed surgically on an elective basis. The volume of thoracic aortic procedures has grown steadily because of factors such as increased public awareness, an aging population, earlier diagnosis, multiple advances in imaging, and advances in surgical techniques including endovascular stenting. Medical centers have emerged that specialize in thoracic aortic diseases, resulting in improved management and survival.[1] This progress has created a set of patients who later require reoperation for long-term complications such as valve or graft failure, pseudoaneurysm at anastomotic sites, endocarditis, and/or progression of the original disease process into the residual native aorta.

The anesthetic management of thoracic aortic diseases has unique considerations, including the temporary interruption of blood flow, often resulting in ischemia of major organ systems. Critical components of anesthetic management include the maintenance of organ perfusion, protection of vital organs during ischemia, and monitoring and management of end-organ ischemia. As a result, the vigilant and skillful anesthesiologist contributes significantly to the overall success of these operations. The procedures performed by the thoracic aortic team for organ protection, such as partial left-heart bypass (PLHB) for distal aortic perfusion, cardiopulmonary bypass (CPB) with deep hypothermic circulatory arrest (DHCA), selective cerebral perfusion, and lumbar cerebrospinal fluid (CSF) drainage, are practiced routinely in no other area of medicine. Several multisociety guidelines represent a contemporary evidence-based, consensus-driven approach to thoracic aortic diseases. Their recommendations are referred to throughout this chapter, based on the well-known classification of recommendations and levels of evidence (Tables 23.1 and 23.2) by the American College of Cardiology (ACC) and American Heart Association (AHA).[2–5]

Anatomy of the Aorta

The aorta is the large artery running from the aortic valve to the iliac bifurcation. It serves both as a conducting vessel and as a secondary passive pump because of its elastic recoil. During ventricular systole, the aortic lumen distends as it receives the entire stroke volume. In diastole, after aortic valve closure, the blood is propelled forward as a result of the aorta's elastic recoil. This pulse wave is transmitted distally at approximately 5 m/second, exceeding the aortic blood flow velocity of 40 to 50 cm/second. The aortic systolic blood pressure results from the summated effects of stroke volume, aortic compliance, and peripheral vascular resistance. Isolated systolic hypertension develops with aging as the aorta loses elasticity and cannot dampen the stroke volume.

During fetal development, the ductus arteriosus diverts blood from the pulmonary artery into the distal aortic arch. After birth,

BOX 23.1 THORACIC AORTIC DISEASES AMENABLE TO SURGICAL TREATMENT

Aneurysm
Congenital or developmental
  Marfan syndrome, Ehlers-Danlos syndrome
Degenerative
  Cystic medial degeneration
  Annuloaortic ectasia
  Atherosclerotic
Traumatic
  Blunt and penetrating trauma
Inflammatory
  Takayasu arteritis, Behçet syndrome, Kawasaki disease
Microvascular diseases (polyarteritis)
Infectious (mycotic)
  Bacterial, fungal, spirochetal, viral
Mechanical
  Poststenotic, associated with an arteriovenous fistula
  Anastomotic (postarteriotomy)
Pseudoaneurysm
Aortic dissection
  Stanford type A
  Stanford type B
Intramural hematoma
Penetrating atherosclerotic ulcer
Traumatic aortic injury
Aortic coarctation

Data from Kouchoukos NT, Dougenis D. Surgery of the aorta. *N Engl J Med.* 1997;336:1876–1878.

TABLE 23.1 Classification Scheme for Clinical Recommendations

Clinical Recommendations	*Definition of Recommendation Class*
Class I	The procedure/treatment should be performed (benefit far outweighs the risk).
Class IIa	It is reasonable to perform the procedure/treatment (benefit still clearly outweighs risk).
Class IIb	It is not unreasonable to perform the procedure/treatment (benefit probably outweighs the risk).
Class III	The procedure/treatment should not be performed as it is not helpful and may be harmful (risk may outweigh benefit).

Data from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. A report of the American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine. *Circulation.* 2010;121:e266–e369.

TABLE 23.2 Classification Scheme for Supporting Evidence for Clinical Recommendations

Supporting Evidence	*Estimate of Certainty*
Level A	Data derived from multiple randomized clinical trials (RCT) or metaanalysis.
Level B	Data derived from a single RCT or nonrandomized studies.
Level C	Only consensus opinions of experts, case studies, or standard of care.

Data from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. A report of the American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine. *Circulation.* 2010;121:e266–e369.

lung expansion and constriction of the ductus arteriosus because of increased blood oxygen content drive the blood from the pulmonary artery into the pulmonary circulation. Typically, the ductus arteriosus is functionally closed by 48 hours and is permanently closed by 3 weeks after birth.[6] It subsequently fibroses to become the ligamentum arteriosum. Occasionally, this process fails and the ductus arteriosus remains patent. Furthermore, occasionally a ductal diverticulum may persist and be confused in later life with an aortic injury during aortic imaging. The pathogenesis of aortic coarctation may be related to residual ductal tissue that narrows the aorta as it constricts.

The aortic wall has three layers: a thin intima or inner layer lined by endothelium, a thick media or middle layer, and a thin adventitia or outermost layer.[3] The endothelium is in direct contact with blood, is easily traumatized, and is the site for atherosclerosis. The media accounts for 80% of the aortic wall thickness and consists of spirally arranged intertwining layers of elastic tissue that provide the aorta's tensile strength and elasticity. The adventitia consists mainly of collagen and contains the vasa vasorum that nourishes the outer half of the aortic wall. The fact that the vasa vasorum are absent in the infrarenal aorta may explain the frequency of infrarenal aortic aneurysms. These three aortic layers typically are indistinguishable by current clinical imaging techniques. Pathologic aortic processes can separate the aortic wall layers to make them evident on computed tomography (CT), magnetic resonance imaging (MRI), or transesophageal echocardiography (TEE).[2–4]

The thoracic aorta comprises the ascending aorta, the aortic arch, and the descending aorta.[2–4] The ascending aorta also includes the aortic root. The aorta begins at the aortic valve just to the right of midline at the left ventricular base. The aortic root and proximal ascending aorta lie within the pericardial sac. The aorta then travels superiorly and anteriorly to the left. It then turns posteriorly and continues to the left to the fourth thoracic vertebra. Thereafter, it travels inferiorly, initially anterior and to the left of the spine to cross the diaphragm, ending in front of the fourth lumbar vertebra. The aortic root includes the aortic valve annulus and the sinuses of Valsalva that terminate at the sinotubular junction.[3,4] The origin of the brachiocephalic artery marks the end of the ascending aorta and the beginning of the aortic arch. The aortic arch lies within the superior mediastinum between the ascending and descending thoracic aorta. The aortic arch ends after the origin of the left subclavian artery. The aortic isthmus is the segment of aorta where the distal aortic arch becomes the descending thoracic aorta. At the aortic isthmus, the relatively mobile ascending aorta and arch join the descending thoracic aorta that is fixed to the posterior thoracic cage by pleural reflections, the intercostal arteries, the ligamentum arteriosum, and the left subclavian artery. As a result, the aortic isthmus is vulnerable to traumatic injury because it is subjected to high shear forces after blunt trauma or rapid deceleration. Furthermore, the aortic isthmus also is the most common site for aortic coarctation.

The coronary arteries are the first branches of the aorta. The aortic arch subsequently gives origin to the brachiocephalic (innominate), left carotid, and left subclavian arteries that supply the head, neck, and arms.[2–4] The brachiocephalic artery is the first branch of the aortic arch, followed by the left common carotid artery, and finally, the left subclavian artery. There are multiple aortic arch anatomic variations, including vascular rings, right-sided aortic arch, and branching anomalies. A right-sided aortic arch is found in about 0.1% of the population. A relatively common aortic arch branch anomaly with a 4% prevalence rate is an isolated left vertebral artery, so named because it arises directly from the aortic arch.[7]

The aortic arch also modulates blood pressure via baroreceptors within its outer wall. The aortic bodies are located inferior to the aortic arch. The aortic baroreceptors respond to a greater threshold pressure and thus are less sensitive when compared with the carotid sinus receptors. These receptors send impulses to the brainstem that interact with the medullary cardiovascular center for modulation of autonomic nervous system activity.[8]

General Considerations for the Perioperative Care of Aortic Surgical Patients

Patients undergoing thoracic aortic surgery require the common considerations for the safe use of anesthesia and perioperative care that are addressed in this section (Box 23.2). The unique considerations and care that apply to specific diseases and procedures are addressed in subsequent sections devoted to their management.

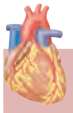
Preanesthetic Assessment

The preanesthetic assessment of the thoracic aorta surgical patient ideally begins before admission to the operating room (OR). The first consideration is whether the planned procedure is emergent, urgent, or elective. For urgent or emergent operations, it is most efficient to assign team members specific tasks for rapid and comprehensive patient and OR preparation. For example, one team member can review the patient chart and diagnostic studies to formulate an anesthetic plan. A second team member can interview the patient and obtain informed consent. The remaining team members can simultaneously prepare the OR, apply physiologic monitors, secure intravascular access, and send laboratory specimens including blood for crossmatching.

The second consideration is to determine the aortic diagnosis because its extent and physiologic consequences dictate both anesthetic management and surgical approach. Aortic diseases proximal to the left carotid artery typically are approached via a median sternotomy, whereas aortic diseases distal to this point usually are approached via a left thoracotomy or thoracoabdominal incision. Although an aortic diagnosis often is established in advance, at times a definitive diagnosis must be verified after OR admission by direct review of diagnostic studies or by subsequent TEE. In every case, a review of the operative plan with the surgical team facilitates thorough anesthetic preparation. Direct review of adequate aortic diagnostic imaging studies not only verifies the operative diagnosis but also determines the surgical possibilities (class I recommendation; level of evidence C).[2,9] The anatomic details of an aortic disease permit the anesthesiologist to anticipate potential perioperative difficulties, including likely postoperative complications.

The systematic assessment of each organ system in the aortic surgical patient should focus on how it will affect the conduct of anesthesia and surgery. The baseline functional reserve of each organ system determines the likely perioperative complications and allows ranking of organ-protective strategies. It is reasonable in nonemergent cases to obtain further tests to quantitate the functional reserve of affected organ systems, for example, neurocognitive testing, brain imaging, noninvasive carotid artery imaging, pulmonary function testing, echocardiography, and cardiac catheterization (class IIa recommendation; level of evidence C).[2] Significant cerebrovascular disease affects blood pressure management to ensure adequate cerebral perfusion. Significant cardiac compromise typically increases the risks for heart failure, myocardial ischemia, and arrhythmias. Significant lung disease often is predictive for postoperative respiratory failure, pneumonia, or both. Significant renal insufficiency affects fluid management, triggers the avoidance of nephrotoxic drugs, and customizes the dosing of renally cleared drugs. Hepatic disease and hematologic dysfunction are risk factors for perioperative bleeding and transfusion. Severe aortic atheroma is a major risk factor for atheroembolism and consequent stroke and limb ischemia.

Because myocardial ischemia is an important predictor of perioperative outcome, it has featured prominently in the guidelines for thoracic aortic diseases.[2–4] Patients with evidence of myocardial ischemia should undergo further evaluation to determine the extent and severity of coronary artery disease (CAD; class I recommendation; level of evidence C).[2] If significant CAD is responsible for an acute coronary syndrome, then coronary revascularization is indicated before or concomitant with the thoracic aortic procedure (class I recommendation; level of evidence C).[2] Concomitant coronary artery bypass grafting (CABG) is reasonable in patients who have significant CAD and are scheduled to undergo surgery for diseases of the ascending aorta or aortic arch, or both (class IIa recommendation; level of evidence C).[2] In contrast, the benefit of coronary revascularization is less clear in patients who have stable CAD and who are scheduled to undergo



BOX 23.2 ANESTHETIC CONSIDERATIONS FOR THE CARE OF THORACIC AORTIC SURGICAL PATIENTS

Preanesthetic Assessment
- Urgency of the operation (emergent, urgent, or elective)
- Pathology and anatomic extent of the disease
- Median sternotomy vs thoracotomy vs endovascular approach
- Mediastinal mass effect
- Airway compression or deviation

Preexisting or Associated Medical Conditions
- Aortic valve disease
- Cardiac tamponade
- Coronary artery stenosis
- Cardiomyopathy
- Cerebrovascular disease
- Pulmonary disease
- Renal insufficiency
- Esophageal disease (contraindications to TEE)
- Coagulopathy
- Prior aortic operations

Preoperative Medications
- Warfarin (Coumadin)
- Antiplatelet therapy
- Antihypertensive therapy

Anesthetic Management
- Hemodynamic monitoring
  - Proximal aortic pressure
  - Distal aortic pressure
  - Central venous pressure
  - Pulmonary artery pressure and cardiac output
  - TEE
- Neurophysiologic monitoring
  - Electroencephalography
  - Somatosensory-evoked potentials
  - Motor-evoked potentials
  - Jugular venous oxygen saturation
  - Lumbar cerebrospinal fluid pressure
  - Body temperature
- Single-lung ventilation for thoracotomy
  - Double-lumen endobronchial tube
  - Endobronchial blocker
- Potential for bleeding
  - Large-bore intravenous access
  - Blood product availability
  - Antifibrinolytic therapy
- Antibiotic prophylaxis

Postoperative Care Considerations and Complications
- Hypothermia
- Hypotension
- Hypertension
- Bleeding
- Spinal cord ischemia
- Stroke
- Renal insufficiency
- Respiratory insufficiency
- Phrenic nerve injury
- Diaphragmatic dysfunction
- Recurrent laryngeal nerve injury
- Pain management

surgical intervention for descending thoracic aortic disease (class IIb recommendation; level of evidence C).[2]

Preoperative Medications

Preoperative medications typically provide detailed information about concomitant medical conditions. As a general rule, all cardiac, pulmonary, and anticonvulsant medications should be continued up until the morning of surgery. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers should be discontinued the day before surgery to minimize the risk for perioperative vasoplegia and adverse outcomes.[10,11] Occasionally, these drugs may be continued with caution in patients with hypertension that is difficult to control. All oral hypoglycemic agents should be discontinued the night before surgery to avoid hypoglycemia. If possible, metformin should be discontinued the day before surgery to minimize the risks for severe lactic acidosis associated with exposure to iodinated contrast agents or perioperative hypovolemia. If a patient is receiving insulin, up to 50% of the typical morning dose should be given the day of surgery with subsequent close glucose monitoring. Finally, the consequences of preoperative medications for anesthetic procedures must be carefully considered. For example, coagulopathy caused by organ dysfunction or concomitant medication, or both, increases the risks for hemorrhagic complications associated with neuraxial techniques such as lumbar CSF drainage and epidural analgesia.

Warfarin should be discontinued for approximately 5 days before surgery to allow for full recovery of coagulation function as verified by a normal international normalized ratio.[12,13] If this is not possible, then the patient should be admitted for heparin bridging until shortly before surgery. Patients chronically exposed to low-molecular-weight heparin, aspirin, adenosine diphosphate platelet-receptor inhibitors (clopidogrel, prasugrel, or ticagrelor), and platelet glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) are typically at increased risk for perioperative bleeding. Aspirin may or may not be discontinued depending on a coexisting acute coronary syndrome, but ideally, agents such as clopidogrel or prasugrel will have been discontinued at least 5 to 7 days before surgery to allow adequate recovery of platelet function for perioperative hemostasis.[12,13] The new oral anticoagulants, including dabigatran, rivaroxaban, apixaban, and edoxaban, should be stopped for longer than three half-lives—ideally, for 3 to 5 days (see Chapter 35).

Anesthetic Management

Overall, the anesthetic plan, including techniques, drugs, and monitoring, should be individualized to enhance the conduct of the procedure, including perfusion technique, hemodynamic monitoring, and preservation of organ function (class I recommendation; level of evidence C).[2] Because thoracic aortic procedures may result in massive bleeding and cardiovascular collapse, it is essential to have immediate availability of packed red blood cells and clotting factors, large-bore vascular access, invasive blood pressure monitoring, and central venous access. Pulmonary artery catheterization assists in the management of cardiac dysfunction associated with CPB, DHCA, and PLHB. Intraoperative TEE is indicated in thoracic aortic procedures, including endovascular interventions, in which it assists in hemodynamic monitoring, procedural guidance, and endoleak detection (class IIa recommendation; level of evidence B).[2,9] A rationale exists for choosing to cannulate the left or right radial artery for intraarterial blood pressure monitoring. Right radial arterial pressure monitoring will often detect compromised flow into the brachiocephalic artery because of aortic cross-clamping too near its origin. Right radial arterial pressure monitoring also makes sense in procedures that require clamping of the left subclavian artery. Left radial arterial pressure monitoring is indicated when selective antegrade cerebral perfusion (ACP) is planned via the right axillary artery; however, a right-sided catheter may be preferred for ACP if direct brachiocephalic cannulation is used by the surgeon. At times, bilateral radial arterial pressure monitoring may be required. Femoral arterial pressure monitoring allows the assessment of distal aortic perfusion in procedures with PLHB. Overall, institutional practices depending on surgical techniques and preferences will also help determine the best location for monitoring.

Large-bore peripheral intravenous cannulation secures vascular access for rapid intravascular volume expansion. Rapid transfusion is desirable via an intravenous set with a fluid-warming device. Alternatively, large-bore central venous cannulation can be utilized for volume expansion. If a pulmonary artery catheter (PAC) is required, a second introducer sheath dedicated to volume expansion also can be placed in the same central vein. Central venous cannulation with ultrasound guidance often increases speed and safety, especially in emergencies.[14] Both a urinary and a nasopharyngeal temperature probe are required for monitoring the absolute temperature of the periphery and core, as well as the rates of change during deliberate hypothermia and subsequent rewarming. The rectum is an alternative site for monitoring peripheral temperature, and the PAC can provide core temperature monitoring.

The induction of general anesthesia requires careful hemodynamic monitoring with anticipation of changes because of anesthetic drugs and tracheal intubation. Appropriate vasoactive drugs should be immediately available as required. Concomitant vasodilator infusions often are discontinued before anesthetic induction. Because etomidate does not attenuate sympathetic responses and has no direct effects on myocardial contractility, it may be preferred in the setting of hemodynamic instability. Thereafter, titration of a narcotic such as fentanyl and a benzodiazepine such as midazolam will provide maintenance of general anesthesia. In elective cases, anesthetic induction can proceed with routine intravenous hypnotics, followed by narcotic titration for attenuation of the hypertensive responses to tracheal intubation and skin incision. Antibiotic therapy optimally should be completed in most cases at least 30 minutes before skin incision to achieve adequate bactericidal tissue levels.

General anesthetic maintenance is typically with a balanced intravenous and inhalation anesthetic technique, and neuromuscular blockade is achieved by titration of a nondepolarizing muscle relaxant. Anesthetics can be reduced during moderate hypothermia and then discontinued during deep hypothermia. With concomitant electroencephalographic (EEG) and/or somatosensory-evoked potential (SSEP) monitoring, anesthetic signal interference is minimized with the avoidance of barbiturates, bolus propofol, and doses of inhaled anesthetic greater than 0.5 minimum alveolar concentration. Propofol infusion, narcotics, and neuromuscular blocking drugs do not interfere with SSEP monitoring. With intraoperative motor-evoked potential (MEP) monitoring, high-quality signals are obtained when the anesthetic technique comprises total intravenous anesthesia with propofol and a narcotic such as remifentanil without neuromuscular blockade. Neuromonitoring (EEG, SSEP, MEP) in thoracic aortic procedures is not only compatible with contemporary anesthetic techniques but is also reasonable when the resulting data will guide perioperative management (class IIa recommendation; level of evidence B).[2] The decision to utilize this monitoring modality should be based on procedural urgency, institutional resources, patient needs, and planned operative technique (class IIa recommendation; level of evidence B)[2] (see Chapter 18).

In most cases, the duration of general anesthesia continues for several hours after admission to the intensive care unit (ICU) to permit a controlled anesthetic emergence. If epidural analgesia is used intraoperatively, a dilute solution of local anesthetic and narcotic is preferred to minimize postoperative hypotension from a concomitant sympathectomy and to minimize motor blockade to permit serial neurologic assessment of lower extremity function. Neuraxial anesthetic techniques are not recommended in patients at risk for neuraxial hematomas in the setting of concomitant thienopyridine antiplatelet therapy, low-molecular-weight heparins, and clinically significant anticoagulation (class III recommendation; level of evidence C).[2,13]

The potential for significant bleeding and rapid transfusion is always relevant in thoracic aortic procedures. Consequently, it is prudent to

have fresh frozen plasma and platelets available for ongoing replacement during massive red blood cell transfusion. The time delay associated with standard laboratory testing severely limits the intraoperative relevance of these data to guide transfusion; however, viscoelastic tests are being used with greater frequency to determine coagulation needs.[15] Strategies to decrease bleeding and transfusion in these procedures include timely preoperative cessation of anticoagulants and platelet blockers, antifibrinolytic therapy, intraoperative cell salvage, biologic glue, activated factor VII, and avoidance of perioperative hypertension. It is reasonable to have an institutional algorithmic approach to the management of bleeding and transfusion for thoracic aortic surgery (class IIa recommendation; level of evidence C).[2] This algorithm will depend significantly on institutional variations in point-of-care coagulation testing, blood component availability, and access to recombinant factor VII (class IIa recommendation; level of evidence C).[2]

Aprotinin, an antifibrinolytic that works by inhibiting serine proteases, has now been widely withdrawn from clinical practice after a large randomized trial demonstrated its significant mortality risk in the setting of high-risk cardiac surgery, including thoracic aortic surgery with DHCA.[16,17] However, the risk-versus-benefit discussion with aprotinin continues to be debated.[18] The antifibrinolytic lysine analogs, epsilon-aminocaproic acid or tranexamic acid, are now the commonly utilized blood conservation agents in thoracic aortic surgery with and without DHCA (class 1 recommendation; level of evidence A).[12,19] Concerns with high-dose tranexamic acid leading to an increased risk for seizures after cardiac surgery remain, and thus, further trials on drug safety are still warranted.[20,21] Recombinant activated factor VII is a synthetic agent that accelerates thrombin production leading to hemostasis, and it may be considered for the management of intractable nonsurgical bleeding after CPB that is unresponsive to routine therapy.[12] Although this agent has demonstrated efficacy in complex aortic surgery, concerns for arterial thrombotic events remain, requiring further trials to investigate perioperative safety.[22–24] Finally, the use of fibrinogen concentrates in the management of coagulopathy continue to be investigated in cardiac surgery, with recent evidence suggesting decreased intraoperative bleeding when fibrinogen concentrates are used as a first-line therapy for coagulopathy after major aortic surgery[25] (see Chapters 34 and 35).

Postoperative Care

With the exception of some endovascular aortic procedures, patients often remain intubated and sedated at the completion of the operation, when they are transported directly from the OR to the ICU. The continuation of care from the OR to the ICU should be seamless and protocol based.[26] In the absence of complications, early anesthetic emergence is preferable for early assessment of neurologic function. If delayed anesthetic emergence is indicated, then sedation and analgesia can be provided. The chest roentgenogram allows confirmation of endotracheal tube and intravascular catheter position, as well as the diagnosis of acute intrathoracic pathologies. Common early complications include hypothermia, coagulopathy, delirium, stroke, hemodynamic lability, respiratory failure, metabolic disturbances, and renal failure. Frequent clinical and laboratory assessment is essential to manage this dynamic postoperative recovery, including the safe conduct of tracheal extubation (see Chapters 38 and 39). Given the risks associated with hyperglycemia after cardiac surgery, management of blood glucose levels should be standardized, with more recent data to suggest more liberal control (glucose less than 180 mg/dL) is acceptable with good outcomes.[27,28] Antibiotic prophylaxis is typically continued for 48 hours after surgery to minimize surgical infection risk.

Thoracic Aortic Aneurysm

A thoracic aortic aneurysm is a permanent localized thoracic aortic dilatation that has at least a 50% diameter increase and three aortic wall layers.[2–4] Localized dilatation of the thoracic aorta less than 150% of normal is termed *ectasis*. Annuloaortic ectasia is defined as isolated dilatation of the ascending aorta, aortic root, and aortic valve annulus. Pseudoaneurysm or a false aneurysm is a localized dilation of the aorta that does not contain all three layers of the vessel wall and instead consists of connective tissue and clot. Pseudoaneurysms are caused by a contained rupture of the aorta or arise from intimal disruptions, penetrating atheromas, or partial dehiscence of the suture line at the site of a previous aortic prosthetic vascular graft.

BOX 23.3 COMPLICATIONS OF THORACIC AORTIC ANEURYSMS

- Aortic rupture
- Aortic regurgitation
- Tracheobronchial and esophageal compression
- Right pulmonary artery or right ventricular outflow tract obstruction
- Systemic embolism from mural thrombus

Thoracic aortic aneurysms are common and are the 15th most common cause of death in people older than 65.[29] This disease process is virulent (Box 23.3) but indolent because it typically grows slowly at an approximate rate of 0.1 cm/year.[29] The most common reason for more rapid degeneration is acute aortic dissection. Besides acquired risk factors such as hypertension, hypercholesterolemia, and smoking, current evidence points to the strong influence of genetic inheritance.[29,30] Genetic analysis suggests that thoracic aortic aneurysms divide into two groups at the level of the ligamentum arteriosum. Above the ligamentum arteriosum, the disease is not related to typical arterial risk factors and has a smooth, noncalcified wall accompanied by no debris or clot. Below the ligamentum arteriosum, the disease process primarily is atherosclerotic, with an irregular calcified wall accompanied by copious debris and clot. This freedom from atheromatous disease in patients with thoracic aortic aneurysms of the ascending aorta has been called a "silver lining."[29] Inflammatory causes for thoracic aortic aneurysm include syphilis, mycotic aneurysm from endocarditis, giant-cell arteritis, and Takayasu arteritis.[2]

The aneurysm's location and extent determine the operative strategy and related perioperative complications. Aneurysms of the aortic root and/or ascending aorta commonly are associated with a bicuspid aortic valve.[31,32] Dilation of the aortic valve annulus, aortic root, and ascending aorta pulls the aortic leaflets apart and causes central aortic regurgitation (AR).[30] Aneurysms involving the aortic arch require temporary interruption of cerebral blood flow to accomplish the operative repair. Endovascular stent repair is an established therapy for aneurysms isolated to the descending thoracic aorta; however, ascending aorta stents have been employed in certain patients considered too high-risk for open surgery.[2,33–35] Repair of descending thoracic aortic aneurysms requires the sacrifice of multiple segmental intercostal artery branches that compromise spinal cord perfusion and results in a significant risk for postoperative paraplegia from spinal cord ischemia.[36]

The shape of thoracic aortic aneurysms can be described as either fusiform or saccular. Fusiform aneurysms are more common, associated with atherosclerotic or collagen vascular disease, and usually affect a longer segment of the aorta, producing a dilation of the entire circumference of the vessel wall. Saccular aneurysms are more localized, confined to an isolated segment of the aorta, and produce a localized outpouching of the vessel wall.

Thoracic aortic aneurysms mostly are asymptomatic and frequently are discovered incidentally.[2–4,29] Common symptoms of thoracic aortic aneurysm include chest and back pain caused by aneurysmal dissection, rupture, or bony erosion. The intrathoracic "mass effect" from a large thoracic aortic aneurysm can compress local structures to cause hoarseness (recurrent laryngeal nerve), dyspnea (trachea, mainstem bronchus, pulmonary artery), central venous hypertension (superior vena cava syndrome), and/or dysphagia (esophagus).[37] Rupture of thoracic aortic aneurysms is a surgical emergency and is often

accompanied with acute pain with or without hypotension. Although rupture of an ascending aortic aneurysm may cause cardiac tamponade, rupture in the descending thoracic aorta may cause hemothorax, aortobronchial fistula, or aortoesophageal fistula.

Diagnostic Imaging for Thoracic Aortic Aneurysms

Multiple imaging modalities are available to diagnose and manage aortic aneurysms. Recent guidelines and standards on imaging diseases of the aorta review the advantages and limitations of various techniques, as well as expected normal ranges for vessel caliber.[38] Imaging begins with the basic chest radiograph, which may suggest a thoracic aortic aneurysm if features such as a widened mediastinum, enlarged aortic knob, dilated descending thoracic aorta, aortic calcifications, leftward tracheal deviation, upward deviation of the left mainstem bronchus, and/or new left pleural effusion are present. Typically, transthoracic echocardiography can provide a reasonable examination of the thoracic aorta, although the acoustic windows are limited by the lungs. The contemporary imaging modalities of choice are CT, MRI, and TEE. Computed tomographic angiography (CTA) images the thoracic aorta during the arterial phase of an intravenous radiocontrast agent injection. It defines vascular anatomy and surrounding nonvascular structures. Aneurysm leak is detected as extravascular contrast extravasation. This imaging modality has multiple advantages, such as high resolution, wide availability, rapid acquisition, imaging in patients with metallic implants, and generation of volumetric aortic images for stent design. Because CTA requires iodinated contrast agents, it carries a risk for contrast nephropathy that can be attenuated by administration of hydration, acetylcysteine, and sodium bicarbonate.[39]

Contrast-enhanced magnetic resonance angiography (MRA) with gadolinium also images the entire thoracic aorta in fine detail. Although the spatial resolution of MRA is slightly inferior to CTA, it does allow for degrees of tissue and fluid characterization. The disadvantages of MRA include its limited availability, lack of imaging in patients with metallic implants, imaging difficulty in the setting of continuous hemodynamic monitoring, and the time required for image acquisition. Its advantages are the avoidance of ionizing radiation and the lack of renal toxicity.[2,29]

TEE can image the thoracic aorta from the aortic valve to the distal ascending aorta and from the distal aortic arch to the proximal abdominal aorta. The distal ascending aorta and proximal aortic arch cannot be reliably imaged by TEE because the intervening trachea and left mainstem bronchus obstruct the acoustic window; this is known as the "blind spot" of TEE.[40] It is possible to overcome this blind spot with modalities such as imaging across the trachea temporarily filled with a saline-filled balloon (the A-view) and utilizing an expanded aortic view.[40,41] The advantages of TEE include its portability, its real-time interpretation, its compatibility at the bedside and in the OR, and its multiple imaging modalities for complete aortic and cardiac assessment. Disadvantages include the requirement for sedation or general anesthesia and the risks for upper gastrointestinal injury.[42]

Surgical Considerations for Thoracic Aortic Aneurysms

Surgical repair aims to replace the aortic aneurysm with a tube graft to prevent further aneurysmal complications (Box 23.4). The first indication for thoracic aortic aneurysm resection is whenever the aneurysm is symptomatic regardless of size (class I recommendation; level of evidence C).[2,29] Symptoms often herald the onset of rupture or dissection and should be interpreted as an urgent indication for surgery. A symptomatic presentation occurs in about 5% of patients. Unfortunately, the first symptom in the remaining 95% of patients often is death.

The second indication for resection is aortic diameter. In the ascending aorta, a diameter of 6.0 cm is the critical hinge point after which the risk for aneurysm rupture increases exponentially. Thus surgical resection is recommended in the ascending aorta when the diameter reaches 5.5 cm (class I recommendation; level of evidence B).[2,29]

BOX 23.4 INDICATIONS FOR SURGICAL REPAIR OF THORACIC AORTIC ANEURYSMS

Atherosclerotic aneurysm diameter
- Ascending aorta ≥5.5 cm
- Descending aorta ≥6.5 cm

Marfan or familial thoracic aneurysm diameter
- Ascending aorta ≥5.0 cm
- Descending aorta ≥6.0 cm

Severe aortic regurgitation
Aortoannular ectasia with aortic root aneurysm
Rupture
Refractory pain

In patients with genetically mediated aortopathies (Marfan syndrome, bicuspid aortic valve, familial thoracic aortic aneurysm, vascular Ehlers-Danlos syndrome, and Turner syndrome), surgical resection is recommended at a lower ascending aortic diameter of 5.0 cm (class I recommendation; level of evidence B); however, a lower threshold of 4.5 cm is acceptable in cases of a family history of aortic dissection.[3,29] Ascending aortic aneurysms with diameters less than 5.5 cm but with an annual growth rate in diameter greater than 0.5 cm/year qualify for surgical resection (class I recommendation; level of evidence B).[3] It is reasonable to consider prophylactic replacement of the aortic root and ascending aorta in a woman with Marfan syndrome who is planning a pregnancy and who has an aortic root or ascending aortic diameter larger than 4.0 cm (class IIa recommendation; level of evidence C).[2] In adults with the aggressive aortopathy of the Loeys-Dietz syndrome, it is reasonable to consider proximal thoracic aortic repair when the internal aortic diameter exceeds 4.2 cm (class I recommendation; level of evidence C).[3,43] The ascending aortic aneurysm diameter also must be indexed to body size.[44] For example, if the maximal cross-sectional area of the aortic root or ascending aorta (in square centimeters) divided by the patient's height (in meters) exceeds a ratio of 10, then surgical repair is a reasonable option (class IIa recommendation; level of evidence C).[2] The rationale behind indexing the aortic dimensions to body size is that shorter adults dissect and rupture their aortas at smaller diameters.[2,38] Furthermore, those patients who are undergoing open aortic valve procedures and who have an aortic root or ascending aortic diameter larger than 4.5 cm should be considered for concomitant aortic replacement (class I recommendation; level of evidence B).[3]

The hinge point for rupture in the descending thoracic aorta is a diameter of 7.0 cm.[29] Consequently, surgical resection is recommended in thoracoabdominal aneurysms when the aortic diameter exceeds 6.0 cm (or less when it is associated with a connective tissue disorder such as Marfan syndrome) (class I recommendation; level of evidence C).[2] In patients who have aneurysmal degeneration of the descending thoracic aorta associated with prior dissection and/or a connective tissue disorder, surgical resection is recommended when the aortic diameter is more than 5.5 cm (class I recommendation; level of evidence B).[2] Patients with aneurysms of the descending thoracic aorta should be considered for thoracic endovascular aortic repair (TEVAR) when technically feasible (class I recommendation; level of Evidence B).[2,33]

Aneurysms of the ascending aorta and aortic arch are approached from a median sternotomy incision. Standard CPB can be used for the repair of aneurysms limited to the aortic root and ascending aorta that do not extend into the aortic arch by cannulating the distal ascending aorta or proximal aortic arch and applying an aortic cross-clamp between the aortic cannula and the aneurysm. Aneurysms that involve the aortic arch require CPB with temporary interruption of cerebral perfusion (DHCA). Neuroprotection strategies in this setting include deep hypothermia, selective ACP, and retrograde cerebral perfusion (RCP). Aortic aneurysms of the descending thoracic aorta require lateral thoracotomy for open surgical access. Aneurysmal resection requires cross-clamping with or without distal aortic perfusion.

Surgical Repair of Ascending Aortic and Arch Aneurysms

The type of surgical repair depends on aortic valve function and the aneurysm extent. Perioperative TEE can evaluate the aortic valve structure and function to guide and assess the surgical intervention (reimplantation, repair, replacement).[9,38] Furthermore, TEE can assess the diameters of the aortic root, ascending aorta, and aortic arch to guide intervention. The most common aortic valve diseases associated with ascending aortic aneurysm are bicuspid aortic valve or AR caused by dilation of the aortic root (Fig. 23.1). If the aortic valve and aortic root are normal, a simple tube graft can be used to replace the ascending aorta. If the aortic valve is diseased but the sinuses of Valsalva are normal, an aortic valve replacement combined with a tube graft for the ascending aorta without need for reimplantation of the coronary arteries can be performed (Wheat procedure; Fig. 23.2; class I recommendation; level of evidence C).[2]

If disease involves both the aortic valve and the aortic root, the patient requires aortic root replacement and aortic valve intervention. If technically feasible, the aortic valve can be reimplanted with a modified David technique, which includes graft reconstruction of the aortic root with reimplantation of the coronary arteries (class I recommendation; level of evidence C).[2,45] If not feasible, aortic root replacement with a composite valve-graft conduit is indicated (Bentall procedure; Fig. 23.3; class I recommendation; level of evidence C).[2] Aortic root replacement requires coronary reimplantation or aortocoronary bypass grafting (Cabrol technique; Fig. 23.4).

Repairing aortic aneurysms that extend into or involve the aortic arch requires CPB with DHCA with or without perfusion adjuncts. For ascending aortic aneurysms that involve only the proximal aortic arch, partial arch replacement (hemiarch technique) is reasonable in which a tubular graft is interposed between the ascending aorta or aortic root and the lesser curve of the aortic arch (class IIa recommendation; level of evidence B).[2] Ascending aorta with hemiarch reconstruction often is performed using DHCA with or without ACP/RCP to make the distal anastomosis feasible without cross-clamping ("open technique"). In patients who have isolated aortic arch aneurysms and a low operative risk, arch replacement is reasonable when the arch diameter exceeds 5.5 cm (class IIa recommendation; level of evidence B).[2] Total aortic arch replacement is reasonable in aneurysms that involve the entire arch (class IIa recommendation; level of evidence B).[2] Ascending aortic aneurysms that extend through the aortic arch into the descending aorta can be repaired with the "elephant trunk" technique (Fig. 23.5; class IIa recommendation; level of evidence B).[2,46] Aortic arch aneurysms that extend into the aortic branch vessels may require repair with branched or trifurcated tube grafts to permit separate anastomosis to the brachiocephalic, left carotid, and left subclavian arteries.[47] In patients with aortic arch aneurysms and concomitant severe comorbidity, guidelines support an endovascular repair technique (class IIb recommendation; level of evidence C).[2,33] However, in patients who have aortic arch aneurysms and who have reasonable surgical risk, the guidelines advise against an endovascular repair technique (class III recommendation; level of evidence A).[2,33] The use of a hybrid arch approach has gained popularity as it aims to minimize (or avoid) bypass and circulatory arrest times. With this technique, patients with arch aneurysms undergo an open debranching of the great vessels with the creation of appropriate landing zones for an endovascular stent graft of the aortic arch (Fig. 23.6).[48,49]

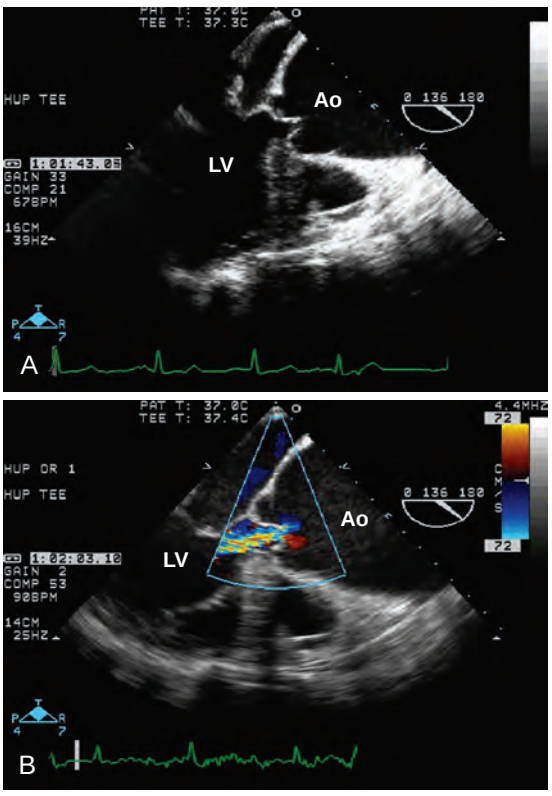


Fig. 23.1 Transesophageal echocardiographic (TEE) midesophageal long-axis images of the aortic valve demonstrating aneurysmal dilation of the aortic root and ascending aorta (A). Doppler color-flow imaging (B) demonstrating severe aortic regurgitation caused by outward tethering of the aortic valve cusps by the aortic aneurysm. *Ao,* Aorta; *LV,* left ventricle.

Anesthetic Management for Ascending Aorta and Arch Aneurysms

The conduct of general anesthesia in this setting has specific concerns. The imaging studies should be reviewed for aneurysm compression of mediastinal structures such as the right pulmonary artery and left mainstem bronchus (Fig. 23.7). Prevention of hypertension increases forward flow in AR and minimizes the risk for aneurysm rupture. As reviewed earlier, the preference for a left or right radial arterial catheter depends on the surgeon's approach to arch repair. Occasionally, bilateral radial arterial catheters can allow for simultaneous monitoring of cerebral and systemic perfusion pressures if arterial cannulation of the right axillary, subclavian, or brachiocephalic artery is planned for CPB and ACP. Nasopharyngeal, tympanic, and bladder temperatures are important for estimating brain and core temperatures for monitoring the conduct of DHCA. Monitoring of jugular bulb venous oxygen saturation and the EEG may reflect cerebral metabolic activity to guide the conduct of DHCA. Intraoperative TEE is essential to guide and assess the surgical interventions. In patients with AR, TEE can assist in the conduct of CPB by guiding placement of cannulae such as the retrograde cardioplegia cannula (coronary sinus) and by monitoring left ventricular (LV) volume to ensure that the LV drainage cannula keeps the ventricle collapsed. Intraoperative TEE is reasonable in thoracic aortic procedures, including endovascular interventions, in which it assists in hemodynamic monitoring, procedural guidance, and endoleak detection (class IIa recommendation; level of evidence B).[2]

Neuroprotection Strategies for Temporary Interruption of Cerebral Blood Flow

The risk for stroke is substantial during the cerebral ischemia that accompanies aortic arch reconstruction.[50] The first mechanism is cerebral ischemia due to hypoperfusion or temporary circulatory arrest during aortic arch repair. The second mechanism is cerebral ischemia due to embolization secondary to CPB and atheroma. Arterial embolic causes include air introduced into the circulation from open cardiac chambers, vascular cannulation sites, or arterial anastomosis. Atherosclerotic particulate debris may be released during clamping and unclamping of the aorta, the creation of anastomoses in

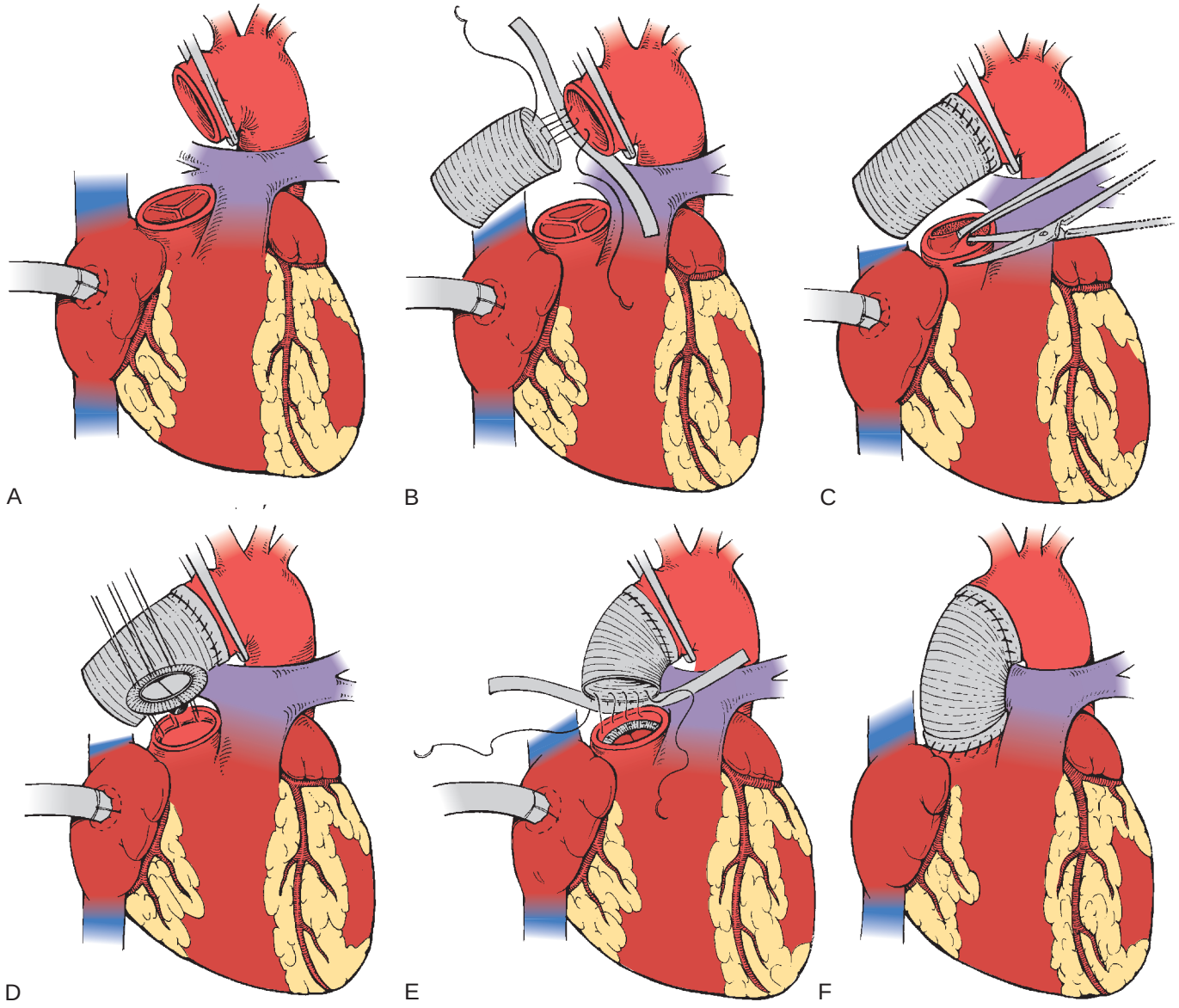


Fig. 23.2 Replacement of the ascending aorta with a prosthetic tube graft for ascending aortic aneurysm or type A aortic dissection (A, B, F). In the presence of aortic valvular disease, the aortic valve can be replaced (C–E) or repaired (not shown). Extension of the aneurysm or dissection into the aortic arch may require replacement of part or all of the aortic arch with a prosthetic tube graft (not shown). A small rim of the native aortic root containing the right and left coronary ostia was left behind in this repair. *(Reproduced with permission from Downing SW, Kouchoukos NT. Ascending aortic aneurysm. In: Edmunds LH, eds.* Cardiac Surgery in the Adult. *New York: McGraw-Hill; 1997:1176.)*

the ascending aorta and aortic arch, or the excision of severely calcified and diseased cardiac valves. CPB may result in the microparticulate aggregates of platelets and fat. The turbulent high-velocity blood flow out of the aortic cannula used for CPB also may dislodge atherosclerotic debris within the aorta. Retrograde blood flow through a diseased descending thoracic aorta as a consequence of CPB conducted with femoral artery cannulation may cause retrograde cerebral embolization. For all these reasons, strategies to provide neurologic protection are essential in thoracic aortic operations (Box 23.5), and there exists a great degree of variation in the approaches used to protect and monitor brain function.[51,52]

Deep Hypothermic Circulatory Arrest

The brain is extremely susceptible to ischemic injury within minutes after the onset of circulatory arrest because it has a high metabolic rate,

BOX 23.5 BRAIN PROTECTION FOR AORTIC ARCH RECONSTRUCTION

- Deep systemic hypothermia
- Topical cerebral cooling
- Retrograde cerebral perfusion
- Selective antegrade cerebral perfusion
- Cerebral hyperthermia prevention during rewarming

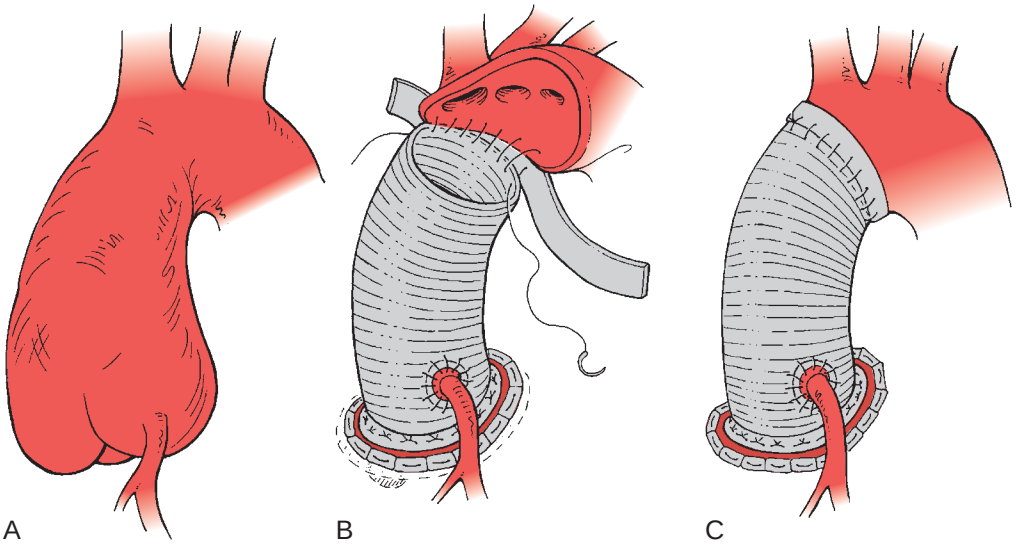


Fig. 23.3 Replacement of the entire aortic root with a composite valved conduit for ascending aortic aneurysm. The underside of the aortic arch was also incorporated into the prosthetic graft. The right and left coronary arteries were reimplanted into the graft (A–C). Alternatively, the aortic root can be replaced with a cryopreserved homograft or porcine bioprosthesis (not shown). *(Reproduced with permission from Griepp RB, Ergin A. Aneurysms of the aortic arch. In: Edmunds LH, ed.* Cardiac Surgery in the Adult. *New York, McGraw-Hill; 1997:1209.)*

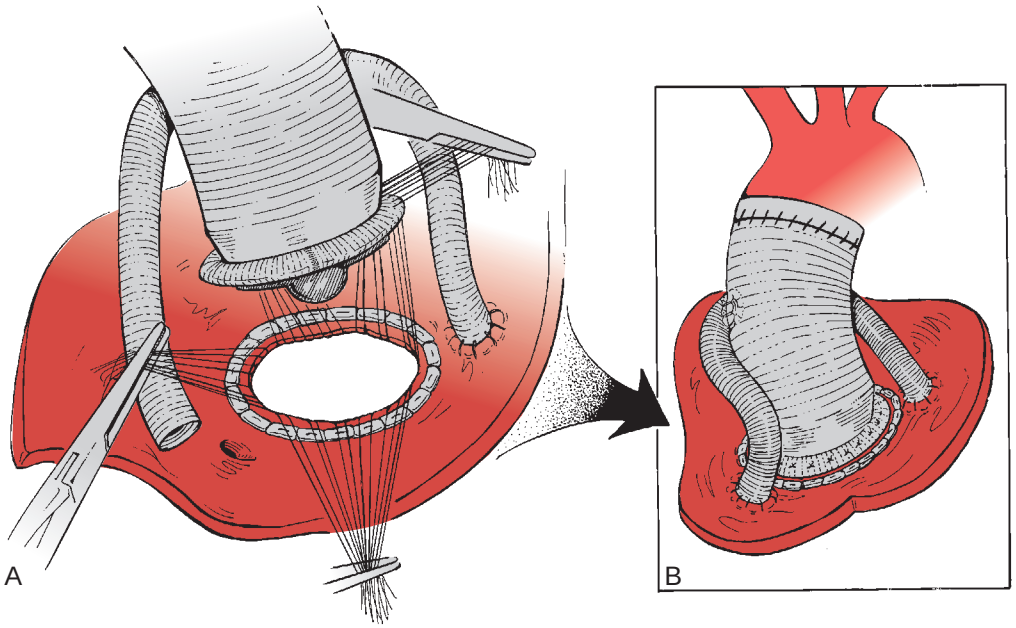


Fig. 23.4 Replacement of the entire aortic root with a composite valved conduit for ascending aortic aneurysm combined with end-to-end anastomosis of the right and left coronary arteries to an 8-mm or 10-mm prosthetic tube graft that was then anastomosed to the aortic root (A, B). *(Reproduced with permission from Downing SW, Kouchoukos NT. Ascending aortic aneurysm. In: Edmunds LH, ed.* Cardiac Surgery in the Adult. *New York, McGraw-Hill; 1997:1181.)*

continuous requirement for metabolic substrate, and limited reserves of high-energy phosphates. The physiologic basis for deep hypothermia as a neuroprotection strategy is to decrease cerebral metabolic rate and oxygen demands to increase the period that the brain can tolerate circulatory arrest.[53] Existing evidence indicates that autoregulation of cerebral blood flow is maintained during deliberate hypothermia with alpha-stat blood gas management without compromise of clinical outcome.[54] Direct measurement of cerebral metabolites and brainstem electrical activity in adults undergoing DHCA with RCP at 14°C indicated the onset of cerebral ischemia after only 18 to 20 minutes (Fig. 23.8).[55] Despite this observation, the large body of experimental evidence and clinical experience with deliberate hypothermia suggest that it is the single most important intervention for preventing neurologic injury in response to circulatory arrest.

Despite the proven efficacy of hypothermia for operations that require circulatory arrest, no consensus exists on an optimal protocol for the conduct of deliberate hypothermia for circulatory arrest.[56] A strategy to protect the brain during aortic arch surgery must be a high priority in the perioperative management of these procedures to prevent stroke and optimize cognitive function (class I recommendation; level

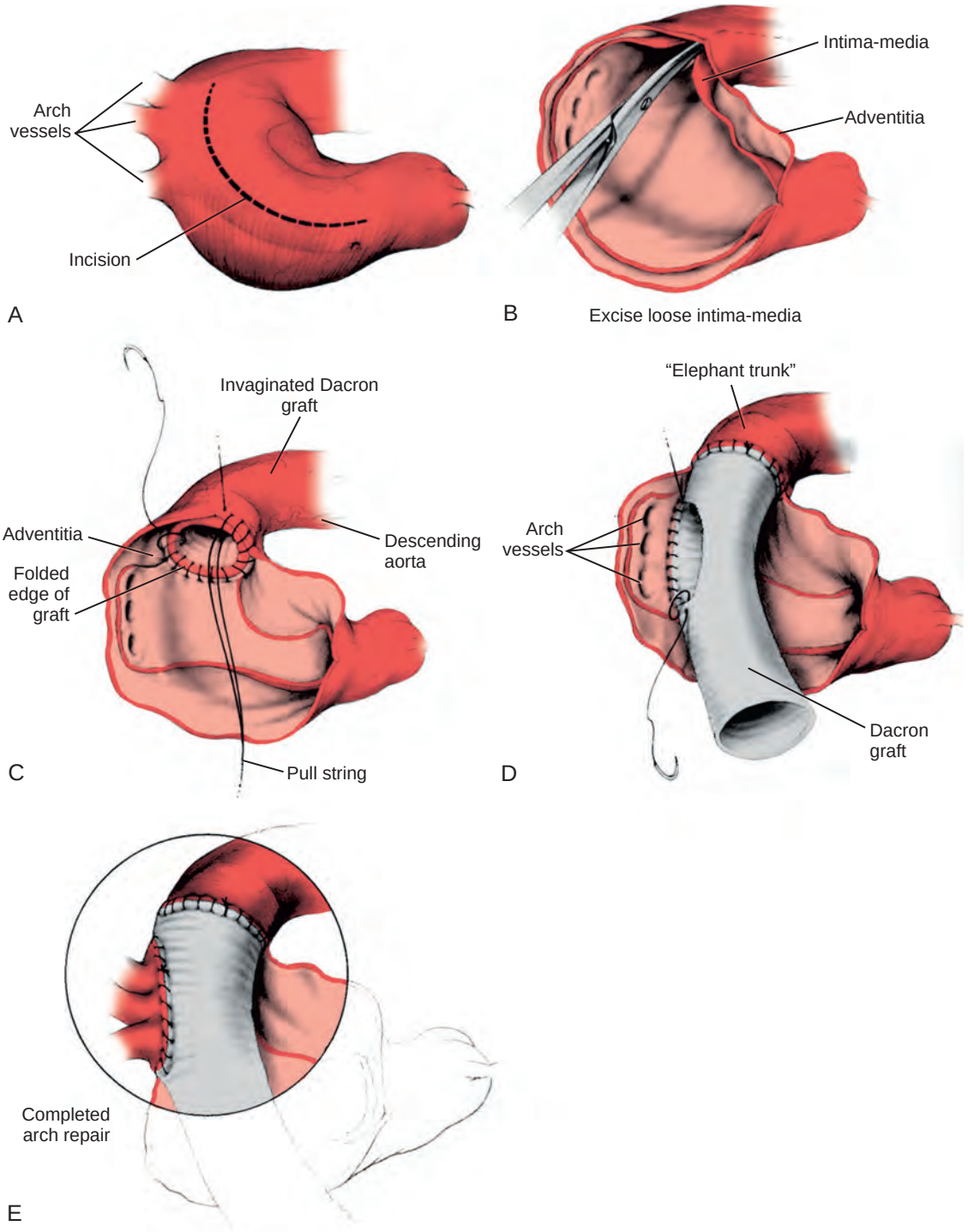


Fig. 23.5 Elephant trunk procedure for prosthetic graft replacement of the ascending aorta, aortic arch, and descending thoracic aorta. The aortic aneurysm or dissection is opened its entire length and extended through the aortic arch (A, B). The prosthetic tube graft is implanted with its distal end extending into the descending thoracic aorta, "elephant trunk" (C, D). The graft is pulled back into the arch for implantation of the arch branch vessels and construction of the proximal anastomosis (D, E). In the second stage of the procedure, the descending thoracic aorta is replaced by constructing a proximal graft-to-graft anastomosis (not shown). *(From Doty DB. Aortic aneurysm. In: Brown M, Baxter S, eds.* Cardiac Surgery: Operative Technique. *St Louis, Mosby-Year Book; 1997:324.)*

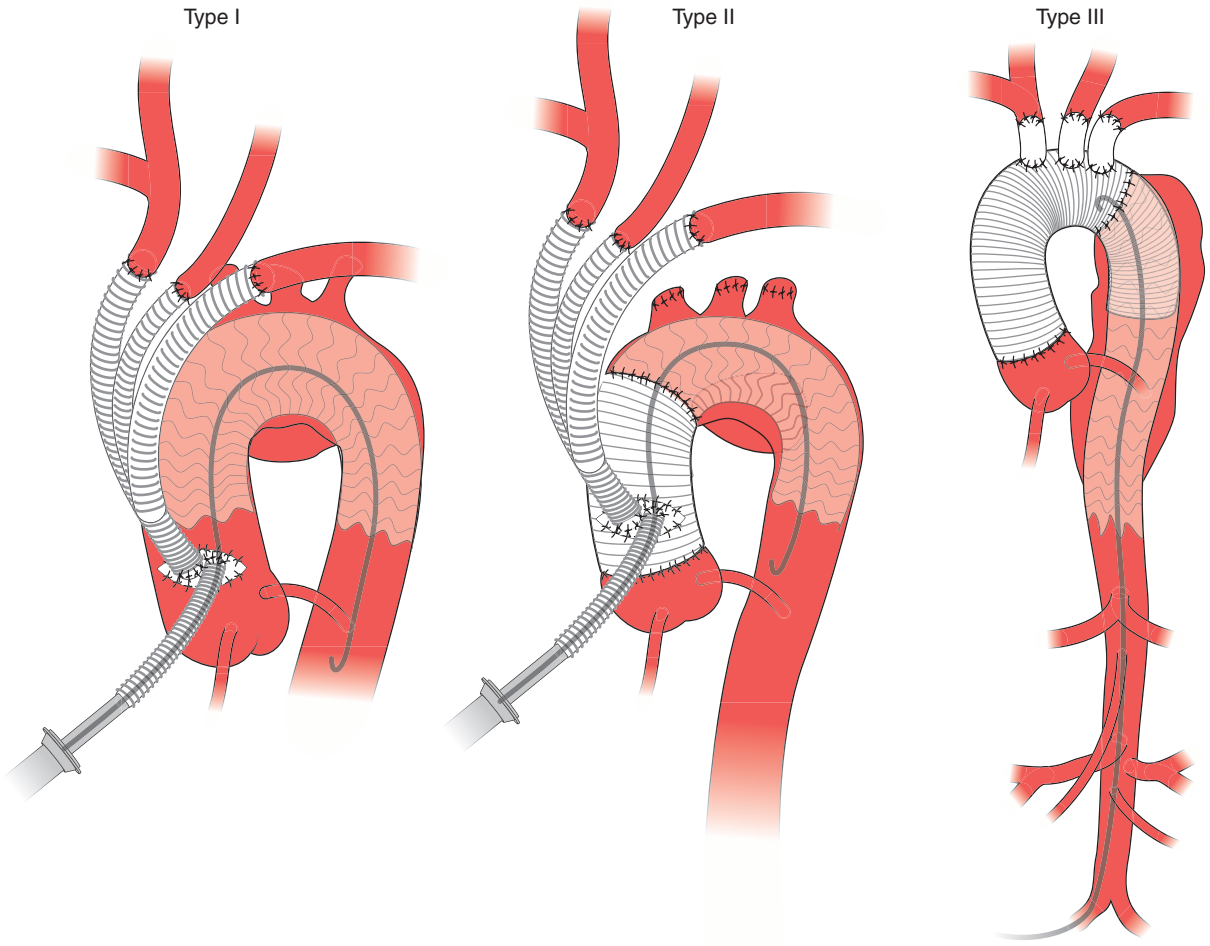


Fig. 23.6 Various debranching procedures and endovascular stent graft placement for aortic arch aneurysms, depending on the extent of ascending and/or descending aorta involvement. Adequate ascending aorta may allow an off-bypass technique. Pathology of the proximal ascending aorta warrants replacement with cardiopulmonary bypass prior to stent deployment, while the addition of diseased descending aorta may require a two-staged procedure with TEVAR performed after the initial debranching procedure. *(From Milewski RK, Szeto WY, Pochettino A, et al. Have hybrid procedures replaced open aortic arch reconstruction in high-risk patients? a comparative study of elective open arch debranching with endovascular stent graft placement and conventional elective open total and distal aortic arch reconstruction.* J Thorac Cardiovasc Surg. *2010;140:590–597.)*

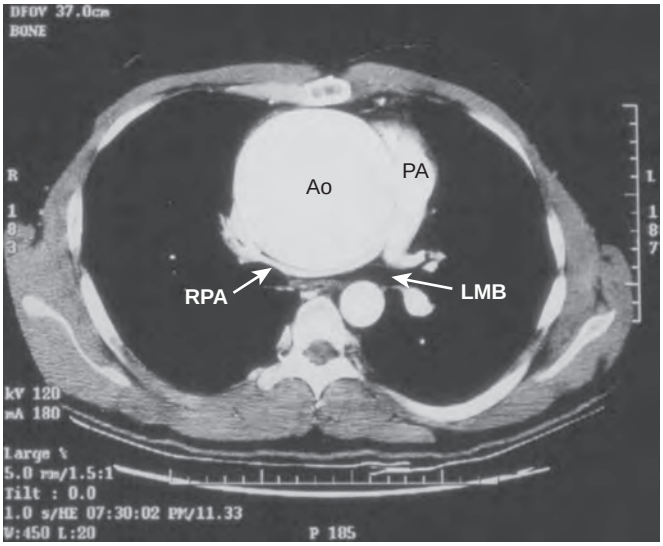


Fig. 23.7 Computed tomographic angiogram of the chest demonstrating a large ascending aortic aneurysm *(Ao)* causing compression of the right pulmonary artery *(RPA)*, distal trachea, and left main stem bronchus *(LMB)*.

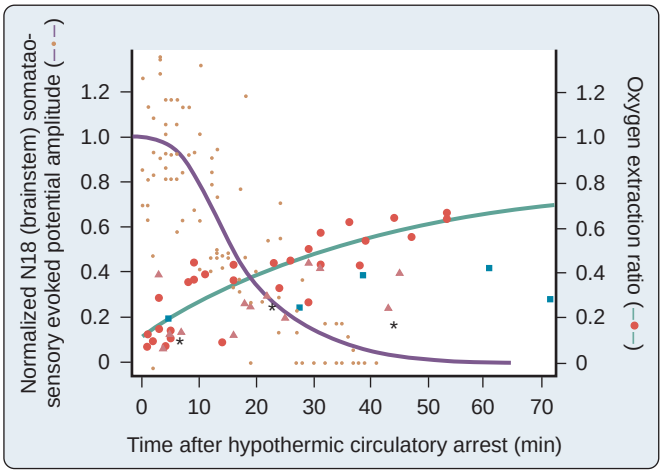


Fig. 23.8 Changes in brainstem (N18) somatosensory-evoked potential amplitudes *(dots)* after initiation of deep hypothermic circulatory arrest with retrograde cerebral perfusion superimposed on the change in brain oxygen extraction ratio (OER) in patients without strokes (*circles;* n = 19), preoperative strokes (*triangles;* n = 4), intraoperative strokes (*squares;* n = 3), and both preoperative and intraoperative strokes (*asterisks;* n = 1). The N18 somatosensory-evoked potential decayed to half its original amplitude at 16 minutes after interruption of antegrade cerebral perfusion. The OER decreased to half its maximal value of 0.66 also at 16 minutes after interruption of antegrade cerebral perfusion. *(Modified from Cheung AT, Bavaria JE, Pochettino A, et al. Oxygen delivery during retrograde cerebral perfusion in humans.* Anesth Analg. *1999;88:14.)*

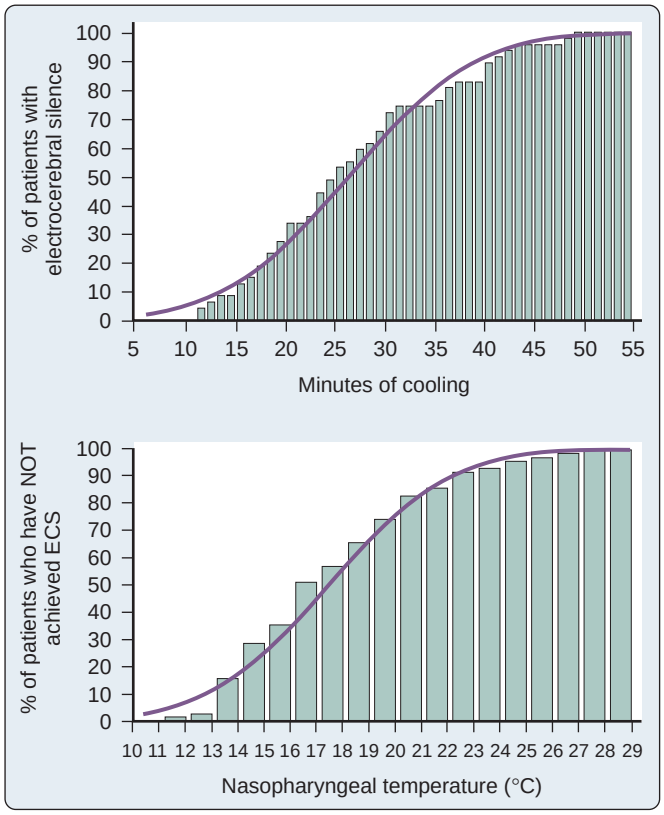


Fig. 23.9 The relation between electroencephalographic activity to minutes of cooling *(top)* and nasopharyngeal temperature *(bottom)* before deep hypothermic circulatory arrest in 109 patients undergoing thoracic aortic operations requiring circulatory arrest. Electrocortical silence (ECS) was achieved by electroencephalogram (EEG) in all patients after 50 minutes of cooling or at a nasopharyngeal temperature of 12.5°C. At a nasopharyngeal temperature of 18°C, only 50% of patients had ECS by EEG. *(Reproduced with permission from The Society of Thoracic Surgeons. Modified from Stecker MM, Cheung AT, Pochettino A, et al. Deep hypothermic circulatory arrest: I. Effects of cooling on electroencephalogram and evoked potentials.* Ann Thorac Surg. *2001;71:19.)*

of evidence C).[2] Although the average nasopharyngeal temperature for DHCA may be about 18°C, the optimal temperature for DHCA has not been established.[50,53] A challenge in the selection of the ideal temperature for DHCA is the inability to directly measure the brain temperature. In an EEG-based approach to this question, the median nasopharyngeal temperature for electrocortical silence was 18°C, although a nasopharyngeal temperature of 12.5°C or cooling on CPB for at least 50 minutes achieved electrocortical silence in 99.5% of cases (Fig. 23.9).[57] Although the EEG functions well as a physiologic endpoint for cerebral metabolic suppression during cooling for DHCA as part of an institutional protocol, its outcome benefit remains to be demonstrated in a randomized trial.[26,50,58] A jugular bulb venous oxygen saturation greater than 95% measured using an oximetric catheter represents an alternative physiologic end point to detect maximum cerebral metabolic suppression for DHCA.[59] It is important to note that deep hypothermia alone to a set temperature (mean = 19°C) as an end point for DHCA without EEG or jugular bulb venous oxygen saturation has been associated with excellent neurologic outcomes.[60,61] Therefore the technique of DHCA alone is a reasonable approach for neuroprotection during aortic arch surgery in the setting of adequate institutional experience (class IIa recommendation; level of evidence B).[2] In addition to systemic hypothermia produced by extracorporeal circulation, topical hypothermia by packing the head in ice has also been incorporated in some institutional DHCA protocols to minimize passive warming of the head.[60,61] However, the value of topical head cooling is questionable, with some evidence actually suggesting no benefit or potential harm.[62,63] Concern for interference with EEG or cerebral oximetry monitors also limits the role of topical cooling.[63]

The conduct of DHCA extends CPB duration with consequent risks for coagulopathy and embolization. Rewarming increases cerebral metabolic rate and can aggravate neuronal injury during ischemia/reperfusion. Consequently, it is important to rewarm gradually by maintaining a temperature gradient of no more than 10°C in the heat exchanger and avoiding cerebral hyperthermia (nasopharyngeal temperature >37.5°C). The current guidelines advise against cerebral hyperthermia in aortic arch procedures (class III recommendation; level of evidence B).[2]

Retrograde Cerebral Perfusion

Although clinical studies would support the practice of limiting the duration of straight DHCA to shorter than 45 minutes to avoid the associated significant increases in stroke and mortality risks, the use of adjunct perfusion techniques for neuroprotection has allowed surgeons to work for longer periods of time in a safe manner.[50,64] Similarly, these cerebral perfusion adjuncts have led to increased use of moderate degrees of hypothermia (20.1 to 28.0 degrees C).[64] RCP is a cerebral perfusion technique performed by infusing cold oxygenated blood into the superior vena cava cannula at a temperature of 8°C to 14°C via CPB (Fig. 23.10) (see Chapter 32). The internal jugular venous pressure is maintained at less than 25 mm Hg to prevent cerebral edema. Internal jugular venous pressure is measured from the introducer port of the internal jugular venous catheter at a site proximal to the superior vena cava perfusion cannula and zeroed at the level of the ear. The patient is positioned in 10 degrees of Trendelenburg to decrease the risk for cerebral air embolism and prevent trapping of air within the cerebral circulation in the presence of an open aortic arch. RCP flow rates of 200 to 600 mL/minute usually can be achieved. The potential benefits of RCP include partial supply of cerebral metabolic substrate,

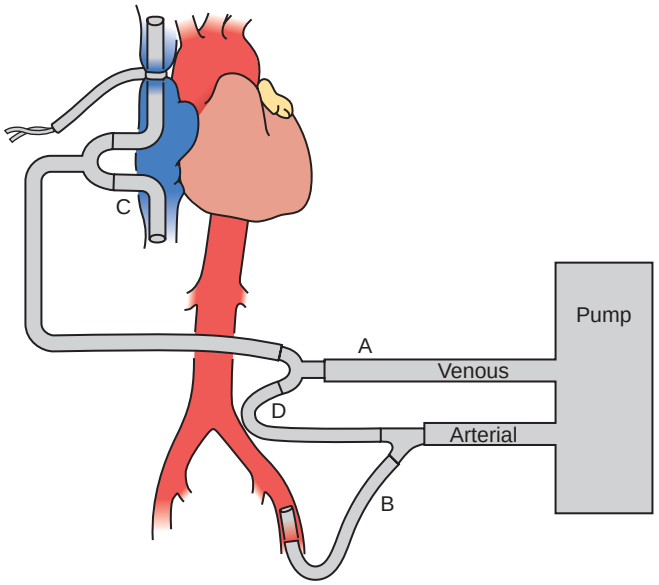


Fig. 23.10 Extracorporeal perfusion circuit used to deliver retrograde cerebral perfusion. The bridge *(D)* is clamped during cardiopulmonary bypass. After initiation of deep hypothermic circulatory arrest, clamps are placed on the venous return line *(A)*, the proximal arterial cannula *(B)*, and inferior vena caval cannula *(C)*, and the bridge *(D)* is unclamped to permit retrograde perfusion into the superior vena cava. *(Reproduced with permission from The Society of Thoracic Surgeons. Modified from Bavaria JE, Woo YJ, Hall RA, et al. Retrograde cerebral and distal aortic perfusion during ascending and thoracoabdominal aortic operations.* Ann Thorac Surg. *1997;60:347.)*

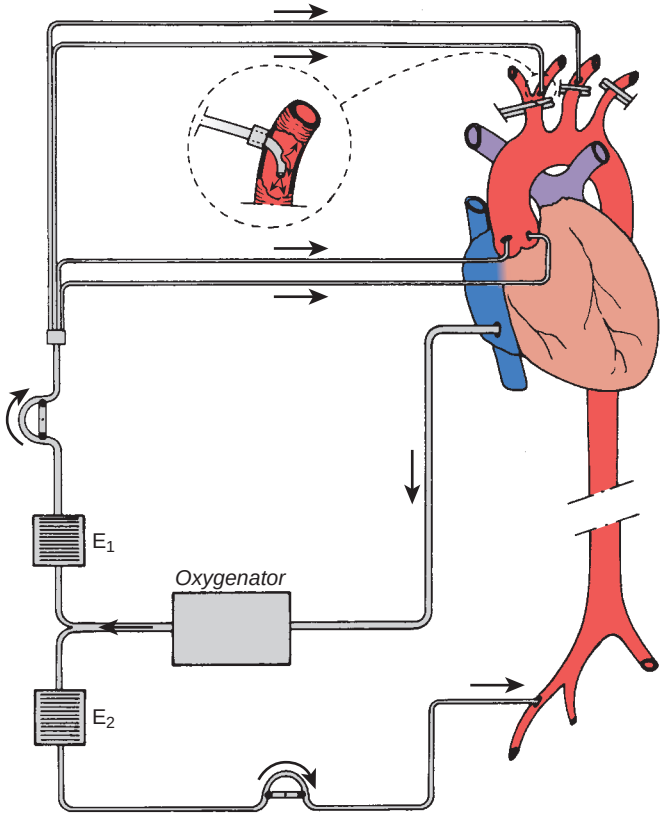


Fig. 23.11 Extracorporeal perfusion circuit used for selective antegrade cerebral perfusion. After achieving deep hypothermia on cardiopulmonary bypass, individual cannulas are inserted into the coronary, innominate, and left carotid arteries for selective antegrade perfusion of the heart and brain. *(From Bachet J, Teodori G, Goudot B, et al. Replacement of the transverse aortic arch during emergency operations for type A acute aortic dissection.* J Thorac Cardiovasc Surg. *1988;96:878.)*

cerebral embolic washout, and maintenance of cerebral hypothermia.[65] Although RCP has been associated with excellent clinical results in aortic arch repair, it has not become the standard technique for neuroprotection in DHCA.[26,66] A large, single-center study (1991–2007; $N = 1107$; RCP in 82%) evaluated the role of RCP in proximal thoracic aortic repair.[67] The perioperative rates for mortality and stroke in this series were 10.4% and 2.8%, respectively. The application of RCP was significantly protective against mortality (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.25–0.70; $P = 0.0009$) and stroke (OR, 0.35; 95% CI, 0.15–0.81; $P = 0.02$).[67] Therefore RCP is safe and easily implemented in aortic arch repair as an adjunct to maintain cerebral hypothermia, provide partial metabolic substrate delivery, and decrease the risk for cerebral embolization.[58–61,65–67] The technique of DHCA with RCP is a reasonable approach for neuroprotection during aortic arch surgery in the setting of adequate institutional experience (class IIa recommendation; level of evidence B).[2] A large recent metaanalysis ($N = 5060$: 15 trials) has demonstrated that with deep hypothermia RCP provides similar cerebral protection as compared with ACP.[68]Although RCP is clinically effective at deep hypothermia, the clinical movement towards moderate hypothermia with ACP in contemporary aortic arch reconstruction will likely limits its application in the future.[69]

Selective Antegrade Cerebral Perfusion

Selective ACP should be considered for aortic arch repairs longer than 45 minutes.[50] Compared with DHCA alone, the combined use of DHCA and selective ACP has been associated with superiority in terms of mortality outcomes.[70] ACP typically is initiated during DHCA by selective cannulation of the right axillary artery, right subclavian artery, brachiocephalic artery, or left common carotid artery (Fig. 23.11).[71,72] In transverse aortic arch reconstruction procedures, ACP can be accomplished by inserting individual perfusion cannulae into the open end of the aortic branch vessels after opening the aortic arch. After reattachment of the aortic arch branch vessels to the vascular graft, ACP can be provided through a separate arm of the vascular graft or by direct cannulation of the graft. A functional circle of Willis may provide contralateral brain perfusion during interruption of antegrade perfusion in the brachiocephalic or left carotid arteries during construction of the vascular anastomoses. ACP with oxygenated blood at 10°C to 14°C at flow rates in the range of 250 to 1000 mL/minute typically achieves a cerebral perfusion pressure in the range of 50 to 80 mm Hg.

Unilateral ACP via right axillary arterial cannulation is a popular technique for adult aortic repair.[71] This technique assumes an adequate circle of Willis; however, the anatomic completeness of the circle of Willis does not guarantee adequate cerebral cross-perfusion during aortic arch repair.[73,74] Consequently, it remains essential to monitor the contralateral hemisphere in unilateral ACP with modalities such as cerebral oximetry, carotid artery scanning, and transcranial Doppler.[75–77]

Given that ACP may be unilateral or bilateral, there remains controversy about which ACP technique is superior.[78] A large analysis that combined 17 studies for a total sample size of 3548 patients compared bilateral ACP (83.1%) with unilateral ACP (16.9%).[79] Although the stroke rates were less than 5% regardless of technique, the period of safe ACP was significantly prolonged with bilateral ACP (86–164 minutes) compared with unilateral ACP (30–50 minutes). The evidence favors bilateral ACP in the setting of aortic arch repair times longer than 60 minutes.[79] Further, a recent metaanalysis ($N = 5100$; 28 trials) has demonstrated that unilateral and bilateral ACP in aortic arch reconstruction achieve similar clinical outcomes for perioperative mortality, stroke, and delirium.[80]

Pilot clinical series in adult aortic arch repair also have been undertaken in the setting of ACP with moderate hypothermic circulatory arrest (MHCA; systemic temperature = 25°C).[81,82] A large, single-center study (1999–2006; $N = 501$ [36.1% emergency cases]; median age, 64 years; 63.9% male sex) evaluated perioperative outcomes with this technique.[83] With a perioperative mortality rate of 11.6%, multivariate predictors for mortality included age and CPB time. The stroke rate was 9.6% with operative time and renal dysfunction as its multivariate predictors for stroke. The rate of temporary neurologic dysfunction was 13.4%, with MHCA duration (OR, 1.015; $P = 0.01$) as a multivariate predictor. Although MHCA with cold ACP appears to be an adequate technique for adult aortic arch repair, its safety is limited in the settings of the elderly, multiple comorbidities, and extended operative time. A more recent metaanalysis of patients undergoing arch surgery actually demonstrates that the use of MHCA with selective ACP is a superior technique in terms of stroke risk.[84] However, the safety of MHCA with ACP for ischemic protection of the spinal cord and kidney are still questioned.[85,86] Overall, the technique of DHCA with ACP is a reasonable approach for neuroprotection during aortic arch surgery in the setting of adequate institutional experience (class IIa recommendation; level of evidence B).[2]

Pharmacologic Neuroprotection Strategies for Deep Hypothermic Circulatory Arrest

There are no proven pharmacologic regimens that have demonstrated effectiveness for decreasing the risk or severity of neurologic injury in the setting of thoracic aortic operations.[58] The agents that have been reported in aortic arch series include thiopental, propofol, steroids, magnesium sulfate, and lidocaine.[26,53,87] Furthermore, there is considerable variation in practice with these agents in aortic arch repair.[87] A recent analysis of a large clinical registry in surgical management for acute type A dissection ($N = 2137$ over 4 years) suggested that steroids may improve neurologic outcome by protecting against stroke (adjusted OR, 0.50; 95% CI 0.24–0.96; $P = 0.049$).[88] In general, the existing evidence suggests that pharmacologic neuroprotection should be considered as a neuroprotective adjunct and not a substitute for hypothermia to protect against cerebral ischemia in the setting of hypoperfusion. The technique of DHCA with pharmacologic adjuncts is a reasonable approach for neuroprotection during aortic arch surgery in the setting of an institutional protocol and adequate institutional experience (class IIa recommendation; level of evidence B).[2]

Descending Thoracic and Thoracoabdominal Aortic Aneurysms

Surgical therapy for descending thoracic and thoracoabdominal aortic aneurysms is to replace the aneurysmal aorta with a prosthetic tube graft. Surgical access is via lateral thoracotomy or thoracoabdominal incision. Despite recent advances, major surgical challenges remain because the typical patient is elderly with multiple significant comorbidities. The risks for spinal, mesenteric, renal, and lower extremity ischemia are significant because of thromboembolism, loss of collateral vascular networks, temporary interruption of blood flow, and reperfusion injury. The risks for wound dehiscence and respiratory failure remain significant because of the large incisions and diaphragmatic division, as well as injuries to the phrenic and recurrent laryngeal nerves. Consequently, TAAA repair is high risk (Table 23.3).[89]

Aneurysms of the descending thoracic aorta are classified by considering which third(s) of the descending thoracic aorta is (are) involved.[2] Extent A involves the proximal third, extent B involves the middle third, and extent C involves the distal third. If more than one-third is involved, then the extent is classified according to which thirds are involved; for example, an aneurysm involving the proximal two-thirds is classified as extent AB. Essentially, multisegment aneurysms can be classified as proximal or distal because these extents influence the risk for spinal cord ischemia after surgical repair, whether open or endovascular.

TABLE 23.3 Clinical Outcomes of Open Thoracoabdominal Aortic Aneurysm (TAAA) Repair (United States: 2005–2012; n = 823)

Complication	*No. of Patients (%)*
Any adverse outcome	131 (15.9%)
Operative mortality	69 (8.4%)
Permanent spinal cord deficits	42 (5.1%)
Stroke	27 (3.3%)
Acute renal dysfunction	95 (11.5%)
Cardiac complication	250 (30.4%)
Pulmonary complication	338 (41.1%)
Bleeding requiring re-exploration	48 (5.8%)

Data from LeMaire SA, Price MD, Green SY, et al. Results of open thoracoabdominal aortic aneurysm repair. *Ann Cardiothorac Surg.* 2012;1:286–292.

TABLE 23.4 Mortality and Paraplegia After Thoracoabdominal Aortic Aneurysm Repair (n = 823)

TAAA Extent	*No. of Patients*	*Operative Mortality*	*Permanent Paraplegia*	*Permanent Paraparesis*
I	209	14 (6.7%)	3 (1.4%)	4 (1.9%)
II	264	24 (9.1%)	12 (4.5%)	3 (1.1%)
III	157	20 (12.7%)	12 (7.6%)	2 (1.3%)
IV	193	11 (5.7%)	4 (2.1%)	2 (1.0%)

Data from LeMaire SA, Price MD, Green SY, et al. Results of open thoracoabdominal aortic aneurysm repair. *Ann Cardiothorac Surg.* 2012;1:286–292.

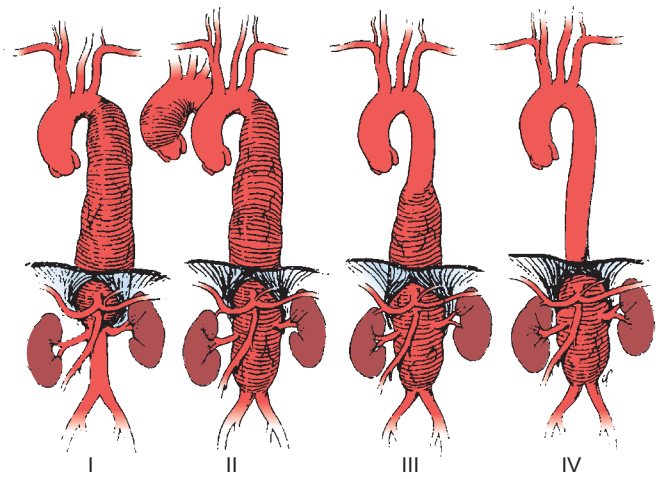


Fig. 23.12 Crawford classification of thoracoabdominal aortic aneurysm extent. *(From Coselli JS. Descending thoracoabdominal aortic aneurysms. In: Edmunds LH, ed.* Cardiac Surgery in the Adult. *New York: McGraw-Hill; 1997:1232.)*

Aneurysms of the thoracoabdominal aorta typically are defined by the Crawford classification (Fig. 23.12).[90] Extent I TAAA begins at the left subclavian artery and ends below the diaphragm, but above the renal arteries. Extent II TAAA involves the entire descending thoracic aorta and ends below the diaphragm at the aortic bifurcation. Extent III TAAA begins in the lower half of the descending thoracic aorta and ends below the diaphragm at the aortic bifurcation. Extent IV TAAA is confined to the entire abdominal aorta. If an extent I or extent II TAAA involves the distal aortic arch, its surgical replacement often requires DHCA for the proximal anastomosis. The Crawford classification stratifies operative risk and guides perioperative management (Table 23.4). Open repair of TAAA typically is accomplished by aortic cross-clamping with or without the addition of a shunt, PLHB, or partial CPB (Fig. 23.13).

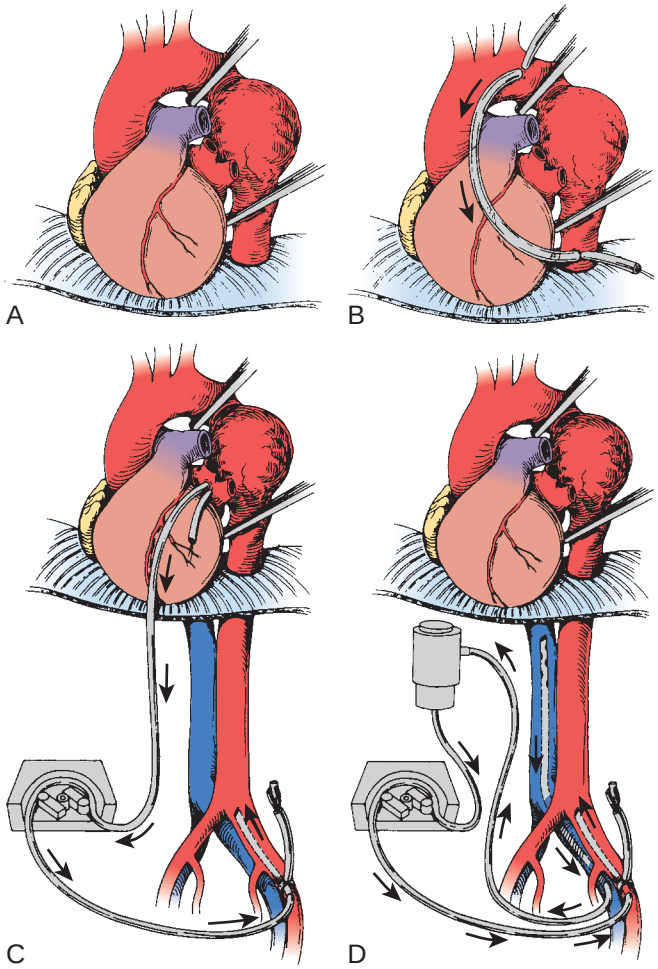


Fig. 23.13 Operative techniques for repair of thoracic or thoracoabdominal aortic aneurysms. In the clamp-and-sew technique, the distal aorta is not perfused (A). Alternatively, distal aortic perfusion during repair can be provided by a passive Gott shunt (B), partial left heart bypass (C), or partial cardiopulmonary bypass (D). Deep hypothermic circulatory arrest may be necessary if the proximal cross-clamp cannot be safely applied in aneurysms extending into the distal aortic arch (not shown). *(From O'Connor CJ, Rothenberg DM: Anesthetic considerations for descending thoracic aortic surgery: Part II.* J Cardiothorac Vasc Anesth. *1995;9:734.)*

Simple Aortic Cross-Clamp Technique

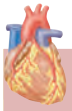
The major disadvantage of this technique, developed by Crawford, is the concomitant vital organ ischemia below the aortic clamp. Consequently, surgical speed is critical to achieve an ischemic time less than 30 minutes to limit the risk for vital organ dysfunction.[91] Its further disadvantages include proximal aortic hypertension, bleeding, and hemodynamic instability on reperfusion. Despite anesthetic interventions, this proximal aortic hypertension may induce LV ischemia.[92] Blood loss can be minimized with intraoperative red blood cell salvaging. Hemodynamic instability during reperfusion can be minimized with correction of metabolic acidosis, rapid intravascular volume expansion, vasopressor therapy, and/or gradual clamp release. Mild systemic hypothermia and selective spinal cooling protect against the ischemia associated with this technique.[93,94] Despite its physiologic consequences, this technique remains popular because it is simple and has proven clinical outcomes (Box 23.6).

Gott Shunt

Passive shunts allow for blood to be diverted from the proximal aorta to the distal aorta during aortic cross-clamping for thoracic aortic repair. One specific type is the heparin-coated Gott shunt (Fig. 23.13B).[95] Blood flow from the proximal to distal aorta through the shunt depends on proximal aortic pressure, shunt length and diameter, and distal aortic pressure. Monitoring the femoral arterial pressure facilitates assessment of distal aortic perfusion and shunt flow. The advantages of the Gott shunt are its simplicity, its low cost, and its requirement for only partial anticoagulation. Its disadvantages include vessel injury, dislodgment, bleeding, and atheroembolism.

Partial Left-Heart Bypass

The control of both proximal and distal aortic perfusion during TAAA repair can be achieved with PLHB. This technique requires left atrial cannulation, usually via a left pulmonary vein (Fig. 23.13C). Oxygenated blood from the left atrium flows through the CPB circuit into the distal aorta or a major branch via the arterial cannula.[93] The CPB circuit can include a heat exchanger, membrane oxygenator, and/or a venous reservoir. The degree of heparinization for PLHB is minimal with heparin-coated circuits without an oxygenator. Full systemic anticoagulation with ACT greater than 400 seconds is required for CPB circuits with membrane oxygenators and heat exchangers.[96] During PLHB, the proximal mean arterial pressure (MAP; radial artery) is generally maintained in the 80 to 90 mm Hg range. Flow rates in the range of 1.5 to 2.5 L/minute typically maintain a distal aortic MAP in the 60 to 70 mm Hg range, monitored via a femoral arterial catheter.[96] Sequential advancement of the aortic cross-clamp during PLHB permits segmental aortic reconstruction with a decrease in end-organ ischemia. The advantages of PLHB include control of aortic pressures and systemic temperature, reliable distal aortic perfusion, and selective antegrade perfusion of important branch vessels (Fig. 23.14).[93] Its disadvantages include increased expense, increased complexity, and requirement for systemic anticoagulation (see Box 23.6). An alternative technique uses partial CPB by femoral vein to femoral artery perfusion with or without an oxygenator. This can allow for distal perfusion without the need for cannulation of the heart or aorta. However, it does not offer the control that is achieved with proper PLHB.



BOX 23.6 ADVANTAGES AND DISADVANTAGES OF DISTAL PERFUSION TECHNIQUES

Potential Advantages

- Control of proximal hypertension
- Decrease left ventricular afterload
- Less hemodynamic perturbations with aortic clamping and unclamping
- Decrease duration of mesenteric ischemia
- Decrease risk for paraplegia from spinal cord ischemia
- Ability to control systemic temperature with heat exchanger
- Vascular access for rapid volume expansion
- Ability to oxygenate blood with extracorporeal oxygenator
- Capability to selectively perfuse mesenteric organs or aortic branch vessels
- Maintain lower extremity SSEPs and MEPs for neurophysiologic monitoring

Potential Disadvantages

- Require greater level of systemic anticoagulation
- Increase risk for vascular injury at cannulation sites
- Increase risk for thromboembolic events.
- Require perfusion team
- Need to monitor and control upper and lower body arterial pressure and flow
- Increase technical complexity of operation

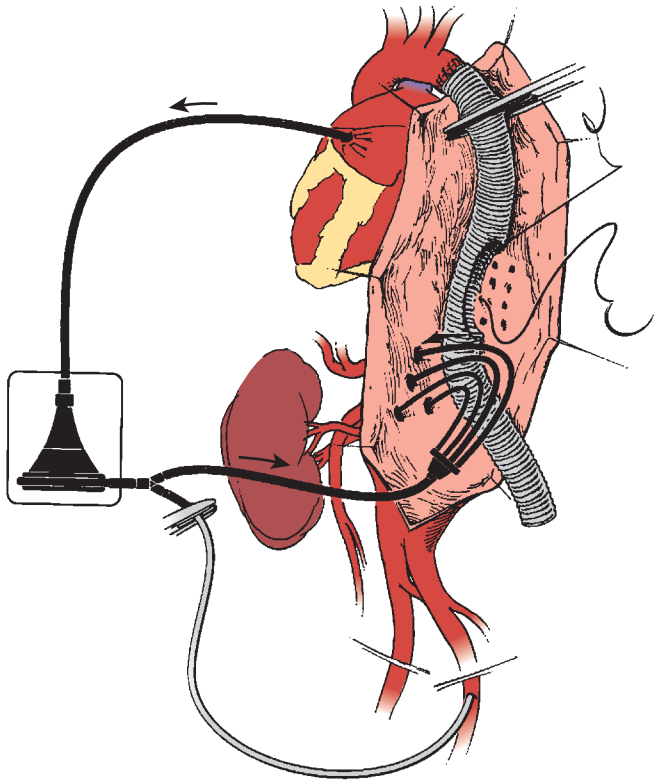


Fig. 23.14 Extracorporeal perfusion circuit for repair of an extensive thoracoabdominal aortic aneurysm. Cannulation of the left atrium and femoral artery provides distal aortic perfusion by partial left heart bypass. Visceral perfusion can be provided by selective cannulation of the celiac, superior mesenteric, and renal arteries. *(Modified from Coselli JS: Descending thoracoabdominal aortic aneurysms. In: Edmunds LH, ed.* Cardiac Surgery in the Adult. *New York: McGraw-Hill; 1997:1237.)*

Cardiopulmonary Bypass With Deep Hypothermic Circulatory Arrest

When a TAAA involves the distal aortic arch precluding an adequate cross-clamp site, CPB with DHCA is required to allow completion of the distal anastomosis. This technique has acceptable perioperative outcome for major reconstruction of the thoracoabdominal aorta because it also protects the spinal cord and mesenteric organs from ischemia.[97] If CPB with DHCA is planned for TAAA repair through a left thoracotomy incision, TEE should monitor for aortic regurgitation so that any LV distention with the onset of asystole during deliberate hypothermia can be managed with insertion of a drainage cannula. The disadvantages of CPB with DHCA include the limited safe period for DHCA, risk for stroke from retrograde aortic perfusion, increased CPB duration, and bleeding. For TAAA with extension into the distal aortic arch, a two-stage elephant-trunk procedure can be performed instead of using CPB with DHCA.[98] In the two-stage elephant-trunk procedure, the transverse aortic arch graft is performed first through a median sternotomy, leaving a short segment of graft extending into the descending aorta (see Fig. 23.5). The second stage of the repair is performed through a left thoracotomy incision to access and anastomose the distal end of the transverse arch graft to the proximal end of the descending thoracic aortic graft. This two-stage repair avoids the need for retrograde CPB perfusion through the diseased descending thoracic aorta and decreases the risk for injury to the recurrent laryngeal nerve, esophagus, and pulmonary artery located in the proximity of the distal aortic arch.

Endovascular Stent Graft Repair of Thoracic Aortic Aneurysms

TEVAR was established for the management of thoracic aortic aneurysms and now has recent management guidelines.[33] Endovascular stent grafts are tube grafts reinforced by a wire frame that are collapsed within a catheter for delivery and deployment within the aortic lumen. The principle of TEVAR is that the deployed stent complex spans the length of diseased aorta to exclude blood flow into the aneurysm cavity. TEVAR requires a landing zone for each end of the tubular graft. Endoleak is defined as blood flow within the aneurysm but outside the endovascular graft (Table 23.5).

TABLE 23.5 Classification of Endoleaks

Type	*Cause of Perigraft Flow*	*Consequences and Therapeutic Strategy*
I	Inadequate seal at proximal and/or distal landing zone	Systemic blood pressure is transmitted to aneurysm with risk for rupture: timely repair is indicated.
II	Retrograde flow from aortic branches into aneurysm	It may thrombose. If aneurysm is expanding, aortic branch embolization is indicated.
III	Structural failure of stent (eg, perforations, fractures)	Systemic blood pressure is transmitted to aneurysm with risk for rupture: timely repair is indicated.
IV	Stent graft fabric porosity	This usually occurs at implantation and disappears with anticoagulation reversal.
V	Aneurysm expansion without obvious endoleak ("endodistention")	The endovascular repair can be strengthened with a second stent.

Data from Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: Executive summary. A report of the American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine. *Circulation.* 2010;121:e266–e369.

The current guidelines from The Society of Thoracic Surgeons (STS) suggest TEVAR for aneurysms of the descending thoracic aorta when the aortic diameter is larger than 5.5 cm (class IIa recommendation; level of evidence B, when the patient has significant comorbidity; class IIb recommendation; level of evidence C, when the patient has no significant comorbidity).[33] When the aortic diameter is less than 5.5 cm, the STS guidelines advise against TEVAR (class III recommendation; level of evidence C).[33] In the setting of TAAA, the STS guidelines support TEVAR in patients with severe comorbidity (class IIb recommendation; level of evidence C).[33] In patients with severe comorbidity and aortic arch aneurysm with distal extension, the STS guidelines support an endovascular repair technique (class IIb recommendation; level of evidence C).[2,33] In patients who have reasonable surgical risk and who have aortic arch aneurysms with distal extension, the STS guidelines advise against an endovascular repair technique (class III recommendation; level of evidence A).[2,33]

Endovascular stent graft repair for isolated descending thoracic aortic aneurysms with a proximal landing zone that involves the left subclavian artery can be accomplished using a two-stage procedure (Fig. 23.15). In the first stage, the left subclavian artery can be divided and anastomosed onto the left common carotid artery. This first stage of the procedure provides a proximal landing zone, allowing the deployment of the endovascular stent graft over the left subclavian artery branch in the distal aortic arch in the second stage of the procedure without compromising flow through the vessel. Multiple recent metaanalyses have demonstrated the outcome importance of not sacrificing the left subclavian artery during TEVAR to avoid the risks for stroke, paraplegia, and left upper extremity ischemia.[99–101] The recent guidelines from the Society of Vascular Surgery strongly support this principle but also recognize that in urgent TEVAR for life-threatening acute aortic syndromes, left subclavian artery coverage is unavoidable.[102]

There are currently two major options for endovascular TAAA repair, namely, total TEVAR and hybrid TEVAR. Total endovascular TAAA repair requires customized stents that preserve major aortic branches with fenestrations or side branches.[103] Multiple series have

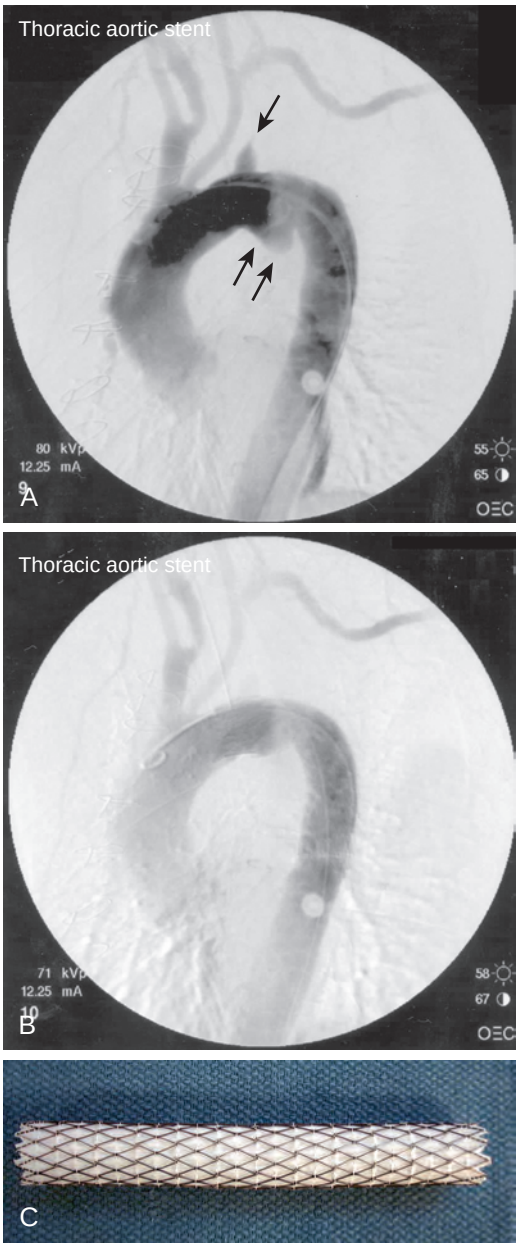


Fig. 23.15 Intraoperative angiogram demonstrating an isolated saccular aneurysm *(double arrows)* of the thoracic aorta (A). The left subclavian artery *(single arrow)* was previously divided and transposed onto the left carotid artery to create a proximal landing site for endovascular stent repair (A). Intraoperative angiogram (B) after deployment of the endovascular stent graft (C) demonstrated exclusion of the aneurysm.

demonstrated the safety and efficacy of this TEVAR modality in high-risk TAAA patients.[104–106] In hybrid TAAA repair, the landing zone for the nonfenestrated endovascular graft is created by aortic debranching procedures, for example, the renal and mesenteric arteries are anastomosed to the iliac arteries. Multiple series and metaanalyses have demonstrated the safety and efficacy of this TEVAR modality as well in high-risk patients.[107–111] This hybrid approach also has been used in aortic arch reconstruction for high-risk patients with aortic arch aneurysms.[49,112] Furthermore, TEVAR recently has extended proximally for therapy of select aneurysms of the ascending aorta.[35,113] In summary, TEVAR for TAAA, whether entirely endovascular or hybrid, is in recent clinical development with an established niche in patients with excessive operative risk. It is likely that these technologies will mature further in the coming years. This maturation of TEVAR for

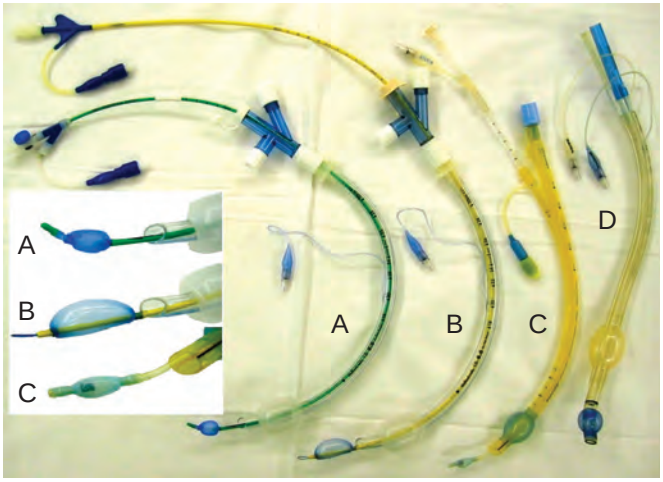


Fig. 23.16 Single-lung ventilation for thoracic or thoracoabdominal aortic aneurysm repair requiring a left thoracotomy can be accomplished using a Cohen bronchial blocker inserted through a standard endotracheal tube *(A)*, an Arndt wire-guided bronchial blocker inserted through a standard endotracheal tube *(B)*, a Univent endotracheal tube with an integrated bronchial blocker *(C)*, or a left-sided double-lumen endobronchial tube *(D)*.

diseases of the descending thoracic aorta likely will be rapid given that recent metaanalysis ($N = 5888$, 42 nonrandomized studies) demonstrated that TEVAR as compared with open aortic repair reduced perioperative mortality (OR, 0.44; 95% CI, 0.33–0.59), paraplegia (OR, 0.42; 95% CI, 0.28–0.63), pneumonia, cardiac complications, renal failure, bleeding, and transfusion, as well as length of hospital stay.[114]

Anesthetic Management for Thoracoabdominal Aortic Aneurysm Repair

The anesthetic management of patients undergoing TAAA repair often requires selective right lung ventilation in the setting of a major left thoracotomy and anesthetic interventions to prevent spinal cord ischemia. Right radial arterial pressure monitoring typically is preferred, especially if the aortic repair involves clamping the left subclavian artery or surgical endovascular access via the left brachial artery. Femoral arterial pressure monitoring is required when distal aortic perfusion is planned either with PLHB or a passive shunt. Hemodynamic monitoring with a PAC usually is helpful for the management of the concomitant specialized perfusion techniques already discussed. The anesthetic plan must allow for spinal cord monitoring with SSEPs, MEPs, or both to account for decreases in renal function and decreases in spinal cord perfusion. Finally, a strategy for postoperative analgesia should be planned.

Lung Isolation Techniques

Selective ventilation of the right lung with concomitant left lung collapse during TAAA repair enhances surgical access and protects the right lung from left lung bleeding. Collapse of the left lung typically is achieved when the left main bronchus is intubated either with a double-lumen endobronchial tube (DLT) or a bronchial blocker. Routine fiberoptic bronchoscopic guidance guarantees the effectiveness of either technique. The increased length of the left mainstem bronchus facilitates placement of a left-sided DLT and subsequently anchors it during surgery. Endobronchial blockade is achieved with one of the following devices: the Arndt blocker, the Cohen blocker, or the Univent tube (Fig. 23.16).[115] Wire-guided endobronchial blocking catheters permit the balloon-tipped catheter to be guided and positioned precisely in the left mainstem bronchus with a fiberoptic bronchoscope. The advantages of a left DLT include the ability to apply selective continuous positive airway pressure to the left lung.

BOX 23.7 FACTORS THAT CONTRIBUTE TO PARAPLEGIA AFTER THORACIC OR THORACOABDOMINAL AORTIC PROCEDURES

- Thoracoabdominal aortic aneurysm extent
- Hypotension or cardiogenic shock
- Emergency surgery
- Aortic rupture
- Presence of aortic dissection
- Duration of aortic cross-clamp
- Sacrifice of intercostal or segmental artery branches
- Prior thoracic or abdominal aortic aneurysm repair
- Prior repair of type A aortic dissection
- Occlusive peripheral vascular disease
- Anemia

BOX 23.8 MINIMIZING PARAPLEGIC RISK AFTER THORACIC OR THORACOABDOMINAL AORTIC PROCEDURES

Minimize Aortic Cross-Clamp Time
- Distal aortic perfusion
- Passive shunt (Gott)
- Partial left heart bypass
- Partial cardiopulmonary bypass

Deliberate Hypothermia
- Mild-to-moderate systemic hypothermia (32°C to 35°C)
- Deep hypothermic circulatory arrest (14°C to 18°C)
- Selective spinal cord hypothermia (epidural cooling, 25°C)

Increase Spinal Cord Perfusion Pressure
- Reimplantation of critical intercostal and segmental arterial branches
- Lumbar cerebrospinal fluid (CSF) drainage (CSF pressure ≤10 mm Hg)
- Arterial pressure augmentation (mean arterial pressure ≥85 mm Hg)

Intraoperative Monitoring of Lower Extremity Neurophysiologic Function
- Somatosensory-evoked potentials
- Motor-evoked potentials

Postoperative Neurologic Assessment for Early Detection of Delayed-Onset Paraplegia
- Serial neurologic examinations

Pharmacologic Neuroprotection
- Glucocorticoid
- Barbiturate or central nervous system depressants
- Magnesium sulfate
- Mannitol
- Naloxone
- Lidocaine
- Intrathecal papaverine

Its disadvantages include increased difficulty in difficult airways and bronchial injury in distorted endobronchial anatomy. The major advantage of endobronchial blockade is its compatibility with an existing standard 8.0-mm endotracheal tube. This is advantageous in emergencies and in difficult airways.[115] The disadvantages of endobronchial blockade include increased time for left-lung collapse and dislodgement during surgery. The majority of patients will require temporary postoperative mechanical ventilation, usually via a single-lumen endotracheal tube. ICU personnel often are unaccustomed to managing patients with DLTs with their risks for malposition, airway obstruction, and difficulty with airway secretions. Endotracheal tube exchange may be challenging if there is airway edema. An endotracheal tube exchange catheter in combination with direct laryngoscopy often facilitates safe endotracheal tube exchange.[116] It is recommended that in the setting of upper airway edema, DLTs are not routinely exchanged for single-lumen tubes (class III recommendation; level of evidence C)[2] (see Chapter 49).

Paraplegia After Thoracoabdominal Aortic Aneurysm Repair

Paraplegia after TAAA repair is a devastating complication. The temporary interruption of distal aortic perfusion and sacrifice of spinal segmental arteries during TAAA repair are central events in the pathogenesis of spinal cord ischemia and paraplegia. There are multiple contributing factors (Box 23.7).[36] The typical level of spinal cord ischemia after TAAA is midthoracic and is associated with a high perioperative mortality. There are many management strategies for prevention of this devastating complication after TAAA (Box 23.8).[2,36]

The spinal cord arterial supply provides a partial explanation for the clinical features of paraplegia after TAAA repair (Fig. 23.17).[36,117,118] The anterior spinal artery supplies the anterior two thirds of the spinal cord, and the posterior spinal arteries supply the posterior third. Branches from each vertebral artery join to form the anterior spinal artery that descends along the midline of the anterior surface of the spinal cord. The anterior spinal artery sometimes is discontinuous and fed in a variable extent by radicular arteries derived from ascending cervical, deep cervical, intercostal, lumbar, and sacral segmental arteries. The posterior spinal arteries also are derived from the vertebral arteries and receive collateral supply from posterior radicular arteries. The terminal cord segments are supplied by radicular arteries that arise from the internal iliac and sacral arterial network. The thoracolumbar spinal cord typically has multiple arterial sources with a clinical vulnerability to significant ischemia. In this watershed region, an important blood supply is derived from a large radicular artery (intercostal arteries T9–T12 in 75% of patients, T8–L3 in 15%, and L1–L2 in 10%).[119,120] This important artery is known as the arteria magna or the artery of Adamkiewicz. Ischemia in the anterior spinal artery territory classically causes motor paralysis with preservation of proprioception.[36] Clinical experience, however, has demonstrated that spinal cord ischemia after TAAA repair is variable, asymmetric, and can affect motor or sensory function, or both.[36,121]

Paraplegia is defined as lower extremity motor weakness with muscle strength weaker than gravity. Paraparesis is defined as lower extremity weakness with muscle power that allows movement at least against gravity (Table 23.6).[118,121] Spinal cord ischemia may have an immediate onset, defined as lower extremity weakness on emergence from anesthesia within 24 hours of the procedure.[36,121] Delayed-onset spinal cord ischemia is defined as lower extremity weakness that follows a normal postoperative neurologic examination after emergence from anesthesia. In the largest series of TAAA repairs ever reported ($N = 2286$; 1986–2006), the incidence rate of symptomatic spinal cord ischemia was 3.8%, with 63% of these cases having an immediate onset and 37% a delayed onset.[93] Multiple series have indicated that delayed-onset spinal cord ischemia can present days, weeks, or even months after TAAA repair.[36,93,121,122]

Immediate-onset paraplegia likely is a consequence of intraoperative spinal cord ischemia, leading to infarction that occurred during surgery. In contrast with delayed-onset paraplegia, recovery with intervention in immediate-onset paraplegia has not been consistently demonstrated. This lack of therapeutic response likely indicates that irreversible spinal cord injury has occurred. Consequently, strategies to prevent immediate-onset paraplegia are directed toward intraoperative spinal cord protection (Box 23.9). The objective of intraoperative spinal cord monitoring is to detect spinal cord ischemia for immediate intervention to improve spinal cord perfusion. Distal aortic perfusion

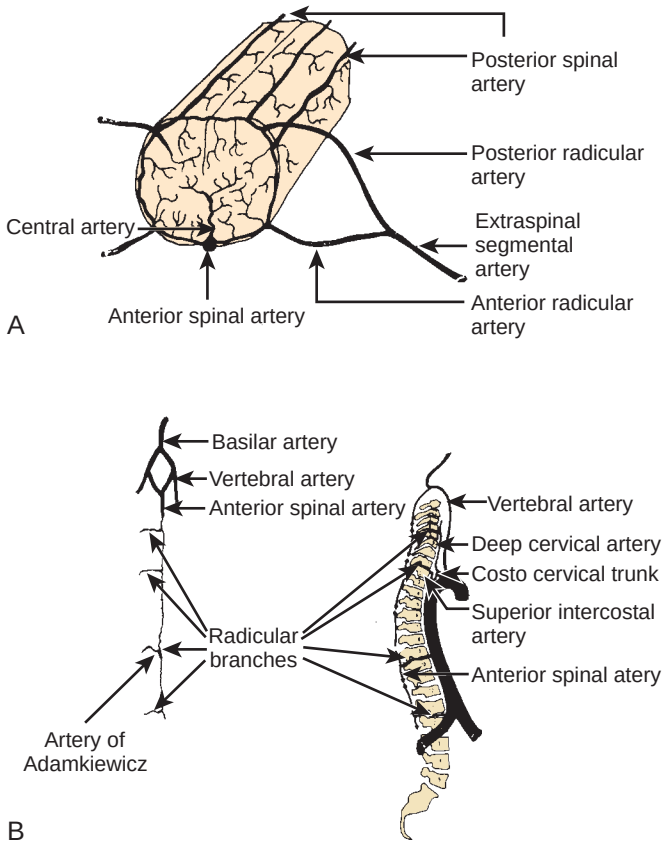


Fig. 23.17 The arterial supply to the spinal cord is provided by the anterior spinal artery and paired posterior spinal arteries that branch off the vertebral arteries (A). Radicular arterial branches off the descending thoracic aorta provide collateral arterial supply to the anterior and posterior spinal arteries (B). The arteria magna or artery of Adamkiewicz refers to a large radicular branch, located between the T9 and L2 vertebral levels, that supplies the anterior spinal artery (B).

TABLE 23.6 Description of Lower Extremity Weakness Caused by Spinal Cord Ischemia

Score	*Description*
Paraplegia	
0	No movement of lower extremity
1	Minimal movement or flicker of lower extremity
2	Movement of lower extremity but not against resistance or gravity (eg, bend knee, move leg)
Paraparesis	
3	Movement of lower extremity against resistance and gravity but without ability to stand or walk
4	Ability to stand and walk with assistance

Data from Greenberg RK, Lu Q, Roselli E, et al. Contemporary analysis of descending thoracic and thoracoabdominal aneurysm repair: a comparison of endovascular and open techniques. *Circulation.* 2008;118:808.

maintains spinal cord function during aortic cross-clamping and improves the ability to monitor spinal cord integrity during surgery with SSEP or MEPs.[118]

Delayed-onset paraplegia indicates that, although the spinal cord was protected intraoperatively, it remains vulnerable to ischemia after surgery. Although the causes of this syndrome are incompletely understood, it often is preceded by hypotension.[123] Strategies to minimize delayed-onset paraplegia include the prevention of perioperative hypotension, early anesthetic emergence for early and subsequent serial neurologic assessment, and lumbar CSF drainage (Box 23.10). Given the catastrophic sequelae of permanent paraplegia after TAAA repair, all reasonable attempts to treat delayed-onset paraplegia can be justified.[36,117]

BOX 23.9 TECHNIQUES TO DECREASE THE RISK FOR INTRAOPERATIVE SPINAL CORD ISCHEMIA

- Mild systemic hypothermia
- Lumbar cerebrospinal fluid drainage
- Selective spinal cord cooling
- Distal aortic perfusion
- Minimizing the ischemic time
- Segmental aortic reconstruction
- Intercostal artery preservation
- Pharmacologic neuroprotection
- Intraoperative motor- or somatosensory-evoked potential monitoring
- Arterial pressure augmentation

BOX 23.10 PREVENTION AND TREATMENT OF DELAYED-ONSET SPINAL CORD ISCHEMIA

- Maintain mean arterial pressure ≥85 mm Hg
- Serial neurologic assessment for lower extremity weakness or sensory loss
- Immediate treatment to augment spinal cord perfusion pressure
- Arterial pressure augmentation with vasopressor therapy
- Lumbar cerebrospinal fluid drainage
- Prevent hypotension

Lumbar Cerebrospinal Fluid Drainage

Lumbar CSF drainage is a strongly recommended spinal cord protective strategy for TAAA repair (class I recommendation; level of evidence B).[2,124–127] The physiologic rationale is that reduction of CSF pressure improves spinal cord perfusion pressure (SCPP) and also may counter CSF pressure increases caused by aortic cross-clamping, reperfusion, increased central venous pressure, and/or spinal cord edema.[36,118]

Lumbar CSF drainage is performed by the insertion of a silicon elastomer ventriculostomy catheter via a 14-gauge Tuohy needle at the L3-L4 vertebral interspace. The catheter is advanced into the subarachnoid space and securely fastened to the skin at approximately 15 cm to prevent catheter movement while the patient is anticoagulated. The open end of the catheter is attached to a sterile reservoir, and CSF is drained when the lumbar CSF pressure exceeds 10 mm Hg. The lumbar CSF pressure is measured with a pressure transducer zero-referenced to the midline of the brain. Currently, the best strategy to manage a traumatic lumbar puncture or the drainage of blood-tinged CSF has not been determined.[128,129] The lumbar CSF drainage catheter is inserted before or at the time of surgery for CSF drainage up to the first 24 hours after surgery. The lumbar drainage catheter subsequently can be capped and left in place for the next 24 hours. It then can be removed, assuming a normal neurologic examination and adequate coagulation.

The complications of lumbar CSF drainage include neuraxial hematoma, catheter fracture, meningitis, intracranial hypotension, and spinal headache.[36,96,130] Neuraxial hemorrhage after lumbar drain insertion remains a risk in patients subsequently subjected to systemic anticoagulation for CPB. Despite this risk, the overall safety of this technique has been established in multiple case series.[96,131,132] Measures to minimize neuraxial hematoma include establishing normal coagulation for both CSF catheter insertion and removal, as well as allowing a few hours between its insertion and heparinization for CPB.[36,131] In

two large contemporary series (combined $N = 2001$), the complication rate associated with CSF drainage for thoracic aortic repair was about 1% with no spinal hematomas. Both series identified excessive CSF drainage as a principal risk factor for intracranial hypotension and subsequent subdural hematoma and emphasized the outcome benefit associated with a limited CSF drainage protocol.[131,132] For routine use, CSF only should be drained, using a closed circuit reservoir, when the lumbar CSF pressure exceeds 10 mm Hg. Meningitis is characterized by high fever, altered mentation, and CSF pleocytosis often with bacteria. The risk for catheter fracture can be minimized by careful catheter removal.

Arterial Pressure Augmentation

The optimization of SCPP for spinal cord protection is recommended as part of an institutional perioperative protocol (class IIa recommendation; level of evidence B).[2] This recommendation also recognized the variety of suitable techniques such as maintenance of proximal aortic pressure and distal aortic perfusion with the caveat that technique selection often is a function of institutional experience.[2] The principles of arterial pressure augmentation and CSF drainage for prevention and management of postoperative spinal cord ischemia are in keeping with this recommendation (Fig. 23.18).[122] Spinal cord ischemia after TAAA repair is more likely in the setting of hypotension because the spinal arterial collateral network has been reduced due to factors such as intercostal artery sacrifice.[123,133,134] Surgical techniques to preserve SCPP include selective intraoperative spinal cord perfusion and intercostal artery revascularization with interposition grafts.[135,136]

SCPP is estimated as the MAP minus the lumbar CSF pressure. In general, the SCPP should be maintained greater than 70 mm Hg after TAAA repair; that is, a MAP of 80 to 100 mm Hg.[36,122,133] Because spinal cord ischemia often involves the thoracolumbar cord, it often is accompanied by a significant sympathectomy known as spinal vasodilatory shock.[2,36,122] Early intervention to treat hypotension with vasopressor therapy may counter the autonomic nervous system dysfunction accompanying spinal cord ischemia and also augment SCPP. As in the treatment of neurogenic shock, high-dose vasopressor therapy with norepinephrine, phenylephrine, epinephrine, and/or vasopressin typically is required to restore systemic vascular resistance and spinal cord perfusion, with a MAP in the 80 to 100 mm Hg range.[122] Recovery from spinal cord ischemia often is heralded by recovery of systemic vascular tone and a decreasing vasopressor requirement. Therapeutic hypertension, as discussed here, for the management of spinal cord ischemia after TAAA must be weighed against the risks for arterial bleeding.

Intraoperative Neurophysiologic Monitoring

Neurophysiologic monitoring of the spinal cord (SSEPs and/or MEPs) is recommended as a strategy for the diagnosis of spinal cord ischemia so as to allow immediate intraoperative neuroprotective interventions such as intercostal artery implantation, relative arterial hypertension, and CSF drainage (class IIb recommendation; level of evidence B)[2] (see Chapter 18). This management strategy may prevent immediate-onset postoperative paraplegia. SSEP monitoring is performed by applying electrical stimuli to peripheral nerves and recording the evoked potential that is generated at the level of the peripheral nerves, spinal cord,

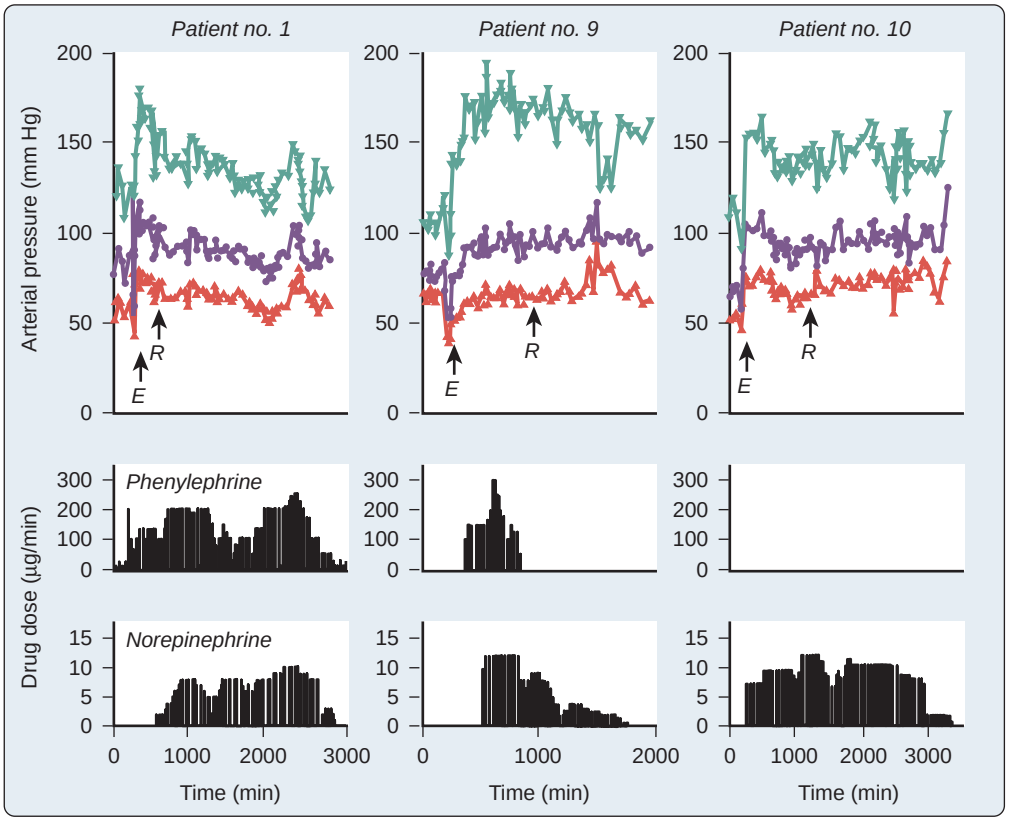


Fig. 23.18 Systolic, mean, and diastolic blood pressures in the period surrounding the onset *(E)* and recovery *(R)* from delayed-onset paraplegia in three patients after thoracoabdominal aortic aneurysm repair. Autonomic nervous system dysfunction caused by spinal cord ischemia may have contributed to the decrease in arterial pressure during the events. Arterial pressures were augmented with vasopressor therapy *(bottom)*. Vasopressor requirements decreased after recovery from spinal cord ischemia. *(Reproduced with permission from The Society of Thoracic Surgeons. From Cheung AT, Weiss SJ, McGarvey ML, et al. Interventions for reversing delayed-onset postoperative paraplegia after thoracic aortic reconstruction.* Ann Thorac Surg. *2002;74:417.)*

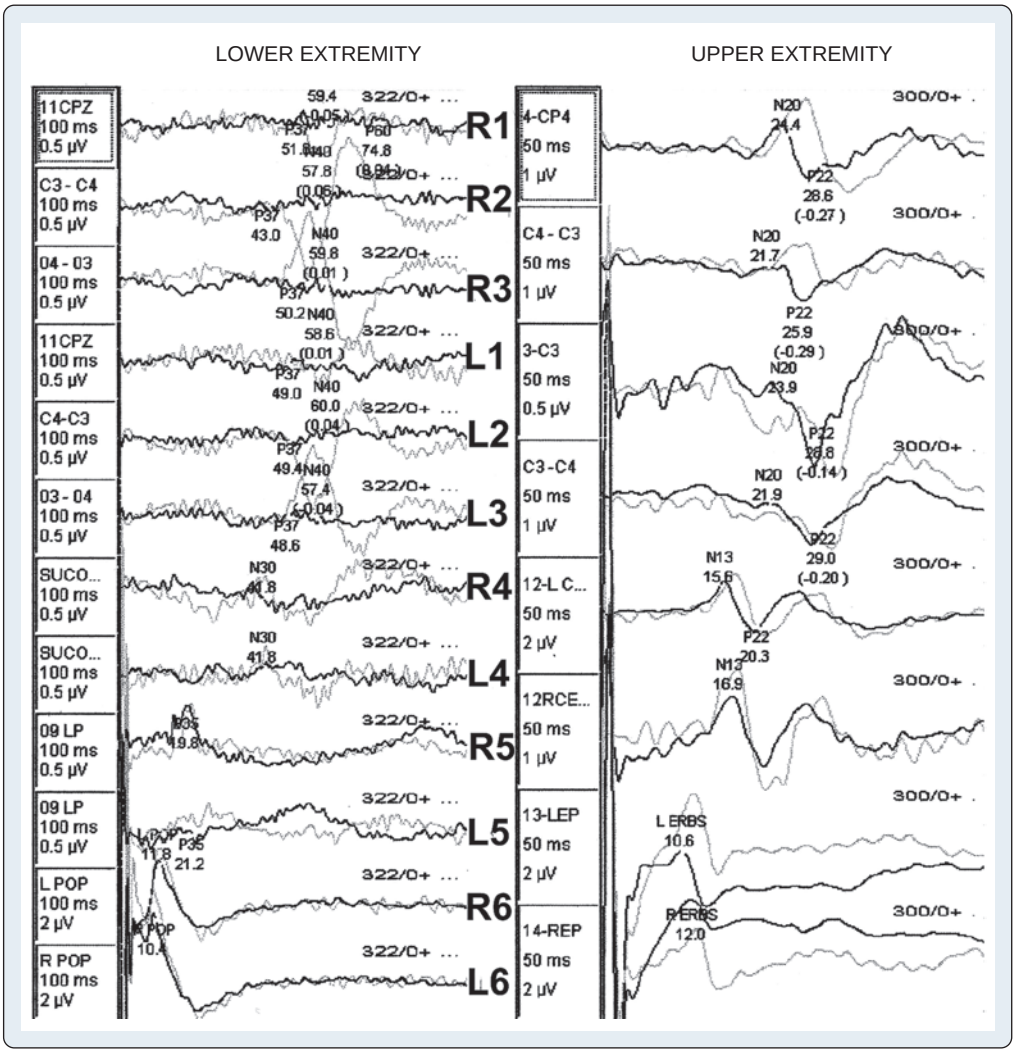


Fig. 23.19 Intraoperative somatosensory-evoked potential (SSEP) recordings from the lower *(left)* and upper *(right)* extremities that demonstrated spinal cord ischemia during thoracoabdominal aortic aneurysm repair. Disappearance of SSEP signals from the right *(R)* and left *(L)* lower extremities recorded at the cortex *(R1, R2, R3, L1, L2, L3)* and spine *(R4, L4)* with preservation of SSEP signals from the lumbar plexus (R5, L5) and popliteal nerves *(R6, L6)* indicated the acute onset of spinal cord ischemia. Upper extremity SSEP signals were maintained during the episode. The *light gray tracings* were the baseline SSEP signals used for comparison.

brainstem, thalamus, and cerebral cortex.[137] Because SSEP monitors posterior spinal column integrity, MEPs have been advocated because they monitor the anterior spinal columns that are typically at risk during TAAA repair. MEP monitoring is performed by applying paired stimuli to the scalp and recording the evoked potential that is generated in the anterior tibialis muscle.[138,139] Paraplegia caused by spinal cord ischemia significantly dampens lower extremity evoked potentials as compared with the upper extremity (Fig. 23.19). Intraoperative comparison of upper and lower extremity evoked potentials distinguishes spinal cord ischemia from the generalized effects of anesthetics, hypothermia, and/or electrical interference (see Chapter 18). As discussed earlier, the anesthetic must be designed for minimal interference with the selected neuromonitoring strategy. Although SSEPs can reliably exclude spinal cord ischemia with a negative predictive value of 99.2%, their sensitivity for its detection is only 62.5%, with no clinically useful predictive value for delayed-onset paraplegia.[140] A recent study (N = 233) compared both MEPs and SSEPs for spinal cord monitoring in extensive descending thoracic and TAAA repairs.[141] Both monitoring modalities had a nearly 90% correlation for spinal cord infarction (correlation statistic = 0.896; $P < 0.0001$), as well as a 98% negative predictive value for immediate-onset paraplegia. Furthermore, reversible changes in MEPs and SSEPs had no correlation with permanent paraplegia. In summary, despite the theoretic advantages of MEPs for monitoring the at-risk anterior spinal columns, in practice, data suggest that SSEPs alone suffice for clinical purposes, and that MEPs did not add significantly to clinical management.[141] This assessment also is reflected in the neuromonitoring recommendations of the latest thoracic aortic disease guidelines[2] (see Chapter 18).

Spinal Cord Hypothermia

Although DHCA is effective, moderate systemic hypothermia is also reasonable for spinal cord protection during TAAA repair (class IIa recommendation; level of evidence B).[2] Furthermore, topical spinal cord hypothermia is possible with cold saline epidural infusion to avoid ischemia during TAAA repair.[142,143] Although clinical experience with this technique has been limited to a few institutions, it has demonstrated clinical benefit as part of a multimodal spinal protection protocol.[127,142,143] Epidural cooling is recommended as an adjunctive technique for spinal cord protection during major distal thoracic aortic reconstructions (class IIb recommendation; level of evidence B).[2] This

technique may disseminate further, given its adjunctive benefit and the recent clinical development of a specialized countercurrent closed-lumen epidural catheter for epidural cooling during major distal aortic reconstructions.[144]

Pharmacologic Protection of the Spinal Cord

Pharmacologic spinal cord protection with agents such as high-dose systemic glucocorticoids, mannitol, intrathecal papaverine, and anesthetic agents is recommended as an adjunctive technique in a multimodal neuroprotective protocol (class IIb recommendation; level of evidence B).[2,127] Additional neuroprotective agents that have been studied in this regard include lidocaine, naloxone, and magnesium.[127,145,146] Although there are multiple agents with potential benefit, only a few are utilized routinely in clinical practice.[145]

Renal Protection During Thoracoabdominal Aortic Aneurysm Repair

Even though there has been major progress in TAAA repair, renal dysfunction remains common and still independently predicts adverse clinical outcomes.[93,147,148] The thoracic aortic guidelines recommend preoperative hydration and intraoperative mannitol administration as reasonable nephroprotective strategies in extensive distal open thoracic aortic repairs, including TAAA repair (class IIb recommendation; level of evidence C).[2] Furthermore, intraoperative cold renal perfusion with blood or crystalloid is recommended as a reasonable intraoperative nephroprotective strategy during TAAA repair (class IIb recommendation; level of evidence C).[2,149,150] The administration of furosemide, mannitol, or dopamine for the sole purpose of renal preservation is not recommended in distal thoracic aortic repairs (class IIb recommendation; level of evidence B).[2] Rhabdomyolysis from lower extremity ischemia has also been identified as a mechanism for renal dysfunction after TAAA repair.[151–153] The maintenance of lower extremity perfusion bilaterally during distal aortic perfusion has been shown to ameliorate this rhabdomyolysis with a significant nephroprotective effect.[151–153] Although these multimodal contemporary nephroprotective strategies have reduced renal complications after TAAA repair, further research is required to enhance renal preservation because renal failure remains a challenge, especially in extent II and III TAAA procedures.[154]

Postoperative Analgesia After Thoracoabdominal Aortic Aneurysm Repair

It is well recognized that the extensive thoracoabdominal incision is very painful. Because epidural analgesia has proven outcome utility in this type of extensive incision, it typically is part of the analgesic plan after TAAA repair.[155] The timing of epidural catheter placement and analgesia must take into account the perioperative anticoagulation status of the patient to minimize the risk for neuraxial hematoma.[13] Furthermore, the epidural analgesia regimen should be formulated for a predominantly sensory block to allow serial motor assessment of the lower extremities and to minimize systemic vasodilation from a sympathectomy. For example, bupivacaine (0.05%), combined with fentanyl (2 µg/mL), can be initiated at a basal rate of 4 to 8 mL/hour after the patient exhibits normal neurologic function.[122] Bolus administration of concentrated local anesthetic through the epidural catheter should be discouraged to avoid sympathetic blockade and associated hypotension. The epidural catheter can be inserted before surgery, at the time of surgery, or in the postoperative period.

Anesthetic Management for Thoracic Endovascular Aortic Repair

TEVAR has revolutionized the management of descending thoracic and TAAAs with significant clinical outcome benefit.[33,114,156] The anesthetic management is based on the principles of care for patients undergoing endovascular abdominal aortic repair, but with the additional concerns of spinal cord ischemia and stroke.[157,158] Typically, these patients undergo a balanced general anesthetic with invasive blood pressure monitoring and central venous access. Some centers have successfully performed these endovascular procedures using a local or regional anesthetic technique.[159] However, it is important to differentiate neuraxial blockade effects from the effects of spinal cord ischemia. The right radial artery is preferred for blood pressure monitoring, given that the left subclavian artery frequently may be covered and/or the left brachial artery may be accessed as part of the procedure.[99–102] PAC monitoring may be helpful in the setting of significant cardiac disease. TEE is reasonable in TEVAR in which it may assist in hemodynamic monitoring, procedural guidance, and endoleak detection (class IIa recommendation; level of evidence B).[2] As discussed earlier, if spinal cord monitoring is planned (SSEPs and/or MEPs), the anesthetic technique must be designed not to interfere with their signal quality (see Chapter 18).[160] The risk factors for stroke after TEVAR include a history of prior stroke, mobile aortic arch atheroma, and TEVAR of the proximal or entire descending thoracic aorta.[157,161] Therefore the detection of mobile atheroma in the aortic arch is an important TEE finding in TEVAR because it predicts a greater stroke risk. The risk factors for spinal cord ischemia after TEVAR include perioperative hypotension (decreased SCPP), prior abdominal/descending thoracic aortic procedures (compromised spinal collateral arterial network), and coverage of the entire descending thoracic aorta (significant loss of intercostal arteries).[157,162] Consequently, indications for CSF lumbar drainage in TEVAR include planned extensive coverage of the descending thoracic aorta, history of prior abdominal/descending thoracic aortic procedures, and postoperative paraparesis/paraplegia despite relative hypertension.[157,162] Lumbar CSF drainage is a strongly recommended for spinal cord protection strategy for TEVAR in patients with identified risk factors (class I recommendation; level of evidence B).[2,157–162]

Aortic Dissection

Aortic dissection results from an intimal tear that exposes the media to the pulsatile force of blood within the aortic lumen (Fig. 23.20).[2,163] Blood may exit the true aortic lumen and dissect the aortic wall to create a false lumen. The aortic dissection may remain localized at the primary entry site at the original intimal tear, or it may extend proximally, distally, or both. It also may extend into the aortic branch vessels to cause branch occlusion, or the intimal layer may shear at the site of branch vessels to result in intimal fenestrations. Propagation of the dissection into the aortic root can cause AR.[2,4] The weakened

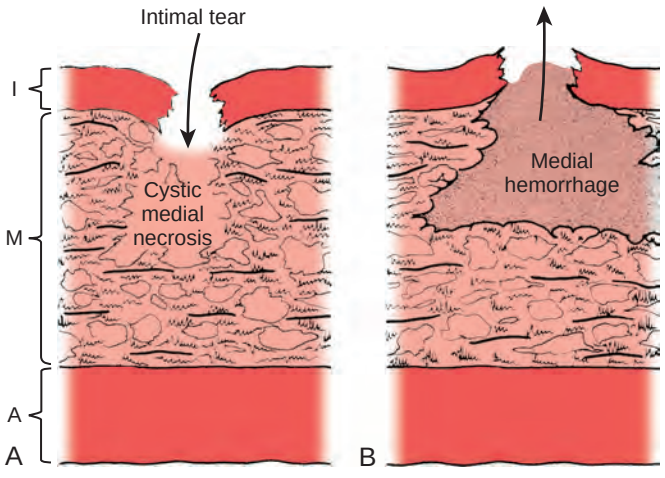


Fig. 23.20 A potential mechanism for aortic dissection is cystic medial necrosis with an intimal tear allowing blood from the aortic lumen to enter the medial layer of the aorta *(M)*, leading to separation of the intima *(I)* from the adventitia *(A)*. *(From Eagle KA, De Sanctis RW. Diseases of the aorta. In: Braunwald E, ed.* Heart disease *[4th ed]. Philadelphia; Saunders; 1992:1528.)*

BOX 23.11 CLASSIFICATION OF ACUTE AORTIC DISSECTION

DeBakey Classification

- Type I: The entire aorta is involved (ascending, arch, and descending)
- Type II: Confined to the ascending aorta
- Type III: Intimal tear originating in the descending aorta with either distal or retrograde extension
- Type IIIA: Intimal tear originating in the descending aorta with extension distally to the diaphragm or proximally into the aortic arch
- Type IIIB: Intimal tear originating in the descending aorta with extension below the diaphragm or proximally into the aortic arch

Stanford Classification

- Type A: Involvement of the ascending aorta and/or aortic arch regardless of the site of origin or distal extent
- Type B: Confined to the descending aorta distal to the origin of the left subclavian artery

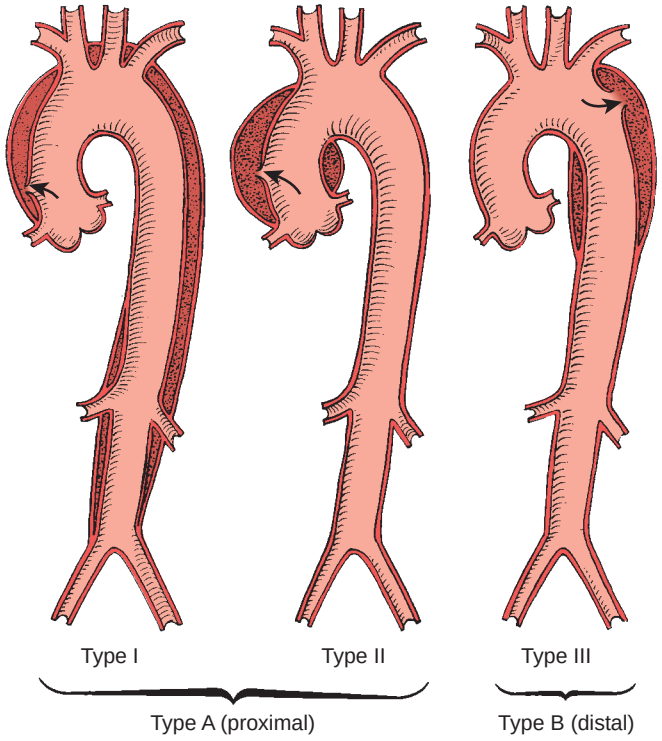


Fig. 23.21 DeBakey classification of aortic dissections. Type I: intimal tear in the ascending aorta with extension of the dissection to the descending aorta. Type II: ascending intimal tear with dissection limited to the ascending aorta. Type III: intimal tear in the descending aorta with proximal extension of the dissection to involve the ascending aorta. Type IIIB: intimal tear in the descending aorta with dissection limited to the descending aorta. *(Reprinted by permission from Excerpta Medica, Inc. From Larson EW, Edwards WD. Risk factors for aortic dissection: A necropsy study of 161 cases.* Am J Cardiol. *1984;53:849.)*

aortic wall often results in acute aortic dilation, which can progress to rupture resulting in pericardial tamponade, exsanguination, or both.

There are two generally accepted classifications of thoracic aortic dissections (Box 23.11).[2,164] The DeBakey scheme classifies aortic dissections into three groups (Fig. 23.21; Videos 23.1 to 23.5). DeBakey type I dissections originate from a primary entry site in the ascending aorta and extend to involve the entire aorta. DeBakey type II dissections originate from a primary entry site in the ascending aorta and are confined to the ascending aorta. DeBakey type III dissections originate from a primary entry site in the descending thoracic aorta and are confined to the descending thoracic aorta distal to the origin of the left subclavian artery. DeBakey type III dissections also can be subdivided into subtype IIIA that are confined to the descending thoracic aorta above the diaphragm and subtype IIIB that extend below the diaphragm into the abdominal aorta. The Stanford scheme classifies aortic dissections into two groups (Fig. 23.22).[165] Stanford type A dissections are aortic dissections that involve the ascending aorta regardless of extent, origin, or entry sites. Stanford type B dissections are confined to the descending thoracic aorta distal to the origin of the left subclavian artery regardless of the extent or entry sites (see Videos 23.1 and 23.2).

BOX 23.12 POTENTIAL COMPLICATIONS OF ACUTE TYPE A AORTIC DISSECTION

- Cardiac tamponade
- Aortic regurgitation
- Myocardial infarction
- Stroke
- Limb ischemia
- Mesenteric ischemia

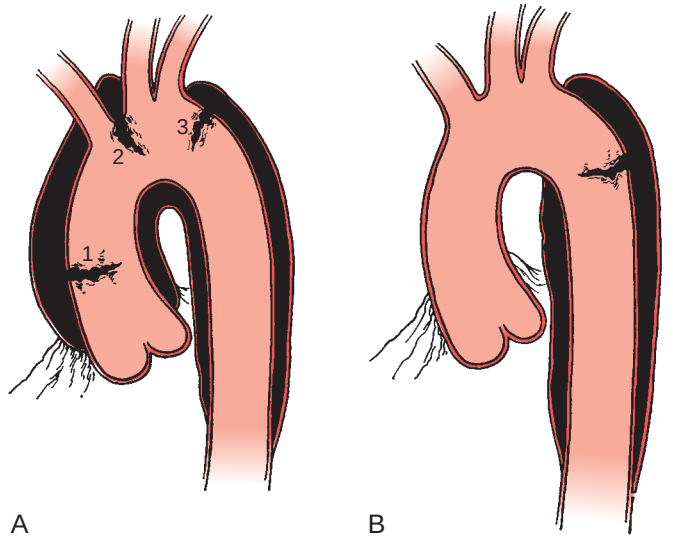


Fig. 23.22 Stanford classification of aortic dissection. In type A aortic dissection, the ascending aorta is dissected regardless of the location or number of intimal tears (A). In type B aortic dissection, the dissection is limited to the descending aorta (B) distal to the origin of the left subclavian artery. *(Reproduced with permission from The Society of Thoracic Surgeons. From Daily PO, Trueblood HW, Stinson EB, et al. Management of acute aortic dissections.* Ann Thorac Surg. *1970;10:237–247.)*

Type A Aortic Dissection

Aortic dissections that involve the ascending aorta (Stanford type A) are considered surgical emergencies (Box 23.12) (class I recommendation; level of evidence B).[2] The mortality rate without emergency surgery is about 1% per hour for the first 48 hours, 60% by about 1 week, 74% by 2 weeks, and 91% by 6 months (Fig. 23.23).[2,163,166] Immediate surgical intervention significantly improves the mortality rate (Table 23.7), especially in patients younger than 80 years.[2,163–167] The principal causes of mortality include rupture, cardiac tamponade, myocardial ischemia from coronary dissection, severe acute AR,

stroke caused by brachiocephalic dissection, and malperfusion syndromes including renal failure, ischemic bowel, and limb ischemia (Table 23.8).[168] An aortic dissection less than 2 weeks old is classified as acute and older than 2 weeks is classified as chronic.[169] This distinction is clinically important because after 2 weeks, mortality risk has plateaued and thus emergency surgery is not necessarily indicated. Although this time-based classification has prevailed, a recent registry analysis demonstrated four distinct time periods as follows: hyperacute (symptom onset to 24 hours), acute (2–7 days), subacute (8–30 days), and chronic (greater than 30 days).[169] Survival was progressively compromised through these four time periods in the presentation of acute type A dissection.[169] The type of preoperative presentation in type A dissection also significantly determines operative mortality, prompting a clinical classification developed at the University of Pennsylvania (Penn classification; Table 23.9).[170] The Penn classification for describing localized or generalized ischemia has been shown to serve as a useful risk assessment tool for predicting mortality, with class Abc (branch vessel malperfusion and circulatory collapse) carrying the highest mortality risk.[171–173]

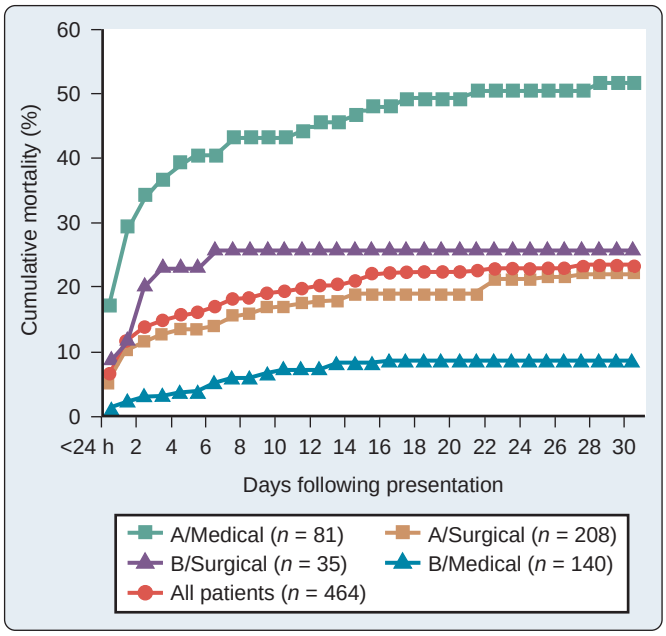


Fig. 23.23 Thirty-day mortality in 464 patients from the International Registry of Aortic Dissection (IRAD) stratified by medical and surgical treatment in both type A and type B aortic dissection. *(From Nienaber CA, Eagle KA. Aortic dissection: New frontiers in diagnosis and management. Part I: From etiology to diagnostic strategies.* Circulation. *2003;108:631.)*

TABLE 23.7 Mortality in Acute Aortic Dissection According to Dissection Type and Management

Dissection Type	*N*	*Hospital Mortality (%)*
Stanford Type A	289	101 (34.9%)
Medical management	81	47 (58%)
Surgical management	208	54 (26%)
Stanford Type B	175	26 (14.9%)
Medical management	140	15 (10.7%)
Surgical management	35	11 (31.4%)

Data from Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA.* 2000;283:897.

TABLE 23.8 Complications of Acute Stanford Type A Aortic Dissection (n = 513)

Complications	*Percentage*
All neurologic defects	18.0
Coma/altered consciousness	14.0
Myocardial ischemia/infarction	10.0
Limb ischemia	10.0
Mesenteric ischemia/infarction	4.0
Acute renal failure	6.2
Hypotension	26.0
Cardiac tamponade	17.0
Mortality	30.0

Data from Bossone E, Rampoldi V, Nienaber CA, et al. Usefulness of pulse deficit to predict in-hospital complications and mortality in patients with acute type A aortic dissection. *Am J Cardiol.* 2002;89:85.

Type B Aortic Dissection

Aortic dissections confined to the descending thoracic aorta (Stanford type B) should be managed medically unless there are life-threatening complications present such as malperfusion and aortic rupture, as well as severe pain and/or hypertension despite aggressive medical therapy (class I recommendation; level of evidence B).[2,163] Mortality with medical management in this type of aortic dissection is significantly lower than perioperative mortality (see Table 23.7).[2,163,166,174] The greater operative mortality is due to the severe complications of type B aortic dissection and the operation itself. TEVAR for the therapy of complicated acute type B dissection is highly recommended (STS guideline: class I recommendation; level of evidence A).[2,33] Similar to the newest clinical classification scheme for type A dissection, a Penn classification for type B dissection has also been introduced to distinguish complicated and uncomplicated presentations (Table 23.10).[175]

Aortic Intramural Hematoma

Aortic intramural hematoma (IMH) is a variant of the classic aortic dissection (Box 23.13).[2,163,166,176] IMH has no intimal flap with no obvious intimal tear on aortic imaging. This class of intimal tear accounts for about 17% of all dissections, with a 30-day mortality rate of 24%: 36% in type A IMH, and 12% with type B IMH ($P < 0.05$).[177] Surgical management of type A IMH reduces mortality rate by 61.1% (14% vs 36%; $P = 0.02$). Medical management for type B IMH reduced mortality fourfold (8% vs 33%; $P < 0.05$).[177] Surgical indications in type A IMH include ascending aortic diameter larger than 50 mm or IMH thickness more than 12 mm. Surgical indications in type B IMH include rapid progression, rupture, or severe clinical symptoms despite aggressive medical therapy.[1,3] It is, therefore, reasonable to

TABLE 23.9 Penn Classification of Ischemic Presentations in Acute Stanford Type A Aortic Dissection

Type A Dissection Presentation	*Definition*	*Mortality Rate*
Penn presentation a (Type Aa)	Type A dissection with **a**bsence of ischemia	3.1%
Penn presentation b (Type Ab)	Type A dissection with **b**ranch vessel malperfusion producing clinical organ ischemia (eg, stroke, renal failure, ischemic extremity, mesenteric ischemia)	25.6%
Penn presentation c (Type Ac)	Type A dissection with **c**irculatory collapse (systolic blood pressure <80 mm Hg and/or vasopressor therapy) with or without cardiac involvement	17.6%
Penn presentation b + c (Type Abc)	Types Ab and Ac together	40%

Data from Augoustides JG, Geirsson A, Szeto W, et al. Observational study of mortality risk stratification by ischemic presentation in patients with acute type A aortic dissection: the Penn classification. *Nat Clin Pract Cardiovasc Med.* 2009;6:140.

TABLE 23.10 Penn Classification of Ischemic Presentations in Acute Stanford Type B Aortic Dissection

Type B Dissection Presentation	*Definition*
Class A (uncomplicated)	Absence of branch-vessel ischemia or circulatory compromise Type I high risk for future aortic complications Type II low risk for future aortic complications
Class B (complicated)	Branch-vessel malperfusion with visceral, renal, lower-extremity, and/or spinal cord hypoperfusion based on clinical and/or laboratory and/or radiographic evidence.
Class C (complicated)	Circulatory compromise Type I aortic rupture with hemorrhage outside the aortic wall with/without cardiac arrest, shock, and hemothorax Type II threatened aortic rupture typically heralded by refractory pain and/or hypertension
Class BC (complicated)	Branch-vessel malperfusion combined with circulatory compromise

Data from Augoustides JG, Szeto WY, Woo EY, et al: The complications of uncomplicated acute type-B dissection: the introduction of the Penn classification. *J Cardiothorac Vasc Anesth.* 2012;26:1139–1144.

BOX 23.13 AORTIC INTRAMURAL HEMATOMA

Diagnostic Criteria

- Crescent-shaped or circumferential thickening of aortic wall
- Hematoma thickness >7 mm
- No dissection flap
- No intimal tear
- No blood flow within hematoma

Risk Factors for Mortality or Progression

- Ascending aorta or arch involvement (type A)
- Aortic diameter >45 mm
- Hematoma thickness >11 mm

manage IMH similar to classic aortic dissection in the corresponding thoracic aortic segment (class IIa recommendation; level of evidence C).[2] Although IMH may be caused by rupture of the vas vasorum in the aortic wall without intimal hematoma, there are frequently small intimal tears that are beyond the resolution of current aortic scanners and are only identifiable on close aortic inspection during surgery or autopsy.[2,170,177–179]

Clinical Diagnosis and Imaging Studies for Aortic Dissection

Aortic dissection is more common in men and has a peak incidence in later life.[2,163,166] It often has an earlier onset in the setting of Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, bicuspid aortic valve, aortic coarctation, and familial aortic dissection.[2,4,163,166] It also is commonly associated with hypertension but less so with atherosclerosis.[29] Further predisposing factors include pregnancy, cocaine abuse, arteritis, aortic trauma, and aortic instrumentation.[2,4,180]

The pain of aortic dissection typically is severe, abrupt in onset, and has a ripping, tearing, or stabbing quality (class I recommendation; level of evidence B).[2] Highly suggestive physical findings include a pulse deficit, a systolic blood pressure limb differential greater than 20 mm Hg, focal neurologic deficit, and a new murmur of AR (class I recommendation; level of evidence B).[2,4] Electrocardiogram (class I recommendation; level of evidence B), along with urgent and definitive aortic imaging (TEE, CT, MRI), is strongly recommended in suspected aortic dissection (class I recommendation; level of evidence B).[2,5] A negative chest radiograph should not delay aortic imaging, especially in patients suspected of presenting with aortic dissection

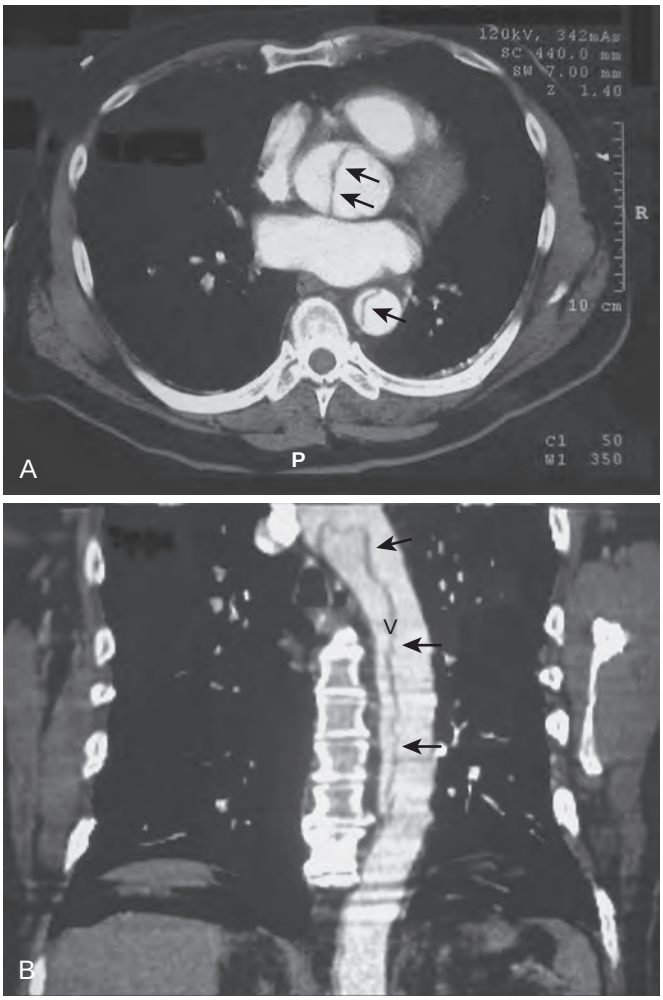


Fig. 23.24 Computed tomographic angiogram in a patient with a type A aortic dissection. Axial images of the chest (A) demonstrated an intimal flap that extended from the ascending aorta *(double arrows)* into the descending thoracic aorta *(single arrow)*. Sagittal reconstruction (B) demonstrated the presence of an intimal flap in the descending thoracic aorta *(single arrows)*.

(class I recommendation; level of evidence B).[2,4] The selection of an aortic imaging modality should be guided by patient and institutional variables, including immediate test availability (class I recommendation; level of evidence C).[2,4] If initial aortic imaging is negative in the setting of high clinical suspicion for dissection, a second imaging study should be arranged (class I recommendation; level of evidence C).[2,38]

The most common imaging study is contrast-enhanced spiral CT or CTA because it is widely available.[181] Typical findings in acute aortic dissection include an intimal flap, luminal displacement of intimal calcifications, and aortic dilation (Fig. 23.24).[163,166,169] IMH appears as a crescent-shaped high-attenuation thickening of the aortic wall in noncontrast CT (Fig. 23.25).[163,166] CT can demonstrate rupture, branch-vessel involvement, and false lumen extent. Although MRI has a near 100% sensitivity and specificity and is widely available, it also takes significantly longer than CT (Fig. 23.26).[2,38,163,166,169]

At experienced centers, TEE provides high-resolution aortic images with comparable sensitivity and specificity to MRI and CT.[2,163,166,182] Furthermore, TEE can look for complications by interrogating the aortic valve (AR severity and mechanism), assessing ventricular function including regional wall motion for coronary dissection, and diagnosing cardiac tamponade and pericardial effusion. Aortic dissection appears on TEE examination as an undulating intimal flap within the aorta separating a true and false lumen (Fig. 23.27). It is sometimes

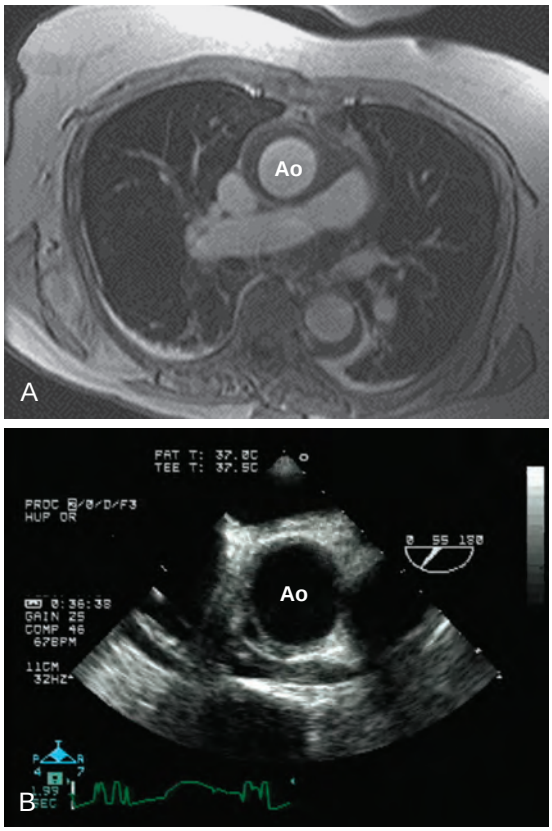


Fig. 23.25 Computed tomographic angiogram of the chest (A) and transesophageal echocardiographic upper esophageal short-axis images of the aorta (B) demonstrating an aortic intramural hematoma that extended from the ascending aorta into the descending thoracic aorta. A crescent-shaped or circumferential thickening of the aortic wall is diagnostic for aortic intramural hematoma. *Ao*, Aorta.

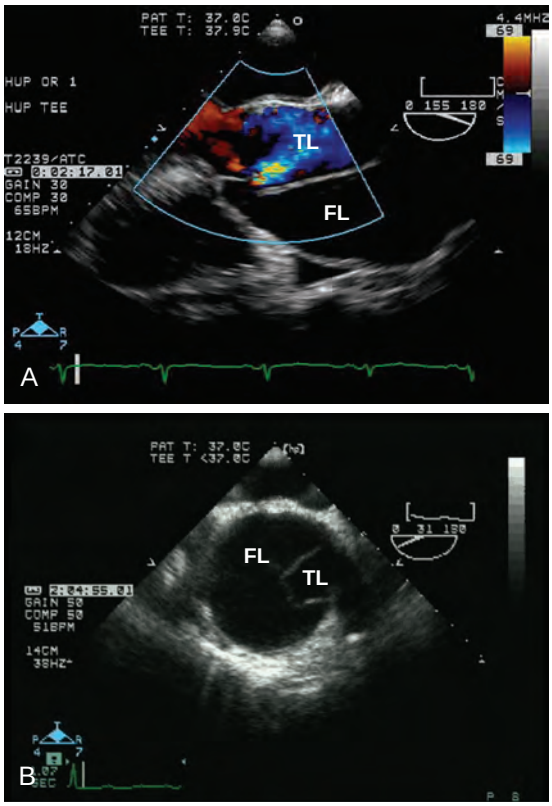


Fig. 23.27 Transesophageal echocardiographic midesophageal long-axis image of the aortic valve (A) and short-axis image of the ascending aorta (B) in a patient with a type A aortic dissection. An intimal flap separating the true lumen *(TL)* of the aorta with the false lumen *(FL)* was demonstrated in the aortic root and ascending aorta. Extension of the dissection into the aortic root may cause aortic regurgitation or coronary insufficiency.

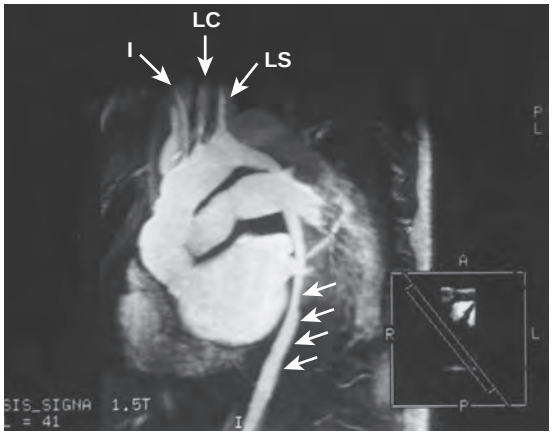


Fig. 23.26 Magnetic resonance imaging of the chest with gadolinium contrast injection in a patient with a type A aortic dissection. The dissection extended into the innominate artery *(I)*, left carotid artery *(LC)*, left subclavian artery *(LS)*, and into the descending aorta *(arrows)*.

difficult to distinguish the true lumen from the false lumen, but the true lumen tends to be smaller with pulsatile high-velocity flow in systole.[38] Doppler color-flow imaging can detect flow communication between the true and false lumens at intimal tear sites. The use of 3D-TEE can also be valuable in determining the size of the entry tear, as well as the relationship to nearby structures.[38] Aortic IMH appears as an echo-dense crescent-shaped thickening (>7 mm) of the aortic wall that may contain echolucent pockets of noncommunicating blood (see Fig. 23.25). TEE also may distinguish clinical mimickers of aortic dissection and can assess the thoracic aortic anatomy in detail to guide surgical decision making.[183,184]

Anesthetic Management for Aortic Dissection

Acute aortic dissection is a medical emergency. Initial medical management is directed at treatment of pain and decreasing the arterial pressure with antihypertensive agents. Vasodilator therapy should be initiated to decrease wall stress with control of heart rate and blood pressure (class I recommendation; level of evidence C).[2,4] In the presence of acute AR, β-blockers should be used with caution because they block the compensatory tachycardia (class I recommendation; level of evidence C).[2] In the absence of contraindications, β-blockers should be titrated to a heart rate of 60 beats/minute (class I recommendation; level of evidence C).[2] Esmolol is a particularly useful β-blocker because it has a short pharmacologic half-life and can be rapidly titrated. Esmolol can be administered as an initial bolus of 5 to 25 mg intravenously, followed by a continuous infusion of 25 to 300 μg/kg per minute. In patients with β-blocker contraindications, heart rate control should be gained with titration of nondihydropyridine calcium channel blockers such as verapamil or diltiazem (class I recommendation; level of evidence C).[2] Alternatively, labetalol, a drug that has a 1:7 ratio of β-blocker to α-blocker activity, can be administered as a 20 to 80 mg intravenous bolus followed by an infusion at 0.5 to 2.0 mg/minute. Metoprolol, a cardioselective β-blocker, may be advantageous in patients with reactive airway disease who are sensitive to β-adrenergic antagonists. Metoprolol is administered at a dose of 5

to 15 mg intravenously every 4 to 6 hours. If the systolic blood pressure remains greater than 120 mm Hg with adequate heart rate control, then vasodilators (e.g., nitroprusside at a dosage of 0.5 to 2.0 μg/kg per minute or nicardipine at a dose of 1 to 15 mg/hour) should be titrated for further reductions of blood pressure while still maintaining adequate vital organ perfusion (class I recommendation; level of evidence C).[2] Vasodilator therapy should not be initiated before heart rate control to avoid the associated reflex tachycardia that might aggravate the aortic dissection (class III recommendation; level of evidence C).[2]

In general, the anesthetic management of type A aortic dissection resembles the management of ascending aortic aneurysms that require DHCA. The anesthetic management of type B aortic dissections resembles the management of TAAA repair. Large-bore intravenous catheters are essential for intravenous medications and rapid volume expansion. A radial arterial catheter for invasive blood pressure monitoring is preferred over a femoral artery catheter to allow for CPB cannulation, depending on surgeon preference. If a pulse deficit is detected, the site for arterial pressure monitoring should be chosen to best represent the central aortic pressure. A central venous or PAC to monitor CVP, pulmonary artery pressure, and cardiac output is useful. TEE insertion is performed after anesthetic induction, and it can be used to verify the diagnosis (class IIa recommendation; level of evidence B).[3,182]

Critically unstable patients should be resuscitated by standard ACC/AHA guidelines or by securing the airway, providing mechanical ventilation, and administering drugs to support the circulation. Emergent TEE should follow to verify the diagnosis of type A aortic dissection and to detect cardiac tamponade, hypovolemia, AR, and/or heart failure.[185] If TEE detects cardiac tamponade, immediate sternotomy with preparations to institute CPB via femoral artery cannulation should be performed. Opening the pericardium and relief of cardiac tamponade can be followed by hypertension causing aortic rupture.

The induction of general anesthesia in hemodynamically stable patients with aortic dissection should proceed in a cautious manner. The dose of intravenous antihypertensive drugs may need to be reduced at the time of anesthetic induction to prevent severe hypotension when combined with anesthetic drugs. Hypotension may also occur on anesthetic induction in response to the attenuation of sympathetic nervous system tone or decreased cardiac preload caused by venodilation and positive pressure ventilation in patients with preexisting concentric left ventricular hypertrophy. The hypertensive response to endotracheal intubation, TEE probe insertion, and sternotomy should be anticipated and attenuated with narcotic analgesics.

Surgical Treatment of Stanford Type A Aortic Dissection

Surgical repair for type A aortic dissection requires resection of the proximal extent of the dissection. A partially dissected aortic root may be repaired with aortic valve resuspension.[186] A destroyed aortic root must be replaced with a composite graft or a valve-sparing root replacement.[3,4] In the setting of a DeBakey type II dissection, the entire dissected aorta merits replacement. CABG sometimes is necessary for aortic dissections that involve the coronary ostia.

Although femoral arterial cannulation is popular for CPB, recent evidence suggests that it is associated with adverse clinical outcomes including death, stroke, and malperfusion syndromes.[187,188] Cannulation of the distal ascending aorta or the axillary artery (ideally with an end-to-end graft) has been associated with significantly enhanced clinical outcome as compared with standard femoral arterial cannulation.[187,188] When central cannulation through dissected aorta is chosen, TEE is mandatory to verify initial wire placement in the true lumen (Fig. 23.28).[189] It remains important to monitor cerebral perfusion throughout the operative procedure for detection and correction of acute malperfusion.[75–77] The use of selective cerebral perfusion techniques with circulatory arrest is reasonable to complete arch reconstructions to reduce neurologic complications (class IIa recommendation; level of evidence B).[3]

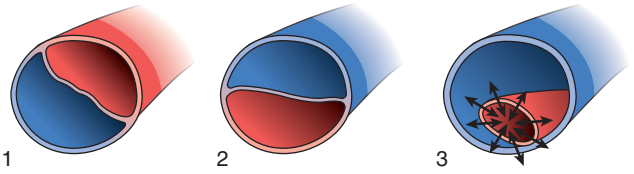


Fig. 23.28 Depiction of the increasing levels of difficulty in direct cannulation of the ascending aorta in acute type A aortic dissection, depending on the location of the true lumen. Level 1 has an anteriorly positioned true lumen, whereas Level 2 includes those patients with a posteriorly positioned true lumen. Level 3 involves cases where there is a near circumferential dissection and essentially a free-floating true lumen. Intraoperative TEE is imperative in verifying wire placement in the correct lumen prior to cannulation. *(From Frederick JR, Wang E, Trubelja A, et al. Ascending aortic cannulation in acute type A dissection repair.* Ann Thorac Surg. *2013;95:1808–1811.)*

In DeBakey type I dissections, the dissected descending thoracic aorta often undergoes aneurysmal degeneration and is responsible for significant aorta-related mortality in the long term.[190] Consequently, long-term outcomes after extensive type A dissection would be significantly improved if this distal aortic degeneration could be prevented.[190,191] Recent clinical series have demonstrated the efficacy and safety of anterograde stenting of the descending thoracic aorta during open aortic arch repair for DeBakey type 1 aortic dissection.[192–194] This technique is also known as the endovascular stented elephant-trunk technique or the frozen elephant-trunk technique.[195] The long-term aneurysmal degeneration of the descending thoracic aorta is prevented by immediate stenting in the acute dissection phase; thus, favorable long-term aortic remodeling is facilitated.

Integrated Management of Stanford Type B Aortic Dissection

Uncomplicated type B aortic dissection currently has the best clinical outcome when managed medically.[33,196] Medical therapy for type B aortic dissection is directed at control of systemic hypertension to prevent aortic aneurysm formation, aortic rupture, and extension of the aortic aneurysm (class I recommendation; level of evidence C).[2] Combination therapy with a diuretic, β-blocker, angiotensin-converting enzyme inhibitor, or other antihypertensive agents usually is necessary to achieve and maintain blood pressure less than 130/80 mm Hg. All patients after repair of type A aortic dissection also should be managed aggressively with antihypertensive therapy because many are left with a residual distal aortic dissection after repair. Serial imaging of the aorta is necessary to detect expansion of the aortic lumen and aneurysm development that may warrant surgical correction.

In the presence of life-threatening complications, TEVAR has emerged as a preferred alternative therapy to surgery.[33,114,196–199] A landmark randomized trial demonstrated that, in the short term, TEVAR added no survival advantage over medical management for uncomplicated type B aortic dissection.[200] However, because TEVAR did improve aortic remodeling in this trial, further adequately powered trials are indicated to test whether this translates into better aortic outcomes.[201] Malperfusion syndromes associated with type B dissection also can be managed with intimal fenestration.[202,203]

Penetrating Atherosclerotic Ulcer

Penetrating atherosclerotic ulcer describes an isolated disruption of the intimal layer of the aortic wall at the site of atheromatous disease (Fig. 23.29).[2,4] This class of intimal tear may occur at any aortic locus but is most common in the descending thoracic aorta. It typically is associated with severe aortic atheroma in the elderly and penetrates through to the aortic adventitia.[2,4] Penetrating atherosclerotic ulcers may be associated with IMH or pseudoaneurysm, and they have been shown to progress to aneurysm in 27.8% and rupture in 4.1% of

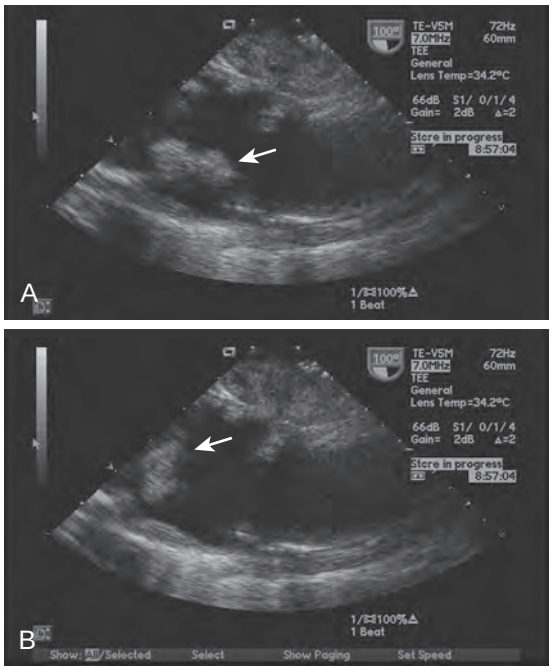


Fig. 23.29 Transesophageal echocardiographic (TEE) long-axis images of the descending thoracic aorta demonstrating severe atherosclerotic disease with atheroma protruding into the vessel lumen. Images obtained in diastole (A) and in systole (B) demonstrated a large mobile atheroma *(arrow)* that may represent an atheromatous plaque that has ruptured and detached from the aortic wall.

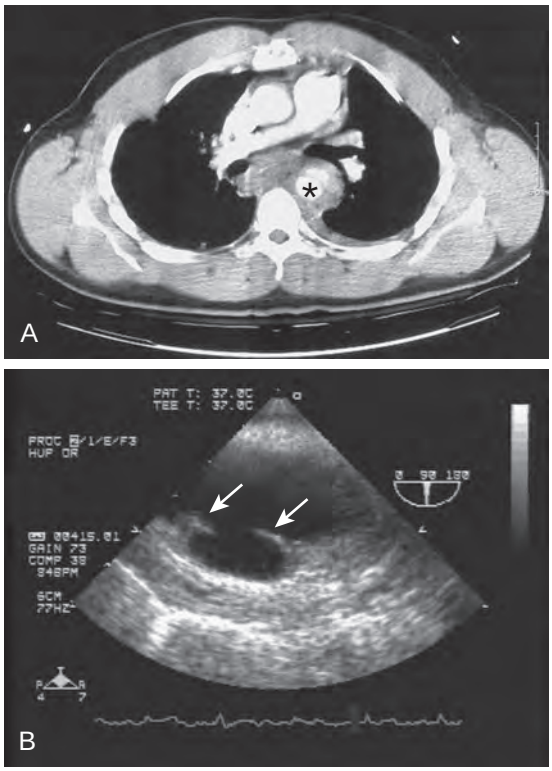


Fig. 23.30 Computed tomographic angiogram of the chest (A) in a trauma patient who presented with a widened mediastinum on the chest roentgenogram demonstrating traumatic intimal disruption of the aorta in the region of the aortic isthmus *(asterisk)*. Perivascular hematoma and extravasation of contrast agent into the mediastinum and left pleural cavity indicated a rupture of the descending aorta. Intraoperative transesophageal echocardiographic (TEE) long-axis image of the proximal descending thoracic aorta (B) demonstrated a thick mural flap *(arrows)* and surrounding hematoma at the site of the intimal disruption.

patients.[204–206] Initial symptoms include chest and back pain similar to aortic dissection.[2] Diagnosis typically is made with contrast-enhanced CT.[207,208] Although patients may be managed medically, TEVAR has emerged as a major management strategy, especially in severely symptomatic or complicated presentations (class IIa recommendation; level of evidence C).[33,209,210] Furthermore, in asymptomatic presentations of this intimal syndrome, TEVAR currently is not recommended (class IIa recommendation; level of evidence C).[33]

Traumatic Aortic Injury

The most common cause of traumatic aortic injury is blunt chest trauma or rapid deceleration injuries associated with motor vehicle accidents or falls. Although this injury may be fatal, the majority of patients have injuries in the region of the aortic isthmus.[211] Patients with traumatic aortic injury commonly will have associated significant injuries. TEE is helpful in the management of traumatic aortic injury because it is portable, is often available in the OR, provides a rapid diagnosis, and does not require aortic instrumentation or radiographic contrast injection. TEE also can detect cardiac tamponade, left pleural effusion, hypovolemia, ventricular dysfunction from myocardial contusion, or vascular injuries from penetrating chest wounds.[212] Its disadvantages include limited imaging in the setting of facial injuries, suspected cervical spine injuries, and lesions in the distal ascending aorta. The characteristic features of traumatic aortic injury detected by TEE are a mural flap at the site of intimal disruption and regional deformities of the aortic wall caused by the contained rupture (Fig. 23.30). The mural flap commonly is limited to a 1- to 2-cm aortic segment located at the aortic isthmus just distal to the origin of the left subclavian artery. This mural flap usually is thick compared with the intimal flap seen in aortic dissection and is less mobile because it usually contains several layers of the vessel wall. Contrast-enhanced CT is frequently selected for aortic imaging because these patients typically require CT scanning as part of their initial diagnostic evaluation.[213,214]

TABLE 23.11 Incidence of Postoperative Paraplegia after Surgical Repair of Traumatic Aortic Injury in Relation to Operative Technique

Operative Technique	*No. of Patients*	*Paraplegia (%)*
Clamp and sew	73	16.4[ab]
Bypass (distal aortic perfusion)	134	4.5[a]
Gott shunt	4	0
Full bypass	22	4.5
Partial bypass	39	7.7
Centrifugal pump	69	2.9[b]

[a]$P < 0.004$, bypass vs clamp and sew; [b]$P < 0.01$, centrifugal pump vs clamp and sew.
Data from Fabian TC, Richardson JD, Croce MA, et al. Prospective study of blunt aortic injury: multicenter trial of the American Association for the Surgery of Trauma. J Trauma. 1997;42:374–380.

Injuries to the ascending aorta or aortic arch typically require CPB with DHCA for repair. Injuries to the aortic isthmus can be repaired via a left thoracotomy. The descending thoracic aorta usually is repaired with an interposition graft with the aid of PLHB. The risk for perioperative spinal cord ischemia is minimal when distal aortic perfusion is provided (Table 23.11) because only a short segment of the thoracic aorta is replaced. Although open repair is possible, TEVAR has emerged as the preferred intervention whenever possible because of the well-documented outcome advantages (STS class I recommendation; level of evidence B).[33,213–217]

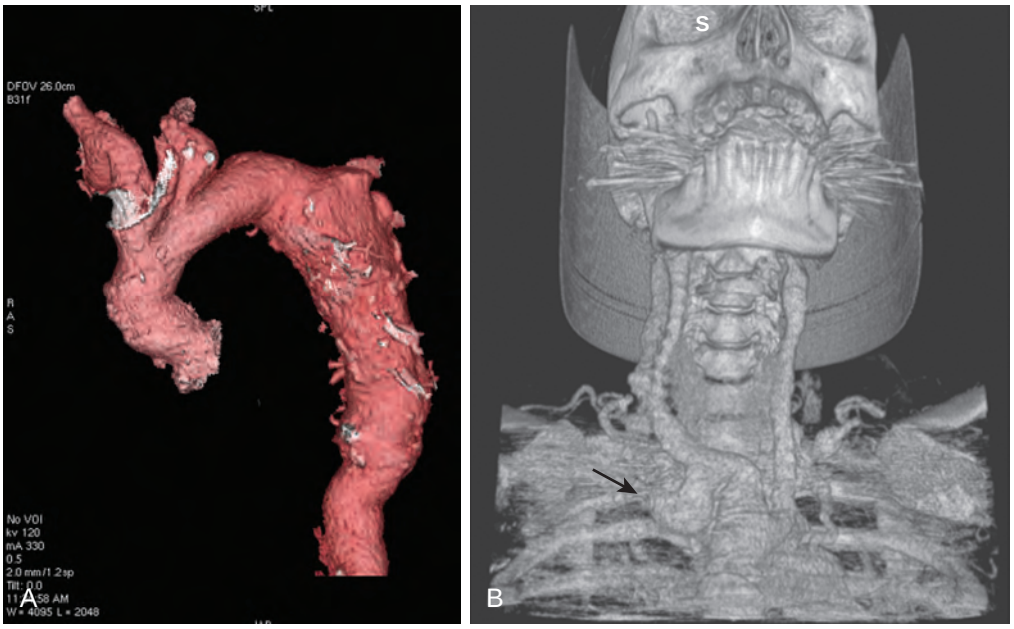


Fig. 23.31 Three-dimensional reconstruction from a computed tomographic angiogram of the aorta (A) and aortic arch branch vessels (B) from a patient with Takayasu arteritis. The reconstructions demonstrated aneurysmal dilation of the descending thoracic aorta, proximal innominate artery, and both subclavian arteries. The left and right *(arrow)* subclavian arteries were occluded distal to the aneurysm.

Aortic Atheromatous Disease

Severe aortic atheroma is a major risk factor for stroke.[2,33] Thoracic aortic replacement is indicated for serious embolism and to facilitate the conduct of concomitant cardiac procedures that require the safe cross-clamping of the aorta (see Fig. 23.29). The anesthetic management of patients undergoing thoracic aortic reconstruction for atheromatous disease resembles the management of thoracic aortic aneurysms for corresponding aortic segments. Intraoperative epiaortic ultrasound imaging is superior to manual palpation or TEE for thoracic aortic atheroma.[218,219] The epiaortic ultrasound is important for selecting the optimal site for aortic cannulation for CPB or placement of the aortic cross-clamp to minimize atheroembolic events such as stroke.[218–220]

Takayasu Arteritis

Takayasu arteritis is a chronic vasculitis that affects primarily the thoracic aorta, its branches, and even the pulmonary artery (Fig. 23.31).[2,4] Takayasu arteritis occurs most frequently in young Asian women and occurs worldwide.[221] Its onset is insidious with the gradual development of vascular insufficiency. Dilation and aneurysm formation also may occur in diseased aortic segments. Diagnostic criteria include onset of disease at age younger than 40 years, claudication of the extremities, decreased brachial pulses, a systolic blood pressure differential of 10 mm Hg between the arms, subclavian or abdominal aortic bruits, and angiographic demonstration of narrowing of the aorta and/or its primary branches.[2,4]

Initial therapy consists of high-dose corticosteroids (class I recommendation; level of evidence B).[2,4] Elective revascularization should be postponed until the acute inflammatory state has been adequately treated (class I recommendation; level of evidence B).[2,4] Once revascularization is feasible, an endovascular approach is a good option that has been shown to have a high success rate with improved quality of life.[222] Anesthetic management of Takayasu arteritis is complicated by limited sites for arterial blood pressure measurement. The femoral artery may be the only site for accurate measurement of central aortic pressure in patients with stenosis of both subclavian arteries.

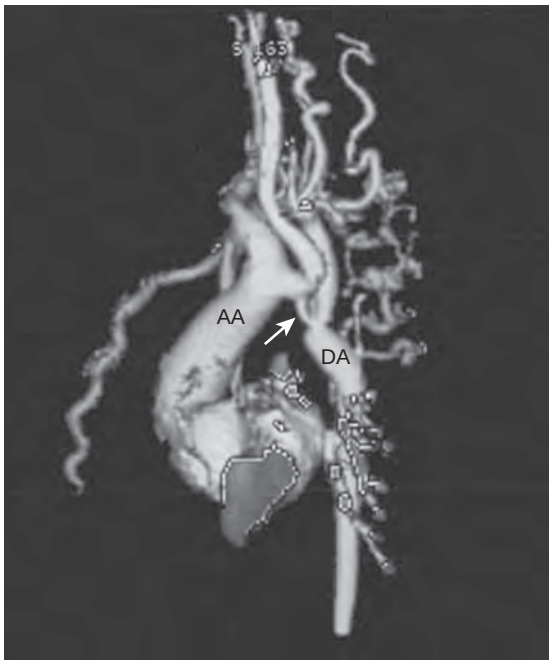


Fig. 23.32 Three-dimensional reconstruction from a computed tomographic angiogram of a patient with aortic coarctation. In this patient, the site of coarctation was located between the left carotid and left subclavian arteries *(arrow)*. Repair was performed by construction of an extra-anatomic bypass graft between the ascending *(AA)* and descending *(DA)* thoracic aorta.

Aortic Coarctation

Aortic coarctation is a common malformation that ranges from a discrete narrowing of the aorta to a long hypoplastic segment of the vessel to complete discontinuity of the aorta (Fig. 23.32).[223] The site of coarctation can be variable but is typically juxtaductal in location, affecting

the proximal descending thoracic aorta just distal to the origin of the left subclavian artery. The distal descending aorta often is hypoplastic in severe cases. Conditions associated with aortic coarctation include Turner syndrome, bicuspid aortic valve, ventricular septal defect, patent ductus arteriosus, and intracerebral aneurysm.[2,223]

Adults with coarctation may present with headache, epistaxis, heart failure, or lower extremity claudication. Its typical hemodynamic profile is upper extremity hypertension combined with lower extremity hypotension and weak pulses. If the origin of the left subclavian artery is distal to the coarctation, blood pressure in the left arm may also be diminished. The chest radiograph often shows rib notching caused by the enlarged intercostal arteries that serve as collateral vessels to supply the lower body. The electrocardiogram often shows left ventricular hypertrophy. The diagnosis is confirmed by definitive aortic imaging.[38] Cardiac catheterization, MRI, and echocardiography are useful to detect associated cardiac abnormalities.

Balloon angioplasty with stenting is the preferred treatment when coarctation is limited to a discrete segment of the aorta.[223–225] Although sedation often will suffice for the procedure, general anesthesia may be required when dilation of the coarctation is expected to be painful or when it is necessary to keep the patient immobile for the procedure. Complications of balloon angioplasty have included residual stenosis, recoarctation, paracoarctation aortic dissection or rupture, aortic aneurysm, and injury to the femoral artery. Aortic dissection or aneurysm at or near the angioplasty site may be a consequence of mechanical damage to the aortic wall or congenital defects of the aortic wall.

Operative repair in adults may involve interposition graft repair or extraanatomic bypass grafting from the proximal aorta or left subclavian artery to the descending aorta.[226] Extraanatomic bypass is advantageous for reoperations or in adults when the distal aortic arch cannot be mobilized to perform an end-to-end anastomosis. Avoiding surgical dissection in the region of the distal aortic arch also decreases the risk for injury to the recurrent laryngeal and phrenic nerves. Although perioperative mortality is low, spinal cord ischemia is possible during repair if collateral circulation is inadequate or if distal aortic perfusion pressure is too low. Preventive strategies include intraoperative monitoring of distal aortic perfusion pressure, neuromonitoring with SSEPs and/or MEPs, deliberate hypothermia, and distal aortic perfusion with PLHB.[227] Postoperative hypertension after repair may require aggressive monitoring and management.

Illustrative Transesophageal Echocardiography Cases

Case Study 1: Thoracic Aortic Atheroma

A 78-year-old man with diabetes and hypertension presents for CABG for triple-vessel disease. He has severe peripheral vascular disease. After induction of general anesthesia, a TEE is performed.

Framing

Because this patient has advanced atherosclerosis with multiple risk factors, it is likely that his thoracic aorta will have extensive atheromatous disease. Thoracic aortic atheroma is a major risk factor for stroke, especially in the setting of intraoperative aortic manipulation and instrumentation. What is the surgical plan in this case: Is this CABG on-pump or off-pump? If there is significant aortic atheroma, then the ascending aortic manipulation associated with aortic cannulation and cross-clamping for on-pump CABG would likely be associated with significant atheroembolism and a significant stroke risk. The cardiac surgeon requests an assessment of the atheroma burden in the thoracic aorta to guide the conduct of the CABG.

Questions

What is the extent of the thoracic aortic atheroma? Which aortic segments are involved? What is the severity of the aortic atheroma? Is there severe atheroma with a high embolic risk in the thoracic aortic segment involved in the planned procedure? In this case of planned CABG, the ascending aorta is the aortic segment of interest.

Data Collection

Severe thoracic aortic atheroma is characterized by atheroma protrusion larger than 5 mm into the aortic lumen or mobile atheroma, or both. Severe protruding and mobile atheroma, as depicted in Figs. 23.33 to 23.37, disseminated throughout the descending thoracic aorta and aortic arch, make it likely that the ascending aorta also is involved with severe atheroma because advanced atheroma is a disseminated arterial process. The detection of severe thoracic aortic atheroma by TEE, therefore, represents a major opportunity to modify surgical decision making to minimize stroke risk in the setting of heavy aortic atheroma burden.

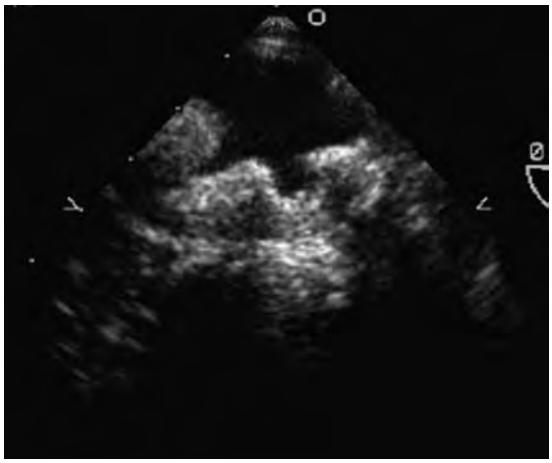


Fig. 23.33 Short-axis view of the descending thoracic aorta. There is severe aortic atheroma greater than 5 mm in diameter. This large atheroma is sessile and does not appear to have any mobile components. There are no associated complications of aneurysm or dissection apparent on this view. This severe aortic atheroma predicts severe atheroma in the aortic arch and ascending aorta, as well as a high perioperative stroke risk associated with surgical aortic manipulation.

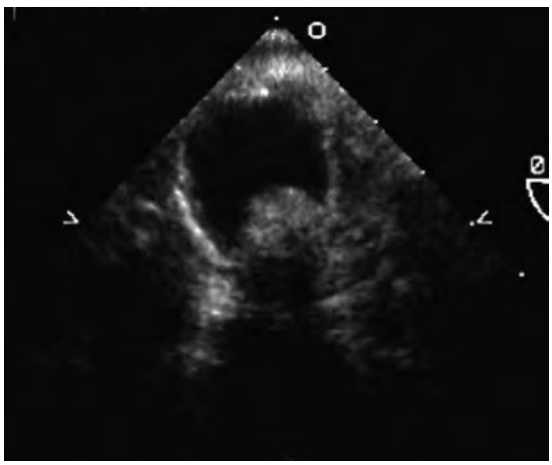


Fig. 23.34 Short-axis view of the descending thoracic aorta. In this aortic segment, there is also severe sessile aortic atheroma with a diameter greater than 5 mm. Notice the variation in morphology as compared with another descending thoracic aortic segment, as in Fig. 23.33. When severe atheroma is detected, it is important to comprehensively evaluate the entire thoracic aorta as in this patient. Multiple thoracic aortic views demonstrate severe aortic atheroma. It is clear that this patient has a severe atheroma burden based not only on the severity but also on the extent.

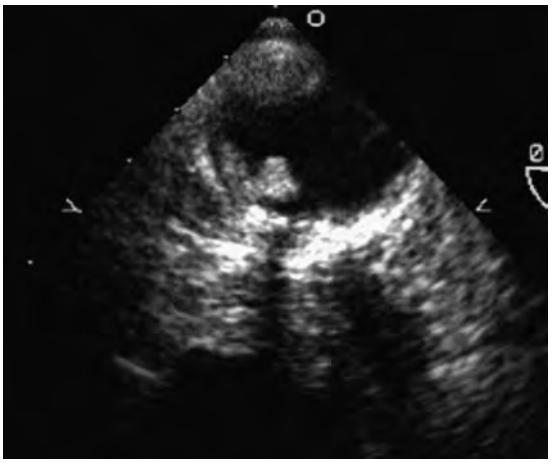


Fig. 23.35 Short-axis view of the descending thoracic aorta. Again, there is severe aortic atheroma with variations in morphology. There is a pedunculated mobile atheroma that is at high risk for embolism downstream in the aorta. Taken together, Figs. 23.33 through 23.35 show that this patient has a heavy atheroma burden throughout his descending thoracic aorta. Because atheroma is seldom a selective disease process, this atheroma burden is likely in the ascending aorta and aortic arch.

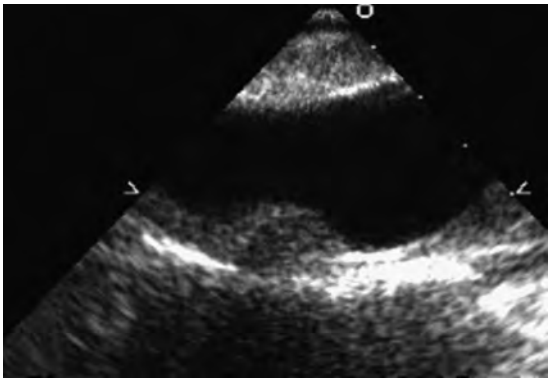


Fig. 23.36 Long-axis view of the aortic arch. There is severe focal sessile aortic atheroma evident in this view. Notice that there is relative sparing of the surrounding intima. There is no evidence of penetrating atheromatous ulceration with associated aneurysm or intramural hematoma. This severe atheromatous disease present in the aortic arch is in keeping with the atheroma burden in the descending thoracic aorta. This patient has a high perioperative stroke risk that focuses attention on the conduct of the coronary artery surgery to minimize this risk.

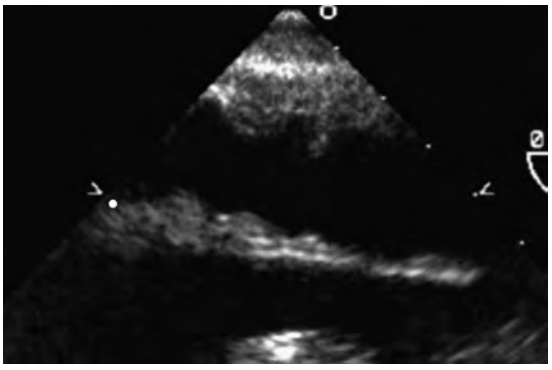


Fig. 23.37 Long-axis view of the aortic arch. There is severe aortic atheroma not only because of a thickness greater than 5 mm but also because of the presence of a mobile pedunculated atheroma. These features further highlight the heavy atheroma burden of the aortic arch and the high stroke risk in this patient associated with on-pump coronary artery bypass grafting.

Discussion

In this CABG scenario, there are at least three broad options for minimizing aortic atheroembolism and stroke:

1. Guided by epiaortic scanning, manipulate the least-diseased ascending aortic segments and proceed with on-pump CABG.
2. Avoid ascending aortic manipulation and proceed with off-pump CABG with a no-touch aortic technique.
3. Cannulate the axillary artery for CPB and replace the severely diseased ascending aorta and proximal arch under DHCA. This would not only minimize the long-term stroke risk because of massive proximal aortic atheroma burden, but would allow completion of the CABG on-pump with minimal risk for cerebral atheroembolism.

In this case, after extensive discussion with the cardiac surgeon, the joint decision was to proceed with off-pump CABG, given the high likelihood of severe ascending aortic disease and the considerable experience of the surgeon with this off-pump CABG technique.

Severe aortic arch and descending thoracic aortic atheroma also are major risk factors for stroke after TEVAR, especially with lesions of the proximal descending thoracic aorta that necessitate hardware manipulation in the aortic arch with the associated risk for arch atheromatous cerebral embolism. This principle also is applicable to the stroke risk associated with transfemoral transcatheter aortic valve implantation in which the hardware has to cross retrograde across the aortic arch to reach the aortic valve. In this scenario, the detection of severe mobile atheroma provides a strong rationale to proceed with transapical aortic valve implantation because the hardware would not cross the aortic arch.

Severe atheroma of the aortic arch and distal thoracic aorta is an important factor in procedures such as acute type A dissection in which femoral arterial cannulation commonly is performed for arterial access required for bypass. This cannulation strategy would carry a significant retrograde cerebral atheroembolic risk. The presence of severe atheroma, as demonstrated by TEE, provides a strong rationale to proceed with antegrade arterial flow via cannulation of the axillary artery. Furthermore, the atheroma burden of this patient also provides a strong rationale to avoid intraaortic balloon counterpulsation. In summary, the assessment of thoracic aortic atheroma (extent, severity, embolic risk) should be related to the operative plan to minimize the risks for vital organ atheroembolism.

Case Study 2: Acute Thoracic Aortic Dissection

A 45-year-old man with known Marfan syndrome presents to the emergency department with severe acute tearing back pain. Physical signs suggestive of acute aortic dissection include a pulse deficit, severe jugular venous distention, and a new precordial murmur. His chest radiograph shows a widened mediastinum, and his electrocardiogram is consistent with sinus tachycardia with no acute ischemia. Because of severe hemodynamic instability, he is transferred emergently to the OR before definitive aortic imaging can be undertaken. After his resuscitation and anesthetic induction, a TEE is performed.

Framing

Because this patient has multiple highly suggestive features, there is a high pre-TEE probability of acute thoracic aortic dissection. Time matters here because the mortality rate is about 1% to 2% per hour. The diagnosis needs to be confirmed. The dissection extent should be characterized to guide definitive management. The known complications of acute aortic dissection should be assessed. The TEE examination serves multiple purposes including establishing the diagnosis, characterizing the full extent of the disease process, providing the data to guide operative decision making, and assessing the results of the surgical repair. The cardiac surgeon requests a comprehensive echocardiographic assessment to guide surgical management of this hemodynamic emergency.

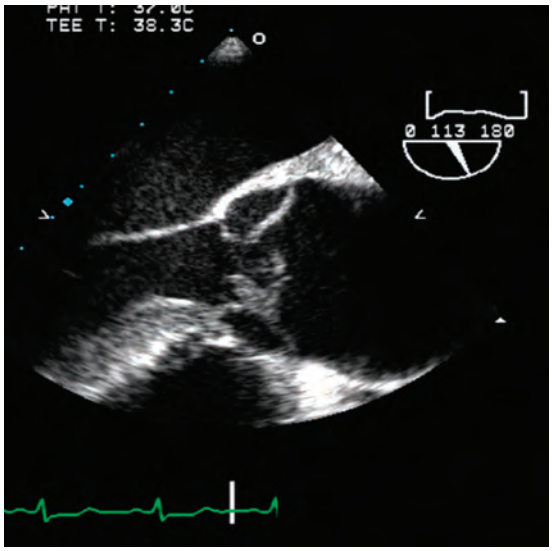


Fig. 23.38 Midesophageal long-axis view of the aortic valve and ascending aorta in systole before cardiopulmonary bypass (at 113 degrees of rotation). There is an intimal dissection flap in the ascending aorta that not only has a large fenestration but is also prolapsing into the left ventricular outflow tract. This view confirms dissection proximal to the left subclavian artery (Stanford type A); thus immediate surgical repair is indicated.

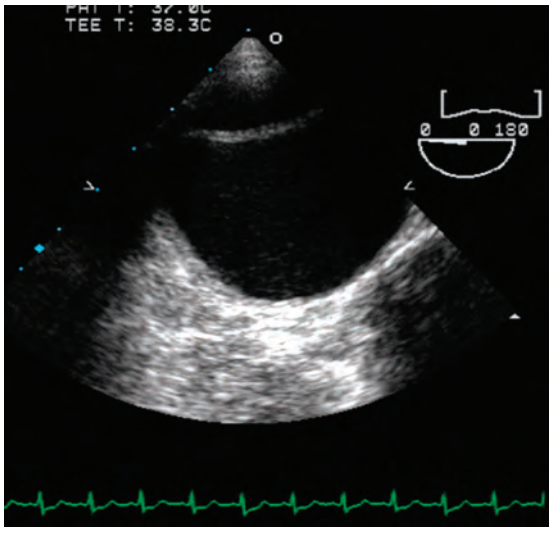


Fig. 23.39 Midesophageal short-axis view of the descending thoracic aorta (at zero degree of rotation). An intimal dissection flap is evident. This view demonstrates that the extent of this type A dissection is compatible with a DeBakey type I aortic dissection. The descending thoracic aortic dissection can be addressed during open aortic arch repair with a thoracic endovascular aortic stent deployed anterograde through the open aortic arch. This is an example of the frozen elephant trunk technique, which is designed to improve long-term aortic remodeling and thus minimize the adverse outcomes associated with aneurysmal degeneration of the dissected descending thoracic aorta.

Questions

Is there an intimal flap compatible with acute aortic dissection? Is it type A or type B aortic dissection? Are there associated complications of the dissection process? Is there a pericardial effusion with tamponade physiology? What is the status of biventricular function? Are there regional wall motion abnormalities compatible with dissection of a major coronary artery? If so, which coronary artery? Is CABG required? Is there AR? If so, what is the severity and mechanism? Can the native aortic valve be resuspended or is aortic valve replacement required? Can the aortic root be spared or is aortic root replacement required? Does the descending thoracic aorta require endovascular stenting?

Data Collection

There is a type A dissection that requires surgical intervention (Figs. 23.38 to 23.43). The aortic root is dilated and dissected. The ascending aorta is dilated and dissected with extension into the aortic arch and descending thoracic aorta (DeBakey I extent) (see Videos 23.3 and 23.4). Severe AR is caused by intimal prolapse and aortic root dilation without native aortic cusp destruction. There are no regional wall motion abnormalities to suggest myocardial ischemia from coronary dissection. There is cardiac tamponade.

Discussion

In the emergency management of acute aortic dissection, the OR can function as a diagnostic suite where TEE is promptly performed after anesthetic induction, endotracheal intubation, and hemodynamic resuscitation. TEE is ideally suited for the fast-track management of this acute aortic syndrome. TEE offers near-100% sensitivity and specificity for the diagnosis and localization of aortic dissection. There are three possibilities in this diagnostic process: (1) surgery for type A dissection or complicated type B dissection; (2) medical therapy for uncomplicated type B dissection; and (3) no acute aortic syndrome present, in which case, further diagnostic workup should proceed to identify and manage the cause.

In this case of type A dissection, the TEE examination not only provides the rationale for immediate surgical intervention but also guides the operative plan. The tense hemopericardium with clinical tamponade was managed with pericardiotomy; the immediate hemodynamic

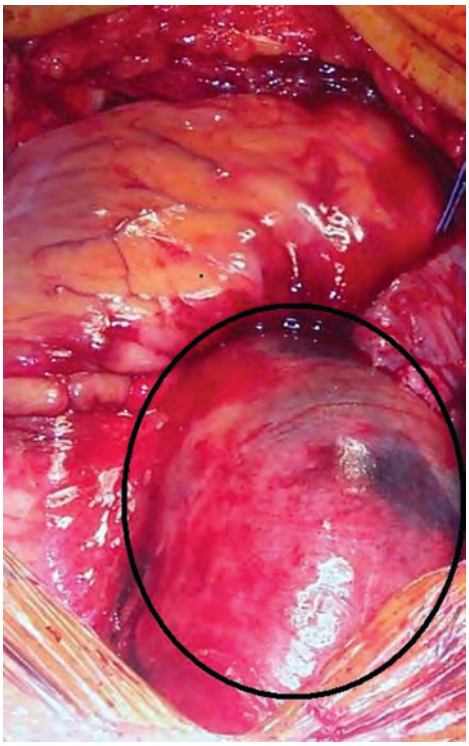


Fig. 23.40 Intraoperative photograph of the ascending aorta after sternotomy and pericardiotomy. The ascending aorta is dissected: The wall is hemorrhagic and in places transparent through the adventitia (area indicated within the *black circle*). Aortic rupture was imminent in this case. The decision to operate emergently and proceed with proximal thoracic aortic replacement on cardiopulmonary bypass with deep hypothermic circulatory arrest was based on the transesophageal echocardiographic findings, as shown in Figs. 23.38 and 23.39.

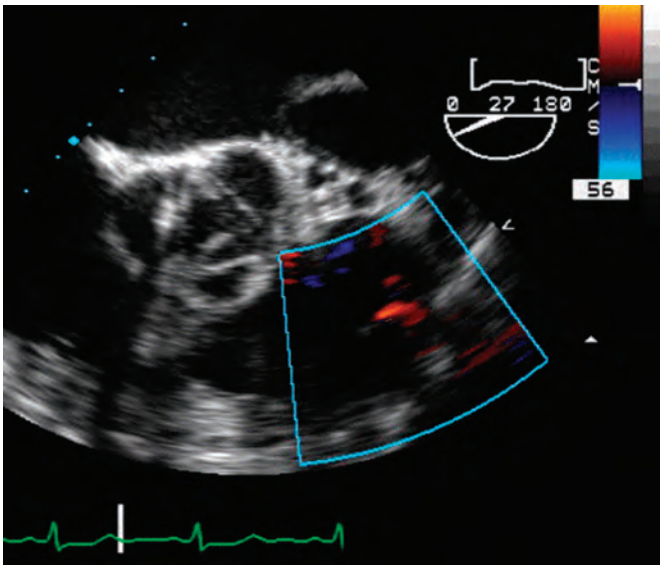


Fig. 23.41 Midesophageal short-axis view of the aortic valve in diastole (at 27 degrees of rotation). The aortic leaflets appear normal. There is prolapse of the intimal dissection flap through the aortic valve, preventing diastolic coaptation and giving the appearance of a "double aortic valve." Severe aortic regurgitation results from this mechanism, as shown in Fig. 23.43. This view also allows for assessment of right ventricular function, in particular, right ventricular hypokinesis caused by ischemia from right coronary dissection. Color-flow Doppler interrogation in this view shows trace pulmonic insufficiency, a common incidental finding. There is also a small pericardial collection evident: This is the residual from the hemopericardium that was drained at pericardiotomy. Before pericardiotomy, the hemopericardium was under tension and had resulted in severe cardiac tamponade.

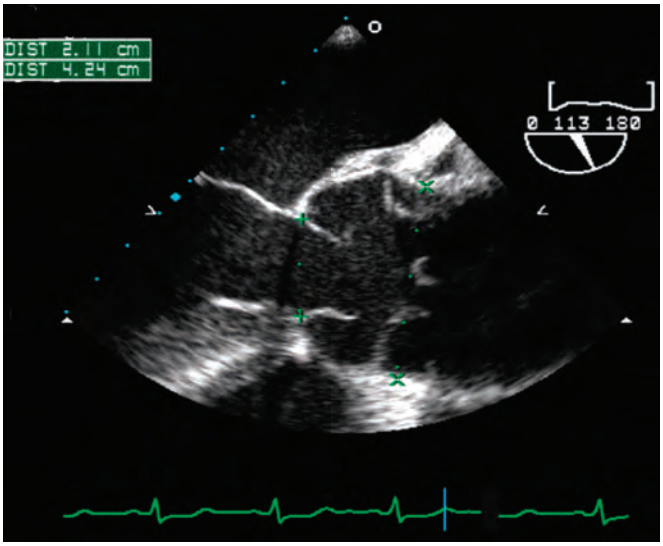


Fig. 23.42 Midesophageal long-axis view of the aortic valve and ascending aorta in systole before cardiopulmonary bypass (at 113 degrees of rotation). An intimal dissection flap in the ascending aorta has a large fenestration. The sinotubular junction is splayed and dilated because of the dissection. This is a second mechanism for aortic regurgitation, as the dilated aortic root will result in diastolic aortic cusp separation. In this case, the intimal flap is also responsible for the severe aortic insufficiency, as shown in Fig. 23.43.

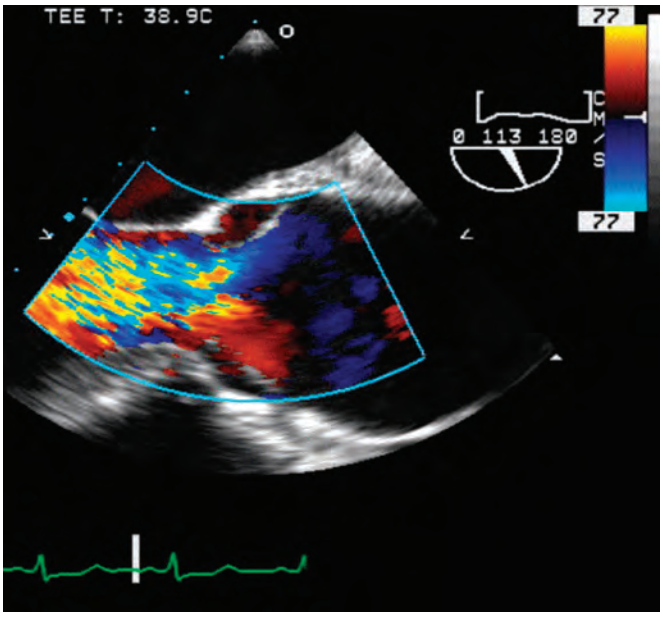


Fig. 23.43 Midesophageal long-axis view of the aortic valve and ascending aorta in systole before cardiopulmonary bypass (at 113 degrees of rotation). Color-flow Doppler interrogation reveals severe aortic regurgitation, as the diastolic jet visualized by color Doppler imaging fills the entire left ventricular outflow tract. The mechanisms of this severe aortic regurgitation, namely, intimal prolapse and aortic root dilation, are more fully explained in Figs. 23.41 and 23.42.

improvement and consequent hypertension were managed immediately to avoid aortic rupture. Because the AR was not related to native aortic cusp destruction, aortic valve resuspension was undertaken. The dissected aortic root was replaced and coronary reimplantation was by means of the button technique. The dissected ascending aorta and aortic arch were replaced. The aortic arch repair was with the hemiarch technique with DHCA. During the open aortic arch anastomosis, the dissected descending thoracic aorta was repaired by means of anterograde deployment of an endovascular stent (frozen elephant-trunk technique). After separation from CPB, TEE demonstrated normal native aortic valve function, normal biventricular function with no regional wall motion abnormalities, and an endovascular stent in the descending thoracic aorta with no flow in the false lumen.

Acute type A dissection is a life-threatening surgical emergency. TEE is a standard of care in this acute aortic syndrome at all stages of its definitive management: prompt diagnosis, detection of complications, conduct of the operative repair, and acute evaluation of surgical results.

Case Study 3: Thoracic Aortic Transection

A 42-year-old woman was involved in a motor vehicle accident. She was an unrestrained driver and sustained a side impact injury with no loss of consciousness. She had no significant medical history. She presented to the emergency department for evaluation. Her physical examination was within normal limits. Her chest radiograph showed a widened mediastinum. Although initially stable, the patient developed shock that was unresponsive to pressors and fluid resuscitation, and so she was emergently transferred to the OR for a diagnostic TEE and possible operative aortic repair. She underwent a TEE after induction of general anesthesia.

Framing

Because this patient likely has an acute aortic syndrome resulting from traumatic aortic transection, it is essential that TEE not only confirm the diagnosis but also fully characterize the aortic lesion. The location and extent of the aortic transection will determine the operative plan.

The cardiac surgeon requests a detailed echocardiographic interrogation of the thoracic aorta to plan the surgical intervention. The surgeon asks whether the incision should be a sternotomy or left thoracotomy.

Clinical Questions

Is there a thoracic aortic transection? If so, what is the extent? Which thoracic aortic segments are involved? Is endovascular aortic repair possible? If not, should the surgeon expose the thoracic aorta via sternotomy or left thoracotomy? What perfusion techniques are required? Is full CPB with DHCA required? Is PLHB required?

Data Collection

The TEE examination confirms thoracic aortic transection localized to the aortic arch with brachiocephalic involvement (Figs. 23.44 to 23.50). The ascending aorta and descending thoracic aorta, including the isthmus, are not involved. In other words, there is no extension either proximal or distal to the aortic arch. This transection and associated IMH involve most of the aortic arch. There is contained rupture of the aortic arch.

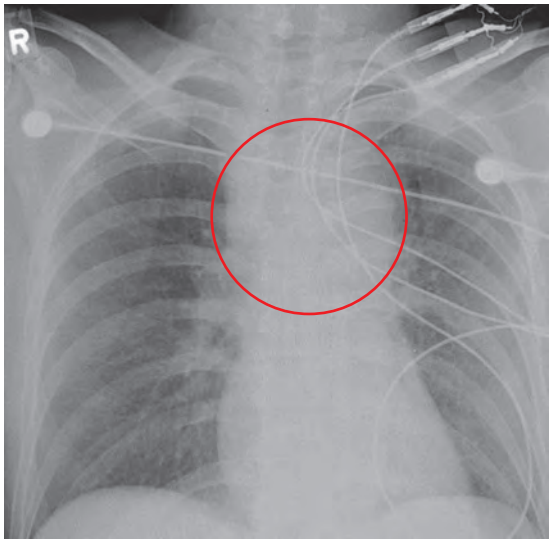


Fig. 23.44 Chest radiograph taken on hospital admission. Note the widened mediastinum (area enclosed by the *red circle*). This finding is suggestive of a thoracic aortic syndrome. Although a chest radiograph may be suggestive, it is important to remember that a normal chest radiograph does not reliably rule out major thoracic aortic pathology.

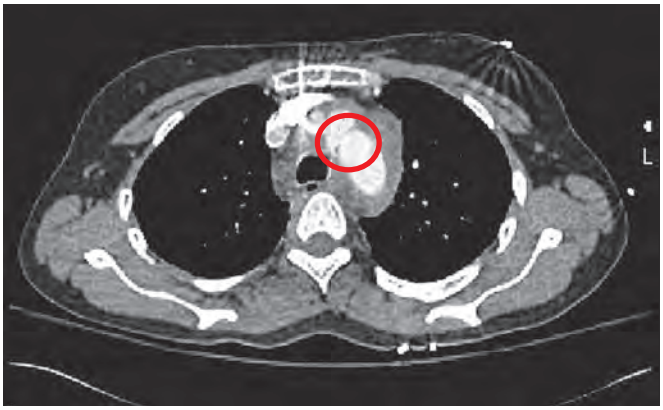


Fig. 23.45 Computed tomographic scan of the thoracic aorta done soon after hospital admission. The aortic arch is *circled in red*. This aortic arch view shows aortic arch disruption compatible with a transection, given the history of a recent automobile accident.

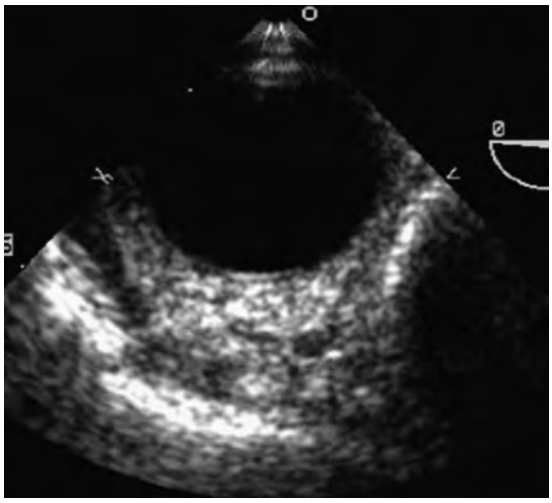


Fig. 23.46 Upper esophageal transesophageal echocardiographic short-axis view of the distal ascending aorta (at zero degree of rotation). No intimal flap is compatible with dissection. However, there is extensive anterior intramural hematoma.

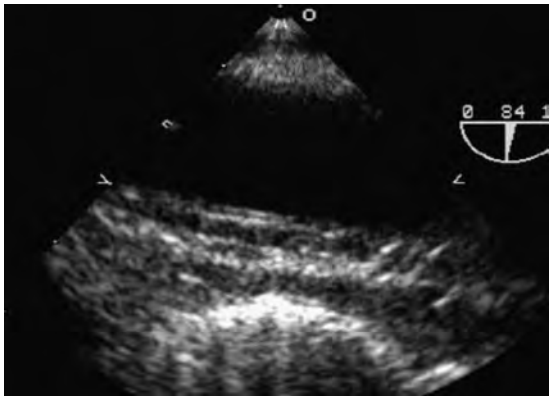


Fig. 23.47 Upper esophageal transesophageal echocardiographic (TEE) long-axis view of the midaortic arch (at 84 degrees of rotation). There is no intimal flap compatible with dissection. There is extensive anterior intramural hematoma, as evidenced by the extensive anterior aortic wall thickening.

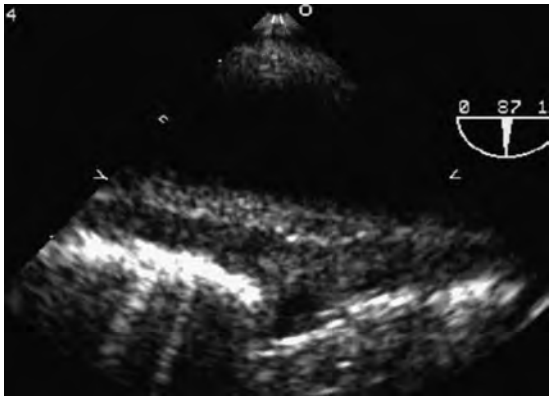


Fig. 23.48 Upper esophageal transesophageal echocardiographic (TEE) long-axis view of the midaortic arch (at 87 degrees of rotation). There is extensive anterior intramural hematoma with a break in the aortic wall, compatible with a significant near-full thickness tear in the aortic arch. This view is diagnostic of focal traumatic transection of the aortic arch.

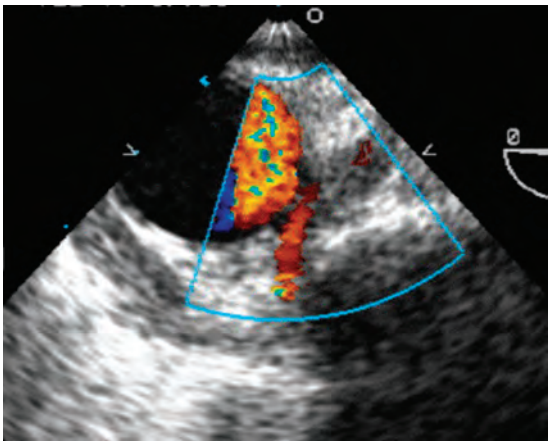


Fig. 23.49 Upper esophageal transesophageal echocardiographic (TEE) short-axis view of the distal aortic arch (at zero degree of rotation). Color-flow Doppler interrogation in this view shows flow into the site of the arch transection. This flow is still contained by periaortic hematoma evident at this aortic level. The next step in the evolution of this pathology is free aortic rupture, a lethal event.

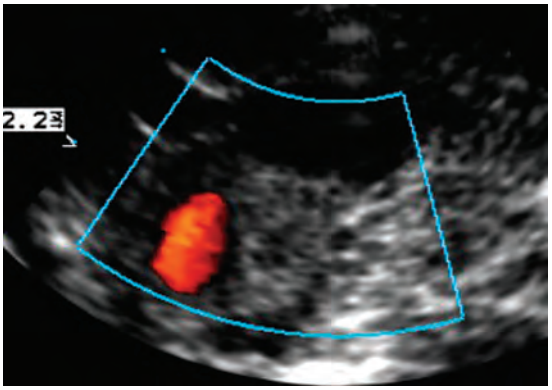


Fig. 23.50 Transcutaneous short-axis views of the right carotid artery and right internal jugular vein. There is extensive hematoma around the lumen of the carotid artery. Color-flow Doppler interrogation of the carotid artery demonstrates intact flow. There is no obvious carotid dissection. These views indicate extension of the mural hematoma into the brachiocephalic vessels. Hence the brachiocephalic vessels at the level of the aortic arch may require reconstruction. These findings suggest a total aortic arch replacement with brachiocephalic reconstruction, a major surgical procedure.

Discussion

The TEE examination suggests that the aortic arch requires extensive acute repair. Although acute endovascular aortic arch repair may be possible in the future, acute total arch endovascular repair is not currently part of standard thoracic aortic endovascular intervention. The current endovascular technology still consists mainly of tubular components with no fenestrations or branches. Given that this is a young patient with minimal comorbidities, the thoracic aorta was accessed anteriorly via sternotomy, and a total aortic arch repair with CPB and DHCA was performed (Figs. 23.51 and 23.52). If the patient was elderly with multiple comorbidities, a hybrid aortic arch repair might have been considered. In this procedure, the brachiocephalic arteries are transposed to the ascending aorta to create the landing zone for aortic arch stenting. This procedure is typically performed off-pump via sternotomy: Stent deployment can be antegrade through the ascending aorta or retrograde via the femoral artery.

This case of aortic arch transection is unusual. About 85% to 90% of aortic transactions occur at the aortic isthmus, just distal to the left subclavian artery. The remaining 10% occur in the remainder of the

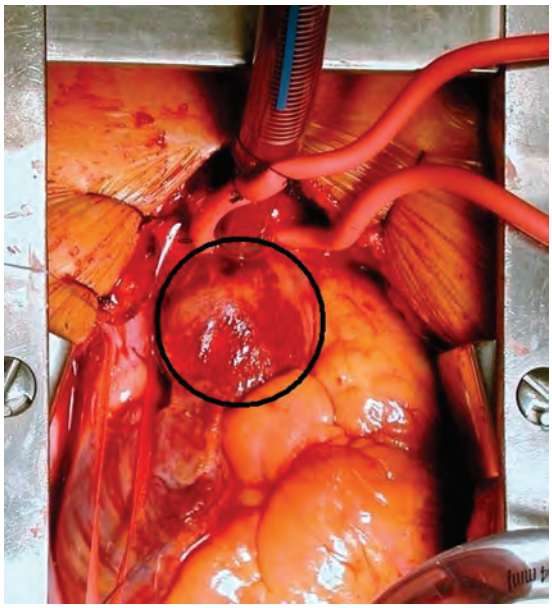


Fig. 23.51 Intraoperative photograph of the thoracic aorta after sternotomy. There is extensive intramural hematoma evident in the proximal aortic arch (area enclosed by the *black circle*).

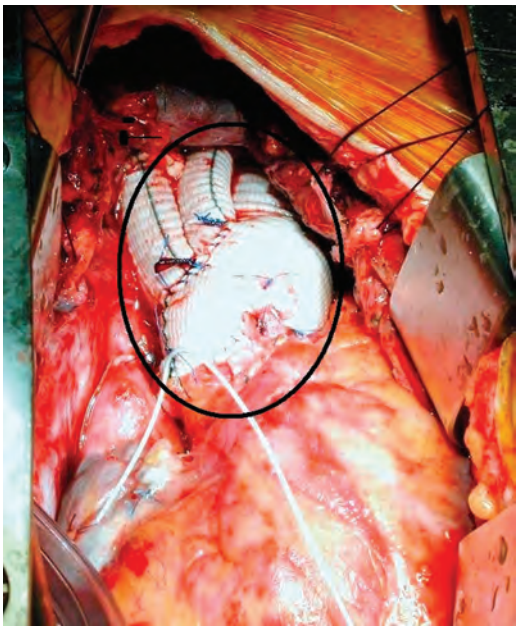


Fig. 23.52 Intraoperative photograph of the aortic arch after cardiopulmonary bypass and deep hypothermic circulatory arrest (area enclosed by the *black circle*). The entire aortic arch has been replaced with a trifurcated prosthetic graft.

thoracic aorta, including the ascending aorta, the aortic arch, and the distal descending aorta. TEE clearly images the thoracic aortic segments where the overwhelming majority of aortic transections occur. The blind spot of TEE is the distal ascending aorta and proximal aortic arch, where transections are rare. Furthermore, in the setting of chest trauma, TEE also can evaluate the heart for evidence of further traumatic injury that may significantly affect perioperative management. Traumatic myocardial contusion may be evidenced by regional wall motion abnormalities that may be severe enough to mandate inotropic support. Traumatic hemopericardium with cardiac tamponade may require surgical drainage. The tricuspid valve also is at risk for

traumatic rupture. Significant tricuspid regurgitation may mandate surgical repair or replacement.

In this case, TEE showed an acute aortic arch transection with extensive brachiocephalic vessel involvement. After total aortic arch replacement, the patient had an uncomplicated hospital course and a complete recovery.

Case Study 4: Bicuspid Aortic Valve

A 43-year-old man presented with progressive heart failure. His father had undergone aortic valve replacement at 50 years of age. His physical examination was compatible with advanced AR. Transthoracic echocardiography showed severe AR and a possible bicuspid valve. Coronary catheterization excluded significant CAD. He was referred for aortic valve surgery. The patient expressed a strong preference to avoid chronic anticoagulation after surgery. He requested aortic valve repair.

Framing

Because this patient has symptomatic AR, he has qualified for surgical intervention. In the setting of a bicuspid aortic valve and patient preference for valve repair, valve anatomy and the mechanism of AR strongly determine the feasibility of successful valve repair. Furthermore, because the bicuspid valve is associated with aortic dilation, the diameters of the aortic root and ascending aorta must be assessed for possible replacement at the time of surgery. The current thoracic aortic guidelines recommend consideration of proximal thoracic aortic replacement when the diameter exceeds 4.5 cm to avoid the future risks for rupture and dissection (class I recommendation; level of evidence B).[2]

Questions

Is there a bicuspid valve? Is the valve calcified? Is there aortic stenosis? Is there AR? If so, what are the severity and mechanism of the AR? Is the valve anatomy compatible with successful valve repair? What are the aortic root diameters? What is the diameter of the ascending aorta? Is the proximal thoracic aorta dissected? Does the patient qualify for aortic root replacement? Does the patient qualify for ascending aortic replacement?

Data Collection

The aortic valve is bicuspid (Figs. 23.53 to 23.59). There is no detectable aortic valve calcification and no aortic stenosis. There is severe eccentric AR because of anterior leaflet prolapse in the region of the raphe. Although mildly dilated, the aortic root does not qualify for replacement at this point. The ascending aorta is not dissected but has a diameter at the level of the pulmonary artery of 4.6 cm.

Discussion

Bicuspid aortic valve is common and is an established risk factor for ascending aortic aneurysm and type A aortic dissection. Although the anatomic orientation of bicuspid aortic cusps varies, the most common arrangement is anterior-posterior, as in this case. The anterior cusp has a raphe where the commissure between the right and left cusps would be in a tricuspid aortic valve. The anterior cusp usually is elongated and thus is prone to diastolic prolapse, as in this case. The posterior cusp usually is normal. The TEE examination should focus on the anatomy, orientation, and mechanism of aortic insufficiency in bicuspid aortic valve cases. As in this case, the delineation of an otherwise competent aortic valve with focal prolapse merits strong consideration for repair. The ascending aorta and not the aortic root met criteria for aortic replacement in this young patient. The aortic arch also was mildly dilated.

In this case, surgical inspection of the aortic valve confirmed the TEE findings. The aortic root, although mildly dilated, did not merit intervention. The raphe of the anterior cusp was excised. The free prolapsing edge was excised in a triangular fashion as part of the anterior aortic leaflet valvuloplasty. The ascending aorta was replaced under

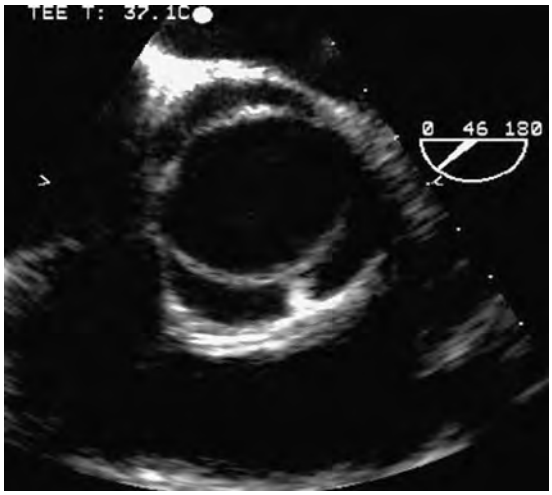


Fig. 23.53 Midesophageal short-axis view of the aortic valve in systole (imaging angle of 46 degrees). The aortic valve is bicuspid with an anterior raphe evident. The aortic cusps appear normal. There is no restricted mobility evident in systole. The cross-sectional area of this bicuspid valve measured 3.2 cm^2. This was within the normal range even when indexed for body surface area.

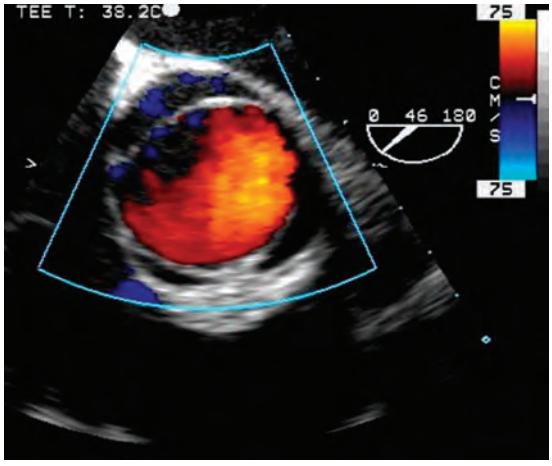


Fig. 23.54 Midesophageal short-axis view of the aortic valve in systole (imaging angle of 46 degrees). Color-flow Doppler mapping shows laminar flow through the aortic valve consistent with an adequate valve area. There is no suggestion of aortic stenosis.

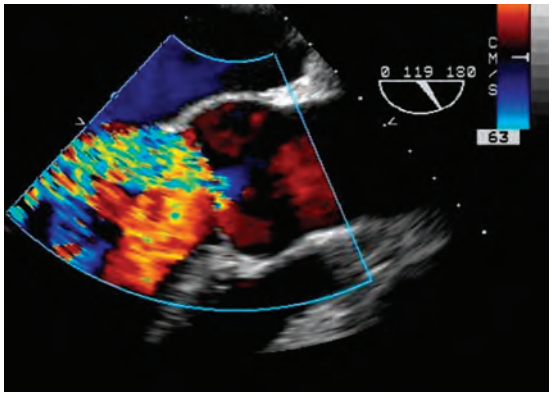


Fig. 23.55 Midesophageal long-axis view of the aortic valve (imaging angle of 119 degrees). Color-flow Doppler imaging reveals severe aortic regurgitation. The jet of aortic regurgitation almost fills the entire left ventricular outflow tract. It is partly directed posteriorly toward the anterior mitral leaflet. This posterior eccentric flow may be caused by prolapse of the anterior aortic cusp or a perforation in the posterior cusp.

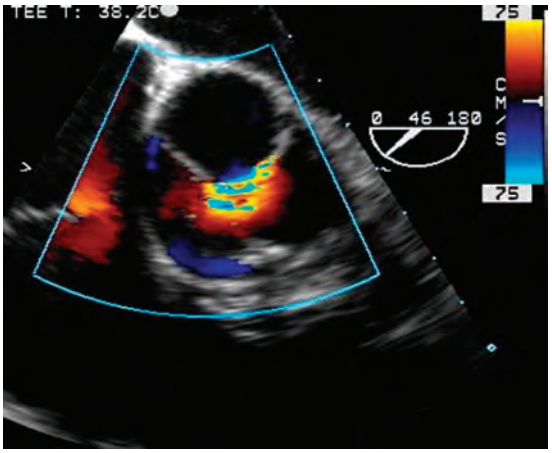


Fig. 23.56 Midesophageal short-axis view of the aortic valve in diastole (imaging angle of 46 degrees). Color-flow Doppler imaging shows central commissural aortic regurgitation at the midpoint of the anterior cusp. This location of the regurgitation suggests focal prolapse of an aortic cusp. When considered together with the posterior eccentric flow evident in Fig. 23.55, the mechanism for the aortic regurgitation in this case is focal prolapse of the anterior cusp in the region of the raphe. This identification of this focal mechanism suggests the possibility of a focal aortic valve repair.

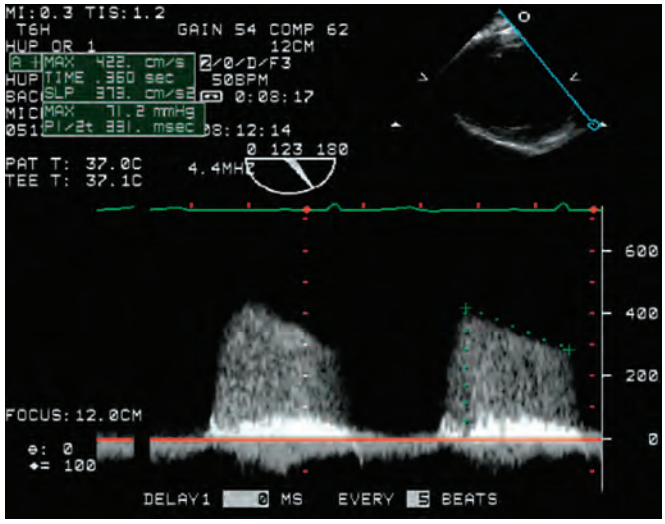


Fig. 23.57 Transgastric long-axis view of the aortic valve (imaging angle of 123 degrees). Continuous-wave Doppler interrogation of the aortic valve shows significant aortic regurgitation (flow above the baseline). The pressure half-time has been quantified at 331 milliseconds, consistent with moderate aortic insufficiency. However, the final grading of the aortic insufficiency was severe when considered together with color-flow Doppler in Fig. 23.55 and effects on the left ventricle in Fig. 23.58. Because the jet of insufficiency is eccentric, it is possible to underestimate the peak diastolic velocity with continuous-wave Doppler. This is the probable explanation for the underestimation of the aortic regurgitation by the pressure half-time method. This underlines the importance of quantifying the valve lesion by multiple methods.

DHCA with the addition of an aortic arch repair (hemiarch technique; DHCA time = 15 minutes). This complete resection of the ascending aorta was undertaken to avoid leaving the cross-clamped ascending aorta in situ because it was judged to be at a greater risk for future dissection. Furthermore, the aortic arch also was mildly dilated. This lower threshold for aggressive proximal thoracic aortic resection was undertaken because of the bicuspid aortic valve, the low operative risk of the patient, and the extensive experience of the thoracic aortic team.

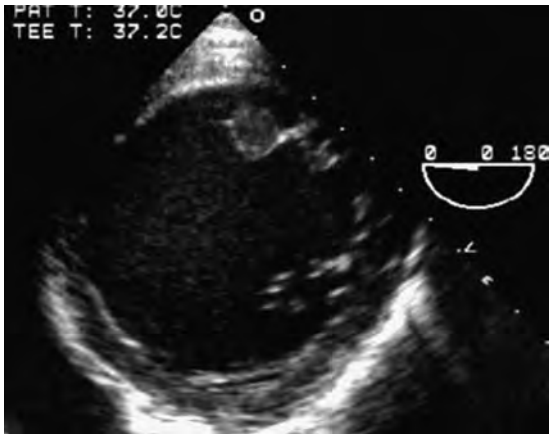


Fig. 23.58 Transgastric midpapillary short-axis view of the left ventricle at end-diastole (imaging angle of zero degree). The left ventricle is severely dilated with an end-diastolic diameter of 6.5 cm. This is consistent with chronic severe aortic regurgitation.

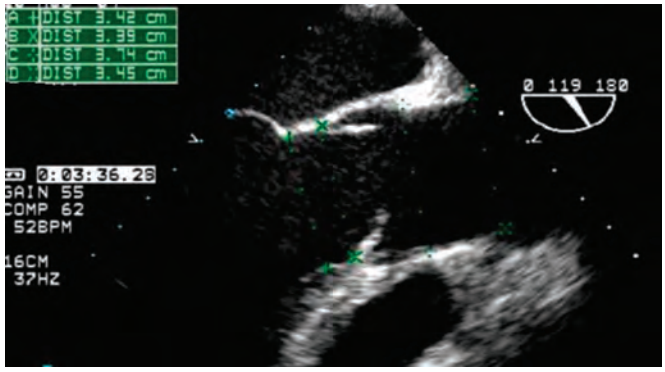


Fig. 23.59 Midesophageal long-axis view of the aortic root (imaging angle of 119 degrees). The diameters of the left ventricular outflow tract *(A)*, the aortic annulus *(B)*, the sinuses of Valsalva *(C)*, and the sinotubular junction *(D)* have been measured. These diameters are consistent with a mild degree of annular and root dilation, a common association with a bicuspid aortic valve. It is important that these diameters are accurately measured because excessive annuloaortic ectasia may dictate aortic root replacement with or without native aortic valve sparing. Furthermore, ascending aorta diameters closer to the level of the pulmonary artery (not shown) should also help determine if ascending aorta replacement is warranted.

After separation from CPB, TEE demonstrated normal aortic valve function with no AR. There was no dissection in the residual native thoracic aorta. There was improved LV function. The patient had an uneventful recovery.

TEE provides important information in the planning of proximal thoracic aortic intervention in the setting of a bicuspid aortic valve. Thorough echocardiographic interrogation of the aortic valve, the aortic root, the ascending aorta, and aortic arch typically provides all the data required for operative decision making. The bicuspid aortic valve signals the presence of an abnormal proximal thoracic aorta that should be managed as carefully as the associated aortic valve dysfunction.

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24 Uncommon Cardiac Diseases

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KEY POINTS

1. Patients with uncommon cardiac diseases frequently have complicated medical conditions, the treatment for which should take place in the context of an institution capable of providing coordinated multidisciplinary care.
2. Cardiac tumors are rare. In general, a cardiac mass is more likely a vegetation or a thrombus than a tumor. Secondary (metastatic) tumors are far more common than primary cardiac tumors. Among primary cardiac tumors, benign lesions are more common than malignant tumors. Anesthetic management for tumor resection is likely to depend more on a patient's comorbidities and tumor location than on the tumor's pathologic condition.
3. Cardiac myxomas historically have been considered the most common benign cardiac tumor. Although most commonly solitary, sporadic, and located on the left atrial side of the fossa ovalis, they may also occur as multiple, simultaneous tumors inherited in cases of Carney complex. Patients with myxomas typically exhibit signs and symptoms attributable to one of the triad of intracardiac obstruction, embolism, or constitutional symptoms.
4. Papillary fibroelastomas are the most common valvular cardiac tumor and may be the most common benign lesion as well. Typically solitary, fibroelastomas occur most frequently on the mitral and aortic valve leaflets. Once considered an incidental, benign finding, they have a high incidence of coronary and cerebral embolization.
5. Primary malignant cardiac tumors are less common than benign tumors. The overwhelming majority of primary malignant tumors are sarcomas.
6. Metastatic cardiac tumors are far more common than primary tumors. Metastatic tumors may involve the heart by direct extension (breast, lung, esophageal), by venous extension (renal cell carcinoma, hepatocellular carcinoma), or by hematogenous (melanoma) or lymphatic (lymphoma, leukemia) spread. Although metastatic cardiac tumors may affect the pericardium, epicardium, myocardium, or endocardium, pericardial involvement is the most common.
7. Carcinoid tumors are metastasizing neuroendocrine tumors. In patients with carcinoid syndrome, carcinoid heart disease is common and characterized by tricuspid regurgitation, mixed pulmonic regurgitation and stenosis, and right-sided heart failure. The management of patients with carcinoid heart disease, similar to the management of many patients with uncommon cardiac conditions, is complex and requires coordinated care at specialty referral centers. The mainstays of treatment are symptom management with somatostatin analogs, antitumor therapy, and cardiac surgical intervention. Successful perioperative management depends on optimal preoperative symptom control with long-acting somatostatin analogs.
8. Renal cell carcinomas are the most common renal tumors. Clear cell carcinomas are the most common subtype of renal cell carcinoma and tend to produce venous extension into the renal veins and the inferior vena cava. Surgical resection of tumor thrombus extending into the intrahepatic inferior vena cava (New York Heart Association [NYHA] level III tumor) or above the diaphragm (NYHA level IV tumor) may require cardiac surgical and anesthesia involvement, although some institutions are now performing resections of proximal lesions involving the right-sided heart without the assistance of cardiopulmonary bypass.
9. Cardiomyopathies are a heterogeneous group of diseases that may be acquired or genetic and may be confined to the heart (primary) or may be part of a systemic disorder (secondary). The American Heart Association classifies cardiomyopathies as primary or secondary and subclassifies primary processes as genetic, acquired, or mixed. The European Society of Cardiology, however, classifies the cardiomyopathies morphologically and functionally into hypertrophic, dilated, arrhythmogenic, restrictive, and unclassified, each of which, in turn, may be considered genetic or nongenetic.
10. Dilated cardiomyopathy is the most common of the cardiomyopathies and may be acquired, hereditary, or idiopathic. Hearts affected with dilated cardiomyopathy show four-chamber dilatation, myocyte hypertrophy, and disproportionate impairment of systolic heart function. The goals of perioperative management of patients with dilated cardiomyopathy, who most frequently require correction of tricuspid or mitral regurgitation, device implantation, or transplantation, include minimizing further myocardial depression, reducing afterload, and maintaining preload.
11. The first case series of patients with hypertrophic cardiomyopathy was published in 1957 and highlights

both the understandings and misunderstandings that continue to affect the current thinking of the disease. Contrary to common belief, hypertrophic cardiomyopathy need not be obstructive, need not be fatal, and need not entail massive left ventricular hypertrophy.

12. Hypertrophic cardiomyopathy is likely the most common inherited cardiac disease and may progress along one or more of three pathways: (1) sudden cardiac death, (2) heart failure, or (3) atrial fibrillation, with or without cardioembolic stroke. Hypertrophic cardiomyopathy is morphologically heterogeneous and includes variants with asymmetric basal septal hypertrophy, midventricular hypertrophy, and apical hypertrophy. Surgical intervention may require transaortic and/or transapical approaches. Anesthetic management requires an intimate knowledge of the patient's anatomy and physiologic characteristics and may differ considerably, depending on whether the patient has a basal lesion with dynamic obstruction or an apical lesion with significant impairment of ventricular filling.
13. The restrictive cardiomyopathies, less common than either the dilated or the hypertrophic cardiomyopathies, are heterogeneous and characterized by impaired myocardial relaxation and decreased ventricular compliance. Although diastolic dysfunction is the hallmark of restrictive cardiomyopathies, systolic function may not be normal, although gross indicators of systolic function such as ejection fraction may be unimpaired. Considering that their treatments are significantly different, restrictive cardiomyopathy and constrictive pericarditis must be distinguished. The patients with restrictive cardiomyopathy who are most likely seen in a cardiac surgical unit are patients with cardiac amyloidosis.
14. Mitral valve prolapse is a relatively common cardiac condition. Most patients remain clinically asymptomatic with normal life expectancies. Progression of mitral valve disease and the development of severe mitral regurgitation are rare; however, severe regurgitation represents a common indication for cardiac surgery. Current approaches to mitral valve prolapse are reviewed, including the range of clinical presentations from mitral valve prolapse syndrome to degenerative valve disease and severe mitral regurgitation.
15. Management of patent foramen ovale has received considerable attention with the widespread use of percutaneous closure devices. Determining the superiority of percutaneous device closure to medical management is heavily debated. The management of an incidental patent foramen ovale found during cardiac surgery via transesophageal echocardiography continues to evolve; however, few data suggest that closure offers morbidity or mortality benefit and may actually increase the risk of postoperative stroke.
16. The definitive approach to a patient with both carotid and coronary artery disease requires a large multicenter, randomized trial; however, the many approaches to the surgical management of combined procedures are described.
17. Heart disease continues to be the leading cause of maternal and fetal death during pregnancy; consequently, the important features of managing the pregnant patient who requires cardiopulmonary bypass and cardiac surgery is updated.
18. With newly developed therapies, the incubation time to develop acquired immune deficiency syndrome after infection and the life expectancy of those with human immunodeficiency virus have been extended; therefore the likelihood of cardiac surgery is greater. Consequently, the rates of exposure, types of procedures, and the precautions of the individuals are addressed.
19. The number of individuals with chronic renal failure, not necessarily dialysis dependent before surgery, are more frequently undergoing cardiac surgery and are likely to develop worsening renal function after cardiopulmonary bypass; therefore the identification of steps that may improve outcome are discussed.
20. Anesthetic concerns for patients with hematologic problems who undergo cardiac surgery are further complicated by the stress cardiopulmonary bypass places on coagulation and oxygen-carrying systems and require special considerations and techniques.

In this chapter, uncommon cardiac diseases and coexisting problems of patients undergoing cardiac surgery are reviewed. Each subsection includes a general overview of the disease or condition, followed by anesthetic considerations for cardiac surgery. Although some of the diseases discussed are quite rare and unlikely to be encountered regularly outside of large referral centers, other conditions, such as chronic kidney disease, are exceedingly common and likely to be routinely found in the patient population. Regardless of the prevalence of the disease or condition, however, optimal anesthetic management will depend both on a thorough understanding of the underlying pathologic and pathophysiologic findings, and on the recognition that the disease process may affect the anesthetic just as much as the anesthetic may exacerbate the disease process. For many conditions, preoperative evaluation and medical optimization in the context of an institution capable of providing coordinated multidisciplinary care may be as important in the intraoperative management of these patients as are the details of any particular anesthesia plan. Furthermore, provider vigilance and sound clinical judgment exercised in the context of intimate knowledge of a given patient's pathologic and pathophysiologic nature under specific clinical circumstances are likely to be more important for ensuring the optimal and safe care of the patient than is any specific combination of medications and monitors.

Cardiac Tumors

Cardiac tumors belong to the class of cardiac masses that includes vegetations and thrombi, for which tumors may be mistaken. Cardiac tumors may be classified as primary or secondary (metastatic). Primary tumors may be benign or malignant, whereas secondary tumors may involve the heart by direct extension (breast and lung), by venous extension (renal cell and hepatocellular carcinoma), or by hematogenous (melanoma, breast, and carcinoid) or lymphatic (lymphoma) spread (Table 24.1).[1]

In general, cardiac tumors are rare, and a cardiac mass encountered echocardiographically or radiographically is more likely to be a thrombus or a vegetation than a tumor. Metastatic tumors are more common than primary cardiac tumors, with an incidence at autopsy between 2.3% and 18.3%, whereas primary tumors have an incidence rate between 0.0014% and 0.33%.[2–7] Among primary tumors, benign lesions are more common than malignant masses. In adults,

TABLE 24.1 Cardiac Masses

Neoplastic			Nonneoplastic	Other
Primary		*Secondary*	*Nonneoplastic*	*Other*
Benign	Malignant	Direct extension	Hamartomas	Thrombus
Myxoma	Sarcoma	Breast	Rhabdomyoma	Vegetation
PFE[a]	Lymphoma	Lung	Fibroma	CAT
Lipoma		Esophagus	PFE[a]	Normal structure
		Mediastinal tumor	Age-related growths	Image artifact
		Hematogenous	Lipomatous hypertrophy	
		Melanoma	Reactive proliferation	
		Lung	Lambl excrescence	
		Breast	PFE[b]	
		Genitourinary		
		Gastrointestinal		
		Venous		
		Renal		
		Adrenal		
		Thyroid		
		Lung		
		Hepatoma		
		Lymphatic		
		Lymphoma		
		Leukemia		

[a]PFE arising de-novo.
[b]PFE arising in the setting of hypertrophic obstructive cardiomyopathy or after endocardial injury.
CAT, Calcified amorphous tumor; *PFE,* papillary fibroelastoma.
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TABLE 24.2 Incidence of Benign Cardiac Tumors in Adults and Children

	Incidence (%)	
Neoplasms	*Adults*	*Children*
Myxoma	45	15
Lipoma	20	—
Papillary fibroelastoma	15	—
Angioma	5	5
Fibroma	3	15
Hemangioma	5	5
Rhabdomyoma	1	45
Teratoma	<1	15

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the most common primary benign tumors are myxomas, although several series now suggest that papillary fibroelastomas may, in fact, be more common (Table 24.2).[1,8] In children, rhabdomyomas are the most common benign tumor. Approximately 15% to 25% of primary cardiac tumors are malignant, with sarcomas being the most common in both adults and children.[1,3,9] Tumors with high rates of cardiac metastases include pleural mesothelioma, melanoma, lung adenocarcinoma and squamous cell carcinoma, and breast carcinoma.[7,10] Although metastases may involve the pericardium, epicardium, myocardium, or endocardium, pericardial involvement is most common.[2]

Although cardiac tumors may be clinically silent and diagnosed only at autopsy, advancements in imaging have facilitated both their often-incidental antemortem diagnosis and their characterization once detected. The increasing sophistication of two-dimensional echocardiography, the advent of three-dimensional echocardiographic imaging, and the continued refinement of computed tomography (CT) and magnetic resonance imaging (MRI) have all allowed earlier, more frequent, and more complete assessment of cardiac tumors.[11–15] When tumors do produce symptoms, the symptoms are frequently nonspecific and more likely to reflect a tumor's location or size than its histopathologic characteristics (Box 24.1).[1,8] Although malignant primary lesions and metastatic tumors may produce constitutional symptoms, even histologically benign masses may cause concerning signs and symptoms associated with intracardiac obstruction and extracardiac embolization.[8] A tumor's location, however, as well as the age of the patient in whom it occurs, and its imaging characteristics may facilitate tumor diagnosis, especially when the cause of the cardiac tumor is taken into account; that is, metastatic lesions are more common than primary lesions, and benign tumors are more common than malignant tumors among primary lesions.[1,14]

Based on a recent retrospective study, the most effective treatment of primary tumors is generally surgical resection with an approximate 2% operative mortality. This study involved 323 consecutive patients who underwent surgical resection of primary cardiac tumors over a period of 48 years in one institution.[16] Recurrence rate in these tumors varied between 3% and 13% but appeared to be related to a biologic propensity rather than the surgical technique as was previously believed. The overall rate of tumor embolization was 25%, compared with previous reports of 12% to 45%. Embolic complications were seen more often in patients with minimal or no symptoms than in those with large tumors associated with hemodynamic changes. Papillary fibroelastoma and aortic valve tumors are most commonly preceded by an embolic event. Even patients who are diagnosed by an embolic event benefit greatly from surgical resection with excellent short- and long-term survival that is comparable with a cohort of patients with tumors undergoing surgery for other reasons.[12] Orthotopic cardiac transplantation has been recommended for unresectable tumors, but the benefit is indeterminate.[17] Although malignant lesions are less common, the surgical risk and outcome for their resection, compared with benign tumor resection, is usually significantly worse, especially in younger patients.[18,19]

In this section, the most common primary benign cardiac tumors in adults (myxomas and papillary fibroelastomas) are discussed, and an overview of adult primary malignant cardiac tumors and metastatic tumors is provided, followed by a review of the anesthetic management for tumor resection. Next, two frequently encountered systemic malignancies with cardiac involvement—carcinoid heart disease and renal cell carcinoma—are discussed, along with their respective anesthetic management.

Primary Benign Tumors

Myxoma

Often a diagnostic challenge, myxomas are benign, solitary, and slow-proliferating neoplasms. Microscopically, they often resemble

BOX 24.1 CLINICAL PRESENTATION OF CARDIAC TUMORS

Benign Tumors

Cardiac myxomas
- Obstructive cardiac symptoms: pulmonary edema or progressive cardiac failure
- Embolic symptoms
- Constitutional symptoms

Papillary fibroelastoma
- Embolic symptoms of obstruction of coronary or cerebral circulation
- Sudden death by prolapse into coronary ostia or occlusion of a large coronary branch

Rhabdomyoma
- Possible cardiomegaly, congestive heart failure, and cardiac arrhythmias, dependent on size
- Sudden death or stillbirth

Fibroma
- One third asymptomatic; two thirds with heart failure, cyanosis, arrhythmias, syncope, chest pain, or sudden death

Atrioventricular nodal tumours
- Asymptomatic sudden death

Cardiac lipomas
- Asymptomatic
- Rare extrinsic compression of heart, dependent on size and location

Malignant Tumors

Angiosarcoma
- Nonspecific, possible chest pain, shortness of breath, malaise, and/or fever

Osteosarcoma
- Atrial involvement with respiratory symptoms
- Ventricular involvement with recurrent ventricular tachyarrhythmia

Leiomyosarcoma
- Pulmonary lesions with dyspnea, chest pain, and nonproductive cough
- Cardiac dysfunctions, including right-sided heart failure, valve stenosis, rhythm alterations, conduction abnormalities, hemopericardial anomalies, and/or sudden death

Rhabdomyosarcoma
- Nonspecific symptoms; possible pleuropericardial symptoms and distal embolization
- Arrhythmias and obstructive symptoms

Cardiac lymphoma
- Cardiac tamponade, heart failure, exertional dyspnea, atrial fibrillation, and features of right-sided heart obstruction

Pericardial mesothelioma
- Chest pain, cough, dyspnea, and palpitations

Metastatic cardiac tumor
- Tachycardia arrhythmias, cardiomegaly, or heart failure in a patient with carcinoma, raising the suspicion of cardiac metastasis (Rarely, cardiac involvement such as pericardial effusion or incipient cardiac tamponade can be first clinical feature of malignant disease, although 90% are clinically silent.)

Reproduced with permission from Butany J, Nair V, Naseemuddin A, et al. Cardiac tumours: diagnosis and management. *Lancet Oncol.* 2005;6:220.

organized thrombi, which may obscure their identity as a primary cardiac tumor (Fig. 24.1).[20] The pedunculated mass is believed to arise from undifferentiated cells in the fossa ovalis and adjoining endocardium, projecting into the left atrium (LA) and the right atrium (RA) 75% and 20% of the time, respectively. However, myxomas appear in other locations of the heart, even occupying more than one chamber.[21] The undifferentiated cells of a myxoma may develop along a variety of cell lines, accounting for the multiple presentations and pathologic observations.[22] Besides a variable amount of stroma, myxomas include hemorrhage, hemosiderin, thrombus, and calcium. Myxomas predominate in the 30- to 60-year-old age range, but any age group may be affected.[20] More than 75% of the affected patients are women.[23] Although most cases occur sporadically, 7% to 10% of atrial myxomas will occur in a familial pattern with an autosomal dominant transmission pattern known as Carney complex.[20,24,25]

Occasionally, an incidental finding on echocardiography, myxomas may produce a variety of symptoms. The classic triad includes embolism, intracardiac obstruction, and constitutional symptoms.[26] Approximately 80%[21] of individuals will exhibit one component of the triad. Up to 10% of people may be asymptomatic, even with mitral myxomas arising from both atrial and ventricular sides of the anterior leaflet of the mitral valve.[27] The most common initial symptom, dyspnea on exertion,[23] reflects mitral valve obstruction associated with left atrial myxomas (Figs. 24.2 and 24.3). Because of the pedunculated nature of some myxomas, temporary obstruction of blood flow may cause hemolysis, hypotension, syncope, or sudden death. Other symptoms of mitral obstruction, similar to mitral stenosis, may occur, including hemoptysis, systemic embolization, fever, and weight loss. If the tumor is obstructing the mitral valve, then a *tumor plop* may be heard after the second heart sound on chest auscultation. The persistent sinus rhythm in the presence of such symptoms may help distinguish an atrial myxoma from mitral stenosis. Severe pulmonary hypertension without significant mitral valve involvement suggests recurrent pulmonary emboli, which is known to occur with a myxoma in the RA or right ventricle (RV). Occasionally, right-sided heart tumors may appear as cyanotic congenital heart lesions attributable to intracardiac shunting.[28]

Recurrent fragmentation and embolization of the gelatinous-like tumor usually appears with systemic manifestations and is characteristic of myxoma. The smaller myxoma in the LA that does not create hemodynamic complications, but can exists undiagnosed for years, is more likely to cause embolization.[12] Cerebral aneurysms often exist in persons with recurrent systemic embolization from intracardiac myxoma, probably secondary to damage by the systemic tumor emboli. The kidneys are also more susceptible to damage from myxoma emboli. Constitutional symptoms such as malaise, fever, and weight loss occur in approximately one third of patients, reflecting a possible autoimmune component to the disease process. The lack of symptoms specific to the tumor frequently delays its diagnosis. The differential diagnosis includes endocarditis, connective tissue disorders, and malignancies. In general, the anatomic type of myxoma portends the clinical presentation. The solid, ovoid tumors are more often associated with congestive heart failure (CHF), whereas papillary myxomas are linked with cerebral embolization.[29] Tumor size does not correlate with symptoms.[23]

Findings on a chest roentgenogram of a myxoma may be absent in approximately one third of persons. Calcification on the chest roentgenogram is more diagnostic of right atrial myxoma but may occasionally be present with left atrial myxomas. Before the availability of echocardiography, angiography was used to identify myxomas; currently, however, angiography is probably only useful to determine coronary anatomy, if considered necessary.[18,30] CT and MRI can help delineate the extent of a tumor and its relation to surrounding cardiac and thoracic structures.[31] MRI is especially valuable in the diagnosis of myxoma when masses are equivocal or suboptimal with echocardiography or if the tumor is atypical in presentation.[21] Difficulty may arise in differentiating a thrombus from a myxoma, because both are so heterogeneous.

Transthoracic echocardiography (TTE) is excellent for identifying intracavitary tumors, because it is noninvasive, identifies tumor type, and permits complete visualization of each cardiac chamber. TTE is the predominate imaging modality for screening.[18] Transesophageal echocardiography (TEE) allows for better definition of tumor size and location and can be used to identify the site of tumor attachment and the presence of multiple lesions.[1,14,32]

Myxomas have a typical echocardiographic appearance and are often irregular in shape with protruding fronds of tissue. Areas of

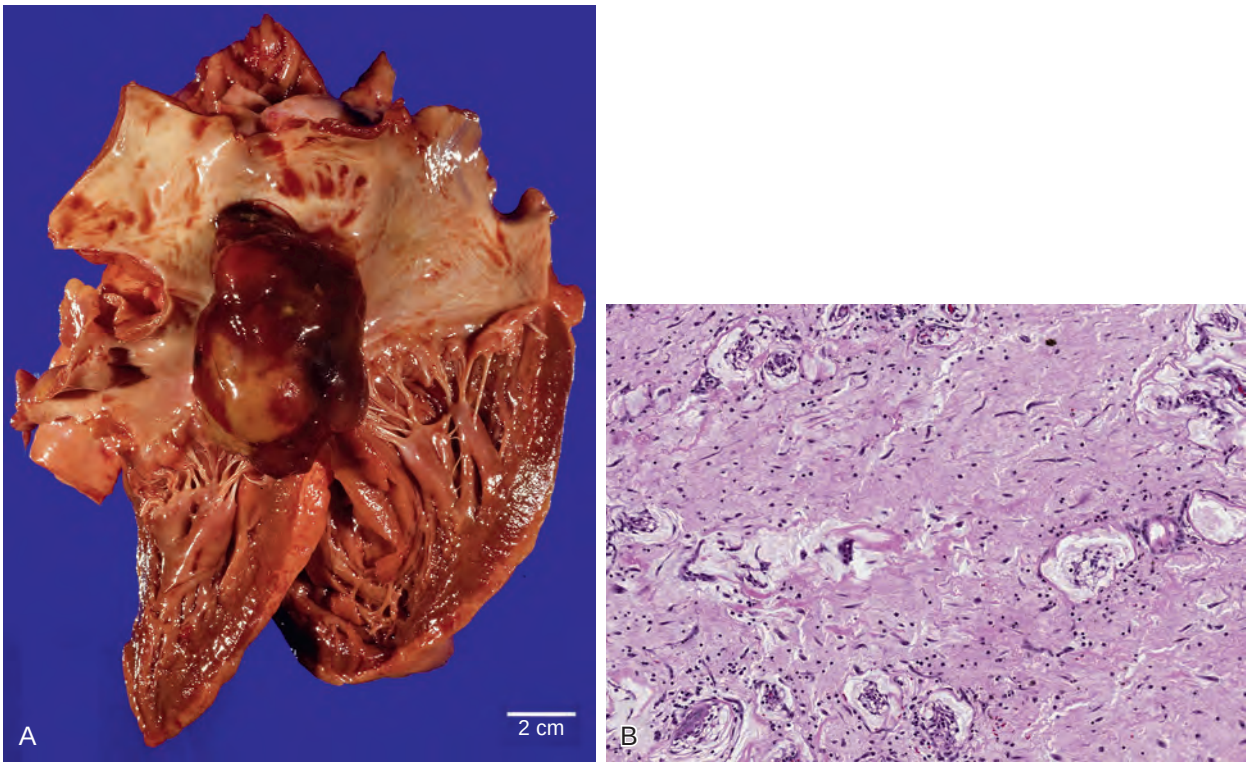


Fig. 24.1 Cardiac myxoma. (A) Gross specimen, solid type, with a typical smooth, lobular, mucoid appearance and location in the fossa ovalis. (B) Microscopic specimen, with small, stellate myxoma or lepidic cells forming rings and strands around vascular structures set against a myxoid background. *(Reproduced with permission from Jain D, Maleszewski JJ, Halushka MK. Benign cardiac tumors and tumorlike conditions.* Ann Diagn Pathol. *2010;14:217.)*

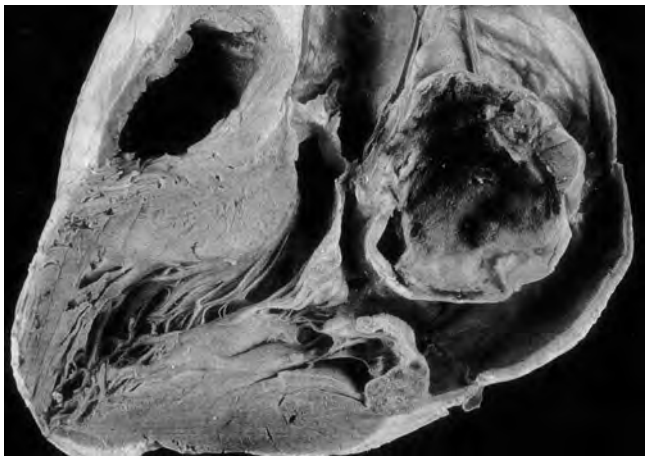


Fig. 24.2 Postmortem specimen of a large left atrial myxoma prolapsing into the orifice of the mitral valve. *(Reproduced with permission from Schaff HV, Mullany CJ. Surgery for cardiac myxomas.* Semin Thorac Cardiovasc Surg. *2000;12:81.)*

calcification may be evident, and the echogenicity of the mass may not be homogeneous.[1,14,15] The presence of a large mass in the LA with an attachment to the interatrial septum is highly suggestive of myxoma; however, echocardiography cannot, of course, provide a definitive tissue diagnosis. Rarely is a thrombus attached to the atrial septum.[33] The degree of obstruction to ventricular filling caused by the tumor may be evaluated with Doppler echocardiography (see Fig. 24.3). Qualitatively, color-Doppler imaging will show aliasing and flow acceleration through the atrioventricular valve when obstruction is present. Continuous-wave Doppler imaging is able to quantify the gradient between the atrium and the ventricle. Preoperatively, the goal of echocardiographic evaluation is to determine the site of tumor attachment, to characterize a tumor's relationship, in particular, to the cardiac valves and their leaflets, and to assess for the presence of multiple masses as in the case of Carney complex.[34] If this cannot be accomplished with TTE, then TEE should be performed to aid in surgical planning.

Although professional societies have specified appropriate use criteria for TEE, most are based on opinion rather than on evidence.[35–37] Whereas TEE may be appropriate to evaluate for a cardiac source of embolus when no noncardiac source has been identified, it may be inappropriate when a noncardiac source has already been located or when the results of the examination are unlikely to change patient management.[35] When the primary reason for cardiac surgery is the removal of an intracardiac mass, an intraoperative transesophageal echocardiographic evaluation should take place before the surgical incision to ensure that the mass is still present and has not embolized or even dissolved, as in the case of intracardiac thrombus. In the case of myxoma, an intraoperative examination in the presence of the surgeon can aid in finalizing the surgical plan and in detecting previously unseen tumors. After tumor removal, the goal of TEE is to ensure that all visible mass was removed and that no damage occurred to adjacent structures. Specifically, in the case of a myxoma attached to the atrial septum, ensuring that no interatrial shunting has occurred after resection is important. If the tumor was attached on or adjacent to the valvular apparatus, then the examiner must determine whether the valve is competent after removing the tumor.

The first surgical resection of an atrial myxoma was performed in 1954.[30] Subsequently, surgical resection has been recommended even if the myxoma is discovered incidentally, primarily because the risk of embolization to the central nervous system may be 30% to 40%.

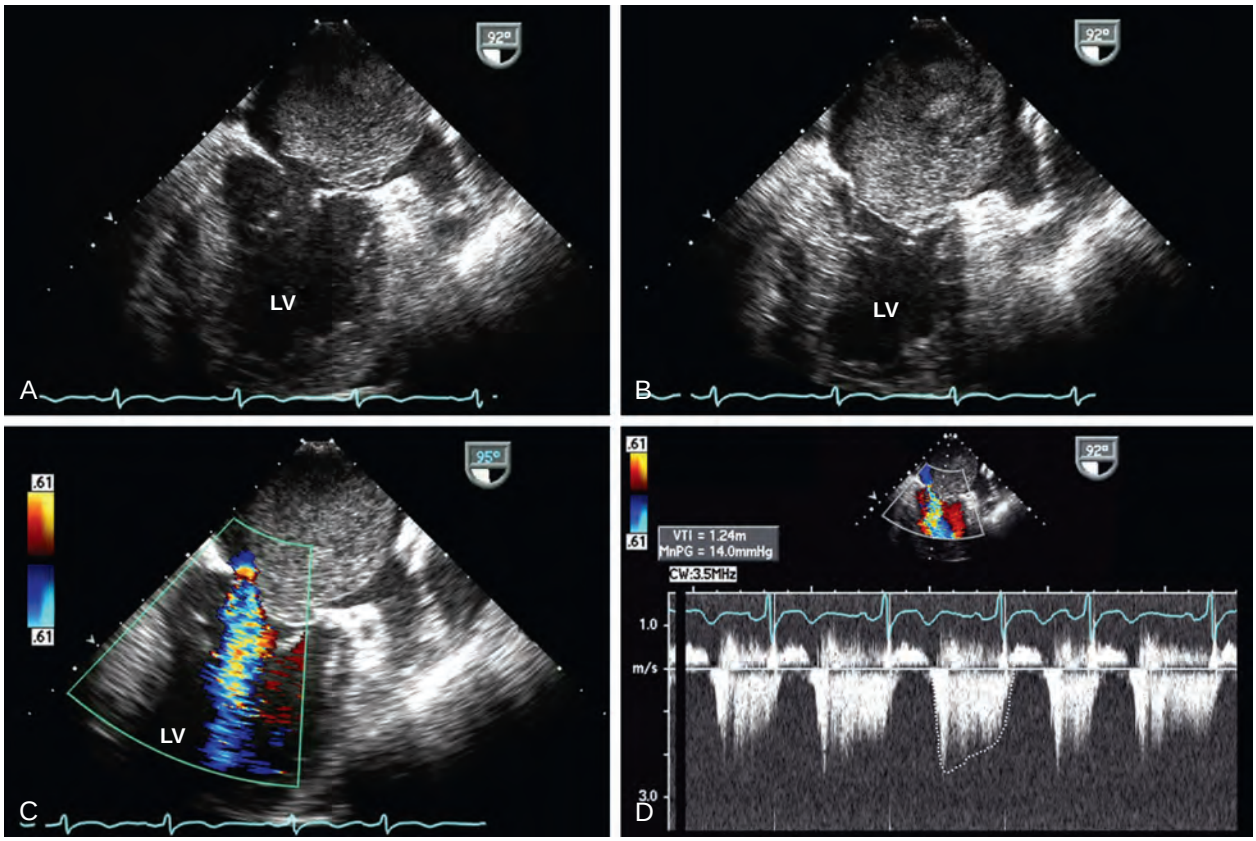


Fig. 24.3 Transesophageal echocardiographic characteristics of a large left atrial myxoma. (A) Midesophageal two-chamber view during systole shows a 5 × 7 cm mass located in the left atrium. (B) Two-dimensional and (C) color-flow Doppler images show that during diastole, the mass obstructs flow across the mitral valve, creating severe functional mitral stenosis. (D) Continuous-wave Doppler across the mitral valve demonstrates a mean gradient of 14 mm Hg. *LV,* Left ventricle. *(Reproduced with permission from Otto CM, ed.* Practice of Clinical Echocardiography. *4th ed. Philadelphia: Saunders/Elsevier; 2012.)*

Generally, the time interval between the onset of symptoms and surgical resection is approximately 4 months, although surgery has been delayed for as long as 10 years in some cases.[23] Surgery is associated with a mortality rate between 0% and 7%.[4,12] More importantly, recent studies show that the long-term survival of an individual who has undergone myxoma resection is no different from age- and gender-matched populations.[16]

Papillary Fibroelastoma

Papillomas (papillary fibroelastoma) are rare, benign tumors that tend to affect the cardiac valves. Although large surgical series count them as the second most common primary cardiac tumor, several series now suggest that papillary fibroelastomas may, in fact, be more common than myxomas.[1,8] Initially thought to be incidental findings during autopsies, most papillary fibroelastomas are currently discovered in living patients.[38] Mostly singular (90%), 1 to 4 cm in size, highly papillary, pedunculated, and avascular, papillomas are covered by a single layer of endothelium containing fine elastic fibrils in a hyaline stroma.[20,39,40] Macroscopically, they resemble sea anemones (Fig. 24.4). They originate most commonly from valvular endocardium,[41] usually involving the ventricular surface of the aortic valve or the atrial surface of the mitral valve, but they only infrequently render the involved valve incompetent. Papillary fibroelastomas account for 75% of all primary cardiac valvular tumors.[16,42] Adults between the ages of 40 and 80 years are primarily affected, with a mean age of 60 years at the time of detection.[43] Many patients are asymptomatic; therefore it is not surprising that 47% of these tumors are discovered incidentally during echocardiography, catheterization, or even cardiac surgery. Echocardiographically, fibroelastomas have a typical appearance (Figs. 24.5 and 24.6; see also Fig. 24.4).[40,44] They are usually small (mean size 12 × 9 mm), and their motion is independent of that of the attached valve leaflet.[45] They may appear similar to vegetations seen in endocarditis or they may be confused with Lambl excrescences, which tend to be more nodular in appearance.[1,14]

Currently, many tumors are detected during the search to find the cause of embolic symptoms. These symptoms are most common when the aortic valve is involved.[12] Although papillary fibroelastomas were previously believed to be harmless, postmortem studies have shown a high incidence of embolization to the cerebral and coronary circulations.[9] Not surprisingly, symptoms are often related to stroke or transient ischemic attack and myocardial infarction (MI). Although embolization may be a tumor, it may be a thrombus because tumors are excellent sites for thrombus formation.[43] Making the diagnosis is very important, because acute valvular dysfunction and even sudden death may occur.[41] Surgical resection is curative but may require valvular repair or replacement in one-third of cases.[38] Recurrence is very rare.

Primary Malignant Tumors

Approximately 25% of primary cardiac tumors are malignant,[43] and 95% of these are sarcomas (Fig. 24.7). They are found infiltrating the RA and causing cavitary obstruction but may have variable clinical presentations based on the location, causing the diagnosis to be elusive. Primary malignant tumors usually occur between the ages of 30 and 50 years and are preceded by vague symptoms such as dyspnea, rapidly

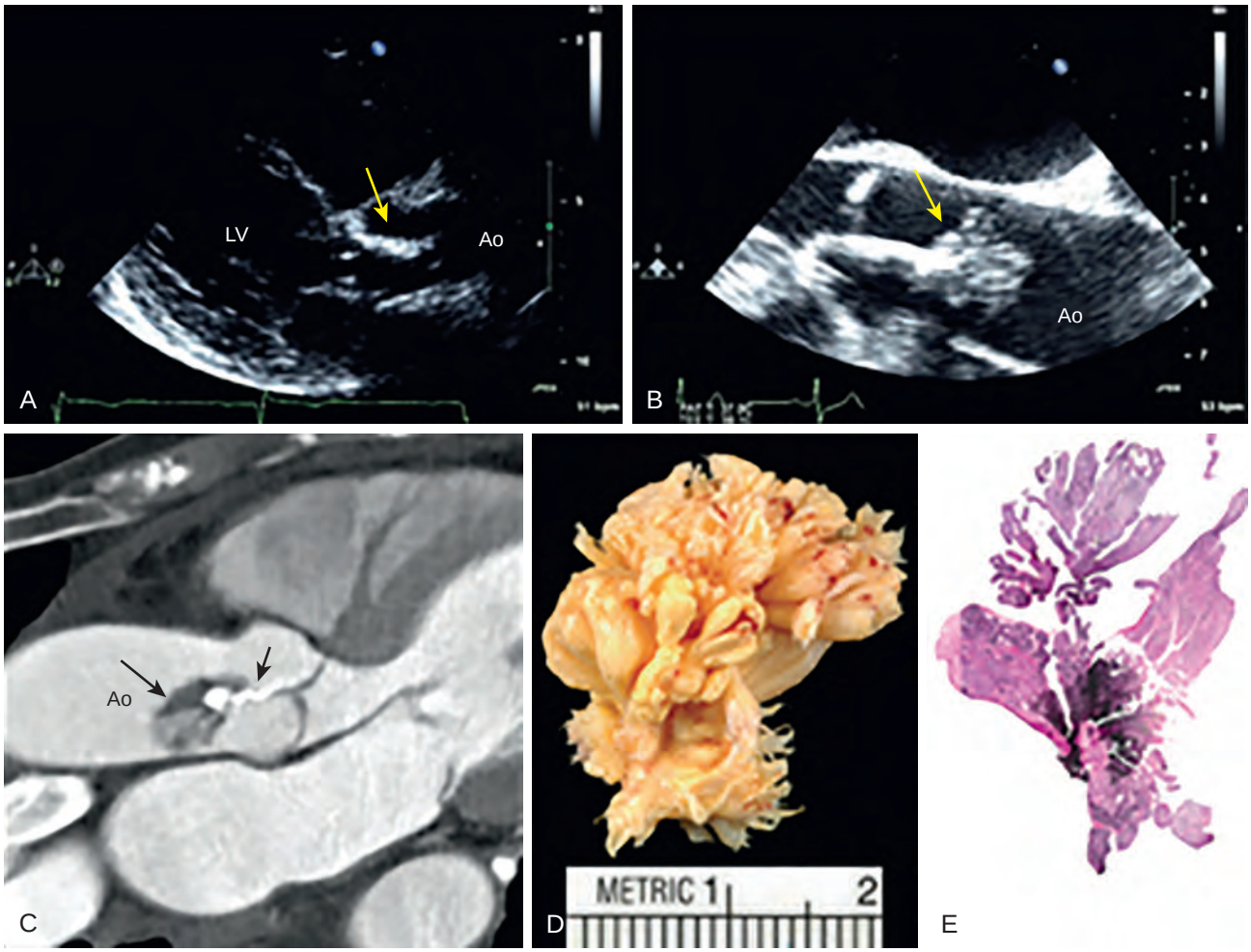


Fig. 24.4 Giant aortic valve papillary fibroelastoma. (A) Transthoracic parasternal long-axis view shows a mass *(yellow arrow)* attached to the aortic valve, extending into the aortic root. (B) Transesophageal midesophageal long-axis view of the aortic valve shows the 4.7 cm, pedunculated mass attached to the right coronary cusp of the aortic valve *(yellow arrow)*. (C) Cardiac-gated CT angiography shows papillary fronds *(long arrow)* extending from a calcified central stalk *(short arrow)*. (D and E) Gross and histologic specimens demonstrate a sea anemone–like appearance with fronds extending from a central fibrocollagenous stalk. *Ao,* Aortic opening; *CT,* computed tomographic; *LV,* left ventricle. *(Reproduced with permission from Fine NM, Foley DA, Breen JF, Maleszewski JJ. Multimodality imaging of a giant aortic valve papillary fibroelastoma.* Case Rep Med. *2013;2013:705101.)*

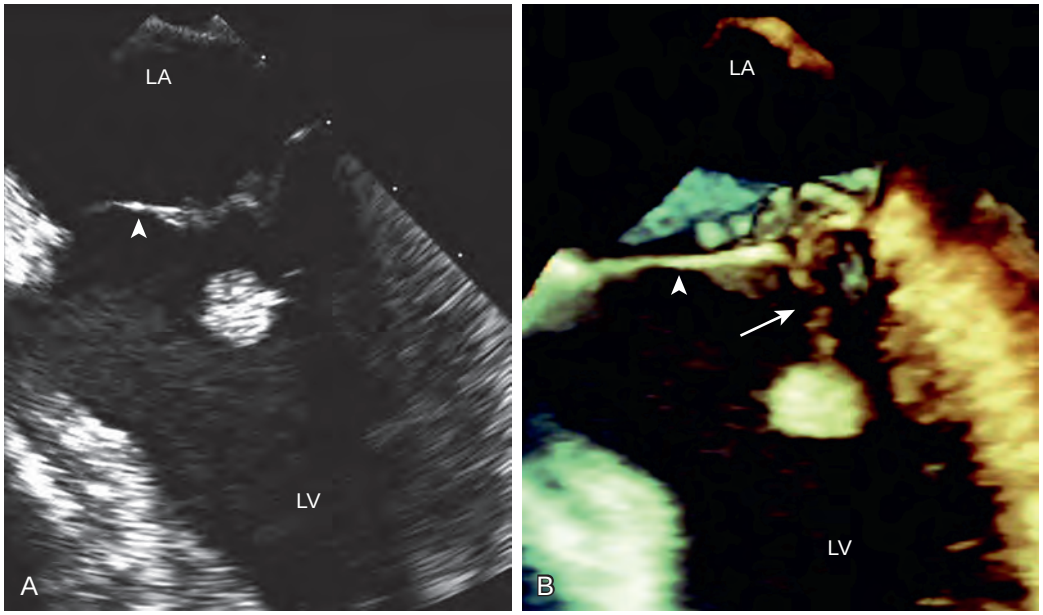
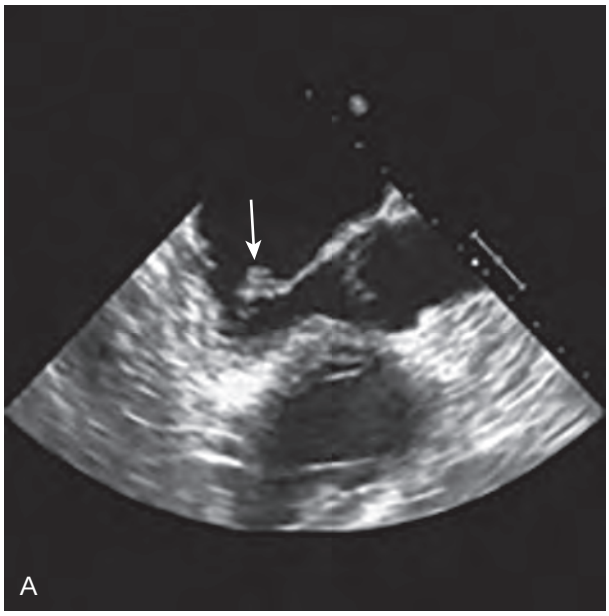
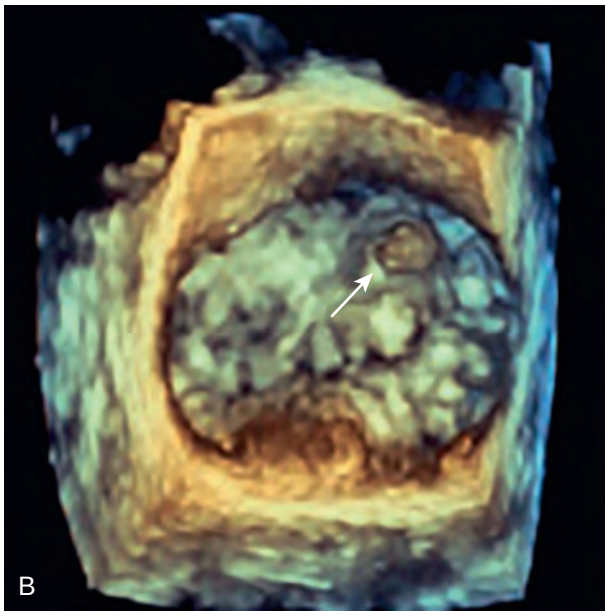


Fig. 24.5 Transesophageal midesophageal two-chamber view focused on the mitral valve shows a papillary fibroelastoma attached to the ventricular surface of the mitral valve. (A) Two-dimensional and (B) three-dimensional images show the 1-cm mass attached by a stalk *(arrow)* to the mitral valve *(arrowhead)*. *LA,* Left atrium; *LV,* left ventricle. *(Reproduced with permission from Bruce CJ. Cardiac tumours: diagnosis and management.* Heart. *2011;97:156.)*





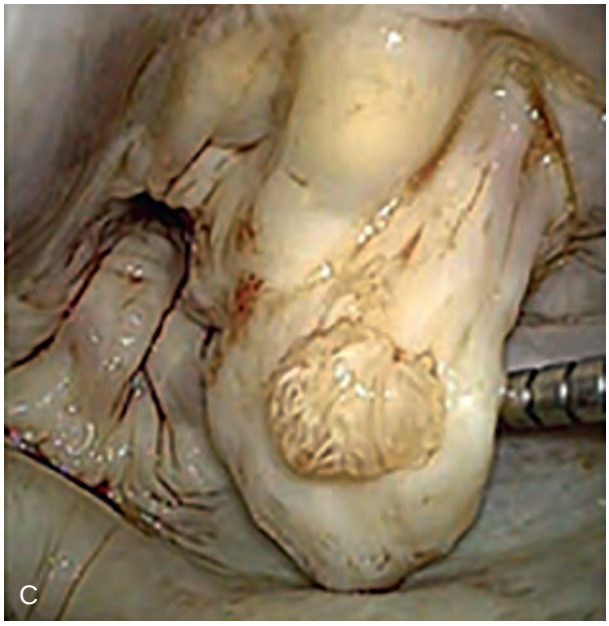
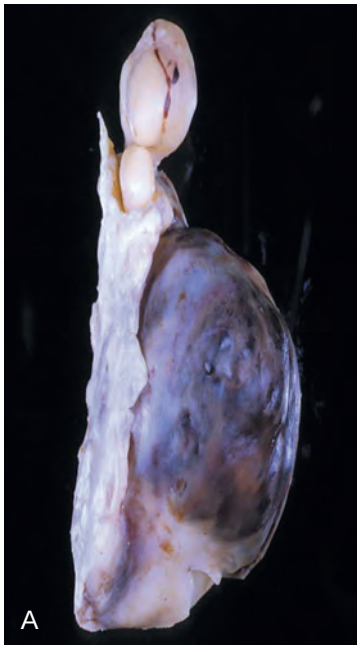


Fig. 24.6 Papillary fibroelastoma. (A) Transesophageal midesophageal long-axis view shows a globular mass *(arrow)* on the anterior leaflet of the mitral valve. (B) Transesophageal three-dimensional echocardiography of the mitral valve (surgeon's perspective from the left atrium) shows the mass on the medial scallop of the anterior mitral valve leaflet. (C) Intraoperative image shows the fibrotic, *pom pom–like* mass arising from the mitral leaflet endocardium. *(Reproduced with permission from Castillo JG, Silvay G. Characterization and management of cardiac tumors.* Semin Cardiothorac Vasc Anesth. *2010;14:10.)*



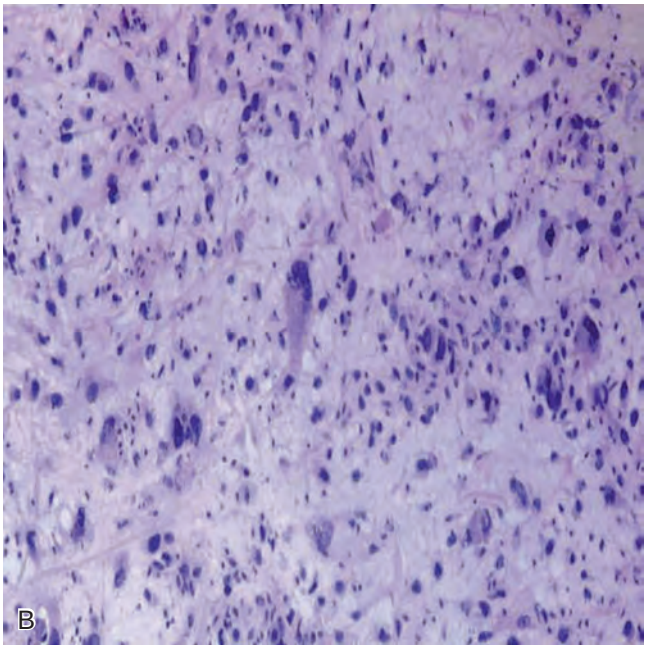


Fig. 24.7 Pleiomorphic sarcoma. (A) Gross specimen of a large, bilobed mass is demonstrated. (B) Histologic specimen shows spindle and polygonal pleomorphic cells arranged in sheets consistent with an undifferentiated, high-grade tumor. *(Reproduced with permission from Butany J, Nair V, Naseemuddin A, et al. Cardiac tumours: diagnosis and management.* Lancet Oncol. *2005;6:223.)*

progressing to death. Angiosarcomas, the most common sarcoma,[9] are rapidly spreading vascular tumors that arise most often from the RA and appear near the inferior vena cava (IVC) with extension to the mediastinum. They occur most commonly in adults and men.[43] Presenting symptoms include chest pain and dyspnea, progressive CHF, and bloody pericardial effusion.[46] There are two clinicopathologic forms of the tumor. The first type deposits a small tumor in the pericardium or epicardium and is associated with skin lesions or risk factors for Kaposi sarcoma. The second involves a large tumor in the RA. Treatment is palliative, because the response to chemotherapy and radiation is poor. Resection may be possible, but survival is less than 2 years. Rhabdomyosarcomas are aggressive tumors that have cellular elements that resemble striated muscle. These tumors occur equally in both sexes. They may originate in any chamber of the heart but, in contrast to angiosarcomas, rarely become diffusely involved with the pericardium. They are bulky and invasive, growing rapidly. Surgical resection is possible, but distant metastasis reduces the chances of success. Chemotherapy and radiation are ineffective.[43]

Echocardiography tends to be less helpful in the management of these patients than it is in patients with benign tumors. It may reveal physiologic complications of the tumor such as cavity obliteration or valvular regurgitation, and it is helpful in finding associated pericardial effusions and physiologic tamponade. However, these tumors have complex anatomy, and the perimeters of the tumor and their involvement in valve apparatuses and coronary anatomy can be difficult to determine even with TEE. In addition, echocardiography does not image adjacent cardiac structures such as the lung and mediastinum in detail. When echocardiography is combined with other imaging modalities such as CT and MRI, the clinician may obtain both the anatomic information needed (from the CT or MRI), as well as the physiologic consequences from echocardiography.[15]

Other primary malignant tumors of the heart include malignant fibrous histiocytoma, fibrosarcomas, osteosarcoma, leiomyosarcoma (the rarest malignant cardiac tumor), undifferentiated sarcoma, neurogenic sarcoma, and lymphomas. Primary cardiac lymphoma is defined as a non-Hodgkin lymphoma and accounts for approximately 1% of primary cardiac tumors.[47] Prevalence of these tumors has been increasing attributable, in part, to acquired immunodeficiency syndrome (AIDS) and to earlier detection with improvements in imaging technology. Lymphomas are generally large masses with extensive infiltration into adjacent areas of the heart from the point of tumor origin and are commonly located in the RA and RV. These primary tumors are very rare, representing less than 2% of all cardiac tumors.[48] Treatment involves a combination of chemotherapy and radiation, occasionally extending survival up to 5 years, but the median survival is 1 year. Malignant fibrous histiocytoma, in contrast to other sarcomas, is generally found in the LA. Despite resection, local recurrence and metastasis are common. Surgical excision may be useful to ameliorate symptoms but ultimately does not improve the poor survival.[49]

In general, malignant primary cardiac tumors may require a combination of surgery, radiation, and chemotherapy to limit cavitary obstruction to blood flow because of rapid growth and metastasis. Local recurrence is more likely to cause death than metastasis.[50] More aggressive approaches for malignant tumors with extensive local disease before metastasis include autotransplantation, during which the heart is removed from the chest cavity and inverted to provide better exposure.[51] Its value is still indeterminate, but no intraoperative deaths have occurred. Although still controversial, orthotopic heart transplantation may be considered for unresectable tumors that involve only the heart, but survival is not extended beyond 1 to 2 years.[18] The rate of intraoperative death with malignant tumor resection is seven times that of benign resection, and the morbidity rate is twice as high.

Metastatic Tumors

Although rare in general, secondary or metastatic cardiac tumors are far more common than primary tumors with an incidence at autopsy between 2.3% and 18.3%.[2,3,6,7,10] Metastatic tumors may involve the heart by direct extension, by venous extension, or by hematogenous or lymphatic spread.[2] These tumors may affect primarily the pericardium, the epicardium, the myocardium, or the endocardium, although one large autopsy series found that the pericardium was involved in approximately two thirds of the cases of metastatic disease (Figs. 24.8 through 24.11).[2] The site of metastasis frequently provides clues to the means of metastasis. Pericardial involvement, for example, often occurs via the direct extension from surrounding intrathoracic structures or from lymphatic spread, whereas endocardial lesions typically reflect hematogenous spread, and epicardial and myocardial lesions tend to arise from lymphatic extension.[2]

Tumors exhibiting high rates of cardiac metastases include mesothelioma (48.4%), melanoma (27.8%), pulmonary adenocarcinoma (21%), undifferentiated lung carcinoma (19.5%), pulmonary squamous cell carcinoma (18.5%), and breast carcinoma (15.5%), although other autopsy series suggest that esophageal carcinoma may also be commonly found in cases of cardiac metastases.[2,6] When considered by means of extension, direct extension is most likely to occur with tumors of the lung, breast, and esophagus, whereas hematogenous seeding is more likely with melanomas, and lymphatic spread is associated with lymphomas and leukemias. Venous extension, primarily involving right-sided cardiac structures, occurs with tumors of the kidneys (renal cell carcinoma), liver (hepatocellular carcinoma), and uterus (uterine leiomyosarcoma).[3,14]

In general, as is the case with most primary cardiac tumors, tumor location determines an individual's clinical presentation.[3] Although cardiac metastasis may be an incidental finding at autopsy, other lesions may exhibit the signs and symptoms of intracardiac or extracardiac obstruction, embolization, or arrhythmia.[52] Left-sided tumors involving the mitral or aortic valves may mimic stenotic lesions, producing angina, syncope, or heart failure with progressive pulmonary venous hypertension, whereas right-sided masses may affect all the manifestations of right-sided heart failure with hepatic congestion, ascites, abdominal distention, and worsening renal function in the face of venous hypertension.[2,52] With lesions affecting the pericardium or epicardium, a large pericardial effusion may develop with the manifestations of tamponade and obstructive shock, depending on the rate of pericardial fluid accumulation.[2] Embolization of right-sided lesions may be clinically silent or may be similar to thrombotic pulmonary emboli with tachycardia, chest pain, dyspnea, or hypoxemia. Embolization of left-sided tumors classically exhibit neurologic manifestations, although systemic embolization may affect the ischemia of any end organ, including the kidneys and abdominal viscera, or produce cutaneous manifestations. When the myocardium is involved, progressive tumor infiltration has the potential to produce any number of atrial and ventricular arrhythmias or conduction abnormalities, depending on tumor location.[2]

Although TTE or TEE may be useful in detecting and localizing metastatic disease, multimodal imaging with CT or MRI may be necessary to determine the extent of cardiac involvement and to facilitate tissue characterization and diagnosis, particularly in cases where the primary lesion is unknown.[14] Unsurprisingly, the prognosis with a diagnosis of metastatic cardiac disease is poor. In one recent small series, 53.4% of patients diagnosed with metastatic lesions were deceased at 1 year.[53] Although surgical intervention is not typically contemplated, 53.5% of the patients with metastatic disease in that series underwent surgical resection. Of those who underwent resection, 56.5% were alive at 1 year.[53]

Anesthetic Considerations

In general, anesthetic management of patients with cardiac tumors is likely guided first by the patient's comorbidities and second by tumor location. Clearly, a patient with an invasive right-sided lesion and the stigmata of right-sided heart failure undergoing a palliative resection will warrant different management than a young, otherwise healthy individual undergoing a minimally invasive papillary fibroelastoma resection.

At the current time, tumor resection is an invasive procedure requiring general anesthesia. However, it is easy to imagine a time in

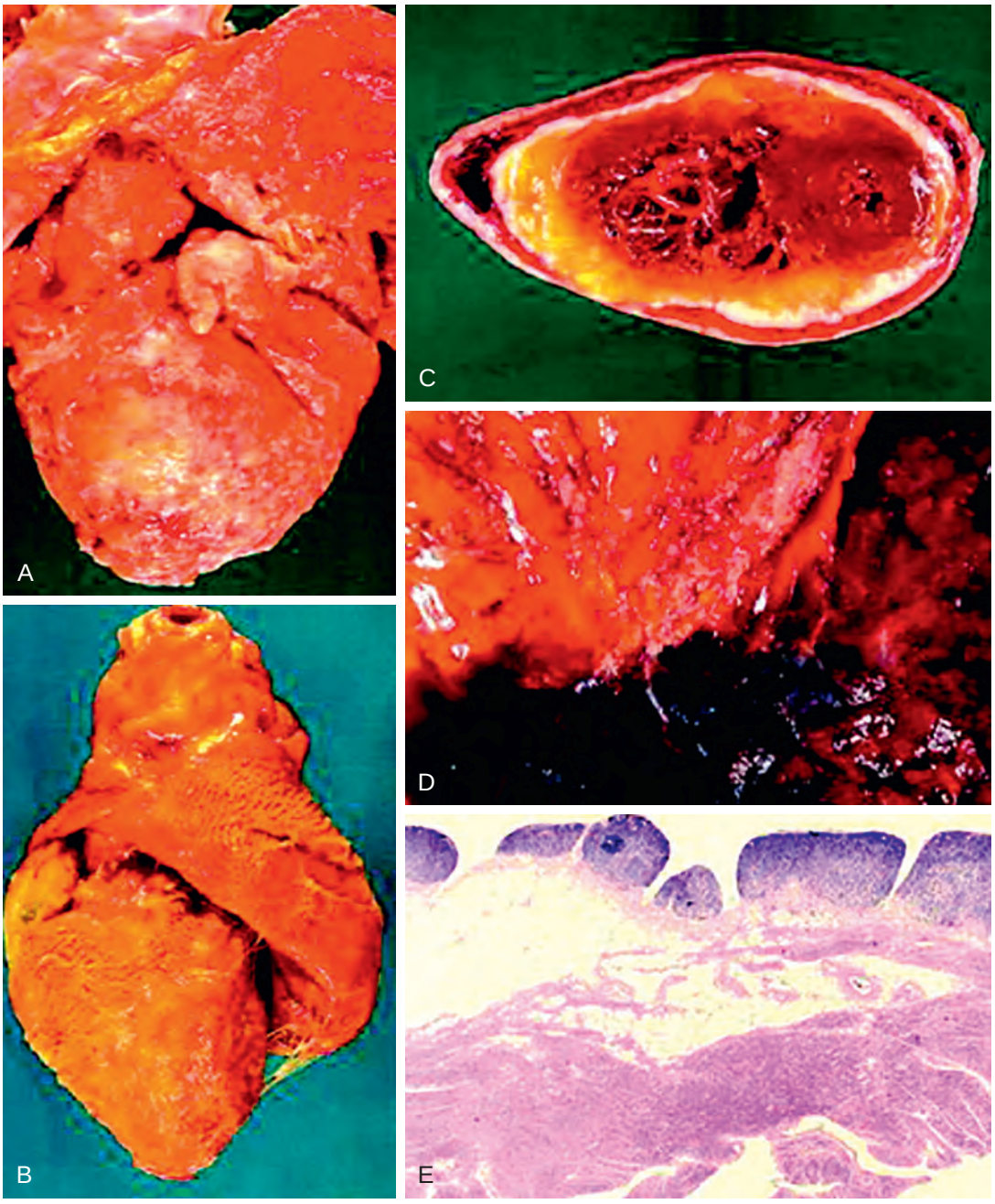


Fig. 24.8 Patterns of tumors metastatic to the heart. Pericardial metastases of esophageal squamous cell carcinoma with fibrinohemorrhagic pericarditis. *(Reproduced with permission from Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases.* J Clin Pathol. *2007;60:29.)*

the not-too-distant future when small, uncomplicated lesions could be resected using catheter-based approaches performed in a cardiac catheterization suite or a hybrid surgical unit under monitored anesthesia care, similar to some transfemoral aortic valve insertions or percutaneous mitral valve repairs that are performed today. At present, however, general anesthesia with an airway secured with an endotracheal tube is required. For minimally invasive or robotic-assisted procedures using limited thoracotomies, lung isolation is required with either a double-lumen endotracheal tube or a bronchial blocker.[54,55]

In addition to the American Society of Anesthesiologists standard monitors providing continual evaluation of oxygenation, ventilation, circulation, and temperature, anesthesia for resectioning a cardiac tumor will undoubtedly involve placing an arterial line for continuous hemodynamic monitoring and establishing central venous access for vasoactive drug administration, volume infusion, and pressure monitoring. For patients with depressed cardiac function in whom mechanical circulatory support may be anticipated at the conclusion of the bypass run or for patients whose surgical resection may be complicated, involving a prolonged bypass run, after which a discrepancy between central and peripheral blood pressures may be significant, consideration may be given to placing a second arterial line in either a femoral or a brachial location. The timing of arterial line placement with respect to anesthetic induction should be guided by the patient's comorbidities and provider experience. Similarly, the choice of catheters and their placement locations for central venous access should be guided by the patient's pathologic condition and the surgical skill

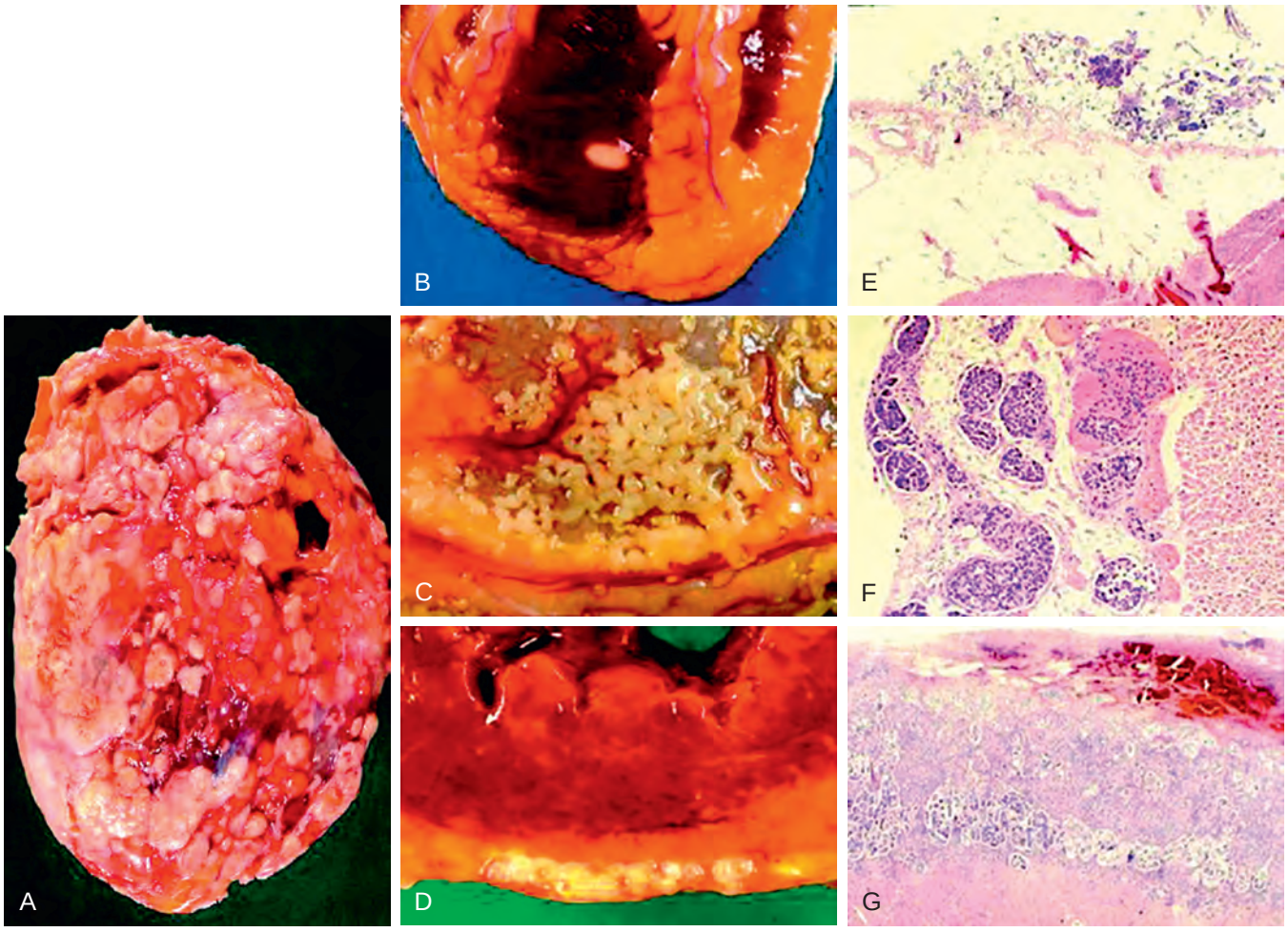


Fig. 24.9 Patterns of tumors metastatic to the heart. Epicardial metastases of malignant mesothelioma. *(Reproduced with permission from Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases.* J Clin Pathol. *2007;60:30.)*

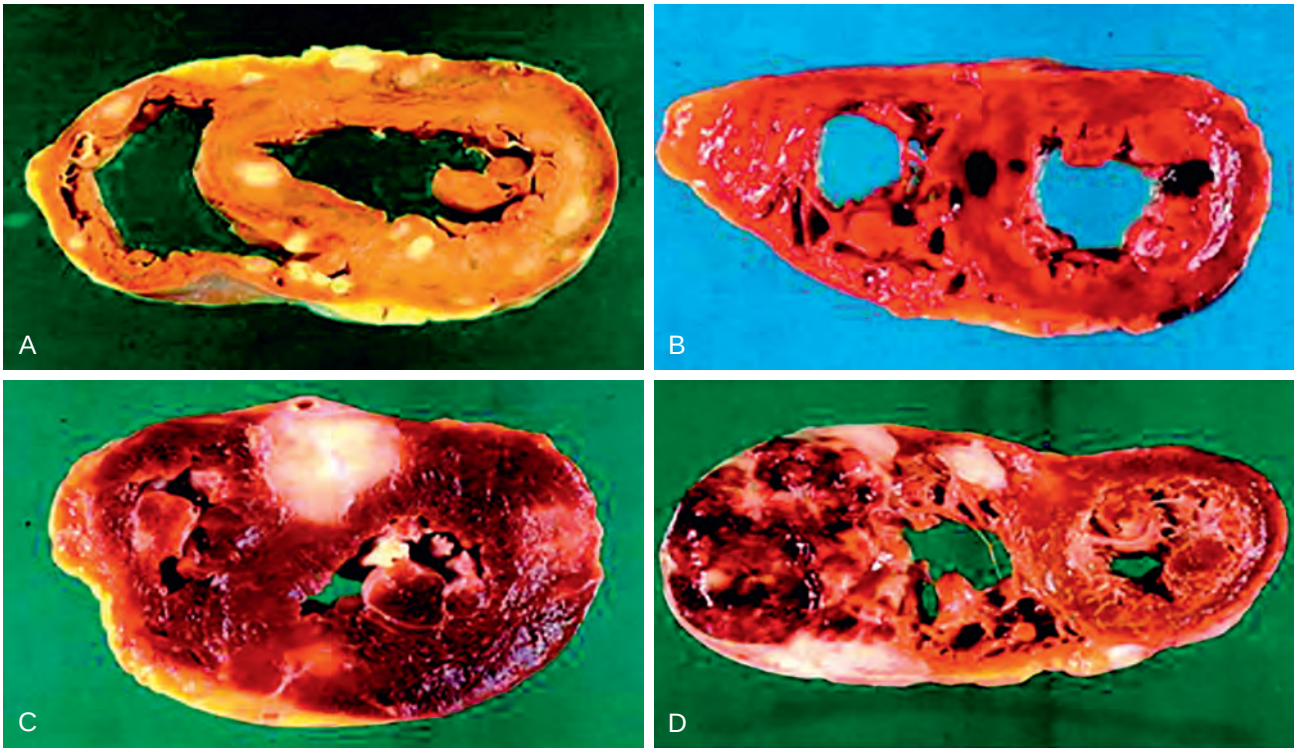


Fig. 24.10 Patterns of tumors metastatic to the heart. Myocardial metastases of malignant melanoma. *(Reproduced with permission from Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases.* J Clin Pathol. *2007;60:31.)*

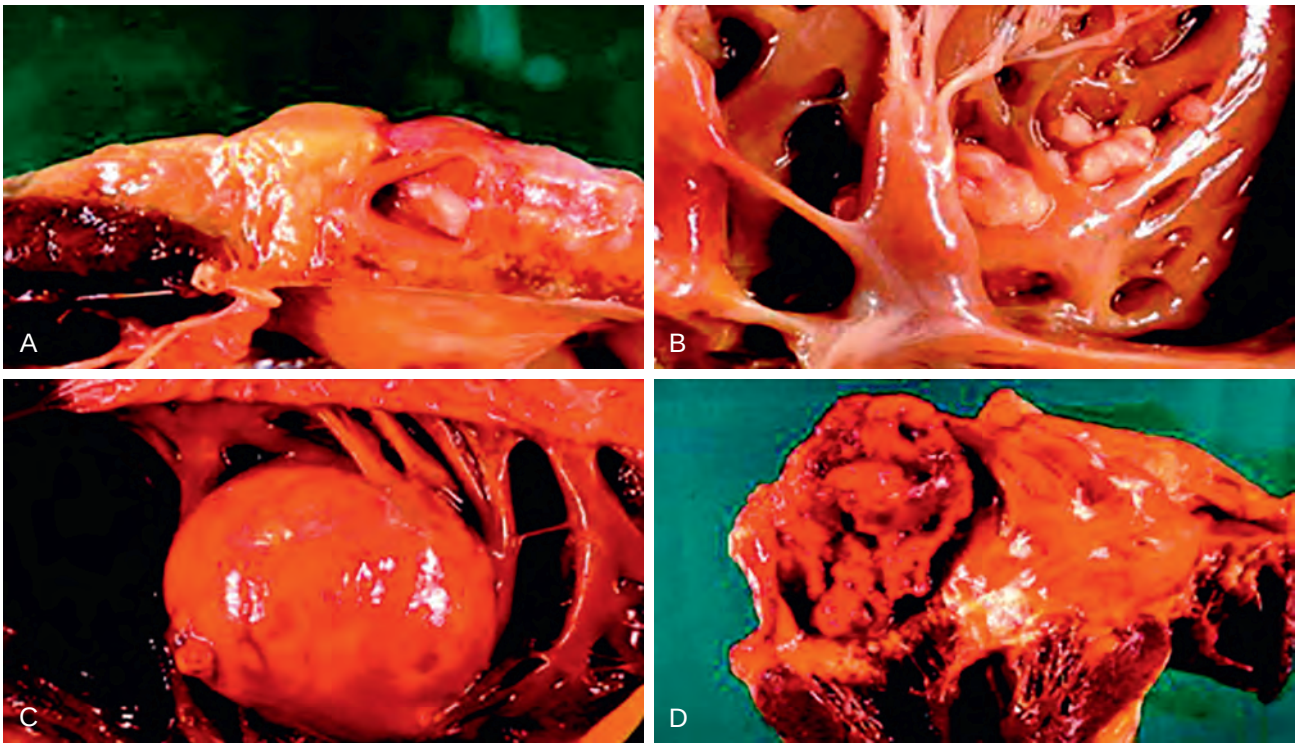


Fig. 24.11 Patterns of tumors metastatic to the heart. Endocardial metastases of renal clear cell carcinoma. *(Reproduced with permission from Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases.* J Clin Pathol. *2007;60:31.)*

of the provider. A healthy 20 year old undergoing resection of a small atrial myxoma may require no more than a triple- or quadruple-lumen infusion catheter, whereas a debilitated 70 year old undergoing resection of a tumor with myocardial involvement and ventricular reconstruction may merit more than one central venous catheter, as well as a pulmonary artery catheter (PAC). Tumors with extensive right-sided involvement and superior vena cava (SVC) compromise may call for the avoidance or delayed (postresection) placement of PACs or the placement of catheters in the femoral vessels rather than in the neck. A skilled surgeon who can resect a tumor with a 20-minute pump run may require different monitoring than a less facile surgeon whose shortest pump times may never be less than an hour.

The choice of induction drugs, again, likely depends less on the tumor's pathologic nature than on patient comorbidity and personal preference. In general, the choice of drug is likely to matter less than how the drug is used. A patient with an effectively stenotic left-sided lesion can just as safely be managed with judicious doses of propofol as with etomidate, ketamine, or barbiturate. The requirement for pharmacologic support with the separation from cardiopulmonary bypass (CPB) will be guided more by patient comorbidity and the details of surgical resection than by the pathologic nature of the tumor.

Anesthetic management is guided by tumor location in addition to patient comorbidity. Left atrial myxomas, for example, will most likely cause mitral valve obstruction, often in conjunction with pulmonary venous hypertension. Anesthetic management will closely resemble that of a patient with mitral stenosis. In contrast, right atrial myxomas may produce signs of right-sided heart failure that correspond to tricuspid valve obstruction. Positioning the patient for surgery must be carefully performed to detect severe restriction of venous return that may often be quickly followed with profound hypotension and arrhythmias. A large tumor may increase the likelihood of hemodynamic instability, whereas small tumors may be associated with increased risk of embolization.[12] Perioperative arrhythmias, especially atrial fibrillation or atrial flutter, may arise in 25% of these patients and may require immediate treatment.

Although median sternotomy may be required for many procedures, others involving isolated, superficial lesions may be performed through an anterior thoracotomy or similar minimally invasive techniques.[18,54–56] Femoral cannulation for the initiation of CPB may minimize the risk of tumor dislodgment or fragmentation. If bicaval venous cannulation is required, then a second venous cannula may be placed in the SVC, often using a small 5 or 6 French sheath placed by the cardiac anesthesia team that is subsequently upsized using the Seldinger technique to an appropriate venous cannula. Cardiac arrest is required for open-chambered procedures. With a prohibitive aorta, ventricular fibrillatory arrest may be used to prevent ejection of blood and embolization of tumor fragments after initiating CPB. For malignant tumors with significant myocardial invasion, deep hypothermic circulatory arrest may be required.

Tumors With Systemic Cardiac Manifestations

Carcinoid Tumors

Carcinoid tumors are metastasizing neuroendocrine tumors that arise primarily from the small bowel, occurring in 1 to 2 per 100,000 people in the population.[57,58] Upon diagnosis, 20% to 30% of individuals with carcinoid tumors exhibit the symptoms of carcinoid syndrome, characterized by episodic vasomotor symptoms, bronchospasm, hypotension, diarrhea, and right-sided heart disease attributed to the release of serotonin, histamine, bradykinins, and prostaglandins, often in response to manipulation or pharmacologic stimulation. Manifestations of carcinoid syndrome occur primarily in patients with liver metastasis that impair the ability of the liver to inactivate large amounts of vasoactive substances.

Initially described in 1952,[57] carcinoid heart disease may occur in 20% to 50% of patients with carcinoid syndrome.[59,60] Carcinoid heart disease may be the initial feature of metastatic carcinoid disease in 20% of patients. The prognosis has improved substantially in the last 20 years for individuals with malignant carcinoid tumors and carcinoid heart disease, but it still causes considerable morbidity and

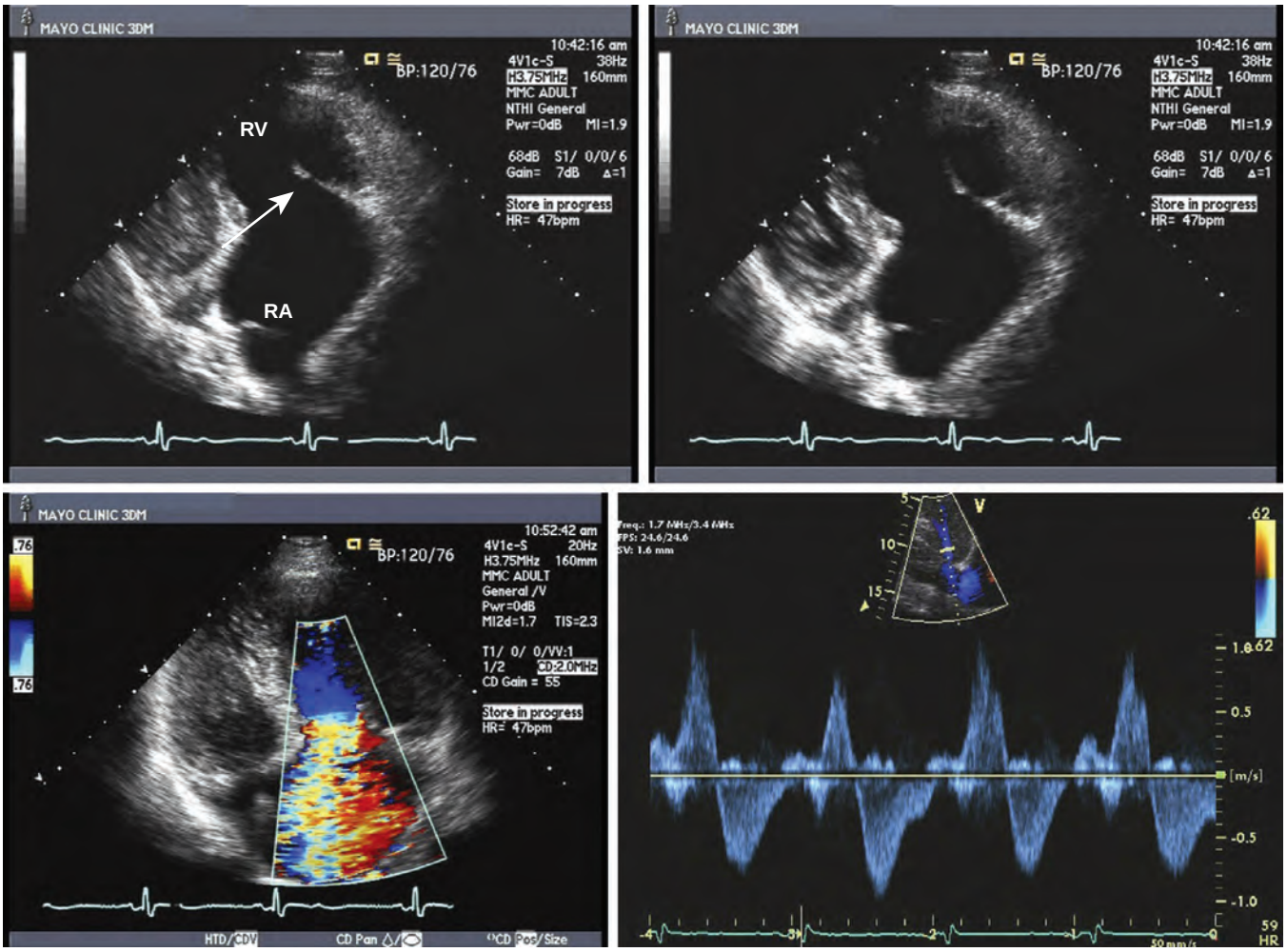


Fig. 24.12 Transthoracic imaging using an apical view in a patient with carcinoid heart disease. The *upper left and right panels* show the tricuspid valve *(arrow)* in both systole and diastole, respectively. The thickened tricuspid leaflets move little between systole and diastole and demonstrate an enormous coaptation defect during systole *(upper left panel)*. Color-flow Doppler imaging *(lower left panel)* reveals massive tricuspid regurgitation that fills the entire right atrium, which is severely dilated. In the *lower right panel*, continuous-wave Doppler imaging of the hepatic veins reveals systolic flow reversals (deflection of Doppler signal above the baseline during systole), which is indicative of severe tricuspid regurgitation. *RA*, Right atrium; *RV*, right ventricle. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:680.)*

mortality. The median life expectancy is 5.9 years without carcinoid heart disease but falls to 2.6 years if it is present.[60] Circulating serotonin levels had once been found to be more than twice as high in persons with carcinoid syndrome who develop carcinoid heart disease,[61] but this is no longer true because most patients receive somatostatin analogs.[60]

Carcinoid heart disease characteristically produces tricuspid regurgitation and mixed pulmonic stenosis and regurgitation resulting in severe right-sided heart failure (Fig. 24.12). Tumor growth in the liver permits large amounts of tumor products to reach the RV without the benefit of first-pass hepatic metabolism (Fig. 24.13). Carcinoid plaques composed of myofibroblasts, collagen, and myxoid matrix[62] are deposited primarily on the tricuspid and pulmonary valves, bringing about immobility and thickening of the valve leaflets, causing the distinctive valvular changes (Figs. 24.14 through 24.16). At the time of surgery, 80% of tricuspid valves are observed to be incompetent with only 20% with stenosis, whereas the affected pulmonary valves tend to be equally divided between incompetence and stenosis.[62] The exact mechanism that causes valve injury is unknown, but high levels of serotonin are sometimes found in patients with carcinoid heart disease.[57] Fewer than 10% of those with carcinoid heart disease have left-sided heart involvement, possibly attributable to inactivation of serotonin in the lungs,[62,63] but either the mitral or aortic valve may be affected in the presence of a bronchial carcinoid, a right-to-left intracardiac shunt, or poorly controlled disease with high levels of circulating vasoactive substances.[58,63,64]

Echocardiographic features of carcinoid heart disease, particularly of the tricuspid valve, are practically diagnostic of the underlying disease process. The leaflets are thickened and retracted. The appearance of the tricuspid leaflets often appears as if the leaflets are curled under. The thickening and retraction of the leaflets result in a large coaptation defect and severe valvular regurgitation. The pulmonic valve may be difficult to image with TTE, but the midesophageal echocardiographic view at 70 to 90 degrees often shows the valve well. With severe tricuspid regurgitation, the RV will dilate and abnormal ventricular septal motion may be noted. Ventricular wall thickness is usually normal. Doppler imaging of the hepatic veins will show systolic flow reversals consistent with severe tricuspid regurgitation.

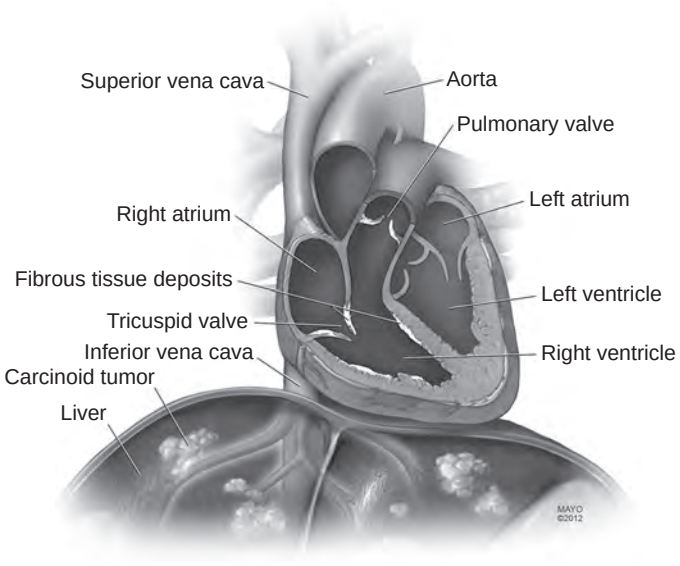


Fig. 24.13 Patterns of carcinoid plaque deposition in carcinoid heart disease. The location of the plaques is predominantly in the right heart and especially on the leaflets of the tricuspid and pulmonary valves. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Illustration No. 3229175-001-0.)*

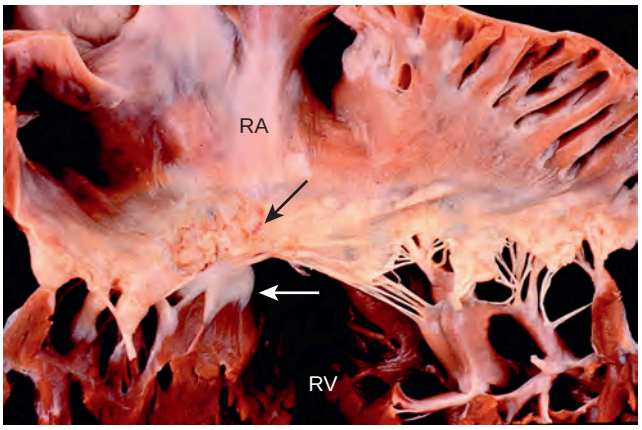


Fig. 24.14 Carcinoid heart disease. A postmortem specimen shows the tricuspid valve with carcinoid deposition, creating thickened, retracted leaflets *(black arrow)* and chordal shortening *(white arrow)*. *RA,* Right atrium; *RV,* right ventricle. *(Reproduced with permission from Weingarten TN, Abel MD, Connolly HM, et al. Intraoperative management of patients with carcinoid heart disease having valvular surgery: a review of one hundred consecutive cases.* Anesth Analg. *2007;105:1193.)*

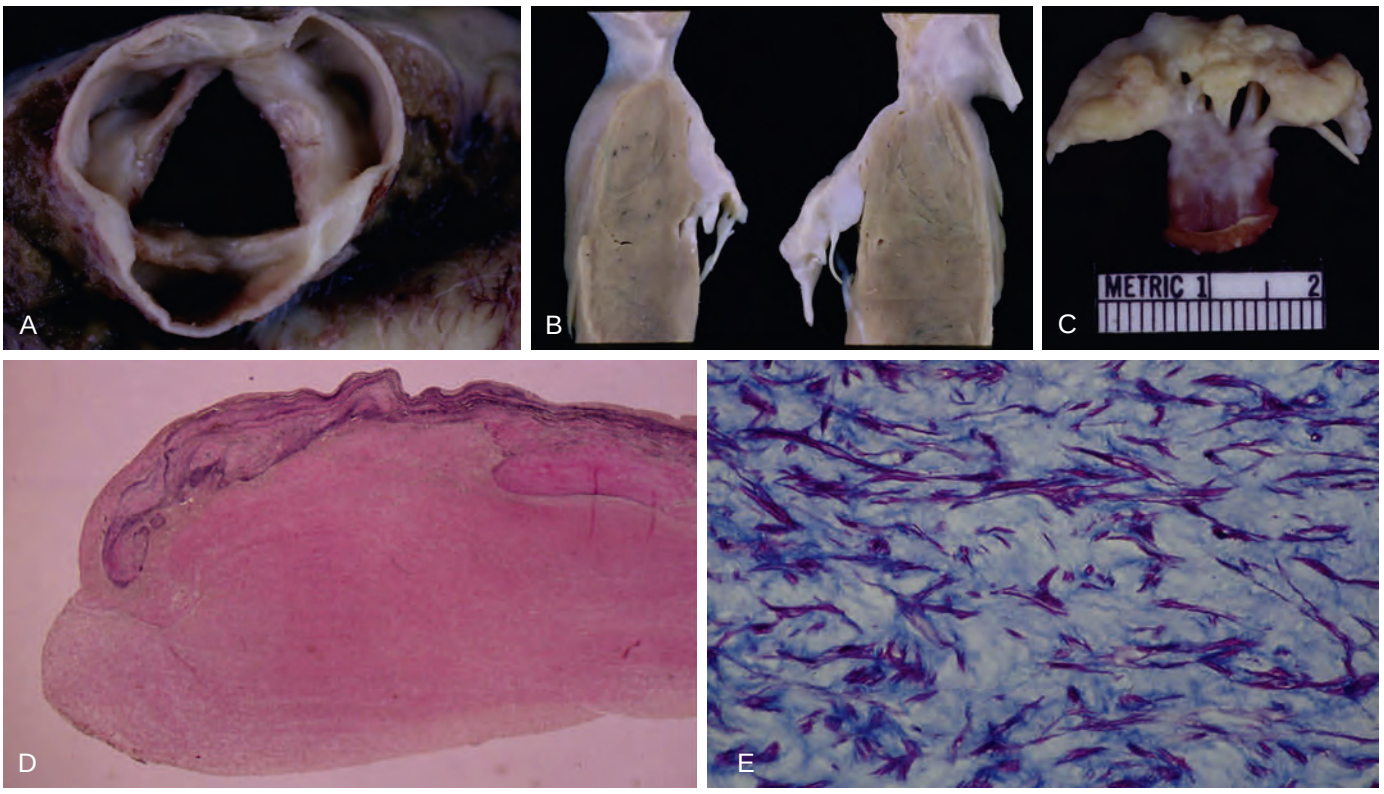


Fig. 24.15 Carcinoid heart disease. (A) Gross specimen of a pulmonic valve with thickened, distorted leaflets is revealed, creating mixed stenosis and regurgitation. (B) Gross cross section of an affected tricuspid valve shows severely thickened and incompetent leaflets. (C) Gross specimen of a tricuspid valve and chordal apparatus is distorted and layered with whitish carcinoid plaques. (D) Histologic specimen of a pulmonary valve cusp reveals a carcinoid plaque, coating its pulmonary arterial *(upper)* surface. (E) Histologic plaque specimen shows characteristic myofibroblast *(red)* proliferation and collagen *(blue)* deposition with Masson trichrome stain. *(Reproduced with permission from Gustafsson BI, Hauso O, Drozdov I, et al. Carcinoid heart disease.* Int J Cardiol. *2008;129:321.)*

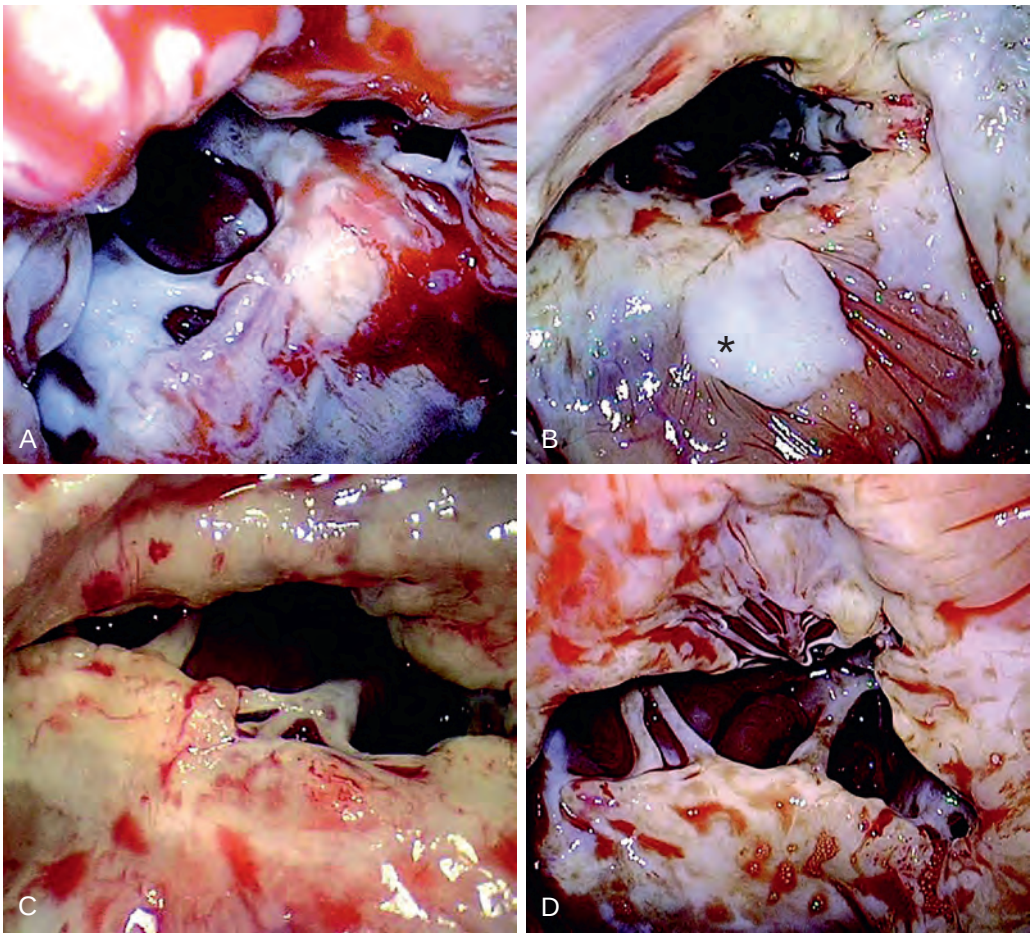


Fig. 24.16 (A–D) Intraoperative views of carcinoid heart disease affecting the tricuspid valve are shown from the right atrium. The thickened, retracted leaflets; the fusion and shortening of the chordal apparatus; and the classic pearly, *stuck-on* appearance of a carcinoid plaque *(asterisk)* are noted. *(Reproduced with permission from Castillo JG, Milla F, Adams DH. Surgical management of carcinoid heart valve disease.* Semin Thorac Cardiovasc Surg. *2012;24:256.)*

A careful search for a patent foramen ovale (PFO) should be undertaken, because its presence raises the possibility of left-sided valvular involvement.[58,64]

Historically, the prognosis of patients with carcinoid syndrome has been poor. In the absence of treatment, median survival was 38 months from the time of development of systemic symptoms.[65] With the development of cardiac involvement and frank carcinoid heart disease, median survival has dropped to a dismal 11 months.[57,65] Improvements in medical management and surgical technique, however, have led to improved symptom control and a lower mortality rate.[57,60] In a retrospective review of 200 patients with carcinoid syndrome referred to the Mayo Clinic, Møller and colleagues[60] found that median survival improved from 1.3 years in the 1980s to longer than 4 years in the late 1990s.[60] Of the 200 patients in the study, 87 underwent cardiac surgery; in addition, when cardiac surgery was included in a multivariate analysis, it was associated with a significant risk reduction. Although the introduction of somatostatin analogues in the mid-1980s was associated with improved symptom control, no evidence suggested that their use was associated with improved survival.[57,60]

The management of patients with carcinoid disease, in general, and carcinoid heart disease, in particular, is complex, requiring a multidisciplinary team of gastroenterologists, endocrinologists, oncologists, general and hepatic surgeons, cardiologists, cardiac surgeons, cardiac anesthesiologists, and surgical intensivists.[58,66] The mainstays of treatment are symptom management with somatostatin analogues and medical management of right-sided heart failure; antitumor therapy with chemotherapy, vascular embolization and surgical debulking; and surgical treatment of carcinoid heart disease.[57,58,66]

First reported in 1985 for the rapid reversal of carcinoid crisis, somatostatin analogues bind somatostatin receptors on carcinoid cells and prevent the release of the vasoactive mediators responsible for the carcinoid syndrome.[67,68] Currently, two somatostatin analogues are available for treatment, octreotide and lanreotide.[69] Octreotide, itself, may be administered as an immediate-release subcutaneous injection, administered two to three times daily at doses between 100 and 500 μg; or it may be administered as a long-acting depot formulation given intramuscularly every 4 weeks at doses between 10 and 60 mg.[69] Although the somatostatin analogues provide symptom relief, their use has not been associated with any demonstrated mortality benefit.[57,66]

A large percentage of patients with carcinoid heart disease are asymptomatic, because the disease is mild. Early detection can affect prognosis as the progression of cardiac disease, especially to right ventricular failure, increases mortality.[59] Treatment of the tumor and the malignant carcinoid syndrome does not result in regression of carcinoid heart disease.[60] The surgical replacement of both the tricuspid and pulmonary valves with either bioprosthetic or mechanical valves is the only viable therapeutic option.[70] The decision regarding mechanical or bioprosthetic valves depends on individual risks and concerns.[57,64,71] The optimal timing of surgical intervention is uncertain but should be considered when signs of right-sided heart failure appear if not before.[64,72] With improvements in surgical technique and perioperative care, postoperative mortality in the large cohort from the

Mayo Clinic improved from 25% in the mid-1980s to 9% in the late 1990s, although this change was not statistically significant.[60]

Anesthetic Considerations

Patients who have carcinoid heart disease and require cardiac surgical intervention pose an anesthetic challenge.[72–77] A carcinoid crisis with exuberant vasoactive-mediator release is a life-threatening event that may be precipitated by endogenous and exogenous stimuli alike. Patient anxiety and fear in anticipation of surgical intervention may provoke a crisis. A variety of pharmacologic agents, including thiopental, meperidine, morphine, atracurium, and succinylcholine, as well as catecholamines such as epinephrine, norepinephrine, dopamine, and dobutamine, have all been implicated, often anecdotally, in crisis precipitation. Furthermore, physical stimulation that may occur with laryngoscopy and endotracheal intubation, vascular access placement and the placement of urinary catheters, and tumor manipulation that may occur during tumor resection may also elicit a brisk release of vasoactive mediators.

Preoperative control of carcinoid activity is a critical aspect of perioperative management.[58,72,77] The importance of a multidisciplinary team coordinating patient care, ensuring optimal preoperative symptom control and anticipating perioperative problems, cannot be overestimated. The perioperative management of a patient with severe disease, although with minimal symptoms, who is maintained on a long-acting somatostatin analogue formulation supplemented preoperatively with additional subcutaneous injections of short-acting drug, is entirely different from that of a severely symptomatic patient who only recently was begun on low doses of short-acting medications. Although the former may be a candidate for a rapid recovery postoperative protocol and may spend only a single night in the intensive care unit, the latter may incur significant morbidity and even mortality.

Perioperative patient management is facilitated with optimal preoperative symptom control with carefully monitored administration and up-titration of a long-acting somatostatin analogue formulation, supplemented preoperatively with additional subcutaneous injections of short-acting medications. Some institutions initiate an octreotide infusion at doses between 50 and 100 μg per hour the night before surgery or the day of surgery in the preoperative holding area, while providing additional intravenous doses of 20 to 100 μg as indicated clinically during anesthetic management.[72,77,78] In the absence of any randomized clinical trials, it remains unclear whether any data, other than institutional experience, can guide the decisions regarding the need for preoperative infusion therapy, the timing of its initiation, the dosing regimen, and the strategy for intraoperative bolusing. It may well be the case that the presence of a well-reasoned institutional protocol designed and monitored by a multidisciplinary team is at least as important, if not more important, than the details of pharmacologic dosing.[72,77] Incidentally, it should be noted that severe hyperglycemia may occur with octreotide because of its inhibition of insulin secretion, especially in combination with steroids. Consequently, regimented glucose monitoring is recommended, especially in an era when hospital reimbursements are tied, in part, to perioperative glycemic control.[68,71]

Because patient anxiety and stress may provoke a carcinoid crisis, consideration should be given to judicious administration of preoperative anxiolytic agents.[73,77] The emphasis, however, should be on judicious, and the dosing should be guided by clinical judgment rather than simply by diagnosis. Liberal preoperative administration of benzodiazepines, especially in conjunction with opioids, to an already sedate patient may result not in the intended plane of hemodynamic stability but in progressive hypoxemia and hypercarbia, leading to right ventricular compromise and the very cardiovascular collapse one meant to avoid. A variety of strategies have been recommended for the induction and maintenance of general anesthesia: use etomidate rather than thiopental; use fentanyl or sufentanil rather than morphine and meperidine; avoid atracurium and succinylcholine, considering vecuronium or cisatracurium; and maintain the patient with isoflurane.[77,78] Without exception, these are anecdotal recommendations. For a patient, even a patient with severe disease, whose symptoms are well-controlled preoperatively on a regimen of long- and short-acting octreotide or its equivalent, it is likely the case that the drugs used matter less than how they are used and matter less than the vigilance of the anesthesiologist directing the patient's care.

One particular challenge with cardiac surgical patients in general and with carcinoid cardiac surgical patients in particular is determining the cause of intraoperative hypotension and thus its appropriate treatment.[72] Clearly, a carcinoid crisis should be at the top of a differential diagnosis, but making that diagnosis with speed and certainty may be difficult, especially when surgical drapes may mask the cutaneous manifestations of a crisis and volatile anesthetics may minimize attendant bronchospasm. Even in the absence of diagnostic certainty, some practitioners may treat each such episode of apparently unprovoked hypotension with a bolus of intravenous octreotide in doses of 20 to 100 μg. Some anesthesiologists may simultaneously administer a subcutaneous dose of 50 to 100 μg with the intention of providing an additional depot of drug to smooth further hemodynamic oscillations. In the face of repeated episodes of apparently unprovoked hypotension, an anesthesiologist may start an octreotide infusion, if he or she has not done so already, at rates of 50 to 100 micrograms per hour, up-titrating it as necessary to a rate of 300 μg/hr. Once started, such infusions are typically continued into the postoperative period. Once the patient is clinically stable, he or she may be weaned and the infusions discontinued, often in accordance with the recommendations of a cardiac surgical critical care pharmacist, over the succeeding 24 to 48 hours. As has been stated repeatedly, evidence-based data for such interventions are absent, and the choice of drug administration, dosing, route, and timing are based largely on institutional protocol and individual provider preference and experience.

In carcinoid patients, acute right ventricular heart failure should also be considered as a potential cause of intraoperative hypotension.[72] Carcinoid heart disease is preferentially a disease of the right-sided heart valves, and it is typically right-sided heart failure that prompts surgical intervention.[57,58] The development of intraoperative hypoxemia, hypercarbia, and acidemia may be sufficient to cause acute right-sided heart failure in an already compromised ventricle. Intraoperative TEE is key for monitoring changes in biventricular function.

When intraoperative hypotension arises, as it inevitably will in patients with carcinoid heart disease, it should be treated promptly even if its cause is unclear. Early and judicious administration of octreotide has been discussed. Previously, certain catecholamines (epinephrine, norepinephrine, dopamine, and isoproterenol) were considered to provoke mediator release in carcinoid syndrome, but a retrospective study of 100 consecutive patients with carcinoid heart disease who underwent cardiac surgery did not show a significant increase in intraoperative octreotide use or mortality with the administration of such vasoactive and inotropic medications.[76] Because nearly 75% of patients with carcinoid heart disease scheduled for cardiac surgical intervention will be in New York Heart Association (NYHA) class III or higher and will require multiple-valve replacement, vasoactive and inotropic medication should be administered according to hemodynamic indices and clinical judgment.[72,77]

Finally, surgical intervention on multiple valves inevitably entails longer aortic cross-clamp and CPB times. In the setting of increased duration of exposure to extracorporeal circulation and hepatic dysfunction associated with liver metastases, coagulopathy and excessive hemorrhage after bypass are anticipated.[77,78] Although malignancy may be associated with a hypercoagulable state, the use of an antifibrinolytic medication is routine in many centers during carcinoid surgery to reduce blood loss and transfusion requirements associated with cardiac surgery.[76,77,79]

Renal Cell Carcinoma

Although renal cell carcinoma may not normally be considered a topic in cardiac anesthesia, cardiac anesthesia team members may increasingly find themselves caring for patients with renal cell carcinoma with significant venous extension.[80] Renal cell cancers represent 2%

to 3% of adult malignancies but are the most common and most deadly of renal neoplasms, accounting for approximately 90% of all renal cancers and conferring historic mortality rates between 30% and 40%.[81–83] Renal cell carcinoma is a disease of the aging, occurring most commonly in patients in their 60s and 70s, with a slight male-to-female predominance (1.5:1).[81,84] Although classically diagnosed by a combination of flank pain, hematuria, and a palpable mass, most renal cell cancers are now found incidentally during radiographic evaluation for other reasons.[81] Largely as a result of the increased frequency of abdominal imaging, the incidence of renal cell cancers has increased in the United States between 3% and 4% annually since the 1970s.[82] A small (2–3%) proportion of the cancers may be associated with familial syndromes, such as von Hippel-Lindau disease, although smoking, obesity, and hypertension are considered the three primary modifiable risk factors.[81–83]

Renal cell malignancies do not represent a single tumor type but, in fact, comprise a number of tumor subtypes, the most common of which are clear cell carcinoma (70–80% of all renal cell tumors), papillary renal cell carcinoma (10–15% of all renal cell tumors), and chromophobe renal cell carcinoma (3–5% of all renal cell tumors).[81–83] Notably, the most common variant of clear cell tumors is that they are highly vascular, confer a worse prognosis than their papillary or chromophobe counterparts, and tend to produce venous tumor extension into the renal veins and the IVC.[82] According to the American Joint Committee on Cancer Staging, a T1 lesion is 7 cm or less and confined to the kidney, whereas a T2 lesion is greater than 7 cm but still confined to the kidney, a T3 lesion extends into major veins and perinephric tissue, and a T4 lesion extends beyond the Gerota fascia.[82] Although the pathologic stage, incorporating tumor size, vascular involvement, and extension, is the most important prognostic factor, an individual's clinical and performance status, tumor histologic anatomy, and tumor molecular markers all combine to influence survival.[81,82] For patients most likely encountered in a cardiac surgical unit with tumor invasion of the IVC extending above the diaphragm (stage T3c), the 5-year survival is between 20% and 40%.[82]

Particularly pertinent to cardiac anesthesiologists is the propensity of clear cell renal cell carcinomas to invade venous vascular structures and produce venous tumor thrombus in 4% to 10% of cases.[82] According to a classification system developed at the Mayo Clinic in the 1980s, level I tumor thrombus is confined to the ipsilateral renal vein or extends 2 cm or less into the IVC. A level II tumor thrombus extends more than 2 cm into the IVC but remains below the hepatic veins, whereas a level III mass involves the intrahepatic IVC but remains below the diaphragm. A level IV thrombus extends above the diaphragm and may involve the RA and right-sided heart structures (Fig. 24.17).[85,86] Tumors demonstrating caval extension are considered locally advanced and curiously may not be associated with metastatic lesions.[82] As such, a combination of radical nephrectomy and IVC tumor thrombectomy may be curative in 45% to 70% of cases, and more cephalad venous extension may not necessarily portend a worse prognosis.[82,84,86]

Historically, surgery for levels III and IV tumors has been performed on CPB, often using deep hypothermic circulatory arrest.[82,86–92] As discussed in other chapters, exposure to extracorporeal circulation and to profound hypothermia is far from benign. In the context of concomitant radical nephrectomy and tumor thrombus resection, procedures performed on CPB, with or without hypothermic arrest, may be associated with a profound hypocoagulable state, requiring transfusion of a significant volume of blood and blood products.[82,86] In an attempt to avoid exposure to extracorporeal circulation, to avoid the neurologic morbidity associated with profound hypothermia and circulatory arrest, and to avoid the ravages of massive transfusion, surgeons have developed strategies for both on-pump resection without hypothermic arrest and off-pump resection, even in the case of lesions extending into the RA (Fig. 24.18).[82,86–89,93–95] Regardless of the surgical technique used, most medical professionals recommend that the care of these complex patients, as the care of other patients with complicated and unusual medical problems discussed in this chapter (carcinoid heart disease, hypertrophic cardiomyopathy [HCM]), be coordinated by a multidisciplinary team, including oncologists; nephrologists; urologic, hepatic, and vascular surgeons; cardiothoracic surgeons; cardiac anesthesiologists; and surgical intensivists.[80,87,95–97]

Anesthetic Considerations

Anesthetically, the most important concerns in caring for patients undergoing radical nephrectomy and tumor thrombectomy will be establishing sufficient venous access and performing a thorough intraoperative transesophageal echocardiogram. All patients will have arterial access for continuous hemodynamic monitoring and for the frequent blood draws that will occur late in the procedure to monitor the adequacy of resuscitation. Central venous access is imperative for volume resuscitation, for monitoring of right-sided heart filling pressures, and for the infusion of vasoactive and inotropic medications. Placement of a PAC may be unnecessary in patients with normal preoperative biventricular function and may be contraindicated in patients with tumor thrombus extending high into the supradiaphragmatic IVC and RA (Figs. 24.19 and 24.20). If monitoring pulmonary pressures after thrombus removal is desired, then a PAC may be placed with its tip just beyond the introducer sheath (approximately 20 cm) and subsequently floated carefully into position once the tumor has been removed, perhaps with direct manual surgical assistance. Placement of femoral venous catheters for volume use intraoperatively may be of little use, considering the need to interrupt IVC blood flow for surgical resection. As indicated, the need for volume resuscitation may be greater than the need for infusion of vasoactive or inotropic medications. Given such, one or two 9 French introducers accompanied by a clip-in infusion catheter may be more useful than a triple- or quadruple-lumen infusion catheter. An upper extremity 8.5 French Rapid Infusion Catheter (Teleflex, Morrisville, NC) may also be used to supplement a central venous line. Depending on the surgical technique and the anticipated volume of blood loss, a rapid infusion device (Belmont Rapid Infuser, Belmont Instrument Corp., Billerica, MA) may be considered. The choice of induction and maintenance medications and the need for vasoactive and inotropic medications will depend on patient comorbidities and provider preference. As has been stated previously, the specific drugs used likely matter less than their means of use. For on-pump procedures, consideration should be given to avoiding the use of antifibrinolytic agents, considering a patient's clear hypercoagulable state, although data to guide a rational choice are practically nonexistent.

Intraoperative TEE will be important for most cases, regardless of the need for CPB.[80,95,98] Although TEE may be used to guide central line placement in patients with tumor extension high in the IVC and RA and to monitor biventricular function, especially during the time of hepatic reperfusion, TEE is particularly useful for reconfirming the proximal extent of tumor burden and for monitoring the adequacy of surgical resection in real time.[80,95,98] Most patients will have undergone high-resolution imaging with either MRI or multiplanar CT before surgery to define the extent of caval tumor burden.[82] However, TEE performed at the time of surgery still has the potential to alter surgical management.[80,99] In one small series from the Mayo Clinic describing concomitant nephrectomy and pulmonary tumor thrombectomy, two of the nine patients developed pulmonary artery tumor embolism intraoperatively that was diagnosed by TEE (see Figs. 24.19 and 24.20).[100]

To date, Fukazawa, Ciancio, and colleagues[80] have recently presented the largest case series, detailing the anesthetic management of patients undergoing radical nephrectomy and tumor thrombectomy. In their report, the authors describe 70 patients (58 with level III thrombus and 12 with level IV thrombus) who underwent surgical resection at the University of Miami between 1997 and 2010.[80] Of the patients with level III lesions, only 2 (3.5%) required the use of CPB for surgical resection, whereas 3 (25%) of those with level IV disease required extracorporeal support. No patients required venovenous bypass. Patients undergoing resection for level IV disease experienced a significantly greater blood loss than those with level III disease (mean

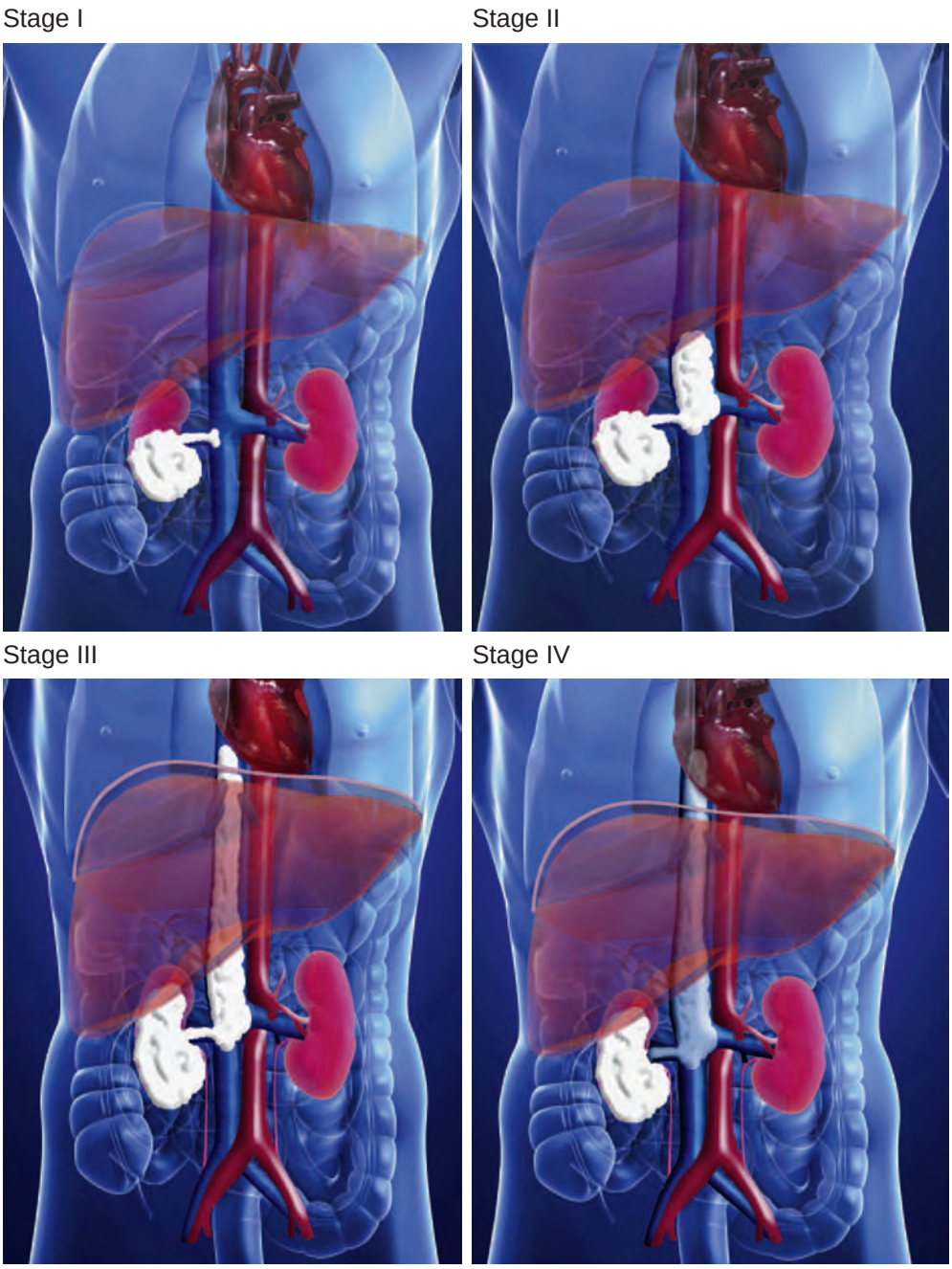


Fig. 24.17 Renal cell carcinoma tumor thrombus staging. Stage I: Is confined to the ipsilateral renal vein or extends up to 2 cm into the IVC. Stage II: Extends more than 2 cm into the IVC but remains below the hepatic veins. Stage III: Involves the intrahepatic IVC but remains below the diaphragm. Stage IV: Extends above the diaphragm and may involve the heart structures. *IVC*, Inferior vena cava. *(Reproduced with permission from Fukazawa K, Gologorsky E, Naguit K, et al. Invasive renal cell carcinoma with inferior vena cava tumor thrombus: cardiac anesthesia in liver transplant settings.* J Cardiothorac Vasc Anesth. *2014;28:641.)*

6978 vs 1540 mL) and received significantly more fluid, blood, and blood products, and were more likely to require a vasopressor infusion.[80] Additionally, patients with level IV disease had longer intensive care unit (ICU) (mean 9.8 vs 4.8 days) and hospital (mean 18.8 vs 8.1 days) lengths of stay.[80] The authors do not provide the details of the anesthetic technique, although all patients had arterial lines placed for hemodynamic monitoring. Of those with level III tumors, 62.1% had central venous cannulas placed, whereas 83.3% of those with level IV tumors had them placed. A second central line was placed in 31% of those with level III disease and in 16.7% of those with level IV disease. PAC placement was uncommon, occurring in only 8.6% of those with level III tumors and 16.7% of those with level IV tumors. Using intraoperative TEE was common, occurring in 77.6% of patients with level III tumors and 100% of patients with level IV tumors and led to significant alteration of the surgical approach in 3 of the 57 patients in whom it was used (5.2%).[80]

In conclusion, as Fukazawa's paper suggests, the optimal anesthetic management of these patients with uncommon diseases should take place in the context of an institution capable of providing a patient with coordinated multidisciplinary support. Although infrequently

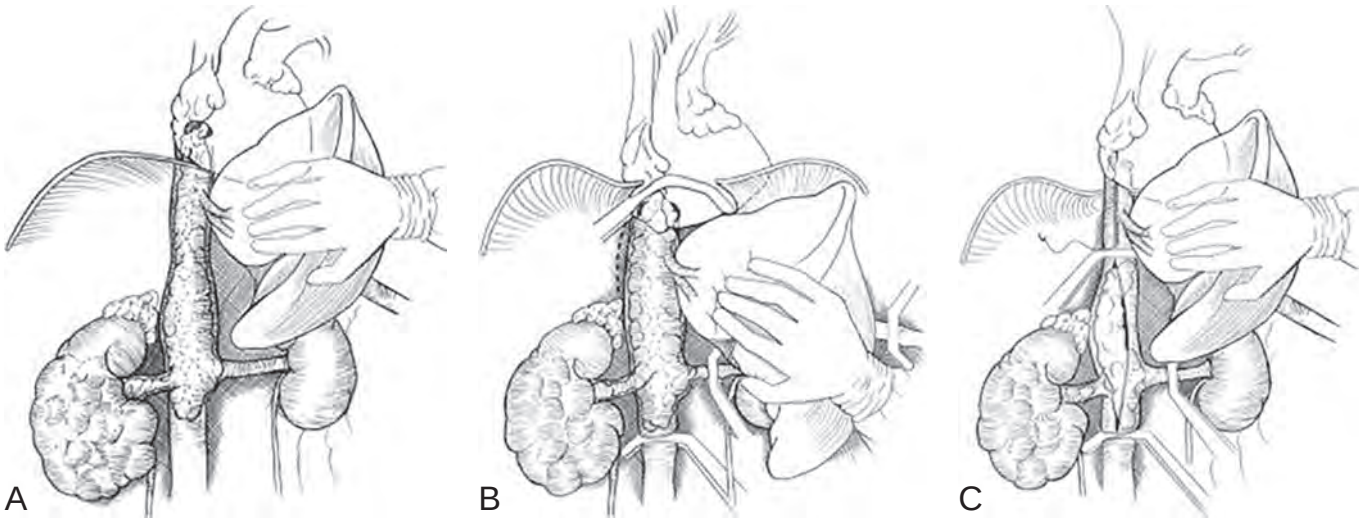


Fig. 24.18 Surgical technique for level IV tumor extraction, avoiding cardiopulmonary bypass. (A) Mobilization of the liver off the retrohepatic inferior vena cava (IVC). (B) Dissection of the IVC and central tendon of the diaphragm off the posterior abdominal wall *(dashed lines)* and clamping of the distal IVC, the right atrium, the left renal vein, and the porta hepatis. (C) Milking the tumor from the supradiaphragmatic IVC, enabling it to be extracted without a sternotomy or the need for cardiopulmonary bypass. *(Reproduced with permission from Ciancio G, Shirodkar SP, Soloway MS, et al. Renal carcinoma with supradiaphragmatic tumor thrombus: avoiding sternotomy and cardiopulmonary bypass.* Ann Thorac Surg. *2010;89:507.)*

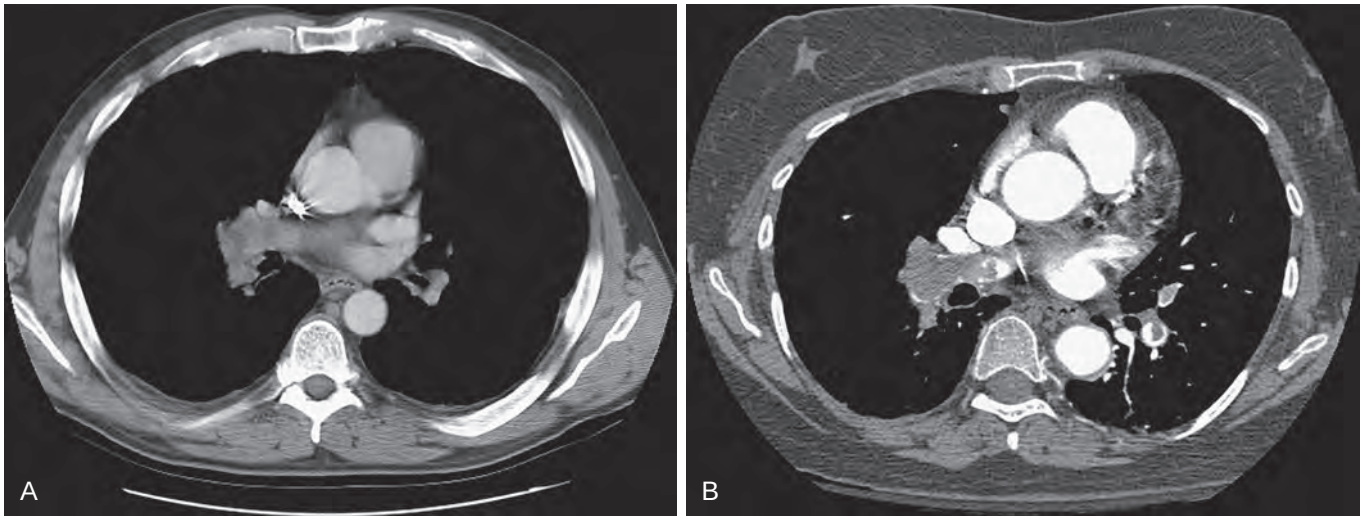


Fig. 24.19 Pulmonary tumor embolism with renal cell carcinoma. (A) Computed tomography angiogram (CTA) of the chest shows a large saddle-tumor thrombus in the main pulmonary artery. (B) A CTA of a second patient with extensive, occlusive tumor thrombus in the right main pulmonary artery and in the branches of the left pulmonary artery tree. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Reprinted in Kayalar N, Leibovich BC, Orszulak TA, et al. Concomitant surgery for renal neoplasm with pulmonary tumor embolism.* J Thorac Cardiovasc Surg. *2010;139:321.)*

recognized, the anesthetic plan for many patients with uncommon conditions, whether locally advanced renal cell carcinoma with caval tumor thrombus or carcinoid heart disease or HCM, will depend as much on the level and quality of institutional support and the skill of a surgical team as it will on the specific pathologic condition of the patient.

Cardiomyopathy

Previously, the World Health Organization (WHO) and the International Society of Cardiology (ISC) defined cardiomyopathy as heart muscle disease of unknown cause, unlike heart muscle disease attributed to a specific cause or associated with a disease process. With more knowledge concerning pathogenetic and etiologic factors, the difference between seemingly idiopathic cardiomyopathy and specific heart diseases has become less distinct. Previously, cardiomyopathy was classified as dilated, hypertrophic, or restrictive. Over time, each classification has become a recognized clinical condition. In 1995 WHO and ISC redefined the cardiomyopathies according to dominant pathophysiologic considerations or, if possible, by "etiological/pathogenetic factors."[101] Cardiomyopathies were then defined as "diseases of the myocardium associated with cardiac dysfunction."

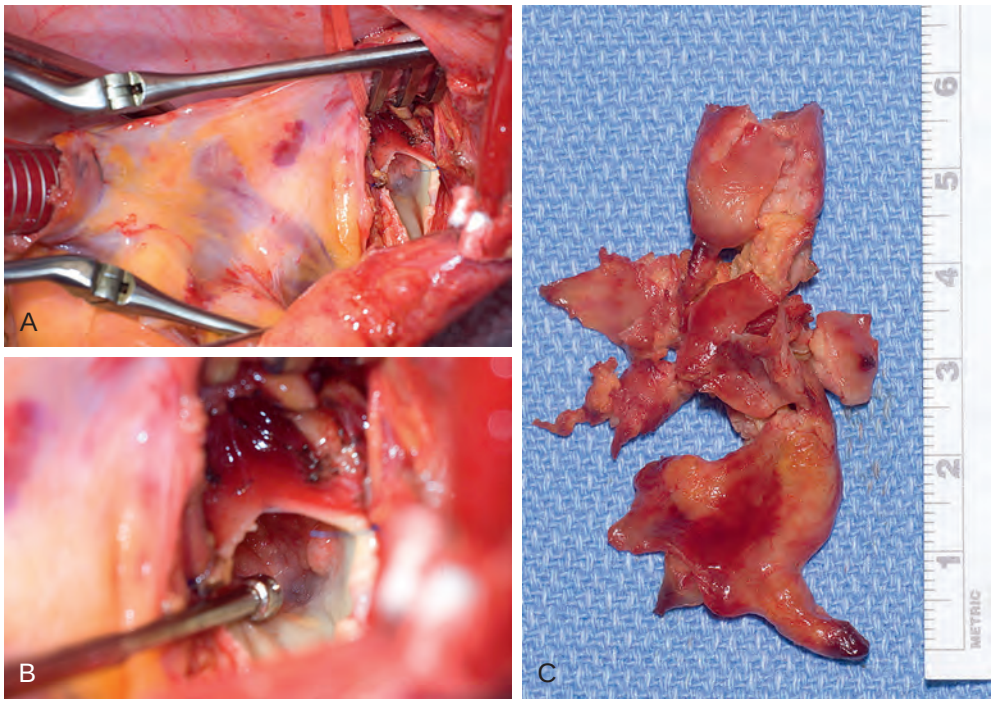


Fig. 24.20 Intraoperative views of pulmonary tumor thrombus with renal cell carcinoma. (A and B) In situ tumor occluding the right main pulmonary artery. (C) Tumor thrombus after surgical extraction. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Reprinted in Kayalar N, Leibovich BC, Orszulak TA, et al. Concomitant surgery for renal neoplasm with pulmonary tumor embolism.* J Thorac Cardiovasc Surg. *2010;139:322.)*

The original cardiomyopathies classified as dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and HCM were preserved, and arrhythmogenic right ventricular cardiomyopathy (ARVC) was added.

In an attempt to incorporate knowledge gleaned in the succeeding decade and the numerous new insights into cardiac molecular genetics, the American Heart Association (AHA) issued a scientific statement in 2006 that proposed to redefine and classify cardiomyopathies.[102] In their words:

> *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that are frequently genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.*[102]

Based on this definition, cardiomyopathies may then be divided into primary and secondary classifications, depending upon the primary organ involvement. Whereas primary cardiomyopathies are confined generally to the myocardium, secondary cardiomyopathies reflect myocardial involvement in the context of a systemic disorder.[102] Primary cardiomyopathies primarily affecting the heart may, in turn, be classified as genetic (eg, HCM, ARVC/dysplasia, left ventricular noncompaction, conduction system disease, ion channelopathies), mixed (DCM, RCM), or acquired (eg, inflammatory, stress-provoked [Takotsubo], peripartum, tachycardia-induced) (Fig. 24.21).[102] Secondary cardiomyopathies, in which cardiac involvement occurs in the context of a systemic disorder, are more numerous and include infiltrative (amyloidosis, Gaucher disease) and storage (hemochromatosis, Fabry disease) diseases, drug toxicities (heavy metals, alcohol, cocaine), chemoradiation side effects (doxorubicin, cyclophosphamide, Adriamycin), nutritional deficiencies (beriberi, scurvy), endocrine abnormalities (diabetes mellitus, hypothyroidism and hyperthyroidism, acromegaly), inflammatory conditions (sarcoidosis, viral), and autoimmune disorders (systemic lupus erythematosus, scleroderma, rheumatoid arthritis), among others (Box 24.2).[102]

As if to confuse the subject further and to take issue with the AHA's proposal, the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases presented its own classification scheme in 2008.[103] Reasoning that distinguishing between primary and secondary cardiomyopathies is not always easy, as many primary disorders may be associated with systemic manifestations and many secondary disorders may almost exclusively affect the heart, The European Society proposed retaining a taxonomy based on ventricular morphologic structure and function.[103] According to the European scheme, cardiomyopathies were divided much as they had been by WHO and the International Society and Federation of Cardiology into hypertrophic, dilated, arrhythmogenic right ventricular, restrictive, and unclassified; and each category, in turn, could be subdivided into familial and genetic or nonfamilial and nongenetic (Fig. 24.22).[101,103]

With the lack of a consensus on a definition of cardiomyopathy and with its numerous subtypes, it is difficult, if not impossible, to speak of its epidemiologic factors, although likely not uncommon. DCM alone, of whatever cause, has been estimated to have an annual incidence of 5 to 8 cases per 100,000 population and a prevalence in the United States of 36 cases per 100,000 population, leading to approximately 10,000 deaths annually.[104] HCM is even more common, if not the most common inherited cardiomyopathy, with an estimated prevalence between 1:500 and 1:200 and an estimated prevalence of at least 700,000 in the United States alone.[105–107] Given this burden of disease, anesthesia providers are likely to encounter patients with a cardiomyopathy in both cardiac and noncardiac surgical units.

In the sections that follow, this text adheres to the WHO and European Society classification, presenting overviews of DCM, HCM, RCM, and ARVC and followed, in turn, by a discussion of the salient points of their anesthetic management (Table 24.3).

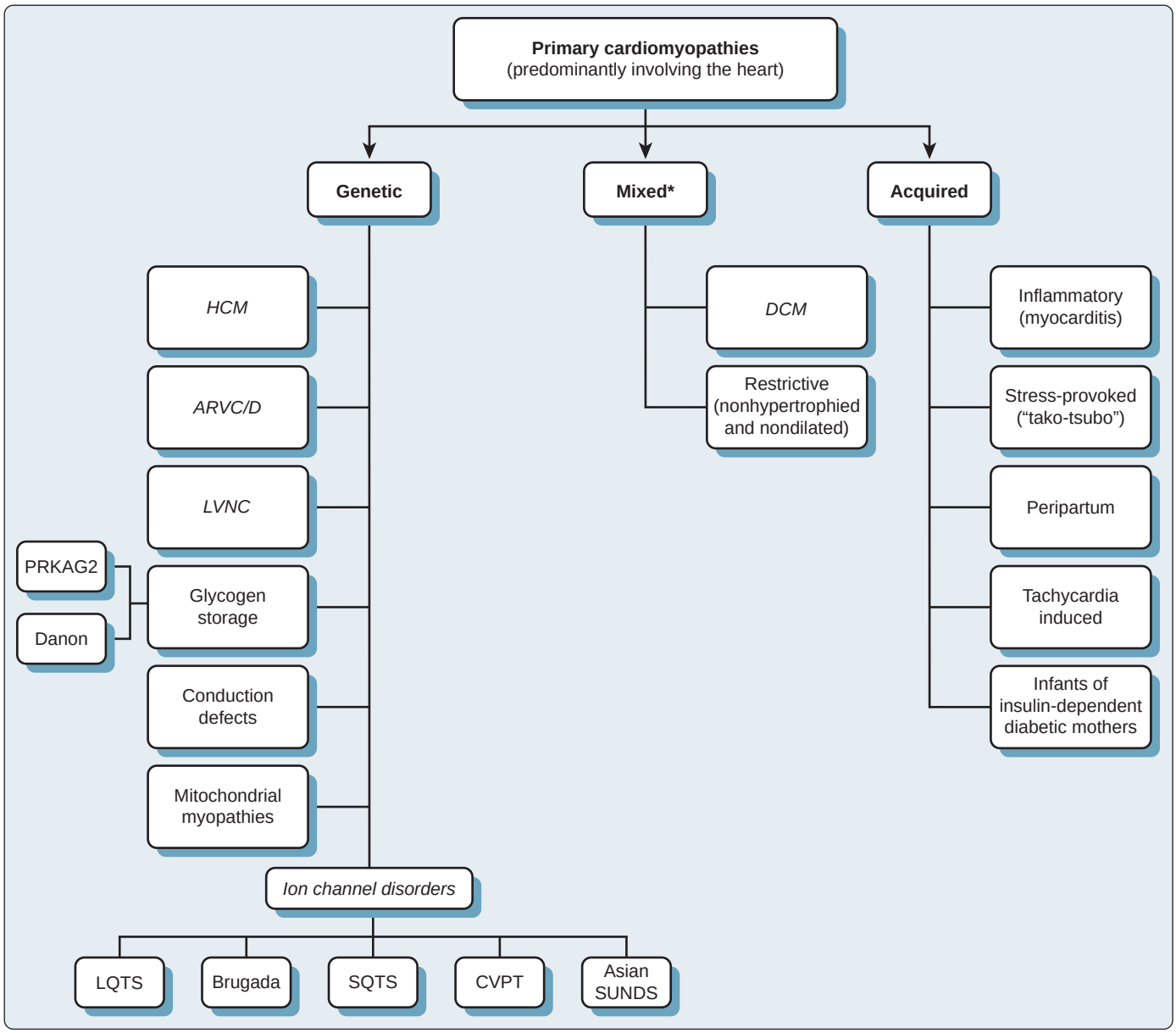


Fig. 24.21 American Heart Association classification of primary cardiomyopathies. Predominantly nongenetic causes, although rare cases of primary cardiomyopathy with a genetic origin, have been reported (see text for details). *ARVC/D,* Arrhythmogenic right ventricular cardiomyopathy/dysplasia; *CVPT,* catecholaminergic polymorphic ventricular tachycardia; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *LQTS,* long QT syndrome; *LVNC,* left ventricular noncompaction; *PRKAG2,* adenosine monophosphate–activated protein kinase, subunit gamma-2; *SQTS,* short QT syndrome; *SUNDS,* sudden unexplained nocturnal death. *(Reproduced with permission from Maron BJ, Towbin JA, Thiene G, et al; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention.* Circulation. *2006;113:181.)*

Dilated Cardiomyopathy

Formerly referred to as congestive cardiomyopathy or idiopathic cardiomyopathy, DCM is by far the most common of the four cardiomyopathies in adults in the WHO and European Society classification. As developments in molecular biology and genetics have provided better insight into the pathogenesis of DCMs, the term, *idiopathic*, has become less applicable. As suggested earlier, the term, *dilated cardiomyopathy*, should likely be replaced with *dilated cardiomyopathies*, because although the end-stage phenotype may be similar with four-chamber dilatation, the insults leading to that phenotype are both numerous and heterogeneous.[102–104,108]

BOX 24.2 AMERICAN HEART ASSOCIATION CLASSIFICATION OF SECONDARY CARDIOMYOPATHIES

- Infiltrative[a]
  - Amyloidosis (primary, familial autosomal dominant,[b] senile, secondary forms)
  - Gaucher disease[b]
  - Hurler disease[b]
  - Hunter disease[b]
- Storage[c]
  - Hemochromatosis
  - Fabry disease[b]
  - Glycogen storage disease[b] (type II, Pompe disease)
  - Niemann-Pick disease[b]
- Toxicity
  - Drugs, heavy metals, chemical agents
- Endomyocardial
  - Endomyocardial fibrosis
  - Hypereosinophilic syndrome (Löffler endocarditis)
- Inflammatory (granulomatous)
  - Sarcoidosis
- Endocrine
  - Diabetes mellitus[b]
  - Hyperthyroidism
  - Hypothyroidism
  - Hyperparathyroidism
  - Pheochromocytoma
  - Acromegaly
- Cardiofacial
  - Noonan syndrome[b]
  - Lentiginosis[b]
- Neuromuscular and neurologic
  - Friedreich ataxia[b]
  - Duchenne muscular dystrophy[b]
  - Becker muscular dystrophy[b]
  - Emery-Dreifuss muscular dystrophy[b]
  - Myotonic dystrophy[b]
  - Neurofibromatosis[b]
  - Tuberous sclerosis[b]
- Nutritional deficiencies
  - Beriberi (thiamine), pellagra, scurvy, selenium, carnitine, kwashiorkor
- Autoimmune and collagen
  - Systemic lupus erythematosus
  - Dermatomyositis
  - Rheumatoid arthritis
  - Scleroderma
  - Polyarteritis nodosa
- Electrolyte imbalance
- Consequence of cancer therapy
  - Anthracyclines: doxorubicin (Adriamycin), daunorubicin
  - Cyclophosphamide
  - Radiation

[a]Extracellular deposition of abnormal substances among myocytes.
[b]Genetic origin.
[c]Extracellular deposition of abnormal substances within myocytes.
Reproduced with permission from Maron BJ, Towbin JA, Thiene G, et al; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation.* 2006;113:1814,.

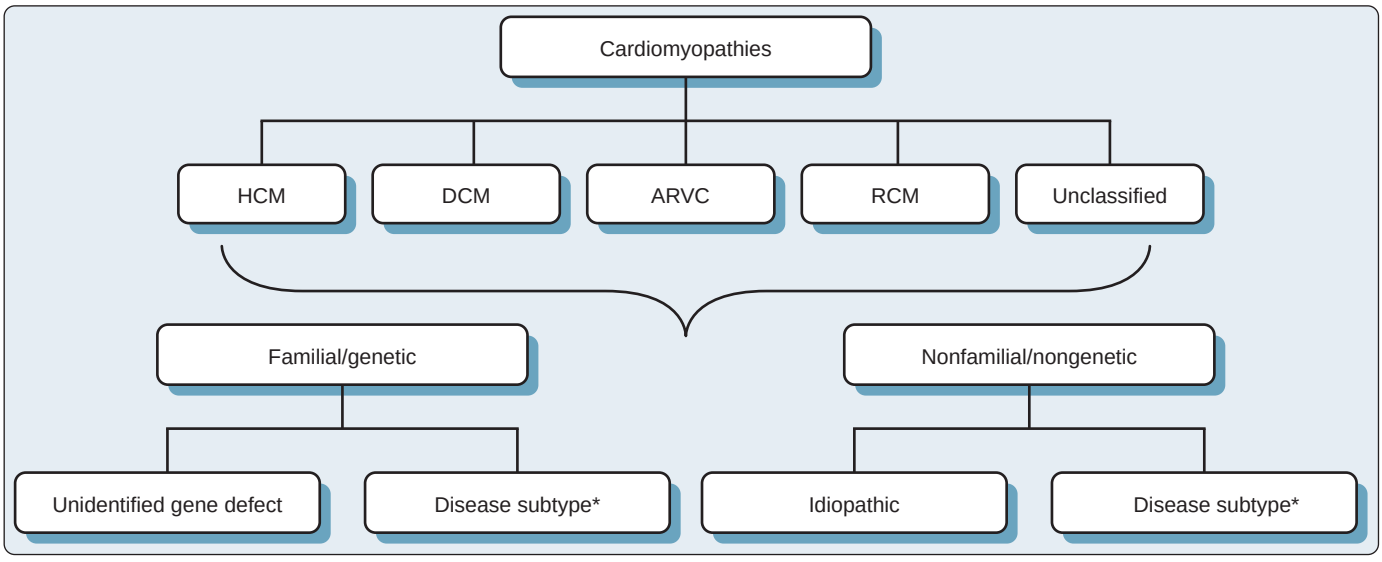


Fig. 24.22 The European Society of Cardiology classification of cardiomyopathies (see text for details). *ARVC,* Arrhythmogenic right ventricular cardiomyopathy; *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *RCM,* restrictive cardiomyopathy. *(Reproduced with permission from Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.* Eur Heart J. *2008;29:271.)*

TABLE 24.3 Characteristics of Cardiomyopathies

Characteristics	*Hypertrophic Cardiomyopathy*	*Dilated Cardiomyopathy*	*Arrhythmogenic Right Ventricular Cardiomyopathy*	*Restrictive Cardiomyopathy*
Clinical				
Heart failure	Occasional (LV)	Frequent (LV or BV)	Frequent (RV)	Frequent (BV)
Arrhythmias	Atrial and ventricular arrhythmias	Atrial and ventricular arrhythmias, conduction defects	Ventricular tachycardia (RV), conduction defects	Atrial fibrillation
Sudden Death	0.7–11% per year	Frequent (ND)	Frequent (ND)	1–5% per year
Hemodynamically				
Systolic function	Hyperdynamic, outflow tract obstruction (occasionally)	Reduced	Normal-reduced	Near normal
Diastolic function	Reduced	Reduced	Reduced	Severely reduced
Morphologic				
Cavity size				
Ventricle	Reduced (LV)	Enlarged (LV or BA)	Enlarged (RV)	Normal or reduced (BV)
Atrium	Normal-enlarged (LA)	Enlarged (LA or BA)	Enlarged (RV)	Enlarged (BA)
Wall thickness	Enlarged, asymmetric (LV)	Normal-reduced (LV or BV)	Normal-reduced (RV)	Normal (BV)

BA, Both atria; *BV,* both ventricles; *LA,* left atrium; *LV,* left ventricle; *ND,* not determined; *RA,* right atrium; *RV,* right ventricle.
Reproduced with permission from Franz WM, Müller OJ, Katus HA. Cardiomyopathies: from genetics to the prospect of treatment. *Lancet.* 2001;358:1628.

Acknowledging the limitations of any taxonomy, the DCMs run a spectrum from genetic to acquired with an overlap in the middle.[102] The genetics of DCMs and the genetics of familial DCM are complicated.[108] For example, if the family members of individuals with apparently idiopathic DCM are screened, as many as 35% will be found to have evidence of DCM, thus suggesting a previously unrecognized familial or genetic basis for the apparently idiopathic presentation of the index individual.[108–110] Although many cases of familial DCM are transmitted in autosomal dominant fashion, the phenotype may not become apparent until later decades in life.[102,103,110] The combination of such age-dependent penetrance with incomplete penetrance and the variable expression of any given mutation makes genealogic analysis difficult.[108] The causes of acquired DCMs are diverse and include toxins, such as ethanol, cocaine, lithium, and chemotherapeutic agents, such as Adriamycin and cyclophosphamide; infectious agents, such as coxsackievirus, human immunodeficiency virus (HIV), syphilis, and Chagas disease; inflammatory and autoimmune conditions, such as lupus erythematosus, sarcoidosis, and rheumatoid arthritis; endocrinopathies, such as diabetes mellitus, hypothyroidism, hyperthyroidism, and acromegaly; metabolic abnormalities, such as thiamine deficiency and scurvy; and a host of miscellaneous causes, such as pregnancy, stress, radiation, and tachycardia (Box 24.3).[102,104]

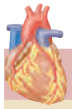
The epidemiologic factors of DCM have already been mentioned. Interestingly, even after controlling for differences in rates of tobacco and alcohol use, hypertension, and socioeconomic disparity, African Americans have three times the risk for developing DCM than do Caucasian Americans. Once they develop DCM, African Americans have a mortality rate almost two times higher.[104] As with many other aspects of the DCMs, their natural history is unclear. In general, the development of symptoms portends a poor prognosis, with 1- and 5-year mortality rates of 25% and 50%, respectively, although as many as one quarter of those with new-onset symptoms will improve without intervention.[104] In an era before the use of ß-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and cardiac implantable cardioverter-defibrillators (ICDs), the mortality rate with the DCMs was due largely to decompensated systolic heart failure (70%) and sudden cardiac death (30%), presumably from malignant arrhythmia.[104]

Phenotypically, the end-stage cardiomyopathies are similar, regardless of the inciting event. There is gross dilatation of all four cardiac chambers, modest thinning of the ventricular walls, and significant hypertrophy of the myocytes and the heart globally, reflecting a myocardium subjected to chronic volume overload (Fig. 24.23).[104,110] At autopsy, these dilated hearts may weigh two to three times normal, exceeding 1000 g.[110] Although valve leaflets may be normal, dilatation of the heart has been associated with regurgitant lesions, secondary to papillary muscle displacement and leaflet malcoaptation, producing the frequently encountered mitral and/or tricuspid regurgitation.[108] Histologic changes are nonspecific and typically shed little insight on the cause. Microscopically, a patchy and diffuse loss of tissue with interstitial fibrosis and scarring is demonstrated. Encroachment on the conduction system produces the bundle branch pattern frequently seen on the electrocardiogram (ECG).[108,110]

With the dilated cardiomyopathies, systolic function is disproportionately impaired, although as systolic functions worsens, diastolic function is compromised as well.[108] As contractile function diminishes, stroke volume is initially maintained by augmentation of end-diastolic volume. Despite a severely decreased ejection fraction, stroke volume may remain almost normal. Eventually, both increased wall stress attributable to significant left ventricular dilatation and normal or thin left ventricular wall thickness occur.[109] Increasing left atrial size may indicate worsening diastolic dysfunction in these patients, contributing significantly to functional mitral regurgitation.[111] Ventricular dilatation, combined with valvular regurgitation, compromises the metabolic capabilities of the heart muscle and produces overt circulatory failure. Compensatory mechanisms may allow symptoms of myocardial dysfunction to go unnoticed for an extended period. However, the onset of mitral regurgitation signals a poor prognosis, because ventricular function progressively worsens without intervention.

Although DCM occurs in children, its presentation is generally in the fourth and fifth decades of life.[110] The clinical picture of DCM typically includes signs and symptoms of CHF often corresponding to months of fatigue, weakness, and reduced exercise tolerance before diagnosis.[112] One third of individuals complain of chest pain.[109] However, the first indication of DCM may be a stroke, arrhythmia, or even sudden death. Increasingly, individuals after routine medical screening are informed of cardiomegaly on a routine chest roentgenogram. Insidious symptoms may appear over a period of years or evolve rapidly after an unrelated illness. Physical signs of DCM, depending on the disease's progression, include pulsus alternans, jugular venous distention, murmurs of atrioventricular valvular regurgitation, tachycardia, and gallop heart sounds.

A chest roentgenogram demonstrates variable degrees of cardiomegaly and pulmonary venous congestion. An ECG may be surprisingly normal or depict low QRS voltage, abnormal axis, nonspecific ST-segment abnormalities, left ventricular hypertrophy, conduction defects, and evidence of atrial enlargement. Atrial fibrillation is common, and approximately one fourth of patients have nonsustained ventricular tachycardia.[112] Although the left ventricle (LV) is affected, the RV may be spared in some patients, and this finding has been associated with improved survival.[113] Coronary catheterization usually reveals normal coronary vessels. Coronary angiography



BOX 24.3 CAUSES OF DILATED CARDIOMYOPATHY

Idiopathic Causes
- Idiopathic dilated cardiomyopathy
- Idiopathic arrhythmogenic right ventricular dysplasia

Familial (Hereditary) Causes
- Autosomal dominant
- X-chromosomal
- Polymorphism
- Other

Toxic Causes
- Ethanol
- Cocaine
- Adriamycin
- Catecholamine excess
- Phenothiazines, antidepressants
- Cobalt
- Carbon monoxide
- Lead
- Lithium
- Cyclophosphamide
- Methysergide
- Amphetamine
- Pseudoephedrine or Ephedrine

Inflammatory: Infectious Causes
- Viral (coxsackievirus, parvovirus, adenovirus, echovirus, influenza virus, HIV)
- Spirochete (leptospirosis, syphilis)
- Protozoal (Chagas disease, toxoplasmosis, trichinosis)

Inflammatory: Noninfectious Causes
- Collagen vascular disease (scleroderma, lupus erythematosus, dermatomyositis, rheumatoid arthritis, sarcoidosis)
- Kawasaki disease
- Hypersensitivity myocarditis

Causes of Miscellaneous Acquired Cardiomyopathies
- Postpartum cardiomyopathy
- Obesity

Metabolic and Nutritional Causes
- Thiamine
- Kwashiorkor, pellagra
- Scurvy
- Selenium deficiency
- Carnitine deficiency

Endocrine Causes
- Diabetes mellitus
- Acromegaly
- Thyrotoxicosis
- Myxedema
- Uremia
- Cushing disease
- Pheochromocytoma

Electrolyte Imbalance
- Hypophosphatemia
- Hypocalcemia

Physiologic Causes
- Tachycardia
- Heat stroke
- Hypothermia
- Radiation

Autoimmune Disorders

Infiltrative cardiomyopathies (dilated cardiomyopathy usually after progression from restrictive cardiomyopathy; in end-stage)
- Cardiac amyloidosis
- Hemochromatosis

Stress- and Catecholamine-Induced Cardiomyopathies

Reproduced with permission from Bozkurt B. Heart failure as a consequence of dilated cardiomyopathy. In: Mann DL, Felker GM, eds. *Heart Failure: A Companion to Braunwald's Heart Disease*, 3rd ed. Philadelphia: Elsevier; 2016:301.

will also distinguish between ischemic and idiopathic DCM, a finding that has therapeutic and prognostic implications. An endomyocardial biopsy is rarely valuable to identify the cause of DCM but may be useful to rule out other pathologic abnormalities that have a similar presentation to DCM.[110] The biopsy has no prognostic value or correlation with ventricular function.

Echocardiography is extremely useful in the outpatient management of patients with DCM. The characteristic two-dimensional findings are a dilated LV with globally decreased systolic function. Indeed, all markers of systolic function (ejection fraction, fractional shortening, stroke volume, cardiac output [CO]) are uniformly decreased.[114] Other associated findings may include a dilated mitral annulus with incomplete mitral leaflet coaptation, dilated atria, right ventricular enlargement, and thrombus in the left ventricular apex (Fig. 24.24). In some instances, regional wall motion abnormalities will be present. Color-Doppler imaging is useful in assessing the presence or absence of valvular regurgitation. Pulsed-wave and continuous-wave Doppler imaging are used to quantify CO and evaluate filling pressures. Well-compensated patients with DCM may have only mild impairment of diastolic function. As the disease progresses and patients become less well compensated, the left ventricular diastolic filling pattern changes to that of restricted filling. Although systolic function may not change in these patients, the increased filling pressures associated with restrictive left ventricular filling will often worsen the symptoms of CHF.

Management of acute decompensated CHF continues to evolve, but the onset of overt CHF is a poor prognostic indicator for persons with DCM.[115] However, compared with ischemic CHF, patients with nonischemic DCM show greater improvement in symptoms, left ventricular function, and remodeling during more contemporary therapy than in the past.[116] In general, treatment of patients with DCM is similar to the treatment of patients with heart failure with reduced ejection fraction and is aimed at improving symptoms, survival, and quality of life while preventing disease progression.[117] Treatment includes medication regimens and device intervention based on symptom class (Table 24.4). Pharmacologically, medications are directed at the management of fluid retention and prevention of disease progression.[117] Although diuretics of various classes are used to treat volume overload, ACE inhibitors, ARBs, ß-blockers, and aldosterone antagonists work to stabilize if not reverse the detrimental effects of cardiac remodeling that accompany DCM.[117] ACE inhibitors work to reduce symptoms, improve exercise tolerance, and reduce cardiovascular mortality without a direct myocardial effect.[112,118,119] Perhaps more important than the hemodynamic effects, ACE inhibitors suppress ventricular remodeling and endothelial dysfunction, accounting for the improvement in mortality noted with this medication in DCM.[120] Other afterload-reducing agents such as selective phosphodiesterase-3 inhibitors may improve quality of life but do not affect mortality; consequently, they are rarely administered in chronic situations. More recently, spironolactone has assumed a greater role in treatment; with the addition of spironolactone in a large double-blind randomized trial,[121] mortality was reduced by 30% from all causes in patients receiving standard ACE inhibitors for DCM. Although aldosterone increases sodium retention and reduces potassium loss, it has also been shown to cause myocardial and vascular fibrosis, impair baroreceptor function, and prevent catecholamine reuptake by the myocardium.

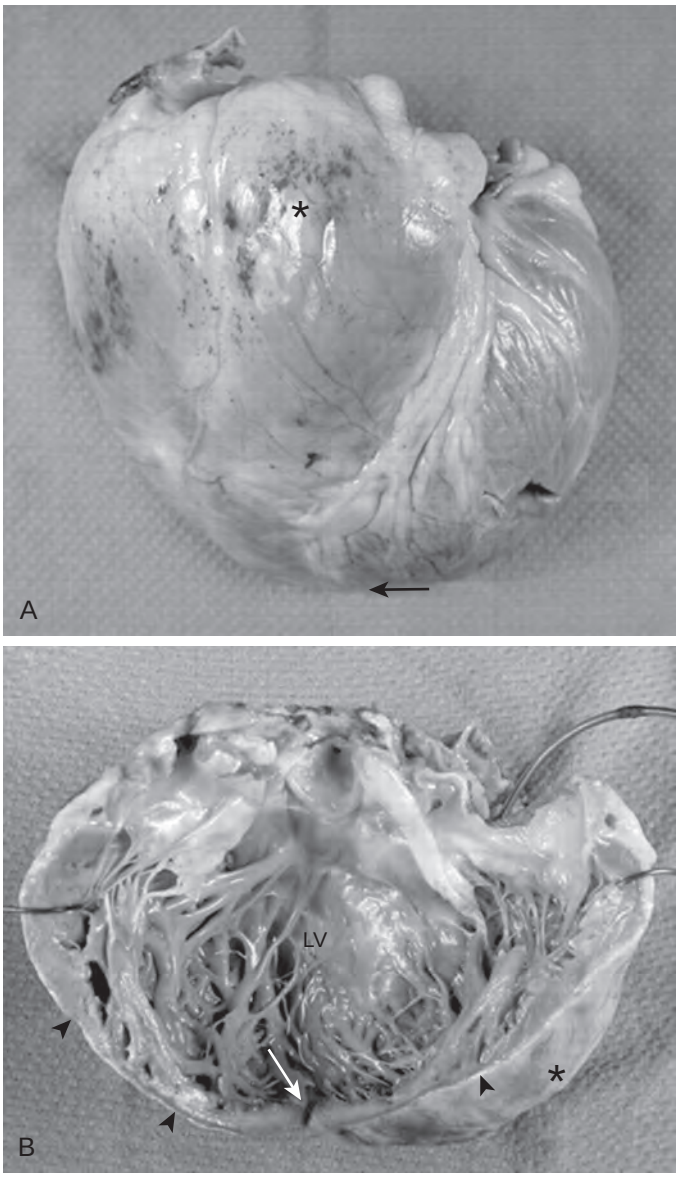


Fig. 24.23 Postmortem specimen of a patient with dilated cardiomyopathy. (A) The spherical shape with biventricular hypertrophy and dilatation is demonstrated, especially at the apex *(black arrow)*. Petechial hemorrhage *(asterisk)* is evident. (B) Cut specimen shows globoid left ventricle, rounded apex *(white arrow)*, and myocardial thinning *(black arrowheads)*. Epicardial fibrosis *(asterisk)* is evident. *LV,* Left ventricle. *(Reproduced with permission from Luk A, Ahn E, Soor GS, Butany J. Dilated cardiomyopathy: a review.* J Clin Pathol. *2009;62:221.)*

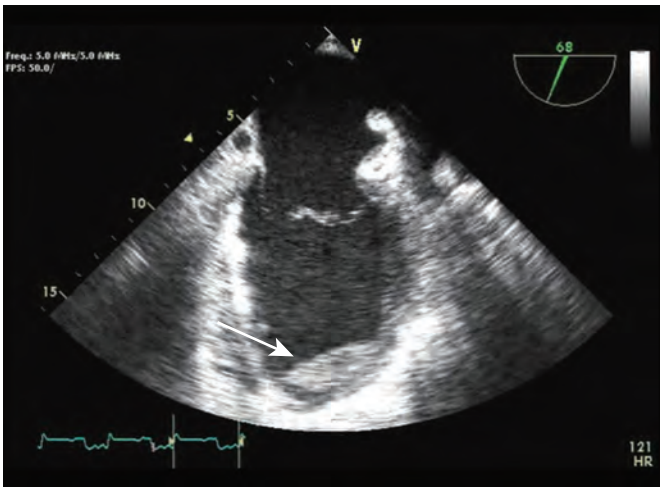


Fig. 24.24 Transesophageal midesophageal two-chamber view shows a thrombus *(arrow)* at the apex of the left ventricle. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:684.)*

Historically, ß-blockers were contraindicated in DCM. In 1982, Bristow and associates[122] found a decreased catecholamine sensitivity and ß-receptor density in the failing human myocardium, leading to loss of contractility. The association between excess sympathetic activity and the failing heart has been demonstrated.[123] Recently, the dobutamine stress test has been shown to identify changes in the ventricle of patients with asymptomatic to mildly symptomatic DCM that reflect increased sympathetic stimulation.[124] This finding may aid in the initiation of ß-blockers in patients with normal resting parameters. The use of ß-blockers in DCM has provided not only symptomatic improvement, but its use has also provided substantial reductions in sudden and progressive death with NYHA functional class II and III heart failure.[125] This finding is especially significant because almost 50% of deaths are sudden.[126]

High-grade ventricular arrhythmias are common with DCM. Approximately 12% of all patients with DCM die suddenly,[127] but overall prediction of sudden death in an individual with DCM is poor.[126] Electrophysiologic testing has a poor negative predictive value that limits its usefulness. The best predictor of sudden death remains the degree of left ventricular dysfunction. Patients who have sustained ventricular tachycardia or out-of-hospital ventricular fibrillation are at increased risk for sudden death, but more than 70% of patients with DCM have nonsustained ventricular tachycardia during ambulatory monitoring.[119] Furthermore, the prognostic significance of ventricular arrhythmias and the response to prophylactic antiarrhythmic therapy in patients with DCM is not well established.

Antiarrhythmic medications are hazardous in patients with poor ventricular function because of their negative inotropic and sometimes proarrhythmic properties. Antiarrhythmic therapy may only be considered in DCM if inducible ventricular tachycardia or symptomatic arrhythmias are present. Class I agents (sodium-channel blockers) are not indicated, because they have clearly demonstrated increased mortality in patients with advanced CHF.[112] Amiodarone is the preferred antiarrhythmic agent in DCM, because its negative inotropic effect is less than other antiarrhythmic medications[126] and its proarrhythmic potential is the lowest.[128] Counter to most trials of antiarrhythmic prophylaxis, results of a large multicenter trial of antiarrhythmic therapy in patients with CHF[128] demonstrated that amiodarone was associated with a significantly lower mortality rate of 38%, compared with 62% without therapy in persons with a high resting heart rate. Notwithstanding these results, ICDs reduce the risk of sudden death and improve mortality.[126,127] Recent evidence has indicated that with previous cardiac arrest or sustained ventricular tachycardia, more benefit is gained from an implantable defibrillator.[129] This conclusion is based on a 27% reduction in the relative risk of death attributed to a 50% reduction in arrhythmia-related mortality, compared with treatment with amiodarone.

Other treatments for DCM include digoxin, which has been reaffirmed as clinically beneficial in two large trials of adults.[113] The risk of thromboembolic complications is significant in DCM for adults. Patients with moderate ventricular dilation and moderate-to-severe systolic dysfunction have intracavitary stasis and a decreased ejection of blood; consequently, they are likely to receive anticoagulant agents if any history of stroke, atrial fibrillation, or intracardiac thrombus exists.

Patients who are resistant to pharmacologic therapy for CHF have received dual-chamber pacing, cardiomyoplasty, left ventricular

TABLE 24.4 Pharmacologic and Device Therapy for Chronic Heart Failure

Indication	*ACE Inhibitor*	*ARB*	*Diuretic Agent*	*Beta Blocker*	*Aldosterone Antagonist*	*Cardiac Glycosides*	*CRT*	*ICD*
Asymptomatic LV dysfunction (NYHA class I)	Indicated	If patient is ACE-intolerant	Not indicated	Post-MI Indicated[a]	Recent MI	(1) For rate control with atrial fibrillation or (2) When improved from more severe HF and in sinus rhythm	May be considered[a]	Indicated
Symptomatic HF (NYHA class II)	Indicated	Indicated with or without ACE inhibitor	Indicated if fluid retention is present	Indicated	Indicated	(1) With atrial fibrillation (2) When improved from more severe HF in sinus rhythm	Indicated[b]	
Worsening HF (NYHA classes III–IV)	Indicated	Indicated with or without ACE inhibitor	Combination of diuretic agents indicated	Indicated (under specialist care)	Indicated	Indicated	Indicated[c]	Indicated
End-stage HF (NYHA class IV)	Indicated	Indicated with or without ACE inhibitor	Combination of diuretic agents indicated	Indicated (under specialist care)	Indicated	Indicated	Indicated[c]	Not indicated[d]

[a]May be considered in patients with LVEF 30% or less, of ischemic cause, in sinus rhythm with a QRS of 150 milliseconds or longer, and with morphologic LBBB.
[b]Indicated with QRS of 130 milliseconds or longer with morphologic LBBB or QRS of 150 milliseconds or longer with nonmorphologic LBBB and EF of 30% or less.
[c]Indicated with QRS of 120 milliseconds or more with LBBB or QRS of 150 milliseconds or longer, nonmorphologic LBBB, and EF of 35% or less.
[d]Use of an ICD may be considered in patients with NYHA class IV HF who are undergoing implantation of a CRT device.
ACE, Angiotensin-converting enzyme; *ARB,* angiotensin-receptor blocker; *CRT,* cardiac resynchronization therapy; *EF,* ejection fraction; *HF,* heart failure; *LBBB,* left bundle branch block; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *ICD,* implantable cardioverter defibrillator; *MI,* myocardial infarction; *NHYA,* New York Heart Association.
Reproduced with permission from Mann DL, Zipes DP, Libby P, et al. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 10th ed. Philadelphia: Saunders; 2015:519.

assist devices (LVADs), cardiac surgical procedures (nontransplantation), and transplantation in recent years. Cardiac resynchronization therapy with dual ventricular pacing improves the NYHA functional class and ejection fraction 6 months after implantation.[130] Placement of implantable LVADs has enabled end-stage patients to reach transplantation or has become destination therapy for those for whom transplantation is not an option.[131] If mitral regurgitation develops in patients with DCM, then mitral valve repair or replacement is recommended. Surgical intervention in this high-risk population is safe and improves NYHA classification and survival.[132] Transplantation can substantially prolong lives with current survival at 15 years of 50% if younger than 55 years of age.[133] However, limited organ availability and drug-related morbidity suggest that improvements in device therapy, either with LVADs or artificial hearts, may provide the best opportunity for increased survival.

Anesthetic Considerations

The most common cardiac procedures for patients with DCM are correction of mitral and tricuspid regurgitation, placement of an ICD for refractory ventricular arrhythmias, and device (LVAD, total artificial heart) placement or orthotopic heart transplantation. Anesthetic management is predicated on minimizing further myocardial depression, optimizing preload, and judiciously reducing afterload.

Individuals with DCM may be extremely sensitive to cardiodepressant anesthetic drugs. Historically, high-dose intravenous opioids, such as fentanyl (30 µg/kg), were considered to provide excellent analgesia and hemodynamic stability in patients with ejection fractions less than 30%,[134] but opioids will likely contribute to prolonged respiratory depression that may delay extubation. Short-acting narcotics such as remifentanil may be unsuitable for patients undergoing cardiac surgery who have poor left ventricular function attributable to a high incidence of bradycardia and severe hypotension.[135] A comparison of the remifentanil-sevoflurane anesthetic with fentanyl-etomidate-isoflurane found significantly greater reduction in mean arterial pressure and greater incidence of bradycardia with the remifentanil anesthetic.[136] Although etomidate has been shown to have little effect on the contractility of the cardiac muscle in patients undergoing cardiac transplantation,[137] ketamine has been recommended often for induction in critically ill patients[138,139] because of its cardiovascular actions attributed primarily to a sympathomimetic effect from the central nervous system. Ketamine is a positive inotrope in the isolated rat papillary muscle and, more importantly, in a model of cardiomyopathic hamsters; it did not display a negative inotropic effect.[140] These findings make ketamine (less than 0.5 mg/kg) an excellent choice to use in combination with fentanyl for induction in patients with severe myocardial dysfunction, secondary to cardiomyopathy. The use of propofol with cardiomyopathy may be a concern, because cardiovascular depression has been observed, possibly attributable to an inhibition of sympathetic activity and a vasodilatory property. However, in a cardiomyopathic hamster model, no direct effect on myocardial contractility was observed with propofol.[141] Caution is still prudent with propofol, as it is with any drug, because of its indirect inhibitory effects on the sympathetic activity on which many patients with cardiomyopathy and reduced left ventricular function may depend for hemodynamic stability. As has been stated previously, however, the choice of a particular drug or drug combination is likely less important than how the drugs are used. If the anesthesiologist is vigilant and judicious with his or her drug dosing, and if he or she anticipates and treats hypotension before it occurs, then induction can likely proceed safely with a variety of pharmacologic regimens, including propofol.

Volatile agents have long been a theoretical concern in persons with failing hearts because of their known depressant effects on myocardial contractility. The effect of currently used volatile anesthetic agents on intrinsic myocardial contractility is difficult to assess. Animal data indicate halogenated volatile agents may have more profound negative inotropic effects in cardiomyopathic muscle than in healthy cardiac muscle.[142] Although an anesthetic technique that minimizes myocardial depression is desirable, there is little support from an evidence-based cardiovascular standpoint for the selection of one agent over another in adults. Although the failing myocardium has been thought to be more sensitive to the depressant effects of volatile agents, synergistic myocardial depression in the presence of moderate left ventricular dysfunction and volatile agents has not been demonstrated.[143] Desflurane, which possesses the lowest blood-gas partition coefficient of the volatile agents and allows for rapid induction and emergence, would appear to have some theoretical benefit for early extubation in patients undergoing cardiac surgery. In healthy hamster papillary muscles, desflurane did not appear to have a negative inotropic effect, although a profound negative inotropic effect was demonstrated in cardiomyopathic papillary muscles.[144] Conversely, sevoflurane and desflurane were not shown to adversely affect the ability of the LV to

respond to increased work, despite their negative inotropic properties, in patients undergoing cardiac surgery and placed on CPB.[145]

Invasive monitoring is commonly used for patients with DCM undergoing surgical procedures during which abrupt hemodynamic changes may be of clinical significance. The use of more aggressive monitoring, however, will depend not only on the patient but also on the procedure that he or she is undergoing. Patients receiving ICDs, for example, although usually having severely depressed left ventricular function, are routinely managed with a peripheral intravenous lines and a noninvasive blood pressure cuff. Echocardiography may be useful for patients undergoing both cardiac and noncardiac surgical procedures, because it can offer real-time information that may be used in conjunction with other data to assess the adequacy of cardiac function for supporting the metabolic needs of the body.

Hypertrophic Cardiomyopathy

Although Brock[146] published a case of functional left ventricular outflow track obstruction, or what he called "acquired aortic subvalvular stenosis" in 1957, Robert Donald Teare, a British pathologist and specialist in forensic medicine who would later perform the autopsy of Jimi Hendrix, presented the first case series of eight patients with HCM under the title of *Asymmetrical Hypertrophy of the Heart in Young Adults* in 1958.[147,148] For those with an interest in the history of medicine and in the evolution in our understanding of what we now call HCM, Teare's publications in 1958 and the succeeding years are fascinating.[147,149–151] More than 50 years later, Teare's original 1958 publication highlights both the understanding and the misunderstandings that continue to affect the thinking of the disease today.[106,152] To begin to understand something of the genetics, the clinical diagnosis, and the natural history of the disease, returning to Teare's 1958 piece is worthwhile.

Teare's first case is that of an apparently healthy 14-year-old boy who first suffers a "blackout" while riding his bike; 5 months later, he collapses suddenly on the playground at school. He is dead when he arrives at the hospital 20 minutes later. At autopsy, he is found to have a heart with "localized and diffuse hypertrophy of the interventricular septum" (Fig. 24.25). Microscopically, the myofibrils are arranged in "bizarre" fashion, "running in divers[e] directions" (Fig. 24.26).[147] Cases two and three appear to have been otherwise healthy young men, each 25 years of age, one of whom is found on a preemployment physical to have a "soft high-pitched systolic murmur just internal to the apex of the heart." An ECG was "grossly abnormal," with T-wave inversions in the anterior precordial leads and Q waves in the anterolateral leads (Fig. 24.27). Although one develops "auricular fibrillation," both develop signs and symptoms of CHF and die suddenly and unexpectedly. On autopsy, their hearts appear similar to that of the 14-year-old boy. Cases four and five are young women, both bearing the stigmata of CHF, both troubled by paroxysmal "auricular fibrillation," in one case complicated by a presumed cardioembolic cerebral infarct. One dies suddenly after collapsing while running to catch a bus, whereas the other dies after an attempt at surgical intervention for decompensated heart failure. Cases six, seven, and eight are but variations on the same theme: three young men, ages 33, 28, and 29 years old, respectively, all previously healthy, and all dead after a sudden collapse under benign circumstances. In each case, "localized hypertrophy of the interventricular septum with a complete absence of vascular, coronary, or aortic disease" is demonstrated.

In closing his series, Teare leaves an Addendum at least as fascinating and provocative as the cases he had just presented: "On December 13, 1956, K. C., aged 16, a brother of Case No. 5, collapsed and died while riding his bicycle. No previous medical history was available." On autopsy, his "heart was virtually identical in appearance with that of his sister, showing localized hypertrophy affecting the anterior wall and interventricular septum." The final line of Teare's report then points in the direction of what the study will come to be known as HCM and followed over the next 50 years: "By coincidence on the day of his death his younger sister attended the outpatient department of

Fig. 24.25 Historical postmortem specimen shows massive hypertrophy of the basal interventricular septum. *(Reproduced with permission from Teare D. Asymmetrical hypertrophy of the heart in young adults.* Br Heart J. *1958;20:2.)*

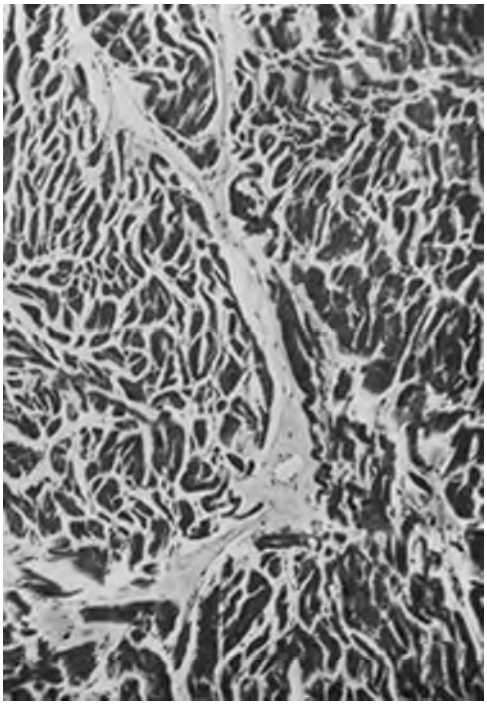


Fig. 24.26 Histologic specimen shows significant myofilament disarray. *(Reproduced with permission from Teare D. Asymmetrical hypertrophy of the heart in young adults.* Br Heart J. *1958;20:2.)*

Hammersmith hospital and was found to have signs identical with her sister. This family will be the subject of another paper."[147] That other paper appears 2 years later in the *British Heart Journal* under the title "A Family with Obstructive Cardiomyopathy (Asymmetrical Hypertrophy)."[150] The findings of the paper are worth reviewing, not

only for its historical significance, but also for its insights, however incipient, into issues still relevant today: the genetics of HCM and the role of genetic testing; the natural history of HCM; and the major sources of morbidity and mortality associated with HCM—sudden death, progressive heart failure, and atrial fibrillation and stroke.[106,152]

In their 1960 publication, Hollman, Teare, and colleagues[150] report on the extended family of case five from his 1957 cases series: a young woman, dead suddenly at age 21 years old, after a prodrome of what was surely progressive heart failure punctuated by atrial fibrillation complicated by a cardioembolic cerebrovascular accident. Having examined two generations of family members, Teare found a striking pattern: all three of the siblings of the young woman and her suddenly deceased brother (whose age had been given as 16 years old in the 1957 publication but as 18 in the 1960 piece) had evidence of a similar cardiomyopathy (Fig. 24.28). Furthermore, their father died suddenly at 40 years of age, also of cardiac causes, and one of their father's brothers, their uncle, had an "abnormal heart" that appeared to affect two of his children, the proband's cousins. Of the 23 individuals who Teare examined, 9, if not as many as 12, had evidence of heart disease, providing strong evidence of an underlying genetic disorder with an autosomal dominant pattern of inheritance.[147] When looking at the age and severity of disease onset, Teare noted that in the proband's generation, the disease was expressed earlier and in more severe fashion than it had in the preceding generation, consistent with what 50 subsequent years of investigation have found; that is, that sudden death is common among the young and less so among the old.[106,152] Finally, Teare found that the histories of the affected individuals were notable for symptomatic themes: atrial fibrillation, progressive exertional dyspnea, and frank heart failure. In closing his sentinel work, Teare, for all his prescient insight, plants the seed of a misunderstanding that has continued in the 5 decades since. Seeking a name to facilitate rather than confuse understanding, Teare writes, "the title *obstructive cardiomyopathy* [italics in the original] is proposed for these and similar cases."[147]

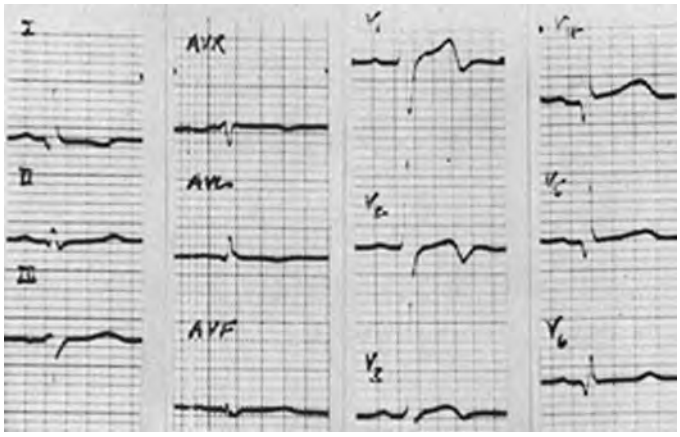


Fig. 24.27 Electrocardiogram from a patient with hypertrophic cardiomyopathy shows anterior and lateral precordial T-wave inversions in V1, V2, V3, and I, as well as Q waves in V4, V5, and V6, consistent with abnormal myocardial function and fibrosis. *(Reproduced with permission from Teare D. Asymmetrical hypertrophy of the heart in young adults.* Br Heart J. *1958;20:2.)*

Now, almost 60 years later, the sudden deaths of young, apparently otherwise healthy athletes has made HCM a seemingly familiar topic, even to the nonmedically trained, but it remains misunderstood. Among the myths, some evident even in Teare's work, that have yet to be dispelled are that HCM is necessarily obstructive (it is not); that the diagnosis is a death sentence and incompatible with a normal life expectancy (it is not); and that the diagnosis requires massive left ventricular hypertrophy that clearly distinguishes it from the physiologic hypertrophy of a performance athlete (it does not).[106,152]

So what is this disease that has been variously named and misnamed *obstructive cardiomyopathy*, *hypertrophic obstructive cardiomyopathy*, *idiopathic hypertrophic subaortic stenosis*, *muscular subaortic stenosis*, and *asymmetric septal hypertrophy*?[153] According to the most recent joint American College of Cardiology (ACC) and AHA guidelines, HCM, the preferred term, is a "disease state characterized by

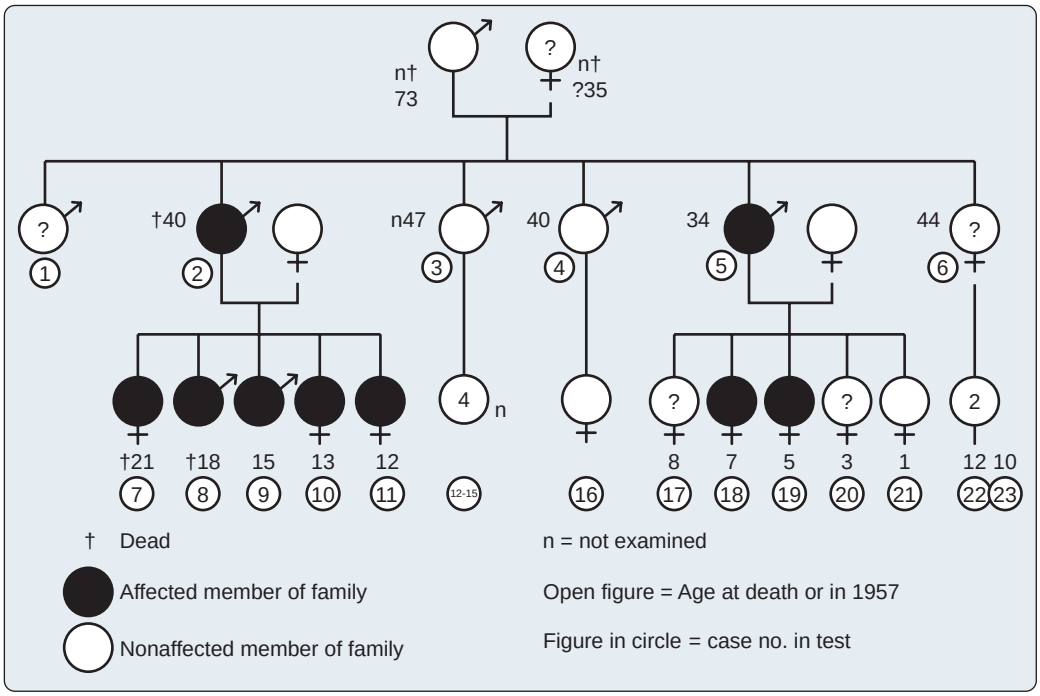


Fig. 24.28 Family tree of a patient with hypertrophic cardiomyopathy is consistent with an autosomal dominant pattern of inheritance. *(Reproduced with permission from Hollman A, Goodwin JF, Teare D, Renwick JW. A family with obstructive cardiomyopathy (asymmetrical hypertrophy).* Br Heart J. *1960;22:449.)*

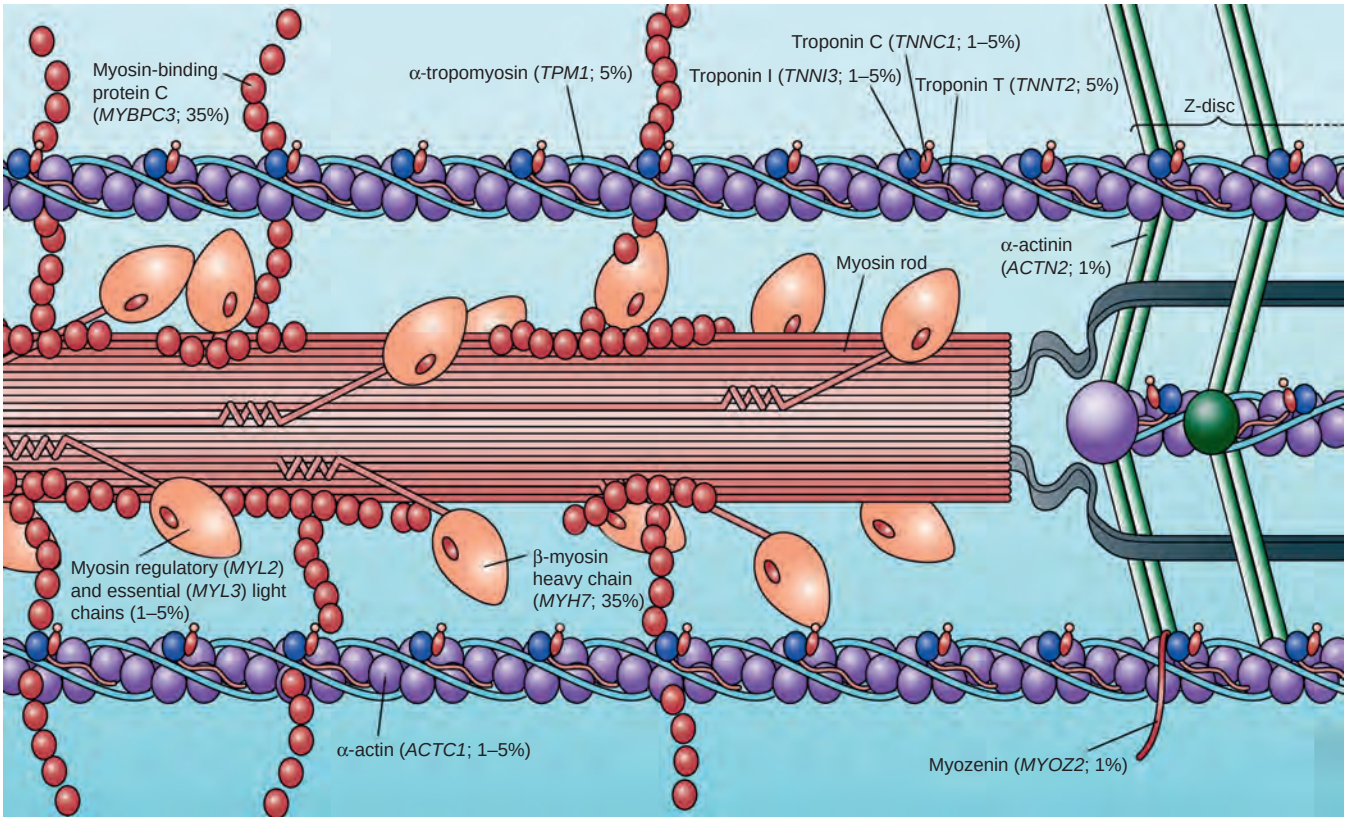


Fig. 24.29 The cardiac sarcomere and the location of genes are known to cause hypertrophic cardiomyopathy. Prevalence of the mutations is shown in parentheses. *(Reproduced with permission from Maron BJ, Maron MS. Hypertrophic cardiomyopathy.* Lancet. *2013;381:24.)*

unexplained left ventricular hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient."[154] Although the left ventricular hypertrophy, typically quantified with TTE but increasingly assessed with cardiac MRI, may be asymmetric, it need not be nor need it show a preference for the basal septum.[154,155] Furthermore, although the clinical diagnosis is often made in the context of a left ventricular wall thickness of at least 15 mm in adults, virtually any wall thickness, even measurements within the normal range, may be compatible with the disease.[154,155] On a microscopic level, as Teare's histopathologic descriptions clearly state, HCM is a primary myocardial abnormality with sarcomeric disarray and asymmetric left ventricular hypertrophy (see Fig. 24.26).[151] The hypertrophied muscle is composed of myocytes with bizarre shapes and multiple intercellular connections arranged in a chaotic pattern.[156] Increased connective tissue, combined with significantly disorganized and hypertrophied myocytes, contributes to the diastolic abnormalities of the disease that exhibit increased chamber stiffness, impaired relaxation, and an unstable electrophysiologic substrate causing complex arrhythmias and sudden death.

HCM is both global and common, perhaps the most common inherited cardiac disease, with a prevalence of at least 1:500 if not closer to 1:200. It is estimated to affect 700,000 Americans if not more.[106,107,153] As Teare correctly inferred, HCM is inherited in autosomal dominant fashion, although with variable expressivity and age-related penetrance.[106,152,153,157] The molecular genetic basis for the disease began to be unraveled in 1989, when HCM was mapped to a locus on chromosome 14.[157–159] A year later, in 1990, the same Harvard laboratory identified in one family a missense mutation in the ß-cardiac myosin heavy chain, leading to the substitution of glutamine for arginine, and in another family an α/β-cardiac myosin heavy chain hybrid gene, thereby discovering the first two genetic bases for HCM.[157,159–161] It is now known that mutations in at least 11 different genes cause HCM and that these genes encode proteins in both the thick and thin myofilaments, as well as the associated terminal Z-disc (Fig. 24.29).[106,152,153,157] The most common of these mutations occur in the ß-myosin heavy chain (40%) and the myosin-binding protein C (40%).[106,152,153,157]

Although genetic testing for individuals with or suspected of having HCM is increasingly common, the interpretation of the results of such tests is complicated. Currently, the results of genetic testing do not predict outcome, do not allow for risk stratification, and do not determine treatment.[106,152–154,157] Genetic testing is, however, useful for identifying family members who may not meet criteria for HCM clinically but who may, nonetheless, be at risk for developing the disease on a genetic basis; that is, gene testing may identify relatives who are genetically positive but phenotypically negative (genotype positive–phenotype negative).[106,152–154,157] The significance of a positive genetic marker in an individual who does not exhibit the disease clinically is unclear. Although such individuals may be at risk of developing the hypertrophic phenotype, quantifying that risk is not currently possible, and the presence of the mutation in the absence of characteristic morphologic changes does not predict outcomes such as sudden cardiac death.[106,152–155,157] Genetic testing is useful, however, to exclude other causes of cardiomyopathy, such as Fabry disease or Danon disease, both of which have a different natural history and a require different treatment.[106,152,153,157] According to current ACC/AHA guidelines, genetic counseling should be offered to individuals with HCM, and screening should be performed in first-degree relatives, even if the prognostic value of such testing is uncertain (both Level of Evidence: B).[154] Genotype positive–phenotype negative individuals should have serial ECGs and clinical evaluations approximately every 5 years for adults and every 12 to 18 months for children and adolescents.[154]

Clinically, HCM is diagnosed most commonly with TTE but also increasingly with cardiac MRI.[106,152–155,162] The characteristic morphologic findings are those of a hypertrophied, nondilated ventricle in the

absence of alternative causes. Although guidelines reference a left ventricular wall thickness 15 mm or greater, any wall thickness, even those in the normal range, may be compatible with the diagnosis in the appropriate clinical context.[106,152–155] In cases in which TTE is inconclusive, cardiac MRI is indicated. Not only does cardiac MRI offer spatial resolution, but it also offers the potential to detect and characterize other morphologic changes that conventional echocardiography may miss: apical-variant hypertrophy, apical aneurysms and thrombus, midventricular cavity obstruction, and anomalous papillary muscle insertions contributing to either midventricular or outflow tract obstruction.[106,152–155] Furthermore, the presence of significant late gadolinium enhancement has predictive value in that its presence in 15% or more of left ventricular mass confers an increased risk of sudden cardiac death and is an indication to consider prophylactic ICD placement.[106,152,153]

In the most familiar manifestation of HCM, asymmetric hypertrophy of the basal left ventricular septum produces dynamic left ventricular outflow tract (LVOT) obstruction. More than 50 years of clinical investigation has taught, however, that there are, in fact, multiple patterns of hypertrophy, and the absence of basal hypertrophy, systolic anterior motion (SAM) of the mitral valve, and associated dynamic LVOT obstruction does not exclude the diagnosis of HCM.[163,164] Other common morphologic types, frequently visualized more clearly with cardiac MRI than with TTE, include a midventricular variant and an apical variant (Figs. 24.30 and 24.31). Defining the location and extent of hypertrophy and the site of obstruction, if any, is important for surgical planning. Although asymmetric hypertrophy of the basal septum can be treated with a standard transaortic extended left ventricular septal myectomy, midventricular and apical variants may require a transapical approach or a combination of transapical and transaortic approaches.[165–172]

As Teare's cases might suggest, the initial investigations of HCM have led many to believe that the diagnosis was the equivalent of a death sentence and the prognosis was uniformly poor. It is now known that both beliefs are clearly not the case.[106,152,153,173,174] With appropriate evaluation, treatment, and surveillance at an institution capable of providing coordinated, multidisciplinary care, HCM is compatible with a normal life expectancy, and mortality in individuals with HCM is most commonly due not to the disease itself but to other causes (Fig. 24.32).[106,152–154,173]

If Teare's early descriptions of HCM led us to believe mistakenly in the disease's poor prognosis, then they presciently and correctly illustrate its untreated and natural history.[147,150] Clinically, patients tend to progress along one or more of three pathways: sudden cardiac death, heart failure, and atrial fibrillation with or without cardioembolic stroke (Fig. 24.33).[106,152–154]

Sudden cardiac death, usually from ventricular tachycardia or ventricular fibrillation, is rare (approximately 1% per year in HCM patients), and the rate is decreasing with the increased placement of ICDs as a primary or secondary prevention.[106,152–155] As Teare's cases again illustrate, sudden cardiac death is more common among the young than the old.[106,147,150,152–154,175] Placement of an ICD is the only treatment proven to improve mortality in HCM patients, but deciding in whom and when to place such a device is complicated.[106,152–155] As the ACC/AHA guidelines make clear, any decision to place a device should take into consideration sound clinical judgment and the preferences of the patient while explicitly acknowledging the risks, benefits, and uncertainties of implantation.[154,155] Clearly, ICDs are recommended as secondary prevention for those HCM patients with a personal history of cardiac arrest, ventricular fibrillation, or ventricular tachycardia (Fig. 24.34).[106,152–155] For patients without such a history in whom placement is contemplated for primary prevention, the decision should take into account the presence of the major proven risk factors for sudden cardiac death, which include a family history of sudden death attributable to HCM in a first-degree relative, unexplained syncope, massive left ventricular hypertrophy with wall thickness 30 mm or greater, repeated episodes of nonsustained ventricular tachycardia, an inappropriate systemic systolic blood pressure response during exercise testing, and, more recently, the presence of significant late gadolinium enhancement (≥15% of left ventricular mass) on cardiac MRI.[106,152–155,176] Other potential sudden cardiac death risk modifiers whose presence or absence may help in the decision of whether to place an ICD include significant resting LVOT obstruction (≥0 mm Hg), the presence of a left ventricular apical aneurysm, end-stage disease with systolic heart failure, and a left ventricular ejection fraction less than 50%, participation in strenuous competitive sports, obstructive coronary artery disease, and age 60 years or older, the latter recognizing that sudden cardiac death is less common among older individuals than it is among the young.[106,152–155,175]

As stated previously, ICD placement is the only intervention proven to prolong life in patients with HCM. Pharmacologic therapy with ß-blockers or calcium-channel blockers may offer symptom relief, but it does not improve mortality.[106,152–153] Defibrillators are not without complications, however, which occur at an estimated annual rate of 4% to 5% and include inappropriate device discharge, lead fracture or dislodgement, device-related infection, and device-associated bleeding or thrombosis.[106,152–154]

When the subject of sudden cardiac death is mentioned, the affected population that comes most frequently to mind is the young, apparently otherwise healthy, competitive, frequently high-performance athletes. In this population, HCM is the most common cause of sudden cardiac death.[106,152–154,177,178] Both American and European cardiology societies recognize that participation in strenuous competitive sports by patients with HCM increases the risk of sudden cardiac death and that refraining from participation can decrease it.[179,180] Patients with HCM are encouraged not to participate in strenuous sports, regardless of the presence of an ICD, regardless of previous septal reduction, and regardless of the presence of LVOT obstruction (Level of Evidence: C).[154] Screening programs have met with mixed success, and American cardiology societies currently do not endorse mandatory electrocardiographic screening of young athletes.[106,153,181]

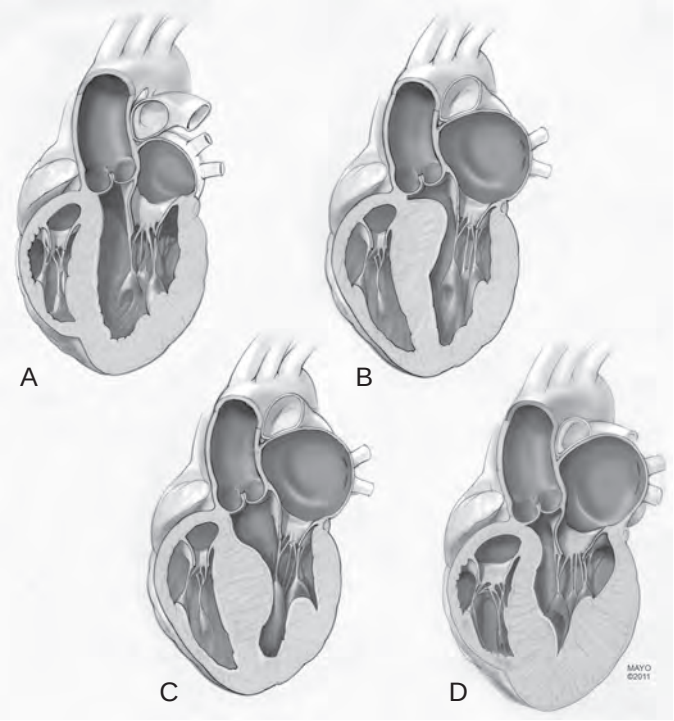


Fig. 24.30 Normal heart and the phenotypic variants of hypertrophic cardiomyopathy. (A) Normal heart. (B) Isolated basal septal hypertrophy. (C) Midventricular septal hypertrophy. (D) Apical hypertrophy. Note that individual patients may have components of more than one type of hypertrophy. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Illustration No. EBW1078418-001-3.)*

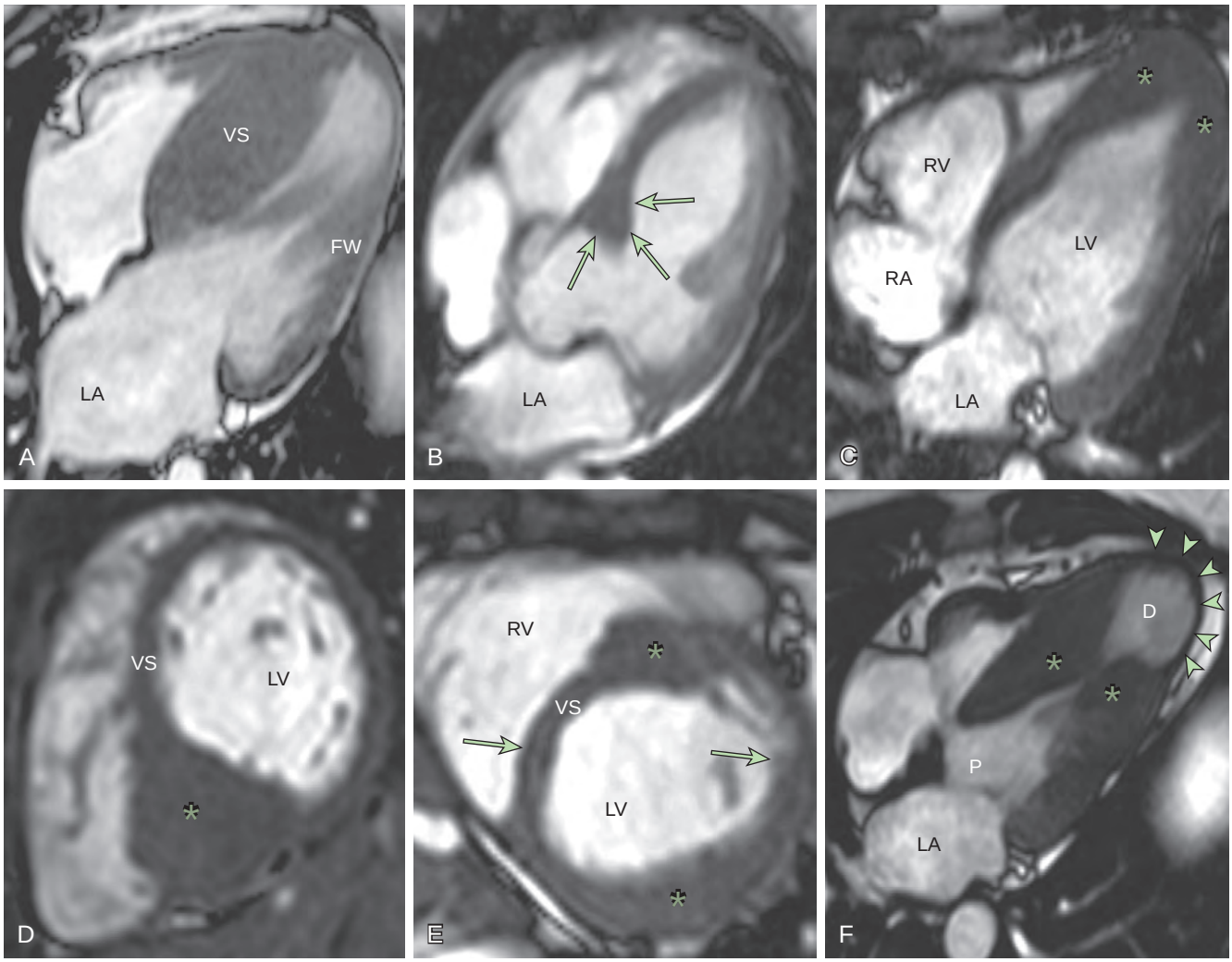


Fig. 24.31 Cardiac magnetic resonance images of the phenotypic variants of hypertrophic cardiomyopathy. (A) Diffuse hypertrophy of the interventricular septum with sparing of the left ventricular free wall. (B) Isolated basal septal hypertrophy *(arrows)*. (C) Apical hypertrophy *(asterisks)*. (D) Posterior left ventricular septal hypertrophy *(asterisk)*. (E) Discontinuous hypertrophy of the basal anterior septum *(uppermost asterisk)* and the posterior free wall *(lower asterisk)* separated by regions of normal left ventricular wall thickness *(arrows)*. (F) Midventricular hypertrophy *(asterisks)*, dividing the left ventricular chamber into proximal *(P)* and distal *(D)* segments with an apical pouch *(arrowheads)*. *D,* Distal (apical) left ventricle; *FW,* free wall; *LA,* left atrium; *LV,* left ventricle; *P,* proximal left ventricle; *RA,* right atrium; *RV,* right ventricle; *VS,* ventricular septum. *(Reproduced with permission from Maron BJ, Maron MS. Hypertrophic cardiomyopathy.* Lancet. *381:242–255.)*

The second pathway along which HCM may progress is that of heart failure, initially diastolic and subsequently systolic.[106,152–155] Although many patients with HCM will remain asymptomatic and enjoy a normal life expectancy, others will become symptomatic, complaining of dyspnea on exertion, palpitations, and chest pain. Almost one half of HCM patients will develop signs and symptoms of heart failure.[106,152–155] Although the symptoms of heart failure frequently reflect dynamic LVOT obstruction and compromise of forward flow, especially under the conditions of hypovolemia, tachycardia, and increased contractility as may occur during exercise or stress, they may occur in the absence of obstruction, reflecting instead an imbalance of myocardial oxygen supply and demand in the context of a grossly hypertrophied heart with an endocardium constantly on the brink of ischemia; impaired left ventricular diastolic function with compromised relaxation and compliance; and the presence of often dynamic mitral regurgitation.[105,105,152–155]

For patients with the classic asymmetric hypertrophy of the basal left ventricular septum, as opposed to those with either the midventricular or apical variant HCM, obstruction occurs as blood ejects from the apex of the LV through the outflow tract and across the aortic valve, passing through a channel of changing caliber created by the hypertrophied basal septum and SAM of the mitral valve apparatus. The outflow tract diameter and thus the obstruction are dynamic and dependent on loading condition. Hypovolemia, decreased systemic vascular resistance (SVR), tachycardia, and increased contractility, all of which may occur with exercise, stress, and surgical intervention under anesthesia, act in concert to exacerbate outflow tract obstruction. For clinical decision-making purposes, it is the peak (or maximum) instantaneous gradient that influences treatment decisions. A resting gradient 30 mm Hg or greater across the LVOT is consistent with basal obstruction and is an independent predictor of heart failure and death, whereas a gradient 50 mm Hg or greater, either with rest or provocation, is considered sufficient to prompt consideration of surgical or percutaneous septal reduction in a severely symptomatic patient.[106,152–154,182]

TTE is the modality of choice for the evaluation of HCM. Two-dimensional echocardiography usually allows the clinician to analyze the morphologic characteristics of the disease and determine the location

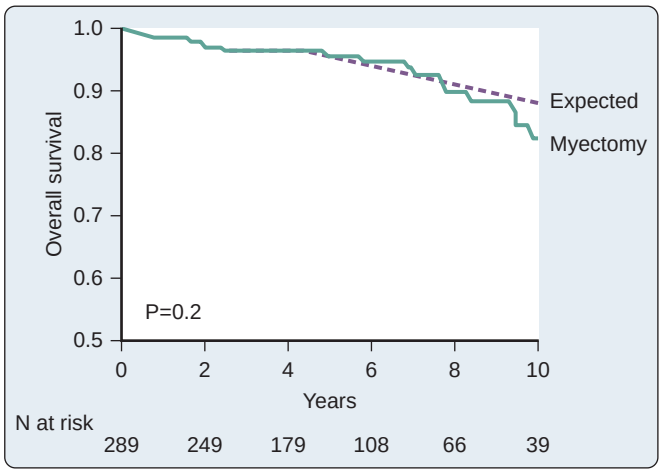


Fig. 24.32 Overall survival after surgical myectomy for obstructive hypertrophic cardiomyopathy is compared with age- and gender-matched general populations. *(Reproduced with permission from Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy.* J Am Coll Cardiol. *2005;46:473.)*

of the hypertrophy. Doppler and color-flow imaging have characteristic appearances in HCM. Continuous-wave Doppler is used to quantify the gradient across the LVOT. The Doppler signal has a unique "dagger-shaped" appearance (Fig. 24.35). The LVOT Doppler signal is typically obtained with an apical position of the transducer during TTE or from a deep transgastric view when TEE is used. If the LVOT gradient is less than expected, then provocative maneuvers should be used in an effort to demonstrate an increased gradient. Decreasing preload and ventricular filling with a Valsalva maneuver or inhalation of amyl nitrite are noninvasive techniques that can be used in the conscious patient (see Fig. 24.35). With severe obstruction, mitral regurgitation usually accompanies LVOT obstruction, in a classic pattern of EJECTION → OBSTRUCTION → REGURGITATION. With the anterior leaflet likely both pushed and drawn into the outflow tract, the jet of mitral regurgitation is typically directed posteriorly (Figs. 24.36 and 24.37).[183] If the jet is not directed posteriorly or if there are multiple jets, then another cause for the regurgitation is likely, and the valve should be interrogated in greater detail. Although posteriorly directed, mitral regurgitation associated with dynamic LVOT obstruction, even when severe, rarely requires surgical intervention and will largely resolve after the cause is addressed (specifically, LVOT obstruction secondary to basal septal hypertrophy). However, mitral regurgitation caused by organic lesions, such as mitral valve prolapse (MVP) or a flail leaflet, will not.[166,168–170,184] An unfortunately common mistake made at institutions unfamiliar with the pathophysiologic implications of basal septal hypertrophy and dynamic

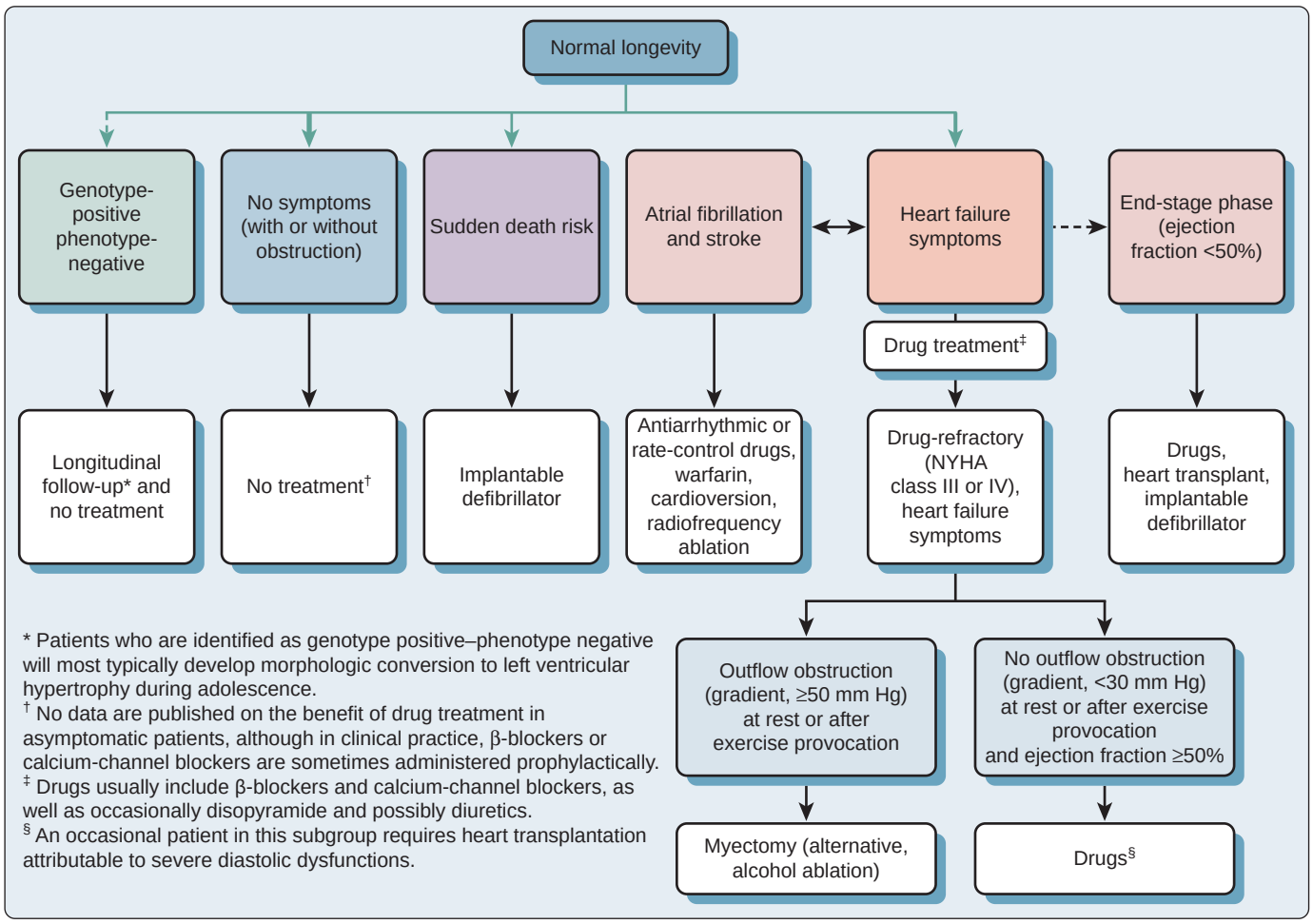
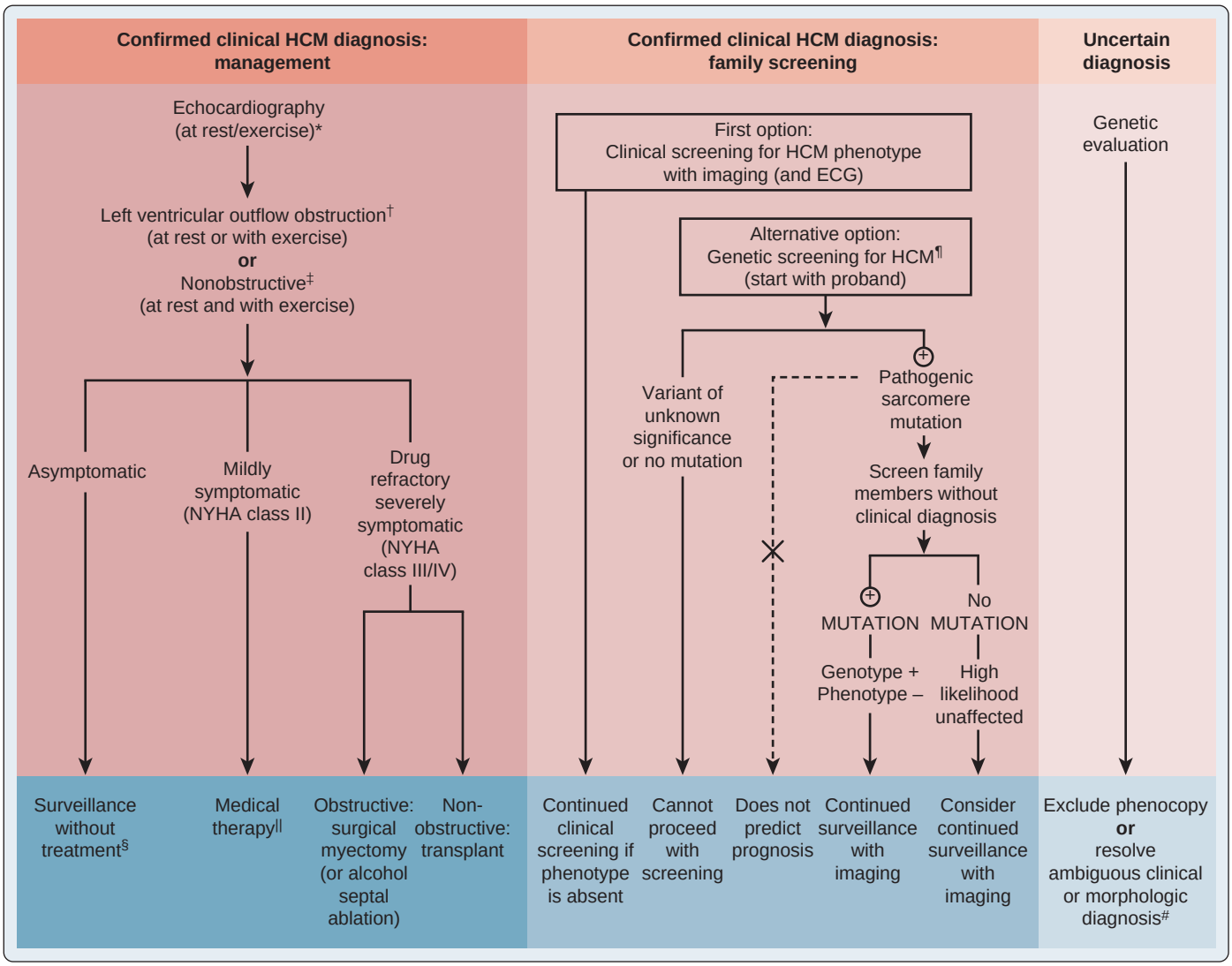


Fig. 24.33 Prognostic pathways and treatment strategies for various presentations of hypertrophic cardiomyopathy. Pathways are not necessarily mutually exclusive. *Colored arrow thickness* represents the proportion of patients affected for every pathway. *NYHA,* New York Heart Association. *(Reproduced with permission from Maron BJ, Maron MS. Hypertrophic cardiomyopathy.* Lancet. *2013;381:247.)*



*Patients without LV outflow tract gradient (<30 mm Hg) at rest should also undergo stress (exercise) echocardiography. Not shown here, on initial evaluation, all HCM patients undergo sudden death risk stratification (see Fig. 5 in Maron BJ, Ommen SR, Semsarian C, et al. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine. *J Am Coll Cardiol.* 2014;64(1); 83–99, available at: <http://www.sciencedirect.com/science/article/pii/S0735109714023390>.)
†Generally regarded as ≥30 mm Hg outflow gradient, but ≥50 mm Hg when septal reduction intervention is considered (ie, septal myectomy, alcohol ablation).
‡No or trivial (<30 mm Hg) outflow gradient at rest and with exercise.
§No data on benefit of pharmacologic therapy, although beta-blockers are often administered prophylactically in clinical practice.
||Obstructive: usually, beta-blockers or possibly calcium channel antagonists (verapamil), or disopyramide. Nonobstructive: beta-blockers, calcium channel antagonists, and possibly diuretics administered judiciously.
¶Screening targets relatives without clinical evidence of HCM phenotype.
#Could differentiate HCM from other causes of LVH, including patients with history of systemic hypertension, or highly trained athletes.

Fig. 24.34 Risk stratification model identifies patients at highest risk of sudden cardiac death who may be candidates for implantable cardioverter-defibrillators (ICDs). Major *(upper box)* and minor *(lower box)* risk markers appear in boxes at the *left*. At *right* are the results of ICD therapy in 730 children, adolescents, and adults assembled from two registry studies. *BP,* Blood pressure; *CAD,* coronary artery disease; *EF,* ejection fraction; *HCM,* hypertrophic cardiomyopathy; *LV,* left ventricular; *LVH,* left ventricular hypertrophy; *NSVT,* nonsustained ventricular tachycardia; *NYHA,* New York Heart Association; *SD,* sudden death; *VT/VF,* ventricular tachycardia/ventricular fibrillation; *Y,* years. *(Reproduced with permission from Maron BJ, Ommen SR, Semsarian C, et al. Hypertrophic cardiomyopathy: present and future, with translation into contemporary cardiovascular medicine.* J Am Coll Cardiol. *2014;64:89.)*

outflow tract obstruction is offering a patient with progressive heart failure from severe mitral regurgitation, secondary to SAM, a mitral valve repair or even replacement without addressing the culprit septal hypertrophy. Almost inevitably, symptoms in these patients will recur, and the patients will return, now for a secondary sternotomy and the indicated procedure that would have likely obviated any intervention on the mitral valve, specifically, a septal myectomy.

The mechanism of outflow tract obstruction and mitral regurgitation in cases of basal septal hypertrophy is complicated and frequently misunderstood.[183] Conventional wisdom would state that flow

acceleration during systolic ejection across a narrowed outflow tract is associated with a region of low pressure that then "sucks" the anterior leaflet of the mitral valve into the outflow tract, producing dynamic obstruction in accordance with Bernoulli principle and the Venturi effect. Whereas early surgical descriptions suggested that outflow tract narrowing was due to a muscular ring or sphincter that contracted during systole, current consensus suggests that the obstruction reflects the interactions of a hypertrophied septum, abnormal anatomy of the mitral valve and its associated apparatus, and abnormal patterns of blood flow in the LV (see Fig. 24.37).[183] An elongated anterior valve leaflet, anterior displacement of the papillary muscles, and a more anterior coaptation margin conspire to create anterior motion of the mitral valve even before aortic valve opening. As blood then courses from the apex across a bulging basal septum, it pushes against the atrial side of the anterior mitral valve leaflet, displacing it into the outflow tract as the aortic valve begins to open. With aortic valve opening and incipient ejection, the Venturi effect may then act in concert to exacerbate outflow tract obstruction, with the anterior leaflet of the mitral valve first pushed and then pulled across the LVOT, resulting in SAM of the anterior mitral leaflet.[183]

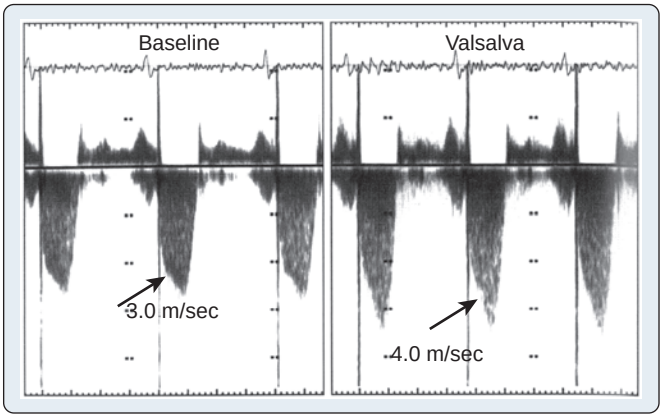


Fig. 24.35 Continuous-wave Doppler spectra obtained from the apex demonstrates dynamic left ventricular (LV) outflow tract obstruction. Note the typical late-peaking configuration resembling a dagger or ski slope *(arrows)*. The baseline *(left)* velocity is 2.8 m/sec, corresponding to the peak LV outflow tract of 31 mm Hg. With the Valsalva maneuver *(right)*, the velocity increases to 3.5 m/sec, corresponding to a gradient of 55 mm Hg. *(From Oh JK, Seward JB, Tajik AJ:* The echo manual*, ed 3, 2006. Used with permission of Mayo Foundation of Medical Education and Research. All rights reserved.)*

For patients with symptoms of heart failure attributable to outflow obstruction, the first-line treatment is pharmacologic therapy with ß-blockers with the express purpose of providing symptom relief. As has been stated previously, pharmacologic therapy has not been shown to improve mortality or to alter the morphologic substrate.[105,106,152–155] ß-Blockers are designed to target the exacerbators of outflow tract obstruction: increased contractility, tachycardia, and hypovolemia with decreased end-diastolic volume and stroke volume. ß-Blockers are negative inotropes and chronotropes, and by slowing the heart rate, they allow for longer diastolic filling and increased stroke volume. For patients unable to tolerate ß-blockers, nondihydropyridine calcium channel blockers such as verapamil and diltiazem are second-line agents, although they may exacerbate outflow tract obstruction by lowering mean arterial pressure, especially in patients with significant resting outflow tract gradients and patients with depressed systolic function. For patients who remain symptomatic, despite treatment with either or both ß-blockers and calcium channel blockers, both of which may lower exercise-induced but not basal gradients, disopyramide can reduce resting outflow tract gradients and afford a degree of symptom relief.[105,106,152–155]

For patients with persistent symptoms despite pharmacologic therapy, interventional therapy with either alcohol septal ablation or surgical myectomy is the next option. For patients with severe symptoms (NYHA functional class III or IV) and severe resting or provoked LVOT obstruction (≥50 mm Hg), despite maximal medical

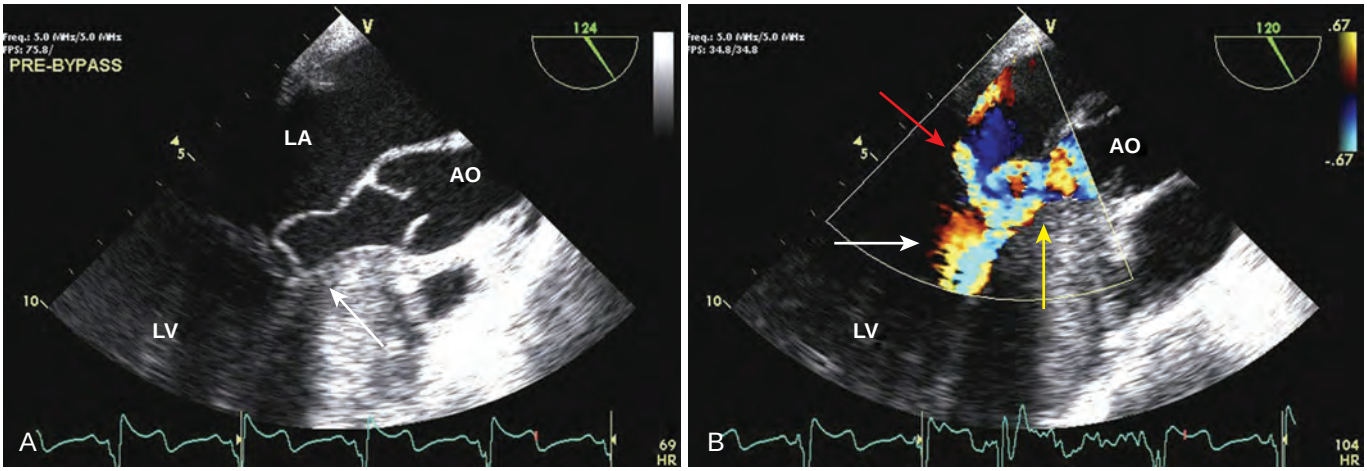


Fig. 24.36 Transesophageal midesophageal long-axis view of the aortic valve and left ventricular outflow tract (LVOT) in a patient with hypertrophic obstructive cardiomyopathy. (A) Two-dimensional echocardiography during systole shows a thickened basal septum *(white arrow)* and systolic anterior motion (SAM) of the anterior leaflet of the mitral valve, creating dynamic LVOT obstruction. (B) Color-flow Doppler shows flow acceleration beginning at the site of the septal hypertrophy *(white arrow)* and becoming more severe in the narrowed LVOT *(yellow arrow)*. Mitral regurgitation associated with SAM is typically directed posterolaterally *(red arrow)* and will typically improve if not resolve after myectomy. Jets of mitral regurgitation directed centrally or anteriorly suggest an additional cause for the regurgitation that may persist after myectomy and may need to be addressed with a separate surgical intervention on the mitral valve. *AO,* Aorta; *LA,* left atrium; *LV,* left ventricle. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:688.)*

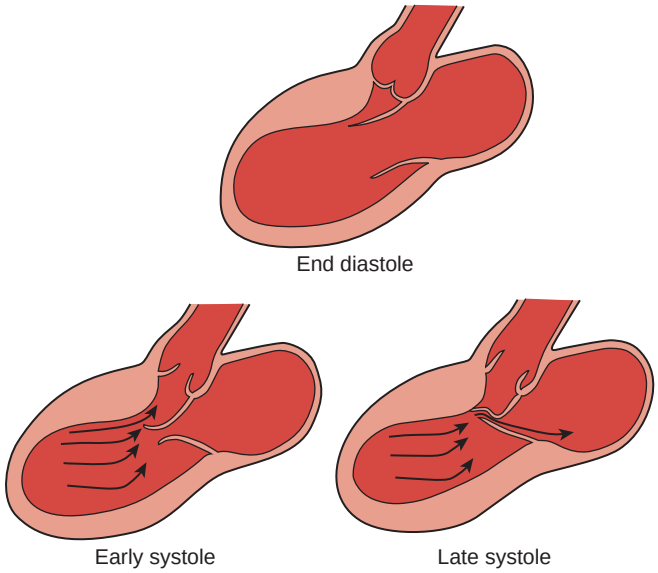


Fig. 24.37 Mechanisms of left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy. The systolic anterior motion (SAM) of the anterior leaflet of the mitral valve begins early in systole, often during isovolemic left ventricular contraction (not depicted) when Venturi effects are negligible. As the aortic valve opens and the ejection phase of systole proceeds *(lower left and right images)*, the anterior mitral valve leaflet is both pushed and pulled into the LVOT. In addition, the jet of mitral regurgitation associated with SAM is classically directed posterolaterally (see text for details). *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 675–736; and from Ommen SR, Shah PM, Tajik AJ. Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: past, present and future.* Heart. *2008;94:1276–1281, 2008.)*

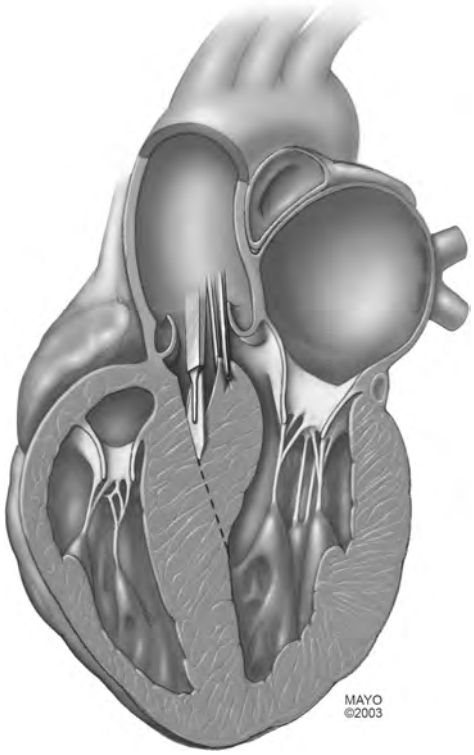


Fig. 24.38 Surgical technique for transaortic extended left ventricular septal myectomy for isolated basal septal hypertrophy. The incision begins at the nadir of the right aortic cusp and continues to the anterior leaflet of the mitral valve. The incision should extend apically past the point of contact between the anterior mitral valve leaflet and the hypertrophied basal septum to the base of the papillary muscles. In the classic technique, the incision is extended only up to 3 cm ventricularly from the aortic valve, whereas in the technique described by Schaff at the Mayo Clinic, the incision extends up to 7 cm ventricularly from the aortic valve, creating an *extended* left ventricular septal myectomy. The surgeon can frequently visualize the point of contact between the anterior mitral valve leaflet and the hypertrophied basal septum as whitish scar tissue discoloring the normally red endocardium. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Reprinted in Brown ML, Schaff HV. Surgical Management of Obstructive Hypertrophic Cardiomyopathy: the Gold Standard.* Expert Rev Cardiovasc Ther. *2008;6(5):715–722.)*

treatment, surgical septal myectomy is a class I indication, provided that it can be performed by an experienced surgeon working at a facility capable of offering patients specialized, multidisciplinary, coordinated care.[106,152–155,185] Surgical intervention has repeatedly been shown to offer durable relief from outflow tract obstruction, thereby decreasing if not abolishing resting and provoked outflow tract gradients, normalizing left ventricular filling pressures, reversing mitral regurgitation, and relieving the symptoms that had been associated with progressive diastolic heart failure.* With operative mortality now less than 1% at major medical centers that specialize in surgical resection, septal myectomy has the potential to normalize life expectancy for affected individuals.[173]

Surgical septal myectomy is both complicated and misunderstood. It is misunderstood, because the surgical technique will vary considerably, depending on the location of the ventricular hypertrophy and the obstruction, if there is any. The most common and familiar phenotype of HCM is asymmetric hypertrophy of the basal septum, producing dynamic LVOT obstruction. When basal septal hypertrophy is the diagnosis, the indicated procedure is a transaortic septal myectomy (Fig. 24.38).[166,168,170] After the initiation of CPB, the application of the aortic cross-clamp, and the administration of cardioplegia, a low transverse aortotomy is made and the subaortic septum is exposed. The prominent basal septum is excised with an excision extending from the nadir of the right aortic sinus leftward to the anterior leaflet of the mitral valve using a meticulous technique to avoid incurring complete heart block, a membranous ventricular septal defect (VSD), or injury to the mitral or aortic valves (Fig. 24.39).[166,168,170] In the classic technique described by Morrow, tissue is removed up to 3 centimeters apically from the aortic valve, whereas the current technique described by Schaff uses an extended resection up to 7 centimeters from the valve.[166,168,170,187,188]

With a midventricular variant of HCM, obstruction occurs at the midventricular level, attributable to the apposition of the ventricular septum and the papillary muscles. Because outflow tract obstruction is not present, at least in the pure form of the midventricular variant, SAM of the mitral valve and associated mitral regurgitation are unlikely. Additionally, the pressure gradient occurs not across the outflow tract but across the cavity of the ventricle, from apex to base. The elevated apical pressures, secondary to midcavitary obstruction, may favor the formation of an apical pouch (Fig. 24.40). Stagnant blood in the pouch may then predispose to apical thrombus formation. Given the location of the obstruction, a transaortic approach may not allow for sufficient exposure for adequate surgical resection; therefore a transapical approach is required (Figs. 24.41 and 24.42).[165,166,171,172] For patients with obstruction at both the base and midventricular levels, the surgeon may need to perform sequential resections from transaortic and transapical approaches, thereby lengthening the surgical procedure.[165,166]

For patients with apical variant HCM, left ventricular hypertrophy occurs predominantly at the apex, producing a small chamber size. The combination of a small volume chamber, a hypertrophied and stiff myocardium, and abnormal diastolic relaxation produces a significant impairment in diastolic filling and results in abnormally low

*References 106, 152–155, 169, 170, 173, 174, 185, 186.

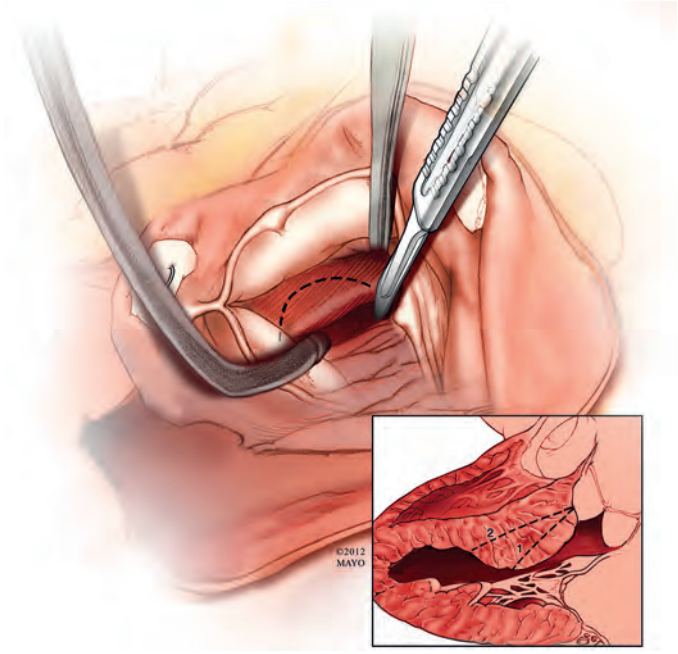


Fig. 24.39 Surgical technique for transaortic extended left ventricular septal myectomy for isolated basal septal hypertrophy. A surgeon's view of the transaortic approach looks from the proximal ascending aorta across the opened aortic valve and apically into the left ventricular cavity. With the patient in the supine position, the right coronary cusp sits anteriorly. The incision begins at the nadir of the right cusp and continues leftward to the anterior leaflet of the mitral valve. Incisions that are begun more rightward than the nadir of the right coronary cusp would risk injury to the membranous ventricular septum and its contained conduction tissue and would result in complete heart block. *(Inset)* The incision is successively deepened and extended apically past the point of contact between the anterior mitral valve leaflet and the hypertrophied basal septum to the base of the papillary muscles. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Illustration No. e3151794-00.)*

stroke volumes. Although the left ventricular ejection fraction may be normal or even supranormal, the low stroke volume leads to a low CO and index and all the classic stigmata of heart failure. Typically, patients with the apical variant do not exhibit LVOT obstruction and do not have SAM of the mitral valve. The resection, itself, is performed transapically, as it is for midventricular variant cases (Figs. 24.43, 24.44 and 24.45).[166,167,172]

Intraoperative TEE is essential in the care of patient undergoing septal myectomy.[189] Before incision, TEE can identify both the location of hypertrophy in relation to the aortic annulus and the thickness of

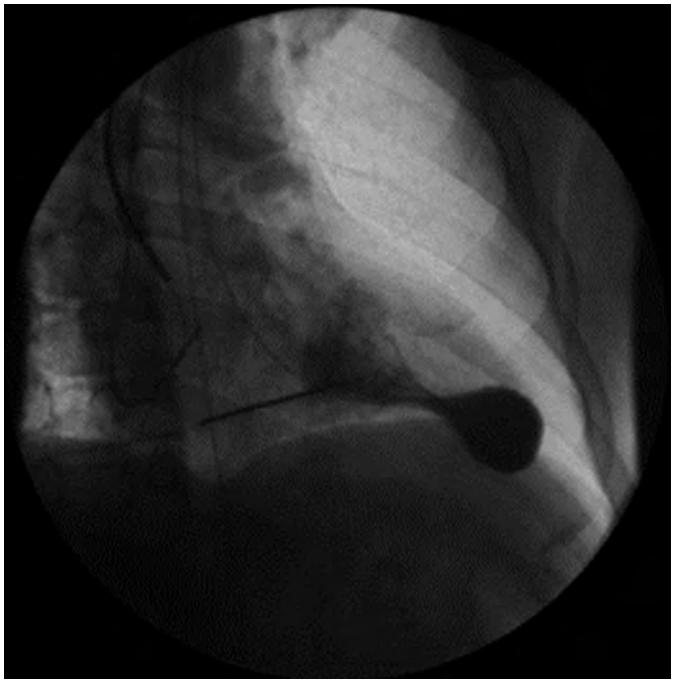


Fig. 24.40 A left ventriculogram demonstrates an apical pouch or aneurysm in a patient with midventricular obstruction. *(Reproduced with permission from Kunkala MR, Schaff HV, Nishimura RA, et al. Transapical approach to myectomy for midventricular obstruction in hypertrophic cardiomyopathy.* Ann Thorac Surg. *2013;96:567.)*

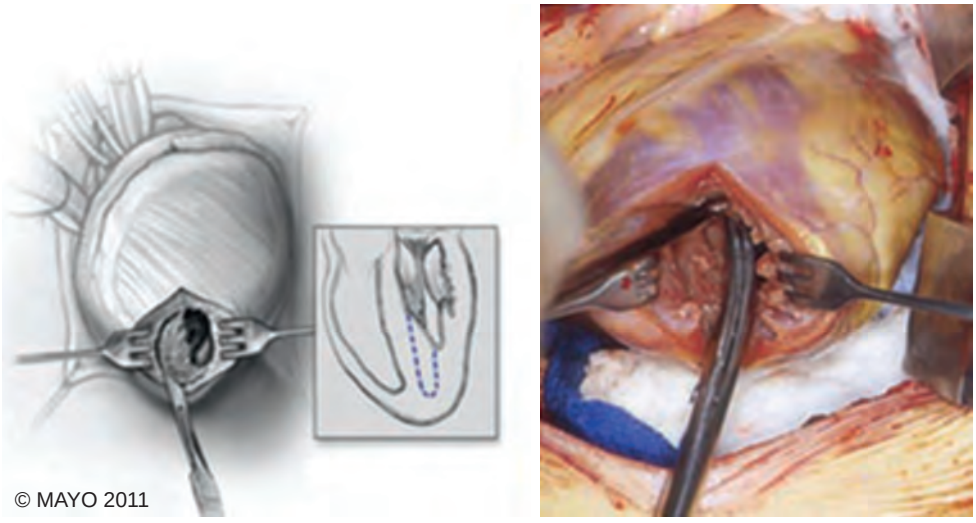


Fig. 24.41 Surgical technique for transapical myectomy for patients with midventricular and/or apical hypertrophy. After the left ventricular apex is opened, the majority of the resection takes place on the interventricular septum and, to a lesser extent, from the left ventricular free wall *(left inset, dashed lines). (Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Reprinted in Said SM, Dearani JA, Ommen SR, Schaff HV. Surgical treatment of hypertrophic cardiomyopathy.* Expert Rev Cardiovasc Ther. *2013;11:623.)*

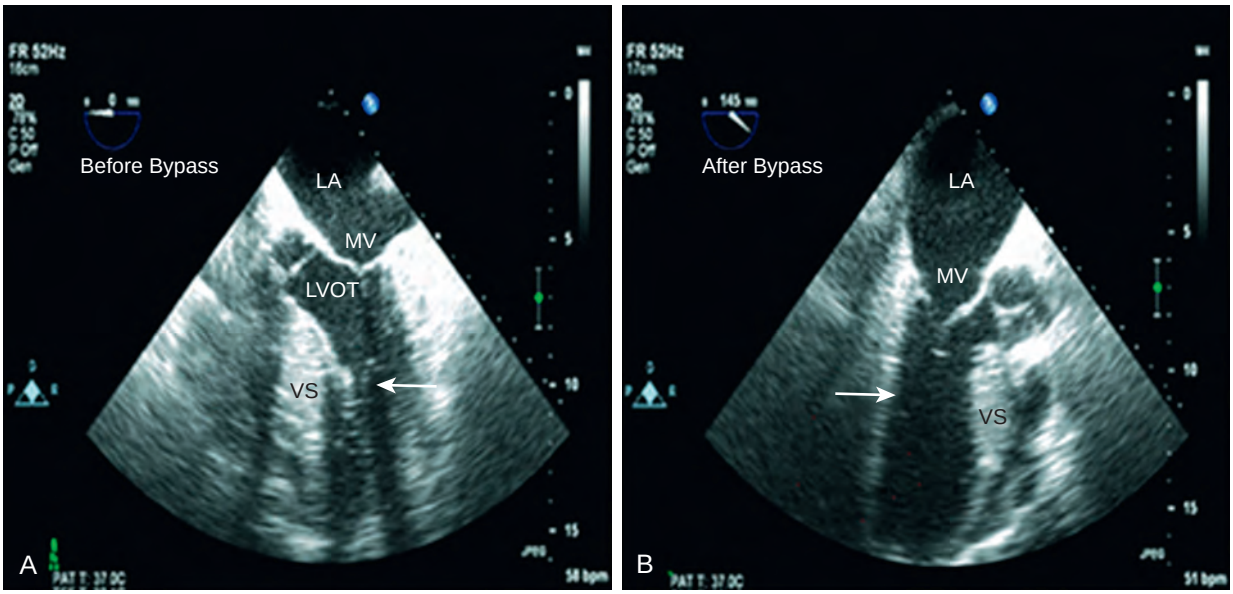


Fig. 24.42 Intraoperative transesophageal echocardiographic images of a patient with midventricular hypertrophy before and after surgical resection. (A) Midesophageal five-chamber view before resection shows the hypertrophied midventricular septum *(arrow)*. (B) Midesophageal long-axis view after resection shows the now-opened left ventricular cavity *(arrow)* after a transapical approach. *LA,* Left atrium; *LVOT,* left ventricular outflow tract; *MV,* mitral valve; *VS,* interventricular septum. *(Reproduced with permission from Said SM, Schaff HV, Abel MD, Dearani JA. Transapical approach for apical myectomy and relief of midventricular obstruction in hypertrophic cardiomyopathy.* J Card Surg. *2012;27:444.)*

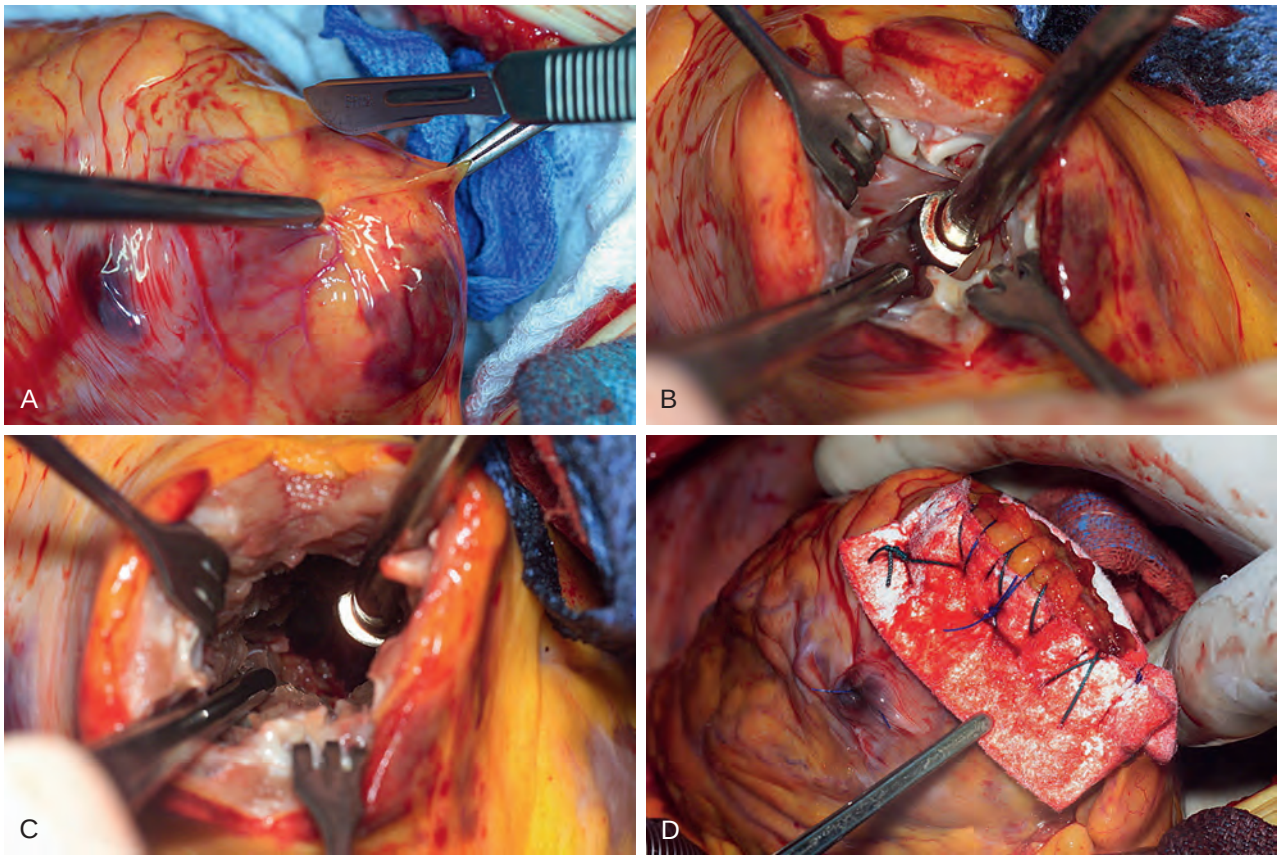


Fig. 24.43 Surgical technique for transapical myectomy for apical hypertrophic cardiomyopathy. (A and B) The left ventricular apex is isolated and incised, exposing apical cavity obliteration by a hypertrophied myocardium. The incision should avoid injury to the distal left anterior descending coronary artery and is made parallel and lateral to it. (C) The hypertrophied muscle is resected, taking care not to injure the papillary muscles and mitral valve apparatus arising from the left ventricular free wall. (D) After the myectomy, the apical ventriculotomy is closed in two layers over felt strips. *(Reproduced with permission from Schaff HV, Brown ML, Dearani JA, et al. Apical myectomy: a new surgical technique for management of severely symptomatic patients with apical hypertrophic cardiomyopathy.* J Thorac Cardiovasc Surg. *2010;139:636.)*

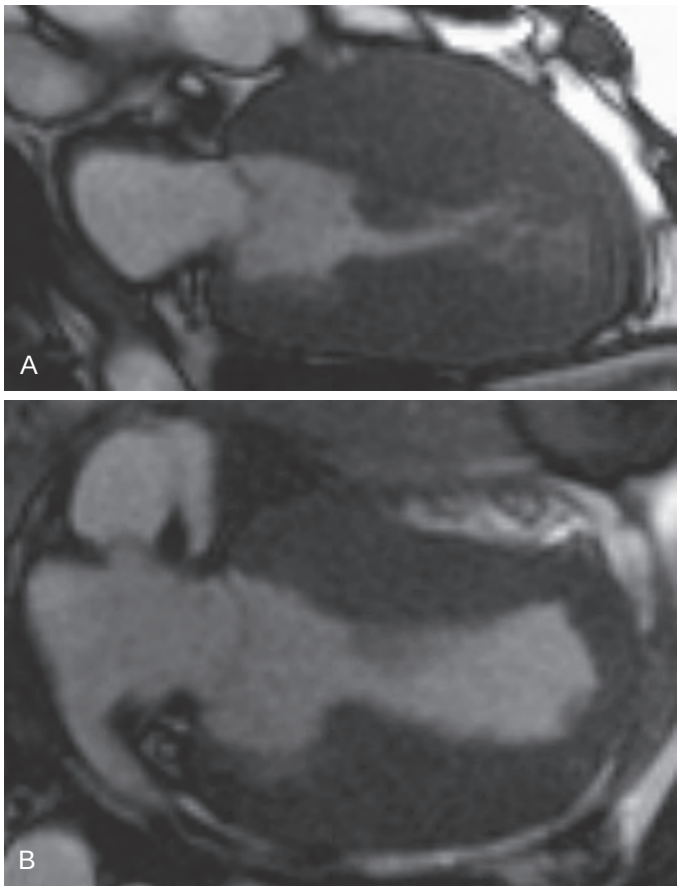


Fig. 24.44 Cardiac magnetic resonance images of a patient with apical variant hypertrophic cardiomyopathy and shown during diastole. (A) Obliteration of the apical cavity is demonstrated before surgical resection. (B) Image depicts the surgical creation of a significantly enlarged left ventricular cavity after resection. *(Reproduced with permission from Schaff HV, Brown ML, Dearani JA, et al. Apical myectomy: a new surgical technique for management of severely symptomatic patients with apical hypertrophic cardiomyopathy.* J Thorac Cardiovasc Surg. *2010;139:635.)*

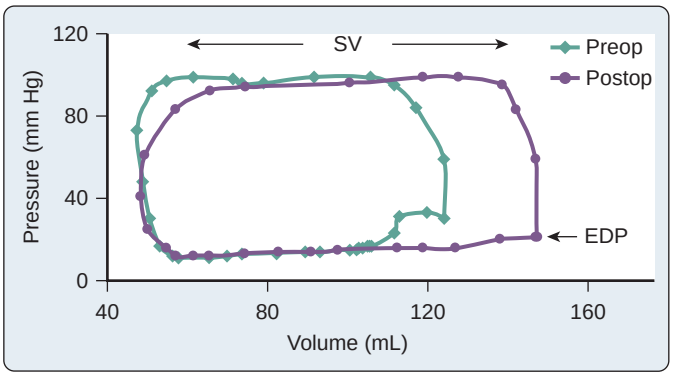


Fig. 24.45 Pressure-volume loops in a patient with apical hypertrophic cardiomyopathy before *(diamonds)* and after *(circles)* surgical resection. Apical myectomy results in an increase in stroke volume and a larger left ventricular end-diastolic volume at lower end-diastolic pressure, suggesting improved left ventricular compliance after the procedure. *EDP,* End-diastolic pressure; *Preop,* preoperative; *Postop,* postoperative; *SV,* stroke volume. *(Reproduced with permission from Schaff HV, Brown ML, Dearani JA, et al. Apical myectomy: a new surgical technique for management of severely symptomatic patients with apical hypertrophic cardiomyopathy.* J Thorac Cardiovasc Surg. *2010;139:635.)*

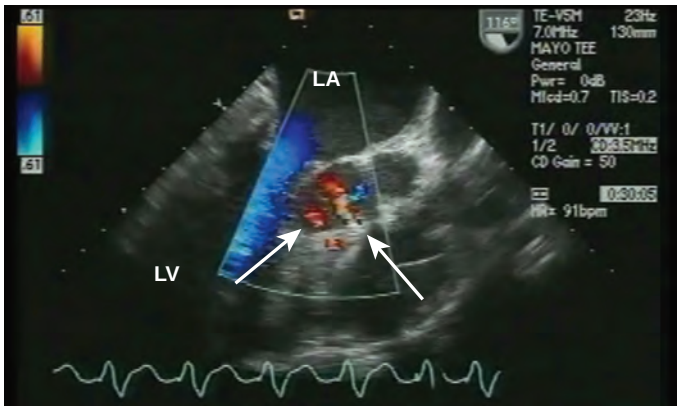


Fig. 24.46 Intraoperative transesophageal midesophageal long-axis view of a patient with basal septal hypertrophy after transaortic extended septal myectomy. Color-flow Doppler imaging reveals two jets of blood flow *(arrows)* into the left ventricular outflow tract from small coronary perforators that were transected during the myectomy. Distinguishing these jets from ventricular septal defects is important. *LA,* Left atrium; *LV,* left ventricle. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:288.)*

the ventricular septum, which assists the surgeon in planning the location and depth of the myectomy. The mitral valve should be closely evaluated for abnormalities that may contribute to mitral regurgitation, particularly if the regurgitant jet is directed centrally or anteriorly. After the myectomy, TEE is used to assess the degree of residual mitral regurgitation and evidence of continued SAM and LVOT obstruction. The ventricular septum must also be closely evaluated for evidence of shunting via an iatrogenic VSD. It is common to see small shunts into the area of the LVOT from transection of coronary vessels at the site of the myectomy (Fig. 24.46). It is important that these shunts are not confused with shunting from a VSD. When an iatrogenic VSD occurs, the expected shunt would be from the LV into the RV, as opposed to the flow observed into the LV from transection of septal coronary artery branches. In addition, shunting through a VSD would be expected to occur predominantly during systole, whereas flow into the LV from septal perforators is predominantly during diastole.

At the Mayo Clinic, surgeons record simultaneous pressure measurements across the level of obstruction both before and after surgical resection to reconfirm and document the degree of obstruction and to ensure the adequacy of the surgical result (Fig. 24.47).[170,184] For patients with asymmetric basal septal hypertrophy and dynamic LVOT obstruction, pressure measurements are made simultaneously in the LV, proximal to the obstruction, and in the ascending aorta, distal to the obstruction (Fig. 24.48). Typically, resting and provocative gradients are recorded. For the latter, the surgeons will tap the ventricle, producing a premature ventricular contraction (PVC) and a post-PVC exacerbation of the outflow tract obstruction and gradient (Brockenbrough-Braunwald-Morrow sign) (Fig. 24.49).[184,190] In cases of gradients that are difficult to elicit, the surgeons may ask the anesthesiologists to administer isoproterenol in increments of 4 µg to produce the hyperdynamic state known to exacerbate outflow tract obstruction. If the latter maneuver is performed, then the patient should be heparinized and cannulated and ready to be placed on bypass emergently in case of profound hemodynamic deterioration. Esmolol should be readily available.

For patients with severe symptoms, despite optimal medical management, and those who are poor surgical candidates or show a strong desire to avoid open-heart surgery, alcohol septal ablation is an alternative to septal myectomy.[106,152–153,185,191] Performed in the cardiac catheterization laboratory under fluoroscopic and echocardiographic guidance, the procedure's objective is to identify a prominent

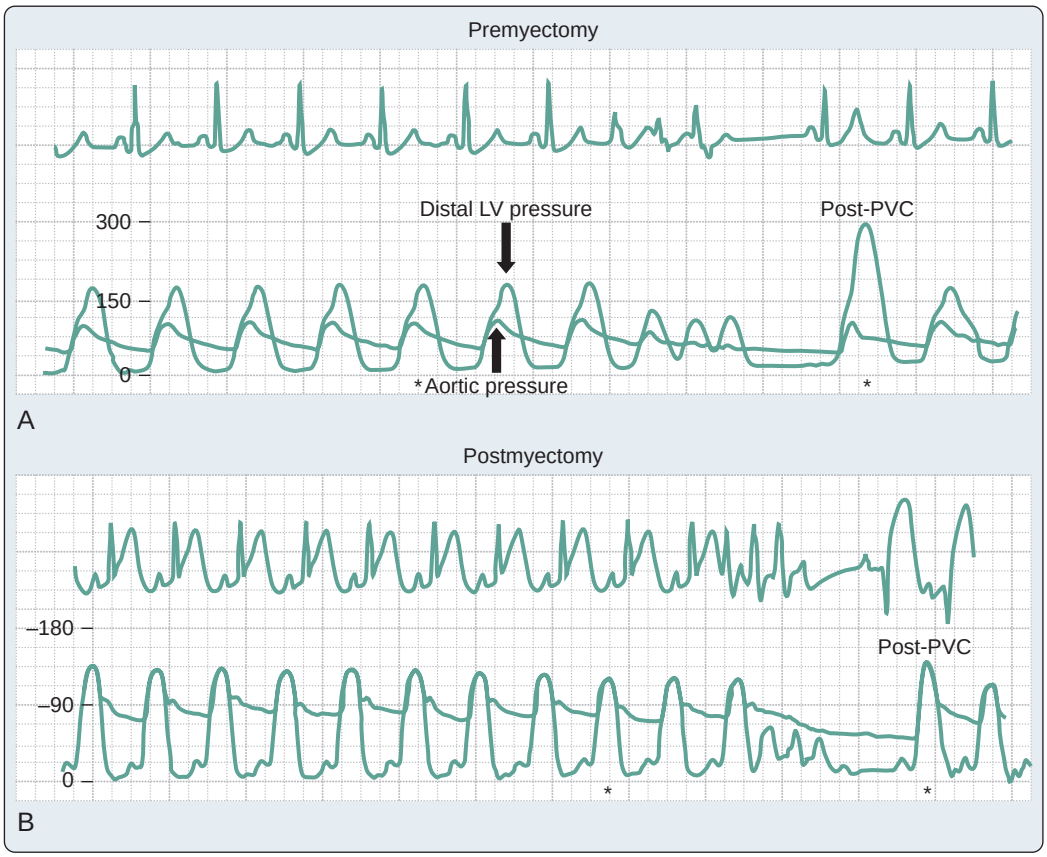


Fig. 24.47 Intraoperative pressure recordings of a patient with hypertrophic cardiomyopathy and midventricular obstruction undergoing transapical resection. (A) Preoperative pressure recording is made with simultaneous measurements in the distal left ventricular cavity and the aortic root. At rest, the left ventricular pressure was 173/8 mm Hg and the aortic pressure 98/38 mm Hg, indicating an obstructive gradient of 75 mm Hg. After a provocative premature ventricular contraction (PVC), the left ventricular pressure rose to 278/8 mm Hg, and the aortic pressure decreased to 90/38 mm Hg, producing an intraventricular gradient of 188 mm Hg. (B) Postoperative pressure recordings were made. At rest, the left ventricular pressure was 139/13 mm Hg and the aortic pressure 138/85 mm Hg, indicating trivial obstruction. After a PVC, the left ventricular pressure was 157/9 mm Hg and the aortic pressure 153/81 mm Hg, consistent with a gradient of only 4 mm Hg across the ventricular chamber. In panel B, typical electrocardiographic ST segment changes are demonstrated. A left bundle branch block pattern is common after resection along the interventricular septum. *LV*, left ventricular. *(Reproduced with permission from Kunkala MR, Schaff HV, Nishimura RA, et al. Transapical approach to myectomy for midventricular obstruction in hypertrophic cardiomyopathy.* Ann Thorac Surg. *2013;96:565.)*

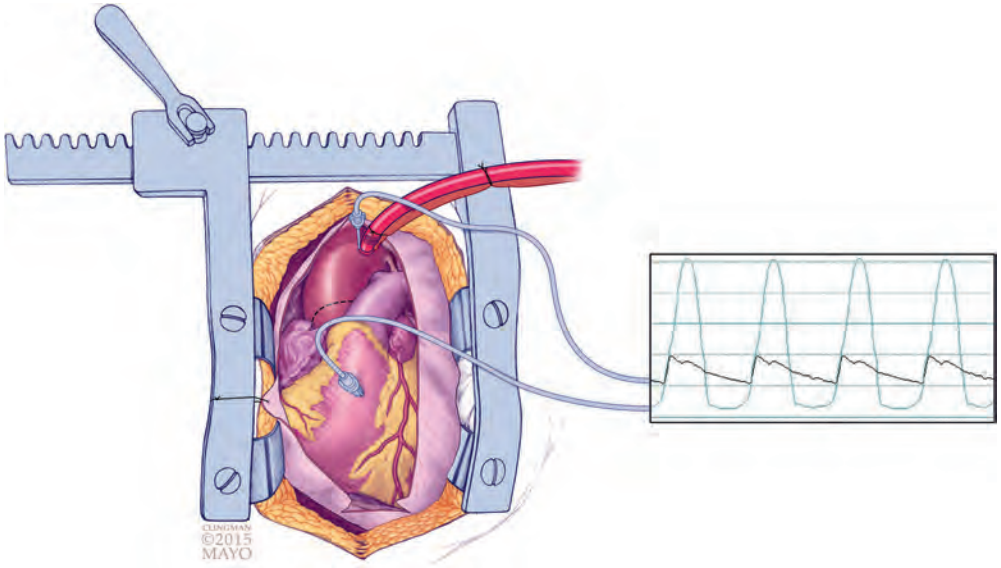


Fig. 24.48 Illustration depicts the needle placement for simultaneous pressure recordings from the left ventricle, proximal to the obstruction, and the ascending aorta, distal to the obstruction. Peak-to-peak gradients are determined by subtracting the peak aortic pressure in systole from the peak left ventricular chamber pressure in systole. *(Reproduced with permission from Mayo Foundation for Medical Education and Research. All rights reserved. Illustration No. 3397674-001.)*

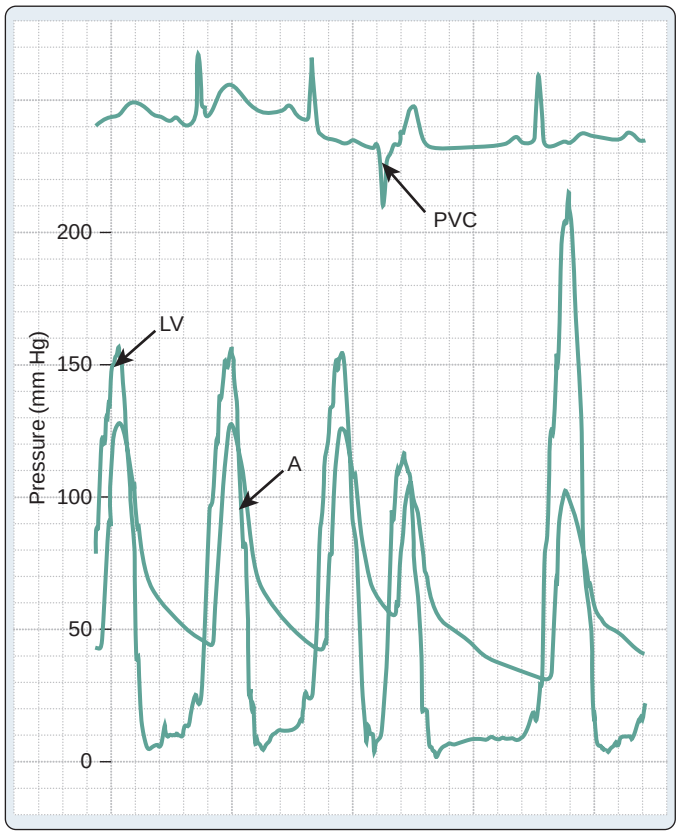


Fig. 24.49 The Brockenbrough-Braunwald-Morrow sign. After a premature ventricular contraction (PVC), the peak systolic pressure gradient increases while the systemic pulse pressure decreases, reflecting decreased stroke volume in the face of increased dynamic left ventricular outflow tract obstruction. The increased outflow tract obstruction, in turn, reflects postextrasystolic potentiation and increased contractility. In contrast, in patients with a fixed obstruction, such as aortic stenosis, the increased contractility with postextrasystolic potentiation after a PVC increases rather than decreases the systemic pulse pressure. *(Reproduced with permission from Pollock SG. Images in clinical medicine. Pressure tracings in obstructive cardiomyopathy.* N Engl J Med. *1994;331:238.)*

anteroseptal-perforating branch of the left anterior descending coronary artery that is supplying the hypertrophied, culprit portion of the basal septum. Once such a vessel is identified, 1 to 3 mL of ethanol alcohol is infused to create a localized infarction, leading to subsequent necrosis and regression of the area of the basal septum contributing to outflow tract obstruction. Although remodeling takes place over the succeeding months, the injection can affect an immediate decrease in gradient as a result of myocardial stunning.[106,152–155,185,191] The advantages of alcohol ablation are that it is minimally invasive, entails a short hospital stay, and may be more appropriate for older patients with more comorbidities. It is, however, associated with a higher risk of need for permanent pacemaker placement; a greater need for repeat procedures, secondary to recurrent or persistent obstruction; and the risk of malignant ventricular arrhythmias attributable to the transmural infarction that is produced. Furthermore, the procedure may offer little benefit to patients with the most severe symptoms and the thickest ventricles (≥30 mm), to patients whose obstruction is not due to a well-localized lesion, or to patients who need concomitant procedures, such as mitral valve intervention or coronary artery bypass grafting.[106,152–155,185,192]

The third and final pathway along which HCM may progress, again illustrated in Teare's cases, is that of atrial fibrillation, the most common arrhythmia in HCM.[106,147,152–155,193] Associated with advanced age and left atrial enlargement, atrial fibrillation occurs in as many as 25% of individuals with HCM, a rate four times greater than that for a similar general population.[106,152–155,193] Expectedly, patients with atrial fibrillation incur significant morbidity, but atrial fibrillation is not an independent risk factor for sudden cardiac death.[106,152–155,193] No strong data support rate versus rhythm control in patients with HCM. For rate control, ß-blockers and nondihydropyridine calcium channel blockers are recommended, whereas amiodarone and disopyramide are acceptable antiarrhythmic agents.[106,152–155] The annual rate of thromboembolic phenomenon has been estimated to be approximately 0.8%; therefore anticoagulation is indicated for those with chronic or paroxysmal, persistent atrial fibrillation. The CHADS (congestive heart failure, hypertension, age of 75 years, diabetes mellitus, stroke) score has not been validated in individuals with hypertrophic disease.[106,152–155]

Anesthetic Considerations

As has been stated, HCM has multiple morphologic variants, the most commonly encountered of which in the surgical unit are the basal septal variant, the midventricular variant, and the apical variant. The pathophysiologic nature and hemodynamics of the three are different. Although the strategies for anesthetic management may be similar, they are not identical.

In general, patients with basal and midventricular hypertrophy in the surgical unit have impaired diastolic and preserved systolic function. There are "burned-out" hypertrophs with severe systolic and diastolic heart failure who will require device implantation or transplantation, but they are rare and can be managed largely as any other patient with end-stage cardiac disease. Both basal and midventricular hypertrophs are physiologically obstructive, the former occurring across the LVOT and the latter occurring across the midventricular cavity, although patients with predominantly midcavitary obstruction may have outflow tract obstruction as well and vice versa. For the cardiac anesthesiologist, reviewing the preoperative ECGs is imperative to know at which level or levels, if at all, ventricular obstruction occurs and its severity.

The patients most challenging to manage hemodynamically are those with asymmetric hypertrophy of the basal septum and dynamic outflow tract obstruction. Frequently, the preoperative ECGs will document maximal instantaneous gradients across the LVOT of more than 50 mm Hg at rest and at times in excess of 100 mm Hg with provocative maneuvers. The conditions that favor obstruction, and thus hypotension, are the conditions to be avoided and treated quickly should they occur: tachycardia, increased contractility, decreased SVR, and hypovolemia.

Essentially, no evidence-based data are available to guide the choice of induction agents and maintenance medications. As mentioned previously, the choice of specific drugs or drug combinations is likely less important than how the drugs are used. Regardless of the drugs chosen, they should be used with the express goal of avoiding the conditions favoring hemodynamic decompensation. As in patients with severe aortic stenosis, hypotension may be poorly tolerated and should be treated quickly with the standard interventions.

Patients who have been followed at large referral centers should arrive to the surgical unit for a myectomy optimally medically managed. ß-Blockers or calcium channel blockers may have been uptitrated to the point of bradycardia, so that with hypotension, phenylephrine may not be the first choice of treatment. A judicious dose of ephedrine (5 mg) or a unit of vasopressin may be more effective and may not risk the loss of atrial kick that could occur as a consequence of aggressive phenylephrine administration. Although surgical myectomy is an elective procedure, for which patients should have been physiologically and pharmacologically prepared, patients with HCM may require emergent noncardiac surgery. Under conditions of pain, stress, and hypovolemia, as may occur with bowel obstruction requiring laparotomy, hemodynamic management during induction may be far more challenging. The management principles should be the same, however, although the choice of drugs and their dosing may be quite different.

Patients undergoing surgical myectomy will require an arterial line for continuous hemodynamic monitoring and will require central venous access for drug infusion and right-sided heart pressure monitoring. Although many would state unequivocally, as they would for patients with severe aortic stenosis, that arterial access needs to be obtained before induction, it does not. With vigilance, sound clinical judgment and an understanding of a given patient's physiologic condition under a given set of conditions, an arterial line may be placed safely before induction, during induction if resources are available to permit such, or after induction. Central venous access typically consists of an introducer and a PAC. The requirement for the latter is not based on evidence. In a young, otherwise healthy individual with preserved biventricular systolic and diastolic heart function undergoing basal resection with a skilled surgeon while being monitored with intraoperative TEE, a PAC may be unnecessary. Some practitioners, however, may feel uncomfortable managing a patient intraoperatively or postoperatively without its data. Intraoperative TEE, however, is essential. TEE should be used to reconfirm the location of hypertrophy and obstruction (if there is any), to characterize the mechanism of associated mitral regurgitation (if there is any), to assess the adequacy of the surgical intervention after bypass, and to look for inadvertent iatrogenic injury, such as a VSD or damage to the mitral or aortic valves.

As was mentioned previously, simultaneous pressure measurements across the level of obstruction both before and after surgical resection are recorded to reconfirm and document the degree of obstruction and to ensure the adequacy of the surgical result (see Figs. 24.47 and 24.48).[170,184] Typically, resting and provocative gradients are recorded (Figs. 24.50 and 24.51). For patients whose gradients are difficult to elicit, surgeons may ask for the administration of isoproterenol in increments of 4 μg to produce the hyperdynamic state known to exacerbate outflow tract obstruction. If the latter maneuver is performed, then the patient should be heparinized and cannulated and ready to be placed on bypass emergently in case of profound hemodynamic deterioration. Esmolol should be readily available.

With removal of the aortic cross-clamp, the myocardium may be quite irritable and the incidence of ventricular fibrillation high.[194] Amiodarone (300 mg) given before cross-clamp removal may decrease the number of defibrillations required to restore a regular, perfusing rhythm, although it does not decrease the incidence of ventricular fibrillation.[194] After myectomy, a left bundle branch block or a partial left bundle branch block is common. Preoperative right bundle branch block increases the risk of postoperative complete heart block.[166,168] Finally, with bypass separation, many patients are found clinically to have a low SVR and require repeated boluses of vasopressin and/or phenylephrine to achieve an acceptable mean arterial pressure. Such vasoplegia usually improves thereafter and typically resolves before the patient leaves the surgical unit.

Patients with apical variant HCM deserve separate mention.[165–167] In these patients, apical hypertrophy is not associated with obstruction or SAM but produces a small chamber size, which, in combination with a hypertrophied and stiff myocardium and abnormal diastolic relaxation, produces a significant impairment in diastolic filling and results in abnormally low stroke volumes. Although their calculated left ventricular ejection fraction may be normal or even supranormal, they have a depressed cardiac index in the context of their low stroke volume. Because outflow tract and even midcavitary obstruction are absent, these patients do not require the considerations of their counterparts with basal or midventricular hypertrophy. Similar to petite female octogenarians with severe aortic stenosis and long-standing hypertension, patients with apical hypertrophy may be very sensitive to

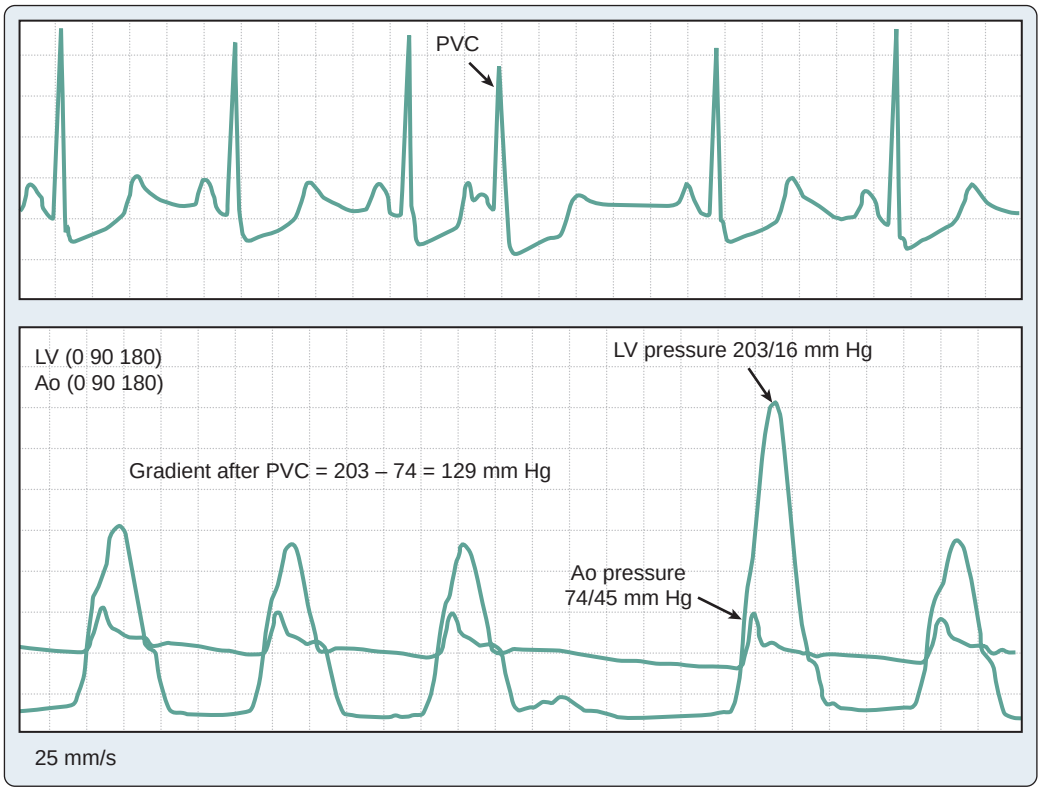


Fig. 24.50 Intraoperative pressure recordings for a patient with hypertrophic cardiomyopathy and dynamic left ventricular outflow tract obstruction. The increase in gradient after a premature ventricular contraction (a positive Brockenbrough-Braunwald-Morrow sign) is noted. *Ao,* Aorta; *LV,* left ventricle; *PVC,* premature ventricular contraction. *(Reproduced with permission from Ashikhmina EA, Schaff HV, Ommen SR, et al. Intraoperative direct measurement of left ventricular outflow tract gradients to guide surgical myectomy for hypertrophic cardiomyopathy.* J Thorac Cardiovasc Surg. *2011;142:55.)*

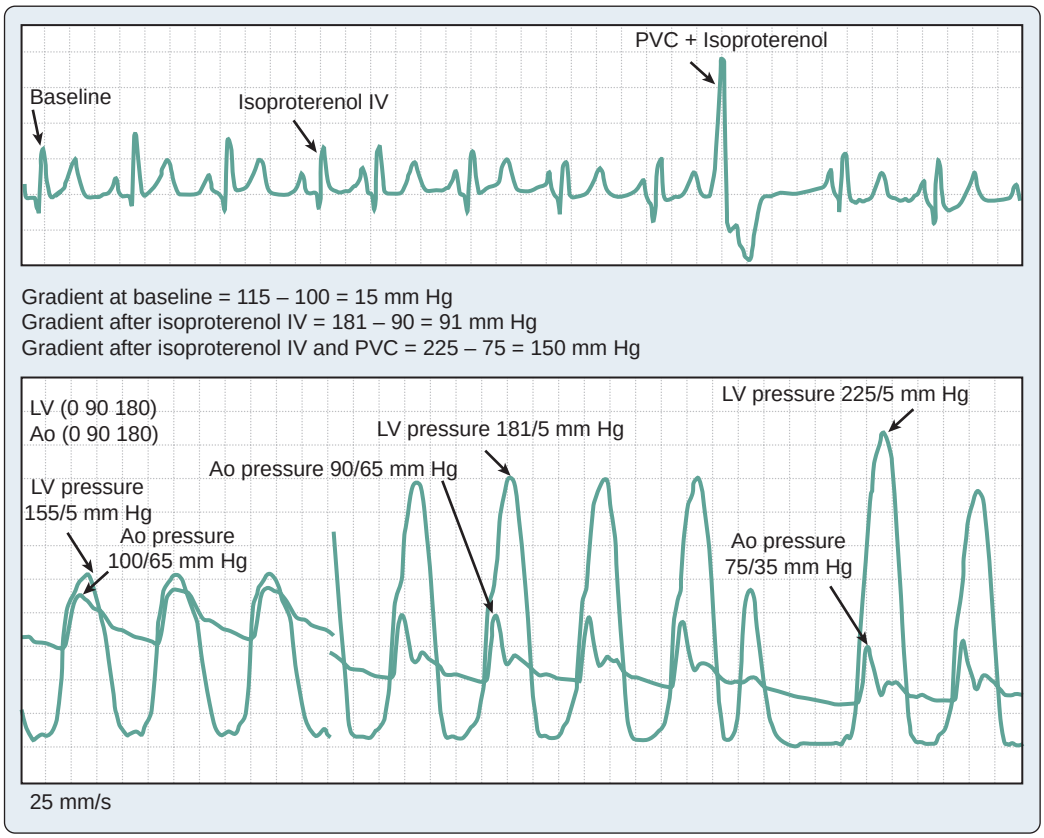


Fig. 24.51 Resting and provocative gradients in a patient with hypertrophic cardiomyopathy and dynamic left ventricular outflow tract obstruction. At baseline, the gradient between the left ventricle and aorta is 15 mm Hg. With isoproterenol infusion, the gradient increased to 91 mm Hg, whereas isoproterenol infusion and a subsequent premature ventricular contraction increased the gradient to 150 mm Hg. *AO,* Aorta; *IV,* intravenous; *LV,* left ventricle; *PVC,* premature ventricular contraction. *(Reproduced with permission from Ashikhmina EA, Schaff HV, Ommen SR, et al. Intraoperative direct measurement of left ventricular outflow tract gradients to guide surgical myectomy for hypertrophic cardiomyopathy.* J Thorac Cardiovasc Surg. *2011;142:56.)*

changes in preload and afterload. It frequently takes very little change in stroke volume to fall from normotensive to uncomfortably hypotensive or to push left-sided filling pressures to the point of pulmonary venous hypertension. As before, drug choice is likely less important than a thorough understanding of a given patient's pathophysiologic condition. Surgically, the resection for a transapical lesion is performed similar to that for midventricular variants through a transapical incision.[166,167,171,172] As is the case with a transaortic resection, transapical resection may be associated with repeated episodes of ventricular fibrillation after cross-clamp removal.

Finally, patients with midventricular obstruction may have components of basal and/or apical hypertrophy. Their intraoperative management will depend on the location of their lesion(s), which must be appreciated by a thorough review of their preoperative imaging studies. Surgical resection may require both transapical and transaortic exposure, thus prolonging modestly the aortic cross-clamp time and the duration of CPB.

Restrictive Cardiomyopathy

Primary RCM is a rare myocardial disease characterized, in the words of the AHA and in concordance with the European Society of Cardiology, "by normal or decreased volume of both ventricles associated with biatrial enlargement, normal LV wall thickness and AV valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function" (Fig. 24.52).[102,103] Whereas DCM is a morphologic definition, RCM is a pathophysiologic one, characterized by impaired myocardial relaxation and decreased ventricular compliance combining to produce elevated filling pressures.[103,108,195,196]

Given the breadth of RCM's definition and its heterogeneous causes, its prevalence is unknown, although it is likely less common than either DCM or HCM.[103,195] RCM may be familial, although not always with an autosomal dominant pattern of inheritance; acquired in the course of a variety of systemic disorders (eg, amyloidosis, hemochromatosis, Fabry disease); or idiopathic.[103,108,195,196] Although its causes are varied, they may be classified as primarily myocardial or endomyocardial. Myocardial disorders are subclassified as noninfiltrative (familial, scleroderma, idiopathic), infiltrative (amyloidosis, sarcoidosis, Gaucher disease), or storage (hemochromatosis, Fabry disease). Endomyocardial disorders may be distinguished by the presence or absence of eosinophilia and include hypereosinophilic syndrome (Löffler endocarditis), endomyocardial fibrosis, and radiation-induced disorders (Box 24.4).[103,108,195,196]

Classically, systolic function is considered normal in RCM, at least by gross indices such as ejection fraction, although some have questioned whether contractile function is completely normal.[103] It may be the case that when myocardial function is interrogated more closely, as it needs to be in patients with the so-called *paradoxic* low-flow, low-gradient severe aortic stenosis, despite preserved ejection fraction, then contractile function in restrictive disease will also be found abnormal.[197,198] Diastolic dysfunction is the hallmark of RCM and is associated with impaired relaxation and compliance. Echocardiographically, RCM is characterized by biatrial enlargement, the absence of ventricular dilatation, and normal ventricular wall thickness, with grossly preserved

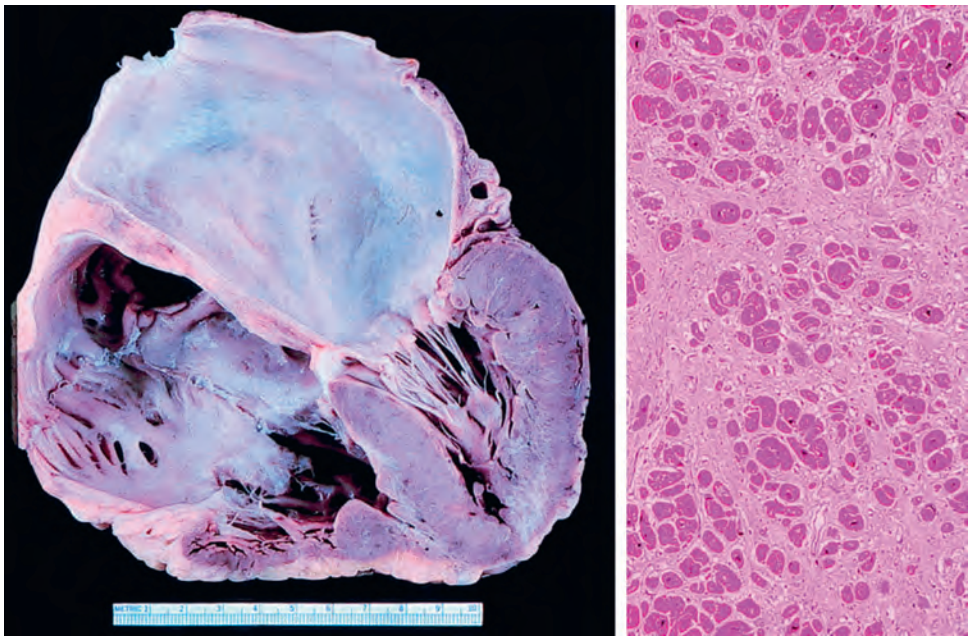
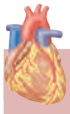


Fig. 24.52 Postmortem specimen of a patient with idiopathic restrictive cardiomyopathy. *(Left)* Gross specimen shows massive biatrial enlargement with normal ventricular size. *(Right)* Histologic section demonstrates significant interstitial fibrosis. *(Reproduced with permission from Ammash NM, Seward JB, Bailey KR, et al. Clinical profile and outcome of idiopathic restrictive cardiomyopathy.* Circulation. *2000;101:2493.)*



BOX 24.4 CLASSIFICATION OF TYPES OF RESTRICTIVE CARDIOMYOPATHY ACCORDING TO CAUSE

Myocardial Causes
Noninfiltrative
- Idiopathic cardiomyopathy[a]
- Familial cardiomyopathy
- Hypertrophic cardiomyopathy
- Scleroderma
- Pseudoxanthoma elasticum
- Diabetic cardiomyopathy

Infiltrative
- Amyloidosis[a]
- Sarcoidosis[a]
- Gaucher disease
- Hurler disease
- Fatty infiltration

Storage diseases
- Hemochromatosis
- Fabry disease
- Glycogen storage disease

Endomyocardial Causes
Endomyocardial fibrosis[a]
Hypereosinophilic syndrome
Carcinoid heart disease
Metastatic cancers
Radiation[a]
Toxic effects of anthracycline[a]
Drugs causing fibrous endocarditis (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

[a]Conditions more likely to be encountered in clinical practice.
Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era*, 6th ed. Philadelphia: Saunders; 2011:693.

systolic function. Diastology is notable for a high E wave, driven by progressively higher left atrial pressures; a shortened deceleration time (less than 160 milliseconds), reflecting a poorly compliant LV and the rapid equalization of left atrial and ventricular pressures; a small A wave of short duration because of the rapid rise in ventricular pressure with filling during atrial kick; and an E/A ratio that frequently exceeds 2.[114,199] In addition to two-dimensional echocardiography and mitral inflow pulsed-wave Doppler, pulmonary vein pulsed-wave Doppler, tissue-Doppler imaging of the mitral annulus, M-mode imaging, and speckle tracking can all be used to establish the diagnosis of RCM and to attempt to determine its cause in a given patient (Fig. 24.53).[199]

With cardiac catheterization, right and left atrial pressures are elevated, and left-sided filling pressures frequently exceed right ventricular diastolic pressures by at least 5 mm Hg.[196] A rapid dip and subsequent early plateau in diastolic ventricular pressure, reflecting filling of a poorly compliant ventricle and rapid equalization of left atrial and ventricular pressures, may produce a characteristic ventricular diastolic waveform, the so-called "square root sign," although it may be absent in up to 50% of affected individuals, because it depends on both the degree of impaired ventricular relaxation and the atrial driving pressure (Fig. 24.54).[200] The atrial pressure waveform may take the appearance of an M or a W, reflecting prominent *a* and *v* waves and rapid *x* and *y* descents, the latter driven by increasingly elevated left atrial pressures. Furthermore, elevation in left-sided filling pressures produce pulmonary venous hypertension and pulmonary artery systolic pressures that may exceed 50 mm Hg.[196]

Diagnostically, distinguishing RCM from constrictive pericarditis (CP) is important, considering that their treatments are quite different (Table 24.5). In both disorders, filling pressures are elevated; although in restrictive disease, elevated pressures reflect a stiffened myocardium, whereas in constrictive disease, they reflect the constraint of a stiff pericardium.[199] With cardiac catheterization, as has been mentioned, left ventricular end-diastolic pressure typically exceeds its right ventricular counterpart by 5 mm Hg or more in RCM, attributable to differences in respective ventricular compliance. In CP, however, ventricular end-diastolic pressures are elevated and equal.[201,202] Additionally, because a

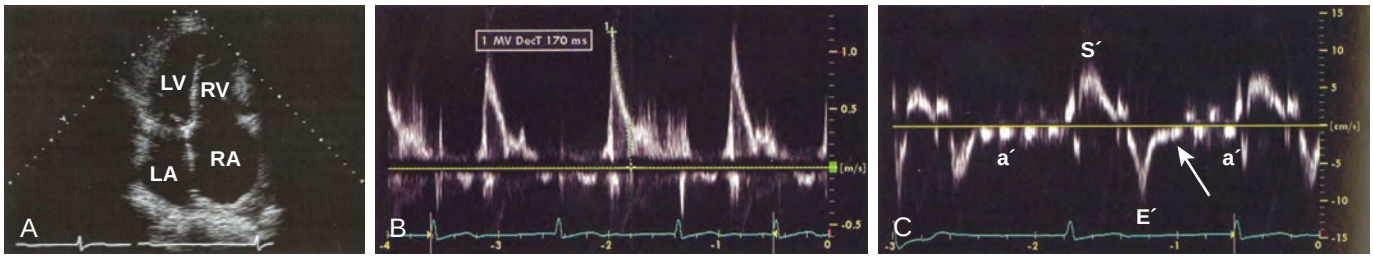


Fig. 24.53 Characteristic echocardiographic findings in a patient with restrictive cardiomyopathy. (A) Transthoracic apical four-chamber view shows significant biatrial enlargement, normal biventricular size, and grossly preserved systolic function *(not shown)*. (B) Mitral inflow pulsed-wave Doppler recording shows a deceleration time of 170 milliseconds and mild variation in E velocities. (C) Mitral annulus tissue velocity recording demonstrates E′ of 8 cm/sec and delayed relaxation *(arrow)*. An a′ reflects atrial fluttering or fibrillating motion. An E/E′ ratio of 100/8 = 13 is consistent with a mild increase in filling pressures. *a′,* Mitral annulus late diastolic velocity (atrial contraction); *DecT,* deceleration time; *E′,* mitral annulus early diastolic velocity; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle; *S′,* systolic velocity of the mitral annulus. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:694.)*

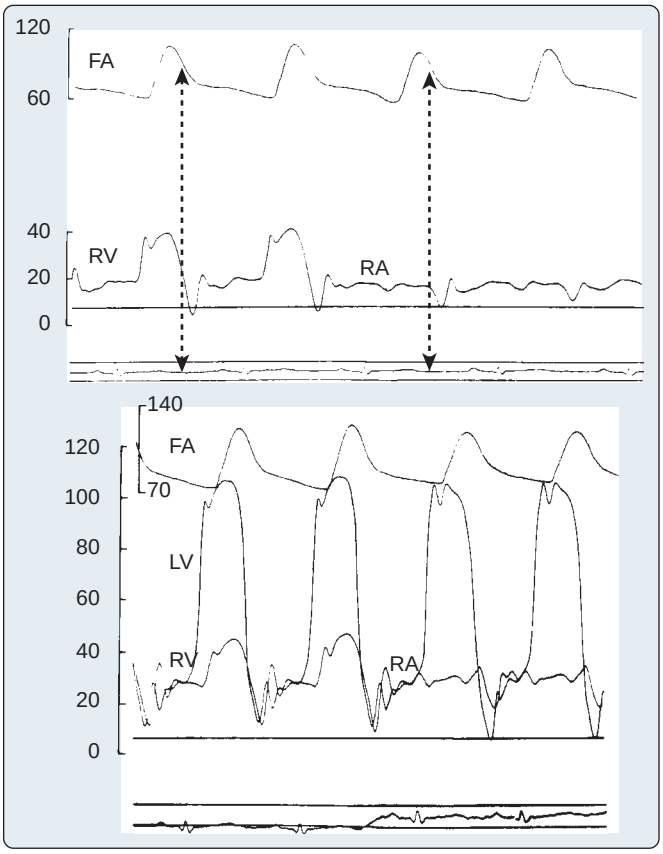


Fig. 24.54 Intracardiac pressure tracings from a patient with idiopathic primary restrictive cardiomyopathy. *(Top)* Right ventricular and right atrial tracings are demonstrated with a typical diastolic square-root configuration in the right ventricular tracing and a prominent y descent in the early diastolic period of the right atrial tracing. *(Bottom)* Simultaneous left ventricular–right ventricular pressures and left ventricular–right atrial pressures show a square-root configuration in the left ventricular tracing and equalization of pressures during diastole in the three chambers. *FA,* Femoral artery; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. *(Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds.* Kaplan's Cardiac Anesthesia: The Echo Era. *6th ed. Philadelphia: Saunders; 2011:693.*

stiff, often thickened pericardium constrains the total cardiac volume in CP, ventricular interdependence is exaggerated. Since a pericardial *shell* affects a dissociation between intrathoracic and intracardiac pressures, decreased filling of the LV during inspiration is matched by enhanced right-sided filling. These respiratory variations, exaggerated in pericardial constriction and indicative of ventricular discordance, are not found in RCM, in which inspiration is met with concordant drops in both right and left ventricular pressures reflective of decreased intrathoracic pressure (Fig. 24.55).[203–205] Echocardiography may also be used to attempt to distinguish between RCM and pericardial constriction. In CP, two-dimensional echocardiography may show a thickened pericardium and may demonstrate a septal bounce consistent with ventricular interdependence and the dissociation of intracardiac and intrathoracic pressures.[199] Mitral inflow pulsed-wave Doppler will show increased E/A ratios in both RCM and CP; however, in the latter case, there should be significant respiratory variation in the E velocity, with at least a 25% increase during expiration (Table 24.6).[199] Radiographically, both CT and cardiac MRI may also be used to distinguish RCM and pericardial constriction. Once a tentative diagnosis of restriction is made, some attempt must be made to determine its cause. Although both CT and cardiac MRI may be useful, definitive diagnosis frequently requires an endomyocardial biopsy.[108,195,196]

Clinically, because either or both ventricles may be involved in RCM, patients may exhibit signs and symptoms of right-sided heart failure (elevated jugular venous pressure, peripheral edema, ascites, cirrhosis, renal failure), left-sided heart failure (dyspnea, orthopnea, exertional chest pain), or both.[108,196] With impaired right ventricular filling, jugular venous pressure is expected to fall during inspiration with decreased intrathoracic pressures, and enhanced right-sided filling may not occur and may, in fact, increase, giving rise to Kussmaul sign.[196,206,207]

Treatment for RCM should be based on the underlying disease process, if it is known (eg, enzyme-replacement therapy for Gaucher and Fabry diseases, steroids for sarcoidosis); otherwise, pharmacotherapy is tailored toward heart failure symptom relief (Table 24.7).[195] With biatrial enlargement, patients with RCM are prone to atrial fibrillation, for which rate therapy and anticoagulation should be used if persistent.[108,195,196]

Prognosis, similar to treatment, depends largely on the cause. For patients with idiopathic disease, 5- and 10-year survival rates of 64% and 37%, respectively, have been observed, which are less than would be expected for age- and sex-matched control subjects.[108,201] Age greater than 70 years, male gender, increasing NYHA functional class, and left atrial diameter greater than 60 mm were independent risk factors for a worse survival.[201]

TABLE 24.5 Differentiation of Pericardial Constriction and Myocardial Restriction

Characteristic	*Constrictive Pericarditis*	*Restrictive Cardiomyopathy*
Jugular venous waveform	Elevated with less rapid *y* descent	Elevated with, more rapid *y* descent Large A waves
LAP > RAP	Absent	Almost always
Auscultation	Early S_3 high pitched; no S_4	Late S_3 low pitched; S_4 in some cases
Mitral or tricuspid regurgitation	Frequently absent	Frequently present
Chest roentgenogram	Calcification of pericardium (20–30%)	Pericardial calcification rare
Heart size	Normal to increased	Normal to increased
Electrocardiogram	Conduction abnormalities rare	Conduction abnormalities common
Echocardiogram	Slight enlargement of atria	Major enlargement of atria
Right ventricular pressure waveform	Square-root pattern	Square-root pattern; dip and plateau often less prominent
Right- and left-sided heart diastolic pressures	Within 5 mm Hg of each other in almost all cases	Seldom within 5 mm Hg of each other
Peak right ventricular systolic pressure	Almost always <60 mm Hg, sometimes <40 mm Hg	Usually >40 mm Hg, sometimes >60 mm Hg
Discordant respiratory variation of peak ventricular systolic pressures	Right and left ventricular systolic pressures are out of phase with respiration	In phase with respiration
Paradoxic pulse	Often present	Rare
CT and MRI imaging	Thickened pericardium	Rarely thickened pericardium
Endomyocardial biopsy	Normal or nonspecific changes	Nonspecific abnormalities

CT, Computed tomography; *LAP,* left atrial pressure; *MRI,* magnetic resonance imaging; *RAP,* right atrial pressure.

Reproduced with permission from Hancock EW: Cardiomyopathy: Differential diagnosis of restrictive cardiomyopathy and constrictive pericarditis. *Heart.* 2001;86:343–349; and Chatterjee K, Alpert J. Constrictive pericarditis and restrictive cardiomyopathy: similarities and differences. *Heart Fail Monit.* 2003;3:118–126.

Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era.* 6th ed. Philadelphia: Saunders; 2011:694.

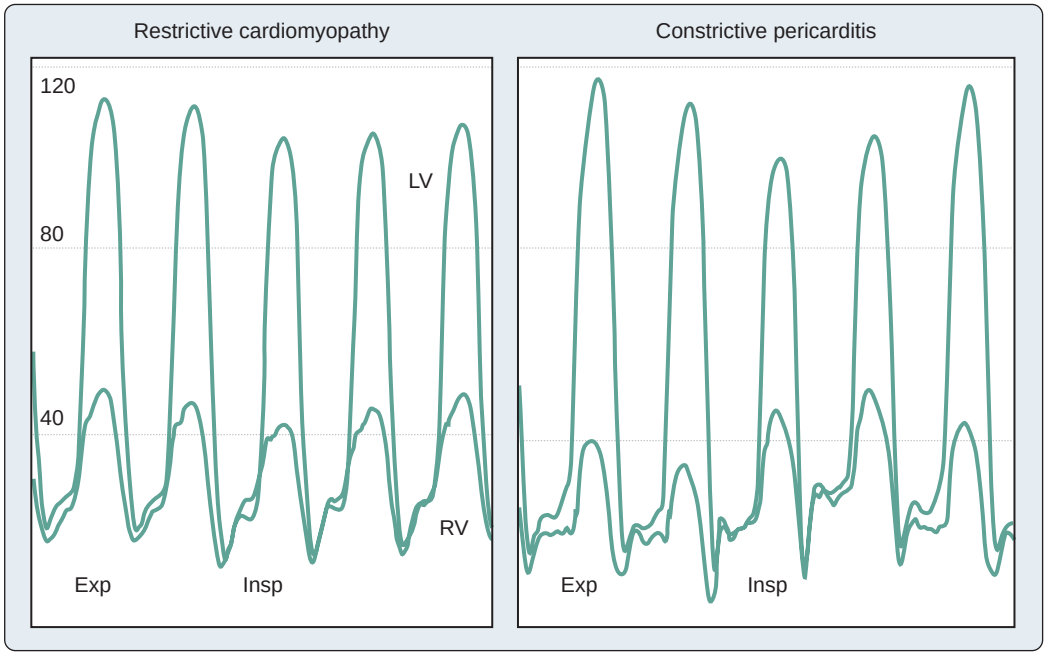


Fig. 24.55 Invasive hemodynamic discrimination of restrictive cardiomyopathy and constrictive pericarditis. In the cardiac catheterization laboratory, high-fidelity manometer-tipped catheters are placed in the left and right ventricles, and recordings are made throughout the respiratory cycle. *(Left)* In a patient with restrictive cardiomyopathy, a drop in left and right ventricular pressures occurs during inspiration, indicating that the elevation of ventricular filling pressures is due to a myocardial restrictive disease. *(Right)* In a patient with constrictive pericarditis, ventricular discordance is noted, with an increase in right ventricular pressure and a decrease in left ventricular pressure during inspiration that is due to the enhancement of ventricular interaction and dissociation of intrathoracic and intracardiac pressures. *Exp,* Expiration; *Insp,* inspiration; *LV,* left ventricle; *RV,* right ventricle. *(Reproduced with permission from Nishimura RA, Carabello BA. Hemodynamics in the cardiac catheterization laboratory of the 21st century.* Circulation. *2012;125:2149.)*

TABLE 24.6 Echocardiographic Features of Restrictive Cardiomyopathy and Constrictive Pericarditis

	Restrictive Cardiomyopathy	*Constrictive Pericarditis*
Pericardium	Normal	Thickened
Left ventricle	Small May show systolic dysfunction No septal bounce	Small Usually intact, may be abnormal, particularly after CABG or radiation Septal bounce
Atria	Usually dilated	Usually nondilated
Mitral inflow	Increase E/A ratio, short DT No significant respiratory variation of E velocity Diastolic MR	Increase E/A ratio, short DT Expiratory increase of >25% in E velocity Diastolic MR
Tissue Doppler long velocities	Significantly reduced	Normal
Circumferential strain	Normal	Reduced
Peak radial strain class IV base	Normal	Reduced
Net twist	Normal	Reduced
Basal longitudinal strain	Reduced	Normal
Apical untwisting velocities	Normal	Reduced
Pulmonary vein inflow	Decreased (0.5) S/D ratio Prominent atrial reversal No significant respiratory change	S/D ratio = 1 Decrease in S and D[a] wave and TR velocity
Tricuspid inflow	Mild respiratory variation	Inspiratory increase of >25% in E wave and TR velocity
Inferior vena cava	Dilated	Dilated
Hepatic veins	Blunted S/D ratio	Inspiration: minimal increase in S and D velocities Expiration: decreased diastolic flow and increase in reversals Increase in atrial reversal of >25% in expiration, compared with inspiration
Peak PA pressure	>40 mm Hg	<40 mm Hg
Color M-mode	Decreased Vp <45 cm/sec	Normal or increase >100 cm/sec
Mitral annular Doppler	Low velocity <8 cm/sec	High velocity >8 cm/sec

[a]One study found significantly greater decrease of D wave only with respiration in constriction.

A, Atrial transmitral filling velocity; *CABG,* coronary artery bypass graft; *D,* diastolic flow; *DT,* deceleration time; *E,* early transmitral filling velocity; *LV,* left ventricle; *MR,* mitral regurgitation. *PA,* pulmonary artery; *S,* systolic flow; *TR,* tricuspid regurgitation; *Vp,* propagation velocity.

Reproduced with permission from Naqvi TZ. Restrictive cardiomyopathy: diagnosis and prognostic implications. Otto CM, ed. *Practice of Clinical Echocardiography*, 4th ed. Philadelphia: Saunders; 2012:557.

TABLE 24.7 Treatment Strategies in Restrictive Cardiomyopathy

Cause	*Specific Symptom*	*Treatment*
Idiopathic	To relieve congestion	Diuretics
	Control of heart rate	ß-Blockers, amiodarone, heart rate–regulating CCBs
	Atrial fibrillation: to maintain sinus rhythm paroxysmal or persistent	Amiodarone, dofetilide Long-term anticoagulation
	To control ventricular rate	ß-Blockers, heart rate–regulating calcium channel blockers, amiodarone, digoxin, atrioventricular node ablation, and pacemaker
	Atrioventricular block	Dual-chamber pacing
	To enhance myocardial relaxation	Calcium channel blockers (unproven), angiotensin inhibition (unproven)
	Refractory heart failure	Cardiac transplantation
Amyloidosis		Melphalan, prednisone, and colchicine; stem cell implant (under investigation); heart and liver transplant (in rare instances)
Hemochromatosis		Phlebotomy, desferrioxamine
Carcinoid heart disease		Somatostatin analogs; serotonin antagonists; valvuloplasty for severe tricuspid and pulmonary stenosis; valve replacement for severe tricuspid and pulmonary regurgitation
Sarcoidosis		Corticosteroids; pacemaker for heart block; implantable cardioverter-defibrillator for ventricular arrhythmias; cardiac transplantation for refractory heart failure
Eosinophilic endocarditis		Initial stage: corticosteroids, hydroxyurea, vincristine
Endomyocardial fibrosis		Endocardectomy with repair or replacement of tricuspid and mitral valves

CCBs, Calcium channel blockers.

Reproduced with permission from Oliver WC, Mauermann WJ, Nuttall GA. Uncommon cardiac diseases. In: Kaplan JA, Reich DL, Savino JS, eds. *Kaplan's Cardiac Anesthesia: The Echo Era*. 6th ed. Philadelphia: Saunders; 2011:695

Anesthetic Considerations

Individuals with RCM only infrequently undergo cardiac surgery. One exception, however, are patients with amyloidosis, who may undergo circulatory-assist device placement, orthotopic heart transplantation, or combined heart and liver transplantation.

The amyloidoses are a family of diseases in which insoluble proteinaceous material is deposited in the extracellular tissues. Amyloid deposition may occur systemically or locally, and cardiac involvement may occur with either phenomenon.[108,196,208–211] Although amyloidosis may be reactive, with increased production and deposition of serum amyloid A (SAA) protein in the context of chronic inflammatory conditions, cardiac involvement in such cases is rare. More commonly encountered variants with cardiac involvement include primary, or systemic (coded as AL), wherein AL fibrils from monoclonal immunoglobulin light chains are overproduced and deposited in the setting of B-cell dyscrasias; hereditary systemic amyloidosis, wherein variants of transthyretin (TTR), amyloid apolipoprotein A1 (AApoA1), and others are produced and deposited systemically; and senile systemic amyloidosis (SSA), in which wild-type rather than mutant TRR is deposited. In addition to these systemic amyloidoses with cardiac involvement, there is also a localized variant, isolated atrial amyloid (IAA) (Table 24.8).[108,196,208–211] AL amyloidosis is the most common

TABLE 24.8 Common Cardiac Amyloidosis[a]

Nomenclature	*Precursor of Amyloid Fiber*	*Type*	*Prevalence*	*Prognosis*
AL (26)	Immunoglobulin light chain	Primary amyloid cardiomyopathy	50% in patients with AL amyloidosis	Median survival –11 mo
ATTR (28, 46, 79, 101)	Mutant transthyretin Wild-type transthyretin	Familial amyloid cardiomyopathy Senile systemic amyloid (SSA) cardiomyopathy	30% in patients with familial amyloidosis In most patients with senile amyloidosis	Median survival 9–13 yr Median survival –75 mo
AA (28)	Serum amyloid A	Secondary amyloid cardiomyopathy	Rare, only 2% in patients with AA amyloidosis	Good
AANF (48, 49)	Atrial natriuretic factor	Isolated atrial amyloidosis	Very common More than 40% in people older than 50	Good

[a]Other cardiac amyloidosis include: AH (24), AApoAI (40, 41, 1, 69), AApoAIV (7, 8), AFib (99), and AGel (12, 60). However, these are rarely occurring with limited literature.
Reproduced with permission from Guan J, Mishra S, Falk RH, Liao R. Current perspectives on cardiac amyloidosis. *Am J Physiol Heart Circ Physiol*. 2012;302:H546.

of the systemic amyloidoses and entails cardiac involvement in 50% of the cases. Median survival is poor at 11 months. ATTR is the next most common form of the disease and involves the heart in approximately 30% of cases. Median survival exceeds 10 years. The clinical manifestation of cardiac amyloidosis is that of restrictive heart disease with signs and symptoms of left-sided heart failure, right-sided heart failure, or biventricular heart failure. With time, diastolic heart failure progresses to systolic heart failure. With infiltration of the conduction system, a variety of arrhythmias and forms of heart block may arise. With compromise of left ventricular filling and CO and with infiltration of the autonomic nervous system, orthostatic hypotension occurs in at least 10% of those with cardiac disease.[196,208] Treatment of cardiac amyloid depends on the variant. Whereas IAA does not affect survival and does not require intervention, secondary amyloidosis relies on treatment of the underlying inflammatory condition. Although treatment of SSA attributable to the deposition of wild-type TTR is confined primarily to investigational drugs, patients with systemic AL amyloidosis and familial amyloidosis with mutant TTR may be candidates for orthotopic heart transplantation or for combined heart and liver transplantation in the case of the latter disease.[196,208–211]

Clearly, patients scheduled for heart transplantation or combined heart and liver transplantation will require full, invasive hemodynamic monitoring, with one if not two arterial lines (one monitoring peripheral pressures and one monitoring central pressures), one if not two introducers (especially in the case of a combined procedure or a *redo* procedure, when large volume blood loss and significant coagulopathy can be expected), perhaps a high-flow peripheral venous cannula, a PAC, and intraoperative TEE. The choice of induction and maintenance drugs may certainly be based on theoretical concerns related to patient physiologic considerations, but no evidenced-based data exist to support a given pharmacologic regimen clinically. The vigilance of the anesthesiologist, his or her understanding of a given patient's physiologic nature under a specific set of clinical conditions, and sound clinical judgment are important. That being said, patients with cardiac amyloid scheduled for transplantation may prove to have particularly labile if not frankly unstable hemodynamics at the time of induction. The combination of severely compromised diastolic function and impaired ventricular filling, likely systolic heart failure, and autonomic instability with amyloid infiltration of the nervous system, can conspire to make the effects of even the most judicious doses of drugs unpredictable.

Arrhythmogenic Right Ventricular Cardiomyopathy

Formerly called *arrhythmogenic right ventricular dysplasia*, arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined by the 1995 WHO as "progressive fibrofatty replacement of RV myocardium, initially with typical regional and later global RV and some LV involvement, with relative sparing of the septum."[101] Evidence of a more progressive involvement of not only the RV but also the LV with long-term follow-up convinced the WHO to classify ARVC as a "disease of the myocardium" that incorporates the many different clinical presentations and aspects of this condition.

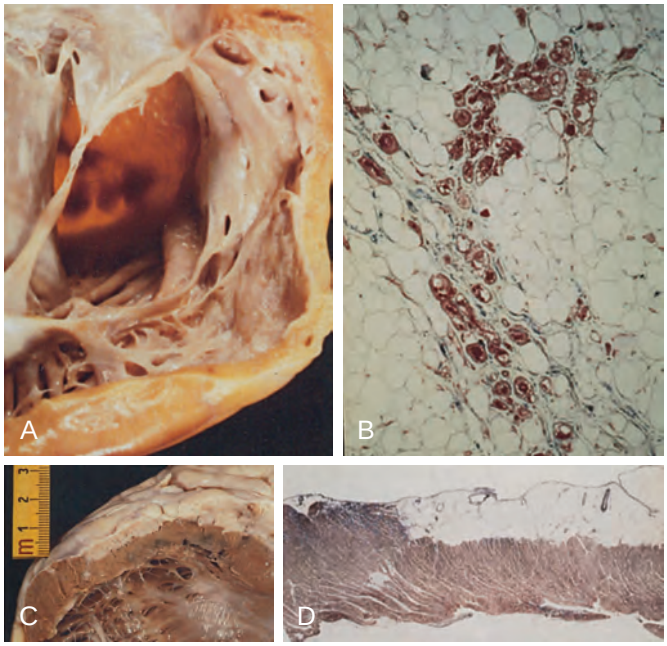


Fig. 24.56 (A) Histologic view at high magnification shows surviving degenerated right ventricular myocytes in the setting of extensive fatty replacement and tiny interstitial fibrosis. (B) Gross (A and C) and histologic (B and D) sections of the anterior left ventricular wall shows striking subepicardial fatty infiltration and fibrosis. *(Reproduced with permission from Corrado D, Basso C, Thiene G, et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study.* J Am Coll Cardiol. *1997;30;1517.)*

ARVC is familial in 30% to 50% of persons with primarily autosomal dominant inheritance, variable expressivity, and reduced penetrance.[212] The prevalence of ARVC has been estimated between 1:2000 and 1:5000 with men affected at a ratio of 3:1.[213] The initial presentation is often during adolescence, although it may occur in younger individuals. Its presentation most commonly begins with the onset of arrhythmias ranging from premature ventricular contractions to ventricular fibrillation originating from the RV. The disease is now known to proceed through three phases: (1) concealed phase without symptoms but some electrophysiologic changes that place one at risk for sudden death; (2) overt dysrhythmias; (3) advanced stage with myocardial loss, biventricular involvement, and CHF.[214] Diagnosis is rare in the early stages[215] but not at autopsy.[216] Standard diagnostic criteria have continued to be revised.[217] Postmortem examination reveals diffuse or segmental loss of the myocardium, primarily in the RV, replaced with fat and fibrous tissue; right ventricular dilation; and thinning of the right ventricular free wall (Fig. 24.56). Right ventricular involvement commonly occurs near the right ventricular outflow tract, infundibulum, and/or the right ventricular apex with reported progression to right ventricular aneurysms in this region,

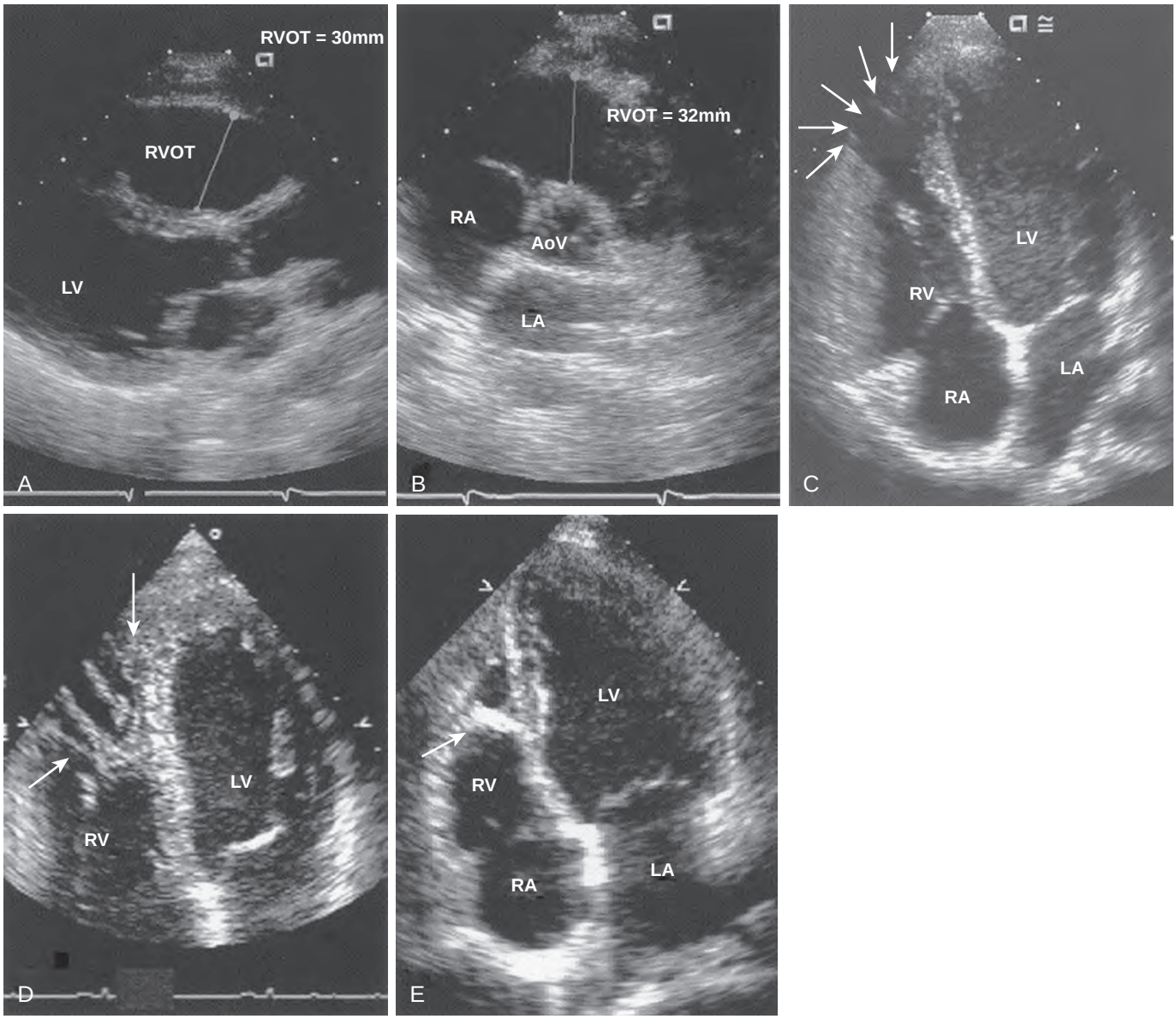


Fig. 24.57 Echocardiographic views from probands meeting Task Force Criteria for arrhythmogenic right ventricular dysplasia. (A) Enlargement from the parasternal long-axis view depicts the right ventricular outflow tract *(RVOT).* (B) RVOT enlargement from the parasternal short-axis view is demonstrated. (C) Apical four-chamber view shows a focal right ventricular apical aneurysm *(arrows).* (D) Apical four-chamber view shows excessive trabeculations *(arrows).* (E) Apical four-chamber view shows a hyperreflective moderator band *(arrow). AoV,* Aortic valve; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. *(Reproduced with permission from Yoerger DM, Marcus F, Sherrill D, et al. Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia.* J Am Coll Cardiol. *2005;45.)*

which are considered pathognomonic.[218] The diagnosis also includes the functional changes associated with the RV beyond the structural alterations. These changes are believed to occur by three possible mechanisms: myoblasts differentiating to (1) adipoblasts, (2) apoptosis, or (3) inflammation.[215] An inflammatory process is evident within the myocardial tissue. The replacement of myocardium with fat and fibrous tissue creates an excellent environment for a fatal arrhythmia, possibly the first sign of ARVC.[214] Although considered a disease of the RV, left ventricular involvement can also occur and even precede right ventricular presentation.[219] Sudden death occurs in up to 75% of patients, although accurately stating the percentage is difficult in view of the number of patients who go undiagnosed. Sudden death occurs most often during sports-related exercise, primarily from ventricular tachycardia and fibrillation.[220] Although a rare disease, ARVC accounts for 20% of sudden death in the young.[221]

The electrical instability, characteristic of ARVC, is not solely responsible for the natural history of the disease. Its clinical presentation may range from asymptomatic myopathic involvement to overt clinical disease with diffuse biventricular involvement.[214,220] Progressive right and left ventricular dysfunction can be appreciated with serial echocardiographic examinations. Echocardiographic findings from 29 patients with ARVC have been described (Fig. 24.57).[222] The systolic and diastolic right ventricular outflow tract dimensions are increased on a two-dimensional ECG. Regional wall motion abnormalities of the

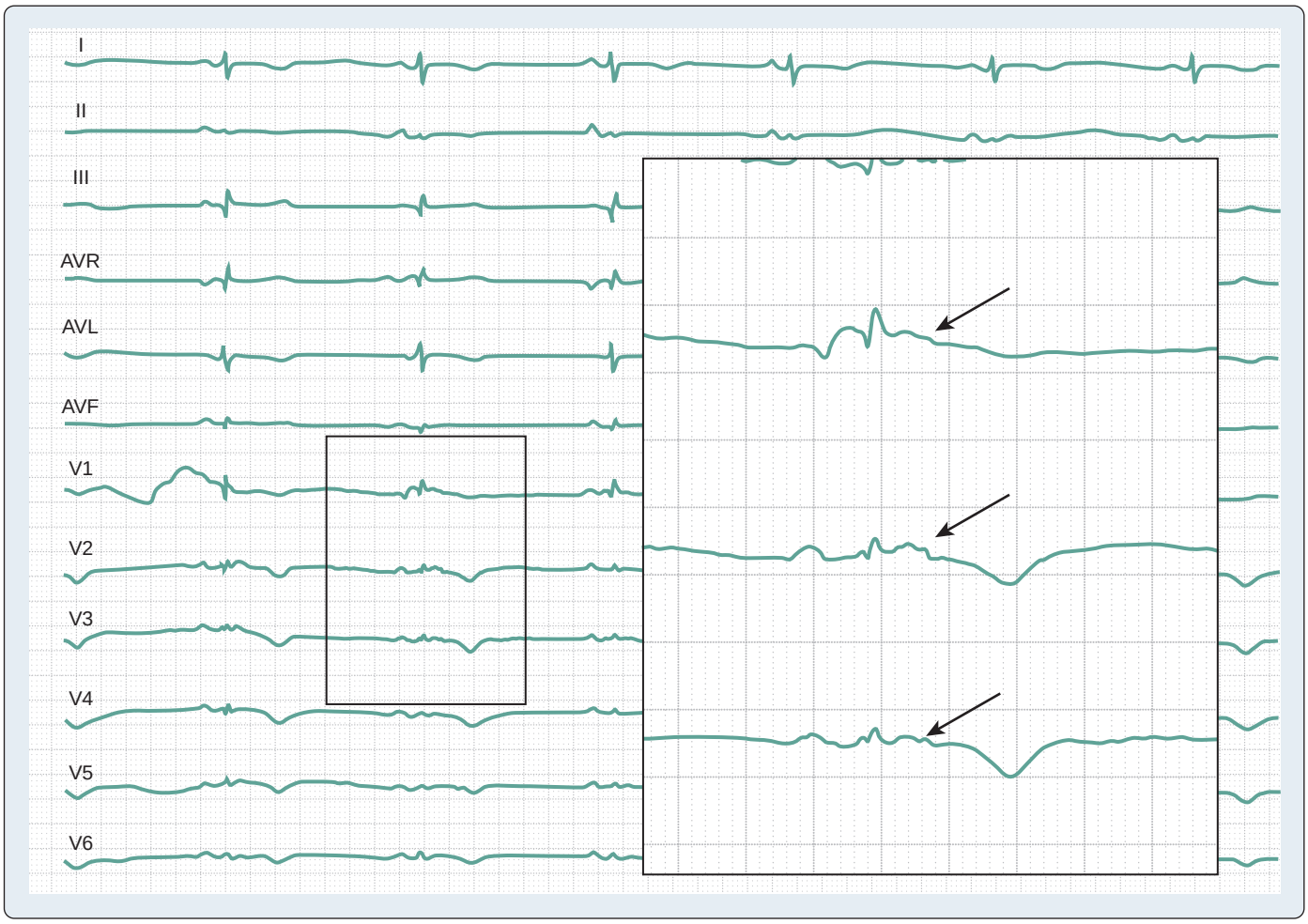


Fig. 24.58 Electrocardiogram demonstrates epsilon waves *(inset; arrows)* between the QRS complex and ST segment. *AVR*, Augmented vector right; *AVL*, augmented vector left; *AVF*, augmented vector foot. *(Reproduced with permission from Rotondi F, Amoroso G, Manganelli F. "Epsilon waves" in peripheral and precordial leads in arrhythmogenic right ventricular cardiomyopathy with severe right ventricular involvement.* J Electrocardiol. *2015;48:210–212.)*

RV were common, and over one half of patients had abnormal right ventricular systolic function. Right ventricular trabeculations were also commonly found. Although typical echocardiographic features are revealed in ARVC, the clinical disease manifestations may precede the appearance of these morphologic features. Recently, it has been shown that significant ventricular mechanical dyssynchrony is present in 50% of patients, which can lead to right ventricular dilatation and impaired systolic function.[223] Myocardial loss with progressive ventricular dysfunction progresses ultimately to CHF, accounting for 20% of deaths. End-stage ARVC may be difficult to distinguish from DCM, because the extent of left ventricular involvement has only recently been appreciated.

Diagnosis based on Revised Task Force Criteria graded aberrations (major and minor) include structural alterations (diagnosed by echocardiography, MRI, and/or right ventricular angiography), histologic evaluation, echocardiographic abnormalities, arrhythmias, genetic studies, and family history.[215,224,225] The characteristic echocardiographic findings include epsilon waves most commonly in precordial leads V1 through V3 (Fig. 24.58), right bundle branch block, inverted T waves in the right precordial leads, QRS prolongation greater than 110 to 120 ms, and extrasystoles with left bundle branch block.[221,224,226] Diagnosis may depend on endomyocardial biopsy to reveal the distinctive changes of ARVC, yet be unrewarding if the biopsy is obtained from the septal area of the myocardium known for its lack of characteristic features.[109] A new immunohistochemical analysis of a biopsy sample has proven to be highly sensitive and specific for the identification of ARVC.[227] The importance of this test is that it has been used to differentiate those patients in the early stages of the disease from those in the more advanced state. A prospective longitudinal study examined 108 newly diagnosed patients over a 2-year period and found that their clinical profile differed from the patient with the more advanced disease. This finding may offer some options for future treatments.[221]

Anesthetic Considerations

A retrospective review of forensic autopsies by the American Society of Anesthesiologists in 50 patients with intraoperative sudden cardiac death related to surgery or anesthesia revealed the presence of ARVC in 18 of the 50 cases.[228] Two adolescents undergoing routine surgical procedures were reported to develop refractory arrhythmias and sudden death after general anesthesia, with the autopsy revealing typical features of ARVC.[216] A family history of sudden death or syncope at an early age should heighten the awareness for the diagnosis of ARVC and merits further evaluation.[215] During the course of ARVC, arrhythmias of both a supraventricular and ventricular nature may occur. Because arrhythmias are more likely in the perioperative period, noxious stimuli, hypovolemia, hypercarbia, and light anesthesia must be minimized intraoperatively and during recovery. However, general

anesthesia, alone, does not appear to be arrhythmogenic. Houfani and colleagues[216] reported that over 200 patients with ARVC underwent general anesthesia without a single cardiac arrest. Anesthesia has been successfully conducted with propofol, midazolam, and alfentanil.[215] Acidosis may be especially detrimental because of its effect on arrhythmia generation and myocardial function.

The prevention of sudden cardiac death and malignant arrhythmias is paramount in the management of ARVC. Consideration for ICD implantation is commonly given in patients surviving sudden cardiac arrest or those with sustained ventricular arrhythmias, nonsustained ventricular tachycardia, syncope, and/or a family history of sudden cardiac death.[229,230] Antiarrhythmic therapy, along with radiofrequency ablation techniques, have also been described for patients with ARVC and underlying electrophysiologic aberrations.[231] Amiodarone and Sotalol have been shown in separate trials to help prevent ventricular arrhythmias in patients with ARVC.[232,233] Management of perioperative malignant dysrhythmias in patients with ARVC targets reversible causes (eg, light anesthesia, pain, electrolyte disturbances) with amiodarone and potentially ß-blockers as antiarrhythmic options.[232,234] TEE is a useful monitoring modality in patients with ARVC undergoing cardiac and other high-risk surgical procedures.[234] Extreme caution should be used if inserting a PAC in patients with ARVC; such intervention may trigger dysrhythmias or potentially cause right ventricular perforation.[234]

Mitral Valve Prolapse

MVP with severe mitral regurgitation is a common reason for cardiac surgery today. MVP is most likely a genetically inherited disease with an autosomal dominant manner. As the most commonly diagnosed cardiac valve abnormality, MVP occurs in adults who are otherwise healthy or in association with many pathologic conditions (Box 24.5) and is equally distributed between men and women.[235]

BOX 24.5 CONDITIONS ASSOCIATED WITH MITRAL VALVE PROLAPSE

Connective Tissue Disorders—Genetic
Mitral valve prolapse—isolated
Marfan syndrome
Ehlers-Danlos syndrome—types I, II, and IV
Pseudoxanthoma elasticum
Osteogenesis imperfecta
Polycystic kidney disease

Other Genetic Disorders
Duchenne muscular dystrophy
Myotonic dystrophy
Fragile X syndrome
Mucopolysaccharidoses

Acquired Collagen—Vascular Disorders
Systemic lupus erythematosus
Relapsing polychondritis
Rheumatic endocarditis
Polyarteritis nodosa

Other Associated Disorders
Atrial septal defect—secundum
Hypertrophic obstructive cardiomyopathy
Wolff-Parkinson-White syndrome
Papillary muscle dysfunction
  Ischemic heart disease
  Myocarditis
Cardiac trauma
Post–mitral valve surgery
von Willebrand disease

From Fontana ME, Sparks EA, Boudoulas H, Wooley CF. Mitral valve prolapse and the mitral valve prolapse syndrome. *Curr Probl Cardiol.* 1991;16(5):309–375.

Knowledge about MVP has evolved significantly over the last 40 years. Unrecognized as a part of the midsystolic click and systolic murmur known as Barlow disease until 1961, the finding of mitral regurgitation in conjunction with the ballooning of the posterior mitral leaflet on angiography resulted in the condition called Barlow syndrome or floppy-valve syndrome.[236] It was during this time that the true cause of MVP was understood to be a degenerative condition with myxoid found on histologic examination that caused thickening, elongation, and a change in the chordae. With the advent of echocardiography in 1970, a diagnosis based on echocardiographic parameters of the normal mitral valve was derived in 1987 for MVP.[237] In essence, only the valve that displayed prolapse in the long-axis view had *true* MVP,[238] which allowed the *true* prevalence of MVP to be determined, as well as the specific process associated with the corresponding mitral regurgitation. Carpentier was further able to differentiate the degenerative changes of MVP from another cause that did not cause billowing of the valve or excess tissue, now referred to as *fibroelastic deficiency*.[239] Currently, MVP is known to be a spectrum of structural and functional valve anomalies affecting 1% to 2% of the population, depending on accepted criteria for diagnosis.[240]

In patients with degenerative mitral valve disease, a spectrum of disease is appreciated, ranging from fibroelastic deficiency to Barlow disease (Fig. 24.59).[240] Fibroelastic deficiency was first identified by Carpentier as a form of MVP without billowing or excess valve tissue as was initially described by Barlow.[239,240] In this situation, the chordae were thin and possibly ruptured, often involving a segment of the posterior leaflet. The mechanism is impaired connective tissue production attributable to a deficiency of collagens, elastins, and proteoglycans, but the cause is unknown. Unlike Barlow disease, symptoms of fibroelastic deficiency generally arrive with chordal rupture, are frequently observed with advancing age, and include a significantly less pronounced, generalized degeneration of the mitral valve than Barlow disease. Surgical repair is also less complex.

Barlow disease is believed to result from myxomatous degeneration of the mitral valve, elongation and thinning of the chordae tendineae, and the presence of redundant and excessive valve tissue. The mechanism is unknown, but regulation of the extracellular matrix components appears to be a primary issue. Normal mitral valve leaflets may billow slightly with closure, but in MVP, redundant mitral leaflets prolapse into the LA during mid-to-late systole (Fig. 24.60). Superior arching of the mitral leaflets above the level of the atrioventricular ring is diagnostic for MVP. Distortion or malfunction of any of the component structures of the mitral valve may cause prolapse and generate audible clicks or regurgitation associated with a murmur. If the chordae tendineae are lengthened, then the valves may billow even more and progress to prolapse when valve leaflets fail to oppose each other. The degree of these changes will determine the presence of mitral regurgitation. The degenerative valve changes that are responsible for

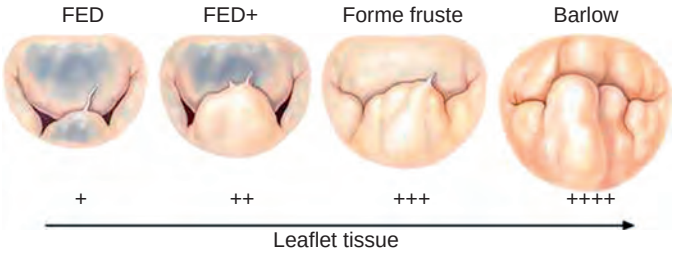


Fig. 24.59 Spectrum of degenerative mitral disease. Degenerative disease spectrum includes: fibroelastic deficiency *(FED)* with thin leaflets and a ruptured chordae *(+)*, long-standing FED leading to myxomatous changes of the prolapsing segment *(++)*, forme frusate with myxomatous disease and excessive tissue in one or more leaflet segments *(+++)*, and Barlow disease with myxomatous changes, excessive leaflet tissue, and large valve size *(++++)*. *(Reproduced with permission from Adams DH, Rosenhek R, Falk V: Degenerative mitral valve regurgitation: best practice revolution.* Eur Heart J. *2010;31:1958–1966.)*

progression from an asymptomatic state with murmurs and systolic clicks to dyspnea with severe mitral regurgitation occur over an average of 25 years.[241] Three-dimensional echocardiography has provided new insight into the characterization of mitral valve disease, as seen in Fig. 24.61, which shows Barlow disease and fibroelastic deficiency with a flail segment.[242]

Finally, even histologically, normal mitral valves may prolapse.[235] Normal mitral valve function depends on a number of factors, including the size of the LV and the mitral leaflets. Changes in these components may cause *innocent* MVP.

No universal criteria for diagnosis of MVP are available. Physical examination and echocardiographic findings are essential for the diagnosis of MVP. Auscultatory criteria that are strictly applied are highly sensitive for the diagnosis but lack specificity. Typical auscultatory features are midsystolic click and late-systolic murmur. The click is related to a deceleration of blood on the undersurface of the valve, prolapsing into the LA. The murmur is late, with progressively increasing regurgitation that results in a crescendo systolic murmur. Certain maneuvers aid with the auscultatory diagnosis of MVP such as Valsalva, squatting, or leg raises that change the left ventricular end-diastolic volume to move the timing of the click within systole.[235] Auscultatory findings may be absent, despite echocardiographic determination of MVP. Currently, MVP is diagnosed more often with two-dimensional echocardiography, because recognition and assessment of the severity is superior. Given the saddle-shaped nature of the mitral annulus, the diagnosis of MVP is typically made from the parasternal long-axis view using TTE. MVP is defined as greater than 2 mm displacement of one or both mitral leaflets into the LA during systole. If the mitral leaflets appear thickened or myxomatous, then the diagnosis is more certain. Color-Doppler and continuous-wave Doppler imaging can quantify the degree of mitral regurgitation when it is present.

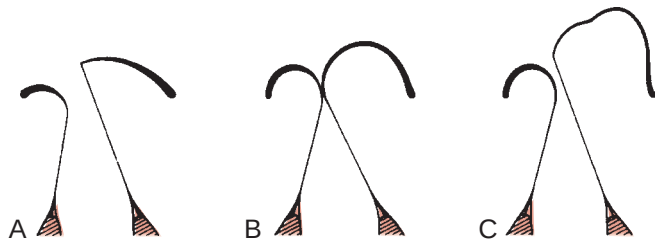


Fig. 24.60 Diagrammatic representation of the pathologic functioning of the mitral valve mechanism. (A) Regurgitation is present with mitral valve prolapse. (B) Billowing mitral valve is demonstrated without prolapse or regurgitation. (C) Billowing and prolapsed mitral leaflets are revealed with regurgitation. *(Reproduced with permission of American Heart Association. From Barlow JB, Pocock WA. Mitral valve prolapse enigma—two decades later.* Mod Concepts Cardiovasc Dis. *1984;53:13.)*

Most patients with MVP are asymptomatic; however, controlled studies have reported the presence of palpitations in 50% of patients.[243] Altered autonomic function, catecholamine responsiveness, or possibly a combination of the two may account for complaints of chest pain, fatigue, palpitations, dyspnea, dizziness, syncope, and panic attacks, among others. These symptoms and some clinical findings of thin body type, low blood pressure, and electrocardiographic repolarization abnormalities have been associated with MVP and are termed *MVP syndrome.*[235] Neuropsychiatric symptoms are no longer considered part of MVP. The possibility of a complex of unexplained cardiovascular symptoms associated with MVP has not been completely eliminated and may exist in a few patients. The cause may be abnormal autonomic activity that leads to symptoms of vasoconstriction, enhanced β-receptor activity, and decreased plasma volume; however, a relationship with MVP remains undefined.

The prognosis for most patients with MVP is excellent with a normal life expectancy.[235] The development of severe echocardiographic abnormalities is rare in patients with MVP. Although a benign course is typical for many patients with MVP, serious complications such as severe mitral regurgitation, infective endocarditis, sudden death, and cerebral ischemia may occur. The incidence of cardiovascular morbidity and mortality in MVP is just under 1% per year.[244] It is a subset of patients who appear to be at increased risk for serious complications who may be defined by echocardiography and clinical findings. These risk factors include reduced left ventricular systolic function and valve thickening greater than 5 mm, among others.[235]

Mitral valve regurgitation is the most serious complication associated with MVP. Severe mitral regurgitation develops in approximately 2% to 4% of patients with MVP, two thirds of whom are male patients.[243] Most patients will have mild-to-moderate mitral regurgitation that does not require surgery. MVP is the most common cause of severe mitral regurgitation, and its onset signals the need for therapeutic intervention. Irrespective of symptoms, the onset of severe mitral regurgitation can result in reduced life expectancy. Patients are usually younger than 60 years of age with the Barlow form of MVP and mitral regurgitation, in contrast, to older than 60 years of age for fibroelastic deficiency. Mitral regurgitation in Barlow disease is not due to the billowing of the leaflet body; rather, it is from the marginal prolapse (Fig. 24.62) and severe annulus dilation.[239] The posterior leaflet is affected more frequently than the anterior leaflet. Changes are often observed

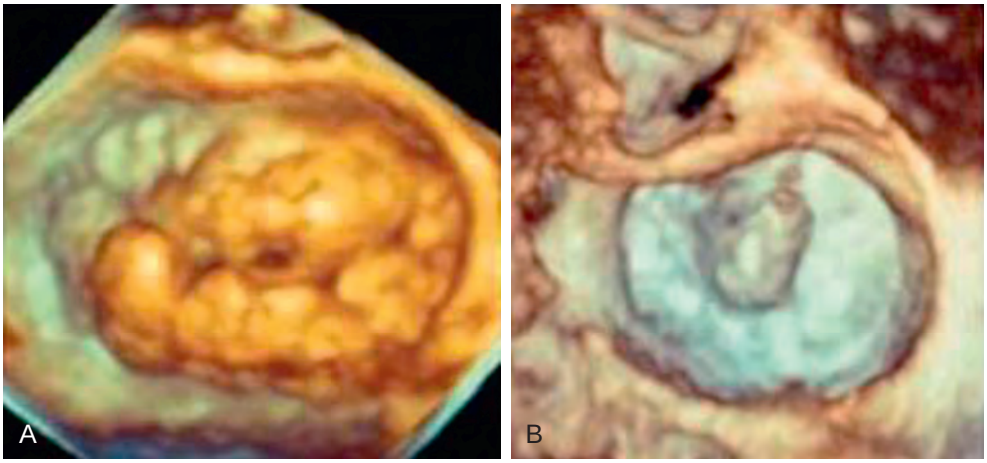


Fig. 24.61 Three-dimensional transesophageal echocardiographic views depict (A) a patient with Barlow disease and (B) fibroelastic deficiency with flail P2 segment. *(Reproduced with permission from Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography.* Eur Heart J Cardiovasc Imaging. *2012;13:1–46.)*

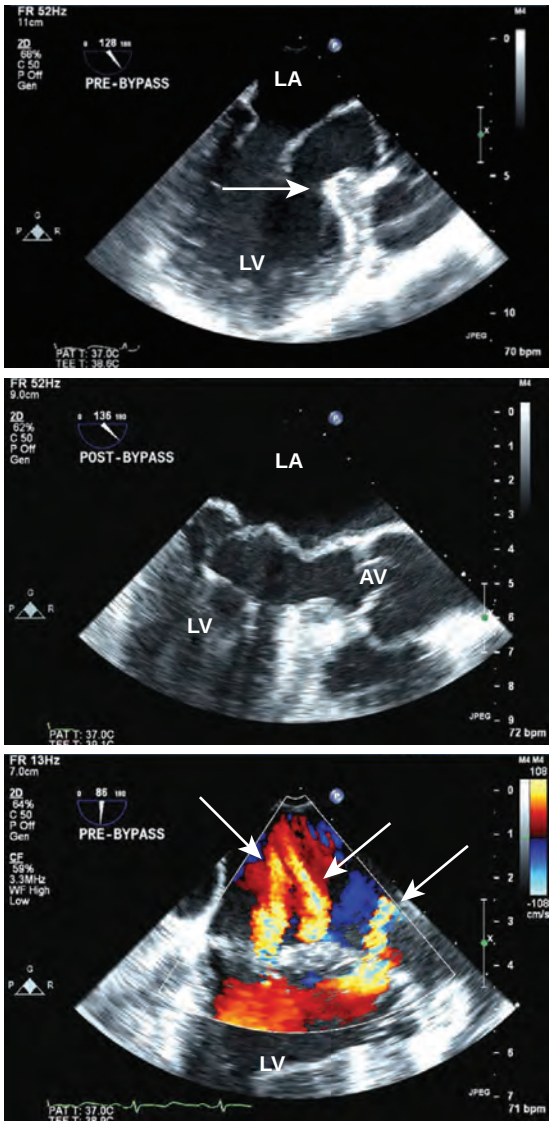


Fig. 24.62 *(Top panel)* A transesophageal long-axis view shows the left ventricular outflow tract and depicts the hypertrophy of the basal portion of the interventricular septum *(arrow)*. *(Middle panel)* A similar image during systole reveals bileaflet prolapse of the mitral valve. *(Bottom panel)* With color-Doppler imaging, at least three jets of mitral regurgitation *(arrows)* are noted. *AV,* Aortic valve; *LA,* left atrium; *LV,* left ventricle.

at the site of chordal insertion, leading to rupture of the chordae and a tethering of the valve leaflet. With the development of severe mitral regurgitation, pulmonary hypertension, left atrial enlargement, and atrial fibrillation frequently emerge. Early repair is recommended to preserve left ventricular function and to reduce the likelihood of atrial fibrillation.

The management of MVP and mitral regurgitation without symptoms continues to be reconsidered in terms of the timing for cardiac surgical intervention, especially in view of the risk of mitral valve repair and the improved outcomes associated with earlier surgery. Without overt symptoms, the degree of ventricular dysfunction may be worsening unknowingly, placing the patient at increased risk for permanent dysfunction and a worse surgical outcome.[235] Men are three times more likely to require surgical intervention, because the progression to severe mitral regurgitation is more common in men with MVP than in women, despite similar overall gender incidence of MVP. Noninvasive monitoring of mitral regurgitation and developing left ventricular dysfunction may help evaluate the optimal time for surgery. Flail mitral leaflet is an especially important risk for a poor surgical outcome if not addressed immediately.

Mitral valve repair is widely recommended for treatment of MVP, compared with replacement. Mitral valve repair confers a significantly improved surgical survival, as well as 5- and 10-year survival, compared with mitral valve replacement.[245] The Cox maze procedure may be added to mitral valve repair safely to effectively reduce late complications of mitral valve disease (eg, atrial fibrillation).[246] Advantages of mitral valve repair, compared with replacement, include a lower risk of thromboembolism, bleeding, infectious endocarditis, and better ventricular function because the valve structure is preserved.[247] Most patients with degenerative mitral disease (90%)[248] are candidates for mitral valve repair, which has been associated with low morbidity and mortality and with excellent long-term outcomes.[249] A prospective, observational study comparing mitral valve repair with mitral valve replacement in patients with mitral valve regurgitation (ischemic and degenerative causes) found a statistically significant survival benefit in patients who underwent repair.[250] Notably, repair of the valve returns the patient to a similar life expectancy as a comparable person who has not undergone a cardiac surgical procedure.

Posterior leaflet prolapse is the most common defect in mitral regurgitation.[235] The posterior leaflet repair is historically low risk, with bileaflet repairs presenting greater technical difficulty. The anterior prolapse repair has a higher rate of reoperation and decreased survival.[249] The use of robotic technology has advanced to a point that allows safe and feasible mitral repair with similar 30-day outcomes to traditional techniques in select patient populations; however, long-term follow-up data in this cohort are not yet available.[251,252] Recently, endovascular mitral valve repair via MitraClip devices (Abbott Vascular, Santa Clara, CA) has emerged as a viable treatment option for select nonoperable candidates with mitral valve regurgitation (Fig. 24.63).[253] All valves unfortunately cannot be successfully repaired, whereupon less than 10% with prolapse of a degenerative mitral posterior leaflet require mitral valve replacement.

The association of arrhythmias and sudden death with MVP is a long-held observation. Premature atrial and ventricular beats, atrioventricular block, and supraventricular or ventricular tachyarrhythmias are common during ambulatory monitoring in adults with MVP.[254] The causes of these arrhythmias are multifactorial, probably combining an anatomic substrate with some form of dysautonomia.[255] Mechanisms that have been proposed for arrhythmias include ventricular enlargement, hyperadrenergic states, electrolyte imbalances, and mechanical irritation of the ventricle because of traction of the chordae tendineae. Arrhythmias may be secondary to mitral regurgitation, not MVP. According to a study of individuals with nonischemic mitral regurgitation, complex arrhythmias were common and equally prevalent whether or not the patient had MVP.[256] Ventricular tachycardia occurred in 35% of those study participants with mitral regurgitation, in contrast to only 5% with MVP alone. Similarly, the risk of sudden death for patients with MVP may be related to mitral regurgitation in view of a reduction in ventricular arrhythmias that occurred with mitral valve repair or replacement.

The occurrence of sudden death with MVP in adults has been debated for years. The risk is low with an estimated yearly rate of 40 in 10,000, but this number is twice the expected rate in the population.[235] Sudden death does occur within families of MVP patients.[254] The ECG is abnormal in approximately two thirds of persons with MVP, but ambulatory electrocardiographic monitoring does not show an excess of atrial or ventricular arrhythmias unless accompanied by severe mitral regurgitation.[235] Electrophysiologic testing has been unable to identify an arrhythmogenic focus or reliably identify those at increased risk but is useful in the pharmacologic management of patients with ongoing complex sustainable arrhythmias. Patients with severe mitral regurgitation, flail segment, and a depressed LV appear to be at greater risk of sudden death. Prophylaxis has not averted sudden death in high-risk patients with severe mitral regurgitation. An ICD is a consideration in patients with inducible ventricular tachycardia or

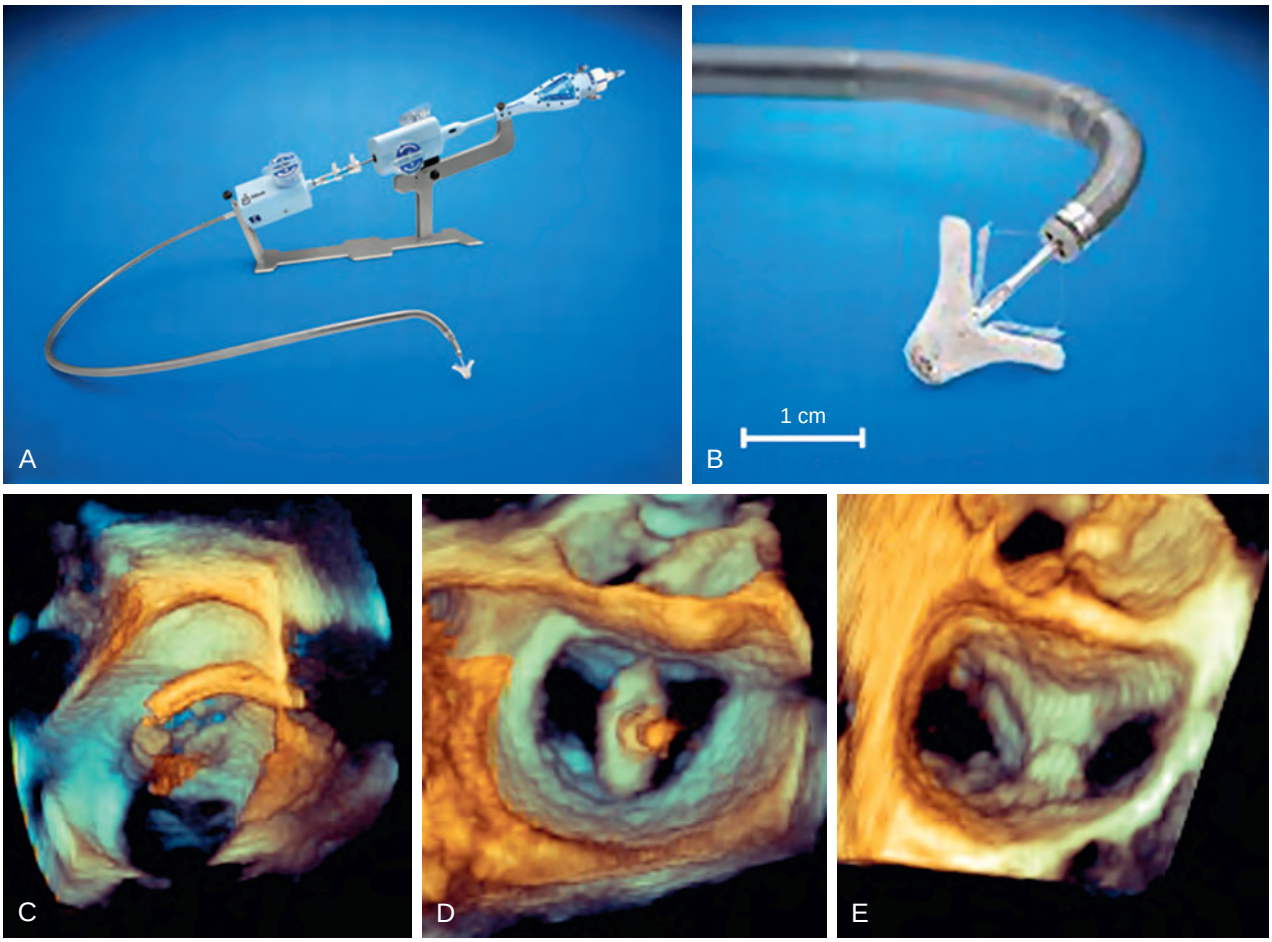


Fig. 24.63 (A) MitraClip delivery system. (B) Enlarged view of MitraClip delivery system with the clip inserted. (C) Three-dimensional transesophageal echocardiographic image shows the delivery system crossing the interatrial septum. (D) MitraClip orientation is perpendicular to the valve coaptation plane. (E) Mitral valve is shown after MitraClip placement at the anterior leaflet (A) and the posterior leaflet (P) interface with the generation of a double-orifice valve. *(Reproduced with permission from Rogers JH, Franzen O. Percutaneous edge-to-edge MitraClip therapy in the management of mitral regurgitation.* Eur Heart J. *2011;32:2350–2357.)*

ventricular fibrillation, but these patients are rare.[257] In general, most low-risk patients do not require treatment for either their symptoms or to prevent sudden death.

MVP has been reported to be associated with cerebral ischemic events, especially in the young. Mitral cusp elongation and expansion that occur with MVP may generate thrombus, vegetation, and calcification of the mitral valve. Mobile masses have been found in conjunction with cerebral events. However, a population-based cohort study involving 1079 patients found no difference in the incidence of strokes in patients under 45 years of age with MVP unless another cardiac disease process was present.[258] In contrast, a study of individuals in Olmsted County of Rochester, Minnesota, found the incidence of stroke was 0.07% per year, almost twice the normal rate.[259] The strongest factors associated with increased risk in these patients with MVP included thick valves, mitral valve surgery, atrial fibrillation, and an age 50 years and older. Factors that were independently associated with stroke were advanced age, coronary artery disease, CHF, and diabetes.

Bacterial endocarditis is an infrequent complication of MVP, but its incidence is three to eight times greater in these individuals than in the general population.[243] Male individuals are three times more likely to develop endocarditis. Current guidelines from the AHA are very specific and do not recommend antibiotic prophylaxis for individuals without a prosthetic cardiac valve, complex congenital heart disease (CHD), postcardiac transplant valvular lesions, or a history of bacterial endocarditis.[260] Patients with isolated clicks probably do not benefit from antibiotic prophylaxis, but cost effectiveness with MVP has been proven nonetheless.[261] Patients at high risk of developing endocarditis (previous bacterial endocarditis, systolic murmurs, thickened leaflets, or mitral regurgitation) should receive antibiotics before undergoing procedures commonly associated with bacteremia, because the risk increases to approximately 0.05% per year.[235] The turbulent flow from the mitral regurgitation and the thickened valve tissue may cause the increased risk of infection. Patients who may require oral endotracheal intubation or fiberoptic bronchoscopy do not require antibiotic prophylaxis.[241] Unfortunately, as recommendations regarding antibiotic prophylaxis have continued to be modified over the years, evidence to guide the physician on the issue of prophylaxis and MVP remains insufficient.

Anesthetic Considerations

Understanding the broad nature of the condition called MVP with respect to anesthetic considerations is important. Most individuals with MVP have an uncomplicated general anesthetic, because they have MVP without serious complications, often referred to as MVP syndrome. These patients are usually younger than 45 years of age with few risk factors for anesthesia. Invasive monitoring is usually unnecessary. Patients may be taking ß-blockers. Preoperative sedation

is useful to suppress a possible increased sensitivity to catecholamines. Painful stimuli may exacerbate the autonomic system, possibly causing arrhythmias, although rarely malignant in nature. Significant decreases in left ventricular end-diastolic volume and SVR or increased contractility and tachycardia should be minimized, because MVP may be enhanced such that CO and coronary perfusion are decreased. Intraoperative arrhythmias usually resolve spontaneously or respond to standard therapy. If an arrhythmia occurs, then adequate oxygenation should be confirmed and other causes of intraoperative arrhythmias investigated. If ß-blockers are required perioperatively, then esmolol will avoid the potential for prolonged blockade that might cause hemodynamically significant bradycardia.

Anticholinergic preoperative medications are best avoided, despite an increased vagal tone in MVP. A moderate anesthetic depth is desirable to minimize catecholamine levels and potential arrhythmias. Ketamine or drugs that have sympathomimetic effects must be cautiously administered. Volatile anesthetics sensitize the heart to catecholamines and thus potentially promote arrhythmias. Isoflurane is probably less sensitizing than halothane, but autonomic imbalance may actually be more important in arrhythmogenesis than any direct effect of volatile agents in patients with MVP. Patients with the MVP syndrome have been shown to possess good left ventricular function if mitral regurgitation or coronary artery disease is absent[262]; therefore myocardial depression from volatile agents will be well tolerated. Narcotics such as fentanyl will block sympathetic responses and promote hemodynamic stability; however, prolonged postoperative respiratory depression is a disadvantage with higher doses. Short-acting narcotics such as alfentanil and remifentanil, as well as other intravenous agents such as propofol, are available to facilitate rapid extubation.[263] Hypercapnia, hypoxia, and electrolyte disturbances increase ventricular excitability and should be corrected. If muscle relaxation is desired, then vecuronium is an excellent choice, because it does not cause tachycardia.

Patients with MVP who have mitral regurgitation are at greater risk for complications and warrant a different anesthetic approach, compared with those with MVP syndrome. Patients with more severe forms of MVP may rapidly progress to CHF and require cardiac surgery. The severity of mitral regurgitation will strongly influence anesthetic management. Invasive monitoring is routinely used during cardiac surgery for such patients and may even be necessary during noncardiac surgical procedures. Intraoperative TEE use is standard for mitral valve repair or replacement procedures. Opioid agents provide excellent hemodynamic stability without depressing myocardial function.[134] Although avoiding ketamine has been recommended by some for patients with the MVP syndrome, doses of ketamine below 0.5 mg/kg preserves hemodynamic stability in patients who are severely ill, especially when used in combination with opioids such as fentanyl. Unique aspects of anesthetic management for robotic mitral valve surgery involve peripheral bypass cannulation, single-lung ventilation, and often regional anesthetic techniques (eg, paravertebral block) to facilitate immediate postoperative extubation.[264,265] Anesthetic management for endovascular mitral valve repair (MitraClip, Abbott Vascular, Santa Clara, CA) typically requires general anesthesia to facilitate frequent transesophageal echocardiographic manipulation for proper device placement. A more extensive review of anesthetic management of valvular disease is found in Chapters 21 and 27.

Case Study 1: Mitral Valve Regurgitation and Septal Hypertrophy

The patient was an otherwise healthy 48-year-old woman referred for mitral valve surgery for severe mitral regurgitation. She was thin and fit. Chest auscultation revealed regular rate and rhythm with a 3/6 systolic murmur. Her preoperative transesophageal echocardiogram was remarkable for bileaflet prolapse and a left ventricular ejection fraction of 68%. The surgeon reviewed the transesophageal echocardiogram and noted that the basal ventricular septum appeared hypertrophied. The surgeon was experienced in complex valve repair and believed the valve was repairable but was concerned that the septal hypertrophy would result in significant postoperative SAM of the mitral leaflet. He requested further evaluation with TEE before CPB was initiated.

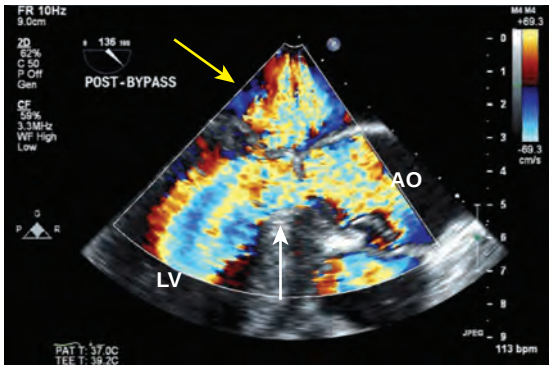


Fig. 24.64 Midesophageal long-axis view reveals the left ventricular outflow tract (LVOT) after the administration of isoproterenol. The heart rate is increased, and the blood pressure is decreased. The mitral regurgitation *(yellow arrow)* worsens, and aliasing of the color-Doppler signal in the LVOT *(white arrow)* now indicates turbulence of blood flow. *AO,* Aorta; *LV,* left ventricle.

Prebypass TEE confirmed the transthoracic echocardiographic findings with the basal ventricular septum measuring 21 mm. At rest, no evidence of SAM or LVOT obstruction was observed. The decision was made to challenge the patient with isoproterenol. With 4 µg of isoproterenol, the heart rate increased from 70 bpm to 135 bpm and the aortic blood pressure decreased from 126/52 to 77/45. Under these conditions, TEE revealed a significant amount of SAM and turbulent flow in the LVOT obstruction (Fig. 24.64). Needles placed in the aorta and LV were transduced and revealed a gradient across the LVOT of 67 mm Hg. Based on these findings, the surgical plan was altered.

CPB was instituted, and the heart arrested. The aorta was opened, and myectomy was performed through the aortic valve. The mitral valve was repaired with a posterior leaflet resection, and neochordae were placed to the anterior leaflet. The patient was weaned from CPB. A residual shelf of septal hypertrophy was seen with TEE. In addition, mild-to-moderate mitral regurgitation was posteriorly directed and assumed to be due to tethering of the anterior leaflet by the neochordae. CPB was reinstituted. A second myectomy was performed, and the neochordae removed. After weaning the patient from CPB, no mitral regurgitation was observed, and the ventricular septum appeared adequately myectomized. With an isoproterenol challenge achieving similar increase in heart rate to those seen before CPB, no evidence of SAM or LVOT obstruction was revealed with TEE. No gradient was demonstrated when needles were placed in the aorta and LV. The patient had an uneventful postoperative course.

In this instance, TEE was absolutely essential in guiding this complex mitral repair. It was able to determine the hemodynamic significance of the septal hypertrophy, the inadequacy of the initial myectomy, and the need to release the neochordae to the anterior leaflet. An alternative surgical procedure would have been mitral valve replacement. However, mitral valve repair is to replacement for the reasons previously indicated.

Patent Foramen Ovale

A PFO is the most common congenital defect involving the atrial septum.[266] It was first recognized as a causal relationship with stroke in 1877[267] and has since been proven one of the mechanisms of stroke.[268] Air, thrombus, or fat may travel from the RA to the LA into the systemic circulation causing a paradoxic embolus that may affect cerebral or coronary circulations. For years, a PFO was identified only in the catheterization laboratory, during surgery, or at autopsy. The availability of noninvasive two-dimensional echocardiography has

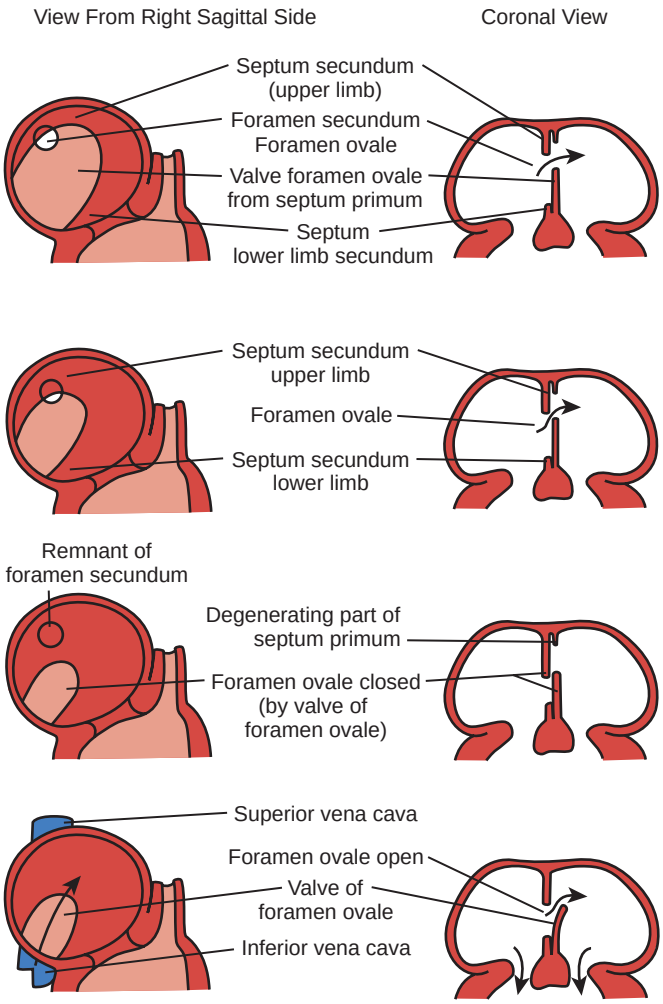


Fig. 24.65 Embryologic development of the interatrial septum. *(Reproduced with permission from Hara H, Virmani R, Ladich E, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status.* J Am Coll Cardiol. *2005;46:1768–1776.)*

considerably increased the annual number of diagnoses of PFO. The ability to so readily and safely close a PFO with minimally invasive techniques has created the need to develop guidelines to address the management of PFO.[269]

The foramen ovale is present during fetal circulation to improve the transport of maternal-oxygenated blood from the umbilical veins across the Eustachian valve selectively into the LA. With birth and the onset of respiration, pulmonary vascular resistance decreases, facilitating functional closure of the foramen ovale. If the flaplike covering from the septum primum does not fuse with the septum secundum over a period of a year, then there is anatomic failure of closure forming a PFO (Fig. 24.65). In patients with a PFO, any condition resulting in right atrial pressures exceeding left atrial pressures will facilitate right-to-left shunting. In contrast, left-sided heart conditions that result in left atrial pressures greatly exceeding right atrial pressures will cause left-to-right shunting. An individual may remain asymptomatic for years with a PFO, depending on the size of the shunt.

The incidence of PFO in the population has varied, depending on the study and diagnostic technique. Hagen and associates[270] reported a 27% incidence of PFO in nearly 1000 autopsies, considered by many, the definitive study on incidence of PFO. Subsequent studies involving various modes of echocardiography have reported the incidence of PFO in the population between 3% and 45%.[271] A recent retrospective study examining over 10 years of cardiac surgery in 13,000

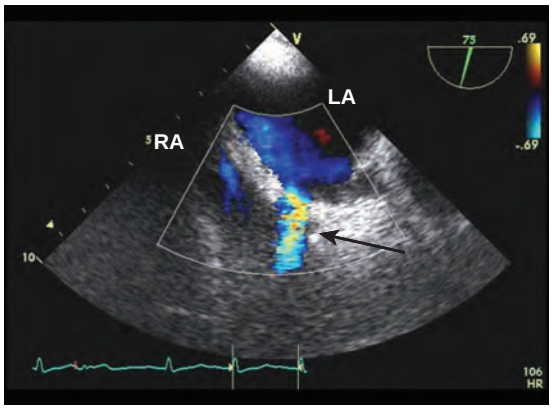


Fig. 24.66 Transesophageal image from the midesophagus at 75 degrees focusing on the interatrial septum. Color-Doppler imaging readily reveals a moderately sized shunt from the left atrium *(LA)* to the right atrium *(RA)* through a patent foramen ovale.

BOX 24.6 DISEASES AND RISKS ASSOCIATED WITH PATENT FORAMEN OVALE

Proved Causal Relationship
Stroke
Transient ischemic attack
Myocardial infarction
Eye infarction
Visceral infarction
Arterial limb embolism
Economy-class stroke syndrome
Platypnea orthodeoxia
Fat embolism in major orthopedic surgery
Air embolism in brain surgery in the sitting position
Decompression illness

Presumed Casual Relationship
Migraine (particularly with aura)
Transitory global amnesia
High-altitude pulmonary edema
Sleep apnea syndrome
Excessive snoring
Increased risk of systemic embolism in:
- Deep sea divers
- Brass musicians
- Glass blowers
- Professionals working in squatting position
- Supersonic jet pilots
- Astronauts

Reproduced with permission from Meier B. Catheter-Based Closure of the Patent Foramen Ovale. *Circulation.* 2009;120:1837–1841.

patients reported an incidence of PFO as 17% with TEE.[272] TTE is now recognized as less sensitive than TEE, possibly accounting for such variation in previous studies regarding the incidence of PFO. TEE has become the gold standard for diagnosing PFO with its higher image resolution than other methods and 100% sensitivity and specificity with autopsy findings (Fig. 24.66).[271] Because TEE is more invasive, additional technical advances in both TTE and transcranial Doppler have improved their sensitivity and, when combined, may be adequate for PFO screening purposes.[273]

Although a number of conditions are associated with PFO (Box 24.6) and may merit consideration for therapy, stroke receives the most attention. Approximately 700,000 strokes occur each year in the United States with 20% considered cryptogenic (ie, without an identifiable cause). In those individuals with a history of cerebral events, the

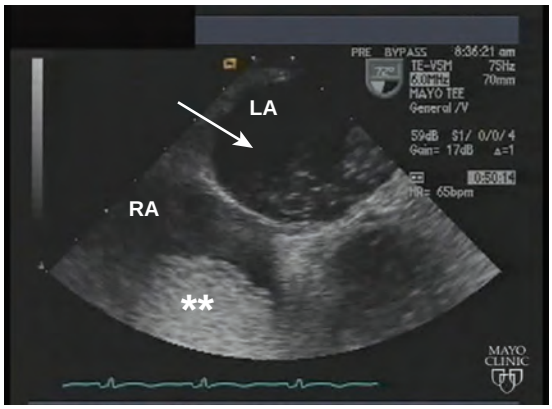


Fig. 24.67 Transesophageal image from the midesophagus at 72 degrees focusing on the interatrial septum. Agitated saline *(double asterisks)* is being used for contrast and can be seen in the right atrium *(RA)*. With the release of a Valsalva maneuver, the contrast is seen to enter the left atrium *(LA)* through a small patent foramen ovale.

prevalence of PFO ranges from 7% to 40%, depending on the diagnostic technique.[274] Several studies show a strong relationship between cryptogenic stroke and PFO, based on epidemiologic evidence,[268] but others dispute it. Petty and colleagues[275] conducted a population-based study looking at TEE in patients with cerebral ischemic events, compared with control subjects who had TEE but did not have cerebral ischemic events to eliminate bias present in other studies regarding PFO. They found that PFO was not an independent risk factor for stroke even when considering the size of the shunt. Although some recognize the PFO as an increased risk for cryptogenic stroke, it remains inconclusive.

The decision to close a PFO will include individual risk factors for stroke or other complications such as migraine headaches and platypnea orthodeoxia syndrome that may occur in the context of a PFO. Paradoxic embolus is more common if an atrial septal aneurysm, a large Eustachian valve, migraines, and an age of 50 years or older are present. Medium-to-large shunts, in combination with coagulation disorders, are highly correlated with paradoxic embolus.[269] In contrast, another study found no relationship to the size of the shunt with PFO and stroke.[275]

To diagnose paradoxic embolus, performing a correct provocative measure to ensure right-to-left movement of air or contrast is essential (Fig. 24.67). Agitated saline directed through an intravenous line with the Valsalva maneuver is most commonly used to confirm the diagnosis. The increased intrathoracic pressure from the Valsalva maneuver will lead to a temporary increased return of venous blood after the maneuver has ended; therefore the right atrial pressure will briefly exceed left atrial pressure to allow contrast administered into the right internal jugular vein to pass to the LA.[273] False-negative results may occur if the left atrial pressure is elevated to such an extent that the provocative measure does not cause right-to-left shunting.

Management of a PFO is dependent on several variables and has been largely debated because of the mixed results of several recent large studies and metaanalyses. Traditional medical therapy consists of various anticoagulation regimens and has been previously believed to be inferior to percutaneous device closure in patients with known PFO.[276] Percutaneous device closure of PFOs has been found to reduce the risk of recurrent strokes in several large studies and metaanalyses, but a recent metaanalysis has challenged the finding that the reduction of recurrent stroke risk is small with complications such as atrial dysthymias not uncommon.[266,277,278] Device closure for patients with PFO has been believed to benefit most those with recurrent stroke who have large PFOs, PFO and failed medical therapy, or who are young and without other contributable risk factors for atherosclerotic disease.[266]

Closure of PFOs can be performed either surgically or percutaneously. Although available in the late 1980s, percutaneous closure of PFOs became popular in the 1990s after a report described the successful closure of PFOs in 36 patients with known right-to-left shunt and presumed paradoxic emboli.[279] Percutaneous closure is generally performed in a catheterization laboratory with conscious sedation. Success rates (incidence of no residual shunting) have been initially very good, but the methods used to evaluate success may have been flawed, accounting for the wide range of success rates between 50% and 100%.[274] With use of transcranial Doppler to assess PFO closure, 9% of patients were found to have significant shunting after only 1 year after percutaneous closure.[280] Although percutaneous closure is routinely performed, it is not free of complications, which include dysrhythmias, cardiac perforation, air embolism, thrombus formation, and even death.[278,280]

Currently, surgically closing an isolated PFO with the safety and availability of percutaneous closure is rare. However, the use of intraoperative TEE during cardiac surgical procedures has increased the number of incidentally diagnosed PFOs. A retrospective review of cardiac surgeries in 13,000 patients found 17% with PFO.[272] The incidence of PFOs was believed to remain relatively static each year; however, the percentage of PFOs that were closed surgically increased to a maximum of 39% over the period. Not only are more PFOs closed as a percentage, but, over time, more surgeons as a percentage are choosing to close them.[269] The cause for these trends is not certain, but a PFO diagnosed incidentally during surgery creates a dilemma for the surgeon.

The decision to close an incidental PFO during cardiac surgery is not always evident, based on short- and long-term risks to the patient. When the finding has been incidental, recurrent paradoxic embolus and neurologic injury have not usually occurred. Certain conditions would almost mandate the closure of the PFO, such as the insertion of LVAD that would promote paradoxic embolus[273] or the onset of severe hypoxia attributable to increased right-sided pressures that cause a large right-to-left shunt. Little evidence suggests that incidentally discovered PFOs in patients without respective history increase morbidity or mortality.[281] In fact, one study demonstrated that an alteration in the surgical plan to include the closure of an incidental PFO actually increased the risk of stroke.[272] Surgical PFO closure when performed is routinely accomplished through a sternotomy, although new techniques of minimally invasive surgery also allow the incision to be a right thoracotomy. Closure requires CPB and cardioplegic arrest. Certain surgical procedures such as tricuspid or mitral valve repair or replacement that includes CPB and atriotomy, require minimal deviation from the originally planned procedure to close the PFO and thus incur little risk. In contrast, coronary artery bypass graft (CABG) surgery performed without CPB would entail the risk of going on CPB, aortic cross-clamping, and other complications associated with extracorporeal circulation. The decision to close an incidental PFO in such circumstances must include careful examination of the perceived risk and benefit for each individual patient.

Based on a survey of cardiac surgeons, 27.9% of respondents always close a PFO if detected during CABG surgery.[273] However, no evidence really indicates that all PFO found incidentally during cardiac surgery merit closure.[272] A retrospective study looking at those with and without PFO showed no differences between stroke, hospital and ICU lengths of stay, MIs, and death when propensity matching was applied for the comparison.[272] Long-term follow-up for 10 years also did not demonstrate any difference between those with a PFO and those without PFO. The outcomes for those who had PFO repaired versus not repaired found no differences except for a slight but significantly increased incidence of stroke postoperatively in the repaired group. In addition to the concern of paradoxic embolism, the risk of severe desaturation postoperatively is possible in patients with unrepaired PFO, but a case series of 11 off-bypass CABG surgeries with incidental PFOs that were not closed showed no adverse desaturation events perioperatively.[282]

Anesthesia Considerations

Anesthesia management for percutaneous PFO closure typically involves conscious sedation. Intraoperative management for the closure of an incidental PFO during cardiac surgery requires very little deviation from the anesthetic management of the scheduled procedure. However, certain precautions should be undertaken once the PFO has been identified.

Routine care for preventing venous air should be standard for cardiac surgery, including careful injection of medications to remove extraneous air from entering the venous system. Some providers use inline air filters on all intravenous lines once the presence of the PFO has been identified, but such practice is not widespread. Appreciating the potential for paradoxic embolus with any patient that requires mechanical ventilation is important. In situations during which the pulmonary vascular resistance may rise, such as during hypercapnia or with positive end-expiratory pressure (PEEP) greater than 15 mm Hg, the potential for right-to-left shunting increases.[283] The choice of anesthetic seems to have very little impact on the management of PFOs.

Case Study 2: Incidental Patent Foramen Ovale Found During Coronary Artery Bypass Graft Surgery

A 60-year-old man with a medical history of hypertension experienced angina on exertion. Specifically, he had bouts of recurring chest pain after jogging for 15 minutes on a treadmill. Previously, he had been able to jog for 30 minutes without difficulty. On physical examination, he appeared thin and fit. The heart was regular in rate and rhythm without a murmur, and the lungs were clear to auscultation. A stress ECG was positive for ischemia with coronary angiography revealing severe three vessel disease. The patient was scheduled for CABG surgery.

In the surgical unit, a transesophageal echocardiographic probe was placed for the purposes of monitoring ventricular function and evaluating regional wall motion abnormalities. The pre–bypass examination revealed an ejection fraction of 65%, normal valve function, and no regional wall motion abnormalities. The interatrial septum appeared redundant. Agitated saline was injected into the central line. After the release of sustained positive pressure ventilation, contrast was seen to enter the LA via a small PFO. No shunt was detected by color-Doppler imaging.

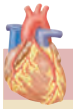
The surgeon was informed of the previously undiagnosed PFO. A discussion ensued regarding the implications of repairing the PFO, compared with leaving it undisturbed. The surgeon had not repaired a small PFO during a previous CABG surgery but learned that the patient had suffered a stroke 2 years later, presumably attributable to paradoxic embolism. Given the patient's young age and previous experience, the surgeon elected to repair the PFO that altered the surgical planning. The cannulation strategy was changed from a single right atrial venous cannula to bicaval cannulation. A right atriotomy was performed, and the PFO was closed with two stitches. The patient was easily weaned from CPB and had an uneventful postoperative course.

Pulmonary Hemorrhage

Pulmonary hemorrhage occurs in approximately 1.5% of patients with hemoptysis[284]; but mortality may reach 85%.[285] The definition of massive hemoptysis varies but is commonly characterized as more than 600 mL of expectorated blood over 24 hours or recurrent bleeding greater than 100 mL per day for several days. Four hundred milliliters of blood in the alveolar space seriously impairs oxygenation. Pulmonary hemorrhage may stabilize, only to worsen again without an obvious explanation, reflecting its unpredictable nature. Notably, death is not attributable to hemodynamic instability with hemorrhage but to excessive blood in the alveoli that causes hypoventilation and refractory hypoxia. Clot formation may lead to occlusion of bronchial segments or even the mainstem bronchus. Mortality is related to the quantity of blood loss within a given period.[285,286] For example, blood loss greater than 600 mL of blood over 16 hours has a mortality rate of 45%, whereas mortality is 5% if blood loss is 600 mL over 48 hours. A delay in initiating treatment because of difficulty in isolating the location of bleeding contributes greatly to the high mortality of pulmonary hemorrhage.

Hemoptysis may occur with various diseases and circumstances (Box 24.7). In the United States, chronic inflammatory lung disease and bronchogenic carcinoma are the most common causes of hemoptysis.[287] Of these causes, bronchitis (26%), lung cancer (23%), pneumonia (10%), and tuberculosis (8%) are most frequent. The inflammatory response is an important factor in the occurrence of bleeding.[288] The combination of chronic infection, inflammation, and vascular growth result in hypervascularization of the bronchial circulation that ultimately erodes into the alveoli.[289] Pulmonary hemorrhage may also result from vigorous suctioning of the lungs, surgery, and improper positioning of a PAC.[290] Massive hemoptysis is usually an emergency, because the underlying pulmonary disorder minimizes the patient's physiologic reserve.

To understand the pathogenesis of pulmonary hemorrhage, appreciating the anatomy of the pulmonary circulation is helpful. The lungs



BOX 24.7 CAUSES OF MASSIVE HEMOPTYSIS

Tracheobronchial Disorders
Amyloidosis
Bronchial adenoma
Bronchiectasis[a]
Bronchogenic carcinoma
Broncholithiasis
Bronchovascular fistula
Cystic fibrosis
Foreign body aspiration
Tracheobronchial trauma

Cardiovascular Disorders
Congenital heart disease
Mitral stenosis
Pulmonary arteriovenous fistula
Septic pulmonary emboli
Ruptured thoracic aneurysm
Arteriovenous malformation

Localized Parenchymal Diseases
Amebiasis
Aspergilloma[a]
Atypical mycobacterial infection[a]
Coccidioidomycosis
Lung abscess
Mucormycosis
Pulmonary tuberculosis[a]

Diffuse Parenchymal Diseases
Goodpasture syndrome
Idiopathic pulmonary hemosiderosis
Polyarteritis nodosa
Systemic lupus erythematosus
Wegener granulomatosis

Other Causes
Pulmonary artery rupture from a pulmonary artery catheter
Iatrogenic (eg, bronchoscopy, cardiac catheterization)
Pulmonary hypertension
Pulmonary edema
Pulmonary infarction

[a]Most common causes.
Reproduced with permission from Thompson AB, Teschler H, Rennard SI. Pathogenesis, evaluation, and therapy for massive hemoptysis. *Clin Chest Med*. 1992;13:69.

have a dual blood supply. The pulmonary arterial circuit is a high-flow, low-pressure circuit. The nutritive supply of the pulmonary structures is the bronchial arteries that originate from the aorta. Bronchial arteries extend into many areas around the lymph nodes, esophagus, and lungs, ultimately penetrating the bronchial wall to supply the bronchial mucosa. The bronchial and pulmonary circulations anastomose at several locations. Massive pulmonary hemorrhage usually involves bleeding attributable to a disruption of the high-pressure bronchial circulation.[284] These high-pressure, tortuous bronchial arteries are found throughout the thoracic cage. The bronchial circulation accounts for 98% of pulmonary hemorrhage, and the pulmonary circulation accounts for the remaining 2%.[286]

Diagnosis of hemoptysis requires a few simple tests. Visual inspection can usually distinguish gastrointestinal bleeding from pulmonary hemorrhage. Hemoptysis is often bright red with some sputum. Hemoptysis attributable to pulmonary artery rupture is usually copious (200 to 2000 mL).[290] Treatment begins with conservative management and simultaneous efforts to locate the bleeding site. A chest roentgenogram may reveal an infiltrate, but neither a chest roentgenogram nor a physical examination has been reliable in localizing the affected lung. Recently, better noninvasive technology such as the multidetector row CT is capable of rapidly and accurately determining the site of bleeding.[287] Flexible fiberoptic bronchoscopy of the airways may be limited by severe bleeding that obscures the view, and persistent attempts should not delay other therapies. Rigid bronchoscopy is better suited for the identification of bleeding during massive hemoptysis and the removal of any large clot that may be obstructing the airway. However, the view of the upper lobes is limited, and the procedure requires general anesthesia. Instillation of epinephrine in the bronchi may facilitate better visualization by slowing the bleeding. Ultimately, angiography of the pulmonary and bronchial arteries may be necessary to localize the source of the bleeding.[285] Imaging for bronchial artery bleeding begins with a thoracic aortogram to localize all the primary systemic arteries to the lungs that may be bronchial or nonbronchial. Once the feeding arteries are localized, selective bronchial arteriography is then used to identify the bleeding vessels.[291]

Therapeutic options for bleeding depend on the extent of bleeding. Flexible bronchoscopy may be able to identify the source of bleeding and perform techniques, such as epinephrine flush and cold-saline lavage to minimize hemorrhage and possible balloon bronchial blockers to tamponade any bleeding.[292] Advancements in bronchoscopy have seen success with the use of topically applied agents consisting of oxidized regenerated cellulose mesh injected at the site of bleeding.[287] Additionally, the use of topically applied factor VIIa (FVIIa) has been reported with success in massive hemolysis, secondary to a medical cause, although its use in this manner is off label.[289] FVIIa has been anecdotally reported beneficial with massive hemoptysis, despite low platelet count, trauma, vasculitis, and bone marrow transplantation. Other medications used to reduce bleeding include Premarin, desmopressin, vasopressin, and tranexamic acid.[293]

With rapid or persistent bleeding, a double-lumen endotracheal tube (ETT) may be necessary to isolate the bleeding from the unaffected lung. Misplacement of a double-lumen ETT occurs in 45% of patients after the initial attempt and 54% after patient positioning.[294] If the patient was administered an anticoagulant drug, then airway manipulation in connection with double-lumen ETT placement may incite further mucosal damage and bleeding. A Fogarty catheter, as described by Larsen and Gasior,[295] may be passed within an existing ETT under bronchoscopic guidance to the affected bronchus, thereby minimizing additional trauma to the airway caused by reintubation and protecting the uninvolved lung. The Univent ETT is an alternative to a double-lumen ETT but requires exchanging the existing ETT for the Univent ETT. A single-lumen ETT should not be advanced into the right main bronchus if bleeding is believed to be in the right lung because of the proximal location of the right upper lobe bronchus. Insertion of a bronchial blocker is another lung isolation strategy, but placement may again be challenging during active bleeding.

Continued bleeding after stabilization and conservative therapy necessitates bronchial artery embolization, which is considered first-line therapy for massive hemoptysis. Although success rates of 75% to 98% have been reported, 16% to 20% of patients rebleed within 1 year.[296–298] Bronchial artery embolization is often performed in conjunction with the thoracic aortogram after identifying the bleeding vessels with polyvinyl alcohol particles, Gelfoam, and/or dextran microspheres. A study found 88% of patients who underwent bronchial artery embolization had immediate control of bleeding, whereas another group of patients (81%) had bleeding cessation within 48 hours.[299] Bronchial artery embolization has greatly advanced treatment success for pulmonary hemorrhage. Immediate recurrence of hemoptysis after embolization may signal that additional contributing vessels were not identified and embolized. Latent hemoptysis is often due to recanalization or collateralization. Although it has proven effective, recanalization is not without complications, especially vascular complications such as coronary artery syndrome, spinal cord ischemia, and esophageal wall necrosis.[291]

The ability to use an array of treatment options in a multidisciplinary approach to this life-threatening condition will increase survival and reduce complications.[292] Efforts to control bleeding for at least 48 hours with nonsurgical alternatives have reduced perioperative morbidity and mortality, compared with early surgical therapy for massive hemoptysis. If bleeding persists and/or nonoperative therapies have either failed or are not feasible, then surgical treatment may be required. A localized bleeding site and sufficient lung function are ideally determined before surgical resection, as total pneumonectomy may be required. Postoperative mortality rates vary tremendously from 1% to 50%.[284] Surgery is contraindicated in those with lung carcinoma invading the trachea, mediastinum, heart or great vessels, terminal malignancy, and progressive pulmonary fibrosis.

The introduction of the PAC in 1970 allowed physicians to obtain CO, SVR, and estimates of left ventricular performance, as well as to detect perioperative myocardial ischemia. As PAC use increased, a rare but often fatal cause of pulmonary hemorrhage—the rupture of the pulmonary artery in patients undergoing cardiac surgery—emerged.[290] The incidence ranges from 0.06% to 0.2% of cases, with a corresponding mortality rate of 45% to 64%.[300] With respect to cardiac surgical patients, death may occur within minutes of pulmonary artery rupture or over a period of 1 to 14 days postoperatively.[301] The diagnosis may be initially missed because patients may be asymptomatic or only mildly symptomatic. A small amount of hemoptysis may herald the onset of severe pulmonary hemorrhage.[302] Other signs of pulmonary artery rupture are hypotension, decreased arterial oxygenation, bronchospasm, pleural effusion, hemothorax, and pneumothorax. Pulmonary hemorrhage rarely occurs during cardiac surgery; however, when present, it is a life-threatening emergency.

Certain factors predispose a patient to pulmonary artery rupture such as age older than 60 years, anticoagulation, and distal migration of PAC.[290] Although pulmonary arterial hypertension (PAH) is often present with pulmonary artery rupture, it is not a risk factor,[301] but PAH may simply promote distal migration of the PAC. Chronic PAH weakens the pulmonary artery and veins; thus a patient's susceptibility to rupture is increased. The mechanism of pulmonary artery rupture is multifactorial, but the catheter balloon is believed to be instrumental.[303] Maximal pressures for balloon inflation are approximately 1700 mm Hg and can easily reach 1000 mm Hg with the start of inflation. PACs that reside distally will lower the inflation pressures necessary to rupture the pulmonary artery, particularly in the older adult. Distal migration of the PAC also occurs more easily in patients undergoing hypothermic CPB, because hypothermia stiffens the PAC. Eccentric inflation of the PAC balloon contributes to pulmonary artery rupture, as evidenced in both cadavers and patients.[304] Inflation that distorts the balloon drives the catheter tip through the vessel wall (Fig. 24.68). Manipulation of the heart may also perforate the pulmonary artery.

The extent of bleeding after pulmonary artery rupture will determine treatment. If the rupture occurs during CPB, then extracorporeal

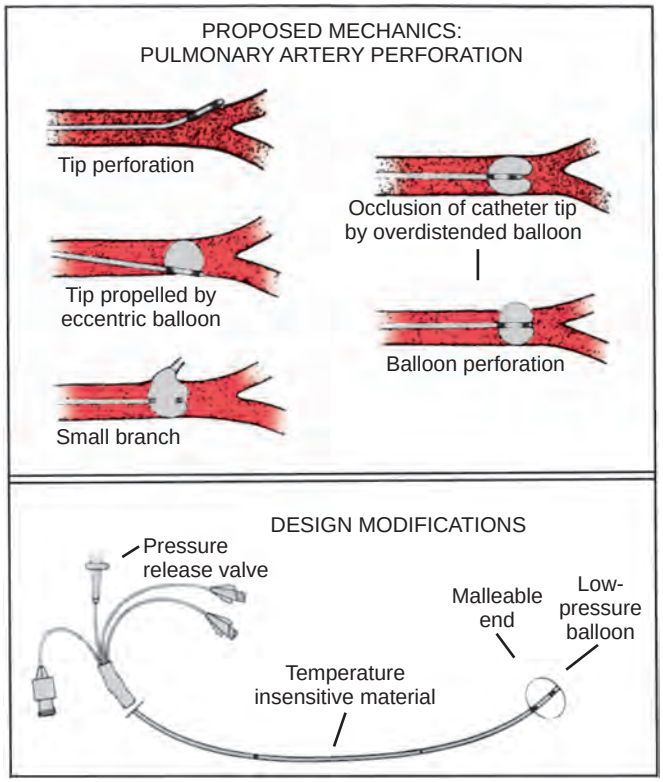


Fig. 24.68 Possible mechanisms of pulmonary artery perforation with balloon-tipped flow-guided catheter are illustrated. These problems require modifications in catheter design. *(Reproduced with permission from Barash PG, Nardi D, Hammond G, et al. Catheter-induced pulmonary artery perforation. Mechanisms, management, and modifications.* J Thorac Cardiovasc Surg. *1981;82:5.)*

support should be maintained to ensure adequate oxygenation and optimal conditions for pulmonary artery repair. If pulmonary artery rupture occurs before CPB, then the use of PEEP and maintaining PAC position with the balloon inflated may provide temporary tamponade effect until more definitive therapies ensue.[301,305] If anticoagulation has been neutralized, then blood loss of 1000 mL or more over 24 hours should merit consideration for surgical intervention, taking into account the patients underlying pulmonary function and tolerance for lobectomy or potentially pneumonectomy.[285,286]

To reduce the risk for pulmonary artery rupture, the placement of a PAC distally in the pulmonary artery should be avoided. Advancing the PAC more than 5 cm beyond the pulmonary valve is not advisable. The balloon should not be inflated against increased resistance, particularly if the patient has been given an anticoagulant drug or after separation from CPB. The pulmonary artery waveform should always be carefully observed with inflation and deflation of the balloon. Retracting the PAC into the RV on the initiation of CPB or withdrawing the PAC 5 cm immediately before CPB is advisable.

Pericardial Heart Disease

The pericardium is a two-layer sac that encloses the heart and great vessels. The inner layer is a serous membrane (visceral pericardium) covering the surface of the heart. The outer layer is a fibrinous sac (parietal pericardium), which is attached to the great vessels, diaphragm, and sternum. The parietal pericardium is a stiff collagenous membrane that is resistant to acute expansion. The space between the two layers is the pericardial space, normally containing up to 50 mL of clear fluid that is an ultrafiltrate of plasma. It can gradually dilate to accept large volumes of fluid if slowly accumulated; however, rapid

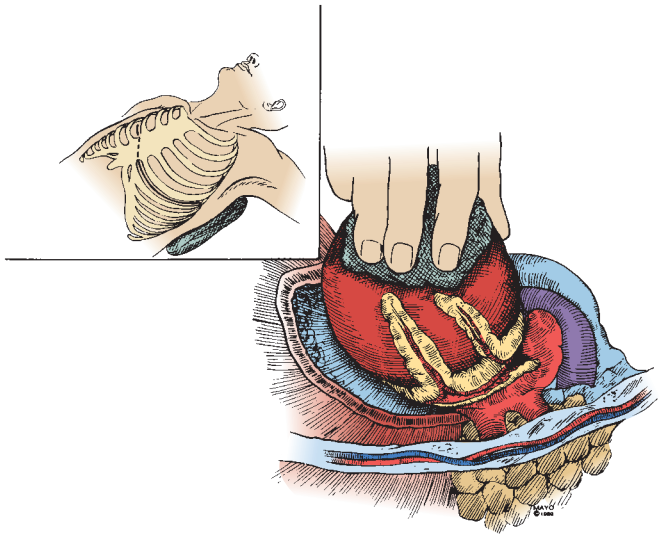


Fig. 24.69 Approach for pericardiectomy through a fifth left intercostal space for anterolateral thoracotomy. The phrenic nerves are preserved on pedicles. The lateral course of the phrenic nerves and the pericardial attachment make the phrenic nerves easily damaged during the removal of the pericardium. *(Reproduced with permission from Tuna IC, Danielson GK. Surgical management of pericardial disease.* Cardiol Clin. *1990;8:683.)*

fluid accumulation leads to cardiac tamponade. The two layers of the pericardium are joined at the level of the great vessels and at the central tendon of the diaphragm caudally, and a serous layer extends past these junctions to line the inside of the fibrinous sac (parietal pericardium). The vagus nerve, left recurrent laryngeal nerve, and esophageal plexus innervate the pericardium, along with sympathetic contributions from the stellate ganglion, first dorsal ganglion, and other ganglia. The lateral course of the phrenic nerve on either side of the heart is an important anatomic relationship because this nerve is encapsulated in the pericardium and thus can easily be damaged during pericardiectomy (Fig. 24.69). The pericardium is not essential for life, and pericardiectomy causes no apparent disability, but it has many subtle functions that are advantageous. Foremost, it acts to minimize torsion of the heart and reduces the friction from surrounding organs. In addition, the pericardium has also shown immunologic, vasomotor, paracrine, metabolic, and fibrinolytic activities.[306]

Acute Pericarditis

Acute pericarditis is common, but the actual incidence is unknown because it often goes unrecognized. It is generally self-limited with symptoms lasting 6 weeks. Acute pericarditis has many causes (Box 24.8), the most common of which is viral (30–50%).[307] Unfortunately, only 25% of cases are diagnosed with a defined cause.[308] Anesthesiologists encounter patients with acute pericarditis in the context of malignancy, MI, postcardiotomy syndrome, uremia, or infection when surgery is required, because symptoms are incapacitating and medical therapy has failed.

Acute pericarditis is characterized by fibrin deposits localized on the pericardial surface. A serous effusion may accompany the fibrinous inflammation. Consequently, the mesothelial cell layer is replaced by a fibrin membrane that has white blood cells scattered throughout. Pericardial fluid may suggest an infectious, neoplastic, or inflammatory cause.[307] Pericarditis occurs in approximately 20% of patients who suffer an MI, primarily within the first week.[309] A distinction is made between pericarditis that occurs during the first week and the Dressler syndrome, which usually appears 2 to 3 months after an MI. With acute pericarditis, pleuritic chest pain is described in the center of the chest, radiating to the back and left trapezius muscle. This

pain is more continuous than the intermittent pain of myocardial ischemia. Some degree of dyspnea may be present with acute pericarditis. Occasionally, the presentation of pericarditis may be right-sided heart failure because large and rapid accumulations of pericardial fluid will sufficiently increase intrapericardial pressure to obstruct right ventricular filling through the SVC and IVC, resulting in tamponade. Atrial arrhythmias may also occur.

In general, acute pericarditis can be differentiated from MI by the measurement of serum cardiac enzymes, but myocardial enzymes are sometimes found in the serum of patients with pericarditis. It is also common to observe the early onset of a low-grade fever that lasts for days to weeks and the presence of a friction rub after the onset of chest pain. Pericardial friction rub is pathognomonic of pericarditis but may be heard only intermittently. Early electrocardiographic changes typical of pericarditis are ST-segment elevation in two or three standard limb leads and in most of the precordial leads. ST-T wave elevation is often present but may be confused with MI (Fig. 24.70). Acute pericarditis generally results in diffuse ST-T changes, whereas an MI usually is associated with more localized ST-T changes. T-wave inversions follow the acute ST-segment abnormalities as pericarditis enters the subacute phase. Q waves usually do not appear during progression of electrocardiographic changes. The echocardiographic findings in a patient with suspected acute pericarditis are variable. A pericardial effusion may be present, the pericardium may be thickened, or it may appear completely normal. If an effusion is present, then cardiac tamponade must be excluded. If the pericardium appears thickened, then additional constrictive physiologic evidence should be sought (see later discussion). The chest roentgenogram may reveal a slightly enlarged cardiac silhouette with a pericardial effusion that indicates the effusion is at least 250 mL. A rapid accumulation of a small volume of pericardial fluid may also cause tamponade. Gradual fluid accumulation may lead to a liter or more of pericardial fluid without symptoms of cardiac tamponade. Pericardial fluid may also be found with CHF, valvular disease, or endocarditis. Pericardiocentesis may be performed in acute pericarditis, either to confirm the diagnosis or to relieve symptoms of cardiac tamponade. Pericardiocentesis is not without risk of complications, including but not limited to coronary artery or ventricular puncture. Echocardiographic evaluation of ventricular contractile function should occur before performing pericardiocentesis. If repeated aspirations are required for relief of tamponade, then a pericardial window or pericardiectomy may be necessary.

Detection of myocardial-directed serum antibodies in the Dressler syndrome and in postpericardiotomy syndrome suggests that these syndromes are immune-related responses. Postpericardiotomy syndrome

BOX 24.8 CAUSES OF ACUTE PERICARDITIS

- Idiopathic
- Infectious
  - Viral
  - Bacterial
  - Fungal
  - Parasitic
- Immunologic
  - Postmyocardial infarction (Dressler syndrome)
  - Postcardiotomy syndrome
  - Still disease
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Polyarteritis
- Neoplastic
- Radiation
- Traumatic
- Renal failure
- Drug induced

Reproduced with permission from Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart.* 2000;84:449–454.

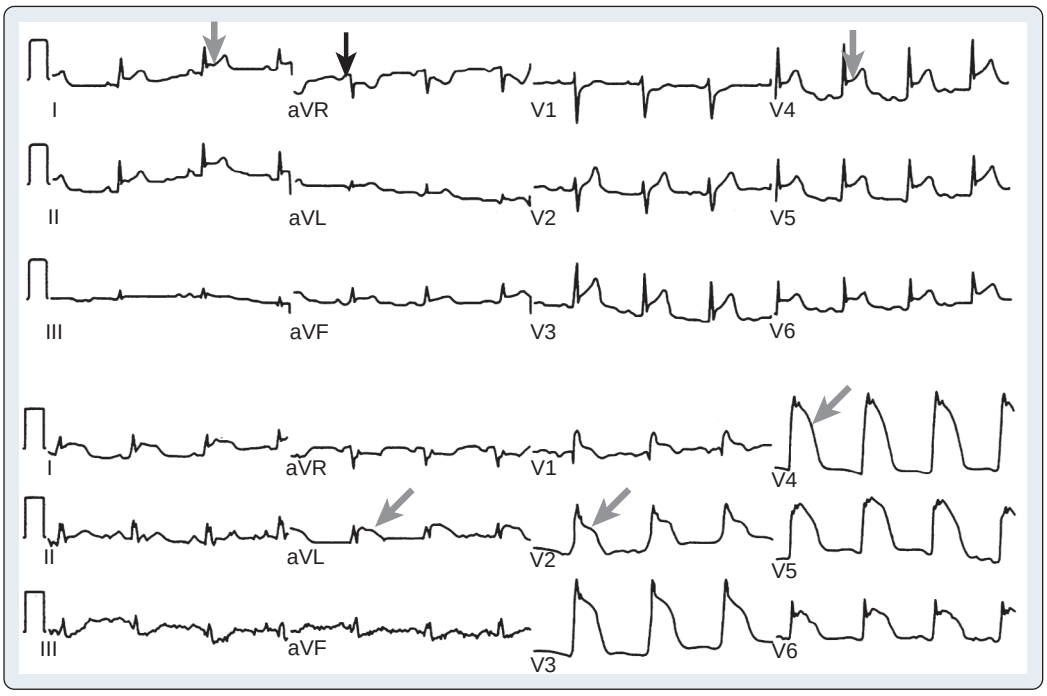


Fig. 24.70 Acute pericarditis: The upward concavity ST elevations in limb leads I, II, aVF, and aVL and in the precordial leads V3, V4, V5, and V6 *(gray arrows)* and the PR-segment elevation in aVR *(black arrow)* are noted. Acute myocardial infarction: The concavity downward ST elevation in leads I, aVL, V1, V2, V3, V4, V5, and V6 *(gray arrows)* indicate a large anterior myocardial infarction. *(Reproduced with permission from Aikat S, Ghaffari S. A review of pericardial diseases: clinical, ECG and hemodynamic features and management.* Cleve Clin J Med. *2000;67.)*

TABLE 24.9 Causes of Constrictive Pericarditis

Cause	*Percentage*
Idiopathic pericarditis	40
After coronary artery bypass grafting	30
Tuberculosis	10
Radiation induced	5
Collagen vascular disease	5
Others (malignancy, uremia, purulent)	5

Reproduced with permission from Kabbani SS, LeWinter MM. Diastolic heart failure. Constrictive, restrictive, and pericardial. *Cardiol Clin.* 2000;18:505.

consists of acute nonspecific pericarditis that usually begins between 10 days and 3 months after cardiac surgery or trauma. In a prospective study of 944 adult patients who underwent cardiac surgery, the incidence of postpericardiotomy syndrome was 17.8%, although the incidence has been reported as high as 50% of patients after cardiac surgery.[310]

Treatment of acute pericarditis consists of symptomatic relief and treating the underlying systemic illness. Symptomatic relief involves support, bed rest, and nonsteroidal antiinflammatory agents for analgesia. Left stellate ganglion block has been used to relieve unremitting pain.

Constrictive Pericarditis

CP is a dense fusion of the parietal and visceral pericardium that limits diastolic filling of the heart, irrespective of the cause. The changes in the pericardium can be due to scarring, induced by a single episode of acute pericarditis, or caused by a prolonged exposure to a recurrent or chronic inflammatory process. Historically, tuberculosis was a major cause of CP, but currently most cases (33%) are believed to be idiopathic.[311] The leading identifiable causes of CP are previous acute pericarditis, cardiac surgery, and mediastinal irradiation in developing countries.[312] Table 24.9 lists some of the causes of chronic CP. Idiopathic, neoplastic, postirradiation, or uremic pericarditis account for most cases of CP that require surgical intervention. Up to 18% of pericardiectomies are attributed to previous cardiac surgeries,[311] which may explain the increase in the number of cases of CP over the last 15 years.[313]

CP clinically resembles the congestive states of myocardial failure and chronic liver disease.[306] The most frequent physical signs are jugular venous distention, hepatomegaly, and ascites. Symptoms are nonspecific and progress over years unless the cause is radiation, cardiac surgery, or trauma that can, instead, develop over a period of months. The normal filling phases of the jugular venous pulse are shown in Fig. 24.71. Venous pressure waves in pericardial constriction are characterized by a prominent Y descent. Kussmaul sign (a paradoxic increase in venous pressure with inspiration) may be present. The elevation of systemic venous pressure accounts for some of the classic symptoms of CP, such as hepatic congestion and peripheral edema.[200] A significant paradoxic pulse occurs in only one third of patients with chronic CP.

Characteristic electrocardiographic changes are P mitrale (broadened P-wave), low QRS voltage, and T-wave inversion.[313] One fourth of patients have atrial fibrillation. Cardiomegaly demonstrated on chest roentgenogram is nonspecific, whereas pericardial calcification is sometimes appreciated (<30%),[312] although it is less common than in the past with the decreased incidence of tuberculosis. Although calcification is very specific for CP, it is not very sensitive. CT and MRI may demonstrate the typically thickened pericardium of CP; however, patients with surgically proven CP may have a normal-appearing pericardium with imaging tests in 28% of individuals.[314]

A comprehensive echocardiographic examination including two-dimensional and Doppler imaging is an essential part of the diagnostic workup and is often adequate for diagnosis. The two-dimensional findings may include a thickened pericardium, abnormal motion of the ventricular septum, IVC dilation, and flattening of the left ventricular posterior wall during diastole.[114] A key diagnostic finding in constriction is ventricular interdependence. Diastolic filling of the ventricles is reliant on each other, because the overall cardiac volume is fixed by the stiffened pericardium. With inspiration, intrathoracic pressure falls, as does the pressure in the pulmonary vasculature. The thickened pericardium prevents the transmission of this pressure decrease to the ventricles. Thus filling of the LV decreases just after inspiration and is due to the fall in pressure within the pulmonary vasculature. Because the intracardiac space is fixed, a decrease in filling pressure to the LV allows increased filling in the RV. The result is a shift in the ventricular septum into the LV during inspiration and an increase in hepatic vein diastolic flow.[114] With expiration, intrathoracic pressure increases, the pressure in the pulmonary vasculature increases, and left ventricular filling is augmented with a shift of the ventricular septum into the RV during diastole. Right ventricular filling is now decreased because of the positive intrathoracic pressure and flow reversals that occur during diastole in the hepatic veins. When several cardiac cycles are viewed consecutively, the ventricular septum appears to *bounce* between the LV and RV.

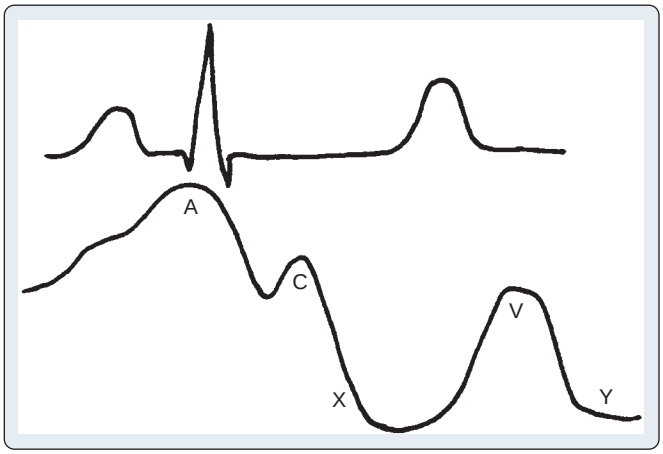


Fig. 24.71 Schematic depiction of normal jugular venous pressure waves in relationship to the electrocardiogram. The A wave is a result of atrial contraction; the prominent negative X descent occurs during ventricular systole and is a result of downward displacement of the base of the heart and tricuspid valve, as well as continued atrial relaxation. The small C wave, which interrupts the X descent, is probably due to the bulging of the tricuspid valve into the right atrium. The V wave represents right atrial filling while the tricuspid valve is closed. Finally, the Y descent occurs after opening of the tricuspid valve and during rapid inflow of blood from the right atrium into the ventricle. *(Reproduced with permission from Legler D. Uncommon diseases and cardiac anesthesia. In: Kaplan JA, ed.* Cardiac Anesthesia. *2nd ed. Philadelphia: Saunders; 1987:785.)*

Echocardiographic findings suggestive of CP include a respiratory variation of 25% or more of early mitral inflow velocity (E velocity), accompanied by expiratory diastolic flow reversals within the hepatic veins (Fig. 24.72).[315,316] These findings, however, are present in only approximately 50% of patients with constriction.[317,318] Respiratory variation of ventricular septal motion is also appreciated with M-mode imaging modality.[315,316] Tissue-Doppler imaging of the mitral annulus has become a valuable tool in the diagnosis of constriction. Under normal conditions, early diastolic mitral annular velocity (e′) is greater at the lateral annulus than the medial annulus. In CP, the medial annular velocity (e′) is often normal or increased (>8 cm/sec) and in excess of lateral annular velocity and has thus been termed *annulus reversus*.[315,316] In myocardial disease such as RCM, relaxation is impaired and the diastolic mitral annular velocity (e′) is low (<6 cm/sec).[315,316] Tissue-Doppler imaging can be a valuable tool in differentiating between restrictive and constrictive diseases, but no uniform acceptance of indices differentiates CP from RCM.[306] Even with Doppler echocardiography, one must be aware of the loading

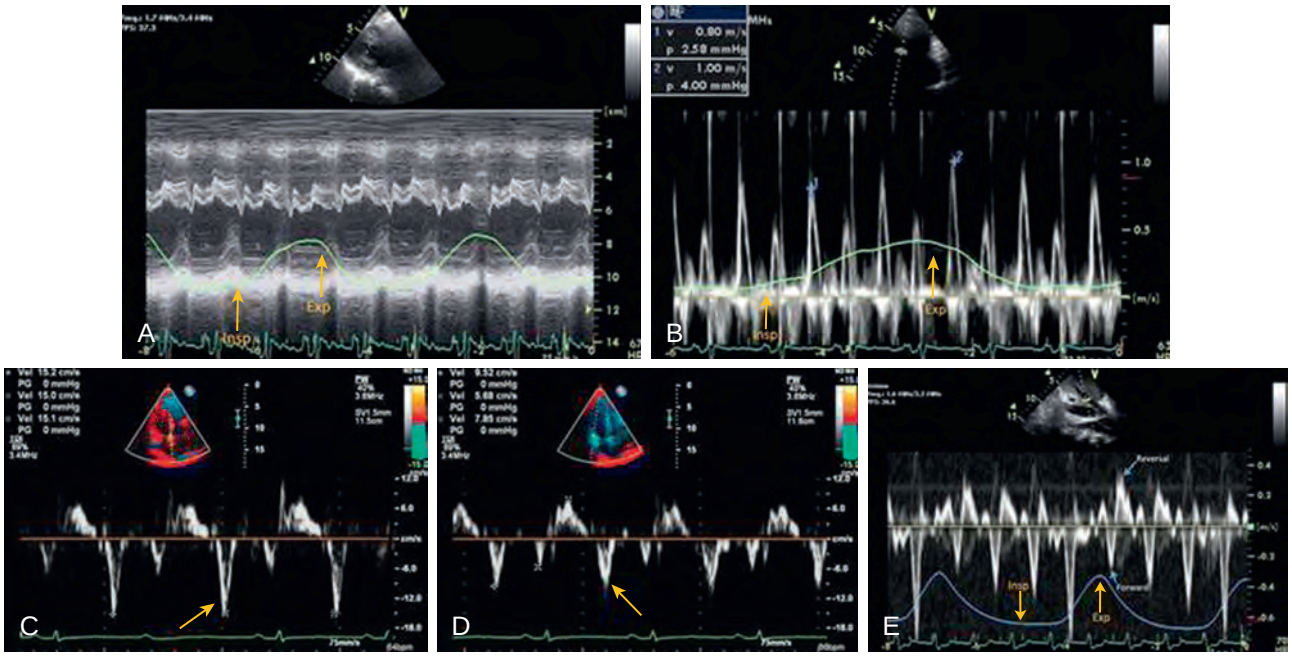


Fig. 24.72 Echocardiographic findings associated with constrictive pericarditis. (A) Transthoracic echocardiography parasternal long-axis M-mode demonstrates leftward septal motion with inspiration. (B) Pulsed-wave Doppler imaging at the mitral valve leaflets demonstrates inspiratory decrease and expiratory increase of early inflow velocity. (C) Medial and (D) lateral mitral annular tissue-Doppler images record increased early relaxation velocity (*e'*) with medial velocity exceeding lateral velocity. (E) Pulsed-wave Doppler within hepatic veins demonstrates flow reversal during expiration. *Exp,* Expiration; *Insp,* inspiration. *(Reproduced with permission from Welch TD, Oh JK. Constrictive pericarditis: old disease, new approaches.* Curr Cardiol Rep. *2015;17:20.)*

conditions and respiratory effort of the patient during the Doppler examination. Gated cardiac MRI is also often used in the workup for CP and allows for an assessment of pericardial inflammation and thickening, along with the characteristic abnormalities in septal motion and mitral inflow.[316] Invasive cardiac catheterization is still regarded as the gold standard for diagnosing CP; however, noninvasive techniques previously described often provide adequate diagnostic data.[316]

TEE is not tremendously helpful in patients undergoing pericardiectomy. When it is used, right ventricular function and the degree of tricuspid regurgitation can be evaluated before and after the procedure. However, remembering that the diagnosis of constriction relies on the Doppler findings in spontaneously breathing individuals is important. These findings are not validated in patients undergoing positive pressure ventilation, thus the surgical unit is not the correct place to confirm or refute a suspected diagnosis of constriction.

The hemodynamic changes of CP are primarily related to the isolation of the cardiac chambers from respiratory effects on thoracic pressure and a fixed end-diastolic ventricular volume.[312] The pericardium limits the filling of the LV during inspiration, which leads to increased filling in the RV because the pericardium is so noncompliant. With expiration, the opposite is observed as the LV is overfilled and the RV is limited. The limitation of right ventricular diastolic filling occurs when the cardiac volume approximates the pericardial volume, usually in mid and late diastole, and is characterized by the square root or dip-and-plateau sign of the right ventricular waveform (Fig. 24.73). Filling is limited by the noncompliant pericardium. The square root sign occurs because the constricting pericardium is essentially part of the ventricular wall. When the ventricle contracts, the pericardium is deformed similar to a spring. As diastole begins, the spring is released and the ventricle fills rapidly, decreasing the ventricular pressure and creating the dip of the dip-and-plateau wave. As cardiac filling approaches the limit set by the fixed pericardium, the plateau of the ventricular filling curve arrives. There is significant elevation of right atrial, left atrial, and ventricular filling pressures. Pulmonary artery

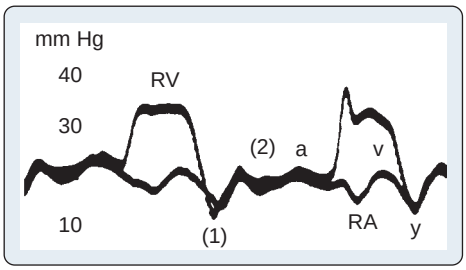


Fig. 24.73 Right ventricular *(RV)* and right atrial *(RA)* pressure tracings recorded with a fluid-filled system from a patient with chronic constrictive pericarditis. *a,* Atrial contraction; *v,* atrial filling; *y,* early ventricular filling. *(Reproduced with permission from Shabetai R. Pathophysiology and differential diagnosis of restrictive cardiomyopathy.* Cardiovasc Clin. *1988;19:123.)*

diastolic pressure, pulmonary capillary wedge pressure, and right atrial pressure are equal and elevated (*pressure plateau*) in CP and attributable to the limitation of the pericardium. Pulmonary artery systolic and right ventricular systolic pressures range from 35 to 45 mm Hg, although PAH is rare. Differences between CP and RCM have been previously reviewed.

Surgical Considerations for Pericardial Disease

Pericardiectomy is performed for recurrent pericardial effusion and CP refractory to conservative therapies. Pericardial dissection for effusive pericarditis is straightforward; however, pericardiectomy for CP is often a surgical challenge with an operative mortality of 5.9% to 11.9%[319] and 5-year survival rate of 78%.[320,321] The occurrence of tricuspid regurgitation may occur, similar to CP with signs of right-sided heart failure and volume overload. In fact, one fifth of patients undergoing surgical intervention for CP have significant tricuspid

regurgitation.[319] Unfortunately, surgical treatment of tricuspid regurgitation with CP has had no effect on long-term survival but also has not increased the risk of surgery. The presence of tricuspid regurgitation may identify a subset of patients with CP who have more advanced disease.

Persistent low CO immediately after pericardiectomy is a major cause of morbidity and mortality occurring in 14% to 28% of patients in the immediate postoperative period.[322] Examination of patients after pericardiectomy for CP found that a significant number of patients had abnormal left ventricular contractility and relaxation abnormalities, based on high-fidelity manometer measurements.[322] More importantly, this group was at a higher risk of operative and long-term mortality. These finding were in contrast to the accepted belief that the pericardium is the problem in these patients and the myocardium is normal. Determination of myocardial function is important as a marker of patient outcome and the need for inotropic support. Although patients with cardiac tamponade usually improve clinically once the pericardium is opened, improvement is not always apparent immediately after pericardiectomy for patients with CP. Noticeable improvement in cardiac function may take weeks; however, 90% of patients will experience relief of symptoms postoperatively.[311]

Median sternotomy provides excellent exposure and access for pericardiectomy, but thoracotomy in the left anterolateral position is also used. Opinions vary regarding the extent of pericardial resection for alleviation of cardiac constriction and the need for CPB. Total pericardiectomy was found to result in superior outcomes, compared with partial pericardiectomy in a retrospective review.[323] Removal of adherent and scarred pericardium to release both the RV and LV involves extensive manipulation of the heart and hemodynamic instability. The decision to use CPB is influenced by the surgeon's confidence in being able to achieve complete pericardial excision with acceptable hemodynamic stability. A more aggressive approach to pericardiectomy with CPB has increased over the years as survival has improved, and this trend may continue.[319] However, good results have been reported with and without CPB.[323] The use of CPB entails full heparinization and may exacerbate blood loss from the many exposed cardiac surfaces. Furthermore, prolonged CPB in debilitated patients contributes to early mortality associated with pericardiectomy. An especially high-risk group of patients undergoing pericardiectomy are those with postradiation CP. They not only suffer from the effects of radiation on the myocardium that may create a more sustained restrictive effect even after pericardiectomy, but they also suffer from radiation-induced pulmonary dysfunction.[319]

Anesthetic Considerations

Anesthetic goals for managing patients with CP for pericardiectomy include minimizing bradycardia, myocardial depression, and decreases in preload and afterload. Monitoring considerations include arterial and central venous pressure catheters. One femoral site should be reserved for femoral cannulation, if necessary, to emergently initiate CPB. PAC monitoring is often used because of the risk of low CO syndrome postoperatively. Low CO syndrome develops in a subset of patients with CP, irrespective of the approach or extent of pericardiectomy.[323] Low CO, hypotension, and arrhythmias (atrial and ventricular) are common during chest dissection. Because of limited and relatively fixed ventricular diastolic filling, CO becomes rate dependent. If myocardial function or heart rate is depressed, then ß-agonists or pacing will improve CO. Catastrophic hemorrhage can occur suddenly if the atrium or ventricle is perforated, necessitating adequate central venous access. Damage to coronary arteries may also occur during dissection; so careful monitoring of the ECG for signs of ischemia is prudent. Pericardiectomy via left anterior thoracotomy requires close monitoring of oxygenation because the left lung is severely compressed during dissection. Currently, the anesthetic technique is based on achieving early extubation similar to other cardiac surgical cases, assuming acceptable hemostasis and hemodynamic parameters.

Cardiac Tamponade

Cardiac tamponade occurs in a variety of clinical situations, most commonly secondary to malignancies or postpericardiocentesis in nonsurgical patients.[324] It is a continuum of physiologic changes that necessitate rapid diagnosis and treatment. Cardiac tamponade may be easily missed in the early stages as the signs and symptoms are often subtle until reaching a critical state. Decompensated cardiac tamponade is an emergency, requiring either immediate pericardiocentesis or surgical intervention.

Tamponade exists when fluid accumulation in the pericardial space dramatically increases intrapericardial pressure and limits filling of the heart. The rate of pericardial fluid accumulation, rather than the absolute fluid volume, is the determinate of tamponade sequelae. Patients with mild tamponade often remain relatively asymptomatic. One of the reasons for delay in the appreciation of tamponade is the tendency of clinicians to overestimate the sensitivity of clinical signs such as hypotension, pulsus paradoxus, and jugular venous distension.[325] In several studies, dyspnea is the earliest and most sensitive of symptoms to indicate tamponade,[325] and severe tamponade is accompanied by both dyspnea and chest discomfort.[306] If an ECG is obtained, then tamponade may show low-voltage QRS complex, electrical alternans (Fig. 24.74), and T-wave abnormalities. Sinus rhythm is usually present in tamponade. A chest roentogram requires at least 200 mL of fluid to accumulate in the pericardium before the silhouette, known as the *water bottle effect*, is seen.[327] The classic Beck triad of acute tamponade, consisting of (1) decreasing arterial pressure, (2) increasing venous pressure, and (3) a small, quiet heart, is only observed in 10% to 40% of patients.[327] Pulsus paradoxus (Fig. 24.75) may also be observed, which is a fall in systolic blood pressure of more than 10 mm Hg during inspiration, caused by a reduced left ventricular stroke volume that is generated by increased filling of the right-sided heart during inspiration. Pulsus paradoxus is not sensitive or specific for tamponade, because it may be present in those with obstructive pulmonary disease, right ventricular infarction, or CP. Pulsus paradoxus may be absent when left ventricular dysfunction, positive pressure breathing, atrial septal defect, or severe aortic regurgitation are present.

Hemodynamic monitoring may aid in the diagnosis of cardiac tamponade. As diastolic filling begins to disappear, the jugular venous pulse loses a prominent Y descent. A prominent X descent remains by the decrease in intrapericardial pressure that occurs during ventricular ejection. Eventually, the pericardial pressure-volume curve becomes almost vertical, causing any additional pericardial fluid to greatly restrict cardiac filling and to reduce diastolic compliance.[328] Ultimately, the right atrial pressure, pulmonary artery diastolic pressure, and pulmonary capillary wedge pressure equilibrate (Fig. 24.76). Equilibration of these pressures (within 5 mm Hg of each other) merit immediate action to rule out acute tamponade. Echocardiography is the current method of choice and the most reliable noninvasive method to detect pericardial effusion and exclude tamponade.

The major hemodynamic changes and compensatory mechanisms of tamponade are outlined in Fig. 24.77. Elevated intrapericardial pressure on the heart during the cardiac cycle is responsible for the hemodynamic changes of cardiac tamponade. Hemodynamic manifestations are primarily due to atrial rather than ventricular compression. Initially with mild tamponade, increased atrial and pericardial pressures limit diastolic filling. Although the intracardiac pressures are elevated with tamponade, the effective preload is greatly reduced, causing lower stroke volume and CO. To maintain CO, sympathetic reflexes are stimulated to increase heart rate and contractility.[313] The rising right atrial pressure also reflexively stimulates tachycardia and peripheral vasoconstriction. Blood pressure is initially maintained by systemic vasoconstriction, but CO begins to fall along with systemic blood pressure as tamponade progresses. Once venous pressure falls below pericardial pressure, the drop in systemic blood pressure is profound and risks inadequate coronary perfusion pressure.[328] This drop in pressure resembles hypovolemic shock and will respond to fluid

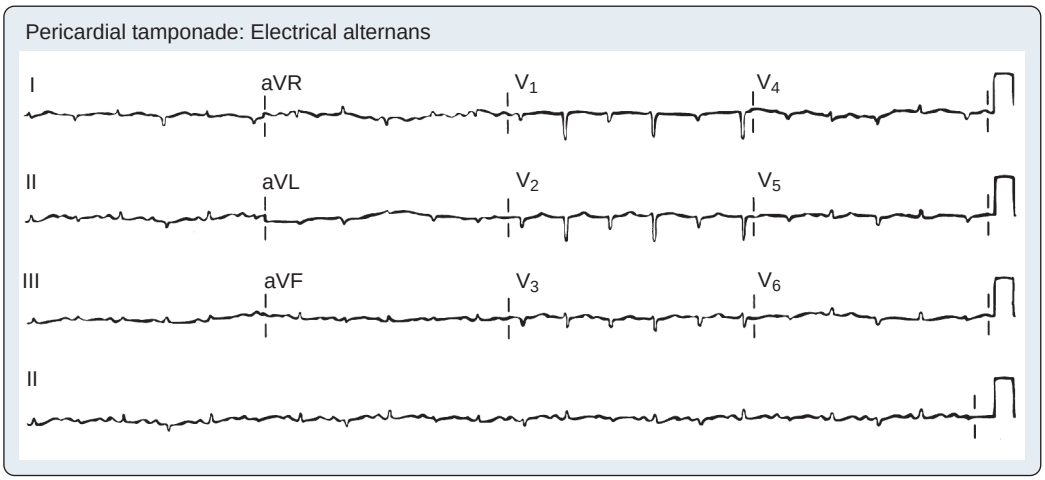


Fig. 24.74 Electrical alternans in pericardial tamponade is due to the swinging of the heart within the pericardial space. *(Reproduced with permission from Aikat S, Ghaffari S. A review of pericardial diseases: clinical, ECG and hemodynamic features and management.* Cleve Clin J Med. *2000;67:909; originally modified from Longo MJ, Jaffe CC. Images in clinical medicine Electrical Alternans.* N Engl J Med. *1999;341:2060.)*

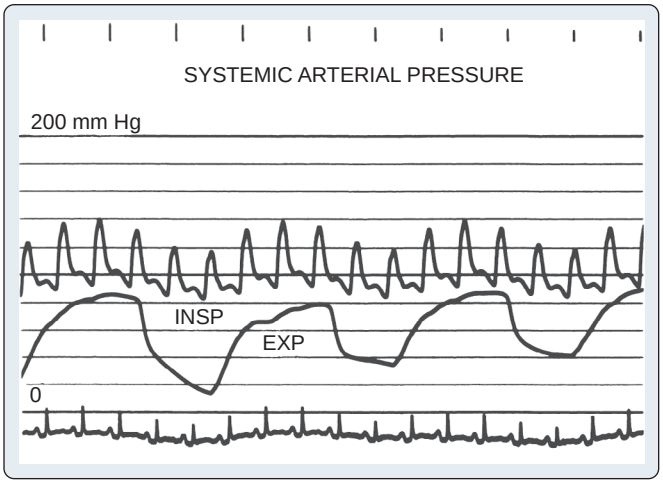


Fig. 24.75 Pulsus paradoxus. During inspiration *(INSP)*, arterial systolic pressure falls by more than 12 mm Hg. *EXP,* Expiration. *(Reproduced with permission from Reddy PS, Curtiss EI. Cardiac tamponade.* Cardiol Clin. *1990;8:628.)*

resuscitation initially, further confusing the diagnosis, but deterioration will soon occur if tamponade is not treated and can become fatal.[306]

Echocardiographic features of tamponade include an exaggerated motion of the heart within the pericardial sac in conjunction with atrial and ventricular collapse (Fig. 24.78).[313] Fluid accumulation greater than 25 mL will result in an anechoic and hypoechoic pericardial space throughout the cardiac cycle.[114] Specific two-dimensional echocardiographic findings that support cardiac tamponade include diastolic collapse of the RV, inversion of the RA during diastole, abnormal ventricular septal motion, and variation of ventricular size with the respiratory cycle.[329] Diastolic collapse of the right-sided chambers occurs because of pericardial pressure exceeding intracardiac pressure during diastole. Right atrial collapse is a specific finding during echocardiographic examination if it is present for more than one third of the cardiac cycle.

Normally, a decrease in intrathoracic pressure during inspiration is transmitted to the pulmonary vasculature and the intrapericardial and intracardiac spaces. In tamponade, this decrease in pressure during inspiration does not occur within the pericardium because of the presence of fluid. Thus the gradient for left-sided filling is decreased, and the early mitral inflow velocity (E velocity) will decrease with inspiration. In addition, right and left ventricular filling display interdependence, similar to that observed in constrictive pericarditis.

Echocardiography can also be used to direct needle or catheter placement for pericardiocentesis. Indeed, the bulk of pericardiocentesis is performed under echocardiographic guidance in some centers.[330] Removal of no more than 50 mL of fluid may be therapeutic for severe tamponade attributable to the steepness of the pericardial pressure volume curve. Typically, a pigtail catheter is left in the pericardial space for several days until drainage becomes minimal. Failure to recognize the insidious nature of tamponade and to anticipate the progression of hemodynamic changes may lead to a delay in using echocardiography to confirm the diagnosis and begin treatment. Examples include unstable hemodynamics after a penetrating chest injury or an abrupt change in chest tube drainage after cardiac surgery, which should prompt rapid assessment for tamponade and possibly emergency sternal opening.

Hemorrhagic tamponade in excessively bleeding patients after CPB is increasingly common and may be fatal. Depending on the diagnostic techniques, cardiac tamponade occurs in up to 8.8% of patients after cardiac surgery. However, almost 75% of postcardiac surgical tamponade occurs late (5–7 days) especially with patients who have undergone valve procedures in contrast to CABG surgery.[331] The causes of early tamponade are due primarily to coagulopathy, secondary to CPB, whereas the cause of late tamponade is multifactorial with aspirin and anticoagulant drugs increasing the risk of bleeding.[331] Persistently poor CO and hypotension with increased and equalized right and left atrial pressures strongly suggest tamponade. However, the multiple causes of hypotension in the postoperative cardiac surgical patient often complicate the diagnosis. The classic features of tamponade may be absent or blunted postoperatively.[332] Arterial hypotension, pulsus paradoxus, and elevated jugular venous pressures were absent in one series of cardiac surgical patients—30%, 40%, and 50%, respectively.[333] A delay in diagnosis contributes greatly to mortality in late cardiac tamponade.

After cardiac surgery, no single clinical, hemodynamic, or echocardiographic finding is sufficient to make a diagnosis of tamponade but requires consideration of the entire clinical picture.[334] Although echocardiography is capable of identifying the size of pericardial effusions postoperatively, it does not necessarily reflect their likelihood of causing tamponade. Most patients after cardiac surgery will have evidence of pericardial effusions, but fewer than 1% will develop

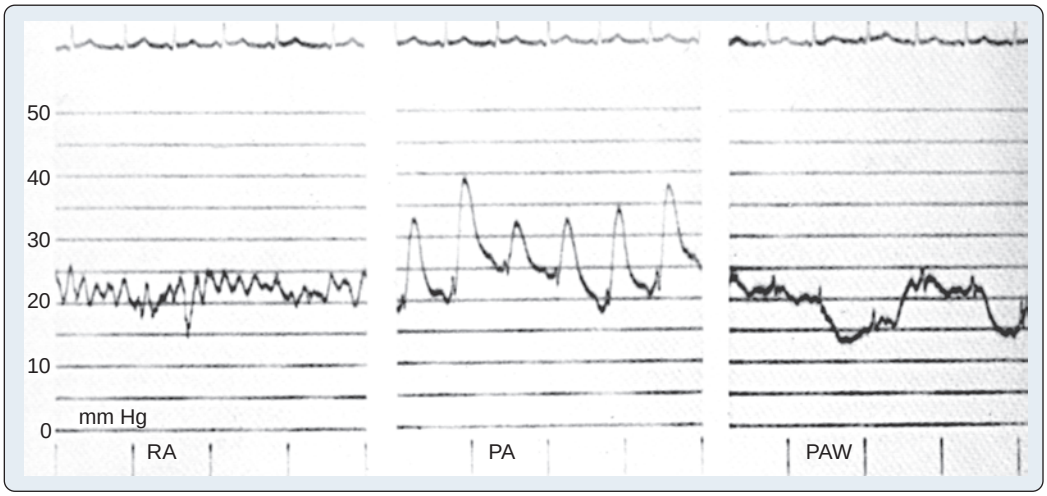


Fig. 24.76 Hemodynamic changes in cardiac tamponade. Equilibration of right atrium *(RA)*, pulmonary artery *(PA)* diastolic, and pulmonary artery wedge *(PAW)* pressures are demonstrated. *(With kind permission from Dr. Thomas J. Conahan.)*

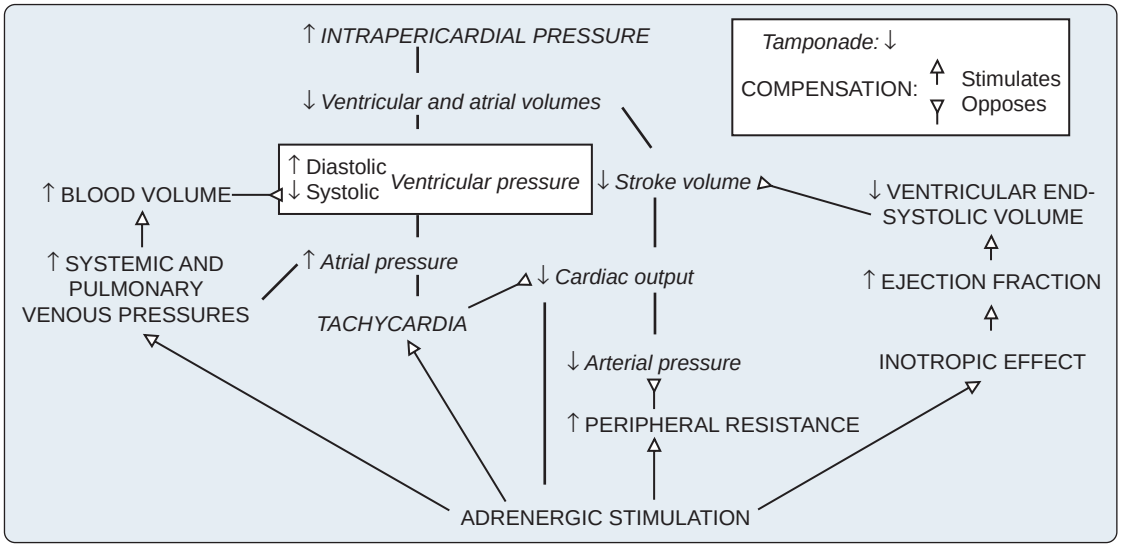


Fig. 24.77 Cardiac tamponade: relationships among major hemodynamic events and major compensatory mechanisms. *Simple arrows* represent tamponade sequences; *pointed arrowheads* represent stimulatory compensatory action; *blunt arrowheads* represent oppositional compensatory actions. *(Reproduced with permission from Spodick DH. Pathophysiology of cardiac tamponade.* Chest. *1998;113:1374; originally modified from Spodick DH, ed.* The Pericardium: A Comprehensive Textbook. *New York: Dekker;1997:182.)*

hemodynamically significant tamponade.[331] TTE may be inadequate in the postoperative cardiac surgical patient, secondary to interference from chest tubes, patient positioning, and other factors necessitating transesophageal echocardiographic consideration.

Pericardiocentesis is indicated for life-threatening cardiac tamponade in conjunction with fluid resuscitation to maintain adequate filling pressures. Hemodynamics improvement should ensue after pericardiocentesis. Although pericardiocentesis relieves the symptoms of tamponade, definitive therapy directed at the underlying cause should be pursued. Major complications of pericardiocentesis include coronary artery laceration, cardiac puncture, and pneumothorax. Tamponade attributable to hemorrhage in the patient after cardiac surgery requires immediate mediastinal exploration to determine the source of bleeding and to stabilize hemodynamics.

Anesthesia Considerations

Severe hypotension or cardiac arrest has followed the induction of general anesthesia in patients with tamponade. The causes include myocardial depression, sympatholysis, decreased venous return, and changes in heart rate that often accompany anesthetic medications and positive pressure ventilation. Resuscitation requires immediate drainage of pericardial fluid. Pericardiotomy via a subxiphoid incision with only local anesthetic infiltration or light sedation is an option. If intrapericardial injury is confirmed, then general anesthesia can be induced after decompression of the pericardial space.[335] Ketamine (0.5 mg/kg) and 100% oxygen have been used with local anesthetic infiltration of the preexisting sternotomy to drain severe pericardial tamponade.[336] Spontaneous respirations, instead of positive-pressure ventilation, will

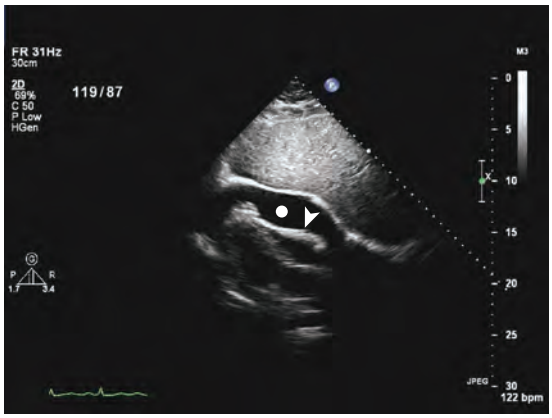


Fig. 24.78 Cardiac tamponade. Subcostal transthoracic view with the liver is seen at the apex of the image. The large echolucent space in the pericardium *(white dot)* is acute accumulation of fluid. Note the collapse of the right side of the heart *(arrowhead)* during diastole. This patient underwent urgent pericardiocentesis under the guidance of echocardiography.

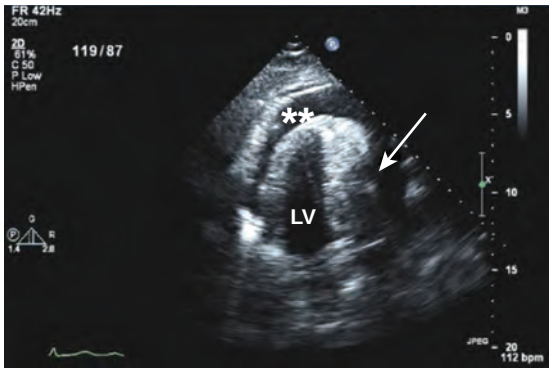


Fig. 24.79 Transthoracic echocardiogram in parasternal four-chamber view. A large echolucency in the pericardium *(double asterisks)* indicates a large pericardial effusion. The right side of the heart completely collapses in diastole *(arrow)*, indicating hemodynamically significant physiologic tamponade. *LV,* Left ventricle.

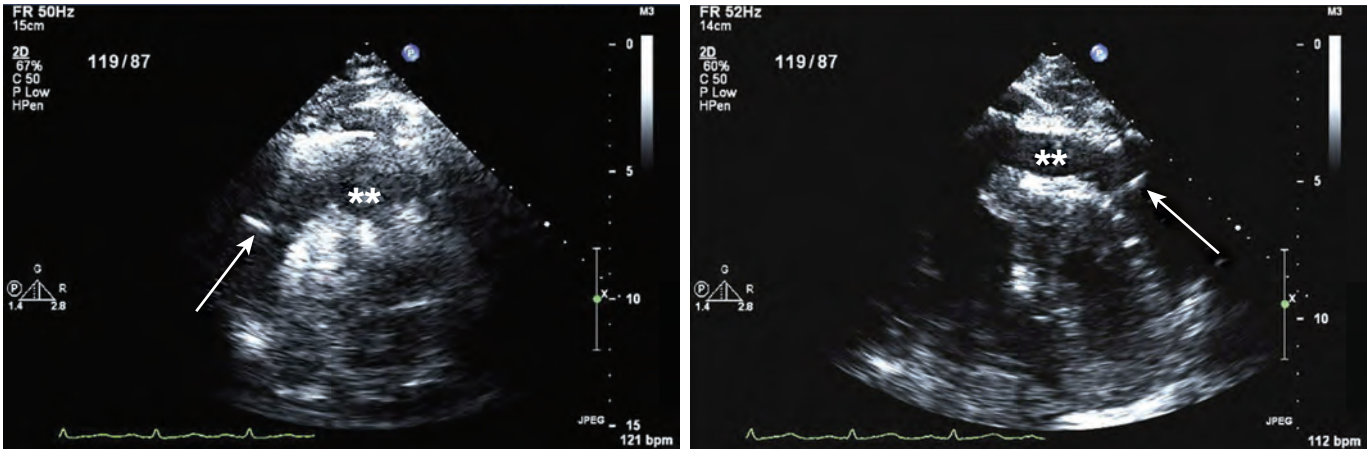


Fig. 24.80 Two transthoracic echocardiographic short-axis views of the heart show a needle *(arrow)* advanced into the pericardial space *(double asterisks)* under echocardiographic guidance.

support CO more effectively until tamponade is relieved. Correction of metabolic derangements is mandatory. Volume expansion is likely warranted in hypotensive patients.[337,338] Similar to CP, patients with tamponade have a relatively low and fixed stroke volume and thus rely on heart rate and adequate filling to maintain CO. Catecholamine infusions or pacing may be used to avoid bradycardia. In a dog model of pericardial tamponade, dobutamine infusion delayed the onset of lactic acidosis by maintaining CO and tissue oxygen delivery.[339]

Case Study 3: Tamponade Case Report

A 65-year-old man with a history of chronic venous insufficiency was hospitalized for a venous stasis ulcer that ultimately required skin grafting. On the day of his planned discharge, he was found to have multiple pulmonary emboli and a large lower extremity deep venous thrombosis. Anticoagulation was initiated, a filter was placed in the IVC, and lower extremity venous catheters were placed for catheter-directed thrombolytic therapy. Two days later, mechanical extraction of the lower extremity thrombus was undertaken without any known complications.

On return to his hospital room after the thrombus extraction, the patient quickly became hemodynamically unstable. He received intravenous fluid administration, however, quickly requiring intubation with mechanical ventilation for respiratory distress. Cardiac arrest resulted, necessitating cardiopulmonary resuscitation and epinephrine administration. An emergent TTE revealed a large pericardial effusion (Fig. 24.79).

Because of the urgency of the situation, a bedside pericardiocentesis was undertaken using echocardiographic guidance (Fig. 24.80). A large amount of blood was removed from the pericardium, and the effusion appeared to resolve (Fig. 24.81). The patient's hemodynamics rapidly improved. He required a period of mechanical ventilation but was ultimately discharged from the hospital in good condition.

Combined Carotid and Coronary Artery Disease

Patients with concomitant symptomatic coronary and carotid disease are few but a significantly higher risk group than either group of patients with carotid or coronary disease alone.[340–342] CABG is proven therapy for ischemic heart disease.[343,344] Advancements in myocardial preservation, CPB technology, and perioperative care over the last three decades have reduced morbidity and mortality associated with cardiac surgery. However, stroke remains the major noncardiac complication of CABG affecting the quality of life, economic well-being,

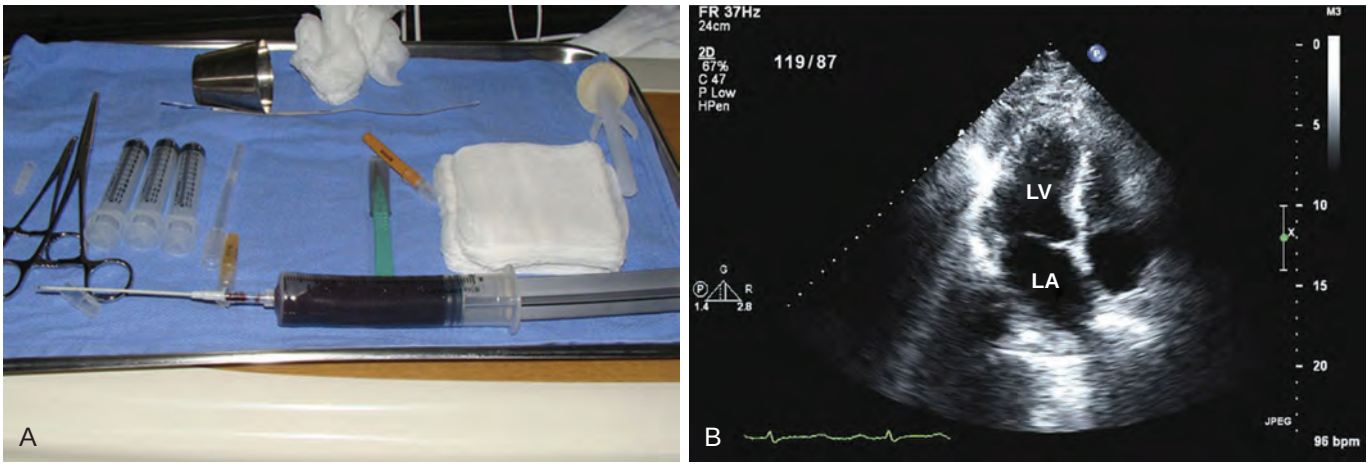


Fig. 24.81 (A) The catheter and syringe that are used for the pericardiocentesis are shown. (B) Transthoracic echocardiogram parasternal four-chamber view shows resolution of the pericardial effusion. The right side of the heart is now well filled in diastole. *LA*, left atrium; *LV*, left ventricle.

and survival. Although the overall incidence of stroke associated with CABG is approximately 2%, the role of extracranial carotid disease to the occurrence of stroke remains indeterminate.

The combination of carotid endarterectomy (CEA) and CABG surgery was first proposed by Bernhard and associates[345] in 1972 to reduce morbidity and mortality from coexistent carotid and coronary disease. Renewed interest in this approach now stems from recent controlled trials that demonstrate the benefits of isolated CEA for both symptomatic and asymptomatic severe carotid stenosis.[346] From 2000 to the end of 2004, 27,084 the combined CEA-CABG procedure was performed according to the Nationwide Inpatient Sample database.[347] According to the same database, the proportion of combined CABG and CEA procedures rose from 1.1% to 1.58% of all CABG surgeries performed from 1993 to 2002.[348] As the population ages, the number of patients with carotid bifurcation stenosis greater than 70% will continue to increase. The result is more patients with combined carotid and coronary disease[346] but with no consensus regarding their treatment. A large multicenter, randomized trial will be necessary to resolve the management of these patients. Unfortunately, the complexities of such a study with the heterogeneity of patients, varying degrees of coronary and carotid disease, and differing institutional preferences for carotid revascularization decrease its likelihood.

Neurologic injury associated with CPB is largely embolic in origin,[349] causing cerebral hypoperfusion and ischemia. Emboli originate primarily from aortic cannulation, aortic cross-clamp release, and cardiac manipulation based on transcranial Doppler ultrasonography. Less common causes of cerebral emboli are left ventricular thrombus and air. However, the cause of stroke after CABG surgery is multifactorial. Univariate analysis of systematic review of stroke associated with the CABG procedure has identified the following risk factors for stroke: carotid stenosis of 80% or more, carotid occlusion, prior stroke or transient ischemic attack, peripheral vascular disease, postinfarction angina, female, prolonged duration of CPB, age (older), previous CEA, diabetes, smoking, hypertension, left main disease, and carotid bruit.[350–352] Carotid bruits may be present in 9.93% of patients undergoing CABG surgery and increases the risk of stroke by a factor of four. Differentiating significant stenosis by auscultation is unreliable.[353] Carotid bruits may be audible with minimal carotid stenosis and silent with a carotid lumen of 1 to 2 mm in diameter. The preexisting presence of subclinical ischemia and cerebral atherosclerosis on MRI or angiography are independent predictors of stroke in CABG patients.[354,355] Atheroma of the arch and ascending aorta were another independent risk factor for stroke in CABG patients.[356] The combination of ultrasonography of the carotid arteries and risk factors are very predictive of patients likely to have a stroke in association with CABG surgery (Fig. 24.82).

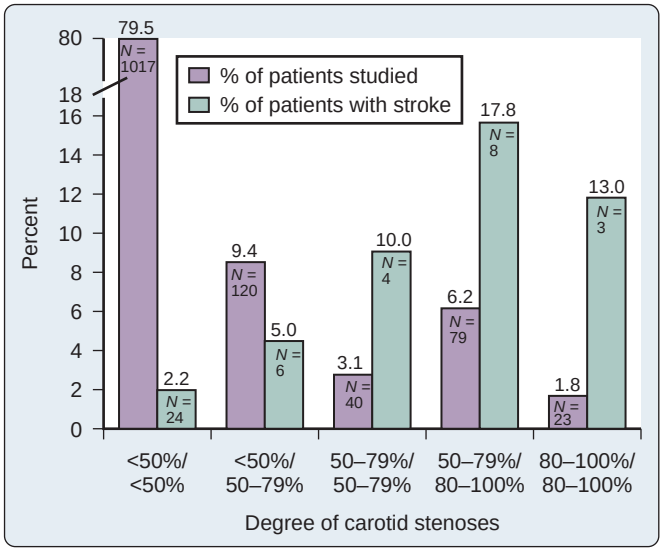


Fig. 24.82 Both the prevalence of carotid stenoses in patients undergoing noninvasive carotid screening and the occurrence of stroke by degree of carotid stenosis are illustrated. *(Reproduced with permission from D'Agostino RS, Svensson LG, Neumann DJ, et al. Screening carotid ultrasonography and risk factors for stroke in coronary artery surgery patients.* Ann Thorac Surg. *1996;62:1714–1723.)*

Carotid artery disease should be considered in all individuals with ischemic heart disease. Severe carotid disease increases the risk of stroke with CABG surgery by a factor of four.[350,357] Early estimates of the incidence of hemodynamically significant carotid stenosis in patients needing the CABG procedure varied between 2% and 16%.[358] Faggioli and associates[359] confirmed the occurrence of severe carotid disease, defined as carotid stenosis greater than 75% in patients more than 60 years of age, to be 11% in patients that underwent CABG surgery. More recently, noninvasive ultrasonography has shown the percentage of persons with severe carotid and coronary disease to be higher than prior studies.[352] Patients undergoing CABG surgery were prospectively evaluated for carotid disease with ultrasonography, and approximately 20% had significant carotid stenosis unilaterally or bilaterally. Large systematic reviews of stroke and the CABG procedure point to a relationship between an increased incidence of stroke with higher degree of carotid stenosis.[350,357,360] The frequency of stroke with cardiac surgery was less than 2% in those with no carotid disease

(0–49% stenosis), increased to 3% with asymptomatic disease (unilateral stenosis 50–99%), 5% in those with bilateral stenosis (50–99%) and 7% to 11% in those with carotid occlusion. These data would support the potential benefit of CEA in either a staged or combined manner with CABG surgery to reduce the chance of stroke in these patients.

It is generally accepted that patients with symptomatic carotid disease undergoing CABG surgery are at a significantly increased risk for stroke and merit revascularization of the carotid and coronary disease as a combined or staged procedure.[352] However, the management of unilateral or bilateral *asymptomatic* carotid stenosis continues to evolve. Asymptomatic severe carotid stenosis is a risk for ipsilateral hemispheric stroke with cardiac surgery and CPB,[342,352,361] but identifying it in the asymptomatic patient hinders determination of this *true* risk assessment. This is important, because isolated CEA was shown to not only reduce the risk of stroke in patients with symptomatic carotid stenosis greater than 70%,[348] but it also was shown to reduce the risk of stroke in asymptomatic patients with severe high-grade carotid stenosis.[346] With the incidence of neurologic injury ipsilateral to the carotid artery encompassing 40% to 50% of strokes associated with cardiac surgery,[362] prophylactic measures to prevent strokes merit consideration.[347]

In most patients, the degree of either carotid or coronary disease will not limit the ability of the patient to undergo the higher priority procedure, CEA or CABG surgery, safely. In contrast, treatment options for those with active concomitant carotid disease and ischemic heart disease are a combined, synchronous, or staged approach. The staged approach does not include CEA and CABG surgery in one anesthetic event but two separate ones. Many surgeons support the combined CABG-CEA procedure, whereas others believe the risk exceeds the benefit.[360,363]

The sequence of CEA and CABG surgery is important regarding the outcome with either the combined or staged approach. Since 1989 when Hertzer and colleagues[340] found a lower incidence of stroke when CEA was performed before rather than after the CABG procedure as a combined approach in one of the few randomized, prospective trial involving this issue, CEA has been commonly performed first. Rizzo and associates[342] confirmed the benefit of performing CEA before CABG surgery by reporting the risk of stroke may reach 14% if the CABG procedure is performed before CEA. More recently, a systematic review of synchronous and staged CEA and CAGB procedures demonstrated that reverse staged procedures (CABG surgery first and then CEA) were associated with the highest ipsilateral and global stroke rate, compared with staged or combined procedures performed with CEA first.[360] Less than 10% of staged procedures are currently performed as CABG surgery and then CEA.

The sequence of performing CEA and CABG surgery is more common than the reverse order but is not without its disadvantages. Myocardial morbidity may reach 20% if CEA is performed before CABG surgery in a staged approach.[342] MI has been recognized for years as the major cause of mortality with isolated CEA. Surgically incorrectable coronary disease may exist in 40% of those undergoing CEA.[358] CEA in patients with severe, symptomatic coronary disease has been associated with a 17% and 20% incidence of MI and mortality, respectively. Most importantly, 20% of the MIs accounted for 60% of deaths.[351] A recent systematic literature review of the combined and staged CEA and CABG procedures confirmed that the incidence of MI was highest if the CEA was performed before the CABG surgery (6.5%) rather than after the CABG procedure (0.9%).[360] Differences in the standards for reporting MI over the last 30 years challenge the accuracy of the incidence of MI after CEA being 6.5%. Without well-defined cardiovascular risks for either the staged or combined approach, the correct decision for the patient is difficult.

The recommendation to perform a combined or staged CEA and CABG surgery for those with concomitant carotid and coronary disease continues to evolve. In a prospective trial, Hertzer and colleagues[340] found a lower incidence of perioperative stroke in with combined rather than staged CABG surgery and CEA. A comparative analysis of studies that included 50 patients or more that underwent the CABG surgery with unoperated major carotid disease found the risk of stroke averaged 5.5% for patients with unoperated carotid disease and the CABG surgery versus 3.1% for patients who underwent combined procedures. However, the role of carotid disease as a direct cause of perioperative stroke after an isolated CABG procedure is not always clear. It is relatively simply to diagnose the likely cause of a perioperative stroke associated with isolated CEA.

Individual studies involving concomitant carotid and coronary disease suffer from great variation in the definition of a stroke, selection bias, patient demographics, and surgical techniques that limit the widespread application of study recommendations. To make up for these deficiencies, large systematic reviews of the studies have attempted to provide insight into the optimal practice of concomitant carotid and coronary disease. A review found no advantage in outcomes for staged or combined procedures.[360] Staged procedures had lower rates of stroke (2.7% vs 4.6%) and death but were not statistically significant. Others have not only found combined surgery unnecessary but potentially detrimental. Gerraty and associates[363] studied prospectively a series of 358 patients undergoing peripheral vascular procedures or CABG surgery that underwent ultrasonography preoperatively. If the carotid stenosis was asymptomatic, then the risk of stroke was so low that it did not merit prophylactic CEA. An audit of one institution's last 5 years with the combined CEA-CABG procedure for asymptomatic carotid stenosis (>50%) found no perioperative strokes at 30 days postoperatively in the 61 patients who had unilateral stenosis that were not revascularized. This finding led to an institutional halt to the performance of combining the procedures.[362] Unfortunately, their studies can do no more than challenge the hypothesis that a combined or staged CEA and CABG surgery will reduce the risk of stroke in asymptomatic, unilateral carotid disease.

A major concern for those who do not support a combined or staged approach for carotid and coronary disease is that some data demonstrate a stroke rate for the combined CEA-CABG procedure of approximately twice the stroke rate of each procedure alone.[342] Safety of the combined CEA-CABG procedure was recently evaluated in 277 patients (3.34%) with carotid stenosis of greater than 70% unilaterally or bilaterally who underwent some form of the combined CEA-CABG procedure, compared with a control group of 8000 isolated CABG surgeries.[364] No statistical difference was found in the mortality or incidence of stroke of those undergoing combined procedures, as compared with those undergoing CABG surgery alone. The increased risk of stroke or even death found in some studies regarding the combined CEA-CABG procedure may be related to the overall severity of the atherosclerotic disease and the likelihood of embolic plaque in the aorta in this particular population of patients. Ricotta and associates[341] were able to define a stroke model through multivariate logistic regression analysis in patients undergoing CABG surgery without carotid stenosis greater than 80%. The risk factors for stroke were age, CPB duration, aortoiliac disease, electrocardiographic evidence of left ventricular hypertrophy, and an extensively calcified aorta. An examination of patients who underwent the combined CEA-CABG procedure revealed three of the four risk factors for postoperative stroke. Although the stroke rate for the combined group was 3.9%, compared with 1.7% for control subjects, the rate was not different from the expected stroke risk based on the inherent risk factors of the patients. One could conclude that patients with combined disease are at higher risk for stroke not attributable to the combined CEA-CABG procedure but from the individual preoperative risk factors. The high-grade carotid disease may be a marker for higher cardiovascular morbidity in these patients and less related directly to the carotid disease.

The risk of mortality and morbidity associated with the combined CEA-CABG procedure was also compared with patients undergoing an isolated CABG surgery in New York state for a control group.[346] Surprisingly, once propensity scores could be matched between isolated CABG surgeries and the combined CEA-CABG procedure, no significant differences were found in the occurrence of stroke, MI, or death between the combined and the isolated CABG groups. Another

important factor in looking at patients for combined procedures is that although, as a group, the mortality may be higher in the combined procedure, compared with an isolated CABG surgery, the risk for the patients vary greatly within their own groups.[364] In a comparison of isolated CABG surgery with the combined procedure, the stroke, mortality, and MI rate was very low in patients who had either unilateral or bilateral carotid stenosis, but those with previous stroke and more advanced age or contralateral internal carotid artery occlusion were at a significantly higher risk of stroke, mortality, and MI, compared with the other patients undergoing the combined procedure.

In conclusion, the intrinsic risk factors of patients who undergo combined procedures contribute more to postoperative stroke than the addition of CEA. The important issue is that the data indicate that combined procedures can be safely performed without an increase in complications attributable to the combination of procedures.

The use of carotid artery stenting (CAS) has gained popularity in recent years as a substitute for CEA in a staged approach but currently only represents a small part of prophylactic carotid revascularization (3.3%), compared with CEA for patients scheduled for CABG surgery.[347] In a comparison with the combined CEA-CABG procedure using a Nationwide Inpatient Sample database including 5 years of patients, the postoperative stroke rate for CAS and CABG surgery was significantly less (2.4%), compared with CEA and CABG surgery (3.9% $P < 0.001$) but no difference in the incidence of death. It was significant that symptomatic patients undergoing both prophylactic procedures before cardiac surgery reported a fivefold increase in stroke associated with CAS and CABG surgery versus CEA and CABG surgery. When CAS was used as the only form of prophylactic treatment of carotid stenosis before CABG surgery in 52 patients in a staged manner, the combination of minor stroke, major stroke, and death rate for this study was 19.2%.[365] Increased stroke rates with CAS and CABG surgery may be attributable to inadequate anticoagulation without clopidogrel to minimize postoperative bleeding after the CABG procedure. The combined CAS-CABG procedure has been performed with an acceptable stroke and death rate if the patient is neurologically asymptomatic; however, Timaran and associates[347] found a fivefold increase in the risk of CAS with CABG surgery for neurologically symptomatic patients, compared with CEA.

A benefit of CAS is that myocardial events may occur less frequently than CEA, perhaps because CAS can be performed with conscious sedation and is less invasive. A serious disadvantage with CAS is the need for multiple antiplatelet therapy and an occasional hemodynamic depression associated with CAS that may limit its role in those with unstable coronary artery disease. Complications from stenting can be as high as 5.7%, and the delay in CABG surgery may be responsible for deaths that occurred; consequently, a more frequent future use of CAS may depend on additional studies. It may be that CAS and CABG surgery will necessarily be less risky if performed as a staged procedure instead of a combined one.

Anesthetic Considerations

Anesthetic management of patients with carotid and coronary disease must provide optimal conditions for the brain and myocardium. Beyond the routine monitoring for cardiac surgery, electroencephalography or other modalities to assess neurophysiologic integrity are useful but have a high false-positive rate. For the anesthesiologist, it is helpful to know that the majority of strokes cannot be ascribed to an adverse intraoperative event such as hypotension or low flow.[350] However, it is more difficult to differentiate a *true* stroke from other states of temporary neurologic impairment associated with CABG surgery, such as heavy sedation, residual muscle weakness from a paralyzing agent, or encephalopathy secondary to cerebral edema. By using general anesthesia for CEA, clinical methods to determine neurologic integrity are delayed, as well as a delay in treatment. In contrast, the use of mild sedation with local anesthesia for CEA has proven to be a more reliable means to detect intraluminal shunting during CEA than other measures of neurologic testing.[366] The sensitivity and specificity of CEA with local anesthesia to detect neurologic deficits has been established. The use of a local anesthetic for CEA in the combined procedure has proven to be valuable in reducing exposure to anesthesia and reducing shunt-related complications, allowing repair with less risk of damage.[367] The use of local anesthesia for the CEA instead of one continuous general anesthetic has become more popular in recent years. The added ability to identify the timing of the neurologic insult may prove valuable, compared with general anesthesia. This is especially true as the neurologic examination in the conscious patient is more reliable than other methods such as stump pressure and electroencephalography. However, anxiety and pain must be controlled to minimize myocardial ischemia during CEA with local anesthesia.

Mean arterial pressure should be maintained in the middle-to-upper normal range without large increases in afterload or heart rate. Normocapnia is recommended. Techniques often used during anesthesia for cerebral protection such as barbiturates, inhalation anesthetics, benzodiazepines, or propofol to decrease cerebral metabolic rate have not been proven beneficial in clinical trials. Attempts to provide cerebral protection should not be used at the expense of myocardial perfusion and function. Usually, if the CEA is performed before CABG surgery, then the site of the CEA will be left open until the cardiac surgery is completed to ensure that bleeding at the site of the CEA is minimal.

Early extubation is desirable to allow earlier neurologic evaluation in combined cases. Fast-track anesthetic management to achieve early extubation is routine. Prompt tracheal extubation after cardiac surgery with CPB may be accomplished with various anesthetic agents. Short-acting opioids have been characterized as achieving more rapid extubation than fentanyl.[368] However, Engoren and colleagues[369] found no difference in the time to extubation with sufentanil or remifentanil, compared with fentanyl with the median time to extubation of 4.75 hours, 3.90 hours, and 2.78 hours, respectively. The combination of remifentanil and propofol was associated with mean extubation times of 163 minutes after arrival in the ICU.[370]

Extubation in the surgical unit is possible with high-thoracic epidural,[371] but early risks of hypothermia, bleeding, and hemodynamic instability may outweigh any benefit of prompt neurologic examination. Furthermore, the need for rapid institution of CPB during an awake CEA may prove challenging. Another possibility is the use of general anesthesia for the CEA, followed by a wake-up test,[372] to allow for the evaluation and treatment of any apparent neurologic injury before initiating CPB. This approach may be more feasible in the low-risk CABG patient who is less likely to have more labile hemodynamics upon waking. Aggressive vasoactive management is frequently required to treat hypertension and tachycardia, resulting from reduced opioids. Shorter-acting muscle relaxants than pancuronium have also been considered to shorten the duration of intubation; however, a large multicenter trial of more than 1100 patients undergoing CABG surgery did not demonstrate a difference in the duration of mechanical ventilation with either vecuronium or pancuronium and a fast-track anesthetic regimen.[368] Postoperatively, hypertension should be aggressively treated to avoid hyperperfusion syndromes leading to transient seizures or intracerebral hemorrhage and to avoid exacerbating bleeding at the site of the CEA.

Coronary Arteriovenous Fistula

Coronary arteriovenous fistula is a rare anomaly that frequently has a silent clinical course. It is an abnormal communication between a coronary artery and another cardiac chamber or venous structure, bypassing the myocardial capillary network. Common sites include coronary sinus, cardiac vein, pulmonary artery, SVC, pulmonary vein, or any one of the cardiac chambers. The incidence in the overall population is 0.002%.[373] Coronary artery fistula is the most common significant coronary artery anomaly and occurs in 0.3% to 0.8% of angiographic series.[374] Coronary arteriovenous fistula is usually congenital but may also occur from acquired (coronary atherosclerosis, Takayasu arteritis), traumatic, or iatrogenic causes. Interestingly, 10% to 30% of

patients with coronary fistulae may have another congenital anomaly such as tetralogy of Fallot, atrial septal defect, and partial anomalous pulmonary venous connection. It is not gender specific. Most congenital arteriovenous fistulas (60%) involve the right coronary artery, are small, and have no clinical significance. The left coronary artery is the site of the fistula in 35% of cases, although more recent studies have suggested that asymptomatic coronary fistulas originate from the left coronary system.[375] Multiple coronary fistulas occur in 5% of patients.[376] The most common distal connection of the fistula with the right coronary artery is the RV that represents 41% of the distal fistula sites. Low-pressure structures are the most common connections for coronary fistula with left-sided connections rarely occurring.[373] Most fistulas are single connections. The most proximal part of the fistula does develop some aneurysmal dilation and is often up to three times the normal diameter of the coronary.[375]

The clinical importance is generally associated with adulthood during which larger fistulas cause significant left-to-right shunts and CHF. Fistulas that connect to the left side do not shunt but cause an effect similar to mitral regurgitation. However, finding a degree of shunting significant enough to see an oxygen step-up effect during right-sided catheterization is rare. Fifty percent of patients with large fistulas develop complications.[373] The most common symptom is dyspnea that occurs in 30% of patients. Most adults are thought to be asymptomatic, but more recent reports suggest that nearly 50% are symptomatic at the time of presentation. The average age of the patient with symptoms is 18 years. Other problems that may lead to the diagnosis are arrhythmias, infective endocarditis, and myocardial ischemia. Usually, myocardial blood flow is not compromised because the shunt is so small, but coronary arteriovenous fistulas may cause angina pectoris by stealing blood from the normal coronary circulation. Usually, this occurrence is limited to exercise.[377] Additional complications of coronary fistulas, such as thrombosis, embolization, PAH, aneurysmal dilation of the involved vessel and even sudden death, may occur in patients diagnosed at later ages. Coronary fistulas rarely lead to aneurysmal rupture. Coronary arteriovenous fistulas can occur after a penetrating injury to the chest and exhibit symptoms of pericardial tamponade.

A continuous murmur with diastolic accentuation suggests an arteriovenous fistula. The murmur is continuous in a crescendo-decrescendo manner that persists through both systole and diastole. The murmur does not peak at the second heart sound, as do most of the other continuous murmurs. The murmur is the loudest at the site of entry into the heart for the fistula. Discovery of a continuous murmur along the upper left sternal border after CABG surgery is an indication for angiography to verify the proper placement of a saphenous vein graft into a coronary artery. Angiography is useful to differentiate this condition from other causes of continuous murmurs, such as patent ductus arteriosus, VSD, and atrial septal defect. Many of these fistulas are found incidentally during angiography. If the coronary artery is significantly enlarged, then echocardiography may be diagnostic. TEE is useful to identify drainage sites of a coronary arteriovenous fistula. More recently, MRI and a CT angiogram have contributed to the diagnostic process, because although angiography is the gold standard for imaging the coronary arteries, it may not provide the course and relationship to other structures as accurately as MRI and CT angiography.[374]

The majority of small symptomatic fistulas do not require intervention.[377] Often with infants who do not demonstrate CHF, medical management may reduce symptoms and, with growth, the size of the fistula and shunt will become smaller and less symptomatic. The natural history of these fistulas is variable. Spontaneous closure has been reported but is very rare and mostly in infants.[373] In some asymptomatic patients, the size of the shunt may reach a pulmonary-to-systemic flow (Qp:Qs) ratio of 1.5 but rarely more than 2, leading to severe fluid overload.

Management is controversial, in part, because treatment is based on anecdotal reports or small case series. Some will start antiplatelet medication, but others oppose it.[373] Symptoms are the primary impetus for closure of the coronary fistula. Asymptomatic patients may be considered for treatment, but the concern is the possibility of future complications. Treatment options to close the fistula include the long-standing therapy of surgery or a variety of percutaneous techniques such as coils, balloons, double-umbrella devices, and vascular-occlusion devices. With any technique, long-term follow-up of the patient is necessary, because recanalization is possible.

Surgical treatment of the coronary fistula with direct endocardial ligation has proven safe with no morbidity or mortality and effective with excellent long-term results of 10 years without problems.[378] Fistulae can be closed either from external placation on a beating heart or from an intracardiac location using CPB. To eliminate the fistulous tract, the distal end of the fistula from within the recipient cavity is closed during CPB.[379] Selected fistulas may be ligated without CPB. The use of coronary revascularization without CPB may be effective to protect the myocardial territories subtended by the fistula.[377] In approximately 50% of cases, when the fistula is corrected with surgery, CPB is used.[375] Cardioplegic arrest may be difficult with aortic cross-clamping of the aorta; therefore the option for temporarily clamping the fistula is acceptable unless the fistula is calcified. Intraoperative TEE can localize fistulas, verify complete repair, and monitor ventricular function to avoid ischemic complications of ligation.[380] Encountering major problems with surgery for coronary fistula is rare, but MI, arrhythmias, and stroke can occur.

The first successful transcatheter closure of a coronary fistula occurred in 1983.[374] This catheter-based technique of closing coronary fistulas has enjoyed success. Although many techniques are available to close the fistula, most have been done with coils.[381] The use of the coils results in thrombosis of the fistula to the level of the first branch, reducing the left-to-right shunt and returning myocardial blood flow. This technique has compared favorably with the surgical option in terms of morbidity, mortality, and effectiveness.[374,375] Series have noted approximately 10% of patients may develop leaks from transcatheter closure.[375] Long-term follow-up care has not been as rigorous or able to determine problems, but nearly one half of follow-up contacts are associated with persistent abnormalities.

Anesthetic Considerations

Anesthetic management of arteriovenous fistulas is similar to anesthetic management for CABG surgery. ECG monitoring for the detection of ischemic changes is invaluable for the ligation of coronary arteriovenous fistulas. The use of echocardiography is extremely valuable to determine myocardial ischemia and the degree of shunt.

Case Study 4: Coronary Artery Fistula

A 56-year-old woman with a history of hypertension reported new onset of dyspnea on exertion. Her physical examination was unremarkable with the exception of a continuous, soft murmur heard on auscultation of the chest. Preoperative TTE revealed normal valves, normal ventricular function, and no regional wall motion abnormalities. However, an area of turbulent flow in the RV raised concern for the presence of a right coronary artery fistula communicating with the RV. This finding was confirmed with a preoperative angiogram, and surgery was recommended. In the surgical unit, the site of communication between the fistula and the RV was identified with TEE. Using color-Doppler imaging, a site of turbulent flow was identified entering the RV. Turbulent flow was also seen outside of the ventricle, presumably occurring within the fistula. The surgeon placed a suture around the coronary fistula at its site of entrance to the RV. As the suture was tightened, the turbulent flow entering the RV was no longer seen with TEE. The result was considered acceptable, and the surgeon proceeded to ligate the fistula. The right coronary artery was assumed to remain intact.

After a short period of observation, it was noted that the ST segments in the inferior leads had become elevated. Ischemia was considered but could not be confirmed as the source of mild ST elevation. When the heart was re-imaged with TEE, right ventricular function was

described as normal. However, new regional wall motion abnormalities were clearly revealed in the inferior wall of the LV. Considering these new wall motion abnormalities, combined with ST segment elevation, it was believed that the right coronary artery had been compromised. CPB was instituted, and a vein graft was placed from the aorta to the distal right coronary artery, followed by easy separation from CPB. Biventricular function was normal, and the wall motion abnormalities were no longer present. The patient had an uncomplicated postoperative course.

In this case, TEE not only guided ligation of the fistula but also confirmed damage to the coronary artery, requiring CABG surgery during the ongoing anesthesia and avoiding another separate procedure and anesthesia.

Cardiac Surgery During Pregnancy

Heart disease is a major risk factor for maternal and fetal death during pregnancy with an incidence of 1% to 3%.[382] It is the most common cause of nonobstetric mortality during pregnancy, accounting for 10% to 15% of maternal mortality. Although maternal cardiac disease represents only 15% of obstetric ICU admissions, it accounts for 50% of the obstetric ICU deaths.[383] Obstetric patients with heart disease are at great risk for serious complications as a result of hemodynamic changes associated with pregnancy and delivery. If cardiac surgery is required during or immediately after pregnancy, then anesthetic management demands an appreciation for the many changes of pregnancy and their effects on the corresponding heart disease and well-being of the fetus.

Certain physiologic changes of pregnancy negatively affect the woman with heart disease. Heart rate and stroke volume are each increased by 25% by the end of the second trimester. Early in the third trimester, intravascular volume has expanded by nearly 50%.[384] These three changes during pregnancy cause a 50% increase in CO that is aggravated by physiologic anemia and aortocaval compression. Labor contractions can rapidly increase the already elevated CO. Such increases in blood volume and CO are especially difficult for a parturient with valvular heart disease. Elevated CO will increase myocardial oxygen demand exacerbating CHF, and low SVR will worsen coronary perfusion, causing myocardial ischemia. Low SVR may also compromise maternal pulmonary blood flow or alter shunt physiologic functioning with certain congenital heart defects. It is not uncommon to see a nonpregnant woman with well-compensated cardiac disease acutely or gradually decompensate as cardiac demands increase during pregnancy.

Cardiovascular morbidity and mortality is strongly associated with maternal functional status. Four major risk factors predict poor maternal outcomes according to a prospective evaluation of more than 600 pregnancies complicated by maternal cardiac disease: (1) CHF and/or a history of transient ischemic attacks, stroke, or arrhythmias; (2) prepregnancy NYHA class higher than II; (3) left-sided heart obstruction; and (4) an ejection fraction greater than 40%.[383] The likelihood of complications rises to 75% if more than one risk factor is present. Most commonly, the complication takes the form of pulmonary edema or arrhythmias.

Rheumatic heart disease accounts for nearly 75% of maternal heart disease, but CHD is increasing its share as more women with CHD are reaching childbearing years. Native valve disease and prosthetic valve dysfunction comprise most of the surgical procedures during pregnancy. Dissecting or traumatic rupture of the aorta, pulmonary embolism, closure of PFO, and cardiac tumors comprise only a small percentage of cases.[385] Mitral valve disease is the most common valvular disorder that requires surgery in pregnancy. Chronic mitral or aortic regurgitation may actually be associated with a small symptomatic improvement, secondary to the normal physiologic changes of pregnancy. In contrast, stenotic valvular lesions tolerate these changes poorly.[382] Aortic and mitral stenosis are common problems that may lead to hemodynamic deterioration, forcing emergency delivery before cardiac surgery. The most frequent indication for emergency cardiac surgery during pregnancy is decompensation from CHF attributable to mitral stenosis.[386] New onset of atrial fibrillation with mitral stenosis causing severe hypotension and decreased CO is one of the more common potentially life-threatening situations to the mother and fetus.

Because cardiac surgical morbidity and mortality is higher in the parturient than the nonpregnant patient undergoing the same cardiac surgical procedure, every effort is made to manage the patient without surgery. Extensive exposure to radiation may, however, limit therapeutic invasive catheterization procedures. If nonsurgical therapy conflicts with fetal interests, cardiac surgery and CPB is reasonable because delaying surgery until after delivery carries a higher maternal mortality than proceeding with the surgery.[382] If the fetus is 24 weeks' gestation, the obstetrician may perform cesarean section just before CPB because of the greater fetal mortality associated with cardiac surgery. Although general anesthesia is recommended for patients requiring cesarean section before CPB, volatile agents may induce uterine atony, resulting in serious bleeding; consequently, total intravenous anesthesia merits consideration.

Weiss and colleagues[385] described the heart surgery requiring CPB in a pregnant patient. Maternal morbidity has fallen from 5%[386] to less than 1%.[387] Fetal mortality remains high, ranging from 16% to 33%.[385,386,388] Unfortunately, fetal mortality is related to the use of CPB, duration of the surgery, and hypothermia. The nonphysiologic nature of CPB combines with the changes of pregnancy for an uncertain response and tolerance by both the mother and the fetus. A recent series of 23 pregnant women with severe cardiac valve malfunction requiring open cardiac surgery demonstrated an in-hospital maternal mortality of 8.7% and a fetal mortality of 43.5%.[389]

CPB exposes the fetus to many undesirable effects that may have unpredictable consequences. Initiation of CPB activates a whole-body inflammatory response[390] with multiple effects on coagulation, autoregulation, release of vasoactive substances, hemodilution, and other physiologic processes that may adversely affect both the fetus and the mother. Maternal blood pressure may fall immediately after or within 5 minutes of initiating CPB, lowering placental perfusion secondary to low SVR, hemodilution, and the release of vasoactive agents.[386] Fetal heart rate variability is often lost, and fetal bradycardia (<80 bpm) may also occur at this time.[391] Because uterine blood flow is not autoregulated and relies on maternal blood flow, decreases of maternal blood pressure cause fetal hypoxia and bradycardia. Increasing CPB flows (>2.5 L/m^2 per minute) or perfusion pressure (>70 mm Hg) will raise maternal blood flow and usually return the fetal heart rate to 120 bpm.[392] A compensatory catecholamine-driven tachycardia (170 bpm) may ensue that suggests an oxygen debt existed.[391] Nonetheless, increasing CPB flow and mean arterial pressure do not always correct fetal bradycardia, and, if not, then other causes must be considered.

Problems with venous return or other mechanical aspects of extracorporeal circulation may also limit systemic flow, causing reduced placental perfusion. If acidosis persists throughout CPB, then other factors may be responsible for it, rather than low maternal blood pressure such as maternal hypothermia, uterine contractions, or medications that are transferable to the fetus. Monitoring the fetal heart rate is important to assess fetal viability and subsequent therapeutic initiatives. Fetal monitoring reduces mortality partially by early recognition of problems.[386] Immediately after delivery, the CO increases suddenly because of mobilization of extracellular fluids and removal of aortocaval compression to greatly burden the diseased cardiovascular system.[382]

Hypothermia has been used for years in cardiac surgery but is not recommended for the pregnant patient. There are reports of fetal survival with maternal core temperatures of 23°C to 25°C, and fetal survival is even documented after 37 minutes of hypothermic (19°C) circulatory arrest.[393,394] However, when hypothermic versus normothermic CPB was examined retrospectively in 69 pregnant patients who underwent cardiac surgery during 1958 to 1992, hypothermia was associated with an embryofetal mortality of 24%, compared with 0% for normothermia (Table 24.10). The fetus appears to maintain

TABLE 24.10 Fetal and Maternal Mortality and Morbidity After Cardiopulmonary Bypass

Variable	*Number of Patients*	*Embryofetal Mortality*	*Maternal Mortality*	*Embryofetal Morbidity*	*Maternal Morbidity*
Total cases	69	14 (20.2%)	2 (2.9%)	5 (7.2%)	3 (4.3%)
1958–1974	29	9 (31.0%)	2 (6.9%)	1 (3.4%)	0
1975–1991	40	5 (12.5%)	0	4 (10.0%)	3 (7.5%)
Less than 15 weeks	24	3 (12.5%)	1 (4.2%)	4 (16.6%)	1 (4.2%)
16 weeks or more	41	9 (21.9%)	0	1 (2.4%)	2 (4.9%)
Hypothermia (<35°C)	25	6 (24.0%)	0	4 (16.0%)	1 (4.0%)
Normothermia (≥36°C)	13	0	0	0	2 (15.3%)

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autoregulation of the heart rate with mild hypothermia, but most functions are reduced with severe hypothermia.[391] Maternal mortality was not influenced by differences in CPB temperature.

Beyond the effect of hypothermia on acid-base status, coagulation, and arrhythmias, it may precipitate uterine contractions that limit placental perfusion and risk fetal ischemia and survival. The explanation for hypothermic-induced contractions may be related to the severe dilution that accompanies CPB and lowers progesterone levels, thus activating uterine contractions. Contractions are more likely to occur the older the gestational age of the fetus.[388,395] Accordingly, uterine monitoring is strongly recommended if CPB is required during pregnancy. If uterine contractions should begin during CPB, then stopping them is vitally important for fetal survival. Treatment includes ethanol infusion, magnesium sulfate, terbutaline, or ritodrine. However, many of these tocolytic agents have potential side effects and toxicities that can be especially detrimental to the patient with heart disease.[396] However, tocolytic agents may be necessary if the contractions are associated with significant fetal decelerations that are indicative of severe oxygen debt. Infants have died from protracted contractions.[397] Prophylactic measures, such as progesterone to prevent contractions, have been of indeterminate value. Pulsatile CPB may lessen the risk of contractions; although fewer premature contractions were noted, the mechanism is unclear and has not gained popularity.[398]

As noted previously, the initiation of CPB is accompanied by moderate hemodilution. It has been recommended that the hematocrit remain above 28% to optimize oxygen-carrying capacity for the mother and fetus.[382] Arterial partial pressure of carbon dioxide ($PaCO_2$) should be slightly hypercapnic, because this increases uterine blood flow. Anticoagulation and its neutralization for CPB should be consistent with routine management for nonmaternal patients, because unfractionated heparin does not cross the placenta and can be used safely. Anticoagulation therapy during pregnancy has been extensively reviewed.[399] A cesarean section has been advised for neonates with a gestational age of more than 28 weeks immediately after heparinization and cannulation but before the commencement of CPB,[400] because at 24 to 28 weeks' gestation, organogenesis is complete, and neonates do well. If the avoidance of CPB with the fetus is not possible, then, unfortunately, the appropriate management to achieve an optimal outcome for the mother and fetus has not been firmly established with prospective randomized trials.

Approximately 30 to 60 minutes after separation from CPB, the fetus develops a severe and progressive respiratory acidosis.[391] Although correctable, hours later, a more severe metabolic acidosis ensues with the potential for fetal death. It has been postulated that catecholamines and the fetal stress response may be responsible for poor CO, secondary to significant vasoconstriction reflected in a persistent acidosis.[388] The effects of vasopressors and inotropic agents on uterine blood flow in pregnant patients with cardiac disease are indeterminate. ACE inhibitors and ACE-receptor antagonists are contraindicated during pregnancy.[382] Current guidelines are based on animal data, not the intact human maternal-fetal unit. Uterine blood flow is directly proportional to mean perfusion pressure and inversely proportional to uterine vascular resistance. The uterine vascular bed is maximally dilated during pregnancy. Stimulation of α-adrenergic receptors increases uterine vascular resistance and potentially decreases uterine blood flow. However, improvements in maternal CO, blood pressure, and uterine blood flow by certain vasopressors may outweigh any detrimental effect on uterine vascular resistance. Ephedrine has been the vasopressor of choice for maternal hypotension for years. Ephedrine and phenylephrine are safe when treating maternal hypotension during cesarean section after spinal or epidural anesthesia.[401,402] In pregnant ewes, dopamine's effect on uterine blood flow is mixed. Epinephrine has been associated with decreased uterine blood flow, although in one clinical report an infusion of epinephrine improved maternal hemodynamics after CPB and resolved fetal bradycardia.[403] Overall, the use of these agents during CPB appear to have few negative effects.[391]

Anesthesia Considerations

Medications for anesthesia must be considered in the context of the maternal heart disease, the influence of CPB, and the effects on the fetus. Maternal safety and optimal fetal outcome must be ensured. Being aware of the safety of the more commonly used drugs in cardiac anesthesia during pregnancy is important. The risk of teratogenesis with a myriad of medications and exposures of the fetus during cardiac surgery and CPB is high, but most infants have successfully avoided the effects.[394,395] No anesthetic agent has been shown to be teratogenic in humans. Fetal teratogenicity is always a concern of anesthetic management, especially during the first trimester when fetal organogenesis occurs. Commonly used induction agents and sedatives, such as thiopental, ketamine, etomidate, propofol, midazolam, and diazepam, rapidly cross the placental barrier to the fetal circulation.[50,404–406] Animal studies show that halothane, enflurane, isoflurane, and sevoflurane appear to be safe anesthetic agents and lack teratogenic effects.[407,408] Despite concerns about the action of nitrous oxide on DNA synthesis, human and animal studies indicate that it is safe to use nitrous oxide for anesthesia during pregnancy. Fentanyl and sufentanil decrease beat-to-beat variability and may mask fetal distress but do not produce teratogenic effects. Both depolarizing and nondepolarizing muscle relaxants cross the placenta to different degrees. Pancuronium, atracurium, and pipecuronium have been administered either intramuscularly or intravenously directly to the human fetus *in utero* without apparent adverse sequelae.

Many medications are administered during cardiac anesthesia that do not provide anesthesia. ß-Blockers such as propranolol, esmolol, and labetalol cross the placenta but appear safe for acute and chronic use.[409] Nitroprusside, nitroglycerin, and hydralazine appear to be safe for treating maternal hypertension. Nitroprusside rapidly crosses the placental membrane in pregnant ewes, but infusion rates of less than 2 μg/kg per minute do not generate toxic levels of cyanide in fetal lambs.[400] Mannitol and furosemide cross the placenta and induce fetal diuresis but have no apparent adverse fetal consequences. Regional anesthesia carries considerable risk in view of the degree of anticoagulation necessary for CPB, although it has been used successfully.

A team approach with the anesthesiologist, surgeon, neonatologist, and obstetrician is critical for the care of mother and fetus, especially if optimal management for the mother does not necessarily coincide with fetal interests. The decision to operate needs to be made in the context of the potential survivability of the fetus outside the uterus should delivery of the baby become probable.

Risks of Human Immunodeficiency Virus Transmission

In the United States, 1.2 million people are infected with HIV, representing 2.5% of the global infections.[410] More than 50,000 new cases occur annually in the United States.[411] Concern exists among health care workers about the risk of infection with HIV. Only 57 cases of documented occupational HIV infection in health care workers in the United States have been reported between 1981 and 2001.[410] Cardiac surgery is one of the highest risk settings for occupational HIV transmission by reason of the considerable blood exposure that often occurs with excessive bleeding after CPB. This risk is not expected to improve greatly in the foreseeable future. However, the pattern of HIV transmission is changing to include more heterosexual and progressively older individuals. New therapies and a delayed incubation time to develop AIDS after infection have extended life expectancy of those with HIV.[412] However, since the introduction of the highly active antiretroviral therapy, reduction in deaths have been slipping in response to a potential resistance to combination drug therapies. Currently, the number of cases has stabilized in the United States. As patients with HIV live longer and reach ages during which the likelihood of cardiac surgery is greater, the number of HIV patients that require cardiac surgery will also rise.

The risk of exposure of HIV for the health care worker continues to evolve. Earlier studies show transmission risks from patients were overall, minimal. Henderson and associates[413] prospectively studied 1344 health care workers over a 6-year period to assess the risk of HIV transmission during occupational activities. The authors combined data from multiple sources and stated, "the risk for HIV-1 transmission associated with percutaneous exposure to blood from an HIV-1 infected patient is approximately 0.3% per exposure." The risk after mucous membrane and cutaneous exposure to an HIV patient is 0.09%. Transmission of HIV has been reported after nonintact skin exposure, but the risk is less than mucous membrane transmission.[414] The Centers for Disease Control and Prevent prospective surveillance project found a 0.36% HIV seroconversion rate in health care workers who sustained percutaneous exposure to HIV-contaminated blood.[415] No seroconversions occurred in health care workers who had mucous membrane or cutaneous exposure to HIV-infected blood.

The rates of exposure are subject to study methods, types of procedures, and the precautions of the individuals involved; consequently, the stated risk of transmission with a single exposure may be greater than initially suspected. Factors that have been identified to alter the rate of conversion are a deep injury contact, injury by a device visibly contaminated with a patient's blood, or injury by a device placed in the artery or vein. These factors are associated with a higher titer of viral exposure; consequently, the rate of conversion is greater than the rate of 0.5% noted previously.[416] The risk of transmission is also greater with exposure to a larger quantity of blood or an HIV-infected person with a terminal illness.[414] Rates of conversion in surgical settings are known to vary widely.[417] The specific occupational risk of bloodborne infections in the health care setting primarily depends on three factors: (1) prevalence of infected patients within the patient population; (2) probability of acquiring a specific infection after a single occupational exposure; and (3) frequency of at-risk exposures.[412] Recently in a study examining the risk of transmission of HIV by surgical subspecialties and occupation, cardiothoracic surgery had the highest rate. The rate of mucocutaneous contamination by blood splashing during surgery has been estimated to be higher, approximately 50% for cardiothoracic surgery. It appears that almost 60% of exposures in cardiac surgery occur in the surgical unit, with suturing representing one third of the contacts. However, HIV infection accounts for only 5% of these exposures, compared with 78% for hepatitis C. Blood-to-hand contacts represent many of the exposures in the cardiac surgical setting.[417] Contact of blood with the body increases the risk of infection dramatically as blood loss exceeds 500 mL.

The best way to prevent occupation-related HIV infection is to prevent exposure to HIV-contaminated bodily fluids, most notably blood. Greene and colleagues[418] using data confined to anesthesia personnel and obtained in 1991 to 1993, found that the majority of percutaneous injuries were from contaminated needles, usually hollow bore and preventable. Hollow-bore needles that have been used in venous or arterial puncture appear to have a higher incidence of HIV transmission than solid needles. Needleless or protected-needle infusion devices and revised anesthesia practice protocols have lowered the incidence of percutaneous injuries.[419] All anesthesia personnel should routinely wear face shields or eye protection and gloves to prevent cutaneous and mucous membrane contamination.

The safety of blood transfusion regarding infection has been confirmed.[420] All donated blood undergoes HIV-antibody screening, but a *window period* of approximately 22 days exists when antigen may exist in a donor's blood without antibody. As of 1995, only 29 documented cases of AIDS have been attributed to receiving HIV-seronegative blood, although the actual number may be higher. Lackritz and associates[421] evaluated the American National Red Cross blood system and estimated that one blood donation in 360,000 occurred during the window period. Furthermore, 15% to 42% of this blood was discarded on account of other laboratory abnormalities. They also estimated that 1 in 2,600,000 donations was HIV positive, but it was missed because of laboratory error. The American Red Cross defined the risk for the administration of HIV-infected blood as 1 in 450,000 to 660,000 donations. Extrapolating their data nationwide to all 12 million annual donations, approximately 18 to 27 HIV-infected donations are available for transfusion. Schreiber and colleagues[422] estimated that one in 493,000 donated units of blood would result in HIV transmission. They also estimated the risks of transmitting human T-cell lymphotropic virus, hepatitis C virus, and hepatitis B virus to be 1 in 641,000; 1 in 103,000; and 1 in 63,000, respectively. Despite the appropriate concern about HIV transmission during blood transfusion, similar attention should also be directed toward the transmission of hepatitis B and C viruses.

The effectiveness of postexposure prophylaxis has been difficult to prove in view of the small number of exposures that prevent an adequate statistical analysis of the rate of seroconversion after contact. In case-controlled trials, zidovudine is the only drug that has been shown to reduce the rate of seroconversion.[423,424] Table 24.11 displays the antiretroviral drugs available in 2009. Table 24.12 outlines the recommendations of the US public health service and from the Centers for Disease Control and Prevention for postexposure prophylaxis. Postexposure chemoprophylaxis with two drugs is indicated when health care workers are at risk for acquiring HIV via percutaneous exposure. The two-drug combination of nucleoside reverse transcriptase inhibitor agents is recommended if significant exposure occurs over a 4-week course. Possible combinations include zidovudine-lamivudine, lamivudine-stavudine, or didanosine-lamivudine.[414] A third drug is recommended if the risk is believed to be even higher

TABLE 24.11 Antiretrovirals Available in 2009

NRTIs	*NNRTIs*	*Protease Inhibitors*	*New Classes*
Abacavir	Delavirdine	Atazanavir	Fusion inhibitors (eg, enfurvitide)
Didanosine	Efavirenz	Darunavir	CCR5 inhibitors (eg, maraviroc)
Emtricitabine	Nevirapine	Fosamprenavir	Integrase inhibitors (eg, raltegravir)
Lamivudine	Etravirine	Indinavir	
Stavudine		Lopinavir	
Tenofovir		Nelfinavir	
Zidovudine		Ritonavir	
		Saquinavir	
		Tipranavir	

CCR5, C-C chemokine receptor type 5; *NRTIs*, nucleoside reverse transcriptase inhibitors; *NNRTIs*, nonnucleoside reverse transcriptase inhibitors.

Reproduced with permission from Dunning J, Nelson M. Novel strategies to treat antiretrovial-naive HIV-infected patients. *J Antimicrob Chemother.* 2009;64:674–679.

TABLE 24.12 Provisional Public Health Service Recommendations for Chemoprophylaxis After Occupational Exposure to Human Immunodeficiency Virus

Type of Exposure	*Source Material*[a]	*Antiretroviral Prophylaxis*[b]	*Antiretroviral Regimen*[c]
Percutaneous	Blood[d]		
	Highest risk	Recommend	ZDV plus 3TC plus IDV
	Increased risk	Recommend	ZDV plus 3TC ± IDV[e]
	No increased risk	Offer	ZDV plus 3TC
	Fluid containing visible blood, other potentially infectious fluid,[f] or tissue	Offer	ZDV plus 3TC
	Other body fluid (eg, urine)	Not offered	
Mucous membrane	Blood	Offer	ZDV plus 3TC ± ID[e]
	Fluid containing visible blood, other potentially infectious fluid,[f] or tissue	Offer	ZDV ± 3TC
	Other body fluid (eg, urine)	Not offered	
Skin	Blood	Offer	ZDV plus 3TC ± IDV[e]
Increased risk[g]	Fluid containing visible blood, other potentially infectious fluid,[f] or tissue	Offer	ZDV ± 3TC
	Other body fluid (eg, urine)	Not offered	

[a]Any exposure to concentrated human immunodeficiency virus (HIV; eg, in a research laboratory or production facility) is treated as percutaneous exposure to blood with the highest risk.

[b]Recommend—Postexposure prophylaxis (PEP) should be recommended to the exposed worker with counseling. Offer—PEP should be offered to the exposed worker with counseling. Not offered—PEP should not be offered because these are not occupational exposures to HIV.

[c]Regimens: zidovudine (ZDV), 200 mg three times a day; lamivudine (3TC), 150 mg twice daily; indinavir (IDV), 800 mg three times a day. (If IDV is not available, then saquinavir may be used, 600 mg three times a day). Prophylaxis is administered for 4 weeks. For full-prescribing information, see package inserts.

[d]Highest risk—Both larger volume of blood (eg, deep injury with large diameter hollow needle previously in source patient's vein or artery, especially involving an injection of source patient's blood) and blood containing high titer of HIV (eg, source patient with acute retroviral illness or end-stage AIDS; viral load measurement may be considered, but its use in relation to PEP has not been evaluated). Increased risk—Either exposure to larger volume of blood or blood with high titer of HIV. No increased risk—No exposure to larger volume of blood or to blood with high titer of HIV (eg, solid suture needle injury from source patient with asymptomatic HIV infection).

[e]Possible toxicity of additional drug may not be warranted.

[f]Includes semen; vaginal secretions; or cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids.

[g]For skin, risk is increased for exposures involving high titer of HIV; prolonged contact, extensive area, or an area in which skin integrity is visibly compromised. For skin exposures without increased risk, the risk of drug toxicity outweighs the benefit of PEP.

Reproduced with permission from Cardo DM, Bell DM. Bloodborne pathogen transmission in health care workers. Risks and prevention strategies. *Infect Dis Clin North Am.* 1997;11:341, and from the Centers for Disease Control and Prevention (CDC). Update: provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV. *MMWR Morb Mortal Wkly Rep.* 1996;45:468,199.)

or the HIV titer is higher in the exposure. Therapy should be initiated as soon as possible, because there is a *window* before the systemic infection occurs. Early exposure to the antiretroviral therapy permits a better chance to preserve immune function and alter the course of the disease. Current recommendations suggest at least 1 to 2 hours from the time of exposure for the initiation of prophylaxis to be successful, but this has not been proven. In some cases, prophylaxis has been successfully administered 36 hours after exposure.[419] It has been shown that those who are exposed to HIV through occupation and who do not seroconvert may still develop markers of T-cell mediated response to the virus. However, the risk of this is lower if the exposed person has received antiretroviral prophylaxis.[419]

All patients at any stage of infection with HIV, even during the "window of opportunity" are at risk for transmission.[425] To date, only 22 patients have HIV seroconversion after prophylaxis, with 6 of those patients receiving combination therapy. Follow-up for the occurrence of side effects should start after 4 weeks and continue for at least 6 months after exposure.[419] Serologic testing for conversion should occur 6 weeks, 3 months, and 6 months from the time of exposure. If hepatitis C was confirmed, then testing for seroconversion should continue for another 12 months because of the effect of hepatitis C to delay HIV seroconversion. Zidovudine has potential complications; therefore its administration should be carefully considered since most exposures to HIV do not result in seroconversion. Additionally, zidovudine has been associated with several failures and complications.[417]

Prophylaxis therapy for occupational exposure should involve investigation into the source of the exposure with the recent rise of resistant strains to carefully design the optimal regimen. Determining the HIV serologic nature of the source for infection as soon as possible is critical to minimize any exposure to prophylaxis if the source is found to be HIV negative. Prophylaxis is not indicated if the patient is negative for HIV. If testing the infecting source is delayed, then at least one dose of prophylactic agents should be administered.[411] The viral load for prophylaxis differs greatly if the donor is chronically infected, and the postexposure prophylaxis will be influenced by it. The proper prophylaxis is important because incremental toxicity increases as the number of antiretroviral agents is increased.

Because new therapies for HIV have become more widespread,[426] patients undergoing cardiac surgery may be receiving these newer medications (see Table 24.11). Triple drug therapy is now the standard of care. The complexity of medications that these patients may receive certainly increases the possibility of drug interactions. The nucleoside analog reverse transcriptase inhibitors are primarily secreted by the kidneys, therefore fewer drug interactions are possible. However, the nonnucleoside analog reverse transcriptase inhibitors and protease inhibitors are metabolized by the liver with the cytochrome P450 mechanism so that many drug interactions are possible, especially with anesthetic agents. Ritonavir, a potent protease inhibitor, can increase the blood concentration levels of amiodarone, midazolam, diazepam, and meperidine, to name a few. Drug interactions should be considered if a patient is taking these medications and requires cardiac surgery.

Renal Insufficiency and Cardiac Surgery

Chronic kidney disease is increasingly common, having a global prevalence of greater than 10%.[427] In recent years, the number of individuals with chronic renal failure (CRF) undergoing cardiac surgery has increased between 2% and 3% of the cardiac surgical population.[428] Patients with CRF may not necessarily be dialysis dependent before surgery but are more likely to develop worsening renal function after CPB than those with normal preoperative renal function.[429] Acute kidney injury occurs frequently (28%) and is associated with increased mortality.[430,431] Morbidity and mortality are especially high in patients on long-term dialysis who are undergoing cardiac surgery and CPB, ranging from 17% to 77% and 8% to 31%, respectively.[432] Because CRF accelerates the development of atherosclerosis, many of these patients will eventually require myocardial revascularization. Irrespective of whether the CRF patient is dialysis dependent, he or she is an anesthetic challenge, especially in regards to fluid management, electrolyte status, and hemostasis. The ability to avoid dialysis in the nondialysis-dependent CRF patient is very important to hospital lengths of stay and long-term mortality. A collaborative effort by the cardiac surgeon, anesthesiologist, nephrologist, and cardiologist is instrumental in the

care of these patients. Unfortunately, long-term survival is still appreciably diminished, even with minimal perioperative morbidity.

Patients with CRF are more prone to fluid overload, hyponatremia, hyperkalemia, and metabolic acidosis. Optimal hemodynamic and fluid status before surgery is important. Hemodialysis should be strongly considered the day before surgery, especially in those who are strictly dialysis dependent. Chronic dialysis patients tend to arrive for surgery with worsened left ventricular function, possibly from an inefficient waste and toxin removal. CHF can occur as a result of hypervolemia and poor left ventricular function, manifesting as pulmonary edema and respiratory distress. Dialysis and medical therapy directed at improving cardiac function may be required to optimize the patient preoperatively. Chronic medications should be carefully reviewed to ensure that certain medications, such as antihypertensive agents, are given. The importance of preoperative preparation for patients with CRF is evident by the significantly high mortality rate associated with urgent surgery.[428]

Perioperative mortality of patients with CRF undergoing cardiac surgery is associated with several risk factors. A preoperative creatinine of 2.5 mg/dL is associated with greater mortality even in those patients with nondialysis-dependent CRF.[432] Late mortality may range from 8.3% to 55% if dialysis is ongoing for longer than 60 months.[428] Pulmonary dysfunction also increases the perioperative mortality of CRF patients.

Patients with CRF differ from those with normal renal function in a variety of ways, which influence anesthesia management. A normochromic, normocytic anemia is common primarily because of decreased or absent erythropoietin secretion for which the kidney is the predominant source. Anemia is now treated with recombinant human erythropoietin therapy instead of blood. The cardiovascular benefits are especially noticeable with the correction of anemia. However, treatment is costly and requires multiple injections weeks before surgery, which may not always be possible.

Efforts to find renoprotective agents for patients that are either at high-risk for renal failure or those with CRF have been unsuccessful. Randomized double-blind prospective trials looking at the use of *N*-acetylcysteine for patients undergoing CPB with CRF have found mixed results.[433–435] *N*-acetylcysteine is an antioxidant and vasodilator with the ability to increase cyclic guanosine monophosphate (cGMP) and nitric oxide, which has shown promise in contrast-related renal failure. Fenoldopam, a dopamine-1 receptor agonist, was studied in patients undergoing CPB with preoperative creatinine levels above 1.5 mg/dL.[436] Patients were given a renal dose of dopamine or fenoldopam perioperatively. Postoperative parameters were only improved in those receiving fenoldopam, suggesting a renal protective effect, but additional studies are needed. Mannitol and Lasix may also prevent early oliguric renal failure.[437]

Anesthesia Considerations

CRF affects dosing of medications that have a large volume of distribution. Decreased serum protein concentration diminishes plasma binding, leading to higher levels of free drug to bind with receptors. Many patients with CRF have hypoalbuminemia. In general, anesthetic induction agents and benzodiazepines are safe to use in patients with CRF. A common induction agent, thiopental, is highly protein bound, therefore the dose should be reduced accordingly. Medications that rely totally on renal excretion have a limited role. Fentanyl and sufentanil may be more effective for pain management because excretion is not renally dependent as morphine sulfate. Currently used volatile anesthetic agents rarely incur any additional renal dysfunction, even with underlying CRF unless severely prolonged duration of anesthesia occurs. Muscle relaxants and agents for antagonism of muscle paralysis have varying degrees of renal excretion (Table 24.13).

A rapid-sequence induction is recommended in those with CRF in response to the likelihood of delayed gastric emptying. Significant extracellular volume contraction may also be present before the induction of anesthesia as a result of the 6- to 8-hour fast before surgery and dialysis within 24 hours of surgery that may lead to hypotension on induction. Because fluid requirements are usually high with CPB, a PAC is especially useful to manage fluid administration. TEE may complement fluid management by assessment of left ventricular volume and function. Before the initiation of CPB, fluid administration should be limited, especially if the patient is dialysis dependent. In the nondialysis-dependent patient, fluid should be given to maintain adequate urine output but to also avoid excessive cardiovascular filling pressures that incite pulmonary edema. Fluids should not be too aggressively restricted, because doing so may cause acute renal failure superimposed on CRF. Low-dose dopamine has been recommended for patients with CRF, but its value is indeterminate.

TABLE 24.13 Commonly Used Muscle Relaxants and Renal Failure

Relaxant	*Acceptable*	*Renal Excretion*
Atracurium	Yes	<5%
Curare	Yes, with caution	60%
Cis-atracurium	Yes	<10%
Doxacurium	Yes, with caution	70%
Gallamine	No	100%
Metocurine	Yes	50%
Pancuronium	Yes, with caution	70%
Pipecuronium	Yes, with caution	70%
Vecuronium	Yes	30%
Rocuronium	Yes	9%[b]
Mivacurium	Yes	7%[c]
Succinylcholine	Yes, with normokalemia	0%

[a]Prolonged neuromuscular blockade has been reported.
[b]Data from Khuenl-Brady K, Castagnoli KP, Canfell PC, et al. The neuromuscular blocking effects and pharmacokinetics of ORG 9426 and ORG 9616 in the cat. *Anesthesiology*. 1990;72: 669–674.
[c]Data from Cook DR, Freeman JA, Lai AA, et al. Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. *Br J Anaesth.* 1992;69: 580–585.
Reproduced with permission and adapted from Barash PG, Cullen BF, Stoelting AK. *Clinical Anesthesia.* Philadelphia: JB Lippincott; 1989, and Miller RD, Savarese JJ. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. *Anesthesia.* New York: Churchill-Livingstone; 1990:389–436.

In general, CRF will worsen after CPB in part because of a combination of nonpulsatile flow, low renal perfusion, and hypothermia.[432] Studies remain mixed regarding the ability of pulsatile flow during CPB to preserve renal function, compared with nonpulsatile CPB.[438] Renal perfusion is lowered as CPB is initiated, increasing the chance for ischemia of the renal cortex. Mean arterial pressure should be kept above 80 mm Hg. The stress of surgery and hypothermia may impair autoregulation so that renal vasoconstriction reduces renal blood flow. The fluid required to initiate CPB may significantly reduce the hemoglobin and oxygen-carrying capacity in view of the preexisting anemia of CRF without the addition of red blood cells (RBCs) to the priming volume or immediately upon initiation of CPB. A hematocrit of 25% should be maintained during CPB.[432] Washed RBCs are recommended for RBC transfusion to lessen excessive potassium and glucose levels intraoperatively. Potassium plasma levels should be checked periodically. Patients with CRF often have glucose intolerance from an abnormal insulin response; therefore more frequent determination of serum glucose levels is advisable.

The anephric patient poorly tolerates post-CPB hypervolemia associated with prolonged duration of CPB. Dialysis can be performed during CPB and is technically easy and effective because small molecules (uremic solutes, electrolytes) are removed.[439] Instead of dialysis during CPB, hemofiltration (ultrafiltration) is more frequently performed effectively, clearing excess water without the hemodynamic instability of dialysis. Circulating blood passes through the hollow fibers of the hemoconcentrators, which have a smaller pore size than albumin (55,000 daltons) that remove water and solutes. These midsize (inflammatory) molecules are small enough to pass through the pores to concentrate the blood. Potassium is eliminated, thereby helping reduce excessive potassium concentration commonly associated with

cardioplegia administration. Hemofiltration during CPB may not achieve a net reduction in the overall total fluid balance of the patient in part because a minimum volume of fluid must be maintained in the venous reservoir of the extracorporeal circuit but may be associated with earlier extubation after CPB.[440]

Excessive bleeding after CPB is not uncommon in those with CRF in part because of preoperative platelet dysfunction. Antifibrinolytic medications are pharmacologic measures used to successfully reduce excessive bleeding and transfusion requirements associated with cardiac surgery.[79] Tranexamic acid, an inexpensive, synthetic antifibrinolytic, is excreted primarily through the kidneys; consequently, a dose reduction will be required, based on the preoperative creatinine level. A newer dosing regimen has been developed, based on levels of tranexamic acid.[441] The drug, aprotinin, a serine protease inhibitor with antiinflammatory and antifibrinolytic properties, is concentrated in the proximal renal tubules. Recently, aprotinin was found to triple the risk of renal failure with dialysis, compared with tranexamic acid and aminocaproic acid in patients undergoing CABG surgery in an observational study involving over 4000 patients.[442] This study was followed by a randomized double-blinded trial of patients undergoing cardiac surgery with aprotinin, aminocaproic acid, or tranexamic acid that was halted before the completion of enrollment as a result of the increase in mortality with aprotinin, compared with the other lysine analog antifibrinolytic agents.[443] Although this trial did not find a statistically significant increase in renal failure or the need for renal replacement therapy, there was an increase in the number of patients who had their creatinine dose doubled. Ultimately, the US Food and Drug Administration (FDA) has removed aprotinin from clinical use.

Postoperatively, if dialysis is required in patients with end-stage renal disease, then the risk of dialysis dependence is greatly increased.[437] If the patient is dialysis-dependent preoperatively, dialysis is usually resumed within 24 to 48 hours of surgery and then according to the patient's preoperative routine to optimize fluid, electrolyte, and metabolic status. Dialysis may be needed soon after return from the surgical unit if mobilization of fluids into the intravascular space causes CHF. Hemodialysis primarily corrects electrolyte imbalances and removes organic acids to correct metabolic acidosis. Dialysis may lessen the platelet dysfunction associated with uremia to minimize hemostatic abnormalities and excessive hemorrhage. Peritoneal dialysis may be preferable if the postoperative hemodynamic status of the patient is unstable. Peritoneal dialysis, compared with hemodialysis, is more convenient to administer and does not require the immediate support of a nephrologist. However, continuous renal replacement therapy can be instituted intraoperatively and postoperatively to manage acute renal failure with volume overload and metabolic instability with great results in cardiac patients after CPB.[444] Continuous renal replacement therapy has become very popular in cardiac surgical patients in the last 10 years because the bedside nurse can direct the degree of fluid pull in response to the patient's changing hemodynamic status. Between 0.7% and 1.4% of patients undergoing cardiac surgery may require this transient form of therapy for renal failure.

Patients with CRF are at high risk for morbidity and mortality with cardiac surgery involving CPB. Attention to the following steps may improve outcome: (1) assessment of conditions associated with CRF that lead to complications such as platelet function, lung function, and anemia; (2) adequate RBC mass; (3) fluid and electrolyte care, particularly after CPB; (4) hemofiltration; (5) blood conservation techniques and treatment of coagulopathy; (6) judicious use of dialysis; and (7) scrutiny for infections that patients with CRF are more susceptible to develop.

Hematologic Problems in Patients Undergoing Cardiac Surgery

Anesthetic concerns for patients with hematologic problems who undergo cardiac surgery are further complicated by the stress CPB places on coagulation and oxygen-carrying systems. Hemophilia, cold agglutinins (CAs), sickle cell disease (SCD), antithrombin (AT) deficiency, and von Willebrand disease (vWD) are a few of the hematologic disorders that may require special consideration if CPB is used. In general, a multidisciplinary approach, including individuals with expertise in these areas, is helpful in providing optimal care with such rare conditions.

Hemophilia

In the 1940s and 1950s, the coagulation factors that separated hemophilia A (factor VIII [FVIII] deficiency) from hemophilia B (factor IX [FIX] deficiency) were identified. Before that discovery, hemophilia was a debilitating disease with a life expectancy of less than 20 years. Subsequently, improvements in FVIII therapy has prolonged life, but the early factor concentrates were not virally safe; consequently, 60% to 95% of individuals with hemophilia beyond 8 years of age were infected with hepatitis C virus,[445] and eventually two thirds of individuals with hemophilia became infected with HIV.[446] Although life expectancy temporarily fell below 40 years of age,[447] new FVIII replacement therapy such as recombinant FVIII (rFVIII) greatly reduced viral transmission. The result was more autonomy for patients with hemophilia, prolonging their life beyond 50 years, and ensuring that they will more likely experience age-related disorders such as coronary artery disease.

Hemophilia A is the third most common X-linked disorder, occurring in 1 in 5000 male births.[445] Hemophilia B, also known as *Christmas disease*, is also an X-linked disorder with one fourth the incidence of hemophilia A. FVIII is instrumental for a normally functioning clotting cascade. With a half-life of only 8 to 12 hours, FVIII and FIXa accelerate activation of factor X. Hemophilia is characterized by spontaneous bleeding in the joints and muscles in its severe form. Hemophilia A or B are very similar in presentation, course, and treatment. Treatment of hemophilia A and B primarily depends on replacement of FVIII or FIX, respectively. Preparations of rFVIII, developed in the 1990s, effectively control 80% of bleeding episodes with a single dose. Viral contamination has been essentially eliminated; therefore the incidence of inhibitors is no more likely than plasma-derived factors. Cardiac surgeries require more intense hemostasis than most other surgical and nonsurgical situations. This requirement is exacerbated by the stress on the coagulation system and increased risk of excessive bleeding associated with cardiac surgery.[448]

Specific challenges are involved in undergoing cardiac surgery and CPB with hemophilia. Management is derived from case reports and series without randomized, prospective trials. Relatively few institutions have experience in performing cardiac surgery in those with hemophilia; systematic information regarding optimal perioperative care is limited. However, a recent study indicated similar outcomes in patients undergoing CPB with or without hemophilia.[449]

Preoperative assessment of the cardiac surgical patient with hemophilia must determine the severity of the patient's hemophilia by history and laboratory tests, because perioperative bleeding is related to the degree of factor deficiency. Mild hemophilia has factor levels between 6% and 30% with occasional symptoms and represent 30% to 40% of hemophilia cases.[450] Moderate hemophilia has factor levels between 1% and 5% and represent 10% of hemophilia cases. Severe hemophilia has factor levels below 1% with easy bleeding that could become severe during surgery if factor activity remains at 1%. Severe hemophilia occurs in approximately 50% of hemophilia cases. Most patients arrive for surgery with an FVIII or FIX activity less than 5%. Although a factor level near 50% of normal is regarded as adequate to achieve noncardiac surgical hemostasis, hemostatic demand and associated coagulation abnormalities[448] with cardiac surgery and CPB will require a higher FVIII level.

Preoperatively, FVIII activity should be 80% to 100% for cardiac surgery. The amount of factor replacement is estimated from the total fluid volume of the extracorporeal circuit (priming volume), plasma volume, and the desired factor activity. If the preoperative FVIII or FIX level is recent (morning of surgery), then this value may be acceptable

for the determination of FVIII and FIX replacement for the initiation of CPB. Otherwise, FVIII and FIX levels should be obtained before initiation of CPB. Replacement of FVIII or FIX during CPB may be achieved by intermittent bolus or continuous infusions, but the optimal factor activity for CPB has not been established. Based on hemodilution that typically occurs during CPB, 30% to 50% FVIII or FIX levels would be consistent with other coagulation factors during this period, but FVIII levels are difficult to obtain during CPB, secondary to the high heparin dosing required. Consequently, a bolus of FVIII or FIX before the initiation of CPB is a consideration.

The disadvantage of bolus administration of factor replacement is the resulting high peak levels, but it ensures that trough levels will be adequate for hemostasis. Continuous infusions may preserve FVIII levels at a constant and "safe" level to minimize bleeding.[451] Currently, only a few forms of rFVIII can be used for continuous infusions because of product instability. Depending on the bolus dose of rFVIII (50 IU/kg), a continuous infusion of 4 IU/k per hour may infuse for 72 hours to maintain FVIII activity greater than 100%.[452] Obtaining FVIII or FIX levels after heparin neutralization is still important to guide factor replacement in combination with attempts to obtain hemostasis after CPB. FVIII levels after heparin neutralization and postoperatively should approach 100% to reduce the risk of excessive bleeding. FVIII levels are helpful every other day for a period of 1 to 2 weeks while the chest tubes remain.[453] FVIII levels will vary tremendously because no treatment provides a sustained FVIII level with the diverse individual requirements and consumption of FVIII among cardiac surgical patients. A platelet antagonist such as aspirin may be recommended to prevent thrombosis because of the excessive levels of FVIII that may occur during bolus dosing.[449]

Antifibrinolytic therapy has been used in patients with hemophilia to inhibit the normal clot lysing process. A recent study has demonstrated a hemostatic benefit with tranexamic acid for cardiac surgery and CPB.[449] Antifibrinolytic agents, tranexamic acid, and epsilon-aminocaproic acid are used prophylactically to reduce blood loss and transfusion requirements in cardiac surgery involving CPB.[79] Another antifibrinolytic, aprotinin, has been removed from clinical use as a result of increased risk of death, compared with the other lysine analog antifibrinolytic agents.[442,443] Antifibrinolytic agents are routinely stopped 2 hours after arrival in the ICU, but some benefit has been seen by extending the duration of administration.[449] Serial thromboelastographies (TEGs) are useful if antifibrinolytic agents are going to be administered an extended duration with close inspection for hypercoagulable changes in the TEG shape. Additional methods and techniques for blood conservation should be considered to reduce the risk of bleeding and transfusion with hemophilia.

1-Desamino-8-D-arginine vasopressin (DDAVP), a vasopressin analog, has been used successfully in mild-to-moderate hemophilia A to decrease intraoperative transfusion requirements.[445,454,455] A rapid increase in all components of FVIII occurs after DDAVP administration, but FVIII level will fall by 50% 10 hours after administration. The response of DDAVP depends on the resting FVIII level and hemostatic demand. If the patient with hemophilia possesses 5% to 20% procoagulant activity, then he or she is more likely to respond to DDAVP, in contrast to those with severe FVIII deficiencies who will not respond to DDAVP.[455] The peak effect occurs 1 hour after an intravenous dose of 0.3 μg/kg is given. DDAVP may be given at 12- to 24-hour intervals, but tachyphylaxis is possible after multiple doses.

Therapy for hemophilia B has changed significantly with the availability of a concentrated purified recombinant FIX (rFIX). rFIX is not exposed to human or animal protein. Previously, individuals with hemophilia B were treated with plasma-derived products called *prothrombin-complex concentrates* that contain factors IX, X, II, and VII. These active complexes have resulted in fatal thrombotic reactions because these complexes are not normally generated or regulated by the coagulation pathway. Circulating FIX levels will not increase as much as FVIII after transfusion because FIX is distributed in both intravascular and extravascular spaces, unlike FVIII; consequently, the calculated dose has to be doubled.[456] FIX activity of approximately 50% is adequate to achieve hemostasis yet minimize the risk of thrombotic complications[457]; however, others have recommended higher dosing to achieve 100% activity.[456,458] Recently, FIX product has been successfully used for continuous infusion for replacement therapy during CPB and cardiac surgery.[458] Typically, rFIX is given as bolus once daily for surgery. Continuous infusion of rFIX has been shown recently to be effective in providing conditions for optimal hemostasis for cardiac surgery with CPB, as well as reducing the overall amount of concentrate administered.[458] Furthermore, the occurrence of inhibitors with rFIX is rare but must be evaluated before treatment. rFIX concentrate is not licensed yet in the United States for continuous infusion. Recommended levels for perioperative FIX levels have not been established for cardiac surgical patients, despite multiple case reports of it effective and safe use in this cardiac population. More information dosing of rFIX is available.[458] A review of the publications of cardiac surgery and hemophilia patients, 30 adults and 3 children, concluded that "routine cardiac surgery can be performed safely in patients with hemophia."[459]

Antibodies to FVIII or FIX may occur in patients with hemophilia who have received replacement therapy. The incidence of FVIII or FIX inhibitors is 18% to 52% and 2% to 16% of the hemophilia population, respectively.[460,461] Inhibitors occur more often in patients receiving the purest replacement factors, which is a major concern for future replacement therapy with purer products.[462] The strength of the immune response is instrumental in the development of inhibitors. For example, HIV-positive patients with hemophilia do not develop FVIII inhibitors. The inhibitor titer will characterize the patients as mild or high responders. High responders are at great risk because the anamnestic response may generate very high antibody titers that can render factor replacement therapy totally ineffective hemostatically.[463] The problem with patients who develop inhibitors and require surgery is the inability to predict hemostasis at any point of the hospitalization.

Cardiac surgery has been successfully performed in patients with FVIII inhibitors.[464] Patients with low antibody titers often tolerate conventional concentrate infusion but require higher and more frequent doses for efficacy. The defect in the intrinsic coagulation pathway must be bypassed and prothrombin-complex concentrates that contain activated forms of factors VII, IX, and X must be administered, which have been largely successful in achieving hemostasis in the presence of FVIII and FIX inhibitors.[446] Recently, a new recombinant FVIIa has become available.[465] FVIIa appears to bind to tissue factor on the surface of the activated platelet to form complexes at the site of injury. This activates other coagulation intrinsic and extrinsic factors and platelets. It causes the generation of thrombin and fibrin to create hemostasis. It is infused as a bolus 90 to 120 μg/kg and repeated at 3-hour intervals for a maximum of four times. In over 1900 surgical and nonsurgical bleeding episodes in more than 400 patients with hemophilia A or B, FVIIa has been shown to be safe with over 103 major surgical procedures with excellent results in 80% of cases.[466] A randomized controlled trial in cardiac surgery with FVIIa has been performed in adults without hemophilia that showed reductions in allogeneic transfusions.[467] Caution should be taken when using FVIIa because two metaanalysis studies of FVIIa safety have shown an increased risk of arterial thromboembolism.[468,469]

Particular caution must be taken in managing the airway in patients with hemophilia to avoid any trauma-induced bleeding. Nonsteroidal pain medications may be counterproductive in these patients because of their effect on platelet function. Strict asepsis must be maintained because the immune system of these patients may be very weak and extremely susceptible to bacterial and viral infections.

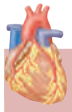
von Willebrand Disease

vWD is the most commonly inherited hemostatic abnormality, with prevalence in the general population of 0.8%.[470] vWD is an autosomal dominant bleeding disorder caused by a deficiency and/or abnormality of von Willebrand factor (vWF). An acquired form of vWD is associated with various disease states and medications.[471] The nomenclature

TABLE 24.14 Classification of von Willebrand Disease

New[a]	*Old*[a]	*Characteristics*
1	I platelet normal, I platelet low, 1A, I-1, I-2, I-3	Partial quantitative deficiency of vWF
2A		Qualitative variants with decreased platelet-dependent function that is associated with the absence of high–molecular-weight vWF multimers
2B		Qualitative variants with increased affinity for platelet GPIb
2M		Qualitative variants with decreased platelet-dependent function that is not caused by the absence of high–molecular-weight vWF multimers
2N		Qualitative variants with significantly decreased affinity for factor VIII
3		Virtually a complete deficiency of vWF

GPIb, Glycoprotein receptor Ib; *vWF,* von Willebrand factor.
[a]Reproduced with permission from Castaman G, Rodeghiero F. Current management of von Willebrand's disease. *Drugs*. 1995;50:602.



BOX 24.9 RECOMMENDED NOMENCLATURE OF FACTOR VIII AND VON WILLEBRAND FACTOR COMPLEX

Factor VIII		von Willebrand Factor	
Protein	VIII	Protein	vWF
Antigen	VIII:Ag	Antigen	vWF:Ag
Function	VIII:C	Function	vWF:RCo[a]

[a]Although not measuring "true" von Willebrand factor (vWF) activity, ristocetin cofactor activity is used as a surrogate test for vWF activity in vitro. This activity depends on both the vWF level and the multimeric structure.
Reproduced with permission from Castaman G, Rodeghiero F. Current management of von Willebrand's disease. *Drugs*.1995;50:602.

of vWF and FVIII complex have been standardized to resolve past confusion (Box 24.9).

vWF is a large, adhesive glycoprotein that is produced by vascular endothelial cells and megakaryocytes. It is found in platelet α-granules, plasma, and subendothelium. It circulates in blood as an array of multimers of various sizes. Large multimers have more binding sites for platelets and therefore augment platelet adhesion and aggregation. Each vWF subunit has a site for a platelet receptor to bind and the extracellular matrix component of the vessel wall to attach.[472] vWF has two major hemostatic functions: (1) a carrier protein and stabilizer for FVIII and (2) mediation of platelet adhesion to injured sites.[473] It plays a crucial role in mediating platelet adhesion, platelet aggregation, and clotting during high shear conditions.[474] Patients with vWD have an abnormality of both vWF and FVIII. vWD is classified into three major types and four subtypes (Table 24.14).[475] Individuals with type 1 and type 2 make up 70% and 20% of people with vWD, respectively.[476] Type 3 vWD represents only 10% of individuals and is autosomal recessive. Type 3 vWD individuals are severely affected and whose presentation is similar to individuals with hemophilia who have a very low FVIII activity (1% to 4%).

Erik von Willebrand first identified the abnormal bleeding time (BT) that characterized vWD. The laboratory diagnosis of vWD is complex because of the broad phenotypes that exist. No single laboratory test is diagnostic for vWD. The BT is sensitive for vWD, but it is prolonged in only 50% of individuals with type 1 vWD. It is significantly prolonged in type 3 vWD. The activated partial thromboplastin time (aPTT) is usually prolonged but not a good screening test for vWD because FVIII activity, which affects the aPTT, varies greatly in

TABLE 24.15 Patterns of von Willebrand Disease

Type	*RIPA*	*Ristocetin Cofactor*	*vWF Antigen*	*Factor VIII*
1	D	D	D	D
2A	D	D or DD	D or N	N or D
2B	I	D	D or N	N or D
2M	D	D or DD	D	N or D
2N	D	D or DD	D	N or D
3	DD	DD	DD	DD

D, Decreased; *I,* increased; *N,* normal; *RIPA,* ristocetin-induced platelet aggregation; *vWF,* von Willebrand factor.

vWD. The ristocetin cofactor assay vWF:ristocetin cofactor (RCo), also known as the *vWF activity*, is the most sensitive and specific test for vWD and the single best test to identify vWD (Table 24.15).[476] It measures the ability of vWF to bind to glycoprotein Ib platelet receptors. The vWF antigen test measures the quantity of vWF protein, not functional activity. vWF multimers can be visualized by electrophoresis and establish the type of vWD by their presence or absence. FVIII activity is frequently low in vWD. In mild cases of vWD, the aPTT, FVIII, and BT may be normal with only a slight decrease in the RCo and vWF antigen.[477] Factors such as age, estrogen levels, adrenergic stimulus, and inflammation can directly affect vWF levels and complicate laboratory evidence of vWD.

A complete medical history is important to complement laboratory testing. Family history is a sensitive indicator of vWD. Individuals with vWD will frequently describe bleeding that is more mucosal in origin (epistaxis), compared with people with hemophilia. Medical history is important because routine laboratory screening may fail to detect vWD. Unlike hemophilia, patients with mild vWD may go unnoticed for years with unremarkable bleeding patterns and rarely need long-term prophylaxis. Variant forms of vWD further increase the possibility of missing the diagnosis. If undiagnosed, then surgical bleeding may be severe, particularly if combined with ingestion of antiplatelet medications. Aspirin and antiinflammatory medication consumption should be identified preoperatively. Questioning the patient individually to determine the severity of bleeding is important, because major differences in the bleeding tendencies can be present within a family and with similar laboratory tests.[471] The severity of bleeding usually determines replacement therapy, instead of DDAVP or the use of antifibrinolytic agents.[478]

Because vWF has a dual role in hemostasis, correction of platelet vessel-wall interaction and deficiency of FVIII must be achieved with a prophylaxis regimen to undergo cardiac surgery requiring CPB. Correction of vWF deficiency may be accomplished by either facilitating vWF release from *in vivo* storage sites or administering exogenous components. Each type of vWD requires a specific therapeutic approach. Preoperative FVIII or RCo levels are recommended to optimize hemostatic capability for surgery. FVIII levels should be obtained intraoperatively and then once per day after surgery. Both FVIII and vWF levels will decrease on initiation of CPB, but vWF will subsequently increase as it is released from storage pools.[474] BT is rarely used anymore to guide therapy because its correlation with surgical hemostasis is poor.[478] FVIII level and vWF should be normalized intraoperatively and 7 days to 10 days after surgery to reach effective hemostasis.[479] The reliability of guides to dosing with vWD is poor, and the achievement of hemostasis should be the catalyst for additional therapy.

DDAVP is a synthetic analog of the natural hormone vasopressin without the pressor effect and is the first choice for treatment in vWD; however, not all types of vWD respond to it. DDAVP is effective in type 1 vWD[480] but ill-advised in type 2B vWD because thrombocytopenia may result. It is useless in type 3 vWD because there are no stores of vWF to release.[481] DDAVP does not directly cause the release of FVIII/vWF from the endothelial cell but stimulates monocytes to produce

TABLE 24.16 Proposed Dosing and Plasmal Levels of Factor VIII Coagulant Activity and von Willebrand Factor: Ristochetin Cofactor During Invasive Procedures and Surgery

			Target Levels (IU mL^{-1})			
			Perioperative		*Postoperative*	
Type of Procedure	*Loading Dose FVIII:C/vWF:RCo (IU mL^{-1})*	*Number of Infusions per Day*	*FVIII:C*	*vWF:RCo*	*FVIII:C*	*vWF:RCo*
Major	0.5–1.0	1–2	1.0	1.0	0.5	0.5
Minor	0.2–0.5	1	0.5	0.5	0.3	0.3

FVIII:C, Factor VIII coagulant activity; *VWF:RCo,* von Willebrand factor: ristocetin cofactor activity. Figures should be adjusted according to frequent clinical observations during and after the procedure. Concomitant treatment with tranexamic acid can usually be recommended.
(Reprinted with permission from Berntorp E. Prophylaxis in von Willebrand disease. *Haemophilia.* 2008;14 Suppl 5:47–53.)

a substance that releases vWF. A response to DDAVP should occur in 30 minutes with a threefold to eightfold increase in FVIII and vWF that may persist for 8 to 10 hours.[480] Hemostasis may require one or two doses of DDAVP at least 12 hours apart. It is readily available, inexpensive, and has minimal risk for patients but may be contraindicated in those with atherosclerosis, CHF, or require diuretic therapy.[482] DDAVP is effective if given in an intravenous, intranasal, or subcutaneous manner, but the intranasal preparation lacks predictability and strength of the intravenous preparation.[476] Intravenous dosing (0.3 μg/kg) requires 20 to 30 minutes to avoid a decline in mean arterial pressure of 15% to 20%. Tachyphylaxis may occur, with a 30% decrease in the effectiveness of the second dose if DDAVP is given more than once in each 24-hour period. For a majority of patients with mild vWD, DDAVP is effective and avoids exposure to plasma products. Side effects of DDAVP include facial flushing, headache, and fluid retention with hyponatremia. Reports of increased thrombosis with DDAVP are anecdotal.

Blood products should not be administered to patients with vWD unless another treatment is ineffective or contraindicated. Plasma-derived factor concentrates are the current standard for replacement therapy if the patient is unresponsive to DDAVP.[482] Factor concentrates in the past were not always effective in vWD because VWF:RCo was low and many of the hemostatically active vWF multimers were absent; as a result, FVIII levels were adequately replenished, but platelet function was impaired. These commercially available concentrates contain large amounts of both vWF and FVIII but differ in their purification and pathogen removal and inactivation techniques. Consequently, there is broad variation in the ratio of vWF and FVIII in the products and their multimer compositions that are so important for effective hemostasis. The various types of products and their dosing have recently been reviewed.[478,479,482] In general, the dosing is 60 to 80 IU/kg for a bolus dose of the factor concentrate to maintain hemostasis. The safety of these purified plasma-derived factor concentrates regarding viral transmission has been shown to be excellent (Table 24.16). An especially good product that contains a ratio of vWF:FVIII (2.4) is Haemate P/Humate-P. Clinicians must be cautious of the ratio of vWF:FVIII in the product and the type of the vWD to correctly treat the patient. The definitive amount of vWF or FVIII that is required to control bleeding for the optimal care is indeterminate. Platelet infusions should be considered in patients with type 3 vWD if bleeding persists after administering replacement concentrates.

Antifibrinolytic agents should be considered in patients with vWD to reduce clot lysis. Tranexamic acid is the most common agent used, whereas aprotinin is no longer available.[443] As in hemophilia, inhibitors can occur in vWD, causing life-threatening bleeding. Prothrombin-complex concentrates have been used to treat bleeding, but inducing a prothrombotic state and thrombosis in cardiac patients with mechanical valves is a risk.[483]

Antithrombin

AT and protein C are two primary inhibitors of coagulation. A delicate balance exists between the procoagulant system and the inhibitors of coagulation (Table 24.17). AT is the most abundant and important of

TABLE 24.17 Balance That Normally Exists Between Prothrombotic and Antithrombotic Forces Within the Circulation

Prothrombotic Factors	*Antithrombotic Factors*
Thrombin	Antithrombin
Factor Xa	Protein C
Factor VIIa	Protein S
Tissue factor	Heparin cofactor II
Activated platelets	Tissue-factor protein inhibitor
Perturbed endothelial cells	Thrombomodulin
Others	Activated protein C cofactor 2
	Others

Reproduced with permission from Blajchman MA. An overview of the mechanism of action of antithrombin and its inherited deficiency states. *Blood Coagul Fibrinolysis.* 1994;5(Suppl 1):S5.)

the coagulation pathway inhibitors. The impact of deficiencies of AT and advisability of restoration of normal levels continues to evolve with respect to cardiac surgery.

AT is an α_2-globulin that is produced primarily in the liver. It binds thrombin, as well as other serine proteases, factors IX, X, XI, and XII, kallikrein, and plasmin irreversibly, which neutralizes their activity. However, only inhibition of thrombin and factor Xa by AT has physiologic and clinical significance.[484] AT deficiency may occur as a congenital or acquired deficiency. Acquired deficiencies are secondary to increased AT consumption, loss of AT from the intravascular compartment (renal failure, nephrotic syndrome) or liver disease (cirrhosis). A normal AT level is 80% to 120%, with activity less than 50% considered clinically important.[485]

Congenital deficiency of AT is the prototypical, hypercoagulable state produced by an imbalance of coagulation and fibrinolytic factors (see Table 24.17). The prevalence is 1 in 2000 to 5000 persons.[486] Congenital AT deficiency is separated into four types (I–IV) and based on the quantitative and qualitative defects of the AT molecule. It is transmitted in an autosomal dominant pattern with affected individuals typically maintaining 50% AT activity. If the levels decline to less than 50% activity, then the risk of venous thrombosis is significant.[485] The only abnormal coagulation test associated with this condition is the assay for AT activity, which is diagnostic. Affected individuals may experience a thromboembolic event at an early age, but arterial thrombosis is encountered in less than 1% of individuals.[487] The advisability of long-term anticoagulation therapy is indeterminate in these individuals. Anticoagulation prophylaxis is recommended in cases in which the risk for thrombosis is temporarily increased, such as surgery.[488] The risk of thrombosis is higher in congenital forms than acquired forms of AT deficiency.[486,489]

In contrast to the rare case of congenital AT deficiency, acquired deficiencies of AT are commonly encountered in cardiac surgical patients. Anticoagulation with heparin for CPB depends on AT to inhibit clotting as heparin, alone, has no effect on coagulation. Heparin catalyzes AT inhibition of thrombin over a 1000-fold by binding to a lysine residue on AT and altering its conformation. Thrombin actually attacks AT, disabling it, but in the process attaches AT to thrombin,

BOX 24.10 DISEASES OR SITUATIONS CAUSING INCREASED HEPARIN RESISTANCE

Infective endocarditis
Intraaortic balloon counterpulsation
Hypereosinophilic syndrome
Oral contraceptives
Shock
Low-grade intravascular coagulation
Previous heparin therapy
Previous streptokinase
Presence of a clot within the body
Congenital antithrombin deficiency
Pregnancy
Neonatal respiratory distress syndrome
Increased platelet levels
Increased factor VIII levels
Secondary decrease in antithrombin levels
Ongoing clotting and utilization of heparin

(Reprinted with permission from Anderson EF. Heparin resistance prior to cardiopulmonary bypass. *Anesthesiology*. 1986;64:504.

forming the AT-thrombin complex. This complex has no activity and is rapidly removed. Thirty percent of AT is consumed during this process; consequently, AT levels are reduced temporarily. If AT levels are not restored, then a condition called *heparin resistance* may arise. The many causes of heparin resistance are listed in Box 24.10. Heparin resistance is defined as the failure of a specific heparin dose (300–400 u/kg) to prolong an activated clotting time beyond 480 seconds in preparation for the initiation of CPB. Failure to reach 480 seconds may be considered inadequate anticoagulation with the risk of thrombus formation during CPB.

Heparin resistance is increasingly common in cardiac surgical practice today because heparin exposure before cardiac surgery is more common. Heparin resistance has been reported to occur in 3% to 13% of cardiac surgical patients. A randomized prospective study, analyzing 2270 cardiac cases, identified only 3.7% of patients to be heparin resistant.[490] Observing a visible clot in the CPB circuit even with inadequate anticoagulation is uncommon. However, inadequate anticoagulation during CPB will systematically activate the hemostatic and inflammatory systems generating thrombin, platelet and clotting factor consumption, and excessive fibrinolysis. This combination of physiologic processes places the patient at risk for both neurologic injury and excessive bleeding.

The importance of AT deficiency in heparin resistance has been demonstrated,[491,492] but it is not the only issue. Platelets, fibrin, vascular surfaces, and plasma proteins all interact to determine the anticoagulant effect of heparin. This is evident from a randomized double-blind, placebo-controlled trial comparing treatments for heparin resistance.[491] Eleven patients remained heparin resistant despite fresh frozen plasma (FFP) and AT administration. Similarly, adequate activated coagulation time values of 480 seconds were not achieved in 30% of patients, even with 800 U/kg of heparin.[493] Typically with heparin resistance, 50% more heparin is given during CPB for anticoagulation. Unfortunately, aggressive heparin dosing in the midst of heparin resistance will further exacerbate a preoperative AT deficiency. On the initiation of CPB, AT activity decreases by 25% to 50%, secondary to dilution and elimination of the AT-thrombin complex.[486,489] Low levels of AT induce a prothrombotic environment that is conducive to thromboembolic behavior based partly on the occurrence of clotting in AT-deficient patients exposed to CPB.[494] The mean baseline AT levels of heparin-resistant patients is 56% ± 25%, which is consistent with previous studies.[490] AT levels may even decrease to less than 40% after deep hypothermic circulatory arrest and prolonged CPB, compared with the average AT level identified as 82% preoperatively in a recent trial.[495]

Heparin resistance was routinely treated with FFP for many years. However, a large disparity between AT levels after recombinant AT, compared with FFP, was noted in a prospective, randomized trial of recombinant AT or FFP for patients who were consistently defined as heparin resistant.[492] More recently, two units of FFP often failed to normalize AT levels in patients who were defined as heparin resistant.[496,497] A 75 μg/kg bolus dose of recombinant AT has effectively improved pre-CPB AT levels from 56% to 75% ± 31%.[490] The use of allogeneic blood products to treat AT deficiency should be discouraged.

In 1974, AT was isolated from human plasma and AT concentrates were discovered.[487] AT concentrate preparations are derived from human plasma pools but are subjected to fractionation procedures and heating to inactivate potential viral contaminants without reducing biologic activity.[489] Recombinant AT concentrates have been studied in cardiac surgical patients.[491,492,498] Single-dose vials of AT contain approximately 500 units and may be given over 10 to 20 minutes safely.[499] AT levels are often low preoperatively for cardiac surgical patients with a further fall attributable to CPB hemodilution and heparinization, leading to mean AT levels of 42% activity.[492] AT concentrates are beneficial in both hereditary and acquired AT deficiency.[486,487] The optimal AT level for CPB has not been defined, but a level greater than 80% is considered less likely to be associated with thrombus formation.

Inadequate anticoagulation during CPB will cause thrombin generation, leading to platelet activation and clotting factor consumption; however, definitive proof that AT supplementation will improve outcome is absent. AT supplementation has demonstrated reduced thrombin and fibrinolytic activity in patients undergoing CPB, based on statistically significant improvement in biochemical markers of hemostatic activation such as prothrombin fragment 1.2 concentrations, D-dimer concentration, and the AT-thrombin complex.[492,498,500] Unfortunately, clinical measures such as mediastinal chest tube drainage and transfusion requirements have been less consistent than biochemical measures.[489,490,492,498,500] Recently, AT supplementation was demonstrated to normalize thrombin generation with an *in vitro* preparation that used the plasma of five patients who had undergone prolonged CPB and deep hypothermic circulatory arrest to measure thrombin generation.[495] The addition of normal donor plasma or AT-deficient plasma to the test plasma resulted in excessive thrombin generation, compared with control blood. It was only the pure AT concentrate that arrested thrombin formation, with the test plasma returning it to below baseline in the control plasma (Fig. 24.83). Two studies have shown increased bleeding and transfusion requirements with AT levels less than 63%[501] and 58%.[493] However, to prove rare clinical endpoints with AT supplementation, compared with placebo in prospective trials, would be problematic.

The benefits of restoring AT levels may go beyond simple heparin responsiveness to an association with postoperative outcome. AT levels of 58% or less, obtained after cardiac surgery in a prospective, observational study, were found to be predictive of an increased incidence of surgical reexploration, adverse neurologic outcomes, thromboembolic events, and prolonged ICU duration.[493] Both duration of CPB and preoperative heparin use were also found to be associated with lower postoperative values of AT. Similarly, low preoperative AT levels were associated with lower postoperative AT levels, worse survival, and longer time to extubation, based on a retrospective analysis of cardiac surgical patients.[501] However, no conclusions can be made about AT supplementation until a prospective trial has been performed in a blinded, randomized fashion to assess the value of AT. An excellent summary of trials evaluating the value of AT concentrate for prophylaxis regarding AT-deficient patients before surgery strongly recommended AT supplementation.[486] Other indications for AT are listed in Box 24.11. Postoperatively, AT levels will continue to decline at a rate dependent on the extent of tissue disruption and hemorrhage. The nadir occurs on the third day and preoperative levels return by the fifth day; therefore supplementation is not required after this time.

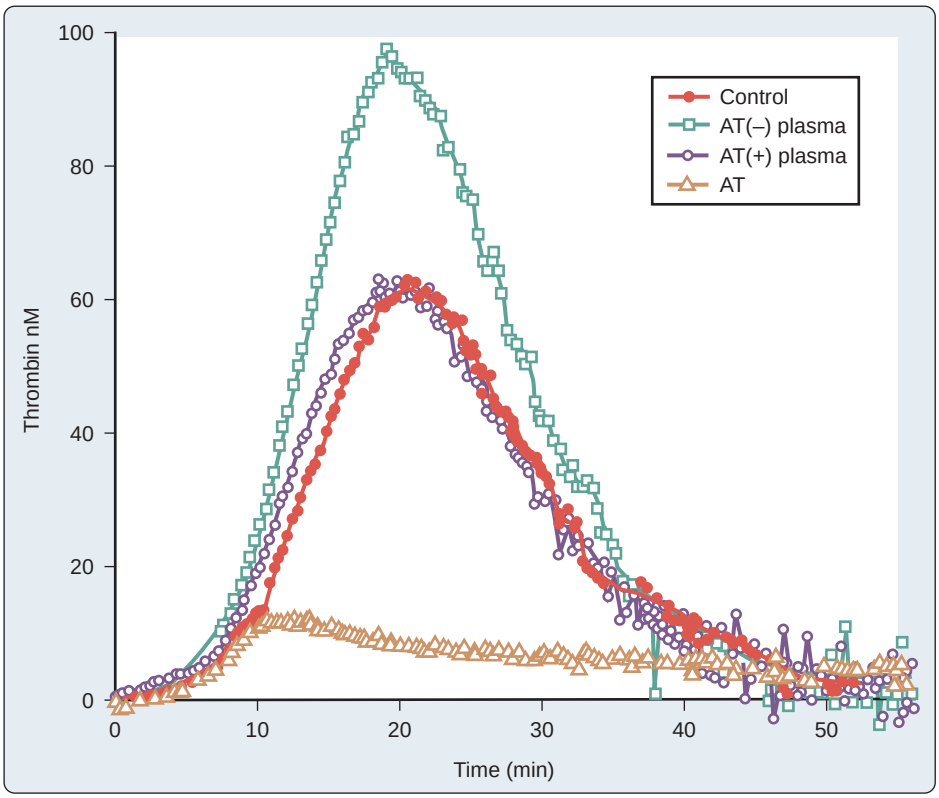


Fig. 24.83 Thrombin generation in platelet-poor plasma after cardiopulmonary bypass surgery is illustrated in representative tracings of five experiments. *Solid red circles* represent control (platelet-poor plasma only); *gold triangles* represent antithrombin (AT) (platelet-poor plasma supplemented with antithrombin concentrate); *green squares* represent AT(–) (platelet-poor plasma supplemented with antithrombin-depleted plasma). *Open purple circles* represent AT(+) (platelet-poor plasma supplemented with normal [non–AT-depleted] plasma). *(Reproduced with permission from Sniecinski R; SzlamF; Chen EP, et al. Antithrombin deficiency increases thrombin activity after prolonged cardiopulmonary bypass.* Anesth Analg. *2008;106:713–718.)*

BOX 24.11 INDICATIONS FOR ANTITHROMBIN REPLACEMENT THERAPY

Approved Indications[a]
Congenital antithrombin deficiency
Perioperative
Postsurgical prophylaxis for deep vein thrombosis
Acute thromboembolism
Pregnancy: delivery and abortion
Neonates with congenital AT deficiency

Probable Indications[b]
Neonates born to mothers with congenital antithrombin deficiency or with strong family history of thrombosis
Disseminated intravascular coagulation attributable to sepsis, trauma, and burns or associated with pregnancy
Heparin resistance associated with low antithrombin levels
Extracorporeal circulation (cardiopulmonary bypass, hemodialysis)
Hepatic artery thrombosis after orthotopic liver transplant

Possible Indications[c]
Venoocclusive disease
Orthotopic liver transplant
LeVeen peritoneovenous shunt
Chronic hepatic insufficiency

Investigational Use
Nephrotic syndrome
Antithrombin deficiency attributable to gastrointestinal loss (inflammatory bowel disease, protein-losing enteropathy)
Pregnancy: preeclampsia, gestational hypertension, and acute fatty liver of pregnancy
Neonatal respiratory distress syndrome

[a]Clinical data suggest efficacy.
[b]Clinical data suggest improvement in laboratory and clinical measures.
[c]Clinical data suggest improvement in laboratory values without proven clinical efficacy.
(Reproduced with permission from Bucur SZ, Levy JH, Despotis GJ, et al. Uses of antithrombin III concentrate in congenital and acquired deficiency states. *Transfusion*. 1998;38:482.)

Cold Agglutinins

CAs are common but rarely clinically important. The incidence rate in cardiac surgical patients varies between 0.8% and 4%.[502] Often associated with lymphoreticular neoplasms, mycoplasma pneumonia, and infectious mononucleosis, they are immunoglobulin M (IgM) class autoantibodies directed against the RBC I-antigen or related antigens.[503] CAs form a complement antigen-antibody reaction on the surface of the RBC membrane that causes lysis. The degree of hemolysis is related to the circulating titer and thermal amplitude of the CAs.[504] Thermal amplitude, that is, the blood temperature below which the CAs will react, is the key information to assign clinical relevance. The titer and thermal amplitude are determined at a range of temperatures in the serum by an indirect hemagglutination test. Most individuals have cold autoantibodies that react at 4°C but in very low titers. Accelerated destruction of RBCs occurs if the thermal amplitude is above 30°C. The more pathologic CAs have a higher thermal amplitude and higher titers at 30°C. From a pathologic standpoint, thermal amplitude is more important than titer. Pathologic CAs cause RBC clumping and vascular occlusion that injures the myocardium, liver, and kidney.[505] Microscopic RBC clumping may erroneously be attributed to other possibilities during hypothermic CPB unless agglutination is observed. Some have reported visible agglutination in the cardioplegic line.[506] Increasing the temperature will rapidly inactivate CAs.[507]

Blood banks routinely screen for the presence of autoantibodies at 37°C, but cold antibodies, only reactive at lower temperatures, are not detected. The significance of CAs is determined by evaluating agglutination of RBC in 20°C saline and 30°C albumin. If there is no agglutination, then significant hemolysis is unlikely.[508] Before the initiation of CPB, the titer and thermal amplitude of CAs must be determined to avoid a temperature during CPB that would cause hemolysis. Intraoperatively, low-thermal amplitude CAs can be determined by mixing cold cardioplegia with some of the patient's blood to check for a separation of cells. If there is concern about CAs after routine testing, then the sample can also be diluted to simulate CPB, cooled, and inspected for RBC agglutination. The occurrence of hemodilution commonly associated with CPB may weaken agglutination and hemolysis in a patient with high reactivity and titer of CAs exposed to hypothermia.

Clinical suspicion is necessary to detect CAs because many other explanations for hemolysis during CPB exist. Consequently, if CAs are suspected or identified preoperatively, then the avoidance of hypothermia is the safest course. Despite normothermic CPB, cold cardioplegia may cause RBC agglutination in small myocardial vessels.[506] Evidence of CAs may also be seen as incomplete cardioplegic delivery or high pressures in the CPB circuit.[509] Hypothermic myocardial protection has been successfully used in some patients with CAs. A review of 832 patients scheduled to undergo surgery and CPB identified only 7 cases of CAs who were strongly positive at 4°C.[507] They concluded that asymptomatic patients with nonspecific, low-titer and low-thermal amplitude CAs might undergo hypothermia and CPB without serious detectable sequelae. However, the possibility of subtle end-organ damage exists.

If hypothermic CPB is necessary, despite the presence of CAs, then the choices are preoperative plasmapheresis, hemodilution, and maintenance of CPB temperature above the CAs thermal amplitude (Fig. 24.84).[504,510] Cold cardioplegia may be used without first undergoing plasmapheresis if normothermic CPB is used and 37°C cardioplegic solution is injected before administering 4°C cardioplegic solution,

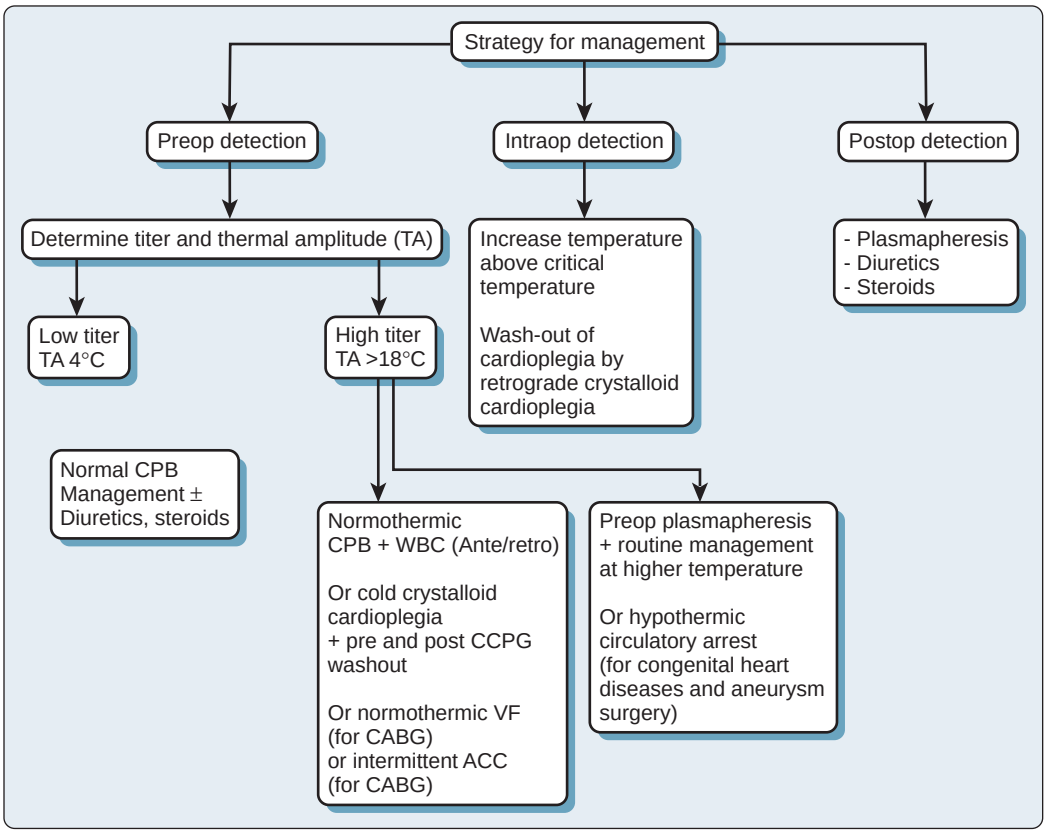


Fig. 24.84 Algorithm illustrates the strategy for the management of cold agglutinin (CA). *ACC*, Aortic cross-clamp; *CABG*, coronary artery bypass grafting; *CCPG*, cold crystalloid cardioplegia; *CPB*, cardiopulmonary bypass; *Intraop*, intraoperative; *Postop*, postoperative; *Preop*, preoperative; *VF*, ventricular fibrillation; *WBC*, warm blood cardioplegia. *(Reproduced with permission from Agarwal SK, Ghosh PK, Gupta D. Cardiac surgery and cold-reactive proteins.* Ann Thorac Surg. *1995;60:1143.)*

clearing all potentially reactive cells. The risk of hemolysis is still high in patients with high-thermal amplitude CAs. If CAs are particularly malignant, then all of the patient's blood from the venous reservoir is drained and discarded. It is replaced entirely by donor blood,[511] unfortunately exposing the patient to the risks of allogeneic blood products. Normothermic CPB and antegrade or retrograde warm blood cardioplegia may be the best option.[512] If CAs should go undetected, then postoperative end-organ damage or low CO may occur. Subsequently, plasma exchange, steroids, elevated urine output, and maintenance of a good CO are recommended.[502] In a case series of 16 patients with CAs who underwent 19 procedures requiring CPB, no patient demonstrated evidence of permanent myocardial dysfunction, had a neurologic event, required dialysis, or died within 30 days.[513] Another case series identified 47 patients out of 14,900 cardiac surgery patients. No difference in composite mortality or severe morbidity was revealed between patients with CAs and those without.[514]

All participants in the care of a patient with CAs should be acutely aware of the potential risk to the patient of hypothermia. Anesthetic gases, intravenous fluids, blood, and plasma should be heated before administration to these individuals. Surgical unit temperature should be warm. Washed RBCs may also be useful if transfusions of fresh components are necessary.[505]

Sickle Cell Disease

SCD is a heterogeneous group of inherited disorders involving the sickle ß-globin gene and was first reported in 1910 by Herrick.[515] Survival in SCD has greatly improved as a result of early diagnosis, antibiotics, and supportive care; however, it remains an important health threat, particularly if major surgery is contemplated.[516,517] Median life expectancy for male and female African Americans with SCD is 42 years and 48 years, respectively. Preparation and meticulous intraoperative care are imperative for the best results.

The ß-globin gene has worldwide distribution but is found most often in West Central Africa. HbA and HbS genes have codominant expression, which allows both genes to be represented in the Hb molecule. One in 10 American blacks are a heterozygous carrier of the ß-globin gene, referred to as sickle cell trait (AS), whereas the homozygous state, sickle cell anemia (SS), occurs in 1 of 400 blacks. The prevalence of SCD in American blacks is 0.2%. HbC disease (SC) occurs in approximately 2% of American blacks; SS accounts for 60% to 70% of SCD in the United States.

The ß-globin gene has a mutation in the DNA that results in a substitution of the amino acid, valine, for glutamic acid in the ß-globin chain that is responsible for normal Hb polymerization upon deoxygenation. The mutated Hb molecule is less negatively charged than the normal Hb, therefore as oxygen saturation approaches 85%, Hb tends to polymerize.[518] As the HbS comes out of solution and gels intracellularly, the RBC sickles (Fig. 24.85). Sickling is a reversible change in the RBC shape. Desaturation is the primary stimulus for sickling. In addition to desaturation, the risk of sickling is related to the amount of HbS in the RBCs. AS individuals do not sickle until the oxygen saturation is less than 40% because their ratio of HbS to total Hb is low. Since SS and SC patients have significantly more HbS, they sickle at an oxygen saturation of 85%, typically, the venous saturation. HbS is responsible for the major hallmarks of SCD: sickling, hemolytic anemia, and vasoocclusive events.[517,519,520] Vasoocclusive events are more likely because sickled RBCs have an increased affinity for the endothelial surface of blood vessels that significantly increases blood viscosity, leading to stasis.[518,521] During a vasoocclusive episode, the endothelium will produce activators such as endothelin that alter the endothelial surface and cause vasoconstriction and injury.

The clinical severity of SS, SC, and AS varies as a function of both inherited (thalassemia or fetal Hb) and acquired factors.[521] Patients with AS are asymptomatic unless they become profoundly hypoxic, acidotic, or hypothermic.[522] On the contrary, individuals with either SS or SC are chronically ill with a life-threatening illness. However, survival for individuals with SS is 95% at 20 years and even longer with

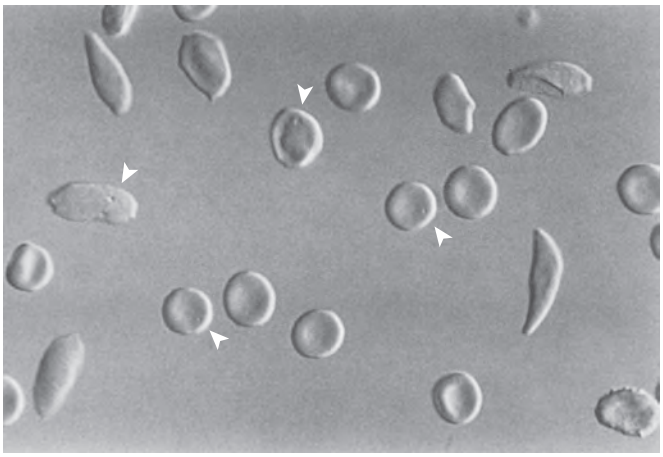


Fig. 24.85 The red cell pit count is used to assess splenic reticuloendothelial function. Erythrocytes from a child with sickle cell anemia were fixed in isotonic buffered glutaraldehyde and viewed by Normarski differential interference contrast microscopy. The increased percentage of red cells with large endocytic vacuoles *(pitted or pocked cells, arrowheads)* indicates functional asplenia. *(Reproduced with permission from Lane PA. Sickle cell disease.* Pediatr Clin North Am. *1996;43[3]:639.)*

SCD.[523] Individuals with SS are usually undersized, skeletally deformed as a result of bone marrow hyperplasia, and may be slightly jaundiced. They are chronically anemic with an Hb concentration often below 8 g/dl. The individual's RBCs are more fragile with a RBC viability of 10% of normal, which accounts for the chronic anemia. As a major site of sickling, the spleen eventually becomes nonfunctional; consequently, individuals with SS are extremely susceptible to infections, especially bacterial infections. Strict asepsis is important.

Three critical conditions may occur in those with SCD: painful crisis, aplastic crisis, and crisis affecting major organs. The painful crisis (sickle cell crisis) is a vasoocclusive, infarctive process, resulting in tissue anoxia exemplified by pulmonary infarctions. Diagnosis is often one of exclusion. Vasoocclusive crises primarily affect male patients 15 to 25 years of age. They are initiated by exertion, infection, dehydration, cold, acidosis, hypoxia, or vascular stasis.[524] The rheologic properties of the sickle RBCs combine with the tendency for adherence to the vessel wall to cause poor microvascular perfusion. Hydration with dextrose and water is important during a crisis, enabling free water to enter the cells and thus lower the Hb concentration; but in this situation, blood transfusion is not helpful.[518] Aplastic crisis is significantly less common than painful crisis but is the most feared hematologic complication of SS. It is characterized by a precipitous fall in Hb, secondary to hemolysis, without the normal bone marrow response. In contrast to vasoocclusive crisis, transfusion is not only helpful, but it is also essential. Aplastic crisis will last 7 to 10 days. Finally, various major organ systems such as the lungs (acute chest syndrome), spleen (splenic infarcts), kidneys, heart (myocardial dysfunction) and the central nervous system (stroke) are poorly perfused, causing permanent injury. Coronary artery occlusions are rare. Stroke is secondary to an intimal injury and thrombosis within the artery. Stroke occurs in approximately 8% of individuals with SS, and children are more likely affected. The lifetime chance of neurologic complications in those with SCD is 25%. Two thirds will have a subsequent stroke within 36 months.

Oral long-term daily use of hydroxyurea has been shown to reduce or prevent many acute and chronic complications of SCD.[516] Hydroxyurea is a ribonucleotide reductase inhibitor and it acts by increasing fetal Hb levels. A prospective randomized trial, the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, enrolled only adults with SCD who experienced more than three vasoocclusive crises during the previous year.[525] The patients who continued hydroxyurea therapy experienced improved outcomes at 2, 9, and 17 years.

Not all individuals with SCD have been identified before general anesthesia, and death has been the first manifestation of the disease.[526] Hb electrophoresis is the most accurate diagnostic test, but peripheral blood smears are not diagnostic. Hematologic consultation should be obtained in any person suspected to have SCD and who is scheduled for any type of surgery or anesthesia. Patients with SS have been considered at increased risk for surgery, general anesthesia, and postoperative complications. Results from the Cooperative Study of SCD, which included 3765 SCD patients in 23 clinical centers across the United States, determined the overall mortality rate was 0.3% with only 3 deaths related to anesthesia or surgery.[527] No deaths occurred in children younger than 14 years of age. Postoperative complications were variable and primarily related to the operative procedure. Despite many different surgical procedures and anesthetics in this large multicenter study, the mortality rate was low with few complications. Modern techniques and monitoring capabilities have enabled individuals with SCD to receive better care and outcome,[517] therefore surgery is a more viable option for consideration.

Preoperatively, complete assessment of the cardiovascular system, specifically looking for myocardial ischemia, PAH,[528] and CHF, is important in the individual anticipating cardiac surgery. Echocardiographic findings indicate that an estimated 20% to 30% of those with SCD have PAH, and its presence increases the risk of death. Problematically, autopsy series have shown that nearly one third of patients at autopsy with SCD had pathologic evidence of PAH without a diagnosis. Until recently, PAH was thought to occur from a thrombotic or embolic cause; now, however, a precapillary form of PAH is evident.[528] Renal function is also likely to be abnormal.[529] Folic acid and careful intravenous hydration in the preoperative period lessens the risk of dehydration, hyperosmolality, and low urine output.[530] An increased incidence of pulmonary dysfunction in patients with SS increases the risk of hypoxia; consequently, preoperative sedation must be carefully titrated along with careful patient observation. The value of prophylactic antibiotics is indeterminate.

The role of preoperative transfusion in the management of patients with SS has been debated for years. The recommendation for preoperative RBC transfusion in patients with SS is based on a reduction in circulating concentration of HbS in an effort to improve oxygen-carrying capacity, suppress the erythropoietic drive, and shift the P_{50} to the left; nevertheless; the possibility of sickling is not eliminated.[521] An HbS less than 30% has been traditionally regarded as necessary for individuals who undergo surgery. To verify this, a multicenter, randomized trial of 551 patients with SCD undergoing various noncardiac surgical procedures was conducted. Preoperative transfusion was designed with either a conservative or aggressive strategy to be evaluated according to the incidence of perioperative complications.[531] The percentage of HbS in the patients managed conservatively was 60%, compared with 30% for the aggressive strategy. The conservative strategy was associated with one half as many transfusion-associated complications. This study supports other work that found maintaining HbS at 50% instead of 30% was as effective in reducing the risk of stroke in nonsurgical situations.[532] For noncardiac surgery, growing evidence suggests that dilution of sickle cells with transfusions should be limited[527] and intraoperative transfusion should reflect standard transfusion guidelines.[517]

For the initiation of CPB, 5% HbS is often recommended,[533] although an HbS of 30% appears suitable.[534] Currently, alternatives to allogeneic transfusion are few for CPB and cardiac surgery. Exchange transfusion has been used successfully to correct anemia preoperatively with less risk of volume overload than simple transfusion.[535] It is important with the exchange transfusion for cardiac surgery to preserve the patient's platelets and plasma to be given after separation from CPB.[536] RBC transfusion, alone, increases blood viscosity more than exchange transfusion because a significant amount of HbS remains. There is concern that increased viscosity may temporarily negate an improvement in oxygen delivery that corresponds to the presence of additional RBCs.[537] The lower blood viscosity and increased oxygen delivery to the tissues derived from the exchange transfusion is probably more efficient. Exchange transfusion has become routine before major surgery, but no prospective trials of exchange transfusion have been conducted to establish its value.

Anesthetic management of individuals with SCD has been reviewed.[522,530] The availability of blood must be established before any surgery because of the possibility of alloimmunization. The incidence of antibodies may approach 50% with more than two thirds being Kell or Rh in SCD.[537] Antibodies may delay the availability of blood and increase the chance of a delayed hemolytic transfusion reaction that can mimic a painful crisis. Therefore any donor blood must be typed to ensure compatibility for ABO, Rh, and Kell antigens. Blood for transfusion should be less than 7 days old and warmed. Before induction of anesthesia, preoxygenation is essential. Maintenance of oxygenation throughout the procedure is critical but in no way guarantees an uncomplicated course. Volatile agents are associated with less sickling.[521] Maintenance of perfusion to the major organs and peripherally is very important to maintain normal acid-base status. The occurrence of hypotension is best treated initially with fluid administration to optimize volume status and to avoid vasopressors. Renal dysfunction causes SCD patients to concentrate urine poorly; therefore volume status is very dynamic. Efforts should be made to maintain the patient's normal body temperature. Intraoperative sickle crisis will sometimes occur, despite the best care, but poses a problem to diagnose during anesthesia. Signs of an intraoperative crisis include seizure, change in respiratory pattern, hypotension, or hematuria but are unfortunately nonspecific and unreliable. Laboratory tests are not helpful either. Nothing pharmacologically, such as alkalinization of the blood or administration of urea, can reduce the tendency to sickle.[521]

CPB has been associated with significant morbidity and mortality in adults and children with SCD.[538] CPB imposes severe physiologic stresses such as low-flow states, circulatory arrest, aortic cross-clamping, mechanical destruction of blood elements, and protein denaturation that predispose the individual to a sickling crisis. No evidence-based guidelines are available for body temperature, cardioplegia, priming solution, and transfusion practice during CPB.[539] The effect and safety of systemic and regional hypothermia (cardioplegia) in patients with SCD is indeterminate. *In vitro*, the solubility of deoxygenated HbS increases as the body temperature is decreased, which reduces sickling. However, decreased temperature increases blood viscosity. Viscosity increases by 30% when the body temperature declines to 30°C.[530] The harmful effects of hypothermia may be primarily related to vasoconstriction and vascular stasis; therefore hypothermia may be tolerated if peripheral perfusion and oxygenation are good. Currently, many patients undergo normothermic instead of hypothermic CPB because of advantages related to postoperative myocardial function.[540] Patients with either AS or SS have been cooled to 26°C or less without a sickling crisis, but partial or total exchange transfusion with a final HbS of 10% was performed in some of the patients.[539] Because oxygenation during CPB is excellent during moderate hypothermia, speculation suggests that sickling may be less common even without partial or full exchange transfusion.[520]

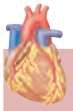
A reduction of HbS has been recommended before initiating CPB, which can be accomplished by dilution with a nonsanguineous priming solution, a blood priming solution, cardioplegia, intravenous fluid, and simple transfusion or blood component sequestration. These measures decrease the percentage of HbS, but a significant number of RBCs remain at risk for sickling. Only a form of exchange transfusion removes sickled cells. Exchange transfusions are advisable if deliberate hypothermia is planned.[539] Automated RBC exchange can be performed in the surgical unit or in the preoperative area. Intraoperative exchange can be performed more safely with the benefit of intraoperative monitoring to guide the transfusion and avoid volume overload and possible cardiac decompensation in patients with serious cardiac conditions. In addition, with CPB, draining blood from the CPB circuit is possible. Another novel approach involves partial RBC removal with the autotransfusion device before CPB to decrease the percentage of HbS, followed by an acute one-volume whole blood exchange during the initiation of CPB. The advantage is the procurement of a platelet-pheresed product with both techniques.[534] Another option is to use

primarily allogeneic blood in the priming volume in which, on the initiation of CPB, venous blood is diverted to other reservoirs and the warmed blood in the priming volume reaches the patient, resulting in an HbS concentration less than 5%. The diverted blood may have the RBCs separated from the plasma and platelets and discarded while the remaining non-RBC components are subsequently infused. This process decreases blood product exposure and allows the transfusion of normal donor blood. These techniques of blood component sequestration may eliminate the need for a hemapheresis procedure. It can also be used in patients with severe SCD who have a history of sickle crisis. Not everyone subscribes to the need for these measures with SCD. Métras and associates[541] described 15 patients with SCD (13 with AS) who underwent cardiac surgery. None of the patients received preoperative exchange transfusions, despite the use of moderate hypothermia, aortic cross-clamping, and cold cardioplegia. There was no evidence of sickling or increased postoperative complications. The authors concluded that as long as hypoxia, acidosis, and dehydration are avoided, preoperative exchange transfusions or blood transfusions are not mandatory; however, they did not study the most severe cases of SCD.

The advisability of cell salvage techniques in SCD is questionable. Intraoperative autotransfusion has been condemned by those who claim an adverse effect on sickling, but is supported by others.[542] The patient's percentage of HbS may influence how well intraoperative autotransfusion is tolerated. If intraoperative autotransfusion is used, then the recommendations are an exchange or a transfusion to an HbS less than 40%, increased hematocrit to greater than 30%, and heparinization until harvesting. Solutions need a physiologic pH.[521]

Individuals with SCD are known to be at risk for a variety of thromboembolic complications such as stroke, MI, pulmonary embolism, and deep vein thrombosis. This considerations may be important in terms of providing anticoagulation in patients for CPB. All aspects of hemostasis, including platelet function, procoagulant proteins, anticoagulant proteins, and fibrinolytic systems, are altered in the direction of procoagulation.[543] Chronic depletion of nitric oxide and arginine may also contribute to the hypercoagulable states in SCD. Evidence suggests that tissue factor expression on circulating endothelial cells may be abnormal with a more procoagulant activity, compared with individuals without SCD. There is also evidence of increased thrombin formation, based on biochemical markers in SCD. Finally, some of the anticoagulant proteins such as protein S and C are below normal levels. The impact on attempts to provide anticoagulation are not known, but carefully assessing the procoagulant state of the patient frequently during treatment of excessive bleeding is important to avoid increasing the risk of thrombotic complications postoperatively. Empirical transfusion may lead to excess blood products after CPB, which may result in a procoagulant state; therefore algorithm-directed transfusion is advantageous.[544] The thromboelastogram is especially useful after CPB to determine whether the patient has developed a hypercoagulable state that may be detrimental to those with SCD.

Larger doses of fentanyl have been reported in children undergoing CPB with SS to attenuate stress during the surgery, especially intubation.[545] Additionally, nearly one third of patients with SS will have PAH, and a high dose of fentanyl will also attenuate pulmonary vascular responses.[528] Early extubation after CABG surgery has minimal risk (Box 24.12). However, reviewing the patient's history regarding analgesia is important, because narcotic intolerance is common; as a result, he or she may require more aggressive perioperative pain therapy.[546] Patients who return from surgery for any reason may be at increased risk for postoperative pneumonia. Acute chest syndrome may appear as pneumonia or mask true pneumonia. Acute chest syndrome has resulted in fatalities. Patients with AS are not at increased risk for postoperative complications.



BOX 24.12 PROPOSED GUIDELINES FOR PERIOPERATIVE MANAGEMENT OF PATIENTS WITH SICKLE CELL DISORDERS UNDERGOING CORONARY ARTERY BYPASS GRAFTING SURGERY

Preoperative Period
Hemoglobin (Hb) electrophoretic studies
Correction of any coexisting infection
Partial or complete exchange transfusions for patients with Hb SS
Light benzodiazepine premedication
Supplemental oxygen to avoid a decrease in oxygen saturation

Intraoperative Period
Preoxygenation for 3 to 5 minutes in all cases
Small dose of opioid and hypnotic induction
Inhaled or intravenous (IV) maintenance of anesthesia
Tepid or warm cardiopulmonary bypass
Mean pump flow >50 mL × kg^{-1} × min^{-1}, perfusion pressure ≥60 mm Hg
Blood transfusion if hematocrit is <20%
Retransfusion of pump blood is not advisable

Postoperative Period
Early extubation within 2 to 6 hours
Maintenance of intravascular volume and body temperature
Avoidance of vasopressors is desirable
Early incentive spirometry
Multimodal approach to pain relief (opioids, nonsteriodal antiinflammatory drugs, acetaminophen)
Warming blankets to maintain temperature ≥37°C
Shivering: meperidine, 10 to 25 mg IV
Routine antibiotic coverage for 2 days
Blood transfusion: Hb <7.5 g/dL for those ≤70 years old; Hb <8.5 g/dL for those >70 years old
Close monitoring of oxygenation, perfusion, and acid-base indices for 12 to 24 hours

(Reproduced with permission from Djaiani GN, Cheng DC, Carroll JA, et al. Fast-track cardiac anesthesia in patients with sickle cell abnormalities. *Anesth Analg*. 1999;89:601.)

Acknowledgments

This chapter is dedicated to the memory of Dwight C. Legler, MD, who first authored this chapter. He is still sadly missed by all members of the Cardiovascular Division of the Department of Anesthesiology at the Mayo Clinic. Many thanks to Maria A. de Castro, MD, Robert A. Strickland, MD, and William J. Mauermann, MD, for their previous excellent contributions to this chapter.

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25

Anesthesia for Heart, Lung, and Heart-Lung Transplantation

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KEY POINTS

1. Cardiac denervation is an unavoidable consequence of heart transplantation, and reinnervation is at best partial and incomplete.
2. Drugs acting directly on the heart are the drugs of choice for altering cardiac physiology after heart transplantation.
3. Allograft coronary vasculopathy remains the greatest threat to long-term survival after heart transplantation.
4. Broadening of donor criteria has decreased time to lung transplantation.
5. Air trapping in patients with severe obstructive lung disease may impair hemodynamics and require deliberate hypoventilation.
6. Newly transplanted lungs should be ventilated with a low tidal volume and inspiratory pressure and as low an inspired oxygen concentration as can be tolerated.
7. Reperfusion injury is the most common cause of perioperative death.
8. The frequency of heart-lung transplantation has decreased as the frequency of lung transplantations has increased.

Heart Transplantation

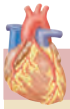
The history of heart transplantation spans almost a century. Canine heterotopic cardiac transplantation was first reported in 1905,[1] but such efforts were doomed by ignorance of the workings of the immune system (Box 25.1). Further research in the late 1950s and early 1960s set the stage for the first human cardiac transplant by Barnard in 1966.[2] However, there were few long-term survivors in this era because of continued deficiency in understanding and modulating the human immune system, and the procedure fell into general disfavor. Continued research at selected centers (such as Stanford University) and lessons learned from renal transplantation led to greater understanding of the technical issues and immunology required, and by the early 1980s, cardiac transplantation gained widespread acceptance as a realistic option for patients with end-stage cardiomyopathy.

Heart transplantation experienced explosive growth in the mid-to-late 1980s, but the annual number of heart transplants worldwide plateaued by the early 1990s at approximately 3500 per year.[3] The factor limiting continued growth has been a shortage of suitable donors. As of February 2015, there were slightly more than 4000 patients on the United Network for Organ Sharing (UNOS) cardiac transplant waiting list (includes all U.S. candidates), an increase of 25% compared with 2004. During that same time period the frequency of heart transplantation also increased (by approximately 17%) but failed to keep pace with the increase in the size of the waiting list. Only 2431 heart transplants were performed in the United States during the 2014 calendar year, slightly above the average of 2290 heart transplants per year over the preceding decade.[4] The median waiting time for a cardiac graft varies widely according to blood type (approximately 52 days for type AB recipients in contrast with 241 days for type O recipients listed for the period 2003–2004, based on OPTN data as of February 1, 2015). Of those patients listed for heart transplantation in 2009, 27.5% had spent more than a year waiting for a transplant. Adult patients on the heart transplant waiting list are assigned a status of 1A, 1B, or 2. Status 1A patients require mechanical circulatory support, mechanical ventilation, high-dose or multiple inotropes, with continuous monitoring of left ventricular filling pressure. Status 1B patients require mechanical circulatory support beyond 30 days or inotropic support without continuous monitoring of left ventricular filling pressure. All other patients are classified as Status 2. The most frequent recipient indications for adult heart transplantation remain either idiopathic or ischemic cardiomyopathy. Other less common diagnoses include viral cardiomyopathy, systemic diseases such as amyloidosis, and complex congenital heart disease (CHD).

The 1-year survival rate after heart transplantation has been reported to be 79%, with a subsequent mortality rate of approximately 4%/year.[3] There has been only slight improvement in the survival statistics over the past decade; the Organ Procurement and Transplant Network reports that the 1- and 3-year survival rates after heart transplantation for those transplanted in the United States during the period 1997 to 2004 were approximately 87% and 78%, respectively.[4] One-year survival rate after repeat heart transplantation more than 6 months after the original procedure is slightly lower (63%) but substantially worse if performed within 6 months of the original grafting (39%).[3] Risk factors for increased mortality have been associated with recipient factors (prior transplantation, poor human leukocyte antigen matching, ventilator dependence, age, and race), medical center factors (volume of heart transplants performed, ischemic time), and donor factors (race, sex, age), and have remained relatively unchanged over the past two decades.[5] Early deaths most frequently are due to graft failure, whereas intermediate-term deaths are caused by acute rejection or infection. Late deaths after heart transplantation most frequently are due to allograft vasculopathy, posttransplant lymphoproliferative disease or other malignancy, and chronic rejection (see Box 25.1).

Recipient Selection

Potential candidates for heart transplantation generally undergo a multidisciplinary evaluation including a complete history and physical examination, routine hematology, chemistries (to assess renal and hepatic function), viral serology, electrocardiography, chest radiography, pulmonary function tests, and right- and left-heart catheterization.



BOX 25.1 HEART TRANSPLANTATION

- Frequency of transplantation remains limited by donor supply.
- Pathophysiology before transplantation is primarily that of end-stage ventricular failure.
- Pathophysiology after transplantation reflects the effects of denervation.
- Allograft coronary vasculopathy is a frequent long-term complication.

Ambulatory electrocardiography, echocardiography, and nuclear gated scans are performed if necessary. The goals of this evaluation are to confirm a diagnosis of end-stage heart disease that is not amenable to other therapies and that will likely lead to death within 1 to 2 years, as well as to exclude extracardiac organ dysfunction that could lead to death soon after heart transplantation. Patients typically have New York Heart Association (NYHA) class IV symptoms and a left ventricular ejection fraction less than 20%. Although most centers eschew a strict age cutoff, the candidate should have a physiologic age younger than 60. Detecting pulmonary hypertension and determining whether it is due to fixed elevation of pulmonary vascular resistance (PVR) is crucial; early mortality because of graft failure is threefold greater in patients with increased PVR (transpulmonary gradient >15 mm Hg or PVR >5 dynes•sec•cm^{-5}).[6] If increased PVR is detected, a larger donor heart, a heterotopic heart transplant, or a heart-lung transplant (HLT) may be more appropriate. Active infection and recent pulmonary thromboembolism with pulmonary infarction are additional contraindications to heart transplantation. The results of this extensive evaluation should be tabulated and available to the anesthesia team at all times because heart transplantation is an emergency procedure.

Donor Selection and Graft Harvest

Once a brain-dead donor has been identified, the accepting transplant center must further evaluate the suitability of the allograft. Centers generally prefer donors to be free of previous cardiac illness and younger than 35 years because the incidence of coronary artery disease markedly increases at older ages. However, the relative shortage of suitable cardiac donors has forced many transplant centers to consider older donors without risk factors and symptoms of coronary artery disease. If it is necessary and the services are available at the donor hospital, the heart can be further evaluated by echocardiography (for regional wall motion abnormalities) or coronary angiography, to complement standard palpation of the coronaries in the operating room. The absence of sepsis, prolonged cardiac arrest, severe chest trauma, and a high inotrope requirement also are important. The donor is matched to the prospective recipient for ABO blood-type compatibility and size (within 20%, especially if the recipient has high PVR); a crossmatch is performed only if the recipient's preformed antibody screen is positive.

Donors can exhibit major hemodynamic and metabolic derangements that can adversely affect organ retrieval.[7] Most brain-dead donors will be hemodynamically unstable.[8] Reasons for such instability include hypovolemia (secondary to diuretics or diabetes insipidus), myocardial injury (possibly a result of catecholamine storm during periods of increased intracranial pressure), and inadequate sympathetic tone because of brainstem infarction. Donors often also have abnormalities of neuroendocrine function such as low T_3 and T_4 levels. Administration of T_3 to brain-dead animals improves ventricular function after transplantation[9]; T_3 administration has enabled decreases in inotropic support in some[10,11] but not all human studies.[12] Donor volume status should be assiduously monitored, and inotropic and vasopressor therapy should be guided by data from invasive monitors.

Donor cardiectomy is performed through a median sternotomy, usually simultaneously with recovery of other organs such as lungs, kidneys, and liver. Just before cardiac harvesting, the donor is heparinized and an intravenous cannula is placed in the ascending aorta for administration of conventional cardioplegia. The superior vena cava (SVC) is ligated and the inferior vena cava (IVC) transected to decompress the heart, simultaneous with the administration of cold hyperkalemic cardioplegia into the aortic root. The aorta is cross-clamped when the heart ceases to eject. The heart also is topically cooled with ice-cold saline. After arrest has been achieved, the pulmonary veins are severed, the SVC is transected, the ascending aorta is divided just proximal to the innominate artery, and the pulmonary artery (PA) is transected at its bifurcation. The heart is then prepared for transport by placing it in a sterile plastic bag that is placed, in turn, in another bag filled with ice-cold saline, all of which are carried in an ice chest. Of all the regimens tested, conventional cardioplegia has proved most effective in maintaining cardiac performance.[13] The upper time limit for ex vivo storage of human hearts appears to be approximately 6 hours.[14]

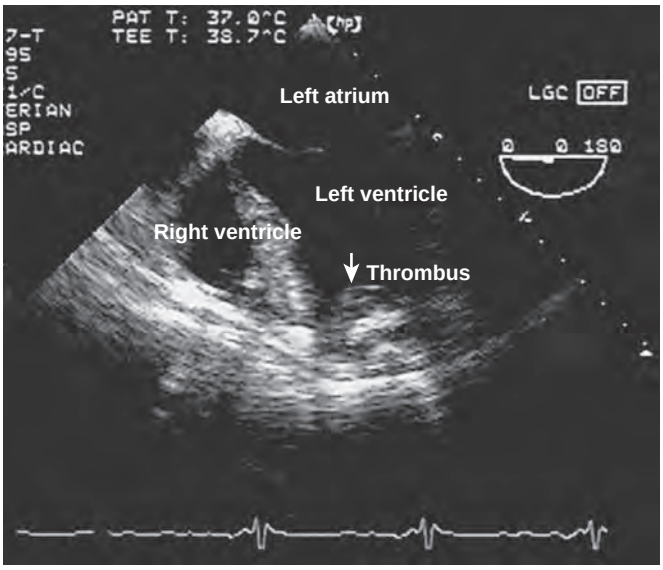


Fig. 25.1 Transesophageal echocardiographic image of laminated intraventricular thrombus in the native left ventricular apex. If intracavitary thrombus is found, great caution is warranted during dissection before cardiopulmonary bypass to avoid systemic embolization.

Surgical Procedures

Orthotopic Heart Transplantation

Orthotopic heart transplantation is carried out via a median sternotomy, and the general approach is similar to that used for coronary revascularization or valve replacement. Frequently, patients will have undergone a prior median sternotomy; repeat sternotomy is cautiously performed using an oscillating saw. The groin should be prepped and draped to provide a rapid route for cannulation for cardiopulmonary bypass (CPB) if necessary. After the pericardium is opened, the aorta is cannulated as distally as possible and the IVC and SVC are individually cannulated via the high right atrium. Manipulation of the heart before institution of CPB is limited if thrombus is detected in the heart with transesophageal echocardiography (TEE; Fig. 25.1). After initiation of CPB and cross-clamping of the aorta, the heart is arrested and excised (Fig. 25.2). The aorta and PA are separated and divided just above the level of their respective valves, and the atria are transected at their grooves. A variant of this classic approach totally excises both atria, mandating bicaval anastomoses. This technique may reduce the incidence of atrial arrhythmias, better preserve atrial function by avoiding tricuspid regurgitation, and enhance cardiac output (CO) after transplantation.[15,16]

The donor graft then is implanted with every effort to maintain a cold tissue temperature, beginning with the left atrial (LA)

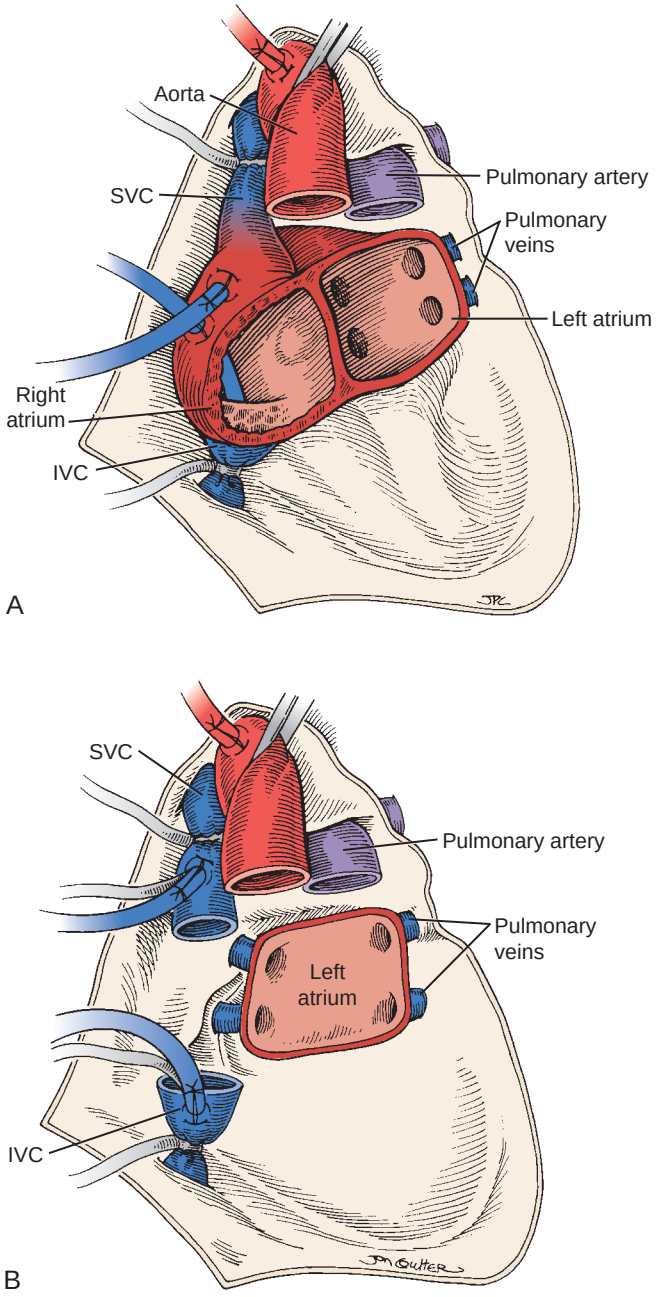


Fig. 25.2 Mediastinum after excision of the heart but before allograft placement. Venous cannulas are present in the superior *(SVC)* and inferior vena cava *(IVC)*, and the arterial cannula is present in the ascending aorta. (A) Classic orthotopic technique. (B) Bicaval anastomotic technique.

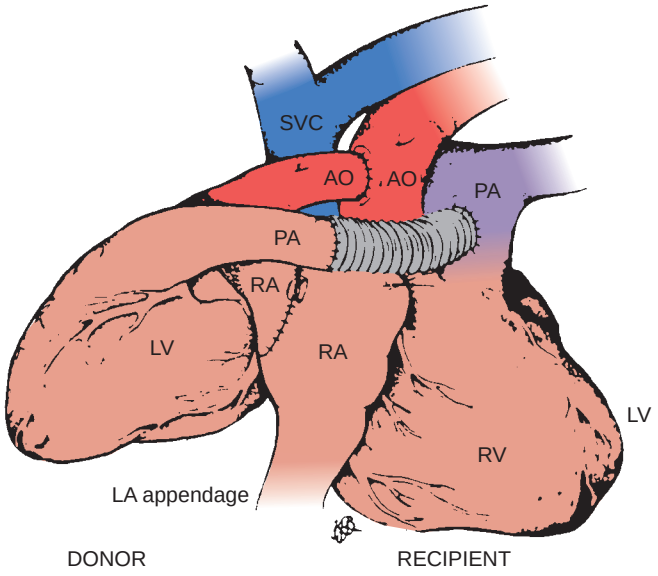


Fig. 25.3 Placement of heterotopic graft in the right chest, with anastomoses to the corresponding native left *(LA)* and right atria *(RA)*, ascending aorta *(AO)*, and an interposition graft to the native pulmonary artery *(PA)*. *LV*, left ventricle; *RV*, right ventricle; *SVC*, superior vena cava. *(From Cooper DKC, Lanza LP.* Heart Transplantation: The Present Status of Orthotopic and Heterotopic Heart Transplantation. *Lancaster, United Kingdom: MTP Press; 1984.)*

anastomosis. If the foramen ovale is patent, it is sutured closed. The donor right atrium is opened by incising it from the IVC to the base of the right atrial (RA) appendage (to preserve the donor sinoatrial node), and the RA anastomosis is constructed. Alternatively, if the bicaval technique is used, individual IVC and SVC anastomoses are sewn. The donor and recipient pulmonary arteries are then brought together in an end-to-end manner, followed by the anastomosis of the donor to the recipient aorta. After removal of the aortic cross-clamp, the heart is de-aired via a vent in the ascending aorta. Just before weaning from CPB, one of the venous cannulae is withdrawn into the right atrium and the other removed. The patient is then weaned from CPB in the usual manner. After hemostasis is achieved, mediastinal tubes are placed for drainage, the pericardium is left open, and the wound is closed in the standard fashion.

Heterotopic Heart Transplantation

Although orthotopic placement of the cardiac graft is optimal for most patients, certain recipients are not candidates for the orthotopic operation, and instead the graft is placed in the right chest and connected to the circulation in parallel with the recipient heart. The two primary indications for heterotopic placement are significant irreversible pulmonary hypertension and gross size mismatch between the donor and recipient. Heterotopic placement may avoid the development of acute right ventricular (RV) failure in the unconditioned donor heart in the face of acutely increased RV afterload.

Donor harvesting for heterotopic placement is performed in the previously described manner, except that the azygos vein is ligated and divided to increase the length of the donor SVC; the PA is extensively dissected to provide the longest possible main and right PA; and the donor IVC and right pulmonary veins are oversewn, with the left pulmonary veins incised to create a single large orifice. The operation is performed via a median sternotomy in the recipient, but the right pleura is entered and excised. The recipient SVC is cannulated via the RA appendage, and the IVC via the lower right atrium. After arresting the recipient heart, the LA anastomosis is constructed by incising the recipient left atrium near the right superior pulmonary vein and extending this incision inferiorly and then anastomosing the respective left atria. The recipient RA-SVC is then incised and anastomosed to the donor RA-SVC, after which the donor aorta is joined to the recipient aorta in an end-to-side manner. Finally, the donor PA is anastomosed to the recipient main PA in an end-to-side manner if it is sufficiently long; otherwise, they are joined via an interposed vascular graft (Fig. 25.3).

Special Situations

Mechanical ventricular assist devices (see Chapters 28 and 36) have been used successfully to bridge patients who would otherwise die of acute heart failure awaiting transplantation.[17] Although ventricular assist devices may improve the survival of patients awaiting transplantation,[18] complications associated with their use may negatively impact

survival after transplantation.[19] The technique of transplantation is virtually identical in such patients to that for ordinary orthotopic transplantation. However, repeat sternotomy is obligatory, and repeat sternotomy is associated with higher morbidity and mortality, as well as higher intraoperative blood use, postoperative length of ICU and hospital stays, and frequency of reoperation for bleeding after subsequent heart transplantation.[20] Placement of large-bore intravenous access is prudent because excessive hemorrhage can occur during or after the transplant procedure.

Rarely, patients will present for cardiac transplantation combined with transplantation of the liver.[21,22] The cardiac allograft usually is implanted first to better enable the patient to survive potential hemodynamic instability associated with reperfusion of the hepatic allograft. Large-bore intravenous access is mandatory. Conventional full heparinization protocols or low-dose heparin with heparin-bonded circuits may be used. A venous cannula can be left in the right atrium at the completion of the heart transplant procedure to serve as a return site for subsequent venovenous bypass during liver transplantation.

Pathophysiology Before Transplantation

The pathophysiology of heart transplant candidates is predominantly end-stage cardiomyopathy. Normally, such patients will have both systolic dysfunction (characterized by decreased stroke volume and increased end-diastolic volume) and diastolic dysfunction, characterized by an increased intracardiac diastolic pressure. As compensatory mechanisms to maintain CO fail, the increased LV pressures lead to increases in pulmonary venous pressures and development of pulmonary vascular congestion and edema. A similar process occurs if RV failure also occurs. Autonomic sympathetic tone is increased in patients with heart failure, leading to generalized vasoconstriction, as well as salt and water retention. Vasoconstriction and ventricular dilation combine to substantially increase myocardial wall tension. Over time, the high levels of catecholamines lead to a decrease in the sensitivity of the heart and vasculature to these agents via a decrease in receptor density (ie, downregulation) and a decrease in myocardial norepinephrine stores.[23]

Therapy of heart failure seeks to reverse or antagonize these processes (see Chapters 11, 36, and 38). Almost all candidates will be maintained on diuretics; hypokalemia and hypomagnesemia secondary to urinary losses are likely, and the anesthesiologist must be alert to the possibility that a patient is hypovolemic from excessive diuresis. Another mainstay of therapy is vasodilators (such as nitrates, hydralazine, and angiotensin-converting enzyme inhibitors), which decrease the impedance to LV emptying and improve cardiac function and survival in patients with end-stage heart failure.[24,25] Paradoxically, slow incremental β-blockade with agents such as the β_1-antagonist metoprolol also can improve hemodynamics and exercise tolerance in some patients awaiting heart transplantation.[26] Patients who are symptomatic despite these measures often will require inotropic therapy. Digoxin is an effective but weak inotrope, and its use is limited by toxic side effects. Phosphodiesterase inhibitors such as amrinone, milrinone, and enoximone are efficacious, but chronic therapy is restricted by concerns about increased mortality in those receiving these agents.[27,28] Therefore inotrope-dependent patients often are treated with intravenous infusions of β-adrenergic agonists such as dopamine or dobutamine. Patients refractory to even these measures may be supported with intraaortic balloon counterpulsation, but its use is fraught with significant vascular complications and essentially immobilizes the patient. Many patients with low CO are maintained on anticoagulants such as warfarin to prevent pulmonary or systemic embolization, especially if they have atrial fibrillation.

Pathophysiology After Transplantation

The physiology of patients after heart transplantation is of interest not only to anesthesiologists in cardiac transplant centers but to the anesthesiology community at large because a substantial portion of these patients return for subsequent surgical procedures (see Chapter 45).[29,30]

Cardiac denervation is an unavoidable consequence of heart transplantation. Many long-term studies indicate that reinnervation is absent,[31,32] or at best partial or incomplete,[33] in humans. Denervation does not significantly change baseline cardiac function,[34,35] but it does substantially alter the cardiac response to demands for increased CO. Normally, increases in heart rate can rapidly increase CO, but this mechanism is not available to the transplanted heart. Heart rate increases only gradually with exercise, and this effect is mediated by circulating catecholamines.[31] Increases in CO in response to exercise are instead mostly mediated via an increase in stroke volume.[36] Therefore maintenance of adequate preload in cardiac transplant recipients is crucial. Lack of parasympathetic innervation probably is responsible for the gradual decrease in heart rate after exercise seen in transplant recipients, rather than the usual sharp decline.

Denervation has important implications in the choice of pharmacologic agents used after cardiac transplantation. Drugs that act indirectly on the heart via either the sympathetic (ephedrine) or parasympathetic (atropine, pancuronium, edrophonium) nervous systems generally will be ineffective. Drugs with a mixture of direct and indirect effects will exhibit only their direct effects (leading to the absence of the normal increase in refractory period of the atrioventricular node with digoxin,[37] tachycardia with norepinephrine infusion, and bradycardia with neostigmine).[38] Thus agents with direct cardiac effects (such as epinephrine or isoproterenol) are the drugs of choice for altering cardiac physiology after transplantation. However, the chronically high catecholamine levels found in cardiac transplant recipients may blunt the effect of α-adrenergic agents, as opposed to normal responses to β-adrenergic agents.[39]

Allograft coronary vasculopathy remains the greatest threat to long-term survival after heart transplantation. Allografts are prone to the accelerated development of an unusual form of coronary atherosclerosis that is characterized by circumferential, diffuse involvement of entire coronary arterial segments, as opposed to the conventional form of coronary atherosclerosis with focal plaques often found in eccentric positions in proximal coronary arteries.[40] The pathophysiologic basis of this process remains elusive, but it is likely due to an immune cell–mediated activation of vascular endothelial cells to upregulate the production of smooth muscle cell growth factors.[41] More than half of all heart transplant recipients have evidence of concentric atherosclerosis 3 years after transplant, and more than 80% at 5 years.[42] Because afferent cardiac reinnervation is rare, a substantial portion of recipients with accelerated vasculopathy will have silent ischemia.[43] Noninvasive methods of detecting coronary atherosclerosis are insensitive for detecting allograft vasculopathy.[44] Furthermore, coronary angiography often underestimates the severity of allograft atherosclerosis[45]; other diagnostic regimens such as intravascular ultrasound and dobutamine stress echocardiography may detect morphologic abnormalities or functional ischemia, respectively, in the absence of angiographically significant lesions.[40,45,46] Therefore the anesthesiologist should assume that there is a substantial risk for coronary vasculopathy in any heart transplant recipient beyond the first 2 years, regardless of symptoms, the results of noninvasive testing, and even angiography.

Anesthetic Management

Preoperative Evaluation and Preparation

The preoperative period often is marked by severe time constraints because of the impending arrival of the donor heart. Nevertheless, a rapid history should screen for last oral intake, recent anticoagulant use, intercurrent deterioration of ventricular function, or change in anginal pattern; a physical examination should evaluate present volume status, and a laboratory review (if available) and a chest radiograph should detect the presence of renal, hepatic, or pulmonary dysfunction. Many hospitalized patients will be supported with inotropic infusions and/or an intraaortic balloon pump, and the infusion rates and timing of the latter should be reviewed.

Equipment and drugs similar to those usually used for routine cases requiring CPB should be prepared. A β-agonist such as epinephrine should be readily available both in bolus form and as an infusion to rapidly treat ventricular failure; and an α-agonist such as phenylephrine or norepinephrine is useful to compensate for the vasodilatory effects of anesthetics because even small decreases in preload and afterload can lead to catastrophic changes in CO and coronary perfusion in these patients.

Placement of invasive monitoring before induction will facilitate rapid and accurate response to hemodynamic events during induction. In addition to standard noninvasive monitoring, an arterial catheter and a PA catheter (with a long sterile sheath to allow partial removal during graft implantation) are placed after judicious use of sedation and local anesthetics. Placing the arterial catheter in a central site rather than the radial artery will avoid the discrepancy between radial and central arterial pressure often seen after CPB, but it also may be necessary to cannulate a femoral artery for arterial inflow for CPB if there has been a prior sternotomy. Floating the PA catheter into correct position may be difficult because of cardiac chamber dilation and severe tricuspid regurgitation. Large-bore intravenous access is mandatory, especially if a sternotomy has been previously performed, in which case external defibrillator/pacing patches also may be useful. The overall hemodynamic picture should be evaluated and optimized insofar as possible just before induction. If the hemodynamics seem tenuous, then starting or increasing an inotrope infusion may be advisable.

Induction

Most patients presenting for heart transplantation will not be in a fasting state and should be considered to have a full stomach. Therefore the induction technique should aim to rapidly achieve control of the airway to prevent aspiration while avoiding myocardial depression. A regimen combining a short-acting hypnotic with minimal myocardial depression (etomidate, 0.3 mg/kg), a moderate dose of narcotic to blunt the tachycardic response to laryngoscopy and intubation (fentanyl, 10 μg/kg), and succinylcholine (1.5 mg/kg) is popular[47]; high-dose narcotic techniques with or without benzodiazepines also have been advocated.[48,49] Vasodilation should be countered with an α-agonist. Anesthesia can be maintained with additional narcotic and sedatives (benzodiazepines or scopolamine).[49,50]

Intraoperative Management

After induction, the stomach can be decompressed with an orogastric tube and a TEE probe introduced while the bladder is catheterized. A complete TEE examination often will reveal useful information not immediately available from other sources, such as the presence of cardiac thrombi (see Fig. 25.1), ventricular volume and contractility, and atherosclerosis of the ascending aorta and aortic arch. Crossmatched blood should be immediately available once surgery commences, especially if the patient has had a previous sternotomy; patients not previously exposed to cytomegalovirus should receive blood from donors who are likewise cytomegalovirus negative. Sternotomy and cannulation for CPB are performed as indicated earlier. The period before CPB often is uneventful, apart from arrhythmias and slow recovery of coronary perfusion because of manipulation of the heart during dissection and cannulation. The PA catheter should be withdrawn from the right heart before completion of bicaval cannulation.

Once CPB is initiated, ventilation is discontinued and the absence of a thrill in the carotid arteries is documented. Most patients will have an excess of intravascular volume, and administration of a diuretic and/or the use of hemofiltration via the pump may be beneficial by increasing the hemoglobin concentration. A dose of glucocorticoid (methylprednisolone, 500 mg) is administered as the last anastomosis is being completed before release of the aortic cross-clamp to attenuate any hyperacute immune response. During the period of reperfusion an infusion of an inotrope is begun for both inotropy and chronotropy. TEE is used to monitor whether the cardiac chambers are adequately de-aired before weaning from CPB.

Weaning from bypass begins after ventilation is resumed and the cannula in the SVC is removed. The donor heart should be paced if bradycardia is present despite the inotropic infusion. Once the patient is separated from CPB, the PA catheter can be advanced into position. Patients with increased PVR are at risk for acute RV failure and may benefit from a pulmonary vasodilator such as prostaglandin E_1 (0.05–0.15 μg/kg/min).[51] Rarely, such patients will require support with a RV assist device.[52] TEE often will provide additional useful information about right- and left-heart function and volume, and document normal flow dynamics through the anastomoses. Unless a bicaval anastomosis was created, a ridge of redundant tissue will be evident in the left atrium and should not cause alarm (see Videos 25.1 and25.2).

Protamine then is given to reverse heparin's effect after satisfactory weaning from CPB. Continued coagulopathy despite adequate protamine is common after heart transplantation, especially if there has been a prior sternotomy. Treatment is similar to that used for other postbypass coagulopathies: meticulous attention to surgical hemostasis, empiric administration of platelets, and subsequent addition of fresh-frozen plasma and cryoprecipitate guided by subsequent coagulation studies (see Chapters 19, 34, and 35). After adequate hemostasis is achieved, the wound is closed in standard fashion and the patient transported to the intensive care unit (ICU).

Postoperative Management and Complications

Management in the ICU after the conclusion of the procedure essentially is a continuation of the anesthetic management after CPB.[53] The electrocardiogram; arterial, central venous, and/or PA pressures; and arterial oxygen saturation are monitored continuously. Cardiac recipients will continue to require β-adrenergic infusions for chronotropy and inotropy for up to 3 to 4 days. Vasodilators may be necessary to control arterial hypertension and decrease impedance to LV ejection. Patients can be weaned from ventilatory support and extubated when the hemodynamics are stable and hemorrhage has ceased. The immunosuppressive regimen of choice (typically consisting of cyclosporine, azathioprine, and prednisone, or tacrolimus and prednisone) should be started after arrival in the ICU. Invasive monitoring can be withdrawn as the inotropic support is weaned, and mediastinal tubes removed after drainage subsides (usually after 24 hours). Patients usually can be discharged from the ICU after 2 or 3 days (see Chapters 37–39).

Early complications after heart transplantation include acute and hyperacute rejection, cardiac failure, systemic and pulmonary hypertension, cardiac arrhythmias, renal failure, and infection. Hyperacute rejection is an extremely rare but devastating syndrome mediated by preformed recipient cytotoxic antibodies against donor heart antigens. The donor heart immediately becomes cyanotic from microvascular thrombosis and ultimately ceases to contract.[54] This syndrome is lethal unless the patient can be supported mechanically until a suitable heart is found. Acute rejection is a constant threat in the early postoperative period and may present in many forms (eg, low CO, arrhythmias). Acute rejection occurs most frequently during the initial 6 months after transplantation, so its presence is monitored by serial endomyocardial biopsies, with additional biopsies to evaluate any acute changes in clinical status. Detection of rejection mandates an aggressive increase in the level of immunosuppression, usually including pulses of glucocorticoid or a change from cyclosporine to tacrolimus. Low CO after transplantation may reflect a number of causative factors: hypovolemia, inadequate adrenergic stimulation, myocardial injury during harvesting, acute rejection, tamponade, or sepsis. Therapy should be guided by invasive monitoring, TEE, and endomyocardial biopsy. Systemic hypertension may be caused by pain, so adequate analgesia should be obtained before treating blood pressure with a vasodilator. Because fixed pulmonary hypertension will have been excluded during the recipient evaluation, pulmonary hypertension after heart transplantation usually will be transient and responsive to vasodilators such as prostaglandin E_1, nitrates, or hydralazine after either orthotopic or heterotopic placement.[55,56] Atrial and ventricular tachyarrhythmias are common after heart transplantation[57]; once rejection has been ruled

out as a cause, antiarrhythmics are used for conversion or control (except those acting via indirect mechanisms such as digoxin, or those with negative inotropic properties such as β-blockers and calcium channel blockers). Almost all recipients will require either β-adrenergic agonists or pacing to increase heart rate in the immediate perioperative period, but 10% to 25% of recipients also will require permanent pacing.[58,59] Renal function often improves immediately after transplantation, but immunosuppressives such as cyclosporine and tacrolimus may impair renal function.[60,61] Finally, infection is a constant threat to immunosuppressed recipients. Bacterial pneumonia is frequent early in the postoperative period, with opportunistic viral and fungal infections becoming more common after the first several weeks (see Chapter 41).

Pediatric Considerations

In the pediatric population, cardiomyopathy, complex CHD, and repeat transplant are the primary indications for heart transplantation. Cardiomyopathy is the most common indication for pediatric heart transplantation and has been an increasing indication over the past 30 years.[62,63] The ages and indications of patients with CHD undergoing heart transplant is changing as surgical management of CHD continues to advance. The most common indication in the CHD population for transplant is failed single-ventricle palliation.[63] Repeat heart transplant is rare in pediatrics and is associated with worse outcomes compared with the original transplant.

A 2007 scientific statement from the American Heart Association presented recommended indications for pediatric heart transplant mostly based on expert consensus.[64] A class I indication for pediatric heart transplant was class D heart failure defined as symptomatic heart failure at rest requiring continuous inotropic support, mechanical ventilation, or mechanical device support. Pediatric patients with class C heart failure (current or past history of symptomatic heart failure) who were at risk of sudden death or development of pulmonary hypertension should also be listed for heart transplant. The biggest challenge for pediatric transplant programs is to determine which CHD patients are symptomatic, at risk for sudden death, or at risk of developing pulmonary hypertension. In general, transplantation is recommended in patients who have decompensated heart failure refractory to medical treatment and CHD patients that are not candidates for reparative surgery or palliation.

Overall survival has improved in children undergoing heart transplantation. Enhanced preservation of the donor heart, improved selection of recipients and donors, and refinements in surgical techniques and immunosuppressive therapy have contributed to this trend.[62,65] Unfortunately, the number of potential recipients will always exceed the supply of organ donors. Strategies to decrease the waiting list include limiting transplantation to patients with CHD to those with ventricular dysfunction, severe valvular dysfunction, or severe coronary anomalies. ABO-incompatible transplantation is also now permitted under UNOS guidelines in children younger than 1 year of age with any isohemagglutinin titer and for children between 1 and 2 years of age with isohemagglutinin titers of 1:4 or lower. Despite strategies to shorten the waiting time, wait list mortality is 17% for pediatric heart transplant candidates with infants currently having the longest waiting time.[66,67]

The preoperative assessment for heart transplantation in the patient with complex CHD can be quite extensive depending on the heart defect and previous corrective or palliative procedures. Similar to the child with dilated cardiomyopathy, assessment of the indexed pulmonary vascular resistance (PVRI) is essential.[59] Transplantation with an increased PVRI is potentially contraindicated because it is associated with acute right ventricular failure and mortality. In adults, a PVRI greater than 5 units and a transpulmonary gradient greater than 15 mm Hg are generally contraindications for transplantation.[6] The upper limit of PVR associated with successful cardiac transplantation has not been established in children. Acceptable PVRI is less than 10 units in children, but it is not unusual for a pediatric heart transplant candidate to have a PVRI greater than 10 units. However, even in the 6 to 10 unit range, the child is at risk for acute RV failure because the donor's right ventricle is thin walled and the myocardium has been ischemic. If the PVRI decreases significantly in the catheterization laboratory, with a trial of vasodilator testing, hyperventilation, administering 100% fraction of inspired oxygen, and nitric oxide, the candidate is deemed acceptable for transplant. If the PVRI remains borderline, the candidate is admitted to the hospital for a 1- or 2-week trial with milrinone and dobutamine. If the PVRI then falls, transplantation is offered with the thought that these patients might benefit from pulmonary vasodilation therapy during weaning from CPB and in the ICU after transplantation.

Another aspect to be emphasized in the pretransplant evaluation of these patients with complex CHD is the need for a detailed anatomic evaluation. It is not uncommon for this group of patients to have branch pulmonary artery stenosis, discontinuous pulmonary arteries, abnormal pulmonary venous return, hypoplastic aortic arch, and coarctation of the aorta. Anomalies of systemic and pulmonary veins are associated with atrial isomerism, and different surgical techniques are needed to address these issues during transplantation. The most common indication for cardiac transplantation in CHD patients is for the so-called failed Fontan for physiologic repair of cardiac defects with single ventricle.[63] They present with protein-losing enteropathy, chronic liver disease, and pulmonary arteriovenous malformations. The existence of large aortopulmonary collaterals can lead to high-output failure or moderate-to-severe hypoxemia that may lead to primary graft failure. Small malformations may regress with time. Although the donor ischemic time, ICU days, and total hospital days are prolonged in CHD patients, the outcome is comparable to the patient with dilated cardiomyopathy after heart transplantation.

In some recipients, the circulation is supported by extracorporeal membrane oxygenation (ECMO) or a ventricular assist device as a bridge to transplantation. Prolonged support is associated with bleeding, sepsis, and multiorgan dysfunction. It is not uncommon to list an infant who is on ECMO for heart transplant after a failed Norwood procedure. The need for ECMO is associated with increased waitlist mortality.[66–68]

Besides determining the blood type (ABO), it is important to assess for the presence of antibodies against human histocompatibility leukocyte antigen (HLA). Anti-HLA antibodies are uncommon in in patients with cardiomyopathy, but may have developed in the recipient who was exposed to blood products during palliation for complex CHD. Transplantation in the setting of elevated panel reactive antibody greater than 10% or allosensitization carries an increased risk of mortality.[69] Techniques to decrease the circulating anti-HLA antibodies (desensitization) include administering IVIG, cyclophosphamide, mycophenolate mofetil or plasmapheresis.[70,71]

Children are naturally anxious before surgery and premedication is provided with benzodiazepines. Preoperative placement of invasive monitors is typically not feasible in children prior to induction; however, noninvasive monitoring should be in place before induction. A peripheral IV or other long-term intravenous access will already be in place, permitting an intravenous induction. Full-stomach precautions are generally recommended; however, children typically do not tolerate prolonged periods of apnea. In addition, hypoxia and hypercarbia will aggravate PVR, necessitating expert airway management. Induction of anesthesia can be accomplished with any sedative-hypnotic agent, including propofol, etomidate, or high-dose narcotic (fentanyl), a benzodiazepine, and a nondepolarizing muscle relaxant. Titration to vital signs is important. Arterial and central venous access is obtained, and large-bore venous access is also recommended because postoperative bleeding is common in patients with CHD owing to extensive scarring and adhesions from previous palliative procedures.

Anesthesia is maintained with an inhalation agent, additional opioid, benzodiazepine, and nondepolarizing muscle relaxants. Frequently, the groin vessels are exposed for urgent cannulation before sternotomy, and during this procedure fewer narcotics are required. A PA catheter can be used in the older child, but direct measurement of

RV pressures in the grafted organ can be transduced by the surgeon if there are concerns about pulmonary hypertension.

Acute RV dysfunction is a major postbypass problem. with acute RV failure occurring in an estimated 15% to 40% of pediatric heart transplants.[72] In pediatric procedures, the donor-recipient heart size matching (by weight) ranges between 80% and 160%; however, the upper limit can be increased for neonates and in cases in which there is concern for pulmonary hypertension. Measures to preserve donor RV function posttransplant include keeping PVR normal by suctioning the endotracheal tube, maintaining adequate oxygenation and moderate hyperventilation, and ensuring adequate anesthesia and analgesia to decrease circulating catecholamines. Milrinone is used for providing inotropy and decreasing PVR, whereas nitric oxide is a useful adjunct. Patients may occasionally need to be placed on ECMO to allow for pulmonary artery pressure normalization and recovery of RV function.

Lung Transplantation

History and Epidemiology

Although the first human lung transplant was performed in 1963, surgical technical problems and inadequate preservation and immunosuppression regimens prevented widespread acceptance of this procedure until the mid-1980s (Box 25.2). Advances in these areas have since made lung transplantation a viable option for many patients with end-stage lung disease. According to data collected by UNOS between 2000 and 2002, the annual frequency of lung transplantation has remained stagnant, with the total number still averaging in the vicinity of 1000. Further growth in lung transplantation was feared to be constrained by a shortage of donor organs, with demand for organs still vastly exceeding supply. This was expected to be potentially exacerbated by data that were published in 2009, revealing that double-lung transplant afforded fewer hospitalizations and potentially better long-term survival.[73] Despite these data, since 2003 the number of double-lung transplants has increased significantly in the United States, whereas the number of single-lung transplants remained stagnant. The greatest growth in double-lung transplant occurred in the population with chronic obstructive pulmonary disease without alpha-1 antitrypsin deficiency and interstitial lung disease.

According to the most recent data available for the Registry of the International Society of Heart and Lung Transplantation for the period January 1, 1985, to June 30, 2013, a total of 47,647 lung transplants were reported.[3] This total was made up of 45,697 first transplants and 1950 retransplantations. Retransplants have consistently remained at about 5% of the total number of transplants in the United States, whereas European data suggested 3.6%. Younger and female patients represented the greatest chance of retransplant. The year 2011 saw the highest number of transplants; there was a decrease in the number of low-volume centers (defined as fewer than 10 transplants per year) with a commensurate increase in the number of high-volume centers performing more procedures. Between 2008 and 2013, 156 centers reported doing lung transplant procedures. Of these, 44 centers accounted for 65% of all lung transplants and 14 centers reported volumes of greater than 50 transplants per year.[74]

It is estimated that more than one million individuals with end-stage lung disease are potential recipients of lung transplants.[75] The Organ Procurement and Transplantation Network has 1643 patients listed as candidates for lung transplantation in the United States. This number does not accurately reflect the number of organs required because some patients will require bilateral lung transplantation. Average time to transplant increased to as high as 451 days in 1999; however, most recently, that time has declined to 325 days for those waiting for 1 to 2 years. After stagnating from 2001 to 2003 at slightly more than 1000 transplants annually, the number of transplants in the United States has grown steadily since 2010 to between 1700 and 1900 annually. Currently, about one-fourth of patients undergo transplant within 251 days. Most of this improvement has been seen with recipients who are 50 years and older. One explanation for this may be increasing leniency in organ-selection criteria. The use of expanded criteria does not appear to have been associated with an increase in mortality. Mortality for patients on the waiting list also has continued to decline, from a 2001 high of about 500 to approximately 198 in 2014.[74] Although some of this improvement may be ascribed to better medical management of patients on the waiting list, it is also likely due to broadened criteria for acceptance for transplantation and the corresponding increase in the number of transplants performed per year.

Data from 1990 to 2012 have shown a median survival of about 5.7 years, with 88% surviving 3 months, 80% surviving 1 year, 65% at 3 years, 53% at 5 years, and 32% at 10 years. Improvement has continued over time; this is reinforced by the increase in 3-month survival from 83% to 91% and by 1-year survival improvement from 72% to 83% over the entire reporting period. Double-lung transplant recipients did better than single-lung transplants, with median survival being 7.0 years as compared for 4.5 years for single-lung transplants.[74]

Younger and female recipients showed improved survival over older and male recipients (Fig. 25.4). Patients who received lungs from CMV-negative donors had better survival over lungs received from CMV-positive donors.

Even better survival data have been reported from centers with extensive experience with these procedures (1-year survival rates of 82% for double-lung recipients and 90% for single-lung recipients).[76] Infection is the most frequent cause of death in the first year after transplant, but this is superseded in later years by bronchiolitis obliterans.[3] Additional causes for mortality are primary graft, failure, technical problems with the procedure, and cardiovascular causes. In patients who have longer survival, the causes shift more toward bronchiolitis obliterans (BO), chronic rejection, and malignancy. Notable is that 21% of all lung transplants were performed at 21 centers around the world averaging 50 procedures per year.[3]

Some of the most challenging patients are those with cystic fibrosis (Fig. 25.5). The 1-year survival rate of 79% and 5-year survival rate of 57% after lung transplantation have shown that despite the high incidence of poor nutrition and the almost ubiquitous colonization by multidrug-resistant organisms, these patients can still successfully undergo lung transplantation with acceptable outcomes data.[77]

It is a sign of the maturity of lung transplantation procedures that survival data for redo lung transplantation also are becoming available. Retransplantation has very high early mortality and a median survival rate of only 2.5 years.[74]

Infection and multiorgan failure before repeat transplant are associated with an almost uniformly fatal outcome. Subsequent data from

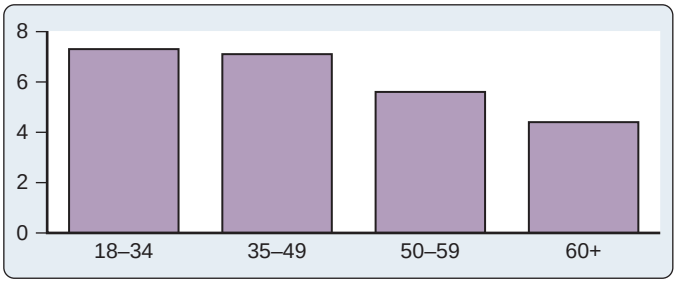


Fig. 25.4 Median survival in years by recipient age.

BOX 25.2 LUNG TRANSPLANTATION

- Broader donor criteria have decreased the time from listing to transplantation.
- Nitric oxide minimizes reperfusion injury.
- Donor lungs should be ventilated with a protective strategy (low inspired oxygen, low tidal volume/inspired pressure) after transplantation.

BOX 25.3 RISK FACTORS FOR INCREASED MORTALITY

- Smaller transplant center: 30 transplants per year
- Greater donor-to-recipient height mismatch
- Older recipient: older than 55
- Higher bilirubin
- Higher supplemental oxygen therapy
- Lower cardiac output
- Lower FVC
- Higher creatinine

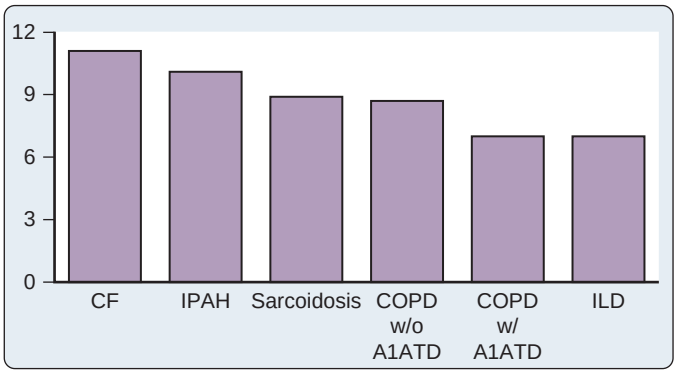


Fig. 25.5 Median survival in 1-year survivors by indication. *A1ATD,* alpha-1 antitrypsin deficiency; *CF,* cystic fibrosis; *COPD,* chronic obstructive pulmonary disease; *ILD,* interstitial lung disease.

UNOS, however, have shown an improvement, with the 1-year survival rate at 66.3% in the retransplant patients as compared with 83.8% in the primary transplant population. This is, however, significantly worse at 3 years, with repeat survival rate at 38.8% compared with 63.2% (Box 25.3).

Recipient Selection

Because donor lungs are scarce, it is important to select those most likely to benefit from lung transplantation as recipients. In general, candidates should be terminally ill with end-stage lung disease (NYHA class III or IV, with a life expectancy of approximately 2 years), be psychologically stable, and be devoid of serious medical illness (especially extrapulmonary infection) compromising other organ systems. Patients already requiring mechanical ventilation are poor candidates, although lung transplantation can be successful in such a setting. Other factors such as advanced age, previous thoracic surgery or deformity, and steroid dependence may be regarded as relative contraindications by individual transplant centers. Hepatic disease solely caused by right-heart dysfunction should not preclude candidacy (Boxes 25.4 and 25.5).

Potential recipients undergo a multidisciplinary assessment of their suitability, including pulmonary spirometry, radiography (plain film and chest CT scan), and echocardiography or multigated image acquisition scan. Patients older than 40 years and those with pulmonary hypertension usually undergo left-heart catheterization to exclude significant coronary atherosclerosis or an intracardiac shunt. TEE may yield data (eg, unanticipated atrial septal defect) that will alter subsequent surgical approach in approximately one-quarter of patients with severe pulmonary hypertension.[78] Candidates who are accepted often are placed on a physical conditioning regimen to reverse muscle atrophy and debilitation and kept within 20% of their ideal body weight. Because lung transplantation is an emergency procedure (limited by a lung preservation time of 6–8 hours),[79] results of this

BOX 25.4 ABSOLUTE CONTRAINDICATIONS FOR LUNG TRANSPLANTATION

- Malignancy within 2 years (preferably 5 years)
- Untreatable significant disease in another organ system
- Atherosclerotic disease not corrected
- Acute medical instability: hepatic failure
- Bleeding diathesis that is not correctable
- Mycobacterium tuberculosis infection
- Highly virulent or resistant microbial infections
- Chest wall deformity
- Obesity
- Medical noncompliance
- Psychiatric disease leading to noncooperation in management plan
- Absent social support system
- Substance abuse/addition
- Severely impaired functional status

BOX 25.5 RELATIVE CONTRAINDICATIONS FOR LUNG TRANSPLANTATION

- Age >65 years with limited functional reserve
- Obesity
- Malnutrition
- Severe osteoporosis
- Prior lung resection surgery
- Mechanical ventilation or ECLS
- Highly resistant bacterial colonization
- Hepatitis B and C
- HIV infection with detectable viral load
- *Burkholderia* and *Mycobacterium abscessus* infection in which good control is not expected

comprehensive evaluation should be readily available to the anesthesiology team at all times. Ideally, the transplant recipient should also see the anesthesiology team at the time of evaluation to determine whether the patient has any specific anesthetic challenges. This will allow for the team taking care of the patient to rapidly assess the patient before transplantation. Weiss[80] published data in 2009 that supported the cautious transplantation of patients older than 60 years but recommended against transplantation of patients older than 70. Data from the same authors suggested that race-matching also provided a survival benefit that manifested itself in the first 2 years after transplant.[81]

Mechanical bridging therapy is now available as a way to provide longer support of the recipient until a suitable organ can be located. Mechanical ventilation is the most commonly used mechanism and often used to support the patient between exacerbations of their underlying disease but is not without risk of develop ventilator-associated infection or injury. Extracorporeal life support (ECLS) has been thought of for a long time but initial survival data were discouraging. The ideal candidate is young with no multiorgan dysfunction and in appropriate medical condition to allow rehabilitation. The outcomes have improved to the degree that post-ECLS transplanted patients have similar outcomes as those without the need for ECLS. The UNOS database has shown improved 1-year survival from 30% in 2005 to an impressive 75% in 2010 for those using ECLS. Despite this promise there are still significant risks of complication related to coagulopathy, infection, and complications arising at sites of vascular access.[82] Fuehner and colleagues described the use of ECLS in awake patients who were allowed to ambulate and receive therapy to maintain their conditioning.[83]

Donor Selection and Graft Harvest

The ongoing shortage of suitable donor organs has led to a liberalization of selection criteria. Prospective lung donors who were cigarette smokers are no longer rejected simply based on a pack-year history. Computed tomography has been used to assess the structural integrity of the lung, particularly in donors who have suffered traumatic chest injury. Lungs that have contusion limited to less than 30% of a single lobe can be considered adequate.[84] Greater use also has been made of organs from older but otherwise healthy donors (55 to 60 years old), especially when the ischemic period will be short.[85] A clear chest radiograph, normal blood gas results, unremarkable findings on bronchoscopy, sputum stain, and direct intraoperative bronchoscopic and gross evaluation confirm satisfactory lung condition. The lungs are matched to the recipient for ABO blood type and size (oversized lungs can result in severe atelectasis and compromise of venous return in the recipient, especially after double-lung transplantation). Donor serology and tracheal cultures will guide subsequent antibacterial and antiviral therapy in the recipient.

Most lung grafts are recovered during a multivisceral donor harvest procedure. The heart is removed as described for heart transplantation, using inflow occlusion and cardioplegic arrest, with division of the IVC and SVC, the aorta, and the main PA. Immediately after cross-clamping, the pulmonary vasculature is flushed with ice-cold extracellular preservative solution, which often contains prostaglandin E_1. This is believed to promote pulmonary vasodilation, which aids homogenous distribution of the preserving solution. Other additives that have been included are nitroglycerin and low-potassium 5% dextran. The left atrium is divided to leave an adequate LA cuff for both the heart graft and lung graft(s) with the pulmonary veins. After explantation, the lung also may be flushed to clear all pulmonary veins of any clots. After the lung is inflated, the trachea (or bronchus for an isolated lung) is clamped, divided, and stapled closed. Inflating the lung has been shown to increase cold ischemia tolerance of the donor organ. The lung graft is removed, bagged, and immersed in ice-cold saline for transport. The use of extracellular preservation fluid has been shown to be beneficial in protecting the lungs from ischemia/reperfusion injury. However, the most important factor to consider when determining resistance to ischemia/reperfusion is the duration of the ischemia itself. When the ischemia time exceeds 330 minutes, the risk of mortality rapidly increases.[86]

Recipients who have donor-specific antibodies (DSA) tend to worse short- and long-term outcomes. These patients may need to be considered for an aggressive desensitization protocol that entails plasma exchange and is carried out immediately after anesthetic induction and terminated before the perfusion of the first donor allograft. In addition to this, patients will receive rabbit antithymocyte globulin (ATG) after the final plasma exchange and mycophenylate in the postoperative period. With this protocol, patients who were sensitized were able to have outcomes similar to those who were not sensitized.[87]

Induction of immunosuppression is becoming more commonplace but has remained controversial. The goal is to decrease the degree of calcineurin inhibitor use and its attendant side effects. Whitson and associates showed in a review of the UNOS database that the use of induction with agents such as alemtuzumab and basiliximab improved outcomes.[88]

Surgical Procedures

Because of the relative shortage of lung donors and the finding that recipients can gain significant exercise tolerance even with only one transplanted lung,[89] single-lung transplantation used to be the procedure of choice for all lung transplant candidates. Subsequently, however, the published data have indicated better outcomes for those patients receiving double-lung transplant. Certain situations exist in which it is, practically speaking, better to transplant both lungs. For example, the presence of lung disease associated with chronic infection (cystic fibrosis and severe bronchiectasis) mandates double-lung transplantation to prevent the recipient lung from acting as a reservoir of infection and subsequently cross-contaminating the allograft. Patients with severe air trapping may require double-lung transplantation if uncontrollable ventilation/perfusion mismatching will be likely after transplantation. Lobar transplantation into children and young adults from living related donors is discussed separately later in this chapter.

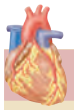
Single-Lung Transplant

The choice of which lung to transplant is usually based on multiple factors, including avoidance of a prior operative site, preference for removing the native lung with the worst ventilation/perfusion ratio, and donor lung availability. The recipient is positioned for a posterolateral thoracotomy, with the ipsilateral groin prepped and exposed in case CPB becomes necessary. With the lung isolated, a pneumonectomy is performed, with special care to preserve as long a PA segment as possible. After removal of the diseased native lung, the allograft is positioned in the chest with particular attention taken to maintaining its cold tissue temperature. The bronchial anastomosis is performed first. A telescoping anastomosis is used if there is significant discrepancy in size between the donor and the recipient. The object of the technique is to minimize the chance of dehiscence. Although it was once common to wrap bronchial anastomoses with omentum, wrapping produces no added benefit when a telescoping anastomosis is performed. The PA is anastomosed next, and finally, the left atrial cuff on the allograft containing the pulmonary venous orifices is anastomosed to the native left atrium. The pulmonary circuit is then flushed with blood and de-aired. The initial flush solution is usually cold (4°C) but is followed by a warm (37°C) flush. The warm flush usually is performed during final completion of the vascular anastomoses. The administration of pulmonoplegia aims to achieve a controlled reperfusion.[90] The contents of this solution are listed in Box 25.6.

After glucocorticoid administration, the vascular clamps are removed and reperfusion is begun. The vascular anastomoses are inspected for any areas of hemorrhage, and then the lung is reinflated with a series of ventilations to full functional residual capacity. After achieving adequate hemostasis and satisfactory blood gases, chest tubes are placed, the wound is closed, and the patient is transported to the ICU.

Double-Lung Transplant

Early attempts at double-lung transplantation using an en bloc technique via a median sternotomy were plagued by frequent postoperative airway dehiscence because of poor vascular supply of the tracheal anastomosis, by hemorrhage caused by extensive mediastinal dissection (which also resulted in cardiac denervation), by the requirement for complete CPB and cardioplegic arrest (to facilitate pulmonary arterial and venous anastomoses), and by poor access to the posterior mediastinum. The subsequent development of the bilateral sequential lung transplant technique via a "clamshell" thoracosternotomy (essentially, two single-lung transplants performed in sequence) has avoided many of the problems inherent in the en bloc technique.[91,92] An alternative to using a clamshell incision in slender patients is an approach



BOX 25.6 WARM PULMONOPLEGIA

- Hematocrit 18 to 20, leukocyte-depleted
- L-Glutamate
- L-Aspartate
- Adenosine
- Lidocaine
- Nitroglycerin
- Verapamil
- Dextrose
- Insulin

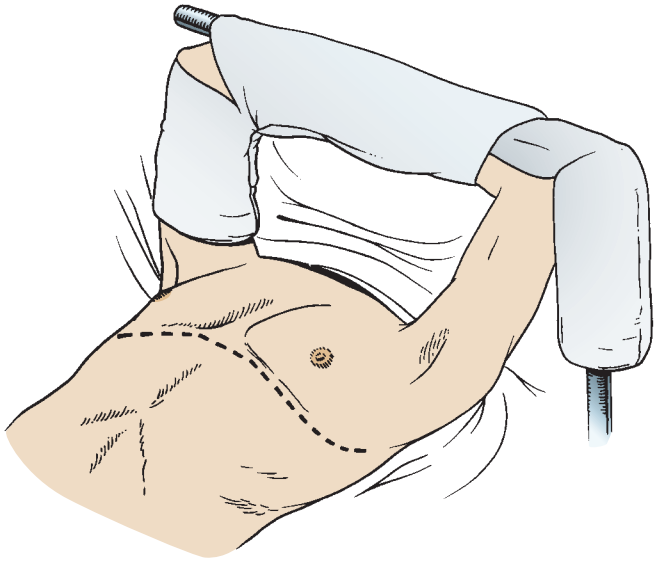


Fig. 25.6 Patient positioning for clamshell thoracosternotomy. The arms are padded and suspended from an ether screen above the head of the patient. Path of surgical incision is shown with *dotted line*. *(From Firestone LL, Firestone S. Organ transplantation. In: Miller RD, ed.* Anesthesia. *4th ed. New York: Churchill Livingstone; 1994, p 1981.)*

through two individual anterolateral thoracotomies. This can result in a particularly pleasing cosmetic result in female patients because the scar can be hidden in the breast crease. Use of CPB is optional, but it does result in better exposure of the posterior mediastinum, thus improving hemostasis, and cardiac denervation usually can be avoided. Pleural scarring usually is extensive in patients with cystic fibrosis, and postoperative hemorrhage and coagulopathy are common and potentially exacerbated if CPB is required. Transplantation of both lungs is performed in the supine position. The groin is prepped and exposed in case CPB is required. If a clamshell incision is used, the arms are padded and suspended over the head on an ether screen (Fig. 25.6). In the slender patient whose anteroposterior chest dimensions are normal, the arms may be tucked at the patient's sides. Recipient pneumonectomy and implantation of the donor lung are performed sequentially on both sides in essentially the same manner as described earlier for a single-lung transplant. The native lung with the worst function should be transplanted first. In patients whose indication for transplantation is suppurative disease, the pleural cavity is pulse-lavaged with antibiotic-containing solution that has been tailored to that patient's antimicrobial sensitivity profile, although it is unclear if this has any effect on subsequent infection. In addition to this, the anesthesiologist irrigates the trachea and bronchi with diluted iodophor solution before the donor lung is brought onto the surgical field.

Pathophysiology Before Transplantation

Patients with highly compliant lungs and obstruction of expiratory airflow cannot completely exhale the delivered tidal volume, resulting in positive intrapleural pressure throughout the respiratory cycle (auto-PEEP [positive end-expiratory pressure] or intrinsic PEEP), which decreases venous return and causes hypotension.[93] The presence of auto-PEEP is highly negatively correlated with forced expiratory volume in 1 second (FEV_1; percentage predicted) and highly positively correlated with pulmonary flow resistance and resting hypercarbia.[94] Hyperinflation is a frequent complication of single-lung ventilation during lung transplantation in patients with obstructive lung disease. Hyperinflation-induced hemodynamic instability can be confirmed by disconnecting the patient from the ventilator for 30 seconds and opening the breathing circuit to the atmosphere. If the blood pressure returns to its baseline value, hyperinflation is most likely the underlying cause. Hyperinflation can be ameliorated with deliberate hypoventilation (decreasing both the tidal volume and rate).[95] Although this may result in profound hypercarbia, high carbon dioxide tensions are often well tolerated in the absence of hypoxemia. PEEP also may decrease air trapping because it decreases expiratory resistance during controlled mechanical ventilation.[96] However, the application of PEEP requires close monitoring because if the level of extrinsic PEEP applied exceeds the level of auto-PEEP, further air trapping may result.

BOX 25.7 TREATMENT OF INTRAOPERATIVE RIGHT VENTRICULAR FAILURE

- Avoid large increases in intrathoracic pressure from:
  - Positive end-expiratory pressure (PEEP)
  - Large tidal volumes
  - Inadequate expiratory time
- Intravascular volume
  - Increase preload if pulmonary vascular resistance is normal
  - Rely on inotropes (dobutamine) if pulmonary vascular resistance is increased
- Maintain right ventricular coronary perfusion pressure with α-adrenergic agonists
- Cautious administration of pulmonary vasodilators (avoid systemic and gas exchange effects)
  - Prostaglandin E_1 (0.05–0.15 μg/kg per min)
  - Inhaled nitric oxide (20–40 ppm)

RV failure frequently is encountered in lung-transplant recipients with pulmonary hypertension because of chronically increased RV afterload. The response of the right ventricle to a chronic increase in afterload is to hypertrophy, but eventually this adaptive response is insufficient. As a result, RV stroke volume decreases and chamber dilation results. The combination of increasing afterload for the RV coupled with decreased stroke volume (and subsequent decrease in the LV stroke volume) creates an unfavorable supply-and-demand situation that makes the RV more prone for failure. The following should be kept in mind when caring for patients with severe dysfunction (Box 25.7). First, increases in intrathoracic pressure may markedly increase PVR,[97] leading to frank RV failure in patients with chronic RV dysfunction. Changes in RV function may occur immediately after adding PEEP, increasing tidal volume or decreasing expiratory time, and can have devastating consequences. In addition, although intravascular volume expansion in the presence of normal PVR increases CO, overzealous infusion in patients with increased PVR will increase RV end-diastolic pressure and RV wall stress, decreasing CO.[98] Inotropes with vasodilating properties (such as dobutamine or milrinone) often are a better choice than volume for augmenting CO in the setting of increased PVR. Furthermore, the right ventricle has a greater metabolic demand yet a lower coronary perfusion pressure than normal. RV performance can be augmented by improving RV coronary perfusion pressure with α-adrenergic agents, provided these vasoconstrictors do not disproportionately increase PVR. Vasopressin is a good choice to achieve this result. This can sometimes be a better choice than augmenting the perfusion pressure with β-adrenergic agents because the oxygen supply is increased without a large increase in oxygen demand. Additionally, the use of norepinephrine has also been shown to improve the ratio of systemic to pulmonary pressures[99] Finally, vasodilators such as nitroprusside or prostaglandin E_1 may be effective in decreasing PVR and improving RV dysfunction early in the disease process, when only mild-to-moderate pulmonary hypertension is present. However, they are of notably limited value in the presence of severe, end-stage pulmonary hypertension. Systemic vasodilation and exacerbation of shunting often limit their use. Inhaled nitric oxide activates the guanylate cyclase and raises the level of cyclic guanosine monophosphate that results in local vasodilation; it has shown promise as a means of acutely decreasing PVR without altering

systemic hemodynamics before and during the explantation phase, as well as after lung transplantation[100-102] Nitric oxide decreases both PA pressure and intrapulmonary shunting. Further, the combination of inhaled nitric oxide and aerosolized prostacyclin had a synergistic effect, without causing deleterious effects on the systemic perfusion pressure. The use of nitric oxide with or without inhaled prostacyclin may be helpful in avoiding CPB in patients having lung transplantation (see Chapters 11, 26, and 38). In addition to the medications just mentioned, patients with pulmonary hypertension may also have been started on phosphodiesterase-5 inhibitors, soluble guanylate cyclase, and endothelin receptor antagonists. Patients may also be on a prostaglandin infusion preoperatively, which should be kept running during the transplant procedure.

Pathophysiology After Lung Transplantation

The implantation of the donor lung(s) causes marked alterations in recipient respiratory physiology. In single-lung recipients, the pattern of ventilation/perfusion matching depends on the original disease process. For example, with pulmonary fibrosis, blood flow and ventilation gradually divert to the transplanted lung, whereas in patients transplanted for diseases associated with pulmonary hypertension, blood flow is almost exclusively diverted to the transplanted lung, which still receives only half of the total ventilation.[103] In such patients the native lung represents mostly dead-pace ventilation. Transplantation results in obligatory sympathetic and parasympathetic denervation of the donor lung and therefore alters the physiologic responses of airway smooth muscle. Exaggerated bronchoconstrictive responses to the muscarinic agonist methacholine have been noted in some (but not all) studies of denervated lung recipients.[104,105] The mechanism of hyperresponsiveness may involve cholinergic synapses, inasmuch as they are the main mediators of bronchoconstriction. For example, electrical stimulation of transplanted bronchi (which activates cholinergic nerves) produces a hypercontractile response.[106] This suggests either enhanced release of acetylcholine from cholinergic nerve endings because of an increased responsiveness of parasympathetic nerves or else a loss of inhibitory innervation. Such effects are unlikely to be postsynaptic in origin because the number and affinity of muscarinic cholinergic receptors on transplanted human bronchi are similar to controls.[107] Reinnervation during subsequent weeks to months has been demonstrated in several animal models,[108,109] but there was no definitive evidence concerning reinnervation of transplanted human lungs until a small study was published in 2008 that showed return of cough reflex to noxious stimuli (distal to the anastomosis) within 12 months. The presence of nerve cells in the anastomoses of deceased patients also was noted.[110] Mucociliary function is transiently severely impaired after lung transplantation and remains depressed for up to a year after the procedure.[111] Thus transplant recipients require particularly aggressive endotracheal suctioning to remove airway secretions.

Lung transplantation also profoundly alters the vascular system. The ischemia and reperfusion that are an obligatory part of the transplantation process damages endothelium. Cold ischemia alone decreases β-adrenergic cyclic adenosine monophosphate–mediated vascular relaxation by approximately 40%, and subsequent reperfusion produces even greater decreases in both cyclic guanosine monophosphate–mediated and β-adrenergic cyclic adenosine monophosphate–mediated pulmonary vascular smooth muscle relaxation.[112] Endothelial damage in the pulmonary allograft also results in leaky alveolar capillaries and the development of pulmonary edema. Pulmonary endothelial permeability is approximately three times greater in donor lungs than in healthy volunteers.[113] Regulation of pulmonary vasomotor tone solely by circulating humoral factors is another side effect of denervation. Changes in either the levels of circulating mediators or in the responsiveness of the pulmonary vasculature to such mediators may result in dramatic effects on the pulmonary vasculature. An example of the former is the finding that the potent vasoconstrictor endothelin is present at markedly increased levels (two to three times normal) immediately after transplantation and remains increased for up to a week thereafter.[114] Alterations in the response of denervated pulmonary vasculature to α_1-adrenergic agents[115] and prostaglandin E_1,[116] as well as a reduction in nitric oxide activity, also have been demonstrated in acutely denervated lung.[115] Dysfunctional responses to mediators may be exaggerated if CPB is required.[115] PVR can be substantially decreased with the administration of inhaled nitric oxide after reperfusion. It remains unclear whether nitric oxide also ameliorates reperfusion injury. Several studies suggest that nitric oxide prevents or modulates reperfusion injury as measured by decreased lung water, lipid peroxidase activity, neutrophil aggregation in the graft, and decreased IL-6, IL-8, and IL-10.[117–120] However, a number of studies suggest that although nitric oxide has an effect on pulmonary hemodynamics, it does not ameliorate reperfusion injury.[121–123]

Aerosolized inhaled prostacyclin also decreases PVR after reperfusion and improves oxygenation without the added theoretic risk for worsening reperfusion injury.[124] Inhaled prostacyclin has approximately the same effectiveness as nitric oxide in treating lungs damaged by reperfusion injury and offers the added benefit of being less expensive.[125]

A number of other agents have shown promise in decreasing postreperfusion injury in animal studies. Tetrahydrobiopterin, an essential cofactor in the nitric oxide synthase pathway, decreased the intracellular water, myeloperoxidase activity, and lipid peroxidation and increased cyclic guanosine monophosphate levels when given during reperfusion.[126] The administration of surfactant into the donor lung before harvest also appeared to ameliorate ischemia/reperfusion injury in pigs. There was a decrease in the PVR, less inflammatory cellular infiltrate, and an increase in nitric oxide levels in the group that received surfactant.[127]

Given these pathophysiologic derangements, it is not surprising that PVR increases in the transplanted lung.[128,129] However, what the clinician observes in the lung-transplant patient will depend on the severity of pulmonary vascular dysfunction present before surgery. PA pressures decrease dramatically during lung transplantation in patients who had pulmonary hypertension before transplantation,[130] and pressures remain decreased for weeks to months thereafter.[130,117] Concomitant with the decrease in PA pressure, there is an immediate decrease in RV size after lung transplantation in those patients with preexisting pulmonary hypertension, as well as a return to a more normal geometry of the interventricular septum.[111] Both of these effects are sustained over several weeks to months.[130–136] Although echocardiographic indices of RV function (RV fractional area change) have not shown a consistent improvement in the immediate posttransplant period,[130] several other studies have documented improvement in RV function during the first several months after lung transplantation.[130,131,133–136] One striking finding was that persistent depression of RV function (defined as baseline RV fractional area change of less than 30% with failure to increase after transplant by either at least 5% or by 20% of baseline) was statistically associated with death in the immediate perioperative period.[130]

Anesthetic Management

Preoperative Evaluation and Preparation

Immediate pretransplant reevaluation pertinent to intraoperative management includes a history and physical examination to screen for intercurrent deterioration or additional abnormalities that affect anesthetic management. Particular attention should be given to recent physical status, especially when the transplant evaluation was performed more than 9 to 12 months previously. A decrease in the maximal level of physical activity from that at the time of initial evaluation can be a sign of progressive pulmonary disease or worsening RV function. Most patients are maintained on supplemental nasal oxygen yet are mildly hypoxemic. Patients who are bedridden or those who must pause between phrases or words while speaking possess little functional reserve and are likely to exhibit hemodynamic instability during induction. The time and nature of the last oral intake should be determined to aid in deciding the appropriate method of securing

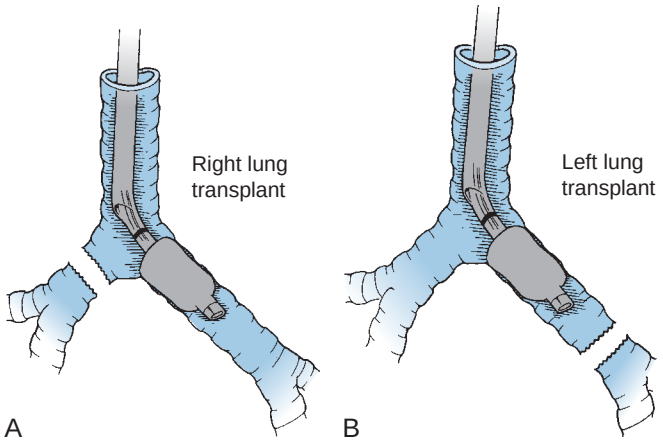


Fig. 25.7 Left endobronchial tube during (A) right- and (B) left-lung transplantation. When the endobronchial tube is correctly positioned, either bronchus may be opened for anastomosis of the donor lung without compromising the surgical field or interfering with isolated lung ventilation.

the airway. The physical examination should focus on evaluation of the airway for ease of laryngoscopy and intubation, on the presence of any reversible pulmonary dysfunction such as bronchospasm, and on signs of cardiac failure. Patients with scleroderma can present difficulty in that they often have a small mouth opening, and in some cases, they can have restricted cervical range of motion. New laboratory data often are not available before the beginning of anesthesia care, but special attention should be directed to evaluation of the chest radiograph for signs of pneumothorax, effusion, or hyperinflation because they may affect subsequent management.

Equipment necessary for this procedure is analogous to that used in any procedure in which CPB and cardiac arrest are real possibilities. Special mandatory pieces of equipment include some method to isolate the ventilation to each lung; although bronchial blockers have their advocates, double-lumen endobronchial tubes offer the advantages of easy switching of the ventilated lung, suctioning of the nonventilated lung, and facile independent lung ventilation after surgery. A left-sided double-lumen endobronchial tube is suitable for virtually all lung transplant cases (even left-lung transplants; Fig. 25.7). Regardless of whether a bronchial blocker or double-lumen tube is used, a fiberoptic bronchoscope is absolutely required to rapidly and unambiguously verify correct tube positioning, evaluate bronchial anastomoses, and clear airway secretions. An adult-sized bronchoscope offers better field of vision and superior suctioning capability but can be used only with 41 or 39 French double-lumen tubes. A ventilator with low internal compliance is necessary to adequately ventilate the noncompliant lungs of recipients with restrictive lung disease or donor lungs suffering from reperfusion injury. The added capability of the ventilator to deliver pressure-controlled ventilation also is important, especially for the patients who have pulmonary fibrotic disease or reperfusion injury. Single-lung recipients with highly compliant lungs may require independent lung ventilation with a second ventilator after transplantation (discussed in detail later). A PA catheter capable of estimating right ventricular ejection fraction (RVEF) can be useful in diagnosing RV failure and its response to inotropes and vasodilators, as well as the response of the right ventricle to clamping of the PA. However, RVEF catheters are not accurate in the presence of significant tricuspid regurgitation or when malpositioned. Continuous mixed venous oximetry is beneficial in evaluating tissue oxygen delivery in patients subject to sudden, severe cardiac decompensation in the course of the operation, as well as the responses to therapy. A rapid-infusion system can be lifesaving in cases in which major hemorrhage occurs because of anastomotic leaks, inadequate surgical ligation of mediastinal collateral vessels, chest wall adhesions, or coagulopathy after CPB.

Induction of Anesthesia

Patients presenting for lung transplantation frequently arrive in the operating room area without premedication. Indeed, many will be admitted directly to the operating room from home. Because of the nature of the procedure planned, and many months on the transplant waiting list, these patients are often extremely anxious. Considering the risk for respiratory depression from sedatives in patients who are chronically hypoxic or hypercapnic, or both, only the most judicious use of intravenous benzodiazepines or narcotics is warranted. Assiduous administration of adequate local anesthesia during placement of invasive monitoring will also considerably improve conditions for both the patient and anesthesiologist. The standard noninvasive monitoring typical of cardiovascular procedures is used (ie, two electrocardiogram leads, including a precordial lead, blood pressure cuff, pulse oximetry, capnography, and temperature measurement). Intravenous access sufficient to rapidly administer large volumes of fluid is required. Generally, two large-bore (16- or, preferably, 14-gauge catheters, or a 9 French introducer sheath) intravenous catheters are placed. Patients for bilateral sequential lung transplantation who will receive a clamshell thoracosternotomy (see Fig. 25.6) should have intravenous catheters placed in the internal or external jugular veins, because peripherally placed intravenous catheters often are unreliable when the arms are bent at the elbow and suspended from the ether screen. An intraarterial catheter is an absolute requirement for blood pressure monitoring and for obtaining specimens for arterial blood gases. Continuous monitoring via a fiberoptic electrode placed in the arterial catheter occasionally may be useful if this technology is available. One femoral artery should be left free of vascular access to allow for cannulation access for CPB or ECMO. Although the radial or brachial artery may be used in single-lung transplantation patients, these sites are not optimal in those who will require CPB (eg, en bloc double-lung transplants or patients with severe pulmonary hypertension) because the transduced pressure may inaccurately reflect central aortic pressure during and after CPB, as well as in patients undergoing a clamshell thoracosternotomy, because of the positioning of the arms. In the authors' institution, the majority of patients now have bilateral limited thoracotomies instead of the thoracosternotomy. An axillary arterial catheter may also be useful in the latter situations because it provides a more accurate measure of central aortic pressure and allows sampling blood closer to that perfusing the brain. This may be important if partial CPB with a femoral arterial cannula is used because differential perfusion of the upper and lower half of the body may result. A PA catheter is inserted via the internal or external jugular veins. A TEE probe is placed after the airway is secured. PA pressure monitoring is most useful in patients who have preexisting pulmonary hypertension, especially during induction and during initial one-lung ventilation (OLV) and PA clamping. Position of the PA catheter must be verified by TEE to ensure that it is residing in the main PA.

If the procedure is planned without CPB, care should be taken to ensure that the patient is kept at ideal physiologic temperature to minimize coagulopathy and increases in the MVO_2. This can be achieved with a warming blanket on the bed, on the patient's head and arms, and on the legs below the knees. A fluid warmer is also useful in this regard.

Three main principles should guide the formulation of a plan for induction: (1) protection of the airway; (2) avoidance of myocardial depression and increases in RV afterload in patients with RV dysfunction; and (3) avoidance and recognition of lung hyperinflation in patients with increased lung compliance and expiratory airflow obstruction (Box 25.8). All lung transplants are done on an emergency basis, and the majority of patients will have recently had oral intake and must be considered to have full stomachs. Because aspiration during induction would be catastrophic, every measure must be taken to protect the airway. Patients with known or suspected abnormalities of airway anatomy should be intubated awake after topical anesthesia is applied to the airway. Although a conventional rapid-sequence intravenous induction with a short-acting hypnotic (such as etomidate, 0.2–0.3 mg/kg), a small amount of narcotic (eg, up to 10 μg/kg of fentanyl) and succinylcholine usually will be tolerated, patients

BOX 25.8 KEY PRINCIPLES OF ANESTHETIC INDUCTION FOR LUNG TRANSPLANTATION

- Secure the airway.
- Intravenous rapid sequence induction versus gradual narcotic induction with continuous cricoid pressure
- Avoid myocardial depression and increases in right ventricular afterload.
- Avoid lung hyperinflation.

with severe RV dysfunction may exhibit profound hemodynamic instability in response to this induction regimen. For such patients, a more gradual induction is recommended, with greater reliance on high doses of narcotics and ventilation with continuous application of cricoid pressure. Consideration should also be given to possibly starting an inotrope or indicator before induction to allow for support of the RV. Patients with bullous disease or fibrotic lungs requiring high inflation pressures may develop a pneumothorax during initiation of positive-pressure ventilation. Acute reductions in Sa_{O_2} accompanied by difficulty in ventilating the lungs and refractory hypotension should generate strong suspicions that a tension pneumothorax has developed. RV function can be impaired during induction by drug-induced myocardial depression, increases in afterload, or by ischemia secondary to acute RV dilation. Agents that act as myocardial depressants should be avoided in such patients. Increases in RV afterload can result from inadequate anesthesia, exacerbation of chronic hypoxemia and hypercarbia and metabolic acidosis, as well as increases in intrathoracic pressure because of positive-pressure ventilation. Systemic hypotension is poorly tolerated because increased RV end-diastolic pressure will diminish net RV coronary perfusion pressure. In addition, chronic increase of RV afterload increases the metabolic requirements of RV myocardium. Once the trachea is intubated and positive-pressure ventilation initiated, the avoidance of hyperinflation in patients with increased pulmonary compliance or bullous disease is crucial. Small tidal volumes, low respiratory rates, and inspiratory/expiratory (I:E) ratios should be used even if this allows increased $etCO_2$ (permissive hypercapnia), although attention should be paid to the effect of this action on the pulmonary artery pressure. If hemodynamic instability does occur with positive-pressure ventilation, the ventilator should be disconnected from the patient. If hyperinflation is the cause of hypotension, blood pressure will increase within 10 to 30 seconds of the onset of apnea. Ventilation then can be resumed at a tidal volume and/or rate compatible with hemodynamic stability.

Anesthesia can be maintained using a variety of techniques. A moderate dose of narcotic (5–15 μg/kg of fentanyl or the equivalent), combined with low doses of a potent inhalation anesthetic, offers the advantages of stable hemodynamics, a high inspired oxygen concentration, a rapidly titratable depth of anesthesia, and the possibility of extubation in the early postoperative period. Patients with severe RV dysfunction who cannot tolerate even low concentrations of inhalation anesthetics may require a pure narcotic technique. Nitrous oxide generally is not used because of the requirement for a high inspired oxygen concentration throughout the procedure and its possible deleterious effects if gaseous emboli or an occult pneumothorax is present.

Intraoperative Management

Institution of OLV occurs before hilar dissection and may compromise hemodynamics or gas exchange, or both (Box 25.9). Patients with diminished lung compliance often can tolerate OLV with normal tidal volumes and little change in hemodynamics. In contrast, patients with increased lung compliance and airway obstruction often will exhibit marked hemodynamic instability, unless the tidal volume is decreased and the expiratory time is increased. The magnitude of hypoxemia generally peaks about 20 minutes after beginning OLV. Hypoxemia during OLV may be treated with continuous positive airway pressure

BOX 25.9 MANAGEMENT PRINCIPLES FOR ONE-LUNG VENTILATION DURING LUNG TRANSPLANTATION

- Tidal volume and respiratory rate
  - Maintain in patients with normal or decreased lung compliance (ie, primary pulmonary hypertension, fibrosis)
  - Decrease both tidal volume and rate in patients with increased compliance (eg, obstructive lung disease) to avoid hyperinflation (permissive hypercapnia)
- Maintain oxygenation by:
  - 100% inspired oxygen
  - Applying CPAP (5–10 cm H_2O) to nonventilated lung
  - Adding PEEP (5–10 cm H_2O) to ventilated lung
  - Intermittent lung reinflation if necessary
  - Surgical ligation of the pulmonary artery of the nonventilated lung
- Be alert for development of pneumothorax on nonoperative side
  - Sharp decline in oxygen saturation, end-tidal carbon dioxide
  - Sharp increase in peak airway pressures
  - Increased risk with bullous lung disease
- Therapy
  - Relieve tension
  - Resume ventilation
  - Emergency cardiopulmonary bypass

CPAP, Continuous positive airway pressure; *PEEP*, positive end-expiratory pressure.

BOX 25.10 INDICATIONS FOR CARDIOPULMONARY BYPASS DURING LUNG TRANSPLANTATION

Cardiac index	<2 L/min/m^2
S_vO_2	<60%
Mean arterial pressure	<50 to 60 mm Hg
S_aO_2	<85% to 90%
pH	<7.00

applied to the nonventilated lung,[137] PEEP to the ventilated lung, or both. Continuous positive airway pressure attempts to oxygenate the shunt fraction but may interfere with surgical exposure. PEEP attempts to minimize atelectasis in the ventilated lung, but may concomitantly increase shunt through the nonventilated lung. Definitive treatment of shunt in the nonventilated lung is provided by rapid isolation and clamping of the PA of the nonventilated lung. Pneumothorax on the nonoperative side may result during OLV if a large tidal volume is used.

PA clamping usually is well tolerated, except in the face of pulmonary hypertension with diminished RV reserve. If the degree of RV compromise is uncertain, a 5- to 10-minute trial of PA clamping is attempted; then the RV is evaluated by serial COs and RVEF measurements and inspection by TEE. A significant decrease in CO may predict patients who will require extracorporeal support.[138] Other indications for CPB in lung transplantation are listed in Box 25.10.[139]

Patients with severe pulmonary hypertension (greater than two-thirds of systemic pressure) generally will be placed on CPB before PA clamping. The intraoperative use of nitric oxide (20 to 40 parts per million [ppm]) may allow some procedures to proceed without the use of CPB.[140]

Lung transplantation usually can be performed without the aid of CPB; even during bilateral sequential lung transplantation, experienced teams use CPB for only about one-quarter of patients.[141,142]

Although CPB may provide stable hemodynamics, it is associated with an increased transfusion requirement.[95] In addition, graft function (as reflected by alveolar-arterial oxygen gradient) may be compromised,[143] endothelium-dependent cyclic guanosine monophosphate–mediated and β-adrenergic cyclic adenosine monophosphate–mediated pulmonary vascular relaxation may be impaired to a greater degree,[144] and a longer period of mechanical ventilation may be necessary.[141] Several exceptional circumstances require CPB: the presence of severe pulmonary hypertension because clamping of the PA will likely result in acute RV failure and flooding of the nonclamped lung, the repair of associated cardiac anomalies (eg, patent foramen ovale, atrial or ventricular septal defects), treatment of severe hemodynamic or gas exchange instabilities, and living-related lobar transplantation. Hypercarbia generally is well tolerated and should not be considered a requirement for CPB per se.[95] Thus the frequency of CPB will depend on recipient population factors such as prevalence of end-stage pulmonary vascular disease and associated cardiac anomalies.[145] The use of femoral venous and arterial cannulae for CPB during lung transplantation may lead to poor venous drainage and/or differential perfusion of the lower and upper body. Moreover, native pulmonary blood flow continues and may act as an intrapulmonary shunt during what will be partial CPB. In this case, the cerebral vessels receive this desaturated blood, whereas the lower body is perfused with fully oxygenated blood from the CPB circuit. This effect is detectable by blood gas analysis of samples drawn from suitable arteries or by appropriately located pulse oximeter probes. Treatment includes conventional measures to increase venous return and augment bypass flow, or placing a venous cannula in the right atrium if this is feasible. The anesthesiologist also should maximize the inspired oxygen concentration and add PEEP to decrease intrapulmonary shunt. If all other measures fail, ventricular fibrillation can be induced using alternating current, although this is exceedingly rare.[146]

ECMO also has been suggested as an alternative method of CPB during lung transplantation. It has been suggested that the use of ECMO with heparin-bonded circuits might improve the outcome of both single- and double-lung transplants by lessening the amount of pulmonary edema, especially in those patients who need CPB because of hemodynamic instability or who have primary pulmonary hypertension. An added benefit of this technique is that it clears the operative field of bypass cannulae, making left-sided transplant as unimpeded as right-sided transplant. There is no apparent increase in transfusion requirement.[147] Another added benefit of using ECMO in situ is that reperfusion of the lungs can be more easily controlled because the CO transiting the newly transplanted lung can be precisely controlled. This is especially the case for patients with advanced pulmonary hypertension.[148]

If CPB is used, weaning from circulatory support occurs when the graft anastomoses are complete. Ventilation is resumed with a lung protection strategy similar to that used in the ARDSnet (Acute Respiratory Distress Syndrome Network) trial.[85] This demonstrated that patients with decreased compliance related to acute respiratory distress syndrome had a 22% decrease in mortality rate when applying tidal volumes of 6 mL/kg and a plateau pressure less than 30 cm H_2O.[85] Minimizing the inspired fraction of O_2 may help prevent generation of oxygen free radicals and modulate reperfusion injury. FiO_2 can be decreased to the minimum necessary to maintain the SpO_2 greater than 90%. Special attention should be directed to assessing and supporting RV function during this period, inasmuch as RV failure is the most frequent reason for failure to wean. Although the right ventricle often can be seen in the surgical field, TEE is more valuable for visualizing this structure's functional properties at this juncture. TEE also allows the evaluation of PA (see Video 25.3) and pulmonary vein anastomoses. The PA diameter should be greater than 1 cm. Interrogating the pulmonary veins should demonstrate a two-dimensional diameter that is at least 0.5 cm with the presence of flow as measured by color-flow Doppler. In addition, pulse wave Doppler interrogation should yield flow rates less than 100 cm/second to indicate adequacy of anastomosis. The operator must align the Doppler beam angle with the pulmonary vein flow because misalignment may lead to underestimation of the true peak venous flow (see Video 25.4). Care should be taken to measure these flow rates with both lungs being perfused because the measurements could be erroneous if measured with one PA clamped (Fig. 25.8).[149,150] Inotropic support with dobutamine or epinephrine, as well as pulmonary vasodilation with nitroglycerin, nitroprusside, milrinone, or nitric oxide, may be necessary if RV dysfunction is evident. Milrinone has the advantage of providing both inotropic and vasodilatory effects; however, its administration can be complicated by significant systemic hypotension, necessitating the concomitant use of epinephrine or norepinephrine (see Chapters 11, 26, 28, 36, and 38).

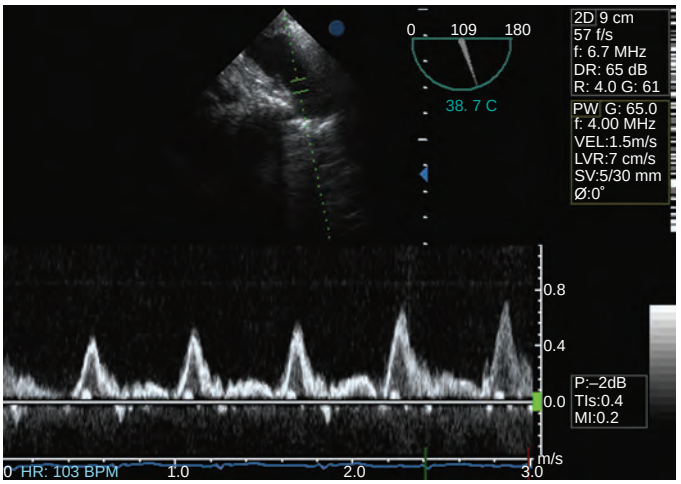


Fig. 25.8 Pulsed-wave Doppler interrogation of the left superior pulmonary vein after lung transplantation.

Coagulopathy after weaning from CPB is common. The severity of coagulopathy may be worse after double- than single-lung transplantation, probably because of the more extensive dissection, presence of collaterals and scarring, and the longer duration of CPB. Factors under the anesthesiologist's control include incomplete reversal of heparin's effects, which should be assayed by the activated coagulation time. Similarly, preexisting deliberate anticoagulation (eg, caused by warfarin) should be aggressively corrected with fresh-frozen plasma. Because platelet dysfunction is common after CPB, empiric administration is justified if coagulopathy persists. The thrombotic and fibrinolytic systems are activated during lung transplantation, especially if CPB is used, and although aprotinin can reduce this activation and perhaps reduce perioperative hemorrhage,[151–153] it has been withdrawn from production. The utility of epsilon-aminocaproic acid, tranexamic acid, and desmopressin (DDAVP) in replacing aprotinin in this setting remains unknown (see Chapter 35), although some preliminary data suggest that tranexamic acid may be similar in efficacy to aprotinin.

Reperfusion without CPB often is accompanied by a mild-to-moderate decrease in systemic blood pressure and occasionally is complicated by severe hypotension. This is usually the result of profound systemic vasodilation. The causative factor is unknown but may be caused by ionic loads such as potassium or additives such as prostaglandin E_1 in preservation solutions or by vasoactive substances generated during ischemia and reperfusion. This hypotension generally responds well to large doses of α-adrenergic agents and fortunately is short-lived. Agents of greatest use in this setting are norepinephrine and vasopressin. Ventilation is resumed with a lung protection strategy identical to that used when weaning from CPB.

Patients with preexisting increased lung compliance, as found in chronic obstructive pulmonary disease, can manifest great disparity in lung compliance after single-lung transplant. The donor lung usually will exhibit normal to decreased compliance, depending on the presence of reperfusion injury. This will result in relative hyperinflation of the native lung and underinflation with loss of functional residual

capacity in the donor lung. Hyperinflation of the native lung may cause hemodynamic instability because of mediastinal shift, especially if PEEP is applied. Therefore patients exhibiting signs of hyperinflation during OLV, which improves with deliberate hypoventilation, should be treated with independent lung ventilation after reperfusion. To accomplish this, the patient's postoperative ventilator is brought to the operating room while the donor lung is being implanted. When all anastomoses are completed, the donor lung is ventilated with a normal tidal volume (8 to 10 mL/kg) and rate, with PEEP initially applied at 10 cm H_2O. These settings can be adjusted according to blood gas analysis. Most gas exchange will take place in the transplanted lung. The native lung is ventilated with a low tidal volume (2 to 3 mL/kg) and a low rate (2 to 4/min) without PEEP. The objective is to prevent this lung from overinflating or developing a large shunt. Carbon dioxide exchange occurs predominantly in the donor lung.

Although some degree of pulmonary edema commonly is detected by chest radiograph after surgery, it is uncommon to encounter severe pulmonary edema in the operating room immediately after reperfusion of the graft. However, when it does occur, postreperfusion pulmonary edema can be dramatic and life-threatening. Copious pink frothy secretions may require almost constant suctioning to maintain a patent airway and may be accompanied by severe gas exchange and compliance abnormalities. Treatment includes high levels of PEEP using selective lung ventilation, diuresis, and volume restriction. Occasionally, patients may require support with ECMO for several days until reperfusion injury resolves; a high percentage of patients so treated ultimately survive.[154,155] Adequate analgesia is crucial for these patients to facilitate the earliest possible extubation, ambulation, and participation in spirometric exercises to enhance or preserve pulmonary function. Lumbar or thoracic epidural narcotic analgesia provides excellent analgesia while minimizing sedation. Epidural catheters can be placed before the procedure if time permits or after conclusion of the procedure. Placement of epidural catheter in cases in which a high expectation exists for the necessity of CPB remains a controversial topic. If CPB has been used or coagulopathy has developed, placement should be deferred until coagulation tests have normalized (see Chapter 42).

Fluid therapy also can impact the outcomes of lung transplantation as was demonstrated by McIlroy and associates, who showed that the greater the amount of colloid (gelatin) that was used, the greater the A-a gradient, and the greater likelihood of delayed extubation. It was unclear, though, whether this effect extended to other colloids.[156]

Postoperative Management and Complications

Routine postoperative management of the lung transplant recipient continues many of the monitoring modes and therapies begun in the operating room. Positive-pressure ventilation is continued for at least several hours; if differential lung ventilation was used intraoperatively, this is continued in the early postoperative period. Because the lung graft is prone to the development of pulmonary edema because of preservation/reperfusion and the loss of lymphatic drainage, fluid administration is minimized and diuresis encouraged when appropriate. When hemorrhage has ceased, the chest radiograph is clear, and the patient meets conventional extubation criteria, the endotracheal tube can be removed. Prophylactic antibacterial, antifungal, and antiviral therapies, as well as the immunosuppressive regimen of choice, are begun after arrival in the ICU.

Surgical technical complications are uncommon immediately after lung transplantation but may be associated with high morbidity.[157] Pulmonary venous obstruction usually presents as acute, persistent pulmonary edema of the transplanted lung.[158] Color-flow and Doppler TEE will show narrowed pulmonary venous orifices with turbulent, high-velocity flow and loss of the normal phasic waveform. PA anastomotic obstruction should be suspected if PA pressures fail to decrease after reperfusion of the lung graft. If the right PA is obstructed, this usually is evident on a TEE examination in the same way as for pulmonary venous obstruction; it is usually much more difficult to adequately inspect the left PA anastomosis with TEE, although some centers have reported a high success rate.[159] The diagnosis can be definitively made by measuring the pressure gradient across the anastomosis either by inserting needles on both sides of the anastomosis to transduce the respective pressures or by advancing the PA catheter across it. However, care should be taken not to measure this gradient while the contralateral PA is clamped, because the shunting of the entire CO through one lung will exaggerate the gradient present.[160] Angiography and perfusion scanning also are useful for making this diagnosis but are not immediately available in the operating room. Bronchial dehiscence or obstruction is extremely rare in the immediate perioperative period and can be evaluated by fiberoptic bronchoscopy.

Pneumothorax must be a constant concern for the anesthesiologist, especially involving the nonoperative side. Diagnosis of pneumothorax on the nonoperative side during a thoracotomy is extremely difficult. A sudden increase in inflation pressures with deterioration of gas exchange and possibly hypotension are characteristic. However, these same findings are possible with hyperinflation, mucous plugging, or malpositioning of the endobronchial tube. Transient cessation of ventilation and immediate fiberoptic bronchoscopy may rule out the former explanations, and the observation of an upward shift of the mediastinum in the surgical field may be observed in the presence of tension pneumothorax. If this diagnosis is strongly suspected, needle thoracostomy on the field may be lifesaving. Alternatively, the surgeon may be able to directly dissect across the mediastinum and decompress the nonoperative thorax, facilitating reinflation.

Tension pneumopericardium and postoperative hemothorax with complete ventilation/perfusion mismatch are other rare complications that have been reported after lung transplantation.[161,162] Patients with pulmonary hypertension and RV hypertrophy occasionally may develop dynamic RV outflow obstruction when transplantation acutely decreases RV afterload; the diagnosis can be confirmed using TEE.[163] Hyperacute rejection of a kind similar to that seen with heart transplantation has not been noted with lung transplantation.

The most common cause of death in the immediate perioperative period is graft dysfunction from reperfusion injury, which usually presents with hypoxemia, pulmonary infiltrates, poor lung compliance, pulmonary hypertension, and RV failure. If there are no technical reasons to account for pulmonary hypertension and RV failure, then graft dysfunction must be suspected. Unfortunately, few treatments will specifically ameliorate graft dysfunction and therapy is largely supportive. Vasodilator therapy to directly decrease PVR and, therefore, RV afterload may improve hemodynamics and, in some cases, may improve gas exchange. Both prostaglandin E_1 and nitrates can reverse severe hypoxemia and pulmonary hypertension after lung transplantation, and the latter attenuate the increase in transcription of vasoconstrictor genes (such as for endothelin and platelet-derived growth factor) induced by hypoxia.[164] Indeed, a prophylactic low-dose infusion of prostaglandin E_1 has been reported to preserve arterial oxygen tension without altering pulmonary hemodynamics in dogs after single-lung transplantation.[165] Improvement in pulmonary hemodynamics and gas exchange in patients with graft dysfunction also have been reported with the administration of nitric oxide.[101,166,167] Compared with historic control patients who developed graft dysfunction before the advent of nitric oxide, inhalation of nitric oxide decreased the duration of mechanical ventilation, frequency of airway complications, and mortality.[167] Improved hemodynamics and gas exchange may reflect the ability of nitric oxide to compensate for the decrease in endothelium-derived relaxant factor activity after transplantation. If nitric oxide has been used to control pulmonary hypertension after surgery, it should be weaned gradually to avoid any rebound pulmonary vasoconstriction.[168] Finally, ECMO may be used to support the patient until there is adequate recovery of pulmonary function.[154,155]

Infection is a constant threat in these immunosuppressed patients. Prophylactic antibiotic coverage is aimed at agents commonly causing nosocomial and aspiration pneumonias because these are common in donors. Coverage can be modified once culture results from the donor trachea are available. Patients with cystic fibrosis should receive

antibiotics targeted at bacteria found in the native lungs before transplantation. Infection should be suspected as the cause of any infiltrate found on chest radiograph, especially if fever or leukocytosis develops, but distinguishing infection from reperfusion injury and rejection may be difficult. Diagnostic bronchoscopy and bronchoalveolar lavage are useful in defining therapy and differentiating infection from rejection,[169,170] but open-lung biopsy occasionally is necessary for definitive diagnosis. Patients who are seronegative to viral agents to which the donor was seropositive (eg, cytomegalovirus) will require prophylactic antiviral therapy. Vadnerkar and colleague's[171] study showed that 43% of patients who had undetected mold infections at the time of transplant were at risk for very poor outcomes, with a mortality rate of 29%.

Rejection episodes are common and may occur as early as several days after transplantation. Rejection often presents as new infiltrates on chest radiograph in the setting of deteriorating gas exchange. Bronchoscopy with transbronchial biopsy helps to rule out other causes of deterioration and document acute changes consistent with rejection. Therapy for acute lung rejection consists of large pulses of steroids such as methylprednisolone or changing the immunosuppressive agents (cyclosporine to tacrolimus or vice versa). Expired nitric oxide has been shown to be an indicator of chronic rejection in post–lung-transplant patients. Measurements of expired nitric oxide have been shown to decrease with the switch of cyclosporine to tacrolimus, reflecting a decrease in the inflammation in the pulmonary mucosa.[172] Expired nitric oxide may be a useful tool to observe patients for the presence or change in chronic graft rejection.[173]

One of the most serious complications of lung transplantation occurs late. Bronchiolitis obliterans is a syndrome characterized by alloimmune injury leading to obstruction of small airways with fibrous scar.[174] Patients with bronchiolitis obliterans present with cough, progressive dyspnea, obstruction on flow spirometry, and interstitial infiltrates on chest radiograph. Therapy for this syndrome includes augmentation of immunosuppression,[175] cytolytic agents (which have been used with varying degrees of success),[176,177] or retransplantation in refractory cases.

Living-Related Lung Transplantation

The scarcity of suitable donor lungs has resulted in waiting times on transplant lists in excess of 2 years, during which time up to 30% of candidates succumb to their illness.[178] Living-related lung transplantation programs have developed to address the needs of lung transplant candidates with acute deterioration expected to preclude survival. Successful grafting of a single lobe for children with bronchopulmonary dysplasia or Eisenmenger syndrome, or two lobes for children and young adults with cystic fibrosis, has encouraged several centers to consider such procedures.[90,179] The anesthetic management issues related to such undertakings have been reviewed.[77] Donor candidates will have undergone a rigorous evaluation to ensure that there are no contraindications to lobe donation and that the donation is not being coerced. Donor lobectomy is performed via a standard posterolateral thoracotomy.[102] Of special note to the anesthesiologist during such procedures is the requirement for OLV to optimize surgical exposure, the continuous infusion of prostaglandin E_1 to promote pulmonary vasodilation, and the administration of heparin and steroids just before lobe harvest. Anesthetic management of the recipient is identical to that for a standard lung transplant, except that the use of CPB is mandatory for bilateral lobar transplant due the fact that sequential off-pump transplantation would warrant the entire RV output going through a single lobe of transplanted lung that would place it at higher risk of pulmonary edema and reperfusion injury.

Pediatric Considerations

Pediatric lung transplant is an attractive option for the treatment of children with end-stage lung disease. There have been nearly 2000 pediatric lung transplants reported to the International Society for Heart and Lung Transplantation since 1986, with 93 in 2012 (the last complete year of reporting) and the most reported having been 126 in 2010.[180] The number of centers performing pediatric lung transplants has also declined from 43 in 2011 to 39 in 2012, with 15 of those centers being in North America (20 in Europe). Only four lung transplants were reported for children younger than 1 year in 2012 with the majority being performed in children 11 to 17 years of age (77%).[180] Over the past 23 years, the most common indications for pediatric lung transplant were surfactant protein B deficiency and CHD in infants (<1 year old), idiopathic pulmonary artery hypertension in toddlers (ages 1–5 years), and cystic fibrosis in older children and adolescents (ages 6–10 and 11–17, respectively).[180] Absolute contraindications to lung transplantation in children are similar to those used for adults; however, relative contraindications may vary between centers.[82]

The majority of pediatric lung transplant recipients are either already inpatients, likely requiring ventilatory and/or hemodynamic support, or chronically ill outpatients who are called in when a potential donor becomes available. Outpatients are often called in on an urgent basis, and because of the sparse number of transplant centers, they may be travel long distances. Care must be coordinated to facilitate appropriate transport, intensive care availability, and an available operating room (OR), equipment, and staff.

A thorough history and physical examination are mandatory to evaluate for indication for transplant, comorbid conditions, cardiac and renal function, as well as current ventilatory and/or hemodynamic support required by the child. There are several reports of children being ambulatory and participating in physical therapy while on venovenous extracorporeal membrane oxygenation (VV-ECMO) as a bridge to lung transplant.[181–183]

Children are expectedly anxious in the preoperative timespan, and judicious premedication is appropriate while transferring to the OR. Oversedation and respiratory depression must be avoided with premedication.

The majority of patients will present to the OR with intravenous access, permitting an intravenous induction. Morbidity during induction anesthesia is increased by hypoxemia, hypercapnea, and systemic hypotension in these critically ill patients. Anesthesia is typically induced with a hypnotic agent (eg, propofol), an opioid, benzodiazepines, and nondepolarizing muscle relaxants titrated to maintain acceptable hemodynamics and expeditiously intubate the trachea. Cardiac arrest and circulatory collapse may occur after induction of anesthesia in the recipient with primary pulmonary hypertension and CHD with pulmonary hypertension.[184] In addition to standard monitors, arterial and central venous access is obtained, and large bore venous access is recommended to facilitate volume administration in the perioperative period. TEE is also useful for assessing cardiac function and volume status children, particularly because the majority of lung transplants in pediatric patients are performed with CPB. Anesthesia is maintained with an inhalation agent and additional opioid, benzodiazepine, and nondepolarizing muscle relaxants. A thickened hypertrophic right ventricle requires additional volume administration. Frequent suctioning of the endotracheal tube may be required for the recipient with cystic fibrosis intraoperatively prior to transplantation.

Unlike adult lung transplantation, CPB is nearly standard in pediatric cases because of several logistical and physiologic reasons. One limitation is the availability of double-lumen endotracheal tubes that would permit adequate one-lung ventilation in pediatric patients. In addition, the majority of pediatric lung recipients would be unlikely to be adequately oxygenated and ventilated with single lung ventilation if isolation were obtained, owing to their morbid status. CPB also allows simultaneous pneumonectomies and anastomoses with reduced risk of bacterial contamination and shortened operative times. The use of CPB is associated with coagulopathy and increased blood product transfusion, necessitating the use of an antifibrinolytic agent (eg, tranexamic acid).

Bronchoscopic evaluation of the bronchial anastomoses is performed if the endotracheal tube is large enough to accommodate a bronchoscope. TEE evaluation of pulmonary arterial and pulmonary venous blood flow is performed during weaning from CPB. Ventilation

strategies that prevent atelectasis and maintain oxygenation without alveolar overdistension, barotrauma, and volutrauma should be employed. This includes the use of PEEP, manipulation of the inspiratory to expiratory time ratio, and weaning to the lowest possible Fio_2. Epinephrine, milrinone, or other cardiovascular support may be beneficial in the perioperative period. Patients are left intubated and sedated for transfer to the intensive care unit, where postoperative management and weaning of support ensue.

Children are often maintained on two to three immunosuppressive agents, a calcineurin inhibitor such as tacrolimus, a cell-cycle inhibitor such as mycophenolate mofetil, and prednisone. Induction immunosuppression has not been shown to provide a survival benefit. Posttransplant morbidities include hypertension, diabetes mellitus, bronchiolitis obliterans syndrome, and renal dysfunction.[180] The most common cause of death within the first month after transplant is primary graft failure. A non-CMV infection is the most common cause of death from the second month after transplant through the first year. Bronchiolitis obliterans syndrome is the most common cause of death after the first year posttransplant.[180] Only 106 pediatric retransplantations have been reported in the last 20 years with survival rates far inferior to that of primary transplantation (82% and 52% for primary transplant 1- and 5-year survival rates, respectively, as compared with 57% and 33% for retransplantation.[180]

Heart-Lung Transplantation

History and Epidemiology

The diminished frequency of heart-lung transplantation since 1990 reflects that it is being supplanted by lung transplantation. The number of HLTs worldwide peaked at 241 in 1989, and there has been a continual decline in subsequent years to approximately half that number.[3] Approximately only 173 HLT candidates were registered with UNOS as of early March 2005, less than 5% of the number on the lung transplant list. The most common recipient indications remain primary pulmonary hypertension, CHD (including Eisenmenger syndrome), and cystic fibrosis.

One-year survival rate after heart-lung transplantation is 60%, significantly less than that for isolated heart or lung transplantation.[3] Mortality in subsequent years is approximately 4% per year, similar to that for heart transplantation. Risk factors for increased mortality after HLT are recipient ventilator dependence, male recipient sex, and a donor age older than 40 years.[3] Early deaths are most often due to graft failure or hemorrhage, whereas midterm and late deaths primarily are due to infection and bronchiolitis obliterans, respectively. Repeat HLT is a rare procedure and likely to remain so because the 1-year survival rate after repeat HLT is dismal (28%).[3]

Recipient Selection

Candidates undergo an evaluation similar to that for lung transplant candidates. As more patients with pulmonary hypertension and cystic fibrosis are treated with isolated lung transplantation, it is likely that the indications for heart-lung transplantation will be limited to CHD with irreversible pulmonary hypertension that is not amenable to repair during simultaneous lung transplantation or diseases with both pulmonary hypertension and concomitant severe left ventricular dysfunction.

Donor Selection and Graft Harvest

Potential heart-lung donors must meet not only the criteria for heart donors but also those for lung donation, both described earlier in this chapter. Graft harvesting is carried out in a manner similar to that previously described for heart transplantation. After mobilization of the major vessels and trachea, cardiac arrest is induced with inflow occlusion and infusion of cold cardioplegia into the aortic root. After arrest, the PA is flushed with a cold preservative solution often containing prostaglandin E_1. The ascending aorta, SVC, and trachea are transected, and the heart-lung bloc removed after it is dissected free of the esophagus. The trachea is clamped and the graft immersed in cold solution before being bagged for transport.

Surgical Procedures

The operation generally is performed through a median sternotomy, but a clamshell thoracosternotomy also is an acceptable approach. Both pleurae are incised. Any pulmonary adhesions are taken down before anticoagulation for bypass. Cannulae for CPB are placed in a manner similar to that for heart transplantation. After the aorta is cross-clamped, the heart is excised in a manner similar to that for orthotopic heart transplant. Each lung is then individually removed, including its pulmonary veins. The airways are divided at the level of the respective main bronchi for bibronchial anastomoses. For a tracheal anastomosis, the trachea is freed to the level of the carina without stripping its blood supply and an anastomosis is constructed just above the level of the carina. The atrial anastomosis is performed in a manner similar to that for orthotopic heart transplantation, and finally, the aorta is joined to the recipient aorta. After de-airing and reperfusion, the patient is weaned from CPB, hemostasis is achieved, and the wound is closed.

Pathophysiology Before Transplantation

The pathophysiology of HLT recipients combines the elements discussed earlier in this chapter. Patients usually will have end-stage biventricular failure with severe pulmonary hypertension. The cardiac anatomy may be characterized by complex congenital malformations. If obstruction of pulmonary airflow is present, there is a danger of hyperinflation after application of positive-pressure ventilation.

Pathophysiology After Transplantation

As with isolated heart recipients, HLT recipients' physiology is characterized by cardiac denervation, transient cardiac ischemic insult during graft harvest, transport, and implantation, and long-term susceptibility to accelerated allograft vasculopathy and rejection. As is the case for lung recipients, heart-lung recipients have denervated pulmonary vascular and airway smooth muscle responses, transient pulmonary ischemic insult, altered pulmonary lymphatic drainage, and impaired mucociliary clearance.

Anesthetic Management

The anesthetic management of heart-lung transplantation more closely resembles that of heart than lung transplantation because the use of CPB is mandatory. After placement of invasive and noninvasive monitoring similar to that used for heart transplantation, anesthesia can be induced with any of the techniques previously described for heart and lung transplantation. As with lung transplantation, avoidance of myocardial depression and protection and control of the airway are paramount. Although a double-lumen endotracheal tube is not mandatory, it will aid in exposure of the posterior mediastinum for hemostasis after weaning from CPB. Otherwise, anesthetic management before CPB is similar to that for heart transplantation.

A bolus of glucocorticoid (eg, methylprednisolone, 500 mg) is given when the aortic cross-clamp is removed. After a period of reperfusion, an inotrope infusion is started and the heart is inspected with TEE for adequate de-airing. Ventilation is resumed with normal tidal volume and rate, along with the addition of PEEP (5–10 cm) before weaning from CPB. After successful weaning from CPB, the PA catheter can be advanced into the PA again. Protamine then is administered to reverse heparin-induced anticoagulation. The inspired oxygen concentration often can be decreased to less toxic levels based on blood gas analysis.

Problems encountered after weaning from CPB are similar to those encountered after isolated heart or lung transplantation. Lung

reperfusion injury and dysfunction may compromise gas exchange, so administration of crystalloid should be minimized. Occasionally, postreperfusion pulmonary edema may require support with high levels of PEEP and inspired oxygen in the operating room. Ventricular failure usually responds to an increase in β-adrenergic support. Unlike isolated heart or lung transplantation, frank RV failure is uncommon immediately after heart-lung transplantation unless lung preservation was grossly inadequate. Coagulopathy often is present after HLT and should be aggressively treated with additional protamine (if indicated), platelets, and fresh-frozen plasma.

Postoperative Management and Complications

The principles of the immediate postoperative care of HLT recipients are a combination of those of isolated heart and lung recipients. Invasive and noninvasive monitoring done in the operating room is continued. Inotropic support is continued in a manner similar to that for heart transplantation. Ventilatory support is similar to that after lung transplantation; the lowest acceptable inspired oxygen concentration is used to avoid oxygen toxicity, and the patient is weaned from the ventilator after hemodynamics have been stable for several hours, hemorrhage has ceased, and satisfactory gas exchange is present. Diuresis is encouraged. Finally, the immunosuppressive regimen of choice is begun.

Infection is a more frequent and serious complication in heart-lung recipients than in isolated heart recipients. Bacterial and fungal infections are especially common in the first month after transplantation, with viral and other pathogens (*Pneumocystis carinii* and *Nocardia*) occurring in subsequent months.[185]

Similar to isolated heart or lung transplants, rejection episodes are common early after heart-lung transplantation. Rejection may occur independently in either the heart or lung.[125] Therapy is similar to that for rejection of isolated heart or lung grafts.

Heart grafts in heart-lung blocs are prone to accelerated coronary vasculopathy in a manner similar to those of isolated heart grafts. As with lung transplantation, a feared late complication of heart-lung transplantation is bronchiolitis obliterans. Clinical presentation is similar to that seen with lung transplant patients. Approximately one-third of heart-lung recipients develop this process. Anecdotal reports indicate that most affected patients also have accelerated coronary vasculopathy.

Pediatric Considerations

Pediatric HLT is an attractive option for the treatment of children with end-stage lung disease and concurrent heart failure either due to cor pulmonale or critical CHD with or without pulmonary artery or pulmonary vein abnormalities. In the 1980s and 1990s, HLT was used more frequently due to technical reasons.[186] As surgical technique and long-term outcomes for palliative procedures like the Norwood operation for hypoplastic left heart syndrome have improved, the need for concurrent HLT has decreased. Furthermore, earlier detection and intervention for CHD has led to a decline in Eisenmenger's syndrome and a subsequent decrease in HLT for this indication.[186]

From 1986 to 2011, 660 pediatric HLTs were reported to the International Society for Heart and Lung Transplantation (188 in the United States since 1988).[180,186] In 2010, only five centers reported pediatric HLTs.[180] The most common indication for pediatric HLT has been CHD in infants (<1 year old), CHD and primary pulmonary hypertension in toddlers (ages 1–5 years old), and primary pulmonary hypertension for older children and adolescents (6–10 years old and 11–17 years old, respectively).[186] Cystic fibrosis as an indication for HLT was more common in Europe than in the United States; however, cystic fibrosis as the indication for HLT has not been reported since 2007.[180,186]

Perioperative anesthetic management for children undergoing pediatric HLT is much the same as describe in the pediatric heart and pediatric lung transplant sections of this chapter.

The 5-year survival rates for HLT have increased from 45% (1997–2003) to 50% (2004–2010).[180] The limiting factor for outcomes in HLT is the lung graft, and therefore survival rates, morbidity, and mortality in HLT mirror those for lung transplantation. As with isolated lung transplantation, bronchiolitis obliterans syndrome remains the predominant cause of graft failure and patient death.[180,186]

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26

Pulmonary Thromboendarterectomy for Chronic Thromboembolic Pulmonary Hypertension

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KEY POINTS

1. The incidence of thromboembolic disease is difficult to estimate because of the nonspecific nature of presenting symptoms and a lack of awareness of the disorder, thus making detection difficult.
2. Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of a pulmonary embolus (PE) or from recurrent PEs. It is an underappreciated phenomenon.
3. The cause of CTEPH after acute PE is not fully understood. Proposed mechanisms include abnormalities in fibrinolytic enzymes or resistance of the thrombus to fibrinolysis.
4. Pulmonary thromboendarterectomy (PTE) is the most effective treatment for patients with CTEPH.
5. Patients typically present with progressive exertional dyspnea and exercise intolerance because of increased pulmonary vascular resistance (PVR), decreased cardiac output, and increased minute ventilation requirements secondary to increased alveolar dead space.
6. Assessment of surgical candidacy should be performed at centers with expertise in the diagnosis and management of CTEPH. Right-sided heart catheterization defines the severity of pulmonary hypertension and the degree of cardiac dysfunction.
7. Patients with preoperative PVR greater than 1000 dynes·s·cm^{-5} have a greater operative mortality rate, but a markedly increased preoperative PVR does not contraindicate surgical treatment.
8. Complications specific to PTE make postsurgical management a challenge: reperfusion pulmonary edema and persistent pulmonary hypertension.
9. A newer surgical classification system has been developed. It describes the different levels of the resected thromboembolic specimen and corresponds to the degree of difficulty of the endarterectomy.
10. Riociguat is the first medication approved by the US Food and Drug Administration for treating certain patients with CTEPH.
11. Balloon pulmonary angioplasty is an alternative approach to PTE in patients believed to have surgically inaccessible chronic thromboembolic disease.
12. Reperfusion pulmonary edema and airway bleeding are two of the most difficult complications of PTE to manage. Anesthesiologists should be prepared to provide diagnostic and therapeutic maneuvers for these complications.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH) that is characterized by complete or partial obstruction of the pulmonary vascular bed as a result of a recurrent or residual intraluminal organized fibrotic clot leading to increased pulmonary vascular resistance (PVR), severe PH, and eventually right-sided heart failure.[1,2]

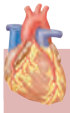
CTEPH is an underappreciated disease, and if left untreated it carries a poor prognosis. Its incidence is difficult to estimate because of the uncertainty regarding the frequency of acute pulmonary embolism (PE) and the percentage of patients in whom emboli fail to resolve. The incidence reflects a wide range, from less than 1% to as high as 9% of patients with acute PE.[3–6]

Screening for CTEPH in patients with PH or unexplained dyspnea is of paramount importance because this form of PH is potentially curable with pulmonary thromboendarterectomy (PTE), also known as pulmonary endarterectomy.[7–10] The success of the operation centers on endarterectomy of the organized fibrous thrombus in the intima and part of the medial layers of the pulmonary vascular tree. Lung transplantation is another potential option, but it is usually not a choice for patients with CTEPH because of the risk of death while on the waiting list, a shortage of organ supply, the expense, the risk of immunosuppressive agents, infection, and rejection.[11]

This chapter is based on the experience of more than 3000 PTE procedures performed at our institution, the University of California San Diego (UCSD). The chapter focuses on classification and pathogenesis of PH, pathophysiology and clinical manifestations of CTEPH, diagnostic workup, surgical approach, anesthetic management including intraoperative echocardiography, management of patients with heparin-induced thrombocytopenia and sickle cell disease (SCD) who are undergoing PTE, postoperative care, and complications such as intraoperative airway bleeding.

Classification of Pulmonary Hypertension

Classifications of PH began in 1973 at the World Health Organization (WHO) conference and have since undergone multiple revisions as the appreciation of the disease and treatment of PH has evolved. The Fourth World Symposium on Pulmonary Hypertension held in 2008



BOX 26.1 REVISED WORLD HEALTH ORGANIZATION CLASSIFICATION OF PULMONARY HYPERTENSION

Group I: Pulmonary arterial hypertension (PAH) and other subtypes of PAH
Group II: Left-sided heart disease
Group III: Respiratory disease and hypoxemia
Group IV: Chronic thromboembolic pulmonary hypertension (CTEPH)
Group V: Miscellaneous causes

Adapted from McLaughlin V, Langer A, Tan M, et al. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension. *Chest.* 2013;143:324–332.

in Dana Point, California was the first international meeting to focus not only on pulmonary arterial hypertension (PAH) but also on PH resulting from left-sided heart disease, chronic lung disease, chronic venous thromboembolism, and other diseases.[12] The consensus during the Fifth World Symposium on Pulmonary Hypertension held in 2013 was to maintain the same classification of PH into five distinct subgroups of patients sharing specific features (Box 26.1).[13]

Further classification of PH by Galie and colleagues[14] and Dadfarmay and associates[15] defined the presence of precapillary (groups I, III, IV, and V) or postcapillary (group II) patterns. CTEPH is precapillary PH, as assessed by right-sided heart catheterization characterized by a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg with normal pulmonary capillary wedge pressure lower than 15 mm Hg and an elevated PVR greater than 300 dynes·s·cm^{-5}. Postcapillary PH secondary to left-sided heart disease is the most frequent form of PH, and it is characterized by mPAP greater than 25 mm Hg and pulmonary capillary wedge pressure greater than 15 mm Hg with normal PVR.[16]

Differentiating PAH from pulmonary venous hypertension in group II is important given the high prevalence of left-sided heart disease (Fig. 26.1).[17] Echocardiography is an essential tool for initial screening and assessment for PH (Table 26.1).

Pathophysiology

Acute or recurrent PE is thought to be the inciting event in the development of CTEPH. Incomplete resolution of the embolus followed by thrombus organization and fibrosis leads to partial or complete vessel obstruction. In addition, vascular remodeling in the distal pulmonary arteries (pulmonary arteriopathy) also may contribute to the increased PVR,[18–20] and it is the cause of residual PH seen in some patients after otherwise successful PTE. Unresolved PE in the proximal pulmonary arterial tree causes vascular obstruction in two ways: canalization of the clot leading to multiple small endothelized channels separated by bands and webs or fibrin clot organization or absent canalization leading to dense fibrous connective tissue that completely occludes the arterial lumen[21–23] This fibrous plug is firm and adherent to the arterial wall, and the surgical challenge is to remove enough of the fibrous plug as one unit to reduce the vascular resistance without disrupting the arterial wall.

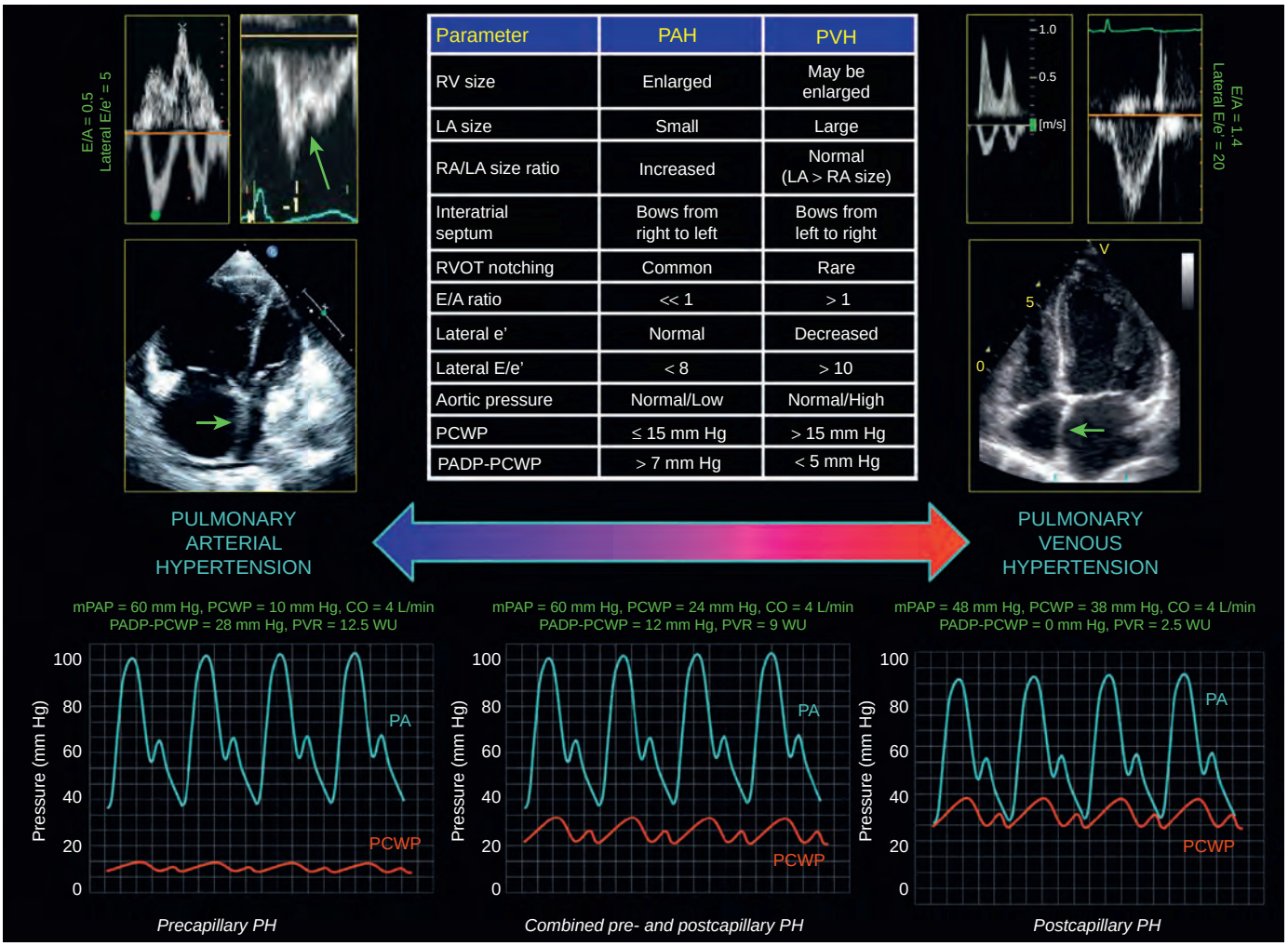
The natural history of PE in most patients is complete resolution of the thromboembolic event with restoration of normal blood flow and hemodynamics. However, in some patients embolic resolution is incomplete, resulting in the development of CTEPH. The mechanism by which thromboembolic material remains unresolved is not fully understood. A variety of factors may play a role: The volume of the embolic substance may simply overwhelm the lytic system, with total occlusion of a major arterial branch preventing the lytic material from reaching and dissolving the embolus completely. The emboli may be made of substances such as well-organized fibrous thrombus that cannot be dissolved by normal mechanisms. Some patients may have tendencies to thrombus formation, a hypercoagulable state, or abnormal lytic mechanisms. Rosenhek and colleagues[24] showed that subjects under normal physiologic conditions have greater levels of tissue plasminogen activator than plasminogen activator inhibitor 1 expression in the pulmonary artery (PA) compared with the aorta, thereby leading to improved natural fibrinolysis. However, Olman and associates[25] and Lang and colleagues[26] were unable to demonstrate a reversal in the tissue plasminogen activator–plasminogen activator inhibitor 1 relationship, thus, favoring incomplete thrombus resolution in patients with a history of CTEPH. The possibility therefore exists that patients with CTEPH either have abnormalities in their fibrinolytic enzymes or have thrombus that is resistant to fibrinolysis.

CTEPH is a common but underrecognized cause of PH. The incidence of CTEPH remains uncertain. Pengo and associates[3] observed 223 patients for a median of 94 months after an acute PE, and 3.8% of these patients developed symptomatic CTEPH. Ribeiro and colleagues[27] examined echocardiograms in 278 patients surviving acute PE for 1 year and performed clinical follow-up for 5 years. Larger perfusion defects at diagnosis, idiopathic thromboembolic disease, high PA pressure (PAP) at the time of presentation, and a history of multiple PEs were risk factors for development of CTEPH after an acute PE.[18] Five percent of patients with PE experienced clinically significant CTEPH. Dentali and associates[28] noted similar findings in 91 patients examined at 6 months after acute PE. PH associated with residual perfusion defects was identified in eight patients (8.8%), four of whom were symptomatic. Unresolved thrombi with recurrent asymptomatic PEs are likely major causes of clinically significant CTEPH.[29]

Bonderman and colleagues[30] identified the following risk factors for CTEPH in a controlled retrospective cohort study: ventriculoatrial shunts, infected pacemakers, splenectomy, previous venous thromboembolism, recurrent venous thromboembolism blood group other than O, lupus anticoagulant or antiphospholipid antibodies, thyroid replacement therapy, or a history of malignant disease. Despite being a risk factor for venous thromboembolism, the prevalence of hereditary thrombophilic states (deficiencies of antithrombin III, protein C, and protein S, and factor II and factor V Leiden mutations) is similar to that in normal control subjects or in patients with idiopathic PH.[31] In contrast, lupus anticoagulant or antiphospholipid antibodies can be found in up to 21% of patients with CTEPH,[1] and Bonderman and associates[32] demonstrated increased levels of factor VIII in 41% of patients with CTEPH. Finally, small, preliminary studies suggest the possibility of structural and functional abnormalities of fibrinogen in patients with CTEPH that perhaps confer resistance to fibrinolysis.[33,34] Morris and colleagues[33] reported relative resistance of fibrin to plasmin-mediated lysis caused by an alteration in fibrin(ogen) structure affecting accessibility to plasmin cleavage sites in patients with CTEPH.

Clinical Manifestations

A history of a previous acute thromboembolic event is not present in 25% to 30% of patients diagnosed with CTEPH.[9,30] The International CTEPH Registry published in 2011 revealed that 25.2% of enrolled patients were without a confirmed diagnosis of a previous PE; 43.9% had not experienced previous deep vein thrombosis.[35] Thus a high index of suspicion is important for the diagnosis of CTEPH in any patient presenting with exertional dyspnea and exercise intolerance, even without evidence of previous PE. Early in the disease process patients may go through a "honeymoon period" in which signs and symptoms of PH are not obvious. Symptoms appear when the right ventricle is unable to increase contractility sufficiently to augment left ventricular (LV) preload and cardiac output (CO) during exercise. Progressive exertional dyspnea is often the initial symptom of CTEPH, and, unfortunately, it is often attributed to more common medical conditions such as obstructive lung disease, obesity, or deconditioning. Exertional dyspnea results from increased PVR limiting CO and increased breathing requirements because of increased alveolar dead space.[18,20]



Parameter	PAH	PVH
RV size	Enlarged	May be enlarged
LA size	Small	Large
RA/LA size ratio	Increased	Normal (LA > RA size)
Interatrial septum	Bows from right to left	Bows from left to right
RVOT notching	Common	Rare
E/A ratio	<< 1	> 1
Lateral e'	Normal	Decreased
Lateral E/e'	< 8	> 10
Aortic pressure	Normal/Low	Normal/High
PCWP	≤ 15 mm Hg	> 15 mm Hg
PADP-PCWP	> 7 mm Hg	< 5 mm Hg

Fig. 26.1 *Left,* Prototypical echocardiographic and invasive hemodynamic findings from a patient with pulmonary arterial hypertension *(PAH).* The right atrium and right ventricle are severely enlarged, and the left ventricle and left atrium are small and underfilled. The interatrial septum bows from right to left. On mitral inflow, the E/A ratio (ratio of early to late (atrial) mitral inflow velocities) is less than 1 because of underfilling of the left atrium and decreased compliance of the left ventricle secondary to extrinsic compression from the enlarged right ventricle. The lateral e' velocity and lateral E/e' ratio (ratio of early mitral inflow velocity to early diastolic mitral annular tissue velocity) are normal (<8), suggesting normal left ventricular (LV) relaxation and filling pressures. Notching is noted in the right ventricular *(RV)* outflow tract *(RVOT)* profile on pulse-wave Doppler imaging because of increased pulmonary artery *(PA)* stiffness. The pulmonary capillary wedge pressure *(PCWP)* is normal, and the pulmonary artery diastolic pressure *(PADP)*-PCWP gradient is severely increased. *Right,* Prototypical echocardiographic and invasive hemodynamic findings from a patient with pulmonary venous hypertension *(PVH).* The left atrium is enlarged, and the interatrial septum bows from left to right. On mitral inflow, the E/A ratio is greater than 1, the lateral e' velocity is reduced, and lateral E/e' ratio is increased, suggestive of grade 2 diastolic dysfunction with impaired LV relaxation and elevated LV filling pressures. No notching is noted in the RVOT profile. The PCWP is elevated, and no gradient is present between the PADP and the PCWP. Although the right ventricle in the *right panel* is not enlarged, RV enlargement and dysfunction can be present in patients with isolated PVH. *Upper middle,* Parameters helpful for differentiating PAH from PVH on echocardiography and invasive hemodynamic testing. *Lower middle,* Invasive hemodynamic findings in a patient with combined precapillary and postcapillary pulmonary hypertension *(PH)* (elevated PCWP and PADP-PCWP gradient). The most challenging patients are in this middle zone (combined precapillary and postcapillary PH), with echocardiographic findings that lie in the middle of the prototypical examples of PAH and PVH shown here. In these patients, careful evaluation of the echocardiogram and invasive hemodynamics will be necessary for an accurate diagnosis.*CO,* Cardiac output; *LA,* left atrial; *mPAP,* mean pulmonary arterial pressure; *PVR,* pulmonary vascular resistance; *RA,* right atrial. *(Reprinted with permission from Vallerie V, McLaughlin V, Shah S, et al. Management of pumonary arterial hypertension.* J Am Coll Cardiol. *2015;65: 1976–1997.)*

TABLE 26.1 Echocardiography in the Initial Screening and Assessment for Pulmonary Hypertension

Completed?	*Action Item*	*Notes*
☐	Record estimated PASP	• Underestimated when Doppler beam alignment is poor or when TR jet is minimal • Overestimated in patients with significant anemia or in some cases of agitated saline-enhanced TR jet on continuous wave Doppler (from feathering) • Assumes absence of pulmonic stenosis • Echocardiographic PASP does not equal mean PA pressure (definition of PH per guidelines is on the basis of invasive hemodynamics: mean PA pressure ≥25 mm Hg)
☐	Evaluate RV size and function	• Signs of RV enlargement (apical four-chamber view): right ventricle shares apex with left ventricle, right ventricle larger than left ventricle, RV basal diameter >4.2 cm • RV hypertrophy (subcostal view): RV end-diastolic wall thickness >5 mm • RV systolic dysfunction: RV fractional area change <35%, TAPSE <1.6 cm, RV tissue Doppler s′ velocity <10 cm/s at base of the RV free wall (tricuspid annulus) • Septal flattening: in systole = RV pressure overload and in diastole = RV volume overload
☐	Evaluate for signs of elevated PVR	• RVOT notching on pulse-wave Doppler profile is a sign of elevated PVR • Peak TR velocity (m/s)/RVOT VTI (cm) <0.18: unlikely PVR is elevated
☐	Estimate volume status	• Use size and collapsibility of IVC (during sniff maneuver) to determine RA pressure • Hepatic vein flow: systolic flow reversal can be a sign of severe TR, RV overload, and/or increased RV stiffness • Signs of RA overload or enlargement: RA area >18 cm^2, interatrial septum bowing from right to left
☐	Evaluate severity of TR	• Features suggestive of severe TR: dense TR jet on continuous-wave Doppler, V-wave cutoff sign, and systolic flow reversal on hepatic vein pulse-wave Doppler imaging
☐	Evaluate for pericardial effusion	• In patients with PAH, the presence of a pericardial effusion = poor prognostic sign
☐	Evaluate for causes of PH (left-sided heart disease, shunt lesions)	• Left-sided heart disease: look for overt LV systolic dysfunction, grade 2 or worse diastolic dysfunction, severe aortic or mitral valvular disease, and less common abnormalities of the left side of the heart (eg, hypertrophic cardiomyopathy, cor triatriatum) • Shunt lesions: perform agitated saline bubble study
☐	Differentiate PAH from PVH	• Signs favoring PVH: LA enlargement (LA size >RA size), interatrial septum bows from left to right, E/A ratio >1.2; *E/e′* (lateral) >11; lateral e″ <8 cm/s • In patients with significantly elevated PASP at rest: grade 1 diastolic dysfunction pattern (E/A ratio <0.8) favors PAH diagnosis because of underfilled LA and decreased LV compliance secondary to RV-LV interaction (extrinsic compression of left ventricle by right ventricle) • See also Fig. 26.1

E/A ratio, Ratio of early to late (atrial) mitral inflow velocities; *IVC,* inferior vena cava; *LA,* left atrial; *LV,* left ventricular; *PA,* pulmonary artery; *PAH,* pulmonary arterial hypertension; *PASP,* pulmonary artery systolic pressure; *PH,* pulmonary hypertension; *PVH,* pulmonary vascular hypertension; *PVR,* pulmonary vascular resistance; *RA,* right atrial; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *TAPSE,* tricuspid annular-plane systolic excursion; *TR,* tricuspid regurgitation; *VTI,* velocity-time integral.
Reprinted with permission from McLaughlin V, Shah S, Souza R, et al. Management of pulmonary arterial hypertension. *J Am Coll Cardiol.* 2015;65;1976–1997.

As the disease progresses and the right side of the heart fails, patients may develop ascites, early satiety, epigastric or right upper quadrant fullness, edema, chest pain, and presyncope or syncope. Other symptoms may include nonproductive cough, hemoptysis, and palpitations. Left vocal cord dysfunction and hoarseness may arise from compression of the left recurrent laryngeal nerve between the aorta and an enlarged left main PA. Early in the disease process the physical examination may be normal or may reveal an accentuated pulmonic component of the second heart sound. Pulmonary flow murmurs or bruits heard over the lung fields are caused by turbulent blood flow through partially occluded or recanalized thrombi. These flow murmurs are heard in 30% of patients with CTEPH and are not found in idiopathic PH.[36]

Late in the disease process patients experience exertion-related syncope and resting dyspnea. The physical signs are far from uniform, and the physical examination may be surprisingly unrewarding if right ventricular (RV) failure is not yet present, even in patients with severe dyspnea. Physical findings of RV failure such as jugular venous distention, RV lift, fixed splitting of the second heart sound, murmur of tricuspid regurgitation (TR), RV gallop, hepatomegaly, ascites, and edema may appear in later stages of the disease. Most patients are hypoxic, with room-air arterial oxygen tension in the range of 65 mm Hg.[37] This hypoxia is a result of ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch and low mixed venous oxygen saturation.[38,39] Marked hypoxemia at rest implies severe RV dysfunction or the presence of a considerable right-to-left shunt, typically through a patent foramen ovale (PFO). Carbon dioxide tension is slightly reduced with metabolic compensation (reduced bicarbonate). Dead-space ventilation is increased, along with $\dot{V}/\dot{Q}$ mismatch, although these features correlate poorly with the degree of pulmonary vascular obstruction.[40]

Diagnostic Evaluation

Pulmonary Function Studies

Basic pulmonary function studies do not provide specific clues to the diagnosis of CTEPH, and these tests are most useful in evaluating patients for coexisting parenchymal lung disease or airflow obstruction. Twenty percent of patients with CTEPH exhibit a mild-to-moderate restrictive defect, often a result of parenchymal scarring from previous lung infarction.[41] Similarly, a modest reduction in single-breath diffusing capacity of the lung for carbon monoxide (DLCO) may be present in some patients with CTEPH. A normal value does not exclude the diagnosis,[38] and severe reduction in DLCO indicates that the distal pulmonary vascular bed is significantly compromised, thus making an alternative diagnosis likely.

Chest Radiography

The chest radiograph may be unremarkable in the early stages of CTEPH. However, as the disease progresses with the development of PH, the proximal pulmonary vascular bed enlarges. In some patients with chronic thromboembolic disease of the main or lobar PAs, this central PA enlargement can be asymmetric (Fig. 26.2). This is not a radiographic finding in those patients with PH resulting from small-vessel disease.[42] As the right ventricle adapts to the rise in PVR, radiographic signs of chamber enlargement such as obliteration of the retrosternal space and prominence of the right heart border can be observed.[43,44] Relatively avascular lung regions can be appreciated if an organized thrombus has compromised blood flow to that area. In these poorly perfused lung regions, peripheral alveolar opacities, linear scarlike lesions, and pleural thickening may be found as a result of parenchymal injury and infarction.

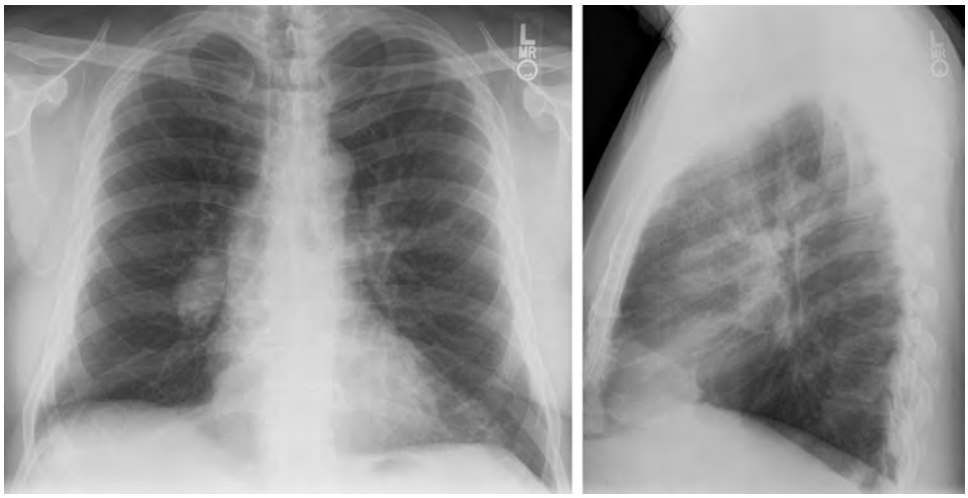


Fig. 26.2 Chest radiographs of a patient with chronic thromboembolic pulmonary hypertension showing asymmetric pulmonary artery enlargement, with a "knobby" appearance of the right pulmonary artery. No cardiomegaly is seen on the posteroanterior view, although the retrosternal space is obliterated on the lateral view.

Transthoracic Echocardiography

Transthoracic echocardiography (TTE) is a frequently used screening modality in patients with suspected PH. It often provides the first objective indication of the presence of elevated PAPs or RV compromise. Current technology allows for estimates of systolic PAP (using Doppler analysis of the velocity of TR), along with CO and RV performance.[45,46] Enlargement of the right heart chambers and the resultant TR, flattening or paradoxical motion of the interventricular septum, and encroachment of an enlarged right ventricle on the LV cavity resulting in impaired LV filling are findings in patients with significant PH.[47] Contrast echocardiography using intravenous agitated saline may show the presence of an intracardiac shunt, as a result of a PFO or another previously undetected septal defect. The echocardiogram is also useful in excluding LV dysfunction, valvular disease, or congenital heart disease, which may cause PH. In some patients with suspected CTEPH, TTE showing normal or minimally elevated PAPs at rest can sometimes demonstrate a substantial rise in PAP or dilatation of the right ventricle with exertion.

Ventilation/Perfusion Scintigraphy

The next step in the evaluation of patients for CTEPH is the acquisition of a $\dot{V}/\dot{Q}$ scan. For those patients with diagnosed PH, and for patients with dyspnea of unclear origin and suspected pulmonary vascular disease, the $\dot{V}/\dot{Q}$ scan is the recommended screening test for CTEPH.[10] In a retrospective survey comparing $\dot{V}/\dot{Q}$ scanning with computed tomography (CT) pulmonary angiography (CTPA) in 227 patients with PH, the sensitivity was 97.4% for $\dot{V}/\dot{Q}$ scanning compared with 51% for CT angiography (CTA) in the detection of CTEPH.[48] In a small study of 12 patients with CTEPH, Soler and associates[49] demonstrated that single-photon emission CT (SPECT) perfusion scintigraphy was more sensitive in detecting obstructed vascular segments when compared with CTPA, with a sensitivity of 62 ± 4.1% versus 47.8 ± 2.9%, respectively. However, a more recent study by He and colleagues[50] comparing the two modalities demonstrated $\dot{V}/\dot{Q}$ sensitivity, specificity, and accuracy of 100%, 93.7%, and 96.5% (high and intermediate probability), respectively, as compared with CTPA sensitivity, specificity, and accuracy of 92.2%, 95.2%, and 93.9%, respectively. These findings suggest that an interpretation of CTPA by an experienced examiner provides comparable detection of chronic thromboembolic disease. In CTEPH, at least one, and more commonly several, segmental or larger mismatched perfusion defects are present (Fig. 26.3). In those patients with small-vessel pulmonary vascular disease, perfusion scan results either are normal or exhibit a "mottled" appearance characterized by nonsegmental defects.[51,52] Exceptions can be seen in pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, in which perfusion scans can demonstrate multiple, large mismatched defects.[53,54] The greatest value of a $\dot{V}/\dot{Q}$ scan as a screening study is that a relatively normal perfusion pattern excludes the diagnosis of surgical CTEPH. Investigators have also observed that the magnitude of perfusion defects exhibited by patients with CTEPH with operable disease may understate the degree of pulmonary vascular obstruction determined by angiography.[55] Therefore CTEPH should be considered and an evaluation for operable disease is warranted even if the $\dot{V}/\dot{Q}$ scan demonstrates a limited number of mismatched perfusion defects or regions of relative hypoperfusion ("gray zones").

Although an abnormal perfusion scan finding is observed in patients with CTEPH, this finding lacks specificity. Several other disorders affecting the proximal pulmonary vessels may result in scan findings similar to those in CTEPH,[56–58] and as such, further diagnostic imaging is necessary. Depending on imaging modality availability, and interpretive expertise, conventional catheter-based angiography, CTPA, and magnetic resonance imaging (MRI) are most valuable methods for defining large-vessel, pulmonary vascular anatomy and providing the necessary diagnostic information for the confirmation of CTEPH.

Catheter-Based Pulmonary Angiography

Catheter-based pulmonary angiography has traditionally been considered the gold standard for confirming the diagnosis of CTEPH and assessing the proximal extent of chronic thromboembolic disease in evaluating patients for PTE. In most circumstances, a properly performed pulmonary angiogram, including lateral projections, provides sufficient information on which to base a decision regarding chronic thrombus location and surgical accessibility. The angiographic appearance of CTEPH is distinct from the well-defined, intraluminal filling defects of acute PE. The angiographic patterns encountered in CTEPH reflect the complex patterns of organization and recanalization that occur following an acute thromboembolic event. Several angiographic patterns have been described in CTEPH, including "pouch defects," PA webs or bands, intimal irregularities, abrupt and frequently angular narrowing of the major PAs, and complete obstruction of main, lobar, or segmental vessels at their point of origin.[22] In most patients with CTEPH, two or more of these angiographic findings are present, typically involving both lungs (Fig. 26.4).

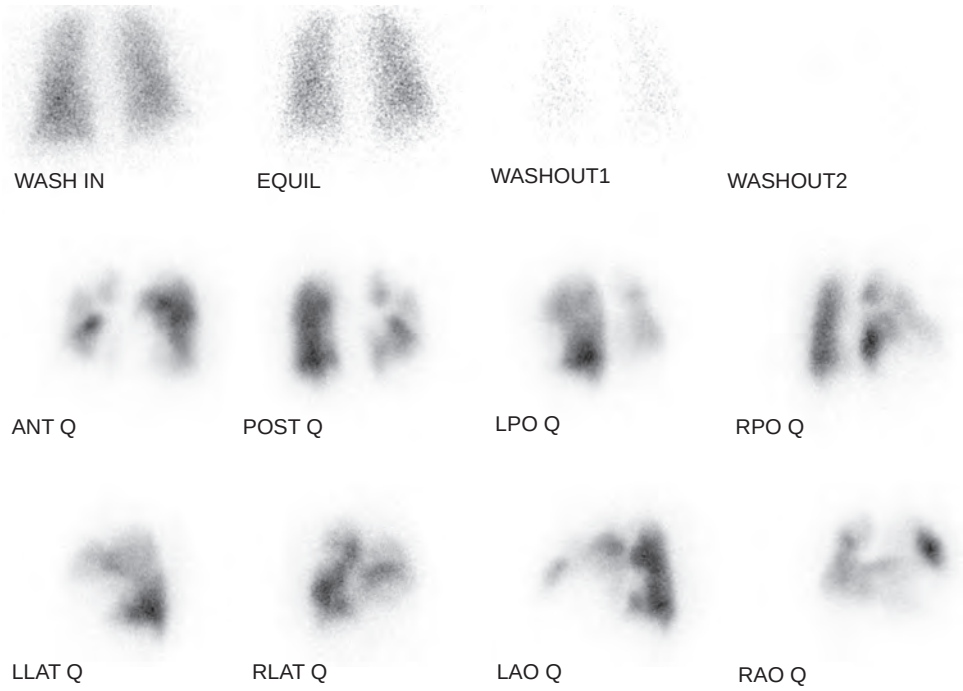


Fig. 26.3 Lung ventilation-perfusion scan of the same patient as in Fig. 26.2. Unmatched perfusion abnormalities include "hypoperfused" left upper lobe, with scattered segmental perfusion defects in the lingula and throughout the right lung. *ANT,* Anterior; *EQUIL,* equilibrium; *LAO,* left anterior oblique; *LLAT,* left lateral; *POST,* posterior; *Q,* perfusion; *RAO,* right anterior oblique; *RLAT,* right lateral.

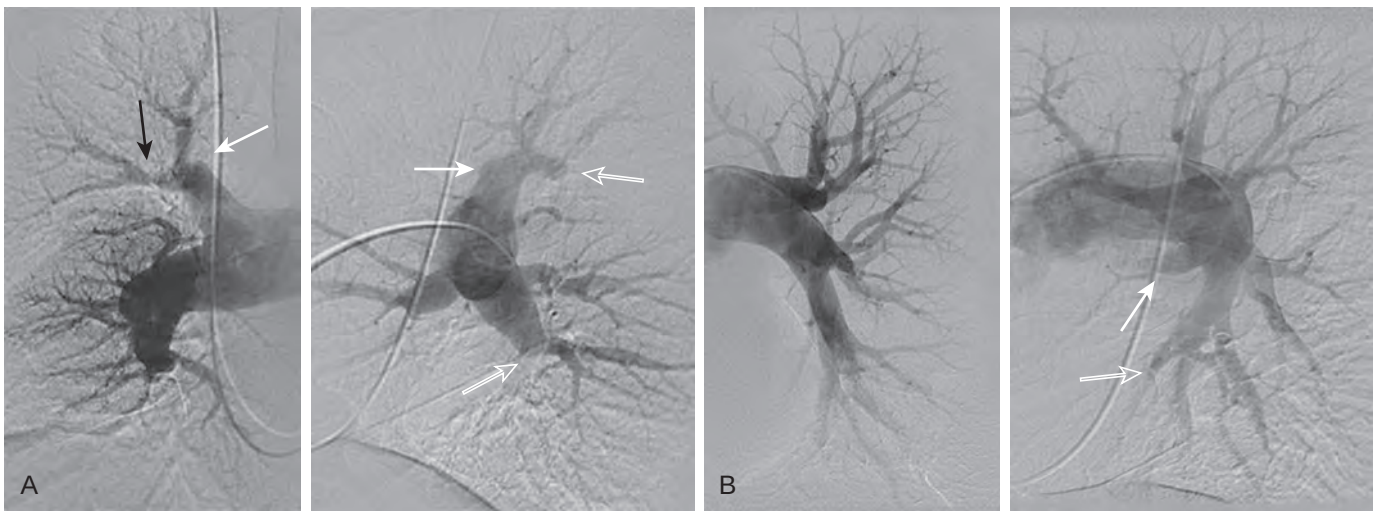


Fig. 26.4 (A) The accompanying pulmonary angiogram of the same patient as in Fig. 26.2, showing angiographic features consistent with chronic thromboembolic disease: "web" narrowing *(black arrow);* proximal vessel occlusion, anterior right upper lobe *(solid white arrows);* and rounded "pouch" lesions of the posterior right upper lobe artery and right descending pulmonary artery *(open white arrow).* (B) The left pulmonary angiogram demonstrates nearly complete occlusion of the proximal lingula *(solid white arrow)* and segmental narrowing of the anterior left lower lobe, best seen on the lateral view *(open white arrow).*

Computed Tomography of the Chest

With advances in technology, CTPA of the chest has played an increasing role in the evaluation for CTEPH. Certain vascular and parenchymal CT findings are seen in patients with chronic thromboembolic disease. These include "mosaic perfusion" of the lung parenchyma, enlargement of the central PAs and right heart chambers, variability in the size of lobar and segmental-level vessels with a reduction in vessel caliber of those involved with chronic thrombi, and peripheral, scarlike lesions in poorly perfused lung regions.[59] With contrast enhancement of the pulmonary vasculature during CT imaging, organized thrombus can be seen to line the pulmonary vessels, often in an eccentric manner. Associated narrowing of PAs, web strictures or bands, poststenotic vessel dilatation, and other irregularities of the intima may also be

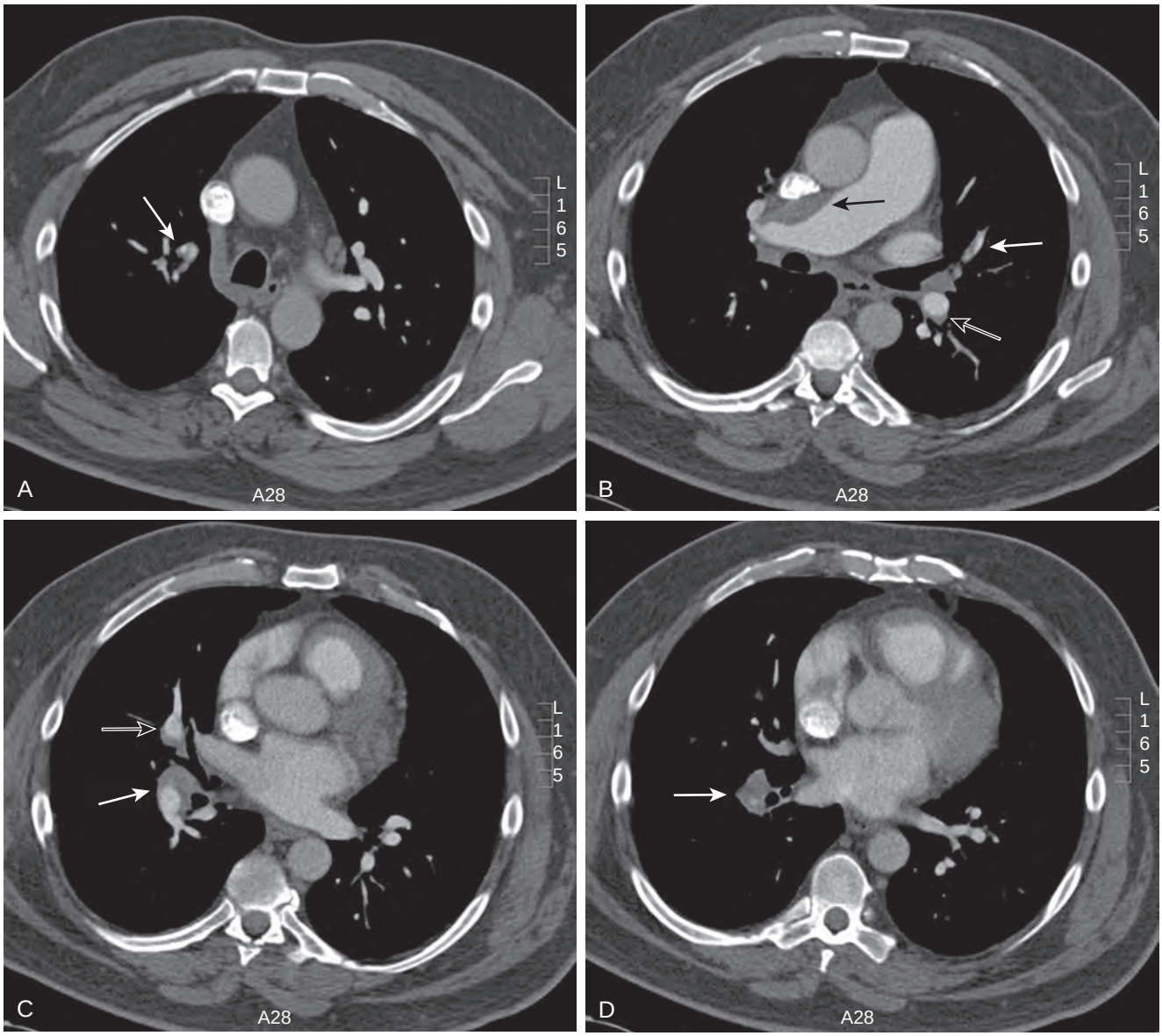


Fig. 26.5 (A–D) Cephalad to caudad presentation of the computed tomography angiogram of the patient undergoing pulmonary thromboendarterectomy who was presented in previous figures showing features of chronic thromboembolic pulmonary hypertension. (A) Intravascular "web" *(solid white arrow),* right upper lobe segmental vessel. (B) Intravascular "web," proximal lingula *(solid white arrow),* lining thrombus, right main pulmonary artery *(PA) (black arrow)* and intimal thickening in distal left descending PA *(open white arrow).* Main PA enlargement was consistent with significant pulmonary hypertension. (C) Eccentric lining thrombus, proximal right middle lobe *(open white arrow)* and right descending PAs *(solid white arrow),* leading to (D) complete occlusion and attenuation at the level of the right lower lobe vessels *(solid white arrow).*

appreciated (Fig. 26.5).[60,61] These radiologic signs are distinct from the isolated finding of intraluminal filling defects observed with acute thromboemboli.[59] With appropriate timing of the intravenous contrast bolus for CTPA, opacification of both the pulmonary and systemic circulation is possible. This type of imaging allows examination of both the pulmonary vascular bed and several cardiac features including cardiac chamber size, the position and shape of the interventricular septum (deviated toward the left ventricle in the setting of significant RV pressure overload), the presence of congenital cardiac abnormalities, anomalous pulmonary venous drainage, and the size and distribution of collateral vessels arising from the systemic arterial circulation, such as bronchial arteries off the aorta and collateral vessels arising from coronary vessels.[59,62,63]

What remains incompletely evaluated is the utility of CTPA in determining operability in certain subgroups of patients with CTEPH. This has become particularly relevant because operative techniques allow for resection of chronic thromboembolic material at the segmental vessel level. Clinical experience has demonstrated that the absence of lining thrombus or thickened intima of the central vessels on CTPA does not exclude the diagnosis of CTEPH or the possibility of surgical resection. Studies directly comparing CTPA with conventional pulmonary angiography are limited. In one such study, CTPA and digital angiography were nearly equivalent in terms of identifying complete vessel occlusion at the segmental level. However, for nonocclusive changes, CTPA was significantly inferior to angiography,[64] although with technologic advances in scanners, the accuracy of CTPA

has improved. A comparative study of electrocardiographically gated multidetector (40-row or 64-row) CTA (MDCTA), contrast-enhanced magnetic resonance angiography (MRA), and selective digital subtraction angiography (DSA) was conducted in 24 patients with CTEPH. The sensitivity and specificity of MDCTA for "CTEPH-related changes" at the main and lobar and segmental level were 100% and 100%, respectively, and 100% and 99%, respectively, in comparison with 65.7% and /100%, respectively, and 75.8% and 100%, respectively for DSA. The image quality of MDCTA in this study was rated as "significantly better" than that of DSA.[65] In a study of 44 patients with suspected CTEPH, Sugiura and associates[66] compared pulmonary DSA with enhanced, electrocardiographically gated 320-slice CT in the detection of thrombi within the pulmonary vascular bed. The sensitivity and specificity of CT to detect chronic thromboembolic lesions were 97.0% and 97.1%, respectively, at the main and lobar vessel level; at the segmental level, the corresponding values for DSA were 85.8% and 94.6%, respectively.[66]

Supplemental information provided by CT is of considerable value, not only in detecting disorders of the pulmonary parenchyma and mediastinum but also in differentiating CTEPH from "radiologic mimics."[59] In patients with CTEPH and coexisting interstitial lung disease or emphysema, CT can define the extent and location of the parenchymal lung process. An attempted PTE leading to diseased lung parenchyma risks an undesirable postoperative outcome; such circumstances therefore should exclude a patient from surgical consideration. When a $\dot{V}/\dot{Q}$ scan demonstrates absence or nearly complete absence of perfusion to an entire lung, CT is an essential study to rule out extrinsic pulmonary vascular compression from mediastinal adenopathy, fibrosis, or neoplasm.[44] CTEPH "mimics" such as primary sarcomas of the proximal pulmonary vessels, arteritis of medium to large pulmonary vessels (eg, Takayasu arteritis or sarcoidosis), and mediastinal fibrosis involving the proximal PAs or pulmonary veins are often revealed with CT.[59]

Magnetic Resonance Imaging

At some CTEPH specialty centers, MRI and MRA to visualize the pulmonary vascular bed have been shown to be reliable methods for diagnosing CTEPH and for determining surgical candidacy.[67] Kreitner and colleagues[68] showed that contrast-enhanced MRA can demonstrate the vascular changes typical of CTEPH. In a study of 34 patients with CTEPH, wall-adherent thromboembolic material involving the central PAs down to the segmental level could be seen. Intraluminal webs and bands, as well as abnormal vessel tapering and cutoffs, were also detected. Additionally, these investigators showed that MRA was superior to DSA in determining the proximal location of resectable chronic thromboembolic material.[68] An additional study comparing MRI techniques with conventional contrast angiography included 29 patients with either CTEPH or idiopathic PAH. The combined interpretation of MRI perfusion imaging and MRA led to a correct diagnosis of idiopathic PAH or CTEPH in 26 (90%) of the 29 patients when compared with the reference diagnosis based on $\dot{V}/\dot{Q}$ scintigraphy, DSA, or CTPA. The interpretation of MRA alone had a sensitivity of 71% for wall-adherent thrombi, 50% for webs and bands, and between 83% and 86% for detection of complete vessel obstruction and free-floating thrombi when compared with DSA or CTA.[69]

More recently, Rajaram and associates[70] retrospectively evaluated the accuracy of contrast-enhanced MRA compared with CTPA in a group of 53 patients with CTEPH. The sensitivity and specificity of MRA in detecting proximal and distal vessel chronic thromboembolic disease were 98% and 94%, respectively, and the sensitivity of MRA diagnosis of central vessel disease considerably improved when images were analyzed with unenhanced proton MRA (50–88%). Overall, MRA identified more stenosis, poststenotic dilatation, and occlusive lesions when compared with CTPA.[70] However, as referenced earlier, in a small study of 24 patients with CTEPH in whom all 3 diagnostic modalities were performed within a 3-day period, Ley and colleagues[65] compared DSA, electrocardiographically gated MDCTA, and contrast-enhanced MRA in the detection of vascular changes associated with chronic thromboembolic disease. Based on comparison with reference standards, the investigators concluded that MDCTA provided the best image quality and highest level of sensitivity and specificity for detection of vascular abnormalities at the main, lobar, and segmental levels.[65]

Additional features of MRI that can be useful in the evaluation of patients with CTEPH include cine imaging, which allows an assessment of RV and LV function and provides data on end-systolic and end-diastolic volumes, ejection fraction, and muscle mass.[71,72] Furthermore, phase-contrast imaging may be used to measure CO, along with pulmonary and systemic arterial flow.[68]

Evaluation of the Patient With Chronic Thromboembolic Pulmonary Hypertension for Pulmonary Thromboendarterectomy

The evaluation of a patient with suspected CTEPH has the objectives of establishing the diagnosis, determining whether PTE is feasible, and, after careful assessment of comorbidities, risks, and anticipated benefits, whether surgical treatment should be pursued. Once the diagnosis of CTEPH has been confirmed, the next consideration in establishing the surgical candidacy of any patient is the determination of surgical accessibility of the chronic thrombotic lesions and, as such, "operability" (Box 26.2). Despite advances in diagnostics and an expanding surgical experience, this assessment remains subjective. Experience with interpretation of the diagnostic studies outlined in the previous sections and knowledge of the capabilities of the surgical team at a specialized center for PTE dictate which chronic thromboembolic lesions can be removed. As surgical experience is gained, it becomes possible to resect not only main PA and lobar level disease, but also more distal, segmental chronic thromboembolic lesions (Fig. 26.6).[73,74] Although early experience with PTE procedures focused on the treatment of patients with PH and RV failure, the indications for surgical intervention have expanded to include those patients with symptomatic chronic thromboembolic disease without PH at rest. A report of 42 patients with symptomatic chronic thromboembolic disease and a baseline mPAP lower than 25 mm Hg concluded that PTE resulted in a significant improvement in functional status and quality of life.[75] Thromboendarterectomy and reperfusion of lung regions before the development of significant PH may prevent the development of the small-vessel arteriopathy in this patient group.

Equally essential in defining surgical candidacy is the assessment of perioperative risks. Properly performed right-sided heart catheterization enables a clinician accurately to determine the severity of PH and the degree of RV dysfunction in patients with CTEPH undergoing surgical evaluation. Early observations indicated that patients with severe PH, as defined by a PVR greater than 1000 dynes·s·cm^{-5}, bear a greater perioperative mortality risk.[76] Hartz and associates[77] reported that a preoperative PVR greater than 1100 dynes·s·cm^{-5} was associated with 41% mortality compared with less than 6% if PVR was less

BOX 26.2 PATIENT SELECTION CRITERIA FOR PULMONARY THROMBOENDARTERECTOMY

- Presence of surgically resectable chronic thromboembolic disease
- Symptomatic chronic thromboembolic disease, with or without pulmonary hypertension and right-sided heart dysfunction at rest
- Absence of concurrent illnesses representing an immediate threat to life
- Patient's desire for surgical treatment based on dissatisfaction with poor cardiorespiratory function or prognosis
- Patient's willingness to accept the mortality risk of the pulmonary thromboendarterectomy surgical procedure

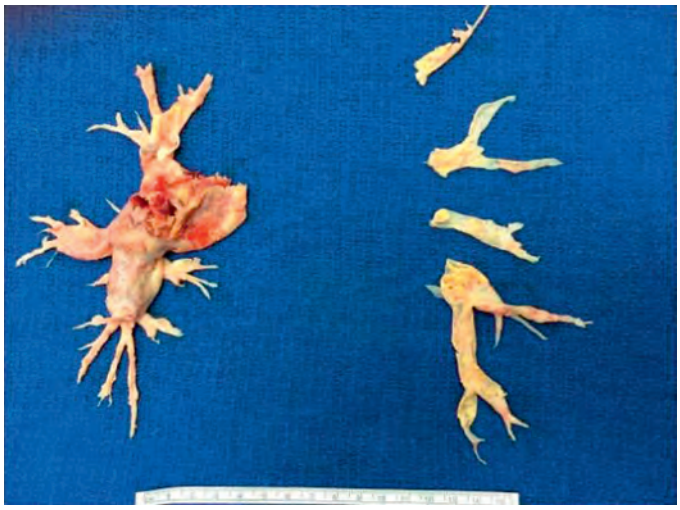


Fig. 26.6 Material removed at the time of pulmonary thromboendarterectomy that shows organized thrombus accompanied by semiorganized clot beginning in the right main pulmonary artery, whereas on the left, segmental level thrombus was endarterectomized. Preoperative pulmonary hemodynamics: mean atrial right pressure, 10; pulmonary artery pressure, 88/33 (55 mean); cardiac index, 2.09 L/min/m^2. Postoperative hemodynamics: central venous pressure, 9; pulmonary artery pressure, 43/15 (24 mean); cardiac index, 4.8 L/min/m^2 per minute.

than 1100 dynes·s·cm^{-5}. Another group later reported an increased postoperative mortality of 20% for patients with preoperative PVR greater than 1,200 dynes·s·cm^{-5} compared with 4% mortality if the preoperative PVR was less than 900 dynes·s·cm^{-5}.[78] Although worldwide perioperative mortality rates have declined, patients with more severe PH and those with decompensated RV failure from CTEPH remain at greater risk.[79] Madani and colleagues[74] reported a declining overall operative mortality risk of 2.2% following PTE in 500 patients operated on between 2006 and 2010; in this same group, those patients with a preoperative PVR greater than 1000 dynes·s·cm^{-5} had a mortality rate of 4.1% compared with 1.6% in those patients with a PVR lower than 1000 dynes·s·cm^{-5}. A subsequent report by de Perrot and colleagues[79] compared PTE outcomes in those patients with CTEPH with a preoperative PVR greater than (n = 26) or less than (n = 78) 1200 dynes·s·cm^{-5}. The overall in-hospital mortality rate after PTE was 4%; all deaths occurred in patients with PVR greater than 1200 dynes·s·cm^{-5} and decompensated RV failure on presentation.[79]

Finally, one should anticipate PTE will result in a meaningful outcome for the patient undergoing this complex and technically challenging procedure. Patients with significant comorbid conditions such as severe emphysema or those with a life-limiting malignant disease are not only at considerable perioperative risk but also are unlikely to realize the functional status benefit from PTE. Although the operation would possibly be technically feasible, such an aggressive intervention could be ill-advised. Furthermore, when the degree of PH appears out of proportion to the extent of accessible chronic thromboembolic disease apparent by angiography, and surgical resection is not expected to result in a substantive improvement in pulmonary hemodynamics, surgical treatment should not be undertaken. Unfortunately, this assessment continues to be subjective. In previous attempts to establish objective criteria whereby small-vessel disease could be contributing to the PVR in patients with CTEPH, PA occlusion waveform analysis was used to "partition" the proximal versus distal components of vascular resistance. Although specialized equipment is required and obtaining adequate occlusion waveforms may be difficult in this patient population, the available data from this technique underscore the heterogeneity of pulmonary vascular lesions present in CTEPH; those patients with operable disease had a greater degree of upstream resistance.[80] In a small series of 26 patients with CTEPH, Kim and associates,[81] using this waveform analysis, demonstrated an inverse correlation between upstream resistance and postoperative mPAP and PVR. In addition, all four deaths in this series occurred in patients with upstream resistance of less than 60%.[81] However, such a discriminatory demarcation was not observed by Toshner and colleagues[80]; both of their patients with CTEPH who died following PTE had an upstream resistance of 68% and 73%. Consequently, available information fails to provide enough "objective data" to exclude patients from surgical consideration on the basis of hemodynamic measures alone.

Operation

Historical Background

Chronic thromboembolic disease was not recognized as a distinct diagnostic entity until the late 1920s. The first surgical attempt to remove the adherent thrombus from the PA wall was reported by Hurwitt and associates in 1958.[82] This landmark operation distinguished endarterectomy, rather than embolectomy, as the surgical procedure of choice for chronic thromboembolic disease. In 1961 and 1962, systemic hypothermia with cardiopulmonary bypass (CPB) standby was used to perform two successful endarterectomies. A historical review of the world's experience with PTE up to 1985, published by Chitwood and colleagues,[83] revealed an overall perioperative mortality rate of 22% in 85 patients who underwent surgical endarterectomy. Moser and associates[37] published their experience of 42 patients with CTEPH who underwent PTE, with an in-hospital mortality rate of 16.6%. Of the 35 survivors (mean follow-up, 28 months), 16 had New York Heart Association (NYHA) functional class I disease, 18 had class II, and 1 had class III. PVR declined significantly after the surgical procedure from 897 ± 352 to 278 ± 135 dynes·s·cm^{-5}. This study confirmed the substantial improvements in functional ability experienced by these patients 1 year postoperatively.[37]

Seven surgeons have been involved with the UCSD program and have performed more than 3300 PTE procedures since 1970. Drs. Braunwald, Utley, Daily, and Dembitsky, who together performed 188 procedures between 1970 and 1989, made progressive modifications to the surgical technique, including the use of median sternotomy and hypothermic circulatory arrest. Drs. Jamieson and Kapelanski performed more than 1400 operations from 1989 to early 2000. Since 2000, Drs. Jamieson and Madani have extended the total number of cases to more than 3000, and Drs. Madani and Pretorius currently perform approximately 180 such procedures annually, with mortality rates of approximately 1% to 2%. UCSD is the world's pioneer in PTE surgery, and most of the surgical experience with PTE to date has been reported from that institution; hence this chapter is based on that extensive experience (Fig. 26.7).

Pulmonary Thromboendarterectomy Procedure

PTE is the only curative treatment for CTEPH, with periprocedural mortality rates lower than 2% to 5% in experienced centers,[74] nearly normalized hemodynamics, and substantial improvement in clinical symptoms in the majority of patients. Treatment decisions in CTEPH should be made by a CTEPH team and based on interdisciplinary discussions among internists, radiologists, and expert surgeons. A patient's condition should not be considered inoperable unless at least two independent experienced PTE surgeons have evaluated the patient. Detailed preoperative patient evaluation and selection, surgical and anesthetic technique, and meticulous postoperative management are essential for surgical success. Following complete endarterectomy, a significant decrease in PVR can be expected with near normalization of pulmonary hemodynamics. A center can be considered to have adequate expertise if it performs at least 20 to 30 operations per year with a mortality rate lower than 10%,[14] although an expert center typically performs more than 50 such operations annually and has a mortality rate of less than 4% to 5% while achieving excellent outcomes even in patients with distal disease. The techniques of this procedure have

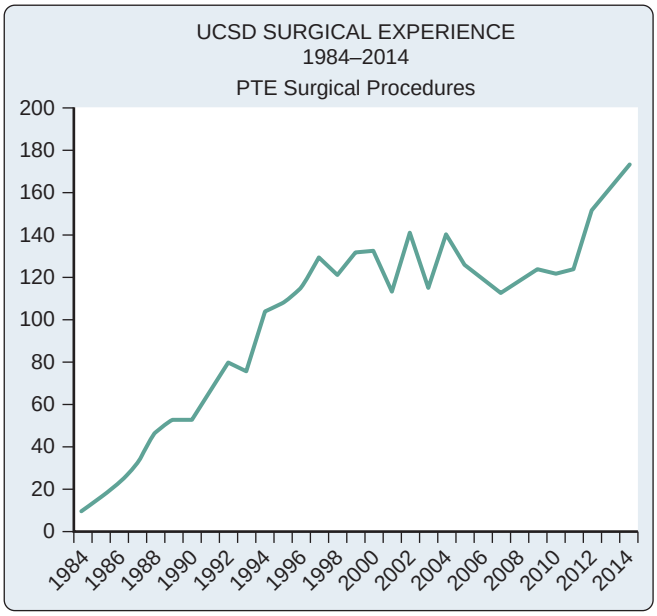


Fig. 26.7 University of California San Diego surgical experience from 1984 to 2014. *PTE,* Pulmonary thromboendarterectomy.

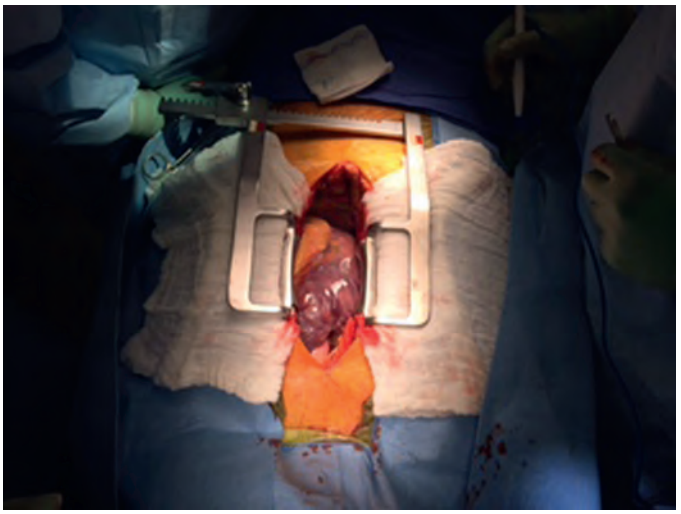


Fig. 26.8 A median sternotomy demonstrating an enlarged, tense right atrium.

been described elsewhere.[84,85] The procedure follows four basic but important principles:

1. The endarterectomy must be bilateral; therefore the approach is through a median sternotomy.
2. Identification of the correct dissection plane is crucial, and the plane must be identified in each of the segmental and subsegmental branches.
3. Perfect visualization is essential, and thorough distal endarterectomy cannot be performed without the use of circulatory arrest. Circulatory arrest is usually limited to 20 minutes at a time and is supported by cooling to 18°C.
4. Complete endarterectomy all the way to the distal ends of the smallest vessels is essential.

The endarterectomy must be bilateral because bilateral thromboembolic disease is present in almost all patients with CTEPH, and PH is a bilateral phenomenon. Historically, many reports described unilateral operations, and, occasionally these are still performed by lateral thoracotomy in inexperienced centers. However, the unilateral approach ignores the disease on the contralateral side, subjects the patient to hemodynamic jeopardy during clamping of the PA, does not allow adequate visibility because of the continued presence of bronchial blood flow, and exposes the patient to a repeat operation on the contralateral side. In addition, collateral channels develop in CTEPH not only through the bronchial arteries, but also from diaphragmatic, intercostal, and pleural vessels. Dissection of the lung in the pleural space through a thoracotomy incision can therefore be extremely bloody. The median sternotomy, apart from providing bilateral access, avoids entry into the pleural cavities and allows the ready institution of CPB.

CPB is essential to ensure cardiovascular stability when the operation is performed and to cool the patient to allow circulatory arrest. Excellent visibility is required, in a bloodless field, to define an adequate endarterectomy plane and to then follow the PTE specimen deep into the subsegmental vessels. Because of the copious bronchial blood flow usually present in these cases, periods of circulatory arrest are necessary to ensure perfect visibility. Although sporadic reports have described the performance of this operation without circulatory arrest, we emphasize that although endarterectomy is possible without circulatory arrest, *complete* endarterectomy is not. We always initiate the procedure without circulatory arrest; a variable amount of dissection is possible before the circulation is stopped, but never complete dissection. The circulatory arrest periods are limited to 20 minutes, with restoration of blood flow between each arrest. With experience, the endarterectomy usually can be performed with a single period of circulatory arrest on each side. A true endarterectomy in the plane of the media must be accomplished. It is essential to appreciate that the removal of visible thrombus is largely incidental to this operation. Indeed, in most patients, no free thrombus is present, and on initial direct examination, the pulmonary vascular bed may appear normal. The early literature on this procedure indicates that thrombectomy was often performed without endarterectomy; in these cases, the PVR did not improve, often with the resultant death of the patient. After median sternotomy the pericardium is incised longitudinally and is attached to the wound edges. Typically, the right side of the heart is enlarged, with a tense right atrium and a variable degree of TR (Fig. 26.8). Severe RV hypertrophy is usually present, and with critical degrees of obstruction, the patient's condition may become unstable with manipulation of the heart.

Anticoagulation is achieved with the use of heparin sodium (400 U/kg, intravenously) administered to prolong the activated coagulation time beyond 400 seconds. Full CPB is instituted with high ascending aortic cannulation and two caval cannulas. The heart is emptied on CPB, and a temporary PA vent is placed in the midline of the main PA 1 cm distal to the pulmonary valve. This location marks the beginning of the left pulmonary arteriotomy.

When CPB is initiated, surface cooling with both a head-wrap jacket and a body cooling blanket is begun, and the blood is cooled with the pump oxygenator. During cooling, no more than a 10°C gradient between arterial blood and bladder or rectal temperature is maintained.[86] Cooling generally takes 45 to 60 minutes. When ventricular fibrillation occurs, an additional vent is placed in the left atrium through the right superior pulmonary vein. This vent prevents left atrial (LA) and LV distention from the large amount of bronchial blood flow.

During the cooling period, some preliminary dissection can be performed, with full mobilization of the right PA from the ascending aorta. The superior vena cava (SVC) also is fully mobilized. The approach to the right PA is made medial, not lateral, to the SVC. All dissection of the PAs takes place intrapericardially, and neither pleural cavity should be entered. An incision then is made in the right PA from beneath the ascending aorta out under the SVC and entering the lower lobe branch of the PA just after the take-off of the middle lobe artery. It is important that the incision stays in the center of the vessel and continues into the lower rather than the middle lobe artery.

Any loose thrombus, if present, is removed. Embolectomy without subsequent endarterectomy is ineffective, and in most patients with

BOX 26.3 UNIVERSITY OF CALIFORNIA SAN DIEGO CHRONIC THROMBOEMBOLI CLASSIFICATION

Level I: Chronic thromboembolic disease in the main pulmonary arteries
Level IC: Complete occlusion of one main pulmonary artery with chronic thromboembolic disease
Level II: Chronic thromboembolic disease starting at the level of the lobar arteries or in the main descending pulmonary arteries
Level III: Chronic thromboembolic disease starting at the level of the segmental arteries
Level IV: Chronic thromboembolic disease starting at the level of the subsegmental arteries
Level 0: No evidence of chronic thromboembolic disease in either lung

From Madani MM, Jamieson SW, Pretorius V, et al. Subsegmental pulmonary endarterectomy: time for new surgical classification. Abstract presented at the International CTEPH Conference, Paris, 2014.

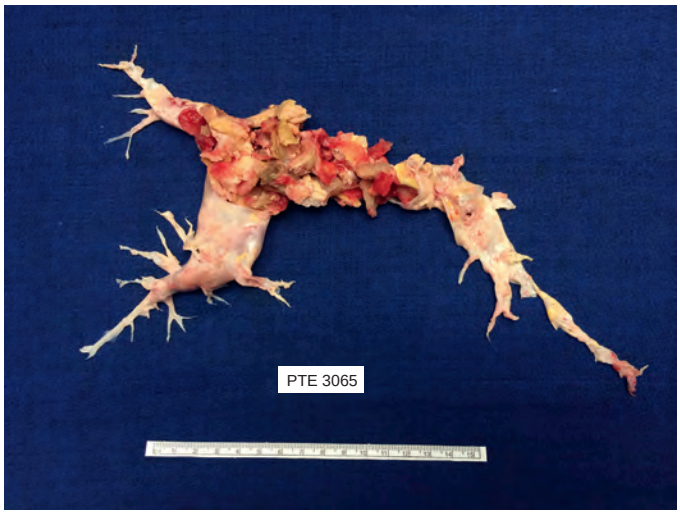


Fig. 26.9 University of California San Diego chronic thromboemboli classification level I, right and left sides. *PTE,* Pulmonary thromboendarterectomy.

CTEPH, direct examination of the pulmonary vascular bed at operation generally shows no obvious embolic material. Therefore, to the inexperienced surgeon or at cursory glance, the pulmonary vascular bed may well appear normal even in patients with severe CTEPH.

If the bronchial circulation is not excessive, the endarterectomy plane can be found during this early dissection. However, although a small amount of dissection can be performed before the initiation of circulatory arrest, it is unwise to proceed unless perfect visibility is obtained because the development of a correct plane is essential.

Five categories of pulmonary occlusive disease related to thrombus can be appreciated. The UCSD classification system describes the different levels of the thromboembolic specimen and corresponds to the degree of difficulty of the endarterectomy (Box 26.3).[87] Level 0 is no evidence of chronic thromboembolic disease present. In other words, a misdiagnosis has occurred, or perhaps one lung is completely unaffected by thromboembolic disease; both situations are rare. This entity is characterized by intrinsic small-vessel disease, although secondary thrombus may occur as a result of stasis. Small-vessel disease may be unrelated to thromboembolic events ("primary" PH) or may occur in relation to thromboembolic hypertension as a result of a high-flow or high-pressure state in previously unaffected vessels similar to the generation of Eisenmenger syndrome. Investigators believe that sympathetic "cross-talk" from the affected contralateral side or stenotic areas in the same lung may also be present.

Level I disease (Fig. 26.9) refers to the condition in which thromboembolic material is present and readily visible on the opening of the main left and right PAs. A subset of level I disease, level Ic, is complete occlusion of either the left or right PA and nonperfusion of that lung. Complete occlusion may represent an entirely different disease, especially when it is unilateral and on the left side (Fig. 26.10). This group of patients, typically young women with complete occlusion of the left PA, may not have reperfusion of their affected lung despite a complete endarterectomy, thus indicating a different intrinsic pulmonary vascular disease unrelated to thromboembolic disease.

In level II (Fig. 26.11), the disease starts at the lobar or intermediate-level arteries, and the main PA is unaffected. Level III disease is limited to thromboembolic disease originating in the segmental vessels only (Fig. 26.12). Level IV is disease of the subsegmental vessels (Fig. 26.13), with no other disease appreciated at more proximal levels. Level III disease and level IV disease present the most challenging surgical situations. The disease is very distal and is confined to the segmental and subsegmental branches. These levels are most often associated with presumed repetitive thrombi from upper extremity sources, long-term indwelling catheters, pacemaker leads, or ventriculoatrial shunts.

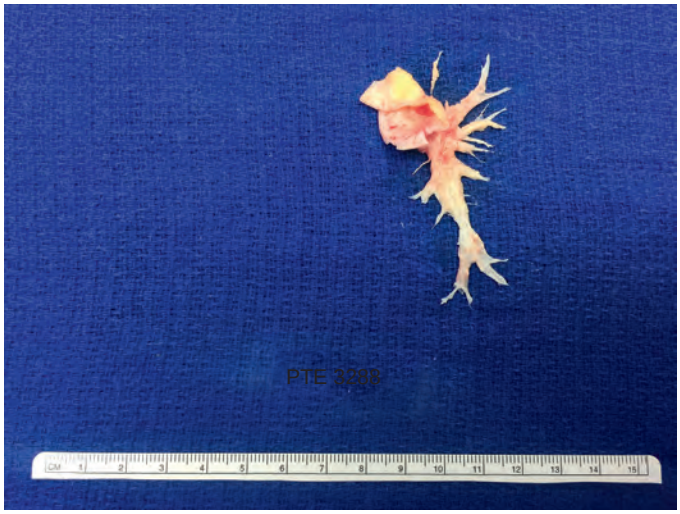


Fig. 26.10 Example where no disease is present on the right side (level 0) and complete occlusion is present on the left side (level 1C). *PTE,* Pulmonary thromboendarterectomy.

When the patient's temperature reaches 18°C, the aorta is cross-clamped, and a single dose of cold cardioplegic solution (1 L) is administered. Additional myocardial protection is obtained by the use of a cooling jacket. The entire procedure is performed with a single aortic cross-clamp period with no further administration of cardioplegia.

When blood obscures direct vision of the pulmonary vascular bed, circulatory arrest is initiated, and the patient undergoes exsanguination. All monitoring catheters to the patient are turned off to prevent aspiration of air. Snares are tightened around the cannulas in the SVC and inferior vena cava (IVC). Although antegrade cerebral perfusion or retrograde cerebral perfusion has been advocated for circulatory arrest in other procedures, these methods are not helpful in this operation because they do not allow a completely bloodless field, and, with the short arrest times that can be achieved with experience, they are not necessary. Any residual loose, thrombotic debris encountered is removed. Then a microtome knife is used to develop the endarterectomy plane posteriorly. Dissection in the correct plane is critical because if the plane is too deep, the PA may perforate, with fatal results; and if the dissection plane is not deep enough, inadequate amounts of the thromboembolic material will be removed. When the proper plane

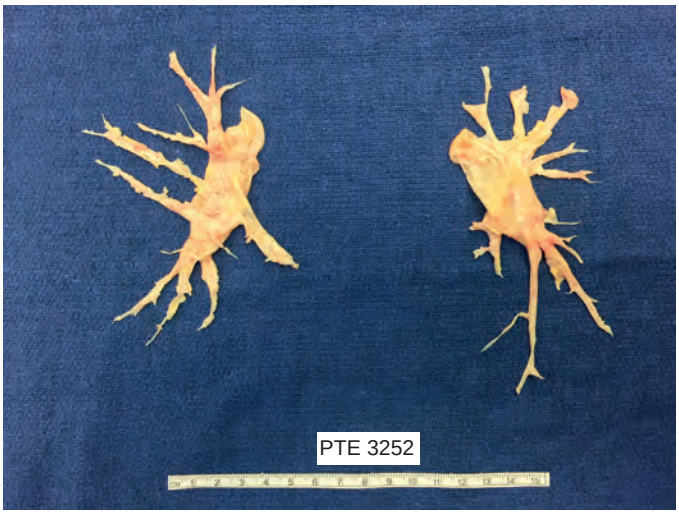


Fig. 26.11 University of California San Diego chronic thromboemboli classification level II, right and left sides. *PTE,* Pulmonary thromboendarterectomy.

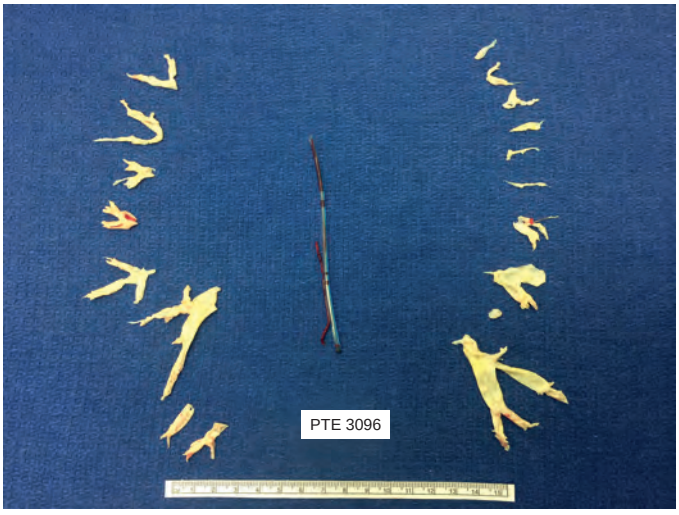


Fig. 26.12 University of California San Diego chronic thromboemboli classification level III, right and left sides. *PTE,* Pulmonary thromboendarterectomy.

Fig. 26.13 University of California San Diego chronic thromboemboli classification level IV, right and left sides. *PTE,* Pulmonary thromboendarterectomy.

is entered, the layer strips easily, and the material left with the outer layers of the PA appears somewhat yellow. The ideal layer is marked with a pearly white plane, which strips easily. No residual yellow plaque should remain. If the dissection is too deep, a reddish or pinkish color indicates that the adventitia has been reached. A more superficial plane should be sought immediately.

Once the plane is correctly developed, a full-thickness layer is left in the region of the incision to ease subsequent repair. The endarterectomy then is performed with an eversion technique, using a specially developed dissection instrument (Jamieson aspirator, Fehling Corporation, Acworth, Ga) and specially designed double-action forceps (Madani PTE Forceps, Wexler Surgical, Houston, Tex). Because the vessel is partly everted and subsegmental branches are being worked on, a perforation here becomes completely inaccessible and invisible later. This is why perfect visualization in a completely bloodless field provided by circulatory arrest is essential. It is important that each subsegmental branch is followed and freed individually until it ends in a "tail," beyond which no further obstruction is encountered. Residual material should never be cut free; the entire specimen should "tail off" and come free spontaneously. Once the right-sided endarterectomy is completed, circulation is restarted, and the arteriotomy is repaired with a continuous 6-0 polypropylene suture. The hemostatic nature of this closure is aided by the nature of the initial dissection, with the full thickness of the PA preserved immediately adjacent to the incision.

After completion of the repair of the right arteriotomy, the surgeon moves to the patient's right side. The pulmonary vent catheter is withdrawn, and an arteriotomy is made laterally beneath the pericardial reflection, and again into the lower lobe, but avoiding entry into the left pleural space. Additional lateral dissection does not enhance intraluminal visibility, may endanger the left phrenic nerve, and makes subsequent repair of the left PA more difficult. A lymphatic vessel is often encountered on the left PA at the level of the pericardial reflection, and it is wise to clip this vessel before it is divided with the PA incision.

The left-sided dissection is virtually analogous in all respects to that accomplished on the right. By the time the circulation is arrested once more, it will have been reinitiated for at least 10 to 15 minutes, by which time the venous oxygen saturations are in excess of 90%. The duration of circulatory arrest intervals during performance of the left-sided dissection is subject to the same restriction (≈20 minutes) as the right.

After completion of the endarterectomies, CPB is reinstituted and warming is commenced. Methylprednisolone (500 mg, intravenously) and mannitol (12.5 g, intravenously) are administered, and during warming no more than a 10°C temperature gradient is maintained between the perfusate and body temperature, with a maximum perfusate temperature of 37°C. If the systemic vascular resistance (SVR) is high, nitroprusside is administered to promote vasodilatation and warming.

When the left pulmonary arteriotomy has been repaired, the PA vent is replaced into the left PA. Once the arteriotomy is closed, the heart is returned to its natural anatomic position. If the intraoperative transesophageal echocardiogram (TEE) showed evidence of a septal defect, the right atrium is opened and examined. Any intraatrial communication is closed. Although TR is invariable in these patients and is often severe, tricuspid valve repair is not performed unless an independent structural abnormality of the tricuspid valve is present. If the tricuspid valve morphology is normal, tricuspid valve competence returns with RV remodeling over the course of a few days postoperatively. If other cardiac procedures are required, such as coronary artery or mitral or aortic valve operations, these are performed during the systemic rewarming period. Myocardial cooling is discontinued once all cardiac procedures have been concluded. The LA vent is removed, and the vent site is repaired. All air is removed from the heart, and the aortic cross-clamp is removed. When the patient has rewarmed, CPB is discontinued. Temporary atrial and ventricular epicardial pacing wires are placed. Despite the duration of CPB, hemostasis is readily achieved, and blood products are generally unnecessary. Wound closure is routine. Vigorous diuresis is usual for the first few hours after CPB.

Anesthetic Management of Patients Undergoing Pulmonary Thromboendarterectomy

Preoperative Assessment

Patients are admitted preoperatively for a full workup. Right-sided heart catheterization is the gold standard for diagnosing PH and the only way of accurately measuring right atrial (RA) pressures and PAP and assessing the severity of PAH. Jamieson and colleagues,[84] in their experience with 1500 cases, found that a postoperative mortality rate of 10% was associated with a preoperative PVR greater than 1000 dynes·s·cm^{-5}, compared with 1.3% in patients with a preoperative PVR lower than 1000 dynes·s·cm^{-5}. PH is defined by mPAP greater than 25 mm Hg and a PVR greater than 300 dynes·s·cm^{-5}. RV diastolic pressures greater than 14 mm Hg together with elevated RA pressures suggest RV failure. An mPAP value greater than 50 mm Hg and PVR greater than 600 dynes·s·cm^{-5} signify severe PH. CO and cardiac index (CI) also provide an insight into RV dysfunction. Preoperatively, all patients who will undergo PTE have IVC filter placement to prevent future PE after the endarterectomy.

Hemodynamic Considerations and Anesthetic Induction

On the day of the operation, a large-bore peripheral intravenous catheter and a radial arterial catheter are placed in the preoperative area. Benzodiazepines occasionally are administered for sedation but with extreme caution, with full monitoring, and preferably in the operating room. Sedation should be individualized on a case-by-case basis, noting that anxiety and pain can increase PVR, whereas excessive sedation can cause hypercarbia and hypoxia, leading to acidosis that exacerbates high PVR. A PA catheter (PAC) may be placed preoperatively but usually is placed after anesthetic induction.

CTEPH, according to its classification as precapillary PH, is characterized by normal LV systolic function and abnormal right-sided hemodynamics. Thus induction and decision making are centered on RV function. The right ventricle typically is hypertrophied and dilated and is associated with a dilated right atrium. Patients undergoing PTE have a fixed PVR and concomitant RV dysfunction; therefore any significant decrease in mean arterial pressure during induction may compromise RV perfusion and cause cardiovascular collapse and death. Maintenance of adequate SVR, an adequate inotropic state, and a normal sinus rhythm serves to preserve systemic hemodynamics, as well as RV coronary perfusion. Attempts to reduce PVR pharmacologically by using nitroglycerin or nitroprusside should be avoided because these agents have minimal efficacy in treating the relatively fixed PVR, and they result in SVR reduction that compromises RV coronary perfusion and RV function, thus rapidly leading to hypotension and cardiovascular collapse. Inhaled nitric oxide (NO) is safe to use, but some patients are not responsive to NO, and it is rarely required on induction. Administration of vasopressors, such as phenylephrine or vasopressin, is vital in treating hypotension and promoting adequate RV perfusion. Despite a relatively fixed PVR, attempts should be made to minimize conditions that increase PVR further such as episodes of hypoxia and hypercarbia.

The choice of anesthetic induction drugs depends on the degree of hemodynamic instability. Etomidate frequently is used because it maintains sympathetic tone and does not have a significant direct myocardial depressant effect. Succinylcholine or rocuronium can be used to achieve a rapid intubation environment and control of the airway. It is recommended that titration of narcotics to blunt the response to intubation takes place after control of ventilation to avoid rigidity and hypoventilation. Inotropic support with an infusion of a catecholamine is used in patients who are at high risk for cardiovascular collapse (Box 26.4).

A PAC is routinely placed after induction rather than before because the right-sided heart catheterization data are usually available for review preoperatively. The TEE can be very useful to guide PAC placement and confirm the position of the PAC in the PA. Patients undergoing PTE tend to have a dilated right atrium and right ventricle, thereby potentially making placement of the PAC difficult. A PAC is vital to assess the impact of surgical intervention on pulmonary vascular reactivity. Patients with advanced disease may be unable to lie supine or in the Trendelenburg position, which sometimes can lead to cardiorespiratory collapse. If the preoperative TTE reveals evidence of RA, RV, or main PA thrombi, TEE is performed immediately after induction and before placement of the PAC. In this instance, PAC placement is guided with TEE, and the PAC is left in the SVC (at 20 cm) until completion of the surgical procedure. Because all patients undergoing PTE also undergo prolonged CPB and circulatory arrest, a femoral arterial catheter is placed after induction to monitor arterial pressure after CPB because a radial artery catheter significantly underestimates systemic arterial pressure with a gradient of as much as 20 mm Hg. This phenomenon has been observed by Mohr and associates[88] and Baba and colleagues,[89] who proposed redistribution of blood flow away from the extremity as the cause. A screen shot displaying all the various hemodynamics used to monitor the patient during PTE is shown in Fig. 26.14.

SEDLine brain-function monitoring (Hospira, Lake Forest, Ill) is used to monitor the electroencephalogram. This four-channel processed electroencephalograph provides confirmation of cerebral isoelectricity and thus minimal use of oxygen by the brain before circulatory arrest. It also serves as a monitor for the level of consciousness during the procedure. Cerebral near-infrared spectroscopy, such as with the FORE-SIGHT (CAS Medical Systems, Branford, Conn) is used to monitor the patient's cerebral oxygen saturation status within tissues of the frontal lobe during the procedure and circulatory arrest. The device is a noninvasive method of estimating jugular bulb venous oxygen saturation ($SjvO_2$) and therefore global cerebral oxygen balance in the clinical setting, as demonstrated by Ikeda and associates.[90] In a retrospective study of more than 2000 patients, Goldman and colleagues[91] confirmed that the institution of cerebral oximetry in their practice decreased the stroke rate in cardiac surgical patients. Yao and associates[92] observed an association between cerebral desaturation and neurocognitive dysfunction in 101 patients undergoing cardiac surgical

BOX 26.4 SIGNS OF IMPENDING COLLAPSE

- Right ventricular end-diastolic pressure >15 mm Hg
- Severe tricuspid regurgitation
- Pulmonary vascular resistance >1000 dynes·s·cm^{-5}

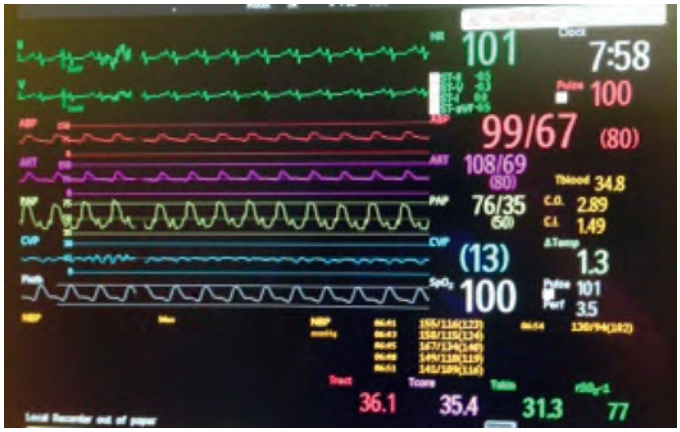


Fig. 26.14 Screen shot displaying all the various hemodynamics used to monitor a patient during the pulmonary thromboendarterectomy procedure.

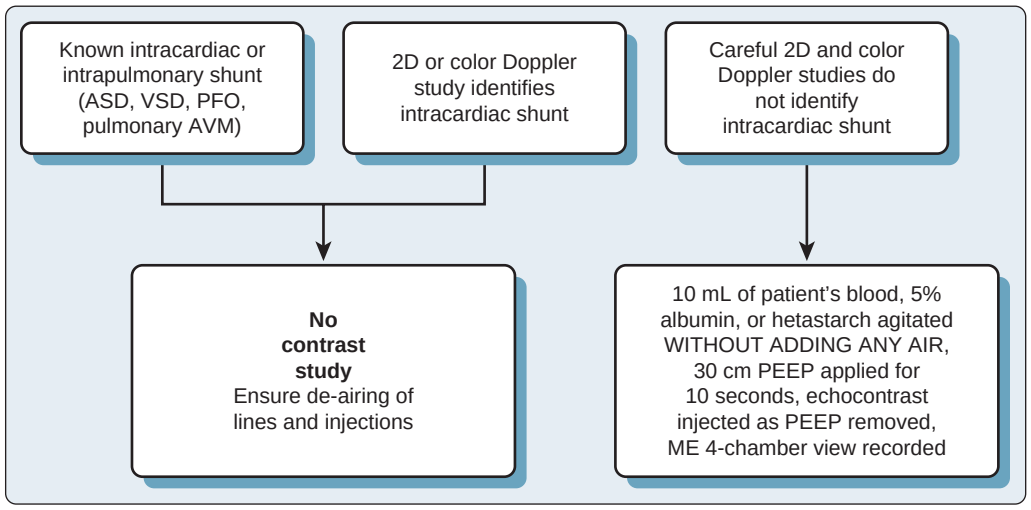


Fig. 26.15 Algorithm for performance of intraoperative echocardiographic contrast study for pulmonary thromboendarterectomy procedures. *ASD,* Atrial septal defect; *AVM,* arteriovenous malformation; *ME,* midesophageal; *PEEP,* positive end-expiratory pressure; *PFO,* patent foramen ovale; *VSD,* ventricular septal defect; *2D,* two-dimensional.

procedures. These investigators found that patients with a cerebral oxygen saturation of less than 40% for longer than 10 minutes had an increased incidence of neurocognitive dysfunction (see Chapter 18).

Temperature monitoring is achieved in several ways during all PTE procedures to allow accurate quantification of thermal gradients and to ensure even cooling and rewarming. Bladder temperature and rectal probes are used for core temperature estimation. A tympanic membrane probe is used for brain temperature estimation, and the PAC measures blood temperature.[93]

Acute normovolemic hemodilution often is used in the setting of an increased starting hematocrit without the presence of any concomitant cardiac disease. Typically, 1 to 2 units of whole blood is harvested after anesthetic induction, depending on the starting hematocrit, and it is replaced with colloid if needed to maintain hemodynamic stability. Acute normovolemic hemodilution has added benefits for deep hypothermic circulatory arrest because it will help decrease blood viscosity, optimize capillary blood flow, and promote uniform cooling.[94] This autologous harvested whole blood is reinfused after protamine administration, thus providing platelets and factors and replacing the diluted clotting factors resulting from the pump prime. Antifibrinolytic agents are not used routinely with PTE because patients are often inherently hypercoagulable.

TEE is used routinely in patients undergoing PTE to monitor hemodynamics, evaluate RV and LV function, identify intracardiac thrombus or valvular disease, and evaluate RV function and de-airing after bypass. A thorough intraatrial septal evaluation is performed to rule out a PFO, which has an incidence of 35% in the PTE population.[95] All patients are evaluated with two methods: color-flow Doppler and agitated echocardiographic contrast. Agitated echocardiographic contrast imaging is particularly useful if results of color-flow Doppler imaging are inconclusive. Positive pressure at 30 cm H_2O is applied for 10 seconds, and with release of the Valsalva maneuver, the agitated echocardiographic contrast (agitated blood or 5% albumin without adding any air) is injected. The echocardiographic contrast study is preferably performed after the patient is prepared and draped because instances of hemodynamic collapse have occurred following contrast injection. Most PFOs are repaired intraoperatively. An algorithm for PFO study assessment is shown in Fig. 26.15. In rare instances when results of the operation are not favorable, and high right-sided pressures are expected, the PFO is left open as a "pop-off" to improve RV function and increase CO at the expense of some hypoxemia. In this instance, closure of a PFO can be detrimental to clinical status by reducing LV filling and increasing filling of the noncompliant right ventricle.[84,96]

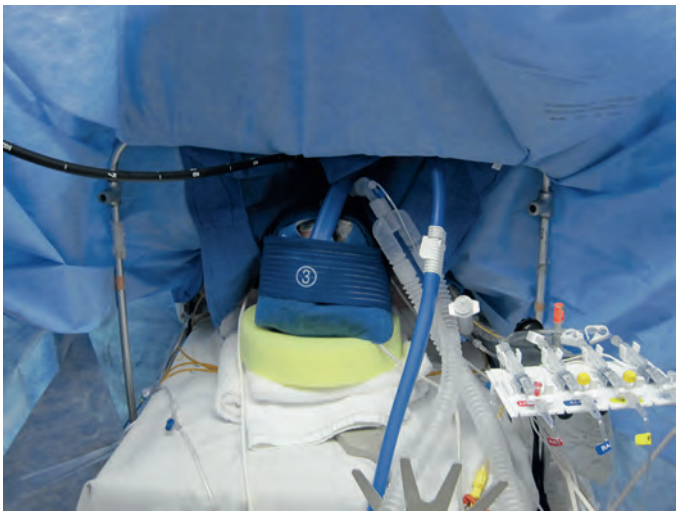


Fig. 26.16 Polar Care 500 cooling blanket used during circulatory arrest during pulmonary thromboendarterectomy procedures. *(Courtesy Breg, Vista, Calif.)*

The patient's head is wrapped in a cooling blanket because all PTE-treated patients undergo circulatory arrest. The head-wrap system (Polar Care, Breg, Vista, Calif) is composed of two items: the Polar Care 500 cooling device (cooling bucket, pump, pump bracket, and AC power transformer), which is reusable, and the actual wrap, which is a single-use item (Fig. 26.16). In a series of 55 patients who used this device during circulatory arrest, the mean tympanic membrane temperature was 15.1°C. The head wrap provides sufficient cooling to the brain, wraps the whole head, and is much easier to use than ice bags. It has been used in more than 3000 cases without any complications.

Cardiopulmonary Bypass Prime, Cooling and Hypothermic Circulatory Arrest

The prebypass time is typically short unless concomitant coronary artery bypass grafting is planned. The bypass system is primed with 1000 mL of Plasma-Lyte A (Baxter, Deerfield, Ill), 100 mL of 25% albumin, 5 to 12 mL (100 units/kg) of heparin, 12.5 g mannitol, and 8.4% 50 mL sodium bicarbonate. For circulatory arrest, 30 mg/kg of

methylprednisolone to a maximum dose of 3 g is added to the prime, and an additional 500 mg is added at rewarming. The steroid theoretically functions as a cell membrane stabilizer and antiinflammatory agent.[97] Phenytoin (15 mg/kg) is administered by the perfusionist for postoperative seizure prophylaxis, after initiation of bypass.

Cooling begins immediately after initiation of bypass, by using CPB temperature adjustment and the cooling blankets present under the patient, together with the head wrap. Allowing appropriate time to cool and warm the patient in each direction using rectal, bladder, tympanic, PA, and perfusate temperatures with appropriate thermal gradients ensures even and thorough cooling and warming, respectively. Propofol, 2.5 mg/kg, is administered immediately before initiation of deep hypothermic circulatory arrest to ensure complete isoelectricity. SEDLine brain-function monitoring is used for this purpose because brain cooling may be uneven or incomplete, and cerebral emboli may occur, given that PTE is an open procedure; in case of sparse electroencephalographic activity, it will monitor for any residual activity (Fig. 26.17).[98]

The following must be confirmed before circulatory arrest: the electroencephalogram is isoelectric, the tympanic membrane temperature is lower than 18°C, bladder and rectal temperatures are lower than 20°C, and all monitoring catheters to the patient are turned off, to decrease the risk for entraining air into the vasculature during exsanguination.

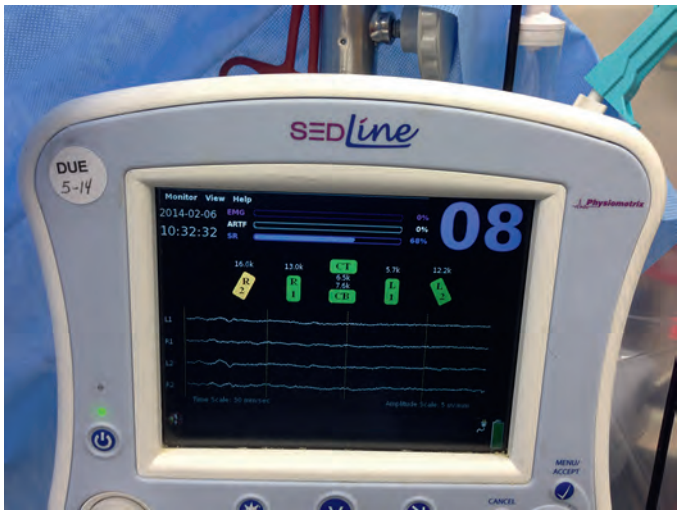


Fig. 26.17 Burst suppression, flat electroencephalogram monitored by SEDLine brain-function monitoring. *(Courtesy Hospira, Lake Forest, Ill.)*

Rewarming Phase and Separation From Bypass

The rewarming perfusate should not exceed 37°C, and the gradient between blood and bladder or rectal temperatures should not be more than 10°C. Warming too quickly promotes systemic gas bubble formation, cerebral oxygen desaturation, and uneven warming, which can aggravate cerebral ischemia and increase the chance of hypothermia in the postoperative period (after-drop). The rewarming period can take up to 120 minutes to achieve a core temperature of 36.5°C, depending on the patient's body mass and systemic perfusion.

Separation from CPB follows the same process as in most other cardiac operations, with a few minor exceptions. Communication with the surgeon is of paramount importance because surgical classification of the thromboembolic disease and the amount of organized clot that was successfully removed will dictate how much inotropic and vasopressor support (if any) is needed to separate from bypass. With successful endarterectomy, substantial reduction in PVR and improved RV function occur, as revealed immediately after bypass with TEE[99] (Fig. 26.18).

If residual PH is observed, the patient may need aggressive inotropic support (eg, dopamine, 3–7 µg/kg per minute; or epinephrine, 0.03–0.15 µg/kg per minute), together with pulmonary vasodilators, such as milrinone, and inhaled prostacyclin or NO. Inhaled NO is preferred because it acts on the pulmonary vasculature with minimal systemic effects. The right atrium is routinely paced at a rate of 90 to 100 beats/min with temporary epicardial pacing electrodes to ensure incomplete RV filling reducing wall tension. Ventricular epicardial electrodes are placed as well, but they are used only if atrioventricular conduction is impaired. End-tidal carbon dioxide is a poor measure of ventilation adequacy and does not represent the true arterial carbon dioxide in these patients both before and after CPB because dead-space ventilation is an integral part of the disease process. The arterial end-tidal carbon dioxide gradient usually improves after successful surgical treatment, but the response and time course vary. Higher minute ventilation is often required to compensate for metabolic acidosis that develops from CPB, circulatory arrest, and hypothermia. Before separation from CPB, intracardiac air and RV and LV function are assessed with TEE and PAC. With successful operative results, immediate improvements of RV function and resolution of the interventricular septal distortion and flattening are seen on intraoperative

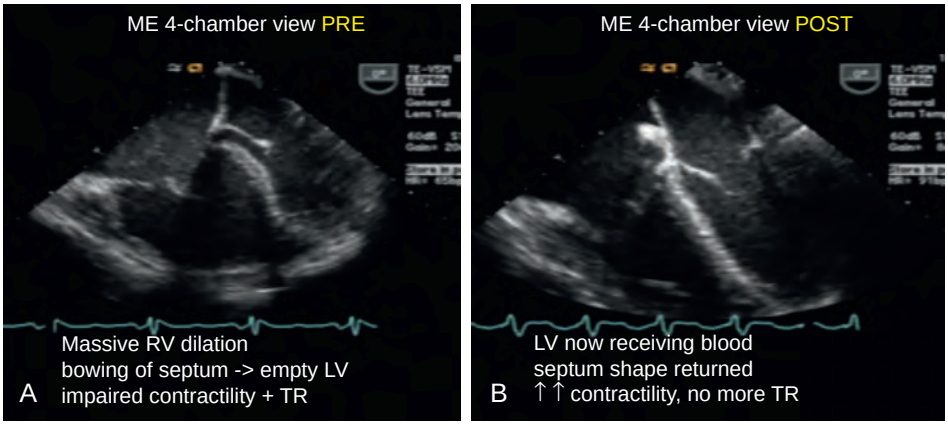


Fig. 26.18 (A) Midesophageal *(ME)* four-chamber view in a patient with chronic thromboembolic pulmonary hypertension before pulmonary thromboendarterectomy (PTE). Note the severely dilated right atrium, right ventricle, and the interatrial and intraventricular septum bulging toward the left atrium and left ventricle *(LV)*. (B) After successful PTE, note the improvement in the right atrial and right ventricular *(RV)* size. *TR,* Tricuspid regurgitation.

TEE. With the dramatic resolution of PH following PTE, transmitral diastolic flow improves in a predictable manner. Not surprisingly, this change correlates with improvements in the CO and CI.[100]

To standardize ventilation and maintain hyperventilation postoperatively, a portable transport ventilator is used to transport patients to the intensive care unit after PTE. If postoperative care is uneventful, most patients are discharged from the unit on the second or third postoperative day, with subsequent hospital discharge approximately 1 to 2 weeks after the operation.

Management of Airway Bleeding

Reperfusion pulmonary edema and airway bleeding are two of the most dreaded complications of PTE. Anesthesiologists must therefore be prepared to provide diagnostic and therapeutic maneuvers for these rare complications and routinely check the endotracheal tube during the rewarming phase before separation from CPB to inspect for bleeding or frothy fluid in the endotracheal tube.[101]

Most cases of bleeding are spontaneous and are discovered only after resuming cardiac ejection. However, the surgeon may anticipate bleeding if an adventitial injury is suspected during PTE and will help in promptly identifying the bronchial side that needs to be isolated. If dark frank blood is seen in the endotracheal tube after separation from CPB, it usually indicates a surgical violation of the blood-airway barrier in one of the PA branches. In contrast, pink frothy blood usually indicates early and severe reperfusion injury and is suspected when the PTE increased blood flow to a previously occluded vessel. Management of airway bleeding centers on prevention of exsanguination and maintenance of adequate gas exchange. Conservative management consists of positive end-expiratory pressure, lung isolation of the segment bleeding with a bronchial blocker, reversal of heparin, and correction of coagulopathies. These maneuvers often reduce minor bleeding and reperfusion injury.[102,103] If bleeding is recognized before separation from CPB, to the surgeon should allow the heart to eject briefly with the bleeding area under direct visualization with fiberoptic bronchoscopy to establish the location of bleeding. An attempt is made to isolate the affected segment by using bronchial blockade to prevent spilling blood into other segments and causing further impaired air flow and gas exchange. Therefore, immediately before separation from CPB, special attention should be paid to optimizing oxygenation and ventilation. In addition, while the patient is undergoing CPB and with the PA vent on suction, an attempt may be made to exchange the endotracheal tube with a larger (9–10 mm) endotracheal tube. This allows the use of a large bronchoscope together with a 9-Fr Uniblocker (LMA North America, San Diego, Calif). We recommend the use of an airway exchange catheter because of the high incidence of poor direct visualization resulting from bleeding, edema, and suboptimal conditions. Use of the Uniblocker is good for isolation of a lung or lobe, and the Arndt blocker (Cook Medical, Bloomington, Ind) is more appropriate for isolation of a specific segment. The use of a double-lumen tube is not recommended because it presents a challenge when using a large bronchoscope that has superior suction and diagnostic capabilities. In cases of minor adventitial injuries, the blocker balloon can be deflated under direct visualization, and normal ventilation can be resumed; however, if persistent hemorrhage is noted, continued lung isolation is needed.

In severe circumstances in which inadequate oxygenation, ventilation, and hemodynamics persist, various forms of extracorporeal life support should be considered. Three options exist:

1. With biventricular dysfunction, venoarterial extracorporeal membrane oxygenation (ECMO) can be used with anticoagulation.
2. With RV dysfunction and persevered LV function, ECMO with RA inflow and PA outflow cannula bypassing and unloading the right ventricle aids in gas exchange and supports RV function.
3. With preserved RV and LV function, venovenous ECMO using a heparin-bonded circuit, without systemic anticoagulation, improves oxygenation but does not provide ventricular support (see Chapters 28 and 33).

An algorithm for management of post-CPB hemorrhage is presented in Fig. 26.19. The Avalon Elite Bicaval Dual-Lumen Catheter (Maquet, Rastatt, Germany) typically is inserted via the Seldinger technique into the right internal jugular vein with ultrasound and TEE guidance. A bicaval view using color-flow Doppler is used to ensure that the outflow jet is toward the tricuspid valve.[102,104,105] This technique is efficient, requires no anticoagulants, and maintains appropriate gas exchange with preservation of pulsatile pulmonary and systemic flow while allowing natural hemostatic processes to repair the affected PA or capillary bed. The natural repair is usually complete after 24 to 48 hours, thus allowing weaning from ECMO. The third most common cause of perioperative death in patients undergoing PTE is massive pulmonary hemorrhage after PTE, with residual PH and reperfusion pulmonary edema as the leading two causes.

Management of the Postoperative Patient

In many respects the principles of postoperative management of patients undergoing PTE are similar to those following other procedures requiring sternotomy and CPB. The desire to minimize the time of mechanical ventilation, the use of vasoactive medications for inotropic and hemodynamic support, wound care, mediastinal chest tube management, the use of "prophylactic" antibiotics, pain management, and treatment of postoperative arrhythmias and coagulopathies are common issues faced by the physicians, nurses, pharmacists, and respiratory therapists caring for patients after PTE.

However, several aspects of this operation frequently present unique postoperative challenges. For example, the median duration of CPB of approximately 4 hours is a risk factor for coagulopathy and a reduction in platelet count that may result in transient, albeit significant, mediastinal blood loss. A modest rise in creatinine level postoperatively is also frequently observed, although the need for dialysis is rare. A transient increase in serum transaminase levels, presumptively from prolonged hypoperfusion, is also observed. Deep hypothermia frequently results in postoperative metabolic acidosis during the rewarming phase, and prolonged circulatory arrest has been associated with postoperative mental status changes and delirium.[106] The endarterectomy procedure itself dramatically alters cardiopulmonary physiology in the immediate postoperative period. After successful PTE, a significant reduction in RV afterload occurs, and lung regions supplied by vessels previously occluded by organized thrombus receive dramatically increased pulmonary blood flow. Understanding of these immediate physiologic changes provides a rationale for the unique management of the post-PTE patient.[107]

Post–Pulmonary Thromboendarterectomy Hemodynamic Management and Persistent Pulmonary Hypertension

The immediate hemodynamic results following effective PTE include reductions in PAP and PVR (RV afterload) and improvements in RV function and CO.[73,78,108–111] However, transient sinus node dysfunction often requiring atrial pacing frequently occurs during the first few postoperative days. This dysfunction likely results from the residual effects of intraoperative hypothermia and cardioplegia. In addition, despite a reduction in RV afterload, some persistent RV dysfunction can be observed. As seen on echocardiography, a degree of RV strain can persist, although the pattern is different from what is noted preoperatively.[9] We believe that this RV strain may result from the residual effects of hypothermia (including the use of a cardiac cooling jacket) and cardioplegia, as a response to poor pulmonary vascular compliance, or from pericardiotomy during PTE. Modest inotropic support is usually effective in maintaining adequate CO during this brief period. Sometimes a persistently low SVR follows PTE in the absence of evidence of infection or medication effect. As in the earlier case, the profound hypothermia may be responsible for this phenomenon, and

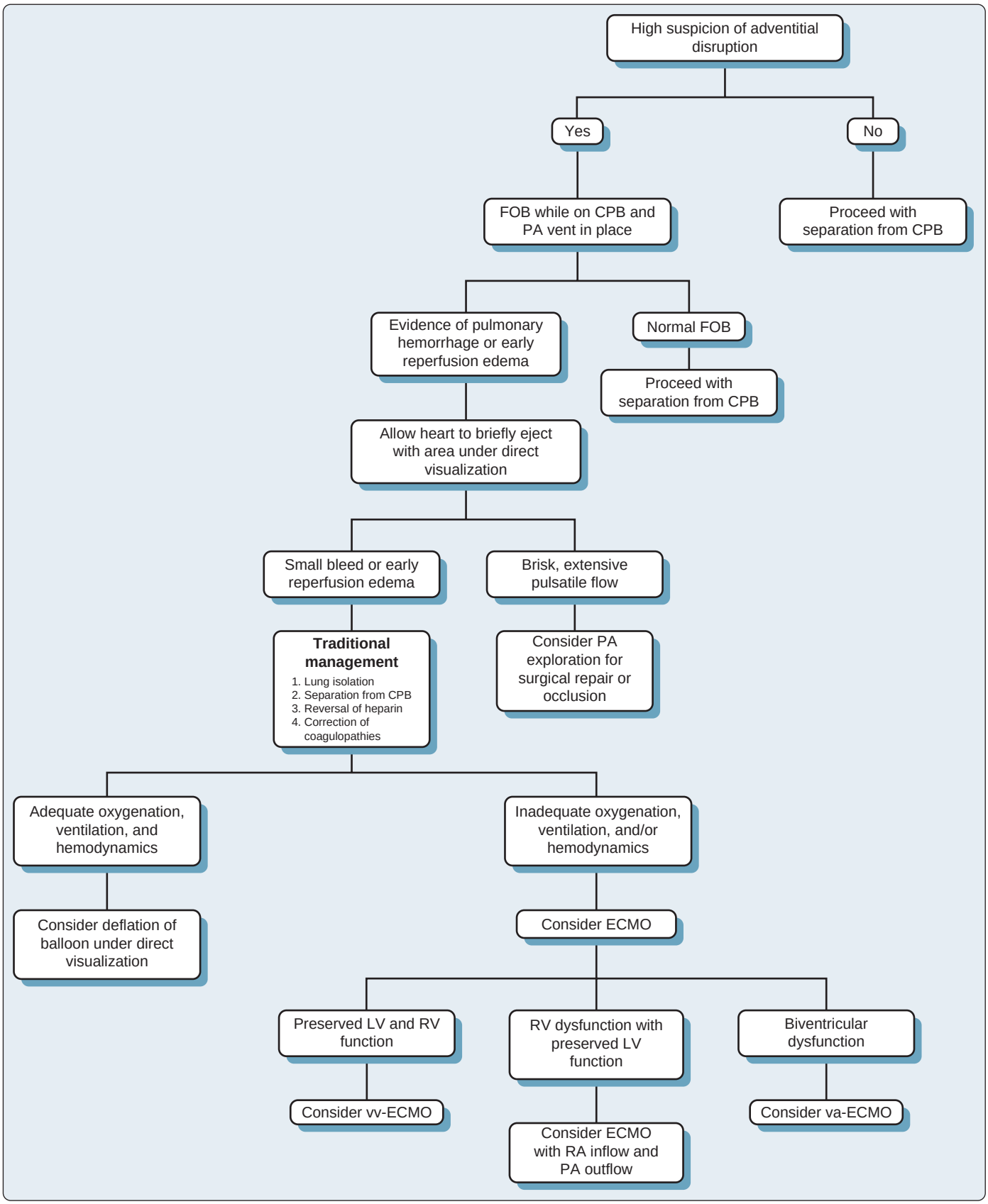


Fig. 26.19 Algorithm for management of post–cardiopulmonary bypass pulmonary hemorrhage for the pulmonary thromboendarterectomy procedure. *CPB,* Cardiopulmonary bypass; *FOB,* fiberoptic bronchoscopy; *ECMO,* extracorporeal membrane oxygenation; *LV,* left ventricular; *PA,* pulmonary artery; *RA,* right atrial; *RV,* right ventricular; *va,* venoarterial; *vv,* venovenous. *(Reprinted with permission from Cronin B, Maus T, Pretorius V, et al. Case 13—2014: management of pulmonary hemorrhage after pulmonary endarterectomy with venovenous extracorporeal membrane oxygenation without systemic anticoagulation.* J Cardiothorac Vasc Anesth. *2014;28(6):1667–1676.)*

an α-adrenergic agonist is generally effective in supporting blood pressure. On rare occasions, adrenal insufficiency may be the basis for this hypotension, and cortisol levels (after administration of adrenocorticotropic hormone) should be assessed to verify this diagnosis. Some patients do not achieve normal PAPs and RV function following PTE; the incidence is between 5% and 35% of operated patients. Plausible explanations include residual chronic thromboembolic disease that could not be surgically resected or a significant amount of coexisting small-vessel arteriopathy.

Long-term information on the level of residual PH that negatively affects functional status and survivorship is lacking.[112–116] In the immediate postoperative period, significant RV dysfunction greatly complicates the clinical course. Attention to oxygenation status and careful volume management, correction of acid-base imbalance, inotropic support, and at times the use of PH-targeted medical therapy with parenteral prostanoid administration may be necessary to support patients through this tenuous postoperative period. In extreme circumstances, ECMO support has been used when other measures fail, particularly when concurrent hypoxic respiratory failure is present.[117] Success with this approach presupposes a reversal component to the cardiopulmonary instability, and sometimes this aggressive management can be viewed as a bridge to organ transplantation in the acute setting.[118]

Other Pulmonary Considerations and Management of Hypoxemia

After successful PTE, lung perfusion shifts, with blood flow preferentially going to regions supplied by PAs that have been opened. This shift is accompanied by a reduction in perfusion in lung regions uninvolved with chronic thrombotic material, a phenomenon termed *perfusion steal*[119] (Fig. 26.20). Although this reperfusion of previously nonperfused lung parenchyma is the basis for the reduction in RV afterload, the postoperative perfusion shifts are responsible for $\dot{V}/\dot{Q}$ mismatch, an important contributor to the development of acute reperfusion lung injury.[120] This form of acute lung injury occurs in the endarterectomized lung region, is associated with varying degrees of hypoxemia (ratio of arterial oxygen partial pressure to fractional inspired oxygen [P/F ratio] <300), begins within 72 hours of operation, and occurs in the absence of an alternative clinical explanation for the pulmonary infiltrates on chest radiograph (Fig. 26.21). The pathophysiologic basis is incompletely understood, although initial observations suggested a high-permeability, inflammatory-mediated mechanism. Such observations were supported by anecdotal experience with high-dose corticosteroids resulting in reductions in both the incidence and the severity of the reperfusion response.[107] Furthermore, a randomized, placebo-controlled clinical trial examining the use of a selectin analogue to block neutrophil adhesion and migration was shown to reduce the relative risk of lung injury by 50% in patients undergoing PTE.[121] However, well-designed follow-up studies investigating the perioperative use of high-dose corticosteroids failed to show effectiveness,[122] and the declining incidence over the years of this postoperative complication without evident cause, or change in surgical or anesthetic management, brings the "inflammatory" response as the sole physiologic basis for this lung injury into question. Furthermore, reports that a higher preoperative PVR is associated with a higher incidence of lung injury after PTE,[123] and more observations that postcapillary microvascular disease can be observed in patients with CTEPH,[124] suggest that a hemodynamic component contributes to reperfusion lung injury after PTE.

The approach to patients with reperfusion lung injury is primarily supportive, and the intensity of intervention depends on the degree of hypoxemia. The difficulties in management of this patient population are augmented by the shift in pulmonary blood flow that occurs as noted previously: the normal compensatory mechanism of hypoxic pulmonary vasoconstriction is blunted in injured lung regions receiving a large percentage of blood flow, thus resulting in regions that are edematous, poorly ventilated, and noncompliant. In the mildest forms, diuresis to decrease lung edema and supplemental oxygen may be the only treatment required. For more severe lung injury, aggressive diuresis, lung-protective ventilator strategies, and prompt treatment of concurrent lung infection (if present) are mainstays of therapy. For severe lung injury, when other measures have failed, ECMO support has been used with success.[117,125] The use of inhaled NO to correct $\dot{V}/\dot{Q}$ mismatch can be associated with an improvement in oxygenation in some patients, at least initially. However, this approach was

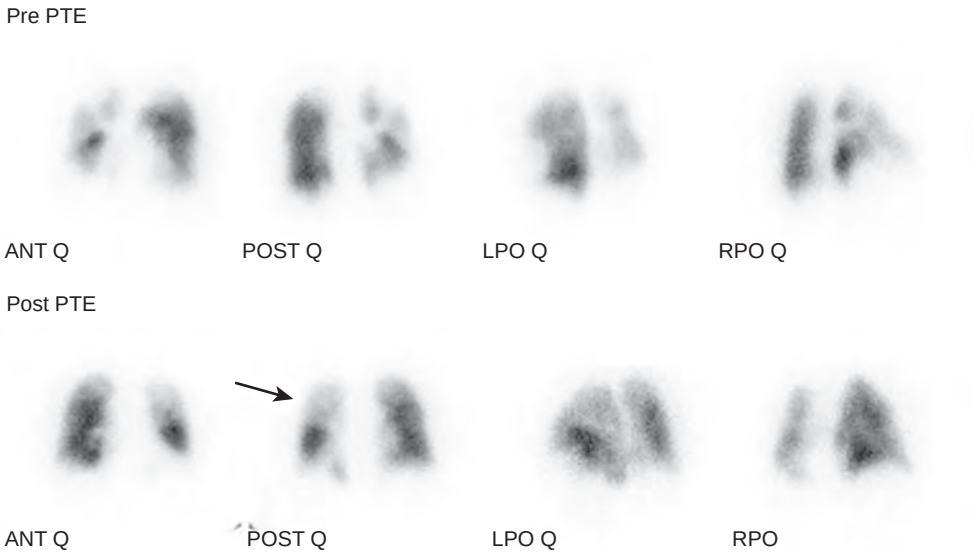


Fig. 26.20 Postoperative shifting of lung perfusion following removal of organized thrombus pictured in Fig. 26.6. The relative increase in perfusion to the right lung where an extensive amount of chronic thromboembolic material was endarterectomized resulted in hypoperfusion of the left upper lobe *(arrow)* after pulmonary thromboendarterectomy *(PTE)* (where minimal amounts of chronic thromboembolic material was endarterectomized), referred to as "perfusion steal." The postoperative scan was obtained 6 days postoperatively. *ANT,* Anterior; *LAO,* left anterior oblique; *POST,* posterior; *Q,* perfusion; *RAO,* right anterior oblique.

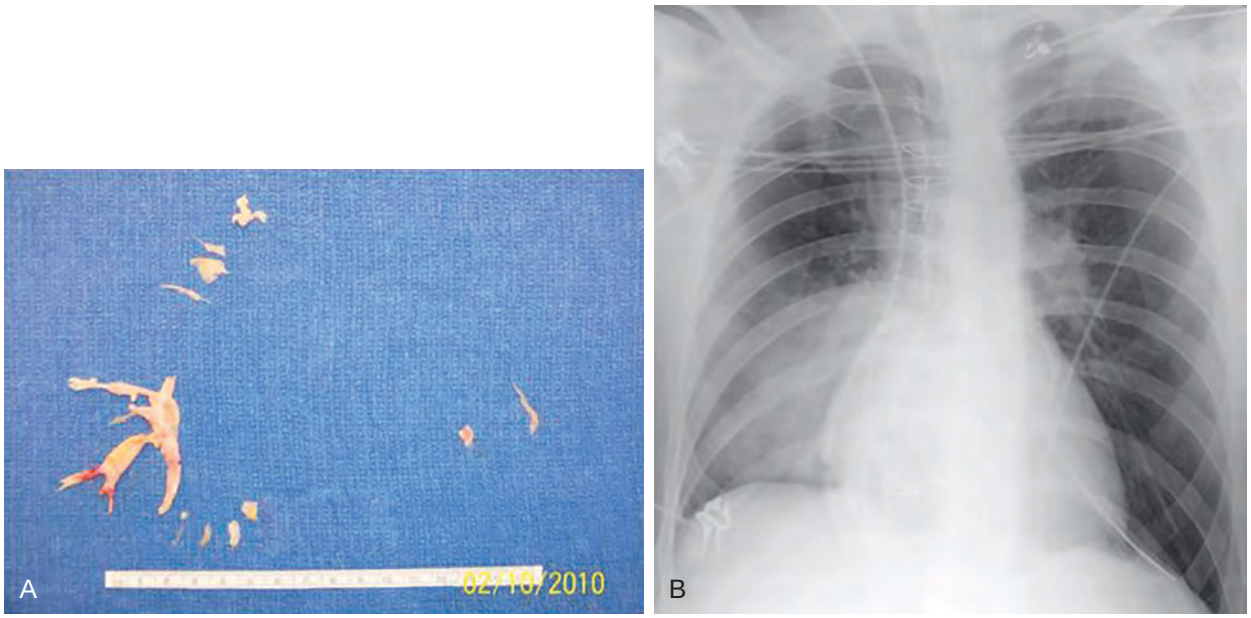


Fig. 26.21 (A) Pulmonary thromboendarterectomy (PTE) specimen from the right lower lobe (RLL). (B) Chest radiograph demonstrating pulmonary infiltrates consistent with reperfusion lung injury in the RLL within 24 hours of PTE. This finding correlates with removal of chronic thromboembolic material from vessels leading to the RLL, as pictured.

not consistently effective in a small trial of patients with other forms of lung injury.[126] Similarly, the use of a low-lung-volume ventilation strategy during the immediate post-PTE period, as an independent factor, is unlikely to prevent reperfusion lung injury.[127]

Hypoxemia during the immediate postoperative period may also simply be secondary to atelectasis in a region of newly reperfused lung. Ventilator adjustments using slightly higher tidal volumes, positive end-expiratory pressure, and lung recruitment maneuvers can be effective in improving $\dot{V}/\dot{Q}$ matching in this setting. For extubated patients, mobilization and aggressive lung recruitment maneuvers to diminish atelectasis usually improve oxygenation.

Low $\dot{V}/\dot{Q}$ and resultant hypoxemia can be observed following PTE operations in the absence of evident lung injury.[128] These findings may be the result of a high perfusion state in relatively small lung regions after endarterectomy of segmental and subsegmental vessels. Other than supportive measures and oxygen supplementation, no specific treatment exists for this condition. This perfusion shift improves over time.

Postoperative Thrombosis Prophylaxis and Anticoagulation

Once hemostasis has been achieved in the early hours following PTE, thrombosis prophylaxis is typically initiated with subcutaneous heparin and the use of pneumatic compression devices. Experience has suggested that patients with a history of antiphospholipid syndrome, those patients with CTEPH who have undergone level 1C resection, and those with evidence of a recent thromboembolic event are at greater risk for postoperative thrombosis, including within the pulmonary vessels. For these patients, therapeutic-level anticoagulation is attempted early postoperatively as long as significant hemorrhage does not occur.

Lifelong anticoagulation is strongly advised in patients who have undergone PTE.[129] Once epicardial pacing wires are removed, and further invasive procedures are unlikely, warfarin is begun with a target international normalized ratio (INR) of 2.5 to 3.5. Although data are lacking on the ideal level of anticoagulation over time, thromboembolic recurrence is rare in patients who have been maintained on long-term anticoagulation. Individualization of the care plan is emphasized. For example, in patients with antiphospholipid syndrome who have considerable thrombophilia, INR targets are frequently higher. For older patients and for those patients concurrently taking antiplatelet agents, targeting an INR between 2.0 and 3.0 is common practice. The use of the newer oral anticoagulants, targeting thrombin or factor Xa, has yet to be examined in this patient population.

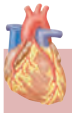
Nonsurgical Approach to Chronic Thromboembolic Disease

Pulmonary Hypertension–Targeted Medical Therapy

PTE is the preferred treatment option for patients with CTEPH. However, patient subgroups in whom PH-targeted medical therapy was examined in randomized, placebo-controlled trials include patients deemed to have inoperable CTEPH and patients with residual PH following PTE. PH-targeted medical therapy is also sometimes beneficial as a bridge to PTE in preoperative patients with severe PH and RV dysfunction (Box 26.5).

A randomized controlled trial examining the efficacy of bosentan in inoperable CTEPH was reported in 2008 by Jais and colleagues,[130] who enrolled 157 patients. Bosentan was used in 77 patients, approximately 28% of whom had previously undergone PTE procedures. Compared with baseline, 16-week treatment with bosentan resulted in an improvement in pulmonary hemodynamic parameters: a 24.1% reduction in PVR, a decline in total pulmonary resistance (treatment effect: decline of 193 dynes·s·m^{-5}), with a rise in CI (treatment effect: improvement of 0.3L/m^2 per minute). The bosentan-treated patients also had a decrease in N-terminal pro–brain natriuretic peptide (NT-proBNP) levels relative to patients receiving placebo. However, at 16 weeks, no definable improvement in exercise capacity and no statistically significant treatment effect of bosentan on WHO functional class were observed.[130]

In a double-blind, placebo-controlled, 12-week pilot study, Suntharalingham and associates[131] enrolled 19 patients with inoperable CTEPH and assessed the benefit of sildenafil with 9 patients receiving the drug. Although no significant difference was detected



BOX 26.5 PATIENT GROUPS WITH CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION TO CONSIDER FOR TARGETED MEDICAL THERAPY FOR PULMONARY HYPERTENSION

- Patients with inoperable chronic thromboembolic pulmonary hypertension
- Patients with residual pulmonary hypertension after a pulmonary thromboendarterectomy surgical procedure
- Patients with chronic thromboembolic pulmonary hypertension in whom comorbidities are so significant that surgical treatment is contraindicated.
- Patients who have severe pulmonary hypertension and right-sided heart failure, in whom targeted medical therapy for pulmonary hypertension may be a "clinically stabilizing bridge" to surgical treatment

in exercise capacity (the primary end point), improvements in WHO functional class and PVR were noted. Control subjects were then transitioned to open-label sildenafil use and were reassessed at 12 months. Significant improvements in 6-minute walk distance (6MWD), activity and symptom scores (Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR]), CI, PVR, and NT-proBNP values (1000–811 pg/mL) were noted.[131]

In an open-label study, Reichenberger and colleagues[132] examined the effectiveness of sildenafil (50 mg three times a day) in 104 patients with inoperable CTEPH. After 3 months of therapy, a modest decrease occurred in PVR (863 ± 38 to 759 ± 62 dynes·s·cm^{-5}), with an increase in 6MWD from 310 ± 11 to 361 ± 15 m; this distance further improved to 366 ± 18 m after 12 months of sildenafil.[132]

The use of intravenous epoprostenol in patients with inoperable CTEPH has been examined. Cabrol and associates[133] retrospectively analyzed 27 patients with inoperable CTEPH who were treated with epoprostenol. After 3 months of therapy, decreases in mPAP (56 ± 9 to 51 ± 8 mm Hg) and total pulmonary resistance (29.3 ± 7.0 to 23.0 ± 5.0 U/m^2) and an increase in 6MWD of 66 m occurred. NYHA functional status was improved by at least one class in 11 of 23 patients.[133]

In a single-center uncontrolled observational study,[134] 28 patients with severe, inoperable CTEPH were treated with subcutaneous treprostinil, a prostacyclin analogue. Right-sided heart catheterization was repeated in 19 patients after 19 ± 6.3 months of treatment. Treprostinil therapy was associated not only with a significant reduction in PVR, but also with an improvement 6MWD, WHO functional class, BNP levels, and CO. The 5-year survival rate was 53% compared with 16% in untreated historical control subjects.[134]

Although the long-term benefit of inhaled iloprost, an aerosolized prostacyclin analogue, in patients with inoperable CTEPH has not been examined, an acute pulmonary hemodynamic benefit has been observed. With the administration of 5 μg of inhaled iloprost to 20 patients with CTEPH (12 with distal chronic thromboembolic lesions), Krug and colleagues[135] were able to show a decline in PVR from 1057 ± 404.3 to 821.3 ± 294.3 dynes·s·cm^{-5} and a reduction in mPAP from 50.55 ± 8.43 to 45.75 ± 8.09 mm Hg. This was accompanied by an increase in CO from 3.66 ± 1.05 to 4.05 ± 0.91 L/min. Of the 20 patients, 16 patients were already receiving one or more PAH-specific medical therapies at the time.[135]

Riociguat, a newer agent that stimulates soluble guanylate cyclase, either directly or by increasing the sensitivity of soluble guanylate cyclase to NO, was examined in patients with inoperable CTEPH or with residual PH after PTE (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With CTEPH [CHEST-1] study).[136] This 16-week, randomized, placebo-controlled trial had 261 enrolled patients, 173 receiving riociguat. Those patients receiving the drug experienced an improvement in exercise capacity (6MWD increased by an average of 39 m), whereas those patients in the placebo group showed a decline in 6MWD by an average of 6 m. The treatment group also had an improvement in WHO functional status and a significant reduction in NT-proBNP levels. A decline in PVR of 226 dynes·s·cm^{-5} was measured in patients receiving riociguat (n = 151), whereas those patients in the placebo group showed an increase of 23 dynes·s·cm^{-5} (least square mean difference of −246 dynes·s·cm^{-5}). Significant improvements in CO and mPAPs were also noted in those patients receiving the drug. No significant difference was observed in the incidence of "clinical worsening events" detected between the two groups, and the occurrence of RV failure (3% in each group) and syncope (2% in the riociguat group vs 3% of placebo patients) was comparable.[136] The results of this study provided the basis for approval by the US Food and Drug Administration of riociguat for those patients with inoperable CTEPH and with residual PH following PTE. A subsequent open-label, long-term extension study (BAY63-2521: Long-term Extension Study in Patients With Chronic Thromboembolic Pulmonary Hypertension [CHEST-2]) providing riociguat to those patients previously receiving placebo confirmed the exercise and functional status benefits of this medication for up to a year, with a similar safety profile achieved in CHEST-1.[137]

PH-targeted medical therapy has also been used as bridging therapy in operable patients with CTEPH, the assumption being that if PH and RV function can be improved in high-risk patients, a reduction in postoperative mortality rates may be realized. The first attempt to prove this thesis was made by Nagaya and associates,[138] who administered intravenous prostacyclin at a mean dose of 6 ± 1 ng/kg per minute for 46 ± 12 days before PTE in 12 patients with operable CTEPH, each with a PVR greater than 1200 dynes·s·cm^{-5}. This treatment resulted in a significant preoperative reduction in PVR (1510 ± 53 to 1088 ± 58 dynes·s·cm^{-5}) and a decline in plasma BNP levels. Postoperatively, 1 patient in the treatment group died (8.3%) during the first 30 days; none died in the group of 21 patients with a preoperative PVR lower than 1200 dynes·s·cm^{-5}. Postoperative pulmonary hemodynamic results in both groups of patients were comparable.[138]

More recently, Reesink and colleagues[139] conducted a randomized, controlled, single-blind study using bosentan as a bridge to PTE. Twenty-five patients with operable CTEPH were enrolled, with 13 patients receiving bosentan for 16 weeks. Comparative differences from baseline between the groups, with therapeutic benefit achieved in those patients receiving bosentan, showed a change in PVR of 299 dynes·s·cm^{-5}, mPAP of 11 mm Hg, CI of 0.3 L/min/m^2 and 6MWD of 33 m. However, postoperative pulmonary hemodynamic outcomes were similar between groups of patients (postoperative mPAP and PVR were lower in the bosentan group; this difference did not achieve statistical significance). Similarly, the short-term postoperative clinical course (days in the intensive care unit, ventilator days, occurrence of lung injury) between groups was similar. Three patients died in the no-bosentan group postoperatively, compared with no deaths in the bosentan-treated patients.[139]

A more recent pilot study of 15 patients with operable CTEPH was conducted to assess the effect of preoperative use of bosentan on RV function.[140] Eight of these 15 patients were randomly assigned to receive bosentan in addition to "best standard of care" for 16 weeks, with pretreatment and posttreatment evaluation of RV function and "remodeling" using cardiac MRI. Discernible improvements in RV stroke volume index, RV ejection fraction, RV mass, RV isovolumic relaxation time, and LV ejection fraction were noted. These improvements were accompanied by a change in mPAP (−11 vs 5 mm Hg in the no-bosentan group), and an increase in 6MWD (20 vs −4 m in the no-bosentan group).[140]

Despite these positive trends, existing data have not justified the routine use of PH-targeted medical therapy in patients with operable CTEPH as a bridge to surgical treatment, although logic dictates that a subgroup of patients with CTEPH with severe PH and RV failure may benefit from hemodynamic stabilization before undergoing anesthetic induction and the cardiopulmonary stress of operation. Despite the uncertainties surrounding medical therapy, increasing numbers of patients with CTEPH with surgical disease are given medical treatment

preoperatively. In a retrospective analysis of patients referred for PTE between 2005 and 2007, Jensen and associates[141] reported that the use of medical therapy for PH in patients with operable CTEPH increased from 19.9% of patients in 2005, to 31.9% in 2006, and to 37.0% in 2007. These investigators additionally observed that this practice was associated with a significant delay in time to referral without having a discernible benefit on measured postoperative outcomes.[141]

Percutaneous Balloon Pulmonary Angioplasty

The use of balloon pulmonary angioplasty (BPA) in the management of selected patients with chronic thromboembolic disease has grown. Application of this technique in a patient with CTEPH was first reported in 1988.[142] In 2001, Feinstein and colleagues[143] expanded on this experience and described BPA as an alternative to PTE in patients believed to have surgically inaccessible CTEPH or in patients whose comorbidities precluded surgical consideration. BPA was performed in 18 patients, averaging 2.6 procedures and 6 balloon dilations per patient, with an overall decrease in mPAP (42 ± 12 to 33 ± 10 mm Hg). Improvements in functional status and 6MWD followed at an average of 35.9 months after the initial catheterization. Only one patient died, on postcatheterization day 7, of RV failure. However, the overall postprocedure CI was not significantly improved, the hemodynamic improvement was not comparable to that obtained in patients undergoing PTE, and the rate of reperfusion lung injury after the procedure was considerable. Those patients with a mPAP greater than 35 mm Hg were at greatest risk (incidence of 61%, 3 patients requiring mechanical ventilation).[143] Two years later, a case report described two patients with surgically inaccessible CTEPH who had hemodynamic improvement after BPA; the investigators noted that this procedure could be viewed as an alternative treatment option for patients deemed "not suited" for surgical treatment.[144]

Specialized centers in Japan have reported the greatest experience with BPA. In a prospective study of 12 patients deemed to have nonsurgical CTEPH and "stabilized" with pulmonary vasodilators (including 2 patients with residual PH after PTE), Sugimura and associates[145] performed multiple angioplasty sessions until the mPAP was less than 30 mm Hg. Not only did this approach result in an overall improvement in pulmonary hemodynamics and functional status, but also, when compared with historical controls, showed an improvement in survivorship. Mild-to-moderate hemoptysis was observed in 50% of patients following this procedure.[145] In 68 patients, Mizoguchi and colleagues[146] reported a refinement of the angioplasty procedure in which the selection of appropriate balloon size was made using intravascular ultrasound; the hypothesis was that this technique could reduce the incidence of postprocedure reperfusion lung injury. Although 60% of patients developed a degree of reperfusion injury (including the development of "hemosputum"), improvements in mPAP (45.4 ± 9.6 to 24.0 ± 6.4 mm Hg) and functional status were reported. One patient died of RV failure 28 days following the procedure. Results of right-sided heart catheterization were available in 57 patients at an average of 1.0 ± 0.9 year after the final angioplasty procedure (range, 0.3–7.0 years). The initial hemodynamic benefit was shown to be sustained, and the mPAP in this group was 24.0 ± 5.8 mm Hg.[146]

A report by Kataoka and associates[147] included 29 patients with CTEPH undergoing BPA. This group demonstrated no immediate hemodynamic improvement in 28 of 29 patients. One patient died of wire perforation 2 days after angioplasty. However, in follow-up at 6.0 ± 6.9 months, functional status, plasma BNP levels, and pulmonary hemodynamics (mPAP 45 ± 9.9 to 31.8 ± 10.0 mm Hg, CO 3.6 ± 1.2 to 4.6 ± 1.7 L/min) improved. Reperfusion lung injury complicated 27 of 51 (53%) procedures.[147]

Andreassen and colleagues[148] from Norway reported similar favorable results of performing BPA in patients with CTEPH with inoperable disease or with persistent PH after PTE. In 20 patients undergoing 18.6 ± 6.1 BPA procedures per patient (segmental and subsegmental arteries), a decrease in mPAP (45 ± 11 to 33 ± 10 mm Hg), an increase in CO (4.9 ±1.6 to 5.4 ±1.9 L/min), and a reduction in RV strain as measured by troponin and NT–proBNP levels were observed 3 months after the last BPA procedure. An overall improvement in functional status (cardiopulmonary exercise testing and NYHA functional class) was also noted. However, a 10% periprocedural mortality rate was observed, with reperfusion injury treated with supplemental oxygen and diuretics following seven procedures.[148]

The ultimate role of BPA in the treatment of patients with CTEPH requires ongoing assessment. Appropriate patient selection, the optimal procedural technique to avoid reperfusion lung injury or pulmonary vascular injury, the appropriate timing of repeated BPAs, hemodynamic benefits, and functional improvement must be determined.[149]

Intraoperative Echocardiography in Patients With Chronic Thromboembolic Pulmonary Hypertension

CTEPH results in myriad changes leading to functional and morphologic alterations of both right and left ventricles. Echocardiographic evaluation of patients with CTEPH includes a complete examination of all cardiac structures, to looking for coexisting LV or valvular disease with particular emphasis on the right side of the heart. This examination encompasses evaluation of RV anatomy and function, including dilation and hypertrophy, with attention to leftward ventricular septal motion. Patients with CTEPH may have thrombus throughout the venous circulation, hence requiring a full examination of the right side of the heart. Therefore the midesophageal (ME) four-chamber, ME ascending aortic short-axis, RV inflow-outflow, and bicaval views are essential.

This section provides a brief description of the intraoperative echocardiographic views required for evaluation of a patient with CTEPH who is undergoing a PTE procedure (see Chapters 14 to 17).

The *ME four-chamber* view is the first view used for assessment of RV dilation and hypertrophy, RA size, and tricuspid valve function. The right ventricle exhibits several changes in response to chronic pressure and volume overload to that ventricle. The response seen as a result of chronic increased afterload include volume-adapting dilatory changes, as well as pressure-related changes such as RV enlargement, hypertrophy, and paradoxical septal motion that eventually lead to RV systolic failure.

The normal right ventricle typically occupies two-thirds, in cross-sectional area, of the LV area. With RV enlargement, its size becomes greater than two-thirds, sharing the cardiac apex; whereas with severe enlargement, the right ventricle becomes larger than the left ventricle, thus forming the cardiac apex (Fig. 26.22A). An effective way to assess the right ventricle rapidly is by looking at the makeup of the cardiac apex in the ME four-chamber view.

RV hypertrophy is the compensatory mechanism for the right ventricle to maintain stroke volume in the presence of increased PVR. Normally, RV free wall thickness at end-diastole is 5 mm in diameter. With long-standing severe chronic PH, RV hypertrophy can exceed 10 mm in thickness, and a prominent moderator band may be noted (Fig. 26.22B). This measurement may be obtained in the ME four-chamber, ME RV inflow-outflow, or transgastric midpapillary views, often aided by the use of M-mode echocardiography.

The right ventricle is normally adapted to eject against a low-pressure pulmonary circuit. With acute or chronic elevation in PAP, RV systolic dysfunction ensues. The right ventricle has a characteristic "peristaltic-like" movement beginning with contraction at the inflow portion, followed by the apex, and ending with contraction of the outflow infundibulum. Several modalities have been suggested for evaluating RV systolic function.[150]

Tricuspid annular plane systolic excursion is a measure of global RV systolic function and a prognostic indicator in PH. This excursion is the amount of shortening of the base of the tricuspid valve annulus toward the apex at peak systole, thus measuring the excursion between end-diastole and end-systole. The normal value is more than 16 mm; a value of less than 15 mm is associated with mortality risk.[150,151]

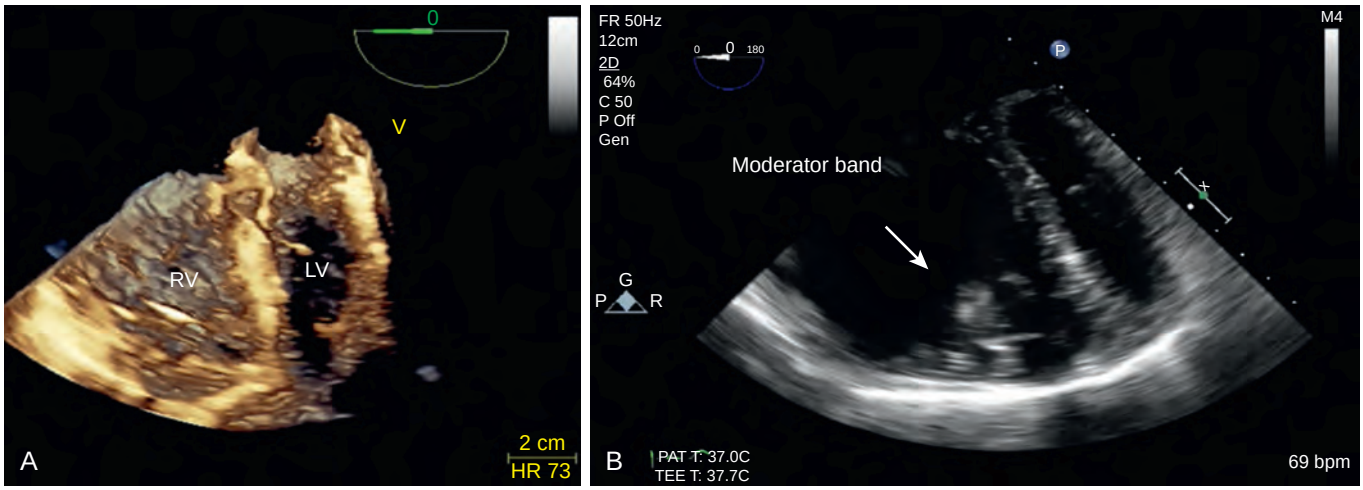


Fig. 26.22 (A) Midesophageal four-chamber view in a patient with severe chronic thromboembolic pulmonary hypertension. Note the dilated and hypertrophied right ventricle *(RV),* which is significantly larger than the left ventricle *(LV).* This is a three-dimensional picture using the General Electric Vivid E9 BT12 system. (B) Midesophageal four-chamber view in two dimensions showing a dilated and hypertrophied RV yielding a prominent moderator band *(arrow)* and an underfilled LV.

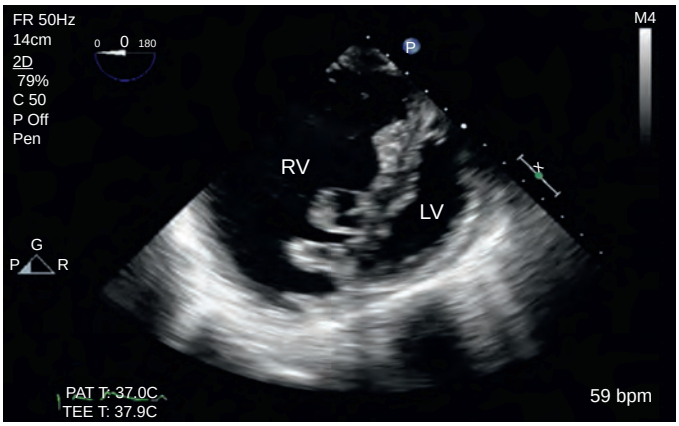


Fig. 26.23 Transgastric midpapillary short-axis view showing flattening of the interventricular septum as a result of right ventricular pressure or volume overload leading to the characteristic D-shaped sign. *LV,* Left ventricle; *RV,* right ventricle.

Interventricular septal motion is seen with RV overload, and it results in flattening of the septum and loss of the natural crescent shape of the RV, thus leading to the characteristic "D-shaped" sign most noticeable in the transgastric midpapillary short-axis view (Fig. 26.23). The right and left ventricles share the interventricular septum, which is usually concave toward the right ventricle during the entire cardiac cycle. Evaluation of the nature and timing of septal flattening relative to diastole versus systole can help differentiate between RV volume overload and RV pressure overload. In conditions characterized by RV volume overload, the septum is flattened at end-diastole, whereas in pressure overload, the septum is flattened at end-systole. With severe CTEPH and pressure overload, right-sided pressures exceed left-sided pressures in both systole and diastole, so the septum may remain deformed throughout the cardiac cycle, a condition that may eventually lead to impaired LV filling and decreased CO (Fig. 26.24). The *eccentricity index* (*EI*) is the ratio of the LV anteroposterior to septolateral diameter of the left ventricle in the transgastric mid–short-axis view.[152] In normal values, the EI has a value of 1 in both systole and diastole. In cases with pressure overload, the EI value is greater than 1 during end-systole, whereas in volume overload it is greater than 1 during end-diastole.[153]

Pulsed-wave Doppler tissue imaging allows evaluation of the peak systolic velocity (S′) of the basal RV free wall in the ME four-chamber view. A peak systolic velocity of less than 10 cm/s suggests abnormal RV function.[150] Pavlicek and associates[153] found that peak systolic velocity correlated well with RV ejection fraction using cardiac MRI.

The *RV myocardial performance index (RV MPI),* also known as the Tei index, is another global assessment of RV systolic and diastolic cardiac performance that combines both systolic and diastolic time intervals.[150] The RV MPI is easily derived using two methods:

1. Pulsed Doppler method from two separate cardiac cycles is used.
2. Tissue Doppler method from a single cardiac cycle. The RV MPI greater than 0.4 by pulsed-wave Doppler and greater than 0.55 by tissue Doppler signifies impaired RV function.[150] The Tei index is simple, noninvasive, and easy to estimate.[154]

Blanchard and colleagues[155] used the Tei index to demonstrate a correlation between improvements in RV function and decrease in the PVR after PTE. The RV Tei index is a valuable parameter for estimating PVR and following disease severity in CTEPH before and after PTE.[154] These investigators were able to demonstrate that patients with CTEPH have an abnormally increased RV Tei index that decreases after successful PTE. Their calculated MPI was 0.52 ± 0.19 in patients with CTEPH, compared with 0.27 ± 0.09 in healthy control subjects ($P > 0.0001$).[155]

Interatrial septum position and motion serve as a surrogate of RV function. In the setting of CTEPH and a failing right ventricle, high right-sided pressure is transmitted to the right atrium, thus leading to dilatation, increasing RA pressure, and shifting the interatrial septum toward the left atrium (Fig. 26.25). In the setting of long-standing PH and overt RV failure, decreased CO leads to increased right-sided volume and diastolic pressure that, when transmitted to the right atrium, causes RA dilatation. Patients with CTEPH often present with pericardial effusions correlating with increased RA pressure. Marked elevations in RV and RA pressures may lead to impaired lymphatic and venous drainage from the pericardium that results in pericardial effusions.[156] Similarly, elevated RA pressure and severe TR may impair coronary sinus drainage and lead to a dilated coronary sinus, best visualized in the deep ME four-chamber view[157] (Fig. 26.26).

Patients with CTEPH with long-standing elevated RA pressure exhibit a higher incidence of PFO than the estimated 25% seen in the adult population. The ME four-chamber, ME RV inflow-outflow, and ME bicaval views are all used to evaluate for PFO, with the aid of color-flow Doppler or agitated saline injection[158,159] (Fig. 26.27).

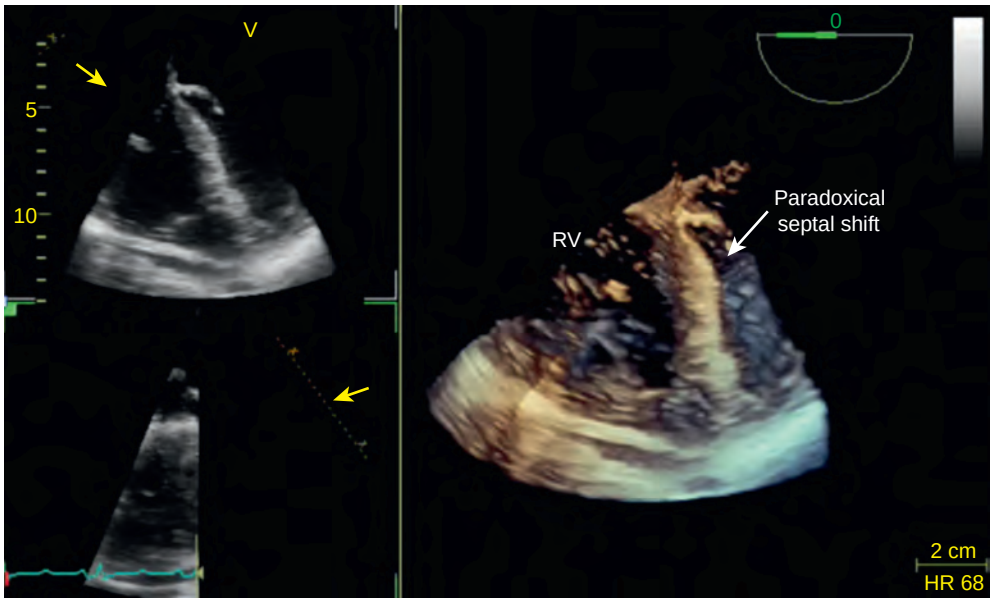


Fig. 26.24 Midesophageal four-chamber view using the General Electric Vivid E9 BT12 system, bird's-eye view showing paradoxical septal shift of the interventricular septum toward the left ventricle in three dimensions *(arrow)*. *HR,* Heart rate; *RV,* right ventricle.

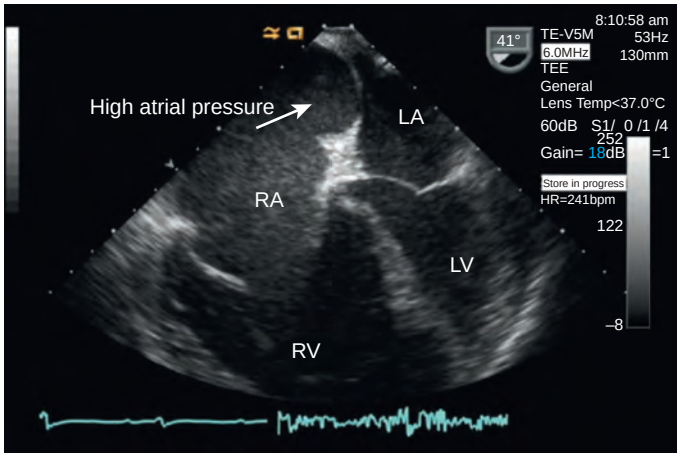


Fig. 26.25 Midesophageal four-chamber view showing a dilated right ventricle *(RV)*, right atrium *(RA)* with increased right atrial pressure *(arrow)*, and an underfilled left ventricle *(LV)*. *HR,* Heart rate; *LA,* left atrium

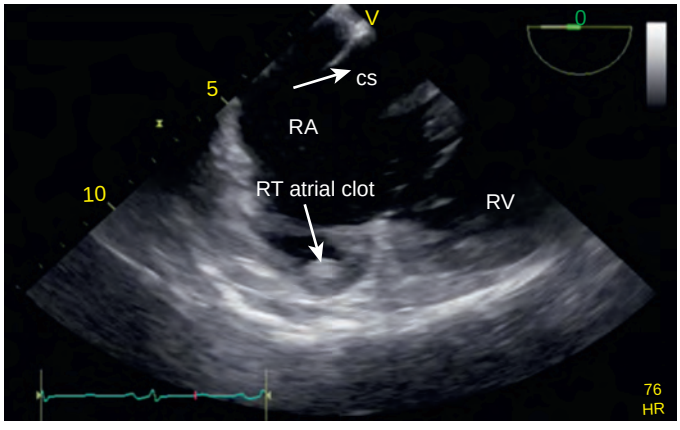
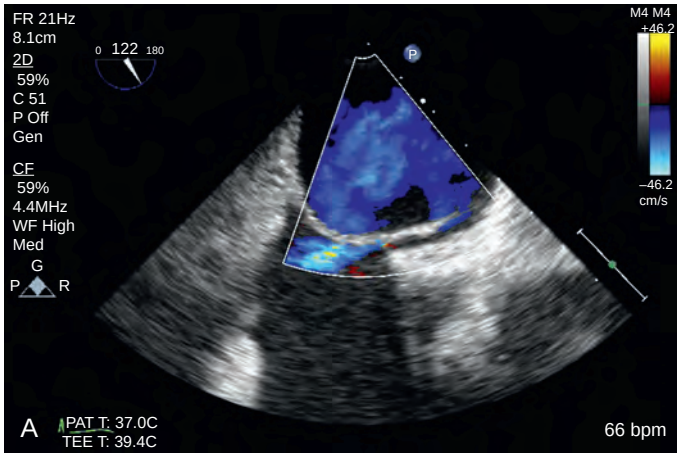


Fig. 26.26 Midesophageal four-chamber view rotated to the right, demonstrating a dilated coronary sinus *(cs; arrow)* and a right *(RT)* atrial clot *(arrow)*. *HR,* Heart rate; *RA,* right atrium; *RV,* right ventricle.



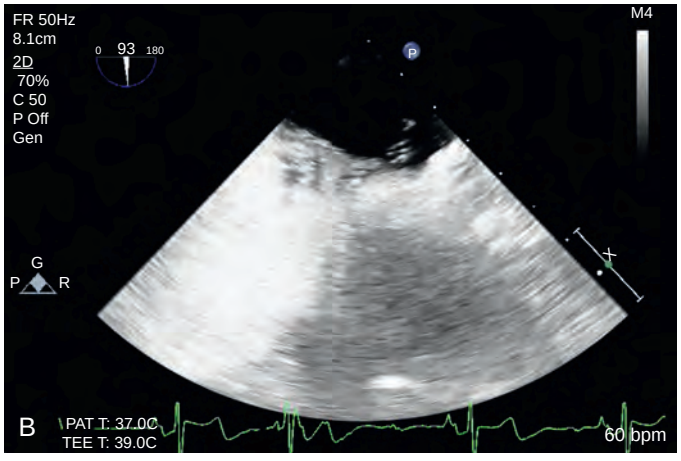


Fig. 26.27 (A) Bicaval view demonstrating flow from left to right with color-flow Doppler echocardiography. (B) Bicaval view demonstrating a positive saline agitated study with right-to-left flow between both atria.

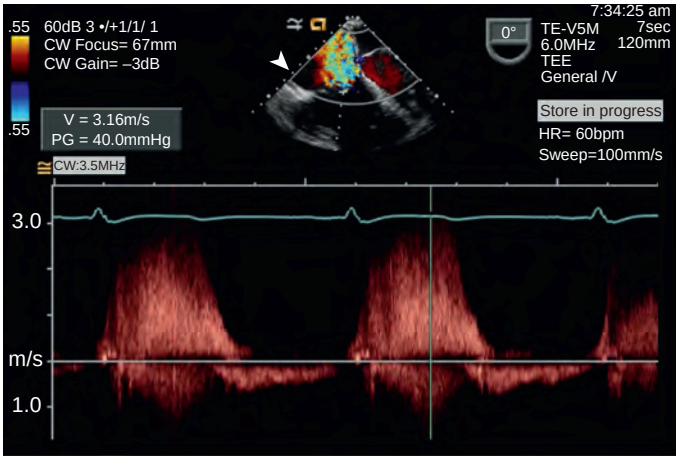


Fig. 26.28 A continuous-wave *(CW)* Doppler used to evaluate the peak regurgitation velocity yields an estimate of pulmonary artery systolic pressure. *HR,* Heart rate.

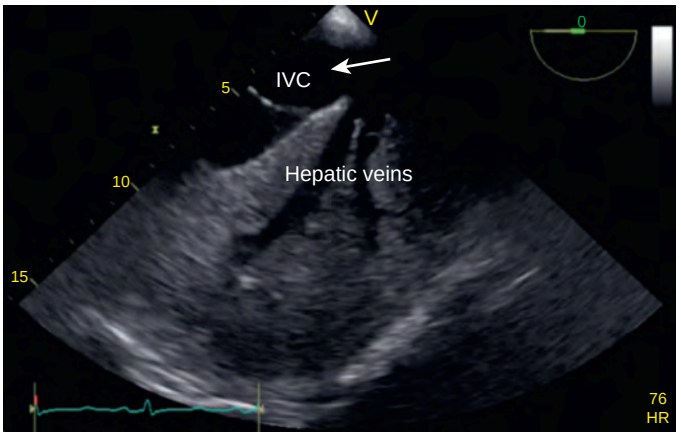


Fig. 26.29 Dilated inferior vena cava (IVC) *(arrow)* and hepatic veins.

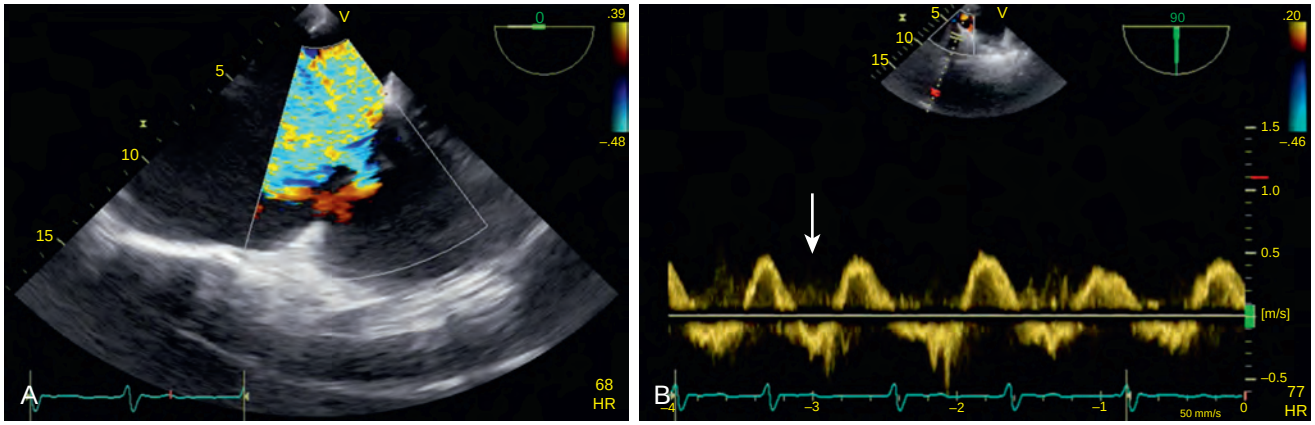


Fig. 26.30 (A) Midesophageal four-chamber view showing a dilated right ventricle with severe tricuspid regurgitation. (B) Hepatic vein reversal, with S-wave reversal *(arrow). HR,* Heart rate.

The *ME RV inflow-outflow* view is often used to assess RV free wall hypertrophy and function, as well as to evaluate peak regurgitation velocity. Systolic PAP can be easily estimated using peak TR velocity (V_{TR}) with continuous-wave Doppler and applying the modified Bernoulli equation ($\Delta P = 4v^2$) with the addition of central venous pressure[150,160] (Fig. 26.28).

It is not uncommon to encounter difficulty in floating the PAC because of severe TR, as well as a dilated right atrium and right ventricle. TEE is routinely used to float the PAC by using the bicaval and ME RV inflow-outflow views.

RA pressure can be approximated by imaging the IVC by echocardiography. The IVC diameter should not exceed 1.7 cm and should collapse by at least 50% during spontaneous inspiration in healthy persons.[161,162] The presence of a dilated IVC and the lack of more than 50% inspiratory collapse implies elevation of RA pressure in the range of 10 to 14 mm Hg. In more severe cases, in which RA pressure is greater than 20 mm Hg, the IVC diameter does not collapse at all with ventilation (Fig. 26.29).

RV failure ultimately leads to RV dilation, with a dilated tricuspid valve annulus together with chordal traction resulting in significant TR. This condition is confirmed by a *vena contracta* greater than 0.7 cm and systolic reversal of hepatic vein flow (Fig. 26.30). Notably, TR does not correlate directly with the degree of PH, but rather with the degree of RV enlargement and alterations in RV geometry. Echocardiography helps appraise the degree of TR before and after surgical treatment. Sadeghi and associates[163] looked at a series of patients with CTEPH undergoing PTE; 19 of 27 patients with baseline severe functional TR with dilated annulus had a significant decrease in TR after PTE without annuloplasty.

The *ME ascending aortic short-axis* and upper esophageal aortic arch short-axis views frequently are used to evaluate the pulmonary vasculature for the presence of clots. Therefore a thorough evaluation throughout the venous system, right side of the heart, and pulmonary vasculature is required (Fig. 26.31A and B). Indirect clues to thrombus formation include a dilated right atrium and right ventricle, intracardiac devices, or the presence of spontaneous echocardiographic contrast. Dilated main PA and RPA are common in CTEPH (Fig. 26.31C).

Mitral valve prolapse (MVP) has been described in patients with CTEPH as "pseudo-MVP." The phenomenon is thought to result from pressure deformation of the left ventricle by the right ventricle, thereby leading to distortion of the mitral valve annulus. The EI was greater for patients with MVP and deformation of the left ventricle compared with patients with no MVP without deformation.[164] Reduction of PH after PTE reversed this deformation and allowed for resolution of "pseudo-MVP."

Impaired LV relaxation seen in patients with CTEPH is largely the result of low LV volume and relative underfilling and is not solely caused by LV chamber distortion secondary to the geometric effects of RV enlargement. LV diastolic filling patterns improve with the resolution of PH after successful PTE. The transmitral E (peak early filling [E-wave]) velocity increases, and pulmonary venous S (systolic forward flow [S wave]) and D (diastolic forward flow wave [D wave])

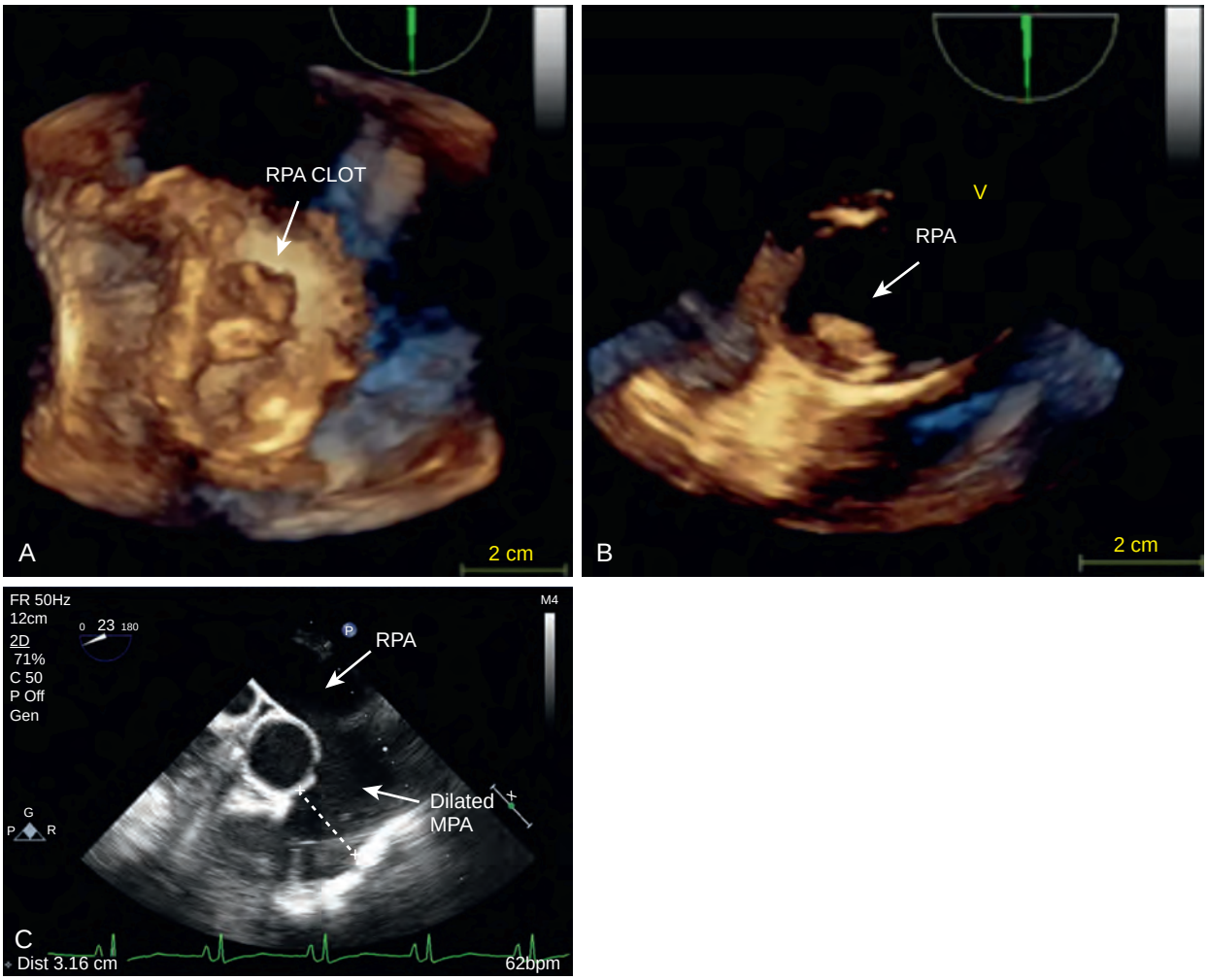


Fig. 26.31 (A) and (B) Right pulmonary artery *(RPA)* clot *(arrows)* in three dimensions using the General Electric Vivid E9 BT12 system. (C) Midesophageal ascending aortic short-axis view shows the relationship of the main pulmonary artery *(MPA)* and RPA with the ascending aorta and superior vena cava and demonstrates a dilated MPA *(arrow)* and dilated RPA *(arrow)*.

velocity increase significantly, suggesting higher preload with improvement in the CO.[165–167] TEE is critical in the intraoperative management of patients with CTEPH for assessment of the right ventricle, tricuspid valve, right atrium, and intracardiac thrombus or other cardiac disease. It also allows for postbypass cardiovascular evaluation and assessment of de-airing of the cardiac chambers, as well as changes affecting the right ventricle.

Pulmonary Thromboendarterectomy in Patients With Sickle Cell Disease

Management of patients with concomitant SCD and CTEPH presents unique challenges. The PTE procedure requires CPB, profound hypothermia, and periods of circulatory arrest, all of which may promote sickling. Reports noted successful completion of PTE with resolution of PH in two patients with SCD complicated with CTEPH.[168] Moser and Shea[169] and Collins and Orringer[170] confirmed the relationships among pulmonary infarction, cor pulmonale, and sickle cell states. In addition, studies by Sutton and colleagues[171] and Simmons and associates[172] reported 20% to 60% prevalence rates of PH in SCD, respectively. With innovations in the management of patients with SCD and their extended life expectancy, clinicians may expect to see more patients with SCD present with CTEPH.

Previous reports of CPB in adults with SCD involved only patients undergoing valvular or septal repair.[173,174] In contrast, patients undergoing PTE require hypothermia to 18°C to 20°C and circulatory arrest. Sickling and hemolysis during or after CPB are known risks.[175,176] Stagnation of blood, hypothermia, anemia, and acidosis resulting from circulatory arrest are expected to increase the likelihood of sickling.[177]

"Prophylactic" exchange transfusion remains controversial. A multicenter trial comparing conservative exchange transfusion with an aggressive transfusion regimen in patients with SCD found no difference, and the conservative approach resulted in dramatically decreased transfusion-associated complications.[178] In major surgical procedures, it is recommended that the level of hemoglobin S should be reduced to less than 30% and to less than 10% for patients undergoing cardiac operations.[179] Several case reports supported exchange transfusion to reduce hemoglobin S to less than10% when deep hypothermic circulatory arrest will be used,[168,180,181] Investigators have proposed that separating plasma and platelet fractions from the patient's native red cell mass in addition to hemoconcentration during CPB may reduce transfusion requirements after bypass.[180]

At our institution, the bypass system is primed with red blood cells, fresh frozen plasma, and albumin to achieve an estimated hematocrit of 25% in the prime. With initiation of CPB, all the venous blood is drained into two reservoirs. Once the desired volume is collected, the venous return is allowed to pass to the venous reservoir in the normal

fashion. In turn, the drained blood is passed through the cell salvage device, and the blood and plasma are separated with the objective of saving all the plasma components and discarding the red blood cells. The plasma products are saved in sterile fashion in a large bag and are returned to the pump circuit just before weaning from CPB. All the excess volume is hemoconcentrated. With this technique, platelet function is well preserved, and postpump hemostasis has been excellent.[180–182]

Tissue hypoxia incites sickling because of increased viscosity from a deoxygenated form of sickle hemoglobin and sickle cell adhesion to endothelial cells. Particular attention should be paid to various hypoxic complications such as atelectasis and reperfusion pulmonary edema during the postoperative period, and oxygen saturation should be maintained at or greater than 95% throughout hospitalization.

Patients with SCD who present for PTE should undergo thorough preoperative evaluation and preparation for operation, with particular attention to correction of anemia, early screening for antibodies in blood typing, preoperative and intraoperative exchange transfusion, maintenance of oxygenation and blood flow to limit end-organ ischemia, maintenance of normal acid-base status, and limitation of the duration of circulatory arrest periods.

Outcome and Future of Chronic Thromboembolic Pulmonary Hypertension

With increased awareness of CTEPH and with several major cardiovascular centers around the world performing the procedure, progress in surgical and medical management has improved outcomes.

The reported world literature on this operation (exclusive of UCSD) is more than 3000 cases. The mortality rate at UCSD has declined significantly from 16% in the 1980s to 1.3% by 2012, and despite a patient population at higher risk, the mortality rate declined to 1% to 2 % (Fig. 26.32). This change likely reflects the evolution and refinements in all aspects of patient care: Correct preoperative diagnosis, meticulous preparation for operation, advances in surgical and anesthetic technique, and improved postoperative management. The secret to the success of this procedure is the close collaboration of multiple medical teams, including pulmonary medicine, anesthesiology, perfusion, and cardiac surgery.

Efforts from the international community have put forth a prospective registry for long-term follow-up and continued awareness of CTEPH.[183] PTE has revolutionized the treatment of CTEPH, by providing significant and permanent lifestyle improvements.[184] With increased awareness of the disease, excellent surgical outcomes in specialized centers, and innovations in medical therapy, treatment of severe PH resulting from CTEPH is now within reach of many patients around the world. However, many questions remain to be answered through future studies and innovations.

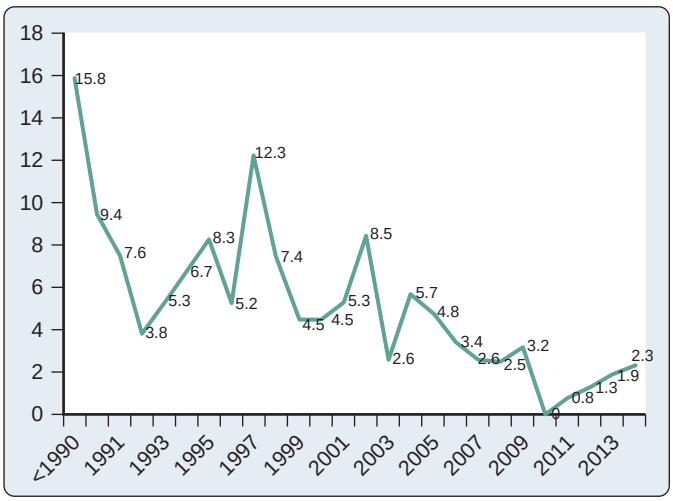


Fig. 26.32 Perioperative mortality rates: University of California San Diego.

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27

Procedures in the Hybrid Operating Room

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KEY POINTS

1. A hybrid operating room combines advanced imaging capabilities with a fully functioning operating suite.
2. Transcatheter aortic valve replacement (TAVR) is recommended for patients with severe symptomatic aortic stenosis who are inoperable or at high risk for needing surgical aortic valve replacement and have a predicted post-TAVR survival of more than 12 months.
3. Vascular complications are the most common complications with the transfemoral approach.
4. The concept of multimodal imaging plays an important role in preprocedural assessment.
5. The presence of a heart team is a prerequisite for establishing a TAVR program.
6. Catheter-based mitral valve repair techniques are primarily guided by transesophageal echocardiography.

Hybrid operating rooms (ORs) were conceived 2 decades ago. They were first designed to combine percutaneous coronary interventions (PCIs) and stent implantations with minimally invasive coronary artery bypass grafting (CABG) procedures. However, widespread building of hybrid ORs started only after the development of transcatheter valve replacements.[1] After the first report of successful percutaneous balloon valvuloplasty in patients with severe aortic stenosis (AS) in 1983,[2] the first human transcatheter aortic valve replacement (TAVR) was performed in 2002.[3] Despite high costs and structural complexity, there has been a steady increase in new hybrid ORs as a result of the development of more and more percutaneous interventions, which require a facility that combines the capabilities of the angiographic catheterization laboratory with the cardiac surgical OR. Typical procedures performed in the hybrid ORs include TAVR, percutaneous mitral valve repair, thoracic endovascular aortic repair (TEVAR), percutaneous pulmonary valve implantation, implantable pacemaker and cardioverter-defibrillator lead explantations, and combined coronary and valve procedures.

Technical Considerations

Definition of a Hybrid Operating Room

A hybrid OR combines advanced imaging capabilities with a fully functioning operating suite. This means that angiographic, fluoroscopic, and other imaging capabilities (eg, computed tomography [CT], echocardiography) are integrated into a cardiac OR.[4]

Equipment and Layout

In addition to components of a surgical suite, the following features should be available[4–6]:

1. High-quality fluoroscopy (generally with flat-panel imaging) in a lead-lined room.
2. Integration of other modalities such as a biplane system, C-arm CT, integrated ultrasound, and electromagnetic navigation systems (optional).
3. A control area for radiologic technicians either inside or outside of the hybrid OR with a direct view to the surgical field.
4. A radiolucent, thin, nonmetallic carbon fiber operating table that can accommodate both angiography and open operations. It must also be integrated to the imaging system to avoid collisions. Because of lack of metal parts, some operating table functions are lost, such as isolated movement of upper or lower parts of the patient's body. Nevertheless, a floating tabletop with multidirectional tilt function is needed for accurate catheter maneuvering.
5. Adequate room size (800 square feet [74.3 m^2] to 1000 square feet or more) to accommodate the equipment required by cardiac or vascular surgeons and interventional cardiologists, as well as the anesthesia team, nursing team, perfusionist, and radiologic technicians. Careful equipment positioning is required to allow fast conversion to conventional surgery if needed.
6. Ceiling-mounted monitors placed in positions that allow all team members (surgeons, anesthesiologists, and interventionists) to visualize the images simultaneously. Images from angiography, echocardiography, and hemodynamic monitoring need to be displayed.
7. Circulating heating, ventilation, and laminar air flow to provide a smooth undisturbed air flow suitable for conventional surgical operations.
8. Adequate high-output lighting for surgical interventions.
9. Other inevitable requirements such as adequate number of power receptacles, gas and suction outlets for both the anesthesia machine and the cardiopulmonary bypass (CPB) system, and hot and cold water outlets for the CPB.
10. Equipment: high-definition displays and monitors, oxygen (O_2) analyzer, suction, O_2 supply, defibrillator/resuscitation cart, echocardiographic equipment, sonographers, anesthesia equipment, CPB equipment, syringe pumps, radiation protection (along with the imaging system), blood warmers and blood bank access, point-of-care laboratory monitoring for blood gases and coagulation parameters, and so on. Because of the life-threatening complications that may be encountered during the procedure, ready-made crash carts consisting of any equipment necessary in an emergency must be available.
11. A complete sterile environment.

An example of the hybrid room setup is shown in Fig. 27.1.

In 2012, the Society for Cardiovascular Angiography and Interventions (SCAI), American Association for Thoracic Surgery

Fig. 27.1 View of a hybrid cardiovascular operating room. The cardiopulmonary bypass circuit is on the far right with its own boom. The operating table is in the middle of the picture, with a floor mounted, fixed biplanar C-arm to the left. *(Courtesy of Alfred I. Dupont Hospital for Children.)*

(AATS), American College of Cardiology Foundation (ACCF), and The Society of Thoracic Surgeons (STS) together published guidelines on hybrid ORs and TAVR. These guidelines did not make the hybrid OR a prerequisite for TAVR or other procedures but allowed for the procedure to be done in a cardiac catheterization laboratory (CCL), an OR, or a hybrid OR located in either the OR suite or a CCL area.[5,7]

Whereas in the United States, 57% of TAVRs were performed in hybrid ORs,[8] in France, 72.7% were done in CCLs.[9] In the United States, hybrid ORs are located either in CCL areas or conventional OR suites, and many centers have hybrid ORs in both locations.[10]

Imaging Systems

Fluoroscopy

Fluoroscopy may be portable or fixed. In general, fixed systems enable higher imaging quality and less radiation exposure compared with portable systems. The fixed C-arm may be mounted on the ceiling or the floor. Ceiling-mounted systems do not occupy OR floor space, but they need higher ceilings, which affects lighting, monitor placement, and laminar air flow. While these disadvantages can be avoided using floor-mounted systems, this comes at the cost of the available floor space. The fluoroscopy operating system generates a considerable amount of heat and noise and it is suitable to put it outside the hybrid OR.[4]

Rotational Angiography

Many of these units have additional properties. Some can rotate fully around the patient and provide cross-sectional or three-dimensional (3D) data in a few minutes. This 3D C-arm CT (eg, Dyna-CT, Siemens, Germany)[11] (also called in-room C-arm CT with rotational angiography)[12] can assist in positioning for TAVR, especially in patients with poor calcification at the annulus, by overlaying a real-time two-dimensional (2D) image and helping to navigate the anatomy. In addition, this technique reduces the amount of contrast agent used during complex endovascular aneurysm repairs with branched grafts[4,13] or TAVR.[12] This technique was found to be comparable to multidetector CT (MDCT) with regard to final valve-visualization angle.[14,15]

Digital Subtraction Angiography

This technique is used to visualize the blood vessels and identify any abnormalities without interference from background structures. In TAVR, it is used for identification of the coronary arteries immediately before valve implantation.

Echocardiography

Transesophageal echocardiography (TEE) is used during TAVR pre-, intra-, and postprocedures for diagnosis of the disease and complications. Real-time 3D TEE can be a helpful tool that facilitates maneuvering of the delivery system and proper positioning of the aortic prosthesis.[12] Transthoracic echocardiography (TTE) may be used in interventions performed under monitored anesthetic care (MAC) in which TEE is not possible.

Systems that allow image fusion of different imaging modalities can be integrated to optimize visualization during interventions (ie, C-THV Paieon, New York, N.Y.; HeartNavigator Philips Healthcare, Andover, Mass) and ValveAssist (GE Healthcare, Little Chalfont, UK).[6] In the future, an electromagnetic navigation system may be integrated in imaging and guidance for TAVR.[16]

Radiation Safety

The most important aspect of radiation safety is education. The whole team must understand how to reduce the radiation dosage and exposure. Certain safety measures should be available during procedures. Hybrid ORs must have lead-lined walls and doors. Both portable and built-in shielding for personnel must be considered during design of a hybrid OR. Moreover, lead aprons must be attached to the table. Enough lead aprons must be hung in a dedicated space outside the hybrid OR for all personnel. Finally, the radiation exposure should be measured regularly for all personnel.[4]

PROCEDURES

Transcatheter Aortic Valve Replacement

Patient Selection and Indications

According to European and American guidelines, TAVR is recommended for patients with severe symptomatic AS who are inoperable or at high risk for needing surgical AVR and have a predicted post-TAVR survival of more than 12 months.[7,17,18] High-risk patients are generally defined as those with an STS score of 10% or European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 20%.[19] According to the American Heart Association (AHA) and the American College of Cardiology (ACC), high risk is defined as STS predicted risk of mortality (PROM) 8% or higher; or two or more indices of frailty (moderate to severe); or up to two major organ systems compromised, not to be improved postoperatively; or possible procedure-specific impediment (Table 27.1).[17]

The approach to patient selection for TAVR is optimal with a multidisciplinary team (MDT)[20] that includes a primary cardiologist, cardiac surgeon, interventional cardiologist, echocardiographer, imaging specialists (CT or cardiac magnetic resonance [CMR]), heart failure and valve disease specialist, cardiac anesthesiologist, nurse practitioner, and cardiac rehabilitation specialists.[7] At minimum, cardiologists, cardiac surgeons, cardiac anesthesiologists, and an imaging specialist should be involved in daily clinical practice.

The following issues must be discussed during the patient selection process:

1. Indication for AVR, either surgical or TAVR
2. Risk assessment and indication for TAVR
3. Feasibility of the procedure for specific patient and choice of most proper access (eg, severe peripheral arterial disease)
4. Selection of specific valve type and size for the individual patient

TABLE 27.1 Risk Assessment for TAVR Candidates

	Low Risk (Must Meet All Criteriain This Column)	*Intermediate Risk (Any One Criterion in This Column)*	*High Risk (Any One Criterion in This Column)*	*Prohibitive Risk (Any One Criterion in This Column)*
STS PROM*	<4% *and*	4%–8% *or*	>8% *or*	Predicted risk with surgery of death or major morbidity (all-cause) *or*
Frailty	None *and*	One index (mild) *or*	>Two indices (moderate to severe) *or*	>50% at 1 yr *or*
Major organ system compromise†	None *and*	One organ system *or*	No more than two organ systems *or*	>Three organ systems *or*
Procedure-specific impediments‡	None	Possible	Possible	Severe

PROM, Predicted risk of mortality; *STS,* The Society of Thoracic Surgeons; *TAVR,* transcatheter aortic valve replacement.
†Not to be improved postoperatively.
‡Examples: tracheostomy present, heavily calcified ascending aorta.
Modified from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg.* 2014;148:e1–e132.

Other factors that may affect the decision-making process include availability, experience, and institutional commitment to managing very high-risk patients, technical skills, local results, referral patterns, and patient preference.

Indication for Aortic Valve Replacement: Surgical or Transcatheter

Diagnosis of AS should not differ according to whether or not a minimally invasive technique is chosen but should be made according to established guidelines.[17,21] Echocardiography and, to some extent, cardiac catheterization are the main diagnostic tools for AS. The echocardiographic criteria to define severe AS include decreased systolic opening of a calcified or congenital stenotic valve with an aortic valve area (AVA) of 1.0 cm^2 or less, indexed AVA 0.6 cm^2/m^2 or less, aortic velocity 4.0 m/s or higher, and/or a mean transvalvular pressure gradient of 40 mm Hg or higher. Symptomatic patients may have heart failure, syncope, exertional dyspnea, angina, or presyncope by history or on exercise testing. AVR is recommended for asymptomatic patients provided that left ventricular ejection fraction (LVEF) 50% or less (Fig. 27.2).[17] Stress echocardiography may be useful during the assessment of low-flow/low-gradient AS.[7] If stress results in increases in stroke volume and AVA larger than 0.2 cm^2 with little change in pressure gradient, it is not severe AS; with true severe AS, patients have a fixed valve area with increases in stroke volume and pressure gradient during a stress state[19] (see Chapters 3 and 21).

Risk Assessment and Indication for TAVR

The recommendations and the data regarding TAVR can be found in the registry experience or from randomized controlled trials.[22] Several multicenter registries, including SAPIEN valves (Edwards Lifesciences, Irvine, Calif) and CoreValves (Medtronic Minneapolis, Minn), have reported outcomes with TAVR. The patient selection criteria and the definitions of events and outcomes vary among these registries, which makes comparisons difficult[7]; however, they provide an overview of indications, complications, and mortality. These registries include the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry,[23] FRench Aortic National CoreValve and Edwards (FRANCE 2),[9] and the German Aortic Valve Registry (GARY).[24]

Placement of AoRtic TraNscatheER valves (PARTNER) trial was designed as a prospective, unblinded, randomized, controlled, multicenter pivotal trial evaluating the safety and effectiveness of the SAPIEN transcatheter aortic valve, in which two patient populations were involved: Cohort A were operable high-risk patients, and Cohort B were inoperable patients. All patients were followed during the hospitalization, at 30 days, 6 months, 1 year, and yearly thereafter. Recently, a group Cohort C was defined as a subset of the inoperable group with relatively poor survival and quality of life, despite TAVR. Comorbidities that defined Cohort C included frailty, malnutrition, cachexia, recent malignancy, stroke, dementia, and dialysis.[25] In Cohort B, there was a 50% decrease in mortality with improvement of all secondary end points. However, there was an increase in strokes,[26] bleeding, and vascular complications. The 30-day mortality in Cohort A was 3.4% and 5% in Cohort B. The risk of clinically apparent major stroke was 3.8% at 30 days and 5.1% at 1 year among the TAVR group compared with 2.1% and 2.4%, respectively, in the surgical group.

In the Medtronic CoreValve U.S. Pivotal Trial, patients were allocated into either an extreme-risk cohort (similar to Cohort B inoperable patients in the PARTNER trial) or a high-risk cohort (similar to PARTNER Cohort A). The incidence of complications used end-point definitions according to the Valve Academic Research Consortium (VARC), aiming for definition uniformity and standardization.[27]

The two most commonly used scores for risk assessment are the STS risk score[28,29] and the EuroSCORE and the related logistic EuroSCORE.[30] Both scores can be calculated online at: http://riskcalc.sts.org and http://www.euroscore.org, respectively. Both scores were used in the PARTNER clinical trials. The EuroSCORE II was recently developed and found to have better predictive capability compared with the logistic EuroSCORE for both surgical AVR and TAVR[31–34]; however, its use was questioned by one study.[35] A simple risk tool (the OBSERVANT Score) consisting of seven parameters for mortality prediction 30 days after TAVR was also developed.[36] Most of these scores were not developed specifically for TAVR, and specific factors that may affect TAVR decisions are not included, such as porcelain aorta, frailty, and TAVR access and approach. These risk scores must be used along with clinical judgment and the heart team's experience during the process of patient selection.

Five risk factors have special importance, either because of their impact on outcome or because they are not presented in risk models in spite of their prevalence. These factors are chronic kidney disease, coronary artery disease, chronic lung disease, mitral valve disease, and systolic dysfunction.[37] Some patients are generally eligible for surgical AVR, but because of local disease abnormalities they may be scheduled for TAVR (eg, severe calcification of ascending aorta, porcelain aorta, friable aortic atheroma, and previous radiation therapy to the mediastinum).[7]

Two other factors that may affect the decision on surgery are (1) very elderly with associated comorbidities, and (2) frailty and futility. Frailty, although it can have significant overlap with disability and comorbidity in old age, is a distinct syndrome with a vicious cycle. It includes decreasing muscle mass, decreasing energy expenditure, and malnutrition, which result in decreased physiologic reserves and resistance to stressors with increased vulnerability to adverse outcomes[38–40] (Table 27.2). Futility means that the clinical condition is too far advanced to be improved even with a successful procedure, and TAVR is not recommended for these patients.[17]

Recent updates to the STS risk score, including frailty as graded by the 5-meter walk test, porcelain aorta, previous radiation therapy, oxygen therapy, and liver disease as graded by the model for end-stage liver disease, were added to increase the reliability of the score with regard to TAVR.[41]

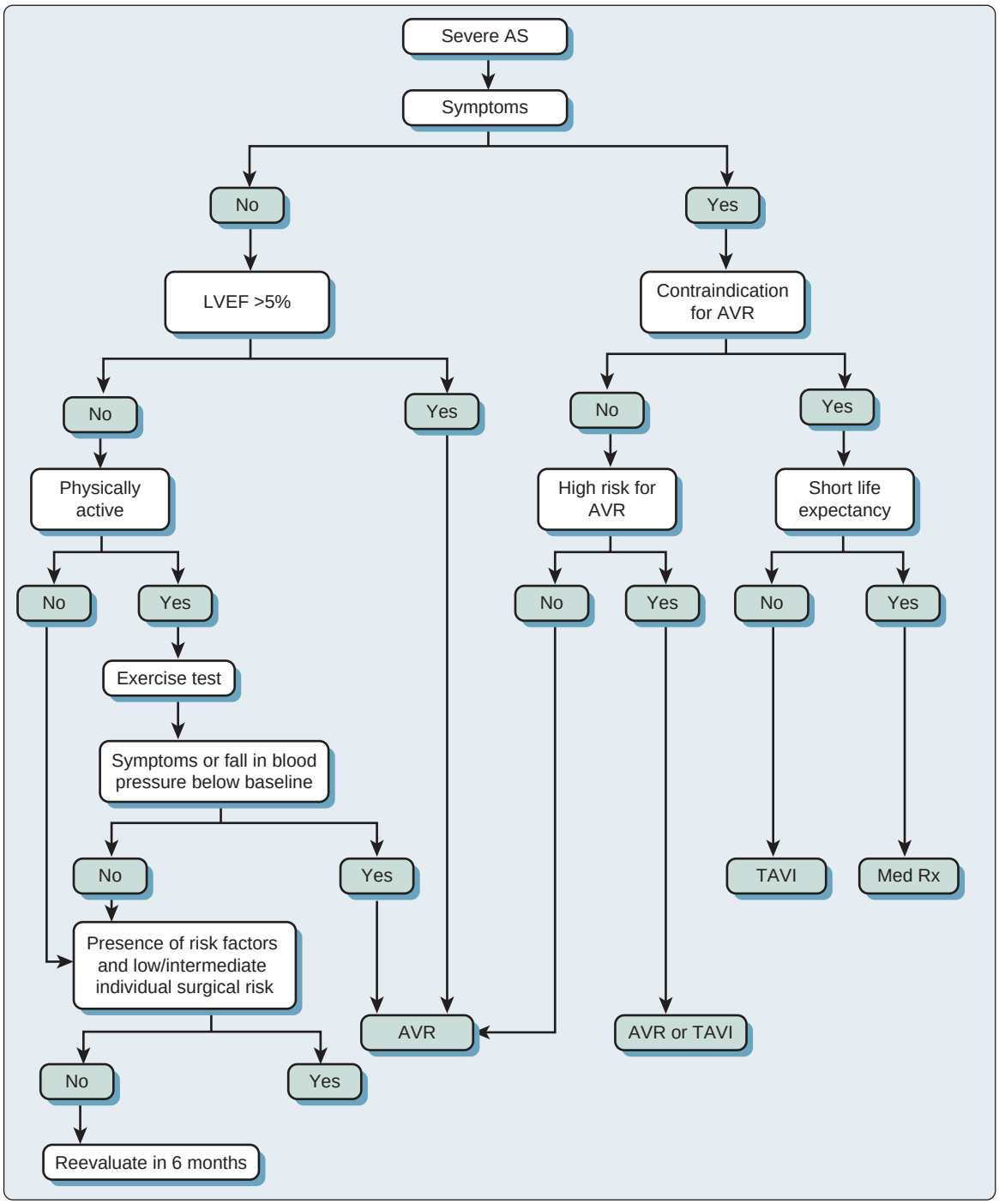

Fig. 27.2 Management of severe aortic stenosis. *AS*, Aortic stenosis; *AVR*, aortic valve replacement; *LVEF*, left ventricular ejection fraction; *TAVR*, transcatheter aortic valve replacement. *(Modified from Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease [version 2012]: the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology [ESC] and the European Association for Cardio-Thoracic Surgery [EACTS].* Eur J Cardiothorac Surg. *2012;42:S1–S44.)*

Arnold and colleagues took a step forward when they considered postoperative poor quality of life as a poor outcome for the procedure. They demonstrated that the most important predictors of poor outcomes were poor functional capacity (as measured by the 6-minute walk test) and lower mean aortic valve gradients.[42,43] Risk assessment algorithms that incorporate hard clinical end points along with quality-of-life measures are likely to become instrumental in the assessment of patients referred for TAVR.[6]

The inclusion and exclusion criteria have been subjected to many modifications as a result of advances in technology and the specifications of next generation valves. Other clinical and anatomic contraindications also must be considered such as valve endocarditis, elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses), and untreated coronary artery disease requiring revascularization[18] (Box 27.1).

TABLE 27.2 Suggested Parameters or Tests to Evaluate Frailty in Patients Referred for TAVR

Frailty Tests or Assessment	*Description*
Grip strength	Dynamometer Abnormal: <30 kg in nonobese males and <18 kg in nonobese females
Gait speed	>7 s to walk 5 m
6-min walk	Abnormal: walk <128.5 m during 6-min walk
CAF	Grip strength, gait speed, instrumental activities of daily living questionnaire, standing balances test, serum albumin, brain natriuretic peptide and creatinine
MGA	Mini-mental state exam, basic and instrumental activities of daily living questionnaires

CAF, Comprehensive Assessment of Frailty[39]; *MGA,* Multidimensional Geriatric Assessment[40]; *TAVR,* transcatheter aortic valve replacement.

Modified from Sintek M, Zajarias A. Patient evaluation and selection for transcatheter aortic valve replacement: the heart team approach. *Prog Cardiovasc Dis.* 2014;56:572–582.

Feasibility of the Procedure for Specific Patients and Choice of Access

Access routes for TAVR include transfemoral, transapical,[44] transaortic (via left anterior minithoracotomy or ministenotomy), suprasternal (aortic/innominate),[45] transcarotid,[46,47] or axillary and subclavian.[48] Caval-aortic access also has been described for TAVR, wherein percutaneous entry is obtained into the abdominal aorta from the femoral vein through the adjoining inferior vena cava.[49] Recently, Cribier performed TAVR through the transseptal route in the absence of suitable iliofemoral access. All of these routes are retrograde except for transapical and transseptal approaches, which are antegrade[6] (Table 27.3).

The most common approaches are transfemoral and transapical. The alternative routes described earlier were investigated only in trials with relatively small patient numbers. In spite of good short-term outcome studies, larger sample sizes and longer follow-up times are needed for these alternative access approaches.[52]

The primary access route is transfemoral as long as the diameter of the femoral vessels are 6 to 8 mm or larger and the degree of atherosclerosis allows.[53] Transfemoral access was compared with transapical

TABLE 27.3 Different Approaches for TAVR

	Retrograde			Antegrade	
	Transfemoral	*Transaortic/Subclavian*	*Transcaval*	*Transseptal*	*Transapical*
Prosthesis	SAPIEN or CoreValve	SAPIEN or CoreValve	SAPIEN or CoreValve	SAPIEN or CoreValve	SAPIEN only
Access	Femoral artery	Aorta (mini-sternotomy) or subclavian artery	Femoral vein into IVC, then abdominal aorta	Femoral vein into IVC	Cardiac apex (mini-thoracotomy)
Type of anesthesia	Sedation (MAC) or general Anesthetic	General anesthetic	General anesthetic	General anesthetic	General anesthetic (less often: thoracic epidural)
Echocardiography	Transthoracic	Transesophageal	Transesophageal	Transesophageal	Transesophageal
Postoperative disposition	Variable, institution dependent: step-down, monitored (telemetry) Setting	Intensive care unit or PACU	Intensive care unit or PACU	Intensive care unit or PACU	Intensive care unit or PACU

IVC, Inferior vena cava; *MAC,* monitored anesthesia care; *PACU,* postanesthesia care unit; *TAVR,* transcatheter aortic valve replacement.

Modified from Klein AA, Skubas NJ, Ender J. Controversies and complications in the perioperative management of transcatheter aortic valve replacement. *Anesth Analg.* 2014;119:784–798.

BOX 27.1 INCLUSION CRITERIA AND CONTRAINDICATIONS FOR TAVR

Inclusion Criteria

- Calcific aortic valve stenosis
- Echocardiography: Mean gradient >40 mm Hg or jet velocity >4.0 m/s and AVA <0.8 cm^2 or indexed EOA <0.5 cm^2/m^2
- High risk for conventional AVR assessed by one cardiac interventionist and two experienced cardiothoracic surgeons
- Symptomatic

Contraindications (Candidates Will Be Excluded if Any of the Following Conditions Are Present)

- Absolute
  - Absence of a heart team and no cardiac surgery on the site
  - Appropriateness of TAVR, as an alternative to AVR, not confirmed by a heart team
- Clinical
  - Estimated life expectancy <1 year
  - Improvement of quality of life by TAVR unlikely because of comorbidities
  - Severe primary associated disease of other valves with major contribution to the patient's symptoms, which can be treated only by surgery
- Anatomic
  - Inadequate annulus size (<18 mm, >29 mm) (when using the current devices)
  - Thrombus in the left ventricle
  - Active endocarditis
  - Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
  - Plaques with mobile thrombi in the ascending aorta or arch
  - For transfemoral/subdavian approach: inadequate vascular access (vessel size, calcification, tortuosity)
- Relative
  - Bicuspid or noncalcified valves
  - Untreated coronary artery disease requiring revascularization
  - Hemodynamic instability
  - LVEF <20%
  - For transapical approach: severe pulmonary disease, LV apex not accessible
  - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+
  - Hypertrophic cardiomyopathy
  - Severe incapacitating dementia
  - Renal insufficiency (creatinine >3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis
  - Severe pulmonary hypertension and RV dysfunction

AVA, Aortic valve area; *AVR,* aortic valve replacement; *EOA,* effective orifice area; *LVEF,* left ventricular ejection fraction; *RV,* Right ventricle; *TAVR,* transcatheter aortic valve replacement.

access and the results were the same according to the PARTNER trial and various other national trials. It seems that because of a "transfemoral first strategy," there may be a selection bias resulting in selection of nontransfemoral access routes for higher risk patients.[54]

Vascular complications are the most common complications with the transfemoral approach and are due to large caliber devices and the atherosclerotic disease of the patients. Peripheral vascular diseases with related vascular calcification, narrow arterial diameter, tortuosity and intramural thrombus or dissection are the most important factors. Planning access requires assessment of the luminal size and the degree of vessel calcification and tortuosity. The high-quality thin-slice CT scan with contrast that extends from the femoral artery to the subclavian artery is considered the key study in this context. Angiography and intravascular ultrasound may be adjuvants.[55] Limitations of the transfemoral approach will be fewer with the use of the newer generation lower-profile valves and reduction in the size of the delivery sheath. Subclavian access is an alternative approach for TAVR with less reported vascular injury, but rare brachial plexus neuropathies have been reported. Left subclavian artery access could be an unsuitable choice for patients who have undergone a previous CABG with left internal mammary anastomosis, because of the risk of myocardial ischemia during temporary occlusion of the artery.[7]

The transapical and direct aortic approaches are comparable. Both have the disadvantage of being a surgical technique that violates the chest wall and the advantage of avoiding the aortic arch with a theoretical reduction of stroke incidence. Moreover, because the distance from the entry point to implantation is short, implantation is easier and more accurate.[55]

The transapical approach has the risk of ventricular rupture and life-threatening bleeding. The concept of multimodal imaging plays an important role in preprocedural assessment, not only in helping determine the feasibility of the procedure but also in evaluating the access size and the size of the aortic annulus.[56] This includes angiography and cardiac catheterization, echocardiography, MDCT, and magnetic resonance imaging (MRI).[37] Some relative or absolute contraindications may be discovered during imaging, such as a bicuspid valve, left ventricular (LV) thrombus, significant mitral regurgitation with mitral annulus calcifications, a substantially high anatomic risk for coronary ostial obstruction (<10 mm), and infective endocarditis.[19]

Selection of Specific Valve Type and Size for the Patient

Because of the variety of the valves present on the market now, many cardiologists use the concept of "anatomy-dependent" valve selection. The close proximity to the coronary ostia, the width and height of the sinuses, the membranous ventricular septum with the His bundle, and the anterior leaflet of the mitral valve are important anatomic considerations.

Imaging techniques play a major role in:

- Identifying suitable prosthesis size.
- Measuring the distance of the coronary ostia from the aortic annulus to avoid occlusion by the valve stent (>11 mm).
- The diameter of the tubular aorta 45 mm from the aortic valve annulus in case of CoreValve use, which is designed to have a frame with hooks deployed in the supraannular aorta. This diameter must be less than 40 to 45 mm according to valve size.[7]
- Presence of atheroma in the thoracic aorta.
- Other valve dysfunctions, especially mitral regurgitation.
- Left ventricular outflow tract (LVOT) and septal hypertrophy
- Diameter of the femoral vessels

Prosthesis size: Slight oversizing is required for prevention of dislocation of these sutureless valves. Undersizing may lead to paravalvular regurgitation or valve embolization, whereas oversizing may lead to incomplete valve deployment or annular rupture. Contrast CT measurement is the ideal technique for aortic annulus sizing before TAVR; the annulus is larger than that measured by TEE by 1.5 ± 1.6 mm.[57]

Three-dimensional TEE measurements have been shown to be superior to 2D TEE measurements and correlate closely with those from MDCT.[58,59] TTE underestimates the annulus size by up to 15% or 1.36 mm.[7,59,60] The 3D TEE is also very accurate in measuring the true aortic annulus diameter via proper alignment of the short and long axes of the aortic valve[57] (Fig. 27.3). It should be used whenever CT is not available.[58] Sizing using cardiac MRI also may be an alternative to CT.[61] For example, patients with heavy annulus calcification, annulus eccentricity, and aorta-LVOT angle are more predisposed to have residual paravalvular leak after CoreValve implantation, but the CoreValve is preferable if the coronary ostia are very low and close to the annulus.[62] Operator experience is the main factor in valve selection.[6]

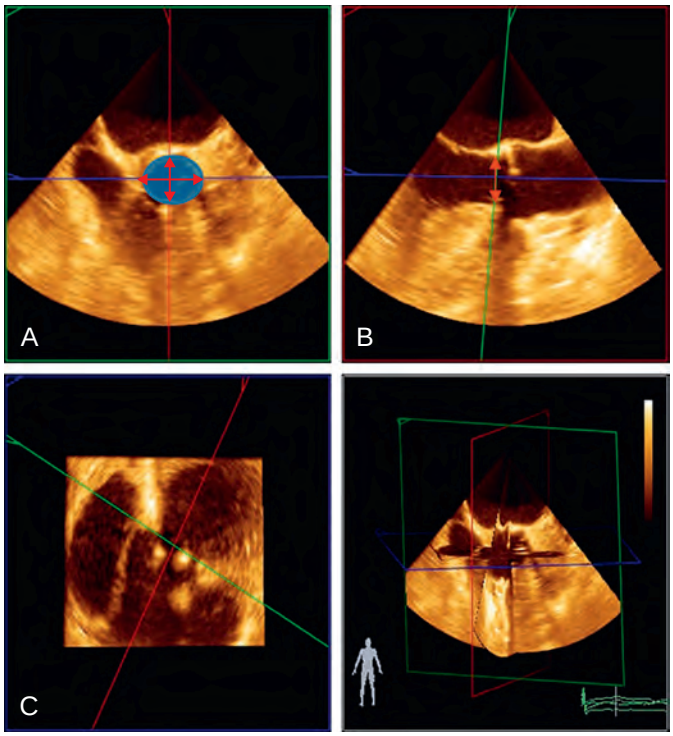

Fig. 27.3 Multiplanar reconstruction from a real-time three-dimensional transesophageal echocardiography of the aortic valve showing (A) the transverse, (B) the sagittal, and (C) the coronal axes. *Red arrows* indicate the annulus measurement.

In the absence of severe atherosclerosis and severe vascular tortuosity, femoral artery size is considered the main limiting factor in determining the most suitable route for TAVR. Sheaths allow access to the vessel without loss of blood when a hemostatic valve is used. Sheath diameter has decreased over time from 25-Fr in the first generation to 18-Fr in the third generation (or even 14-Fr in expandable sheaths [Edwards Lifesciences, Irvine, Calif]). Vessel diameter less than 6 mm (measured by angiography, ultrasound, or CT) presently is considered nonsuitable for the smallest sheath. The operator may puncture the vessel at a more proximal point (external iliac artery) to avoid smaller distal vessels. However, a puncture at or above the level of the inferior epigastric artery (branch of external iliac artery) is often noncompressible and increases the risk of retroperitoneal hemorrhage.[63]

The Edwards SAPIEN valve (initially the Cribier-Edwards valve) consists of a trileaflet bovine pericardium valve, pretreated to decrease calcification, mounted in a balloon-expandable stainless steel stent that can be implanted transfemorally or transapically. The CoreValve (now produced commercially by Medtronic, Irvine, Calif) has an autoexpandable nitinol stent containing a porcine pericardial valve. This valve has only been used by a retrograde approach, either via transfemoral, subclavian, or direct aortic access. Both valves were approved to be used commercially in Europe in 2007, while Edwards SAPIEN valve was approved in the United States in 2011 after the results of the PARTNER study.[64] The CoreValve was approved in the United States in 2014.[65,66] In Europe, the following valves also are approved and

commercially available: the ACURATE TA valve (Symetis, Ecublens, Switzerland),[67] the JenaValve (JenaValve Technology, GmbH, Munich, Germany),[68] and the transapical Medtronic Engager aortic valve system (Medtronic 3F Therapeutics, Inc, Santa Ana, Calif).

Recently, the randomized controlled trial CHOICE compared balloon-expandable versus self-expanding valves and found some advantages of the balloon-expandable valves with regard to device success and paravalvular leakage.[69] In a meta-analysis comparing the SAPIEN and CoreValve complications, increased postoperative permanent pacemaker implantation with the CoreValve was the only difference found between the two valves.[70]

Several newer transcatheter valves are in various stages of evaluation. The Lotus valve (Boston Scientific, Marlborough, Mass) is a repositionable transfemoral valve so the risk of postimplantation paravalvular leak is minimal. REPRISE I and II, dedicated to examining the Lotus valve, found it was safe and effective for high-risk patients.[71] The Direct Flow valve (Direct Flow Medical, Calif), the CENTERA valve (Edwards Lifesciences), SAPIEN XT and SAPIEN 3 valves (Edwards Lifesciences),[72] ACURATE TA transcatheter aortic valve (Symetis, Ecublens, Switzerland), JenaValve (JenaValve Technology, GmbH, Munich, Germany), and Medtronic Engager aortic valve system (Medtronic 3F Therapeutics, Santa Ana, Calif) are all second-generation valves. Some of these valves have already been included in clinical practice; however, experience and data remain limited.[19,67,68,73]

Logistical Considerations

The presence of a heart team is a prerequisite for establishing a TAVR program.[17,18,74] The German TAVR registry emphasized that the presence of on-site cardiac surgery, anesthesiologist, and CPB was essential regardless of the location in the OR, CCL, or hybrid OR.[75] They analyzed the location of emergency conversion from TAVR to open surgery and the mortality rate. They found a 25% mortality rate for surgeries performed in a hybrid OR in a CCL, 37.5% for patients transported from a CCL to an OR for surgery, and 75% for surgeries undertaken in a standard CCL.

During a TAVR procedure, patients may require conversion to emergency cardiac surgery if a complication occurs that cannot be managed conservatively. Although many TAVR patients are not candidates for conventional aortic valve replacements, rescue CPB should be instituted to allow the correction of reversible complications.[76] Further measures in case of major complications should be discussed with the patient before the procedure. These decisions must be documented in the medical notes and discussed with the whole medical team that is involved in the procedure.[51]

Some complications (eg, coronary obstruction, vessel injury) do not require open surgery but instead a lot of support for the interventionist from other team members such as anesthesiologists and radiologists. It is obvious that these complicated procedures need the MDT approach and a hybrid OR that provides an environment suitable for the team to ensure the safety and efficacy of the procedure and to manage complications that may arise.[77]

Multidisciplinary Team

Two important issues must be highlighted when evolving a TAVR program: First, it is not a solo procedure that can be done only by a group of physicians away from other team members. This team approach, which is known also as an MDT approach, is essential for a successful procedure. While the importance of full collaboration between interventional cardiologist and cardiac surgeon is obvious, it is even more critical to incorporate other key providers from other physician groups (eg, anesthesiology, radiology, noninvasive cardiology, intensive care) into the process (Fig. 27.4). Second, it is important to emphasize that TAVR therapy program is a process that starts outside the OR with patient evaluation and selection of suitability for this procedure and does not stop after the procedure, but continues in the postoperative period.[5]

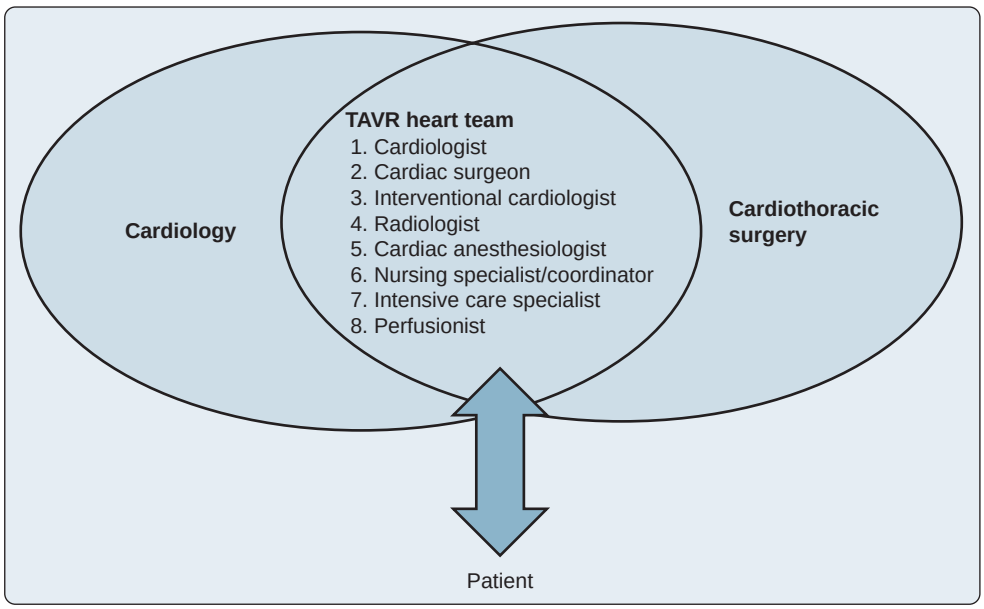

Fig. 27.4 Suggested components of the transcatheter aortic valve replacement *(TAVR)* heart team. *(Modified from Holmes DR, Jr, Mack MJ, Kaul S, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance.* J Thorac Cardiovasc Surg. *2012;144:e29–e84.)*

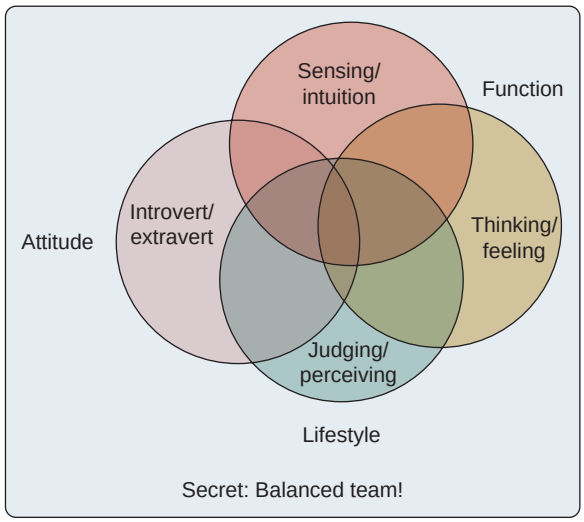

Fig. 27.5 Myers-Briggs Type Indicator.

Considering the different personalities of each team member may help to create a high-performing MDT. To accomplish this, the Myers-Briggs Type Indicator may be useful[78] (Fig. 27.5). A balanced team should have members with comparable personalities in terms of attitude and function to ensure free communication during the procedure. Of course, there must be one in the team who is the *primus inter pares* person (usually the interventionist). However, it is also important that everyone in the team feels free to communicate whenever they think that there is a problem.

Responsibilities for the different heart team members must be assigned before starting the procedure:

- Normally, instrumentation of the patient as well as anesthetic management belongs to the anesthesiologist.
- The intervention itself is performed by cardiologists, cardiac surgeons, or (ideally) both.
- Temporary transvenous pacemaker implantation can be done by the anesthesiologist from the jugular vein or by the interventionist from the femoral vein.
- Rapid pacing can be induced by the anesthesiologist or by the interventionist. No matter who is responsible, clear communication is mandatory.
- Echocardiographic imaging is done by the anesthesiologist or an echocardiographer.

Anesthetic Management

Anesthetic Technique

The decision whether the patient receives general anesthesia (GA) or local anesthesia (LA) of the access site with or without sedation or MAC depends on the route of access, institutional practice, and the patient's comorbidities. GA is still the mainstay in management of patients undergoing TAVR according to a recent survey.[79] In many institutions (especially in Europe), transfemoral TAVR is done under MAC with satisfying results.[80–82] Instead of LA infiltration, some have performed an iliohypogastric and ilioinguinal block during transfemoral TAVR.[83] LA infiltration was also used with the transaxillary approach.[84] The transapical TAVR is done under GA or, in rare cases, using thoracic epidural.[85] Otherwise, other access approaches are done under GA mostly because of lack of experience and familiarity to such procedures.

Advantages to using a MAC technique include avoidance of the circulatory depressant effects of GA, decreased use of vasoactive drugs, easy intraoperative central nervous system monitoring in case of embolic stroke, reduced procedural time, faster patient recovery, need for a lower level of postoperative care, and shorter hospital stay duration.[86] Even when LA or MAC is used, the anesthesiologist has to be prepared to switch to GA in emergency situations.

On the other hand, GA has its own advantages. The airway is secured, avoiding emergency airway intervention in case of an unfavorable hemodynamic situation. The use of TEE under GA is of particular importance in diagnosis and management intraoperatively. No randomized prospective studies have compared the techniques or found an advantage of one over the other.

No anesthetic drug is superior to another. In general, short-acting anesthetics with less hemodynamic effects are preferred to ensure early extubation after the procedure. Etomidate, propofol, remifentanil, sevoflurane, and desflurane are the most frequently used anesthetics.[51]

Procedure-Related Anesthetic Considerations

Monitoring

In addition to standard monitoring (ie, electrocardiography [ECG], pulse oximetry, end-tidal CO_2, anesthetic gas concentration, and noninvasive blood pressure), invasive monitoring is mandatory because of the complicated nature of the procedure, the patient's comorbidities, intraoperative cardiovascular compromise (especially with rapid pacing), and the possibility of life-threatening complications. Both arterial and central venous catheters should be inserted under LA or GA. Although a pulmonary artery catheter has been recommended,[7] there is still debate about whether it is needed in every patient. It may be useful in patients with moderate-to-severe pulmonary hypertension,[87] because pulmonary hypertension per se is an independent risk for mortality in TAVR patients.[88] In these patients, the use of elective femorofemoral CPB also may be considered.[89]At least one large-bore venous access catheter should be inserted for volume resuscitation. Urinary output and temperature monitoring are helpful.

Equipment

All equipment that may be used regularly during the procedure or during treatment of procedure-related complications must be available. This includes cell salvage, infusion pumps, pre-prepared crash carts, heating device, external defibrillator, external pacemaker battery, and intraaortic balloon pump.

Rapid Ventricular Pacing

Rapid ventricular pacing is a special and important issue during the procedure. It is essential to have no ejection with a cardiac arrest during balloon aortic valvuloplasty and during deployment of a balloon-expandable valve such as the SAPIEN valve. On the other hand, the longer profile of the CoreValve, which extends from the aortic annulus to the supracoronary aorta, allows its gradual release without need of rapid pacing.[66] The rapid pacing phase is usually brief and the heart recovers in seconds after stopping rapid pacing. Communication during this period is essential. A clear command "rapid pacing on" has to be followed by the clear reaction that rapid pacing has been started and the heart does not eject anymore. At the end of the maneuver the command "rapid pacing off" has to be followed by the reaction "rapid pacing is off" and the state of the circulation (ie, blood pressure and heart rate recovery).

Imaging Techniques and Guidance

The TAVR procedure creates many challenges throughout the whole process, in which multimodality imaging plays a major role and helps the heart team members to reach the right decision. Imaging is involved in patient selection, procedure planning, procedure performance, and in postoperative follow-up. It is difficult to determine a universal imaging protocol because of the wide variety of imaging modalities available in each institution and operator experience and preferences. The most common available imaging modalities are:

1. Echocardiography (TTE, TEE)
2. Conventional angiography
3. Intraoperative fluoroscopy

4. MDCT
5. Cardiac magnetic resonance

Preprocedural evaluation is the cornerstone in this process. These imaging modalities are used to evaluate the AS pathology, exclude TAVR contraindications (eg, severe aortic regurgitation, valvular vegetation, profound LV dysfunction), evaluate the aortic valve apparatus and dimensions, and evaluate the TAVR access anatomy (eg, iliofemoral vessels, aorta, subclavian vessels).

Transesophageal Echocardiography

TEE is one of two most important intraoperative imaging modalities used during TAVR. It stands side-by-side with fluoroscopy for a successful TAVR process. The radiation exposure to the patient and to the personnel is the major problem with fluoroscopy. In spite of that, it is used extensively because of its ability to better assess the guidewire and catheter locations and the valve stent position. On the other hand, TEE, in spite of being very useful in this context, is used intraoperatively only with patients under GA. Mini-TEE probes are available and can be used with patients under MAC.

The aortic valve has special anatomy that increases the imaging assessment difficulties, and it is important for the echocardiographer to have a good understanding of what is called the functional aortic annulus for good TAVR guidance. The functional aortic annulus contains the following components: the aortic annulus, the sinus segment with the sinuses of Valsalva and the origins of the coronary arteries, and the sinotubular junction where the sinus segment joins the tubular ascending aorta.[90,91] The definition of *aortic annulus* varies significantly among operators.[92] The aortic annulus has at least three definitions. It is either the ring formed by the anatomic ventriculoarterial junction, the ring formed by the hinge point at the attachment of the valve leaflet to the myocardium, or the ring formed at the top of the valve leaflets at the sinotubular junction[93,94] (Fig. 27.6). Actually, the most commonly used "hinge points" ring is a virtual ring, as there is no anatomic plane for this ring. Anatomically, it is located in the upper part of the LVOT, below the other two rings. It was found that the functional aortic annulus is not a spherical but an elliptical structure, with both major and minor diameters, which makes the measurements more difficult, with need for a multiplane, rather than one-plane (2D), assessment.[91] Three-dimensional imaging either by TEE or MDCT plays a major role to overcome this problem.

TEE should be used before, during, and after TAVR procedures to assess various factors.[12,51,95–97]

Preprocedural Assessments

- The severity of AS and associated aortic regurgitation if present
- Aortic valve system (cusps, annulus, root) morphology and abnormalities, which is recommended by the European Association of Echocardiography/American Society of Echocardiography guidelines[95]
- Aortic annulus size: the anterior-posterior aortic annulus diameter in systole at the hinge point of the cusps, either in the 2D long-axis view or 3D in the long-axis and the short-axis views using multiplanar reconstruction mode[51]
- LV size and function
- The aortic annulus to coronary ostia distance, which must be greater than 11 mm to avoid inadvertent coronary occlusion during implantation. Both 2D and 3D modes are used. For left coronary ostium, 3D multiplanar reconstruction must be used, while the right coronary ostium can be measured also in a 2D long-axis view.[51,98]
- Diameter of tubular aorta (a diameter >45 mm is a contraindication for CoreValve implantation)
- Presence of atheroma in thoracic aorta
- Other valve dysfunctions, especially mitral valve regurgitation
- LVOT and septal hypertrophy

Intraprocedural Assessments

- The ventricular puncture site in the transapical approach using the midesophageal two-chamber view
- The proper position of the wires, balloon, and valve delivery systems during and after the implantation. During the transapical approach it is important to ensure that the guidewire is not stuck in the mitral valve apparatus. The mitral valve chordae and the degree of mitral regurgitation must always be reevaluated as catheter advancement in these circumstances risks mitral valve injury and acute mitral regurgitation. Real-time 3D echo is superior in mitral valve apparatus visualization.
- The severity and the location (and sometimes the cause) of transvalvular and paravalvular regurgitation (PVR). The grading recommendation for PVR was recently revised.[99] It is either semi-quantitative or quantitative. The semiquantitative methods include the diastolic flow reversal in the descending aorta and the percentage circumferential extent of PVR. The quantitative parameters in TEE are the regurgitant volume (mL/beat), regurgitant fraction (as percentage), and the effective regurgitation orifice area (cm^2).[100]
- The valve after implantation concerning the pressure gradients, valve area and the dimensionless velocity index when applicable
- Global and regional LV and right ventricular (RV) function, especially after the rapid pacing phases[97]
- Possible complications (ie, new regional wall motion abnormalities, mitral regurgitation, pericardial effusion/tamponade, aortic dissection or trauma,[101] and coronary occlusion of the circumflex artery)[102,103]

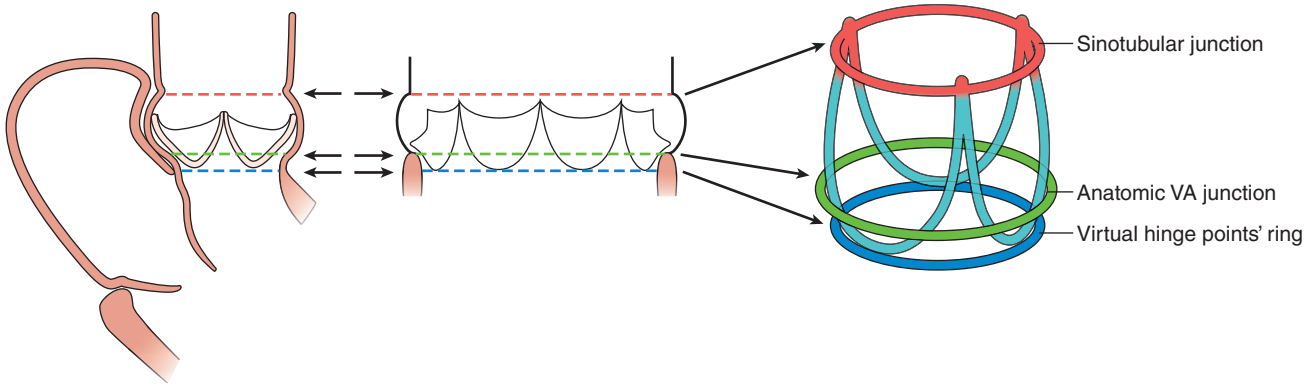

Fig. 27.6 The various rings associated with the aortic annulus. *VA*, Ventriculoarterial. *(Modified from Piazza N, de Jaegere P, Schultz C, et al. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve.* Circ Cardiovasc Interv. *2008;1:74–81.)*

Postprocedural Assessments

- The aortic valve prosthesis function and position
- LV function and mitral regurgitation
- Any possible complication (eg, pericardial tamponade)[12]
- To follow up a paraprosthetic regurgitation, if present

A systematic, comprehensive echocardiographic protocol, incorporating the additional benefits of 3D TEE, is recommended by many experts and is shown to contribute to excellent outcomes of TAVR procedures.[104] Multiple studies have compared TEE (2D and 3D) with MDCT, especially in annulus sizing and aortic root dimensions, and they demonstrated significant measurement differences, where echocardiography usually underestimates the annular size.[61,105]

Conventional Angiography

Conventional angiography is used preoperatively to assess TAVR access (iliofemoral vessels, aorta, subclavian). Also, coronary angiography is done to exclude any significant coronary artery disease.[93] It carries the risk of contrast nephropathy.

Intraoperative Fluoroscopy

Valve positioning is currently based on fluoroscopy with or without (in patients receiving only MAC/LA) TEE guidance. Originally, the operator depends on the aortic calcifications that appear in the 2D view of the fluoroscopy for valve positioning. Some of the fluoroscopy operating systems can rotate fully around the patient and provide cross-sectional or 3D data in a few minutes. This 3D C-arm CT (eg, Dyna-CT, Siemens AG, Erlangen, Germany; and Vitrea, Vital Images [Toshiba], Plymouth, Minn)[11] can assist positioning for TAVR, especially with poor calcification at the annulus, by overlaying real-time 2D images and navigating the anatomy.[11] This technique has been compared with MDCT and found be comparable with regard to final valve-visualization angle.[11,14,15] This recent advance in imaging technology allows comprehensive real-time visualization and/or 3D reconstruction , which helps in optimal positioning of the prosthesis.

Other new imaging systems are also in use. They use either an aortogram acquired before device deployment (C-THV system, Paieon Inc., New York, N.Y.) or the CT data (3mensio valve, 3mensio Medical Imaging, Bilthoven, Netherlands; OsiriX, Pixmeo SARL, Bernex, Switzerland) to predict the optimal angiographic views. The Philips heart navigator system (Philips, Eindhoven, Netherlands) provides 3D reconstruction of the aorta and aortic valve by superimposing the CT data onto the angiographic projections. Small studies have shown the utility of these technologies, with better positioning of the valve.[106]

Digital Subtraction Angiography

DSA is used mainly to visualize the blood vessels and identify any abnormality without interference from background structures. An advanced visualization of the entire DSA flow (iflow) with color coding is another advancement in this field which allows the operator to visualize the entire vascular tree in just one image.

Multidetector Computed Tomography

MDCT is the "gold standard" method in assessment of complex aortic valve geometry. It can give almost all the information needed for TAVR. It is used in the assessment of the annular size and shape, degree of calcification, the distance between annulus and coronary ostia, and in planning for the precise coaxial alignment of the stent-valve along the centerline of the aortic valve and aortic root. In addition, the atherosclerosis of the iliofemoral and the thoracoabdominal aorta can be easily assessed.

Three-dimensional reconstruction of the heart is a very helpful realistic method that can be used at the desired phase of the cardiac cycle (eg, 30–40% of the systole) for valve area and annular assessment.[7] Four-dimensional reconstruction of the heart for the whole cardiac cycle can be done but at the expense of a high radiation dose.[107] Another risk that must be considered is the low-osmolar iodinated contrast agent causing contrast nephropathy. The noncontrast scan is not optimal, but the assessment of the vessel's size, calcification, and tortuosity is feasible.[7]

The elliptical shape of the aortic annulus gives the 3D CT reconstruction special importance, as it allows the measurement of both annular minimal and maximal diameters, which can be measured also by 3D TEE but not with 2D TEE.[61,108] A difference of 2 mm or more between the maximum aortic annulus and nominal prosthesis diameters by MDCT is considered as an independent risk factor for postoperative moderate-to-severe paravalvular regurgitation.[109]

Cardiac Magnetic Resonance

CMR also can give a comprehensive assessment of the aortic valve, annulus, aortic root, coronary ostia, aorta, and iliofemoral vessels. It has the advantage of avoiding radiation exposure and the iodinated contrast. On the other hand, it is time consuming, is contraindicated in patients with pacemakers and defibrillators, and carries the risk of nephrogenic systemic fibrosis if gadolinium is used to enhance CMR imaging.[110]

Although the 2D, ECG-gated, noncontrast cine CMR sequence across the aortic valve provides a good detailed assessment, the 3D whole heart acquisition with or without gadolinium-enhanced imaging gives more precise details for the left ventricle, aortic valve, aorta, and iliopelvic vessels. A navigator-gated, free-breathing, 3D noncontrast steady-state free precession sequence can be used to assess the vessels in patients with renal insufficiency.[7]

After TAVR, CMR can be used to assess the severity of aortic regurgitation. MRI also is used for cases with cerebral embolization.

Complications

In some patients, who have required relatively long rapid pacing because of multiple adjustments to balloon or valve positions before inflation, heart stunning has occurred and has not recovered without medical or mechanical support. Usually a small bolus of metaraminol (0.5–1 mg), phenylephrine (0.1–0.5 mg), or norepinephrine (10–20 μg) is sufficient for recovery. Epinephrine (10–20 μg) sometimes is necessary and can be injected through the central venous catheter or directly into the aortic root pigtail catheter used for contrast administration. This direct injection into the aorta is more effective, especially with a noncontracting heart. External cardiac massage must be initiated, without any delay, to obtain an acceptable cardiac output and coronary perfusion pressure. Failure of these measures must lead the team to move forward to mechanical circulatory support using emergency CPB. Institution of CPB must not take much time and the arterial and venous cannulas are inserted over the femoral guidewires already in situ for emergency situations. During this time, the situation must be assessed to discover any possible complication that led to the condition. Sometimes the only rescue maneuver is conversion to an open surgical operation through a sternotomy. Such a decision must be discussed with the patient before the operation takes place. Patients under LA usually have unpleasant feelings and nausea during the phase of rapid pacing and hypotension, which is distressing when this phase is prolonged. This can require changing to GA and rapidly securing the airway with an endotracheal tube, adding a major burden to the anesthesiologist during this critical situation. Additionally, the anesthesiologist must help to find the reason for the circulatory failure using TEE; however, this must not come before patient care and management.[51] The possible causes of severe acute hemodynamic collapse during the procedure that can be discovered by TEE include valve embolization, severe aortic regurgitation, severe mitral regurgitation, aortic rupture or dissection, LV or RV perforation, and hypovolemia.[104] Ventricular fibrillation is another rare complication that may arise after rapid ventricular pacing that mandates rapid defibrillation. External defibrillator pads should be attached to every patient before the procedure. Electrolytes levels, especially potassium, must be measured and corrected.

The two most common (rare, ≈1% of cases) complications that cause conversion to open surgery are valve embolization into the left ventricle and procedure-related aortic injury, including annular

TABLE 27.4 Complication Rates for TAVR

Complication	*Incidence Rate (%)*	*95% CI (%)*
Major bleeding	22.3	17.8–28.3
Vascular complications	All: 18.8 Major: 11.9	All: 14.5–24.3 Major: 8.6–16.4
Need for permanent pacemaker	13.9	10.6–18.9
Acute kidney injury (moderate to severe)	7.5	5.1–11.4
Aortic insufficiency (moderate to severe)	7.4	4.6–10.2
Stroke	All: 5.7 Major: 3.2	All: 3.7–8.9 Major: 2.1–4.8
Periprocedural MI (<72 h)	1.1	0.2–2.0

CI, Confidence interval; *MI,* myocardial infarction; *TAVR,* transcatheter aortic valve replacement.

Modified from Genereux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol.* 2012;59:2317–2326.

rupture, aortic dissection, and perforation. In spite of active management of such complications, including the surgical team's using CPB, the mortality rate is still very high, ranging from 46% to 67%.[75,111,112] While it is highest in patients with aortic dissection or perforation (80%), it is about 33% following severe aortic regurgitation. For annular rupture, myocardial perforation, and prosthesis embolization, mortality rates are 67%, 50%, and 40%, respectively.

Coronary artery obstruction, which occurs in about 0.7% of cases, affects mainly the left main artery and requires emergency coronary intervention with a success rate of 82% and a 30-day mortality of 41%.[113] Another relatively common complication is vascular injuries; occurrences range from 1.9% to 17.3% of patients and mortality is increased by 2.4- to 8.5-fold.[63] These complications may require surgery, advanced endovascular stenting, ballooning, or intravascular ultrasound.

The common complications of TAVR are major bleeding, vascular injury, heart block, acute kidney injury, paravalvular leak, stroke, and postprocedural MI (Table 27.4).

Vascular Injury

As mentioned earlier, vascular complications (eg, rupture, perforation, dissection, hematoma, and pseudoaneurysm) were common (up to 27%) at the beginning of the era of TAVR, especially with the transfemoral approach because of relatively large valve delivery systems, lack of experience, and inadequate preoperative vascular system assessment tools. These complications have negative effects on morbidity and mortality.[100,115] On the other hand, in the PARTNER A trial, in spite of higher vascular complications (11%) for TAVR compared to 3.2% in the surgical group, there was no significant mortality difference. Over the past few years, the size of the valve delivery systems has been reduced and the precise assessment of the whole vascular system has become available.

Vascular injury must be considered if there is hemodynamic instability or a decrease in hemoglobin concentration at the end of the procedure. Good communication with the operator is essential in this situation.

Pericardial Hemorrhage

This life-threatening complication may arise at any time of the procedure. It occurs either by annular rupture or by wire perforation. The annular rupture and the ventricular or aortic wire perforation are very serious and usually require sternotomy and surgical repair. Venous bleeding by the guidewire or by the pacemaker wire can be managed by pericardial drainage and close observation.

Conduction System Abnormalities and Arrhythmias

As the atrioventricular node and bundle of His pass superficially through the interventricular septum, they are liable to be injured during aortic valve surgical procedures by mechanical trauma, tissue edema, or local inflammation. This dysfunction may be temporary or permanent, for which a permanent pacemaker must be implanted. The same problems occur during TAVR, especially with long valve stents that extend into the LVOT as with the CoreValve, low implantation of the valve, or oversizing. The incidence for a permanent pacemaker after implantation of a CoreValve ranges from 23.4% to 39%, whereas it is only 4.9% to 6% for the SAPIEN valve.[116–118] On the other hand, this pacemaker incidence is only slightly higher for the SAPIEN valve when compared with surgical AVR according to the PARTNER trial.[119] Preoperative predictors of the need for a postoperative permanent pacemaker are left bundle branch block with left-axis deviation, an interventricular septal dimension greater than 17 mm at end-diastole, increased baseline thickness of the native noncoronary aortic valve cusp (>8 mm),[118] or a preexisting right bundle branch block.[120] All patients must be closely monitored for 72 hours after the procedure because the conduction disturbances can occur up to 3 days after the valve implantation.

Valve Malpositioning

This includes either low (in LVOT) or high (in aortic root) valve implantation or valve embolization in the worst-case scenario. Low valve deployment in the LVOT may impinge on the anterior mitral leaflet, in addition to the high risk for postoperative heart block. On the other hand, high valve implantation in the aortic root carries the risk of coronary ostial obstruction leading to myocardial ischemia and potential cardiovascular collapse.

Coronary ostial occlusion occurs in 0.66% of patients[113] and is a life-threatening condition. Diagnosis is usually made by direct coronary angiography. Three-dimensional TEE can predict this problem by accurately measuring the distance between the aortic annulus and the left main coronary ostium.[121] Lifesaving coronary stenting has been attempted in 75% of patients, with a success rate of 82%. In spite of that, the 30-day mortality is very high (41%) with no case of stent thrombosis or reintervention.[113] To avoid delay in stenting for high-risk patients, either a prophylactic stent insertion[122] or at least a wire in the left coronary artery before valve deployment can be used.

Paraprosthetic aortic regurgitation can occur as a result of valve malpositioning, undersizing, extensive valve calcifications, or incomplete expansion of the valve (Fig. 27.7). Mild regurgitation is found in about 70% of patients after TAVR.[123] Moderate-to-severe regurgitation occurs in 11.7% of the patients[124] and is an independent predictor of mid- to long-term mortality.[125] Preoperative cardiac CT allows an accurate assessment of the degree of valve calcification and precise annulus sizing in order to minimize the risk of prosthesis mismatch.[126] This can also be predicted preoperatively using TEE by identifying the calcification of the commissure between the right coronary and noncoronary cusps and the area cover index.[56] Fluoroscopy/aortography or TEE can be used to diagnose the severity of the regurgitation. Management options for moderate and severe regurgitation include a second balloon dilation, snares, and valve-in-valve implantation. Second balloon dilation must be done carefully as it risks valve leaflet disruption. The concept of valve oversizing to reduce postimplantation regurgitation has not yet been investigated or approved.[95]

The rapid pacing technique is very important during valve deployment as any cardiac ejection during this phase may lead to valve malpositioning. Therefore, the temporary pacer must be adjusted to a nonsensing fixed mode with maximum output to minimize ventricular ejection risk.[51]

Embolization of the valve into the left ventricle or into the aorta is a complication that usually needs surgical intervention. It also has been managed by implanting a second device and leaving the dislocated valve safely in the descending aorta.[127]

Stroke

At the beginning of the TAVR era, neurologic complications were cumbersome. Recently, the incidence of stroke has declined from 7.8% to between 2.1% and 2.8%[129] but is still higher than in surgical AVR.

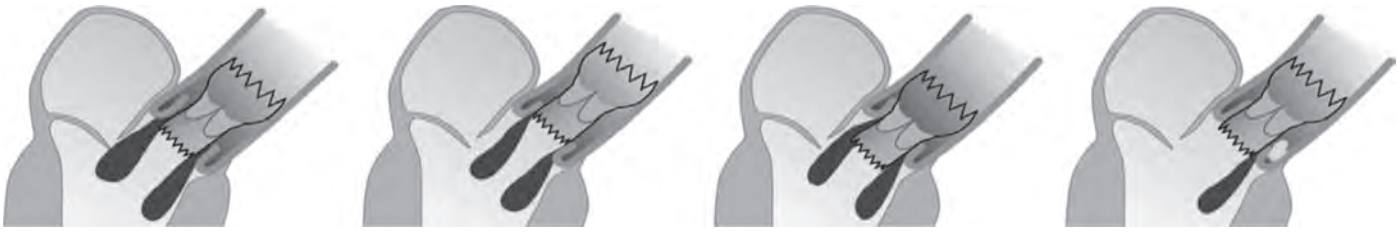

Fig. 27.7 Perivalvular leak can be caused by (A) inappropriate size (undersizing), (B) high or (C) low valve malpositioning, or (D) eccentric or bulky annular or leaflet calcification. *(Modified from Sinning JM, Vasa-Nicotera M, Chin D, et al. Evaluation and management of paravalvular aortic regurgitation after transcatheter aortic valve replacement.* J Am Coll Cardiol *2013;62:11–20.)*

Major stroke was found to occur similarly in TAVR and surgical AVR according to the PARTNER trial, but the central nervous system–associated morbidity was higher in TAVR patients.[130] Stroke in TAVR has many causes, including atherotic material from the ascending aorta or arch, calcific material from the native aortic valve, thromboembolism from the catheters used in the procedure, air microembolism during LV cannulation, prolonged hypotension, or dissection of brachiocephalic vessels.[51] Cerebral microembolism related to TAVR was evaluated with MRI, which demonstrated new foci of reduced diffusion. Manipulation of the aortic root and valve by guidewires and catheters, and during implantation of the prosthesis, are the critical phases in which embolism mostly occurs.[131]

A transcranial Doppler study of embolization during TAVR showed recordings of different rates of high intensity transient signals, yet there is no evidence that TAVR approach (transfemoral or transapical) or valve type is associated with more neurologic insults.[132]

A measure that may be taken to reduce stroke incidence is implantation of temporary carotid artery filters (embolization-protection devices) (debris/calcium-capture devices) at the beginning of the procedure using a radial artery approach with removal at the end of the operation (eg, the Claret Pro system, Claret Medical, Santa Rosa, Calif; the TriGuard, Keystone Heart Ltd, Herzliya, Israel; and the Embrella embolic deflector, Edwards Lifesciences).[106] However, no data support the clinical benefits of these devices in all cases.[19] They may be used in selected cases with a documented history of cerebrovascular disease and significant aortic valve calcifications.[133]

Silent cerebral ischemia occurs in 72% of patients after TAVR as demonstrated by imaging studies. Only 6.6% presented clinically.[131]

Renal Dysfunction

The PARTNER trial did not prove that TAVR has more postprocedural renal morbidity than surgical AVR.[119,130] In spite of that study, many patients required hemodialysis (1.4%) after TAVR. Acute renal injury occurs in 12% to 21% (8.3–57% in other studies) of patients and is mostly reversible. Diabetes mellitus, peripheral vascular disease, chronic renal failure, and the need for blood transfusions increase its incidence.[134,135] Acute kidney injury also occurs more often in surgical AVR patients who suffered preoperatively from chronic renal failure.[136]

Future Perspectives for TAVR

TAVR technology continues to improve the process and overcome the already known problems, as well as to find new applications for the procedure. The trend to smaller introducer systems has reduced vascular complications. New valve sizes are being produced to fit larger patients. Valve-in-valve TAVR,[137] TAVR in bicuspid aortic valve,[138] TAVR in medium- and low-risk surgical groups[139–141] and in younger patients,[19,142] and TAVR for aortic valve regurgitation[73,143] are under clinical investigation. Moreover, new access routes have been used with patients for whom none of known access routes are feasible.

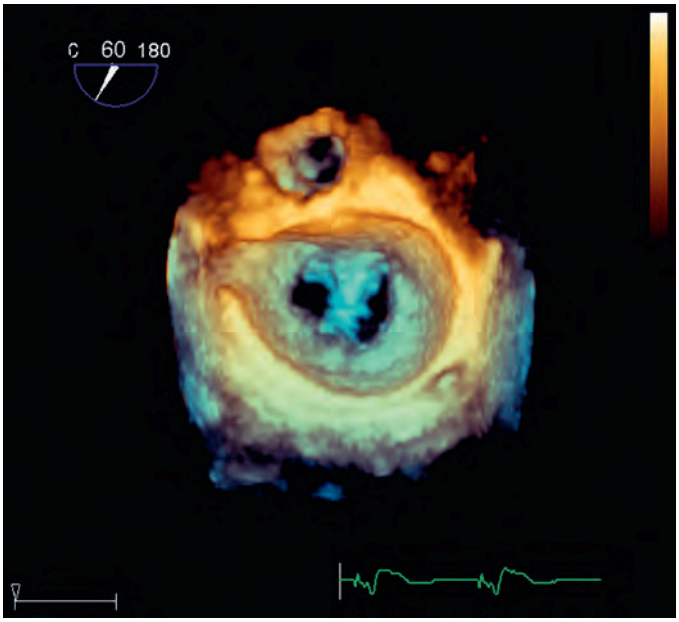

Fig. 27.8 Three-dimensional zoom double-orifice mitral valve after successful MitraClip implantation.

Transcatheter Mitral Valve Repair: MitraClip

Different transcatheter mitral valve repair techniques have been developed over the past few years addressing the leaflets, the mitral annulus, or the left ventricle.[144] These techniques usually mimic well-known surgical techniques.

The MitraClip (Abbott Laboratories, Abbott Park, Ill) is the most commonly used catheter-based mitral valve repair technique. It mimics the surgical edge-to edge technique first described by Alfieri and coworkers[145] and creates a double orifice mitral valve (Figs. 27.8 and 27.9).

Although residual mitral regurgitation is more common compared to surgical mitral valve repair, the reduction in functional class is not different to surgical mitral valve repair, even 4 years after MitraClip.[146]

Patient Selection and Indications

The MitraClip procedure should be considered in patients with chronic severe structural mitral regurgitation (Carpentier classification type II)[147,148] or chronic severe secondary or functional mitral regurgitation[147] in patients who are severely symptomatic (New York Heart Association [NYHA] functional class III or IV) with a prohibitive risk

for surgery or judged inoperable, favorable anatomy for a repair procedure, and a reasonable life expectancy (>1 year). Favorable anatomy with recommended echocardiographic criteria are described in detail in Table 27.5.[149]

Routinely used risk scores like the logistic EuroSCORE, EuroSCORE II, or STS-PROM overestimate the predicted mortality in these patients.[150] The procedure has been found to have a low rate of complications and in-hospital mortality.[151]

Access Routes

The procedure is performed via the left femoral vein. First, a steerable guide is placed through a transseptal puncture into the left atrium. Then, a clip delivery system together with the MitraClip device is introduced via the guide. After capturing both leaflets, the MitraClip is fixed to create the typical double orifice mitral valve.

Anesthetic Management

Usually this procedure is performed under GA to create optimal conditions for the interventionist and the echocardiographer,[152–154] although there have been some attempts to do this procedure in sedated patients.[155,156] Due to the patients' high-risk profile, invasive blood pressure and central venous catheters are mandatory, whereas the use of a pulmonary artery catheter is not recommended. Early extubation right after the procedure can be achieved in most patients. The procedure can be done in the CCL or in the hybrid OR.

Complications

Complications such as atrial perforation with pericardial effusion or tamponade are extremely rare and can be treated without the use of CPB. For a detailed list of complications, see Table 27.6.[157–168]

Imaging Techniques and Guidance

In contrast to TAVR, this procedure is primarily echo-guided. Angiography can be used for transseptal puncture and for visualization of the groin vessels. However, the guidance of the MitraClip system is performed by TEE (see Chapters 3 and 15). The main steps are:

- Transseptal puncture (Fig. 27.10)
- Introduction of the steerable guide catheter into the left atrium (Fig. 27.11)
- Advancement of the clip delivery system into the left atrium (Fig. 27.12)
- Steering and positioning of the MitraClip above the mitral valve (Fig. 27.13)
- Alignment of the clip (Fig. 27.14)

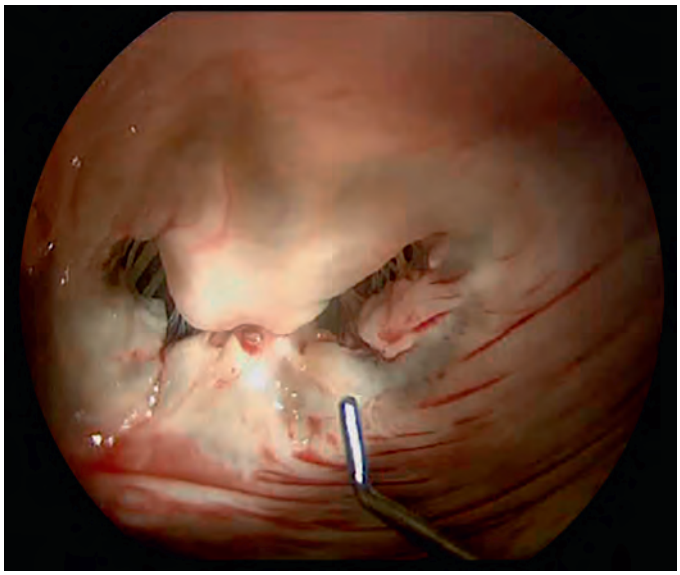

Fig. 27.9 Anatomic picture of double-orifice mitral valve 2 years after MitraClip implantation.

TABLE 27.5 Recommended Criteria for Echocardiographic Analysis of the Mitral Valve for Percutaneous Edge-to-Edge Repair

Criteria	*Assessment*
Mitral leaflet coaptation length	≥2 mm
Mitral leaflet coaptation depth	<11 mm
Flail gap	<10 mm
Width of flail leaflet	<15 mm
Mitral valve opening area	>4 cm^2
Leaflet thickness	≤5 mm
Considerable calcification of the mitral annulus	Should not be present
Marked valvular cleft or leaflet perforation	Should not be present
Marked restriction of posterior leaflet	Should not be present
Lack of primary or secondary chordae support	Should not be present
Calcification of the leaflets in the grasping area	Should not be present
Several significant regurgitant jets	Should not be present

Modified from Flachskampf FA, Wouters PF, Edvardsen T, et al. Recommendations for transoesophageal echocardiography: EACVI update 2014. *Eur Heart J Cardiovasc Imaging.* 2014;15:353–365.

TABLE 27.6 Complications in MitraClip Implantation

Study	*N*	*Logistic EuroSCORE*	*STS*	*30-Day Mortality*	*Transfusion>2 Units of Blood*	*Urgent Surgery*	*Partial Clip Detachment*	*Transseptal Puncture*	*Pericardial Effusion*	*Mitral Steno-*	*Injury MV*	*Major Stroke*
Feldman et al. 2009[157]	107	—	—	0.9	3.7	—	9.0	2.8	—	0	—	0.9
Franzen et al. 2010[158]	51	28.0	16.0	2.0	—	—	3.9	—	0	0	3.9	0
Tamborino et al. 2010[159]	31	—	—	3.2	3.2	3.2	0	3.2	3.2	—	—	0
Pleger et al. 2011[160]	33	41.0	24.0	0	3.0	—	0	—	0	0	—	—
Feldman et al. 2011[161]	178	—	—	1.0	13.0	2.0	5.0	—	3.3	0	—	1.0
Franzen et al. 2011[162]	50	34.0	—	6.0	—	—	—	—	—	21.0	—	—
Van den Branden et al. 2012[163]	52	27.1	10.1	3.6	3.6	1.8	3.6	1.8	1.8	0	0	0
Divchev et al. 2012[164]	33	24.0	30.0	0	—	0	0	0	0	15.2	0	0
Whitlow et al. 2012[165]	78	—	>12.0	7.7	17.9	0	1.3	1.3	1.3	—	—	2.6
Baldus et al. 2012[166]	486	23.0	11.0	2.5	10.4	—	0.2	—	0.9	—	—	0.4
Sürder et al. 2013[167]	100	16.9	—	5.0	—	1.0	5.0	3.0	—	1.0	3.0	1.0

MV, Mitral valve; *STS,* The Society of Thoracic Surgeons.
Modified from Bakker AL, Swaans MJ, van der Heyden JA, et al. Complications during percutaneous edge-to-edge mitral valve repair. *Herz.* 2013;38:484–489.

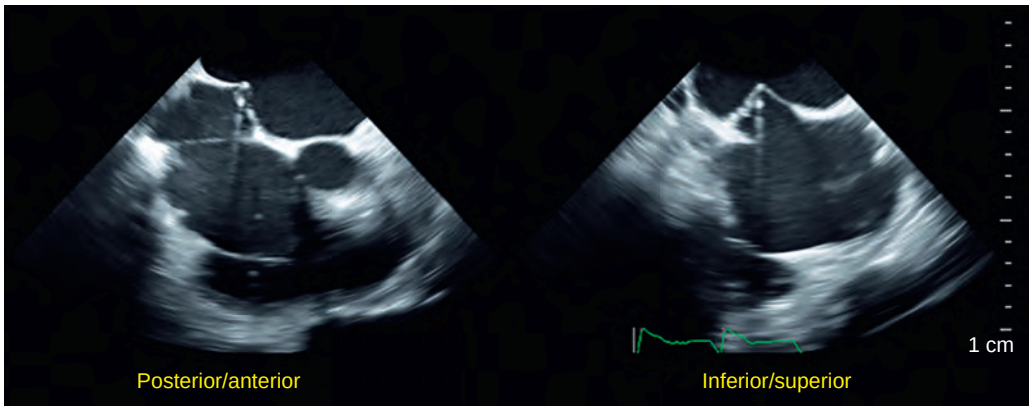

Fig. 27.10 Visualization of transseptal puncture site with X plane. The site of transseptal puncture is important for maneuvering of the delivery system and clearance for capturing the leaflets.

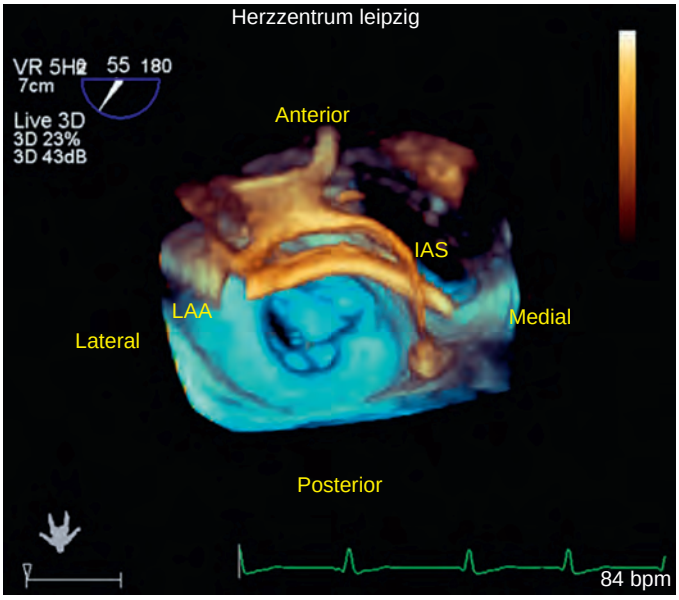

Fig. 27.11 Steerable guide catheter in the left atrium with real-time three-dimensional imaging. *IAS,* Interatrial septum; *LAA,* left atrial appendages.

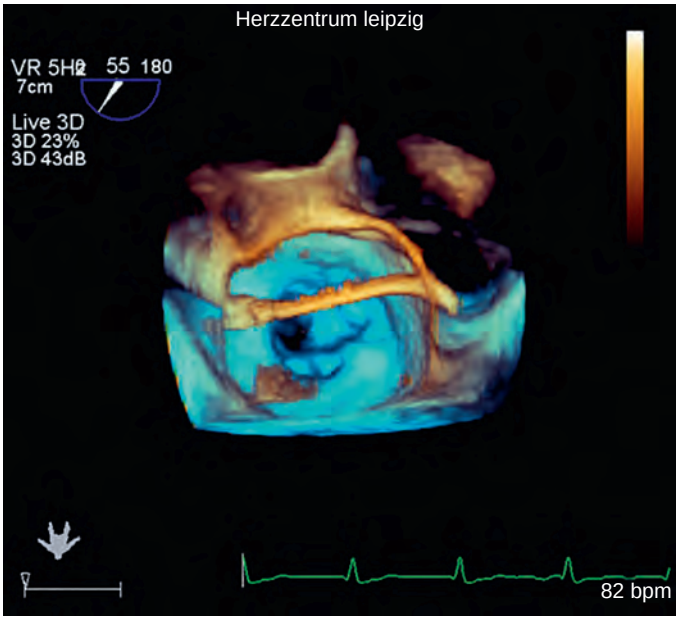

Fig. 27.12 Introduction of clip delivery system into the left atrium.

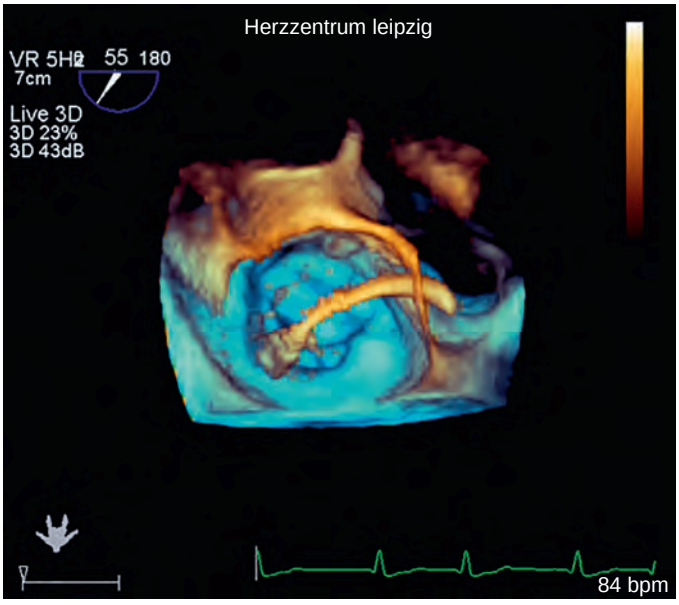

Fig. 27.13 Steering of the clip delivery system.

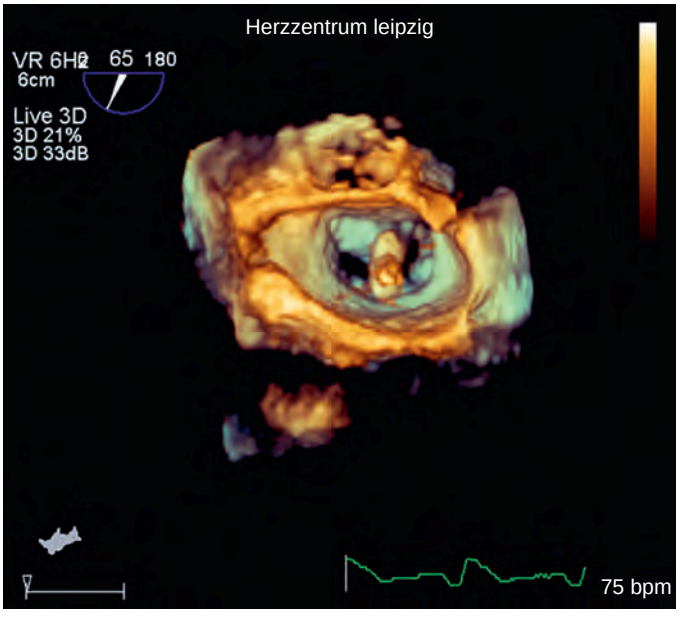

Fig. 27.14 Alignment of the clip to be perpendicular to both leaflets.

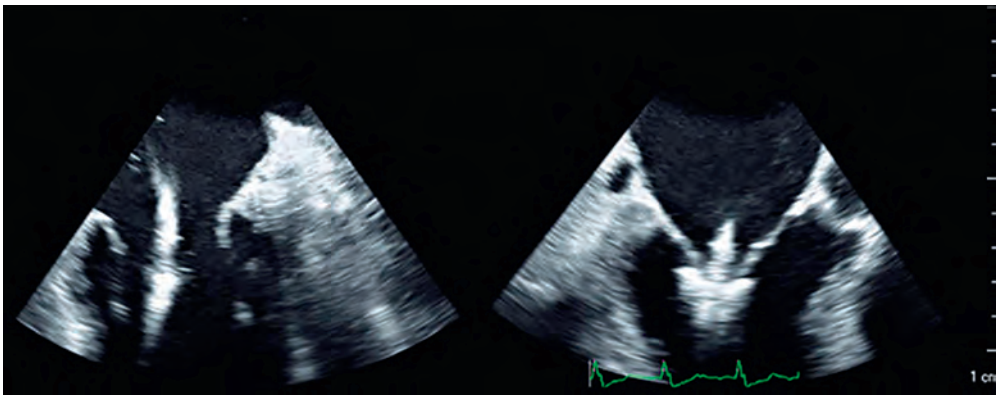

Fig. 27.15 Advancing and positioning of the clip in X-plane.

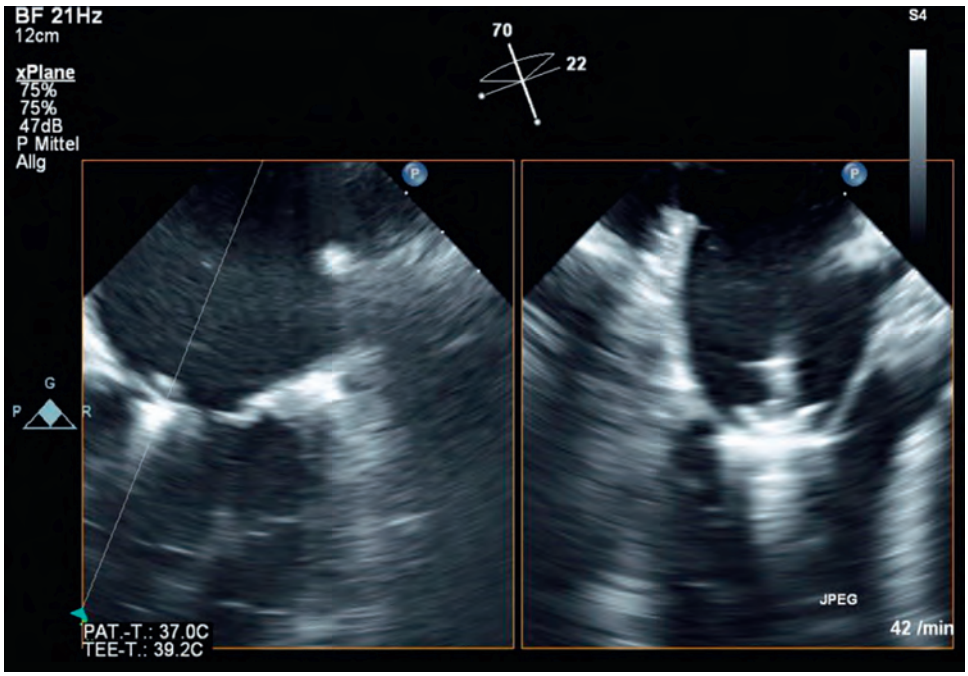

Fig. 27.16 Grasping the leaflets.

- Advancing of the MitraClip into the left ventricle (Fig. 27.15)
- Grasping the leaflets and assessment of proper leaflet insertion (Fig. 27.16)
- Control of leaflet insertion (Fig. 27.17)
- Functional control of the result (ie, residual mitral regurgitation, new mitral stenosis)
- Assessment of iatrogenic residual atrial septal defect after withdrawing of the steerable guide catheter.

For most of the main steps, real-time 3D TEE either in the wide sector zoom mode or in the X-plane mode is preferred over 2D TEE.[152,169,170]

Transcatheter Pulmonary Valve Replacement (Melody Valve)

The right ventricular outflow tract (RVOT) and the pulmonary valve and artery are subjected to many abnormalities of either congenital origin (ie, tetralogy of Fallot with pulmonary atresia and truncus arteriosus) or acquired origin (ie, Ross operation). These patients are often treated with surgical placement of a right ventricular–to–pulmonary artery (RV-PA) conduit. RVOT conduits develop stenosis, insufficiency, or both, over time due to the development of calcification, intimal proliferation, and graft degeneration; consequently, RV dysfunction by volume and/or pressure overload occurs. Such patients are subjected to multiple RVOT conduit reoperations. Bare metal stenting of stenotic conduits decrease RV pressures and is associated with immediate hemodynamic improvement[171] and potentially prolonged conduit life span.[172] Nevertheless, this treatment option comes at the expense of significant pulmonary regurgitation. Transcatheter pulmonary valve replacement (TPVR) provides a good option to treat such cases without the risk of reoperation.[173]

The first reported TPVR with a stent-mounted bovine jugular venous valve was in 2000.[174] The Melody transcatheter pulmonary valve (Medtronic, Minneapolis, Minn) has been used to treat RVOT conduit dysfunction for more than 10 years, with procedural success,

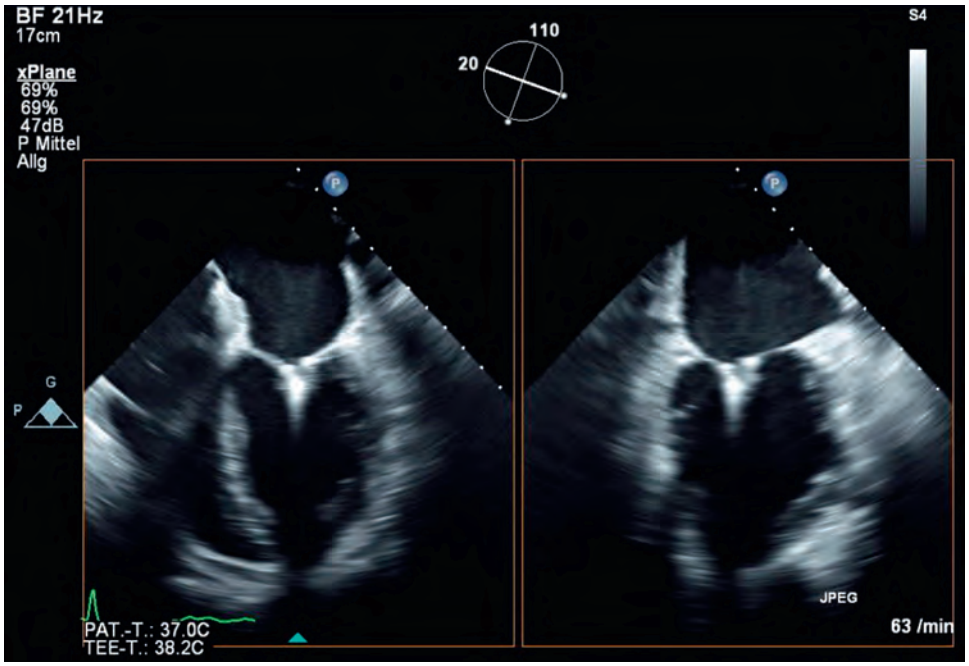

Fig. 27.17 Control of leaflet insertion with X-plane.

excellent short-term TPV function, and low reintervention and reoperation rates at 1 year.[175] It received approval from the U.S. Food and Drug Administration in 2010 as a Humanitarian Use Device.

The Melody valve is composed of a bovine jugular venous valve and a balloon-expandable stent. The valved stent is crimped on a balloon-in-balloon front-loading delivery system (Ensemble, Medtronic). For implantation, the inner balloon is inflated first, followed by inflation of the outer balloon. The utility of a balloon-in-balloon system increases stability of the stent on the balloon during the implantation. The device is available only in one size, while the delivery system comes in three sizes.[176] Larger long-term studies are needed to verify the promising short-term results.[177]

Patient Selection

The transcatheter pulmonary valve is implanted in patients suffering from long-term illness and multiple reoperations. Moreover, the RV pressure should be 65% to 75% of the systemic pressure as an indication for the intervention. Although there is an absence of clear-cut guidelines, these patients must have severe pulmonary regurgitation as assessed by echocardiography or MRI in addition to severe RV dilatation, RV dysfunction, severe symptoms, arrhythmias, or impaired exercise capacity with a peak oxygen uptake of less than 65% of predicted.[178]

Access Route

As in TAVR, the interventionist must consider the anatomic variations when choosing the access route. For sizing of the RVOT and pulmonary valve and artery, the same imaging techniques as in TAVR are used, except for TEE. Because of the limited size of the Melody valve, it is indicated only for patients older than 5 years who weigh more than 20 kg. The conduit RVOT diameter must be smaller than 16 mm, otherwise it cannot be dilated, and must be at least 22 mm, otherwise it is not likely to hold the valve in the landing zone.[179]

The femoral vein is the most common access site for these procedures. The transjugular route has was also been used in smaller patients (<30 kg) with interrupted inferior vena cava.[180] The possibility of additional complications such as injury to the thoracic duct, vagus nerve, carotid artery, and pneumothorax should not be ignored when pursuing this route.

Complications

Major intraprocedural complications have included dislodgement of the device, rupture of a homograft, compression of the main stem of the left coronary artery, obstruction of the origin of the right pulmonary artery (PA), and perforation of the left PA causing severe bleeding. Other complications have included limited perforation of a distal PA resulting in minor bronchial bleeding, partial homograft rupture, and entrapment of the delivery system in the tendinous cords of the tricuspid valve in two patients.[176] Stent fracture is more likely in patients with severely obstructed RVOT conduits[181] and is the most common complication during follow-up, occurring in 20% of cases, most of them having no symptoms. Symptomatic patients may undergo a reintervention by implantation of a second device (valve in valve).[176] If significant pulmonary regurgitation is discovered during the follow-up period, the possibility of endocarditis must be excluded.

During RVOT intervention, coronary compression must be ruled out by coronary angiography at the beginning of the procedure. Using biplane projections, the relationship between the coronaries and the PA can be judged. In unclear situations, a dynamic coronary artery compression test can be performed by simultaneous RVOT balloon angioplasty of the potential implantation site and coronary angiography. This test has been positive in 5% of the patients.[182]

This procedure is preferably done in a hybrid OR with an MDT for optimal complication management.

Anesthetic Management

Patients who undergo TPVR are usually young with chronic illness and a history of multiple reoperations. GA is the method of choice due to the possible length of the procedure. Insertion of arterial and central venous catheters is usually done following induction of anesthesia. It is important to monitor the patient's temperature during the procedure, because of the risk of hypothermia, and active warming is usually required. Rapid pacing is not required because of the low-pressure nature of the right ventricle. Following heparin, the activated

coagulation time at valve implant is targeted at 250 to 300 seconds. TEE evaluation of the pulmonary valve is technically difficult and usually not needed during the procedure. Real-time 3D TEE may be helpful and additive to fluoroscopy but is rarely used.[183]

MISCELLANEOUS PROCEDURES

The uses of hybrid ORs are rapidly expanding due to the wide variety of potential procedures that need both the hybrid OR layout and the heart team concept. Examples include the following procedures.

Hybrid Coronary Artery Revascularization

In addition to transcatheter valve replacement, coronary revascularization may take place in a hybrid OR. Surgical off-pump coronary artery bypass (OPCAB) can be done at the same time as PCI in patients with multivessel disease. This technique may be used in patients with a porcelain aorta, which prohibits proximal anastomoses and aortic clamping. The left internal mammary artery (LIMA) to left anterior descending artery (LAD) graft is performed as OPCAB surgery, in addition to PCIs for the rest of the diseased coronary vessels. The LIMA-LAD graft also may be done with a minimally invasive technique (MIDCAB), especially for patients with a previous sternotomy. These coronary surgical procedures can be combined with PCIs and/or transcatheter valve repairs or replacements.

Hybrid Arrhythmia Procedures

Catheter ablation around the pulmonary vein confluences with the left atrium is used to treat paroxysmal atrial fibrillation. Many techniques can be used ranging from catheter-guided ablation, minimally invasive procedures using video-assisted thoracotomy, or minimally invasive surgical thoracotomy. Combining the transvenous endocardial and the thoracoscopic epicardial approaches may be more effective. Intraoperative mapping allows additional endocardial touch-up when incomplete ablation is detected. The availability of the heart team with on-site CPB is necessary to manage some patients and to treat complications that may arise. Most of these cases are performed under GA with one-lung ventilation using a double lumen tube that gives the anesthesiologist the possibility of ventilating and deflating either lung during the procedure.[4] If mapping is to be done, GA is usually maintained using total intravenous anesthesia to avoid the possible effects of volatile anesthetics on the conduction system.[184]

Implantable Pacemaker and Defibrillator Implantations and Lead Extractions

In general, pacemaker implantation is done under LA with or without sedation. Complications such as pneumothorax, severe arrhythmias, atrial or ventricular perforation, and lesions of the tricuspid valve are rare, but serious, and may need immediate intervention. Therefore, a chest radiograph is mandatory after the procedure. If the patient has a complete heart block, a temporary external pacer is applied and used until permanent pacemaker is implanted.

The same LA/MAC technique can be used during the insertion of an implantable cardioverter-defibrillator (ICD), but with some added considerations (see Chapters 4 and 5). These patients usually have worse general conditions and lower ejection fractions, especially patients undergoing cardiac resynchronization therapy. After implantation, the defibrillating function of the ICD must be tested by inducing ventricular fibrillation, which is to be detected and terminated by the ICD. An arterial catheter should be inserted and external defibrillation pads placed before beginning the procedure. Heparin 5000 IU is usually administered before inducing ventricular fibrillation. During ICD testing, brief GA is needed using propofol or etomidate with oxygen delivered by mask or laryngeal mask airway. Other techniques using GA with endotracheal intubation also have been well tolerated by patients.[185] For procedural analgesia and sedation, propofol and short-acting opioids such as remifentanil have been used.

The number of patients subjected to lead extraction is increasing as a result of increased numbers of implantations. Lead extraction is a difficult procedure and is prone to severe complications due to the adherence of the leads to the myocardium. Ventricular perforation or severe tricuspid regurgitation may occur. Therefore, these patients receive GA with invasive blood pressure monitoring, large-bore intravenous cannula, and intraoperative TEE with the full heart team available if open surgery and CPB are urgently needed.[186]

Endovascular Procedures

Endovascular aortic repairs, either with thoracic (TEVAR), abdominal, or thoracoabdominal extents are also performed in a hybrid OR. Indications include aneurysms, acute and chronic aortic dissection, traumatic disruption, and penetrating ulcers. Hybrid debranching procedures may be done before the endograft implantation, as an open vascular bypass, to create a landing zone for implantation and prevent major vessel obstruction. Again, the presence of the complete heart team with anesthesiologists and perfusionists is mandatory.[4] TEVAR carries the risk of spinal cord ischemia and consequently permanent neurologic deficits. This can be diminished by early detection (using somatosensory or motor-evoked potentials and treatment by blood pressure augmentation (MBP >70 mm Hg) and cerebral spinal fluid drainage (intracranial pressure ≤10 mm Hg) using a subarachnoid catheter inserted at the beginning of the procedure[187] (see Chapters 18 and 23). Deliberate hypotension is usually required during the procedure. Rapid ventricular pacing is the gold standard because of its efficacy, predictability, consistency, rapid reversibility, and potential to assist in hemodynamic recovery after endovascular device deployment. Nitrovasodilators, adenosine, and balloon vena cava occlusion can also be used.[188]

Anesthetic Management

Although many procedures are often performed with MAC/LA, GA is needed during longer and more complex procedures. For success, anesthesiologists need to be familiar with the procedures and their specific complications. Close communication with the interventionist and the other members of the heart team is needed to increase the safety of the procedures. These patients usually suffer from multiple comorbidities, which must be identified and optimized during the preoperative assessment. During the operation, standard monitoring must be established with active warming methods. Invasive monitoring is required because unexpected or sudden changes in hemodynamics are likely to occur. Many interventions are performed under MAC/LA, but all general anesthetic drugs and equipment must be readily available.

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Mechanical Assist Devices for Heart Failure

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KEY POINTS

1. Mechanical circulatory support (MCS) for the failing heart has become a mainstay of the modern management of patients with both acute and chronic heart failure refractory to pharmacologic and other usual interventions.
2. Outcomes with MCS have improved so dramatically that the main focus of this arena has now shifted away from simple survival and toward mitigation of risk and minimization of adverse events.
3. Data taken from experience gained with the first generation of pulsatile devices may no longer be applicable in the current era of nonpulsatile support, but the valuable lessons learned continue to help shape management and clinical decision making.
4. In addition to the traditional indications for MCS (eg, short-term bridge to recovery and long-term bridge to transplantation), MCS is currently employed for a variety of both short- and long-term modern indications, including acute rescue of patients from acute low cardiac output situations (bridge to immediate survival), prevention of further myocardial damage following an ischemic event, prevention of deterioration in multisystem organ function, as a temporizing measure to buy time for recovery, as a bridge to the next step of management (bridge to next decision), as a bridge to improved candidacy (for transplantation), and, increasingly, as a final management strategy for end-stage heart failure (destination therapy).
5. Patient status at the time of implementation of rescue MCS is a key factor determining outcome. Deterioration from delayed implementation is associated with worse outcome.
6. The timing of implantation of a durable left ventricular assist device (LVAD) (eg, as a bridge to transplantation and/or as destination therapy) and perioperative optimization of the patient's nutritional status are key factors determining outcome.
7. Nonpulsatile support devices have supplanted the first generation of pulsatile ventricular assist devices worldwide, and outcomes have improved dramatically with the technology now available.
8. Extracorporeal membrane oxygenation is being incorporated more and more often into modern extracorporeal life support algorithms.
9. The implantable total artificial heart has undergone a resurgence of interest as a bridge to transplantation for patients with biventricular failure and in other scenarios where an LVAD alone would not be ideal.
10. A number of new MCS devices are in various stages of development and clinical trials.

The Current Era of Mechanical Circulatory Support

Mechanical circulatory support (MCS) for the failing heart has become a mainstay of current management of patients with both acute and chronic heart failure refractory to pharmacologic and other usual interventions. In fact, the successes realized to date have been so significant that the main focus of this arena has now shifted away from simple survival and toward mitigation of risk and minimization of adverse events. Undeniably, continued advances in device technology have made this possible, but when coupled with analyses of the enlarging patient management experience, we now have better understandings regarding optimal patient selection and timing of intervention,[1] the expectation of significant improvement in multiorgan function during ventricular assist device (VAD) support,[2–5] and the ways in which preexisting and demographic risk factors may result in complications.[6–9]

Although some of the data taken from the experience with the first generation of pulsatile devices may no longer be applicable in the modern era of nonpulsatile support, the valuable lessons learned help shape management and clinical decision making. All of these factors have now resulted in more widespread acceptance of VADs by physicians and patients as a management strategy, as well as an earlier use of VADs in the course of a patient's cardiac deterioration. As such, in addition to the traditional indications for MCS (eg, short-term bridge to recovery and long-term bridge to transplantation), MCS is currently employed for a variety of both short- and long-term indications, including rescue of patients from acute low cardiac output situations (bridge to immediate survival), prevention of further myocardial damage following an ischemic event, prevention of deterioration in multisystem organ function, as a temporizing measure to buy time for recovery, as a bridge to the next step of management, as a bridge to improved candidacy (for transplantation) and, increasingly, as a final management strategy for end-stage heart failure (destination therapy).

Equally important to the advances in MCS technology has been the formal sharing of outcomes data from centers nationwide through the Interagency Registry for Mechanically Assisted Circulatory Support

(INTERMACS), a North American registry database sponsored by the National Heart, Lung, and Blood Institute; the U.S. Food and Drug Administration (FDA); and the Centers for Medicare and Medicaid Services. INTERMACS was established in 2005 for adult patients receiving long-term MCS device therapy to treat advanced heart failure. A similar European-based database called EuroMACS exists in Europe. Additional databases collect pediatric MCS data (PEDIMACS) and data about adult heart failure patients with higher (less sick) INTERMACS levels (discussed later) still being medically managed (MEDAMACS).

INTERMACS collects clinical data about patients implanted with durable MCS devices at 1 week, 1 month, 3 months, 6 months, and every 6 months thereafter. Major outcomes after implant (eg, death, explant, rehospitalization, and adverse events) are updated frequently and also as part of the defined follow-up intervals. Additional end points include patients' level of function and quality of life, and the reported improvements in both of these areas have been compelling. These data have proven invaluable to appropriate risk stratification and patient selection, and as new devices are introduced, documentation of functional outcomes beyond simple survival assist in differentiating the value of MCS devices.

The sixth INTERMACS annual report, released in 2014, summarizes the enrollment and outcomes of more than 12,300 patients implanted with left ventricular assist devices (LVADs) between 2006 and 2013.[1] This latest INTERMACS report reveals the dynamic and expanding landscape of modern MCS:

- Patient accrual now exceeds 2000 VAD implants per year in the United States alone, and the number of implanting centers in the United States has grown to 158.
- At 1 year, overall survival with a durable MCS device now approaches 80%. This is a marked improvement over the 52% 1-year survival rate demonstrated with the pulsatile HeartMate VE in the REMATCH trial reported in 2001[10] and is a major advance when compared to the medically managed patients in that trial that demonstrated only a 25% 1-year survival rate.
- Overall survival rate at 2 years with a durable MCS device now approaches 70%, 3-year survival rate now approaches 60%, and 4-year survival rate now approaches 50%. Survival rate after destination therapy is now higher than 75% at 1 year and higher than 50% at 3 years.

Survival has improved dramatically in recent years, but this has been also been influenced by the earlier implantation in the course of a patient's cardiac deterioration. Classification in this regard is denoted by INTERMACS level, a scale of clinical condition ranging from 1 to 7. An INTERMACS 7 patient is simply in the advanced stages of heart failure, with the clinical condition of the patient worsening as the INTERMACS profile number gets lower. An INTERMACS 4 has symptoms at rest, an INTERMACS 3 is hemodynamically stable but inotrope-dependent, an INTERMACS 2 is clinically deteriorating with signs of end organ dysfunction despite the use of inotropes, and an INTERMACS 1 is in cardiogenic shock.

Based on the collective outcome data in the INTERMACS registry, guidelines for device implantation have developed. For early elective implantation of a durable LVAD, at numerically higher INTERMACS levels (5–7), the risks of adverse events may outweigh the benefits. Conversely, waiting until the patient is at too low an INTERMACS level (1 or 2) with multisystem organ failure is associated a low probability of ultimate rescue and poor survival. Consequently, at least in the United States, elective LVAD patients are being implanted with durable LVADs when at an INTERMACS level 3 (and in some cases 4), because this seems to be the best timing to balance the risks and benefits and to achieve the best outcomes.

Until 2009, MCS was used most often as a bridge to transplantation. Since 2010, use of destination therapy has grown exponentially, once the HeartMate II received approval as a destination therapy device. INTERMACS data show that destination therapy is now the most common utilization of MCS in the United States, accounting for 41.6% of all LVAD implants in the time period 2011–2013 (compared with 14.7% in 2006–2007). Bridge to candidacy (for transplantation) is now the second most common indication for VADs. The percentage of patients listed for transplantation at the time of VAD implantation has decreased to 21.7% in 2011–2013, compared to 42.4% in 2006–2007. Bridge to recovery and bridge to next decision with short-term VADs and/or extracorporeal membrane oxygenation (ECMO) currently constitutes only a very small percentage of the usage of this technology, compared with the long-term indications.

Mechanical Circulatory Support: Theory and Practice

Cardiogenic shock may be defined as the inability of the heart to deliver sufficient blood flow to meet the metabolic requirements of the body, despite the presence of adequate intravascular volume. Generally, cardiogenic shock entails sustained hypotension (SBP <90 mm Hg or 30 mm Hg below baseline), low cardiac output with high central filling pressures (eg, cardiac index <2.2 L/min/m^2 with pulmonary capillary wedge pressure >12 mm Hg) and signs of diminished tissue perfusion.

What distinguishes cardiogenic shock from the other forms of shock is the mechanical impairment of pump function. Once a patient develops mechanical pump failure and the intracardiac volumes and pressures begin to rise, the vicious cycles (Fig. 28.1) can result in an imbalance of myocardial oxygen supply and demand, worsening ischemia and resulting in further decreases in ventricular function. Cardiogenic shock may ultimately result if the cycle is not broken.

Manipulations and optimization of preload, afterload, heart rate, and contractility are generally the first-line treatment for acute heart failure. Facilitating recovery requires maintaining adequate myocardial oxygen supply, with the lowest feasible myocardial oxygen demand.

Pharmacologic therapies can potentially improve hemodynamics and stabilize the patient with mild or perhaps moderate cardiac failure. In severe failure, however, pharmacologic management with inotropes and vasopressors comes at the cost of increased myocardial oxygen demand and decreased perfusion to the peripheral and splanchnic circulations during attempts to attain acceptable central hemodynamics. For the myocardium, β-adrenergic stimulation may improve contractility of areas that are well perfused, but it will greatly increase myocardial oxygen demand, feeding into and fueling the vicious cycle.

Vasoconstriction may improve coronary and systemic perfusion pressures, but depending on which vasoconstrictor is used, α-adrenergic stimulation will increase both systemic and pulmonary vascular resistances, making it harder for failing ventricles to eject. This is especially problematic when there is right ventricular (RV) failure, because this will increase the workload of the already struggling right ventricle. Furthermore, intentional vasoconstriction often leaves the peripheral and splanchnic beds underperfused.

Afterload reduction with vasodilators is a common strategy to assist the failing heart because the physiologic principle of ventriculoarterial coupling holds that regardless of the poor intrinsic systolic mechanics of the failing ventricle, its overall function as a pump can be improved by decreasing the afterload against which it must pump. However, decreased afterload in the setting of developing cardiogenic shock results in hypotension and poor tissue perfusion that predisposes the patient to multisystem organ failure and a poor outcome.

This is where mechanical circulatory assistance can play an important role, effectively breaking the cycle and improving the balance between myocardial supply and demand as well as systemic perfusion. By decompressing the failing ventricle, the increased wall tension that is adversely affecting the supply-to-demand ratio is addressed, which potentially sets the stage for myocardial recovery. Concurrently, effective perfusion is resumed to the heart and the rest of the body, which can stave off multisystem organ failure.

Thus, by using a mechanical device to take over the pumping function of the failing ventricle, the ravages of cardiogenic shock can often be addressed with the one intervention, albeit an extremely invasive one, with potential advantages and disadvantages. Thus, the

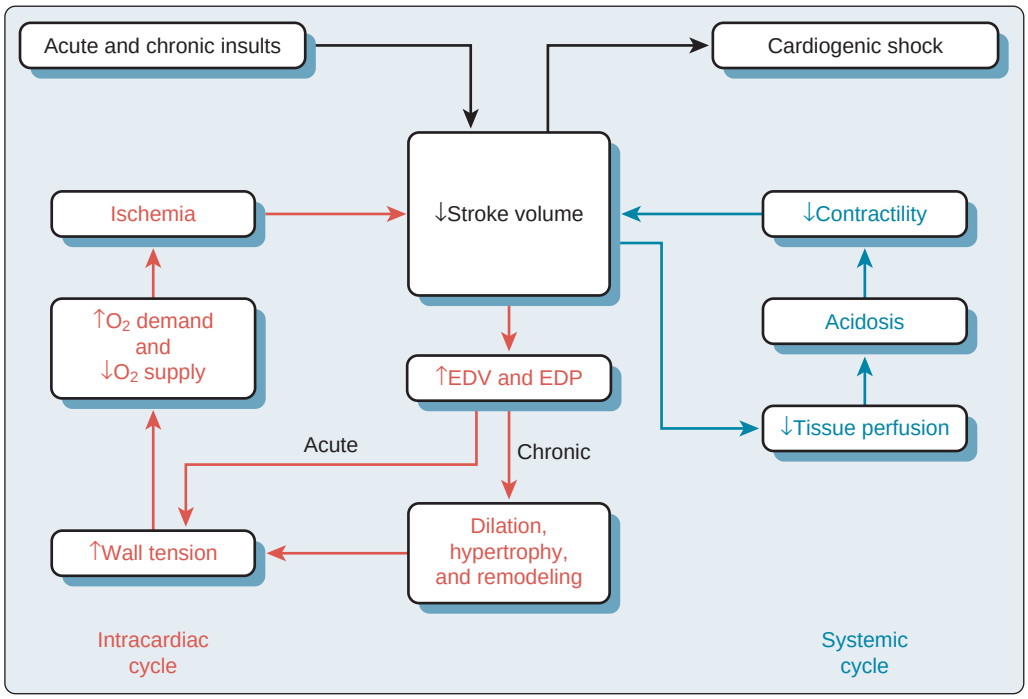


Fig. 28.1 Vicious cycles leading to cardiogenic shock. *EDP,* End-diastolic pressure; *EDV,* end-diastolic volume.

implementation of mechanical assistance is often approached in a stepwise fashion.

The Role of the Intraaortic Balloon Pump

The first step that specifically targets the problem is implementation of intraaortic balloon pump (IABP) counterpulsation. Despite the fact that it was introduced in 1968, the IABP still remains a very commonly used VAD (especially in the United States) because counterpulsation with a properly timed IABP simultaneously increases myocardial oxygen supply and decreases oxygen demand, and is often an effective treatment for left ventricular failure.

Fig. 28.2 demonstrates a deployed IABP. The device has been inserted percutaneously into the femoral artery and then advanced retrograde up the aorta to its correct position that is just distal to the left subclavian artery. Balloon inflation during diastole occludes the aorta and displaces arterial blood, abruptly increasing the aortic root pressure. This increases coronary perfusion pressure, which increases myocardial oxygen supply (assuming the patient has an adequate level of saturated hemoglobin). Abrupt deflation, just before the next systolic ejection decreases the pressure in the aorta in a sudden fashion, facilitating forward ejection from the heart by decreasing impedance to opening of the aortic valve. This results in increased stroke volume and decreased myocardial work and therefore less oxygen demand on the struggling left ventricle. It has been reported that a properly timed, optimally functioning balloon pump can increase cardiac output by 20% or perhaps 30%[11,12] and decrease afterload by as much as 15%. Of the two, it is generally believed that it is the decrease in oxygen demand that most benefits the failing ventricle supported by this device. In the setting of acute myocardial stunning (eg, as a result of an acute myocardial infarction [AMI]), such a decrease in oxygen demand can help to set the stage for myocardial recovery. In the setting of an acute deterioration of a chronically failing ventricle, the IABP may be used to stabilize hemodynamics as a bridge to intervention. Additional reported benefits of IABP counterpulsation include reduction in systemic acidosis and improvements in cerebral and renal microcirculatory perfusion. However, although a balloon pump is well known to improve cardiac function and overall hemodynamics, as mentioned earlier, it augments forward cardiac output by only 25% to 30% at maximum, and it will not augment anything if there is a complete absence of left ventricular output. As a sole intervention, the IABP cannot be expected to rescue a patient from catastrophic myocardial failure.

Appropriate timing of balloon inflation and deflation is key to realizing the hemodynamic benefits of the device. The usual trigger for balloon inflation is the R wave of the patient's ECG; however, an arterial pressure tracing and pacing spikes can also be used. Regardless of the trigger used, as illustrated in Fig. 28.3, inflation should always coincide with the dicrotic notch of the arterial tracing and should continue throughout diastole. Deflation should always occur just at end-diastole, immediately before the next systolic ejection. Inflation and deflation at any other point in the cardiac cycle must be manually corrected by adjustments in balloon timing. Fig. 28.4 shows and discusses potential timing errors. Helium is used as the inflation gas in the IABP because of its low viscosity and inert nature. Depending on the level of assistance required, the balloon can be triggered with each cardiac cycle (so-called 1:1 assistance), every other cycle (1:2), every third cycle (1:3), and so forth. Ratios of 1:2 or 1:3 are ideal for optimizing the timing of inflation and deflation.

Contraindications to the use of the IABP include clinically significant aortic insufficiency, aortic aneurysms, and significant friable atherosclerotic plaques in the aorta. However, the widespread availability of echocardiography to assess patients with cardiac problems, as well as the nearly routine use of transesophageal echocardiography (TEE) during IABP placement in the operative setting, can detect significant atherosclerotic disease in the arch and descending aorta and may help identify patients at high risk. While an ascending aortic dissection still contraindicates IABP use, a descending aortic dissection may no longer constitute an absolute contraindication to IABP use, because, in this era of echocardiography, TEE can be used to ensure the device comes to rest in the true lumen of the aorta.

Indications for the IABP have not changed, but routine IABP usage has recently become somewhat controversial, especially in Europe. It is estimated that 5% to 10% of patients will develop cardiogenic shock following an AMI, and early survival rates for these patients have always been reportedly on the order of 5% to 21%.[13] However, 75% of such patients who were unresponsive to pharmacologic interventions were

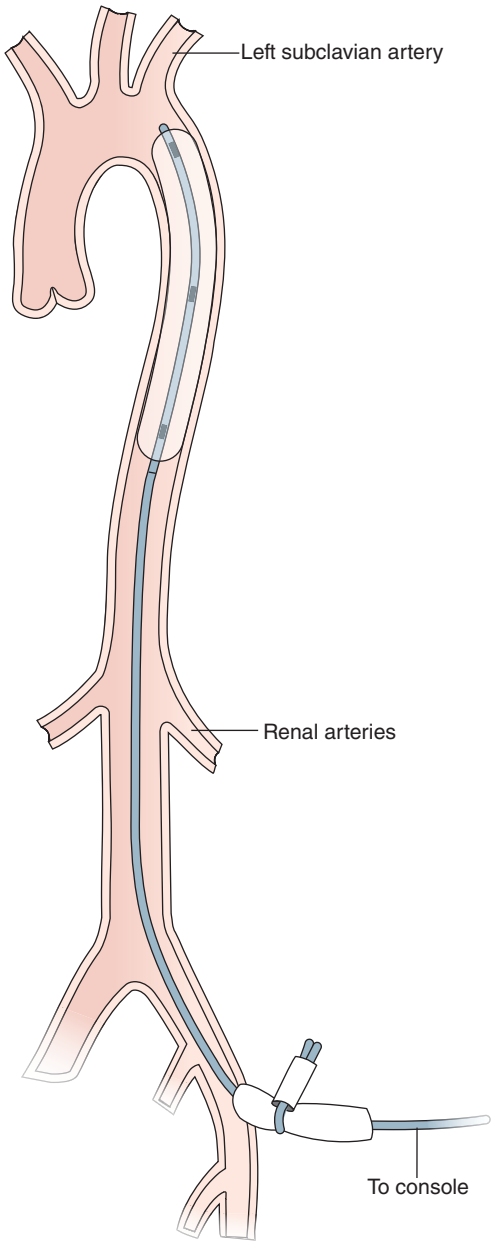


Fig. 28.2 The intraaortic balloon pump.

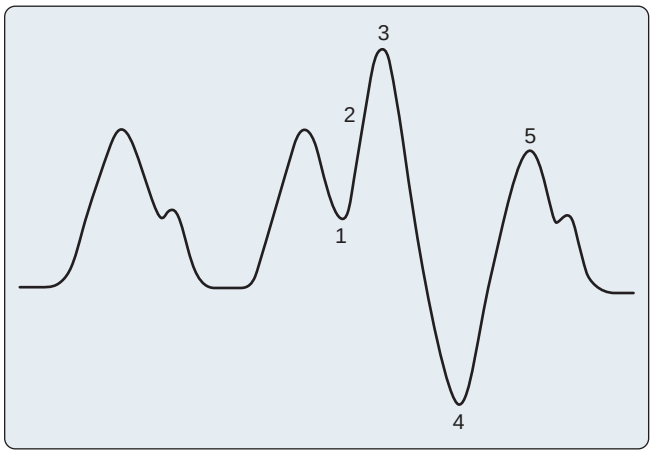


Fig. 28.3 A well-timed intraaortic balloon pump (IABP) inflation. The figure demonstrates an arterial pressure tracing taken from a patient with an IABP. The first pulse seen on the left is the familiar waveform of an arterial pulse. An IABP is triggered to inflate during the second pulse, generating a typical sinusoidal balloon inflation-deflation waveform. The third pulse represents an assisted ejection due to the action of the IABP. Characteristics of the typical balloon waveform include the following: *1,* The balloon inflation point coinciding with the location of the patient's dicrotic notch (representing aortic valve closure at the end of systole). *2,* A steep slope of increasing pressure indicating rapid balloon inflation. This creates a rapid rise in aortic root pressure to reach. *3,* The assisted diastolic peak pressure perfusing the coronary arteries while the IABP is inflated. This increased in coronary perfusion pressure creates the increased myocardial oxygen supply associated with IABP action. *4,* A steep slope of pressure decline indicates a rapid balloon deflation, resulting in a decrease in end-diastolic aortic root pressure. This localized decreased afterload decreases impedance to opening of the aortic valve at the beginning of systole, and creates the decreased myocardial oxygen demand associated with IABP action. *5,* The assisted systolic peak pressure of the next beat perfusing the body. The systolic pressure attained by this ejection was accomplished with less myocardial work thanks to the IABP. Depending on the level of assistance required, the balloon can be triggered with each cardiac cycle (so-called 1 : 1 assistance), every other cycle (1 : 2), every third cycle (1 : 3), and so forth.

well known to exhibit hemodynamic improvement with IABP therapy alone,[14] and early survival rates in these patients were reported to approach 93% when treated with IABP counterpulsation.[15] Although decades of nonrandomized studies and clinical observational trials reported such benefit of IABP use, until recently, limited data were available from randomized trials regarding the outcomes of patients with AMI cardiogenic shock in whom IABP counterpulsation was employed.

In the era of thrombolysis as a primary management of AMI, the IABP enjoyed a class I recommendation in international guidelines, but in current international guidelines (Box 28.1), in the era of percutaneous coronary interventions (PCIs), the recommendation for routine IABP use in the setting of AMI cardiogenic shock has now been downgraded from class I to class IIa in the 2013 American Heart Association (AHA) guidelines and to a class IIb recommendation in European guidelines, on the basis of registry data and a small number of retrospective meta-analyses and randomized trials that failed to demonstrate a mortality benefit from use of the device.[16–19] However, a number of serious concerns and criticisms (eg, regarding patient selection and timing of intervention) have been raised about the methodologies and protocols used in these trials (and thus in trials analyzed in the meta-analyses), and their negative conclusions have been questioned at the international level because several modern-era trials and analyses have demonstrated outcome benefits from IABP use in the AMI cardiogenic shock population.[20–23]

A summary of available published data at the time of this writing regarding the routine use of the IABP to treat patients with AMI cardiogenic shock is as follows:

1. There are no strong data to support the routine use of the IABP in the management of AMI with or without cardiogenic shock, certainly when the device is deployed after PCI.
2. Conversely, no strong data support the avoidance of the use of an IABP in a timely manner in appropriately selected patients who might benefit from the hemodynamic optimization it can provide. Overall, minimal harm has been demonstrated from its use, specifically regarding the incidence of stroke, bleeding, peripheral ischemic complications, and sepsis.[19]
3. There are data suggesting that the routine inclusion of an IABP before high-risk PCI decreases the number of procedural complications[22] and the need for rescue.[24]
4. There are data suggesting that long-term mortality is improved by timely inclusion of an IABP when placed before PCI to ameliorate myocardial ischemia, decompress the ischemic LV, and assist forward flow.[20,22]

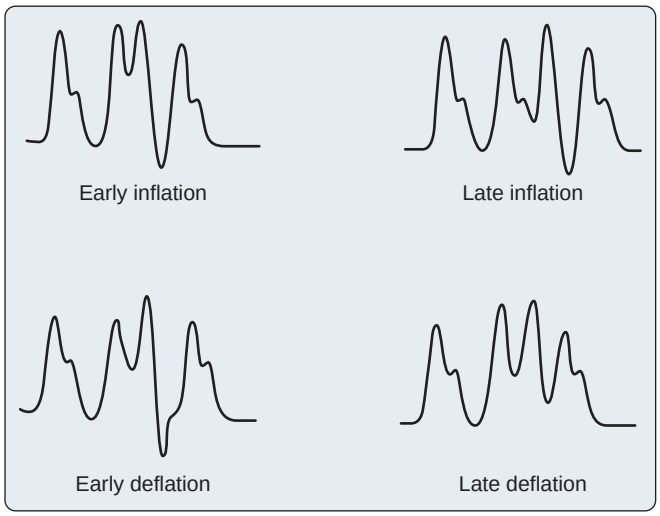


Fig. 28.4 Intraaortic balloon pump (IABP) timing errors. *Early inflation,* before the dicrotic notch (ie, before systolic ejection is completed) immediately forces the aortic valve closed, resulting in prematurely terminated systolic ejection. This results in decreased stroke volume for that cardiac cycle and increased preload for the next cardiac cycle. Not only does this reduce an already impaired cardiac output, but acutely increased end-diastolic volumes stress the failing ventricle by increasing wall tension, which can increase myocardial oxygen demand, impair perfusion, and lead to ischemia. Thus early inflation must be corrected because it increases myocardial oxygen demand and decreases myocardial oxygen supply. *Late inflation,* after the dicrotic notch, fails to augment coronary perfusion pressure optimally. Thus myocardial oxygen supply is not maximally enhanced. *Early deflation* allows time for aortic root pressure to return to baseline before systolic ejection and therefore fails to decrease impedance to opening the aortic valve. Thus myocardial oxygen demand is not decreased. Recall that it is the decrease in myocardial oxygen demand that most benefits the failing ventricle and allows for increased stroke volume with less myocardial work. *Late deflation* can be identified by a failure of the pressure to fall back to baseline or, ideally, below baseline, before the next systolic ejection. Late deflation impedes systolic ejection like an aortic cross clamp. The ventricle is forced to develop such a high pressure to open the aortic valve that ventricular wall tension is significantly increased, which increases myocardial oxygen demand, impairs perfusion, and can lead to ischemia.

Clearly, the IABP remains useful for stabilizing and improving the hemodynamics of selected patients with low cardiac output. It cannot, however, substantially augment forward cardiac output in patients with severe LV failure. This is where more formal MCS comes into play. Despite the absence of strong data and only a class IIb recommendation in current American College of Cardiology (ACC)/AHA guidelines regarding MCS for acute situations (see Box 28.1), the immediate survival of acute cardiogenic shock of any origin will be minimal if nothing is done and disappointingly low (<20%) if medical management alone is instituted.

Implementation of Mechanical Circulatory Support

When the patient with a failing ventricle has failed to improve substantially following all the usual attempts to optimize and maximize, including an IABP, signs that the patient likely needs formal MCS include the following:

- Hypotension (mean arterial pressure [MAP] <60 mm Hg or systolic blood pressure [SBP] <90 mm Hg)
- Cardiac index <2 LPM/m^2
- Pulmonary capillary wedge pressure (PCWP) or right atrial pressure (RAP) >20 mm Hg
- Systemic vascular resistance (SVR) >2000 dyne-sec/cm^5
- Oliguria, low mixed venous oxygen saturation, and rising lactate.

BOX 28.1 2013 ACCF/AHA STEMI GUIDELINES FOR THE USE OF IABP AND VADS

Class I

1. Emergency revascularization with either PCI or CABG is recommended in suitable patients with cardiogenic shock due to pump failure after STEMI irrespective of the time delay from MI onset. (Level of evidence: B)
2. In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI and cardiogenic shock who are unsuitable candidates for either PCI or CABG. (Level of evidence: B)

Class IIa

1. The use of IABP counterpulsation can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacologic therapy. (Level of evidence: B)

Class IIb

1. Alternative LVADs for circulatory support may be considered in patients with refractory cardiogenic shock. (Level of evidence: C)

ACCF, American College of Cardiology Foundation; *AHA,* American Heart Association; *CABG,* coronary artery bypass graft; *IABP,* intraaortic balloon pump; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *STEMI,* ST-segment elevation myocardial infarction; *VAD,* ventricular assist device.

From O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv.* 2013;82(1):E1–E27.

It cannot be overemphasized that fixing numbers will not inevitably improve outcome. Even if somewhat acceptable central hemodynamics can be created pharmacologically, it is very important to consider evidence of poor organ and peripheral perfusion, such as oliguria, low mixed venous oxygen saturation, and rising serum lactate as indications of the need to support the circulation in a more formal way.

Moreover, it is critically important that the failure of the usual maneuvers to adequately stabilize the patient be promptly recognized, because experience of the past few decades has shown that the timing of implementation of MCS is the most important factor in patient outcome.[25]

One cannot wait to initiate support until there is profound cardiogenic shock with deterioration in major organ function. Some recovery may be possible with restoration of adequate perfusion, but it's very difficult to predict, and study after study has shown that patient status at the time of implantation is the primary determinant of outcome. *The longer one waits, the worse the outcome.*

To provide formal MCS, the heart and great vessels must be cannulated and connected to a pump. Fig. 28.5 shows the classic cannulation strategies in the heart and great vessels that, until recently, were the only options, regardless of which manufacturer's device was selected to provide the support. Novel potential cannulation strategies of specific devices are discussed later in the chapter.

While diversion of blood to the pump provides the stroke volume that is ejected, it also facilitates decompression of the failing ventricle, which is critical, because decreased ventricular wall tension dramatically reduces myocardial oxygen demand, interrupting the cycle of worsening ventricular failure. It should also be noted that currently available VADs do not provide any oxygenation or removal of waste from the blood but simply act as pumps that can promote perfusion of the arterial circulation downstream from the failing ventricle. It is possible with some devices, however, to introduce an in-line membrane oxygenator and extracorporeal carbon dioxide (CO_2) removal system for patients with concomitant respiratory failure.

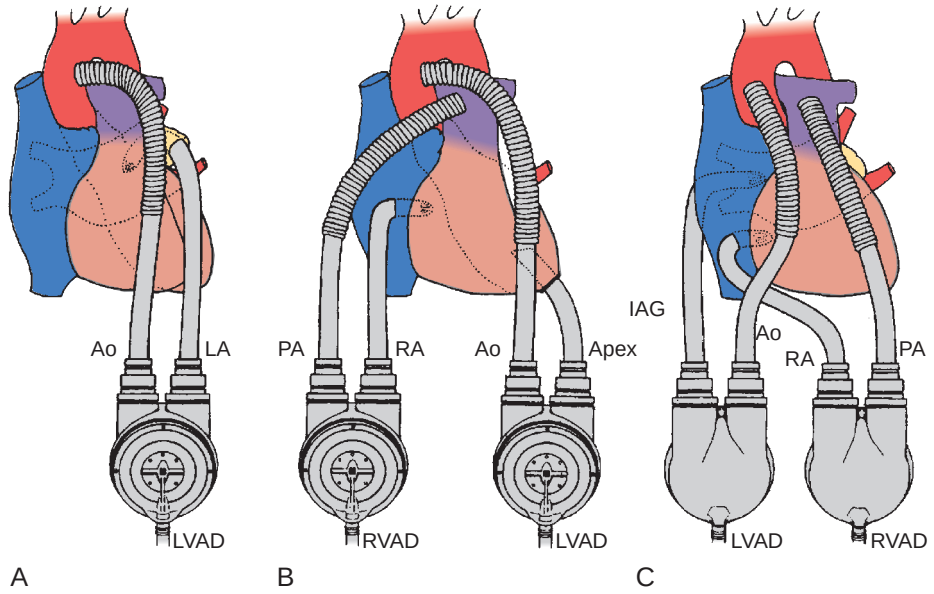


Fig. 28.5 (A–C) Classic cannulation strategies for mechanical circulatory support. *Ao,* Aorta; *IAG,* interatrial groove; *LA,* left atrium; *LVAD,* left ventricular assist device; *PA,* pulmonary artery; *RA,* right atrium; *RVAD,* right ventricular assist device.

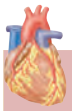
Once the decision to provide MCS has been made, an appropriate device is selected. A number of different devices may be available, and the device selected for a given patient depends primarily on the following factors:

1. The anticipated duration of support required (different devices have different intended durations of use rooted in their engineering, and there are also considerations of FDA approval of the various devices)
2. Whether uni- or biventricular support is required (some devices are intended to support just the left ventricle, although some can be configured to support either, or both simultaneously)
3. The degree of pulmonary dysfunction such that ECMO is required
4. The urgency of the situation (some devices can be deployed rapidly, perhaps even at the bedside, whereas others require transfer to the operating room for sternotomy and cardiopulmonary bypass [CPB])
5. The availability of the device

Before MCS implantation is performed, numerous individual patient factors must be considered, because MCS is fraught with pitfalls, complications, and ethical considerations.

As patient management experience in the field has grown and the outcomes have improved with more advanced devices, there has been an interesting shift away from the question, who needs a VAD? to the more pertinent question, who probably should not receive one? The only absolute contraindications to even temporary VAD use are prognostic factors that would preclude survival even with the restoration of perfusion to the vital organs and peripheral tissues. Thus, the potential for recovery is the paramount consideration. On many occasions, however, the myocardial insult is at least initially the primary problem, and more relative contraindications to VAD support will need to be considered.

Box 28.2 lists a number of commonly encountered considerations and relative contraindications to VAD support that include a variety of anatomic issues and other patient factors that create management issues, make VAD placement or use difficult, make complications more likely, or make meaningful recovery unlikely. Although the advent of modern devices and management strategies has rendered some of these relative contraindications essentially moot, all must be considered and addressed.



BOX 28.2 CONDITIONS OR COMORBIDITIES THAT MAKE VENTRICULAR ASSIST DEVICE PLACEMENT OR USE DIFFICULT, MAKE THE PATIENT MORE LIKELY TO HAVE MAJOR COMPLICATIONS, OR MAKE MEANINGFUL RECOVERY UNLIKELY

Absolute Contraindication

- The patient will not survive regardless of the restoration of adequate systemic perfusion

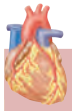
Relative Contraindications or Issues That Need to Be Addressed

- Patient is not a transplant candidate (unless destination therapy or bridging to improved candidacy is the intention and a durable LVAD is being implanted)
- In situ prosthetic valves
- Clinically significant aortic insufficiency
- Clinically significant tricuspid insufficiency
- Mitral or tricuspid stenosis
- Congenital heart disease
- Intracardiac shunts
- Previous cardiac surgery
- Poor nutritional status
- Extremes of body surface area
- Advanced systemic disease (severe COPD, malignancy, ESLD, ESRD, sepsis, progressive neurologic disorder, etc)

COPD, Chronic obstructive pulmonary disease; *ESLD,* end-stage liver disease; *ESRD,* end-stage renal disease; LVAD, left ventricular assist device.

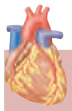
Short-Term Support

INTERMACS data reveal that short-term MCS support constitutes a relative minority of the usage of this technology, but the use of a VAD as a bridge to recovery remains critical to the survival of patients with acute, refractory, severe cardiac failure. However, the traditional conception of short-term use of a VAD only as a bridge to recovery has now been expanded to include concepts such a bridge to immediate



BOX 28.3 COMMON CLINICAL SCENARIOS IN WHICH SHORT-TERM MECHANICAL CIRCULATORY SUPPORT MAY BE INDICATED

- Stunned myocardium following open heart surgery
- Acute myocardial infarction
- Following a failed heart transplantation
- Cardiogenic shock due to acute myocarditis
- Stress-induced cardiomyopathy
- Following a cardiac catheterization lab misadventure
- In the setting of right ventricular failure in the patient already supported by left ventricular assist device



BOX 28.4 POTENTIAL OUTCOMES FROM URGENT IMPLEMENTATION OF SHORT-TERM MECHANICAL CIRCULATORY SUPPORT

- The patient is neurologically intact and multisystem organ function is acceptable; the heart recovers after a period of time and support is weaned to off.
- The patient demonstrates severe neurologic deficits and/or multisystem organ failure; support is withdrawn.
- The patient is neurologically intact and multisystem organ function is acceptable but the heart does not recover; the patient is bridged to either transplantation or destination with a durable mechanical circulatory support device.

survival, bridge to next decision, bridge to a bridge, and bridge to surgery (sometimes at another center). It is common for MCS to be implemented to allow for patient transport to a transplant center, often referred to as a *hub* from an outside hospital or *spoke*.

In general, short-term VAD use is intended for rescue from acute refractory ventricular failure, from which the myocardium is expected to recover.

Thus, as listed in Box 28.3, common scenarios in which temporary VAD insertion may be indicated include ventricular failure due to stunned myocardium following open heart surgery, AMI, following a failed heart transplantation, cardiogenic shock due to acute myocarditis, stress-induced cardiomyopathy, following a cardiac catheterization laboratory complication, and in the setting of RV failure in the patient already supported by an LVAD.

Possible Outcomes From Short-Term VAD Support

An understanding of the limited number potential outcomes from the short-term use of MCS (Box 28.4) helps guide decision making and illustrates some of the current indications for MCS.

1. MCS with a short-term VAD (or ECMO, discussed later) is implemented as a component of an acute rescue strategy; the patient does well on support (eg, the patient is neurologically intact and multisystem organ function is acceptable), and the heart recovers. In this scenario, MCS has been successfully used as a bridge to recovery. Depending on the specific cause of the acute cardiac failure, this could take anywhere from a few days to a few weeks. At that point, MCS flows can be weaned down and the cannulas explanted. It must be appreciated, however, that rates of successful weaning from short-term support were quite low as recently as the late 1990s (eg, 25–30% immediate survival). Over the past decade, however, experienced centers with well-defined protocols for patient selection and optimal timing of intervention have demonstrated survival rates exceeding 50% in the postcardiotomy cardiogenic shock population. Survival following AMI cardiogenic shock that requires VAD support remains in the range of 30%, depending on the device that was used and other critical factors, especially the status of the patient at the time of intervention. Again, the key factor seems to be the time frame in which intervention is implemented; postcardiotomy cardiogenic shock is generally managed immediately, while the management of AMI cardiogenic shock seemingly has a more variable time frame before intervention.
2. Short-term MCS is implemented, but the patient manifests severe neurologic damage and/or progresses to multisystem organ failure before the heart has a chance to recover. Progressive multisystem organ failure and severe neurologic damage are not uncommon in this population, regardless of the restoration of systemic perfusion by a device. In such cases, support is often withdrawn. This reality is one of the reasons why patient selection is so critical and also why it has become popular to use temporary ECMO to determine which patients will recover and likely survive before implanting a formal VAD, even for short-term use. In this case, the use of ECMO would be an example of bridge to next decision.
3. A short-term VAD is implemented as a bridge to recovery; the patient survives and is neurologically intact, but the heart never recovers. If the myocardium does not recover after a period of short-term support, then a decision must be made as to whether the patient is an acceptable transplant candidate. If so, the short-term VAD may be switched to a different device capable of providing long-term support as a bridge to transplantation. In this case, the short-term VAD has been used as a potential bridge to immediate survival and then as a bridge to a bridge. If not transplant-eligible, the patient must be evaluated for permanent implantation of an approved VAD as a permanent management strategy, also known as *destination therapy*. In some cases, the long-term durable LVAD implanted as a bridge to transplantation may be an approved device used in destination therapy. The current generation of durable LVADs has afforded new options for patients with myocardial failure.

Available Devices for Short-Term Support

Before 1992, when the Abiomed BVS 5000 became clinically available, standard centrifugal pumps were used to provide either uni- or biventricular short-term mechanical circulatory assistance. Currently, this type of very basic device would be used for pediatric applications (with small-caliber cannulas to limit flow) or for ECMO; clinicians are beginning to incorporate ECMO more frequently into resuscitative efforts as a bridge to next decision. Such a strategy has been termed *extracorporeal life support*, in which a patient with refractory cardiogenic shock with uncertain outcome is placed on ECMO for a few days. In this fashion, a less expensive centrifugal device is used to determine if there is reasonable likelihood of survival, before committing the patient to a more formal (and much more expensive) VAD. As experience grows, ECMO utilization is likely to increase in these circumstances, concurrent with the availability of more advanced devices that are replacing standard centrifugal pump head technology.

CentriMag

The CentriMag (Thoratec Corporation, Pleasanton, Calif; Fig. 28.6) is a small centrifugal pump with a magnetically levitated impeller that is now being used widely in the United States, in Europe, and in other parts of the world to provide short-term support for almost any modern indication. As with other short-term devices, the pump head itself remains paracorporeal during support, connected to cannulas in the heart and great vessels, so it can be used for left-sided, right-sided, or biventricular support.

Earlier short-term support devices were usually pulsatile and made of polyurethane and other suboptimal materials; they included artificial valves and had a high rate of thrombosis. In contrast, the CentriMag produces nonpulsatile continuous flow, and its design has demonstrable advantages. The impeller of the CentriMag is magnetically levitated and hydrodynamically suspended in the patient's blood;

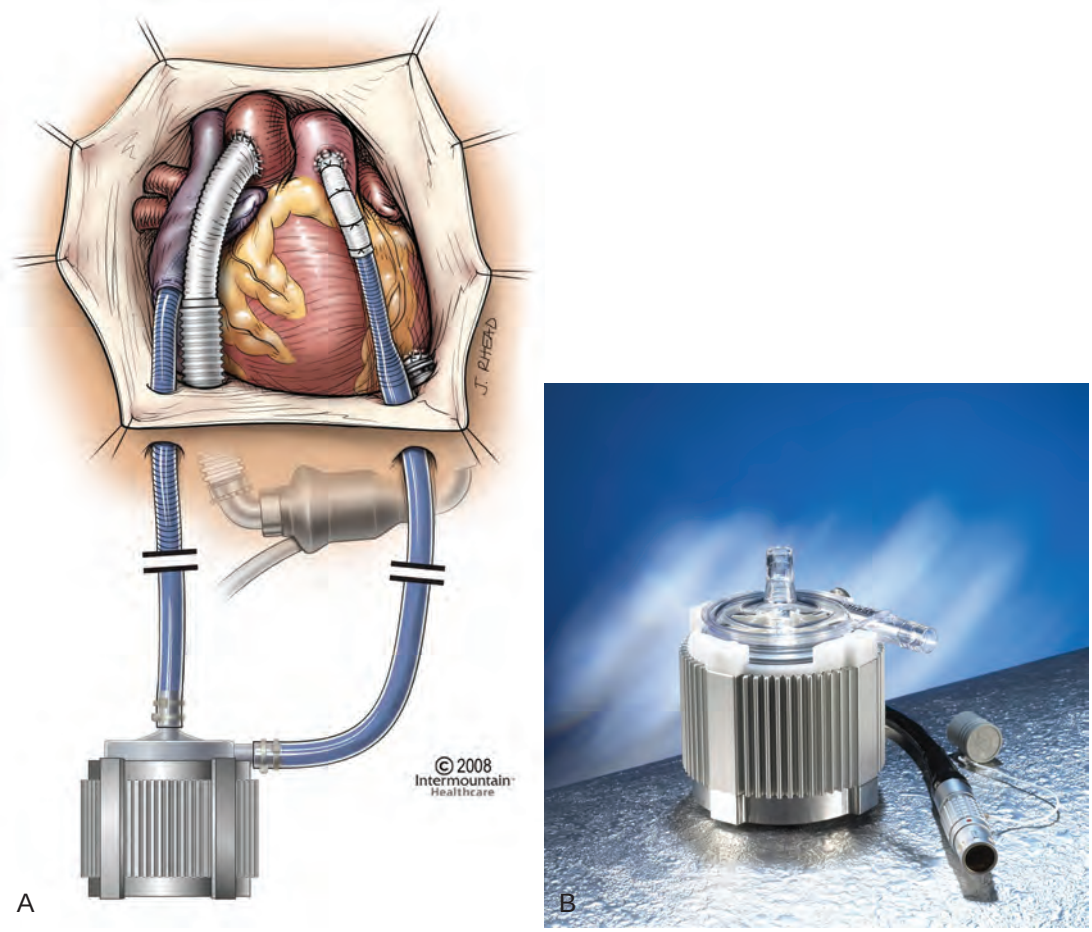


Fig. 28.6 (A) and (B) The Thoratec CentriMag. *(Courtesy of Thoratec Corporation, Pleasanton, Calif.)*

there is no central bearing, and without a bearing, less heat is produced. As a result, there is less hemolysis and therefore less inflammatory response, less peripheral vasoconstriction, and less microvascular occlusion related to plasma free hemoglobin. There may also be a lower incidence of thromboembolic events, and the derangement of liver function tests generally seen after a few days with a standard centrifugal pump head are reportedly not seen to nearly the same extent with the CentriMag.

Despite its small size, the pump itself can provide flow rates of up to 9.9 liters per minute (LPM) and can pump through a membrane oxygenator if ECMO is desired. This versatility coupled with its superior performance profile has made the CentriMag the device of choice for short-term support in many experienced institutions.

At the time of this writing, the CentriMag is FDA cleared for 30 days as a right ventricular assist device (RVAD), but only for 6 hours as an LVAD. It should be understood, however, that the off-label use of the CentriMag as an LVAD for periods longer than 6 hours is common. A smaller version called the PediVAS is approved for 6 hours of use as either an LVAD or an RVAD.

Recent publications of experiences using the CentriMag for biventricular support as a bridge to next decision report 30-day survival in the range of 44% to 73%.[26–28]

Bridge to Immediate Survival: Concepts and Devices

A key determinant of the overall success of bridge to recovery is the rapidity with which the failing ventricle can be decompressed and resumption of adequate systemic perfusion ensured. One of the recognized limitations of currently available devices as a bridge to recovery following an acute myocardial insult is that they must be implanted in a cardiac operating room, often utilizing CPB. Even assuming the immediate availability of the operating room, the device, and the necessary surgical, anesthesia, perfusion, and nursing personnel, delays are inevitable. Poor patient selection aside, it is conceivable that a factor contributing to the low rates of successful bridge to recovery seen in the past was delay in treatment due to operating room and personnel availability. During this interval, the failing ventricle was invariably pressure and volume overloaded, while the splanchnic beds and peripheral tissues were underperfused.

Deploying a rescue device rapidly at the first recognition of refractory ventricular insufficiency (whether acute, or acute on chronic) in the emergency room, the cardiac catheterization laboratory, or an intensive care unit without the need for sternotomy and CPB is theoretically a superior option. Additionally, commonly encountered complications of CPB, such as perioperative bleeding, and the sequelae of the systemic inflammatory response would be minimized. Once immediate survival is ensured, such a strategy/device can conceivably be switched to another that is capable of providing a longer period of support. Considerations such as these led to the development of innovative short-term assist devices and continue to drive the use of time-honored strategies in new ways.

Extracorporeal Membrane Oxygenation

ECMO can be rapidly deployed in experienced centers as a lifesaving intervention to provide temporary cardiopulmonary support as a bridge to immediate survival, a bridge to recovery, and/or as a bridge to support by a longer term support device. Developed from

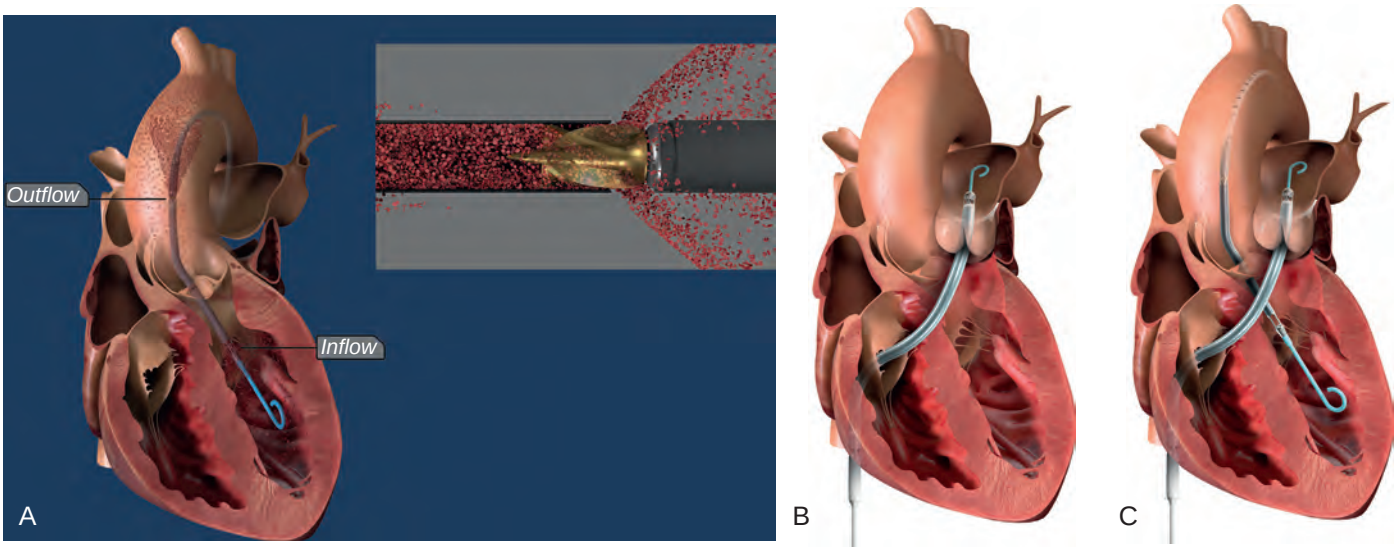


Fig. 28.7 (A–C) The Impella family of support devices. *(Courtesy of Abiomed Inc., Danvers, Mass.)*

CPB technology in the 1970s, a simple ECMO circuit generally uses only a centrifugal pump head, a membrane oxygenator, and a heat exchanger. Survival to hospital discharge has always been the best for full-term neonatal patients with respiratory failure, but experience suggests that appropriately selected adults can also benefit. Clearly, similar considerations govern patient selection for ECMO as for acute implementation of MCS in general (as discussed earlier), with a high likelihood of recovery being the key consideration prior to initiating the therapy. Patients with poor clinical prognosis beyond their respiratory or cardiopulmonary failure, those with multisystem organ failure, and those who have already been intubated and mechanically ventilated for several days at the time of proposed intervention are not likely to demonstrate optimal outcomes from ECMO.

Where respiratory failure is the principal issue and the heart is able to provide adequate output to potentially meet circulatory needs, venovenous (VV) ECMO can provide the necessary oxygenation and ventilation of the blood. In this strategy, venous blood is drained from a caval cannula (introduced through either the femoral or the jugular route), pumped through a membrane oxygenator, and returned to the venous circulation (usually at the level of the right atrium).

Patients with both respiratory and cardiac pump failure are best supported by venoarterial (VA) ECMO, in which venous blood is oxygenated, ventilated, and pumped back into the arterial circulation. Such a strategy is essentially providing CPB. Although cannulations for VA ECMO can be peripheral (eg, femoral vein to femoral artery) or central (eg, right atrium to aorta), central venous cannulation generally provides optimal decompression of the cardiac chambers, which is important for myocardial recovery.

Thus, both VV and VA ECMO provide respiratory support, but only VA ECMO provides MCS. Potential complications of ECMO include all of those inherent to extracorporeal circulation, including bleeding (due to the requisite anticoagulation during support) and limb ischemia distal to peripherally inserted cannulas.

Echocardiography plays an important role in determining the type of ECMO needed (VV vs VA) to ensure proper positioning of cannulas, to assess the extent of ventricular decompression, to monitor potential myocardial recovery, and to aid in subsequent decision making.

Current AHA guidelines for cardiopulmonary resuscitation[29] give ECMO a class IIb recommendation (may be considered, benefit may outweigh risk) for clinical scenarios where recovery is possible. A position article, published in 2011 by the European Extracorporeal Life Support (ECLS) Working Group, outlines the indications, contraindications, and various aspects of patient management regarding ECMO.[30]

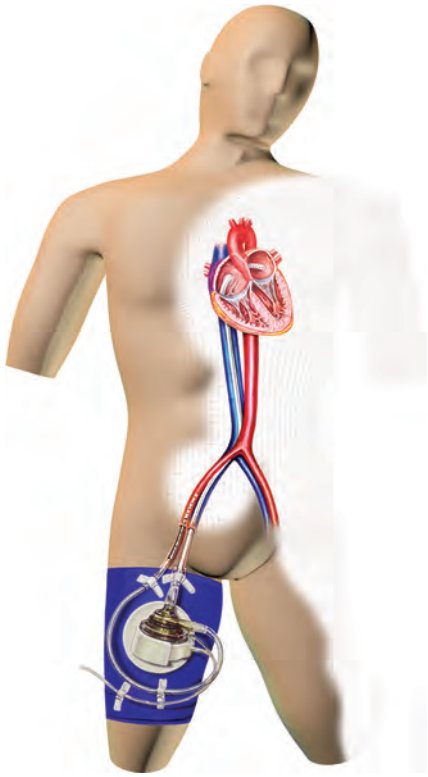


Fig. 28.8 TandemHeart. *(Courtesy of CardiacAssist Inc., Pittsburgh, Penn.)*

Impella and TandemHeart

The Impella (Abiomed, Danvers, Mass; Fig. 28.7) and the TandemHeart (CardiacAssist, Pittsburgh, Pa; Fig. 28.8) percutaneous VADs (pVADs) represent potential bridge-to-immediate-survival devices. Both are designed to support the failing LV, and both are rapidly deployable percutaneously at the time of diagnosis of acute ventricular insufficiency in the emergency room, cardiac catheterization laboratory, or intensive care unit. There is no need for sternotomy and CPB, which has clear potential advantages (as discussed earlier).

Despite the enormous potential of these devices when employed early as a lifesaving intervention, the most frequent use of both

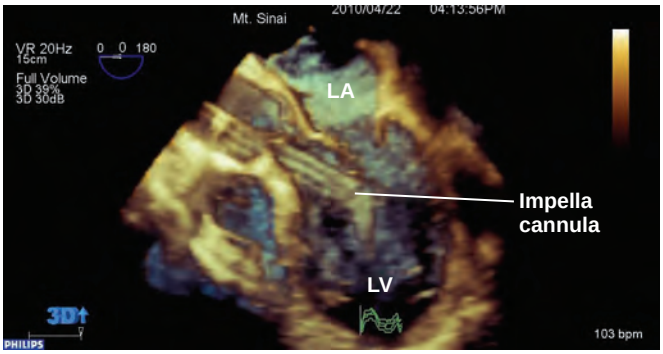


Fig. 28.9 The proper positioning of the inflow cannula of the Impella VAD (ventricular assist device) entering the left ventricle (LV) in a retrograde fashion through the aortic valve. *LA,* Left atrium.

devices has been in the catheterization and electrophysiology labs as an extra margin of safety for high-risk patients undergoing high-risk percutaneous interventions and hemodynamically challenging electrophysiologic interventions (eg, ablation of ventricular tachycardia or fibrillation pathways); the least frequent use has been as a bridge to immediate survival or recovery.

Unfortunately, similar to the initial experience with VADs themselves, when such devices first became available, they were implemented for rescue only as a last resort, once patients had already developed profound cardiogenic shock and organ dysfunction refractory to pharmacology and IABP counterpulsation. Not surprisingly, this led initially to suboptimal results. Outcomes, however, are reportedly improving, and such devices may ultimately demonstrate benefit over ECMO or long-term VADs in the setting of isolated LV or RV failure without pulmonary dysfunction, major valvular abnormality, or biventricular failure. Accordingly, clinical experiences with these devices for acute rescue now appear in the peer-reviewed, published literature. There seems to be an advantage of these devices over the IABP in terms of the level of support provided and the output they can generate, but with a higher risk of bleeding, and the clinical situations in which they might be optimally employed are still being elucidated.

Impella

The Impella pump system is a family of microaxial continuous flow support devices that can be used to support the left, right, or both ventricles. Clinical trials intended to establish the efficacy and optimal utilization of each Impella device are ongoing.

Percutaneously deployable members of the Impella family include the LP 2.5 (provides 2.5 LPM of flow as an LVAD), the LP 5.0 (provides 5 LPM of flow as an LVAD) and the recently approved RP (provides 4 LPM of flow as an RVAD). Other members of the Impella family include directly implantable versions for both left and right ventricular support (LD and RD). All of these devices are FDA cleared, and theoretically all hold the international class IIb recommendation for VAD use in the AMI cardiogenic shock population.

As illustrated in Fig. 28.7, the percutaneous Impella LVAD devices can be inserted from the femoral or subclavian arterial approach retrograde across the aortic valve into the left ventricle to pump blood into the ascending aorta, actively unloading the LV. Relative contraindications to this approach include significant aortic valvular disease or significant atherosclerotic burden in the aorta (eg, mobile plaques or vascular stenosis). The Impella RP is inserted via the femoral vein through the right atrium and into the pulmonary artery, unloading the failing right ventricle and ensuring pulmonary blood flow as an RVAD.

Although reasonably easy to deploy with fluoroscopy or TEE guidance (Fig. 28.9), the majority of use of the LP 2.5 has been in the cardiac catheterization lab or electrophysiology lab as an extra margin of safety for high-risk patients undergoing PCIs and arrhythmia ablations. This is because 2.5 LPM of flow is generally insufficient to rescue by accommodating the circulatory needs of a full grown adult with cardiogenic shock. A recently published analysis of the outcomes with LP 2.5 support in 120 adult patients with acute MI cardiogenic shock at 14 tertiary care centers in 5 European countries demonstrated that although lactate levels came down within 48 hours of device support (demonstrating the positive effects of low flow support), 30-day survival rate remained fairly low (36%).[31] Similar to the situation with the IABP, criticisms of the methodologies used in the practices and studies included patient selection and the timing of intervention.[32]

As discussed earlier, since the mid-1990s, it has been understood that patient status at the time of implementation of MCS is the primary determinant of outcome. Early and sufficient MCS leads to the best possible outcomes. Cardiologists and emergency physicians are the providers who must make the decision to employ MCS when patients present with acute symptoms, typically in the emergency department setting. Cause of the cardiogenic shock and appropriate patient selection are critical factors as well. The outcome of a young person with acute myocarditis cannot be compared to an older person with coronary artery disease, long-standing heart failure, and varying levels of multisystem deterioration. Furthermore, it is also important to consider that simply preventing imminent death is not the same thing as prolonging a high quality of life. Goals of care are important to these decisions.

By comparison to the LP 2.5, the Impella 5.0 can produce a physiologically relevant amount of forward flow, and there is a rapidly growing experience with the use of that device as a bridge to immediate survival, a bridge to recovery, and a bridge to surgery. In contrast to the experience with the LP 2.5 in the setting of AMI cardiogenic shock, a 2013 publication reported the results of a multicenter assessment of the Impella 5.0 as a rescue device for postcardiotomy LV failure.[33] Survival rates were very encouraging, with 30-day, 3-month, and 1-year survival rates of 94%, 81%, and 75%, respectively. It is important to consider that in MCS for postcardiotomy, LV failure is associated with superior outcomes when compared with MCS for AMI cardiogenic shock. This is likely related to shorter intervals separating diagnosis and active management. A recent publication also reported the utility of the Impella 5.0 as a bridge to improved candidacy for transplantation with a durable long-term LVAD.[34]

The TandemHeart

The TandemHeart pVAD (CardiacAssist, Pittsburgh, Pa) uses a full-sized centrifugal pump and a percutaneous cannulation strategy that results in reasonable decompression of the failing LV and rapid resumption of systemic perfusion. As illustrated in Fig. 28.8, with this device, a long percutaneous venous inflow cannula is advanced retrograde from the femoral vein through the RA and across the interatrial septum into the LA. Up to 5 LPM of continuous, nonpulsatile outflow from the centrifugal device (strapped to the patient's leg) is directed into the femoral artery to maintain systemic perfusion. It should be noted that the concept of using LA to femoral artery bypass with an interatrial septal cannula was first described by Dennis and colleagues in the 1960s.[35]

The TandemHeart holds a CE mark in Europe and is FDA cleared in the United States for up to 6 hours of use as an LVAD. In current guidelines, the TandemHeart holds a class IIb recommendation for the management of AMI cardiogenic shock. Although this device was envisioned to be a comparatively rapidly deployable bridge to immediate survival device, the need for a transseptal puncture guided by fluoroscopy and/or echcardiography may limit the ease of implantation, and it would be impossible to implement this device during cardiopulmonary resuscitation.

The superiority of the TandemHeart to provide MCS when compared to a balloon pump was reported in a number of studies, but there is a paucity of published data regarding outcomes with the TandemHeart LVAD by itself. The main complications with the TandemHeart appear to be bleeding at the cannulation sites and limb ischemia. Cannula dislodgment is also a potential issue. The TandemHeart is currently the subject of a multicenter pivotal trial called TRIS (TandemHeart

to Reduce Infarct Size) looking at myocardial salvage in AMI patients, and experience with the use of the TandemHeart as an RVAD is growing.

A 2013 study compared outcomes of 79 patients in acute cardiogenic shock supported by the TandemHeart, the Impella 5.0, and conventional VA ECMO.[36] Overall, in-hospital mortality, rates of successful weaning, rates of successful bridging to a bridge with a longer term device and incidence of limb complications did not differ between the devices. Younger age was the only predictor for improved in-hospital survival, and cost considerations favored ECMO. The manuscript also discussed the advantages and disadvantages of each support strategy. A consensus statement published in 2015 also reviewed and discussed the utility of percutaneous MCS devices.[37]

Fig. 28.10 depicts a logical decision-making algorithm for MCS in the setting of severe refractory cardiogenic shock, but what works well in one institution may not be generalizable to another. Thus, each institution should ideally develop its own algorithm, taking available devices, resources, and experiences into account.

Long-Term Support

As revealed by the INTERMACS data, long-term, durable devices are being implanted in thousands of people each year who otherwise would succumb to heart failure. A number of long-term VADs are available at the time of this writing, but only the HeartMate II (Thoratec Corporation, Pleasanton, Calif; Fig. 28.11) and the HeartWare HVAD (HeartWare, Framingham, Mass; Fig. 28.12) are approved for use and currently in regular use in the United States. Efficacious devices exist in other countries (eg, the Berlin Heart INCOR, Berlin Heart, Berlin, Germany, Fig. 28.13). Several new durable devices are still under investigation in the United States (eg, the HeartMate III, Thoratec Corporation, Pleasanton, Calif; Fig. 28.14). Additionally, some previously used or approved devices may still be employed infrequently in specific centers, but a complete discussion of all potentially available devices is beyond the scope of this chapter. The total artificial heart is indeed in use in the United States and is discussed in detail later.

HeartMate II

The HeartMate II (HM II) is by far the most commonly used long-term LVAD in the United States at the time of this writing. Approved as a bridge to transplantation in 2008 and for destination therapy in 2010, the device is a small axial flow pump, about the size of a D-battery, with a rotating impeller shaped like an Archimedes screw. It has an internal volume of 63 mL and a maximum output of 10 LPM against a mean pressure of 100 mm Hg. This is a continuous flow device that initially results in a mostly nonpulsatile circulation, but pulsatility returns in most patients once the ventricle starts to recover. According to the manufacturer, more than 16,000 patients worldwide have been implanted with the HeartMate II, with the longest duration of support greater than 8 years. Out of all the patients implanted with this device for the purpose of bridge to transplantation, 87% have received a heart transplantation.[1]

Given that the HM II has been the most frequently used, durable LVAD in the United States since the time of its FDA approval for all long-term MCS indications, the 2014 INTERMACS data (presented earlier) are essentially the current data for the HM II.

Figure 28.11 shows how the device is configured internally. The only visible external component is a driveline that exits the skin of the abdomen, usually on the right somewhere convenient between the upper and lower quadrants. The device draws blood from the LV apex and pumps the blood continuously into the ascending aorta. This does not prevent the left ventricle from ejecting through the aortic valve, and the amount of support provided by the device depends on several factors, including intrinsic myocardial function, preload, and afterload. These issues have relevance for the management of a patient on such a support device, as discussed later.

HeartWare HVAD

The HeartWare ventricular assist device (HVAD) is a small intrapericardially positioned continuous flow centrifugal pump, with a bearingless, hydrodynamically suspended, magnetically driven impeller. Technically, the HVAD is a third-generation device because it is bearingless. Typical for a centrifugal pump, rotational speeds of 2000 to 3000 rpm can produce upward of 10 LPM of flow. There are the usual external system controller and power supply that are connected to the device by a tunneled driveline. The configuration of the HVAD is depicted in Fig. 28.12.

The HVAD was CE marked for clinical use in Europe in 2009, was approved by the Australian TGA in 2011, and received FDA approval as a bridge to transplantation in the United States in November 2012 following its demonstration as noninferior to other implantable devices in the ADVANCE trial.[38] In this trial, 140 patients implanted with the HVAD were followed for 180 days or until transplantation or death, and their outcomes compared with 544 patients implanted with other commercially available devices. Of the 140 in the investigational group, at 180 days, 62% were still supported by their original device, 29% had been transplanted, 5% had required device exchange (2% for pump thrombosis), and 4% had died. Overall the 1-year survival rate was 85%.[39]

The HVAD, because of its small size, has also been used as an implantable RVAD. Experience with the use of the HVAD for RV support (while limited at this time) is steadily increasing.[40–42] The HVAD is already approved as a device for use in destination therapy in Ontario (since 2012), and it is anticipated that data from the ENDURANCE trial and the ENDURANCE supplemental trial, which began enrolling patients in late 2013, will establish the HVAD as a device for that use in the United States.

A recent analysis of real-world experience with the HeartWare HVAD over 4 years in the UK revealed a 75% survival rate at 1 year and 66% at 2 years.[43] It should be noted, however, that European patients are generally implanted at lower INTERMACS levels (higher acuity) than in the United States, which may account for the lower rate of survival when compared to the ADVANCE trial conducted in the United States. Interestingly, a multicenter trial conducted at four Canadian centers (where patients were implanted at INTERMACS levels 1 and 2, as they tend to be in Europe) reported an 86% 1-year survival rate. In this trial, 39% were successfully bridged to transplantation, but a 3% incidence of pump thrombosis was seen. It is worrisome that a 36% incidence of adverse neurologic outcome was reported.[44]

Complications of Mechanical Circulatory Support

As outcomes have improved, simple survival of mechanically supported patients has become less of an issue, and the primary focus of MCS research has shifted toward optimizing outcomes through limiting adverse events. Unfortunately, no single risk-stratification method or scoring system has yet been devised to predict the various adverse events inherent to the MCS population. For example, although the preimplant Sequential Organ Failure Assessment (SOFA) score was recently reported to reliably predict survival after 6, 9, 12, 24, and 36 months of support, the SOFA score did not predict other long-term adverse events (eg, stroke, bleeding, infection, need for pump replacement).[45] It is also important to understand that because of the distinct mechanical underpinnings, materials, and functional specifications of modern devices, all data, predictive indices, and risk-stratification scores generated during the era of first-generation pulsatile devices cannot be extrapolated to the current generation of nonpulsatile devices.

Overall, there has been a major decrease in the rates of specific adverse events with the continuous flow devices compared to the first generation of pulsatile devices, according to INTERMACS and other data sources. Conversely, only minor decreases in the total burden of adverse events have been reported in the current era compared to the previous era. Although the rates of some classic problems have

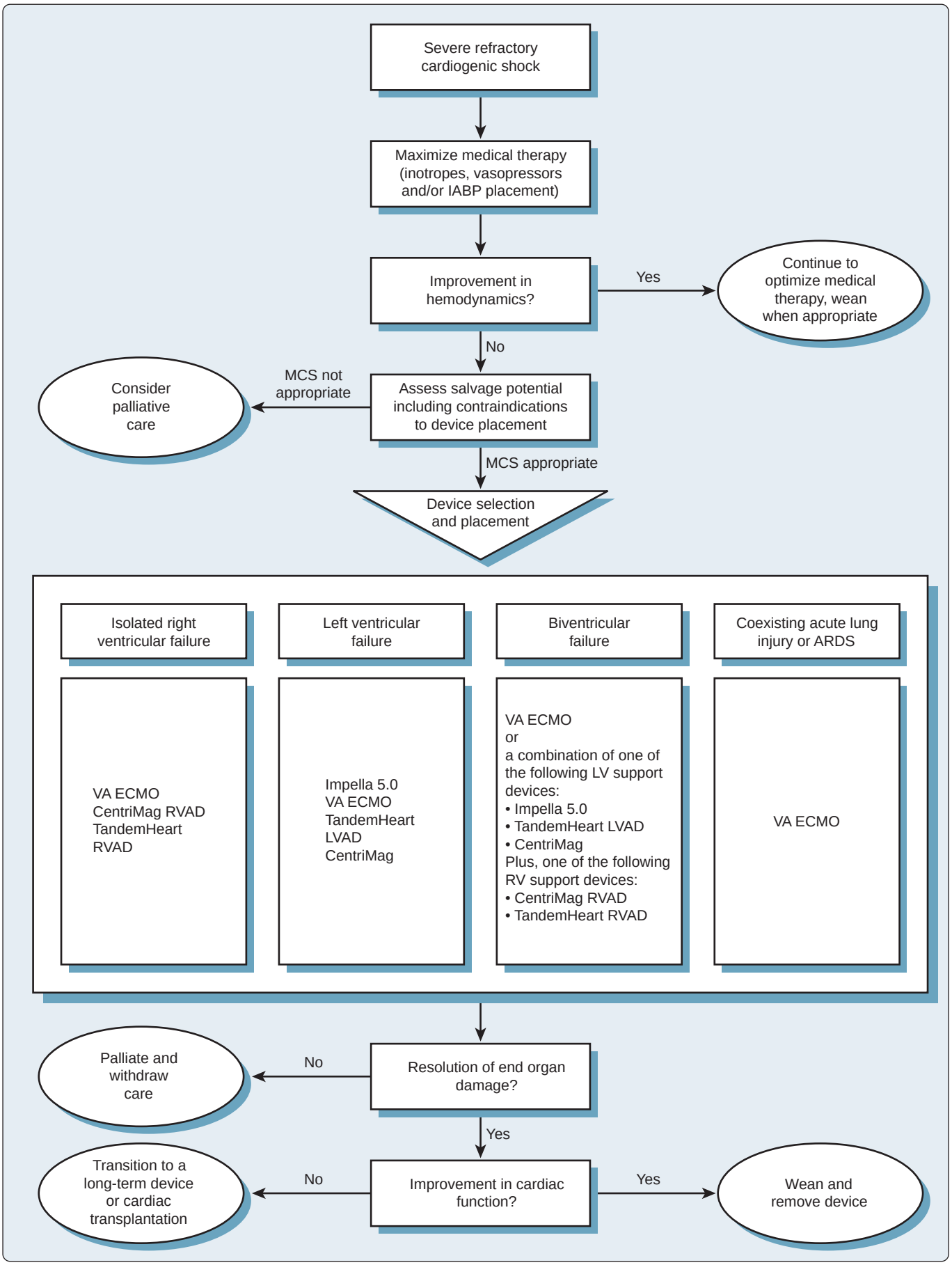


Fig. 28.10 A logical decision-making algorithm for mechanical circulatory support *(MCS)* in the setting of severe refractory cardiac shock. *ARDS,* Acute respiratory distress syndrome; *IABP,* intraaortic balloon pump; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device; *VA ECMO,* venoarterial extracorporeal membrane oxygenation.

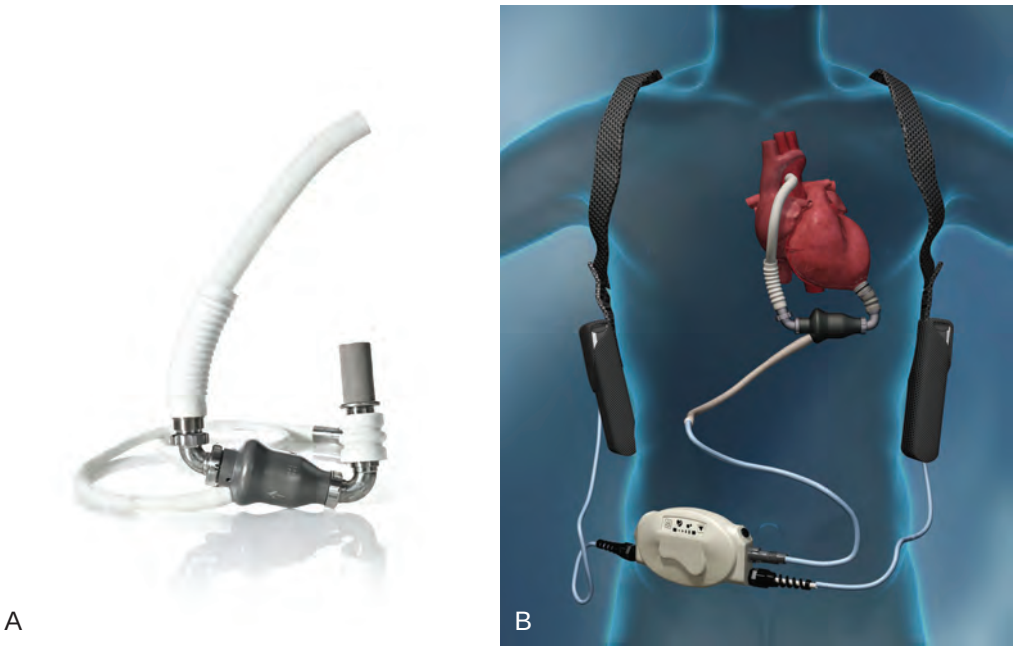


Fig. 28.11 (A) and (B) The HeartMate II. *(Courtesy of Thoratec Corporation, Pleasanton, Calif.)*

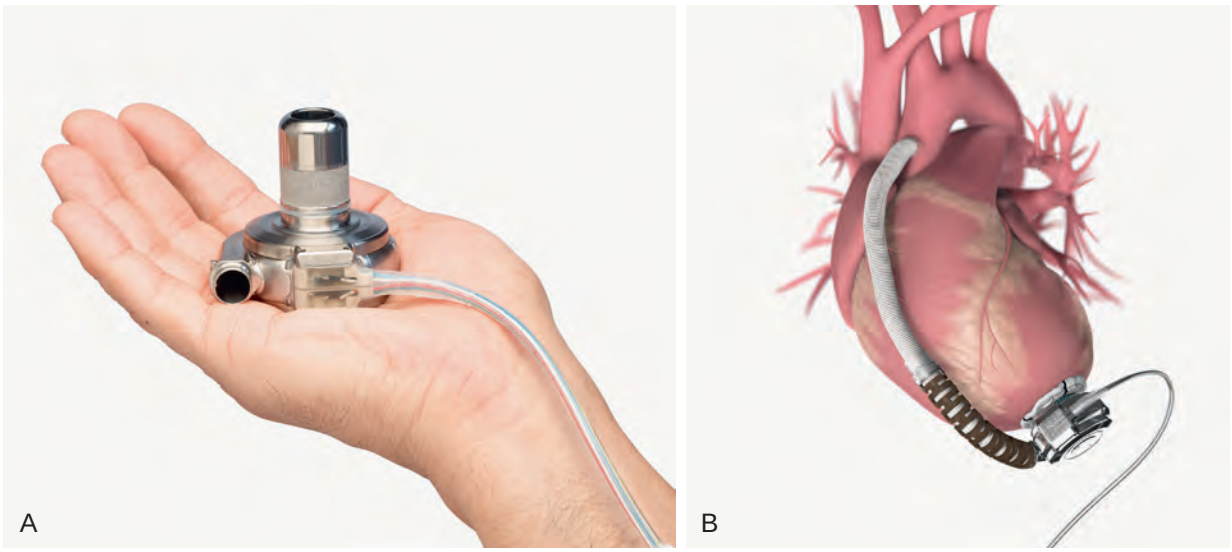


Fig. 28.12 (A) and (B) HeartWare HVAD. *(Courtesy of HeartWare Inc., Framingham, Mass.)*

decreased significantly (eg, mediastinal bleeding, RV failure, perhaps stroke), the rates of some important ones (eg, renal failure and respiratory failure) have not changed. Moreover, new complications have appeared that did not exist with the first generation of pulsatile devices, such as arteriovenous malformations in the gastrointestinal tract, von Willebrand syndrome resulting in gastrointestinal and intracerebral bleeding, and pump thrombosis, among others.

New information is rapidly emerging, and certain modern complications of VAD support have now been linked with certain preexisting factors and/or aspects of modern MCS technology.

- Gastrointestinal arteriovenous malformations are now understood to result from the nonpulsatile flow produced by modern MCS devices, much as they are known to form in patients with severe aortic stenosis (Heyde syndrome).[46–50]
- Acquired von Willebrand syndrome (from the loss of high-molecular-weight von Willebrand monomers) is now understood to result from the shear stresses imposed by the continuous flow devices.[51–55]
- Pump thrombosis has been seen with surprisingly high frequency with both the HM II and the HVAD. As outlined in a 2014 *New England Journal of Medicine* publication, starting in approximately March 2011, the rate of confirmed HM II pump thromboses at 3 months after implantation rose from approximately 2.2% to 8.4% by January 2013.[56] This was alarming, because previously, the median time from implantation to identification of any significant incidence of pump thrombosis had been 18.6 months. To date, any single reason for this increase remains elusive. In all likelihood, this is a multifactorial problem. In addition to design changes to the HM II introduced in 2010 (a new gelatin sealing of the grafts), as reviewed by Lindenfeld and Keebler,[57] additional potential causes of the increased rate and number of HM II thromboses may have

included inadequate anticoagulation and/or antiplatelet therapy during VAD support, overestimation of the actual level of anticoagulation present,[58] the use and dosage of erythropoiesis stimulating agents,[59] abnormal angulation of the inflow and or outflow cannula,[60] strategically decreased rates of flow, heat production by the bearing, infection, atrial fibrillation,[61] and RV failure. For the HVAD, the addition of titanium sintering to the inflow conduit (which should encourage the ingrowth of a nonthrombogenic neointima, as was present in the first-generation, pulsatile HeartMate I) in 2011 appears to have decreased the incidence of HVAD thrombosis seen during early clinical experience with the device.

Hemolysis and increasing LDH levels are now recognized as premonitory signs of thrombosis. These can be monitored, and pharmacologic strategies may be employed in many cases as alternatives to device exchange or transplantation.

Additionally, new associations are being established between adverse events and potentially modifiable risk factors. For example, stroke has recently been linked to vitamin D deficiency[62] and also to elevated systolic blood pressure during support.[63]

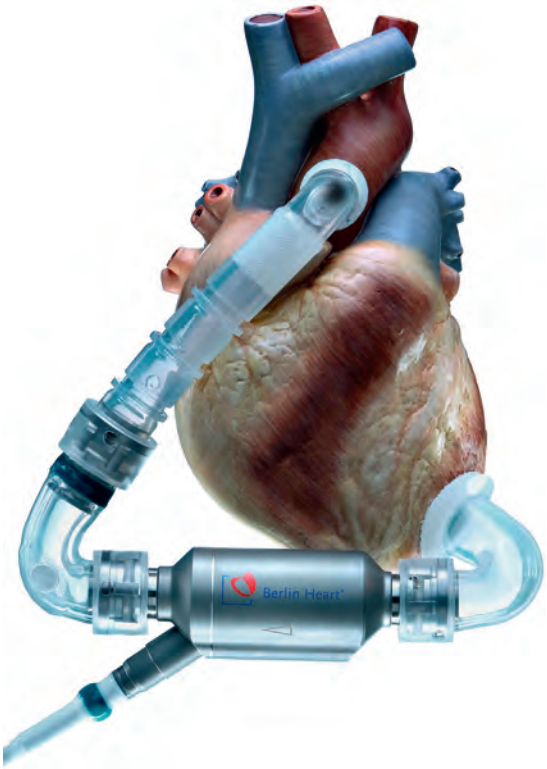


Fig. 28.13 The Berlin Heart INCOR. For the latest information, visit www.berlinheart.de/index.php/mp/content/produkte/incor. *(Courtesy of Berlin Heart AG, Berlin, Germany.)*

Total Artificial Hearts

From the original pneumatically driven devices with their massive external control consoles to the totally implantable computer-controlled AbioCor implantable replacement heart (Abiomed, Danvers, Mass), a mechanical total artificial heart (TAH) that could permanently replace the failing human heart has been the subject of intensive research and development for decades.

The first TAH was a pneumatically driven biventricular pump developed by Dr. Domingo Liotta and colleagues in the 1960s. This device (the Liotta TAH) was first implanted in a 47-year-old patient with severe heart failure by Dr. Denton Cooley on April 4, 1969, and was used for 64 hours as a bridge to heart transplantation.[64] The patient died of Pseudomonas pneumonia 32 hours after his transplantation, but the Liotta heart proved that a mechanical device could be successfully used clinically to sustain a patient, and in fact, the original intention of such a device was the permanent replacement of the failing heart. The second human implantation of a TAH was also performed by Dr. Cooley. In July 1981, the Akutsu III TAH was successfully used for 55 hours as bridge to transplantation in a 36-year-old patient with end-stage heart failure.[65] The Jarvik-7 TAH was first implanted as a permanent replacement heart (destination device) in August 1985 in a 61-year-old man with primary cardiomyopathy and chronic obstructive pulmonary disease.[66] Although the patient survived only 112 days, the duration of his survival was encouraging. The first successful bridge to transplantation with the Jarvik-7 TAH occurred in August 1985.[67]

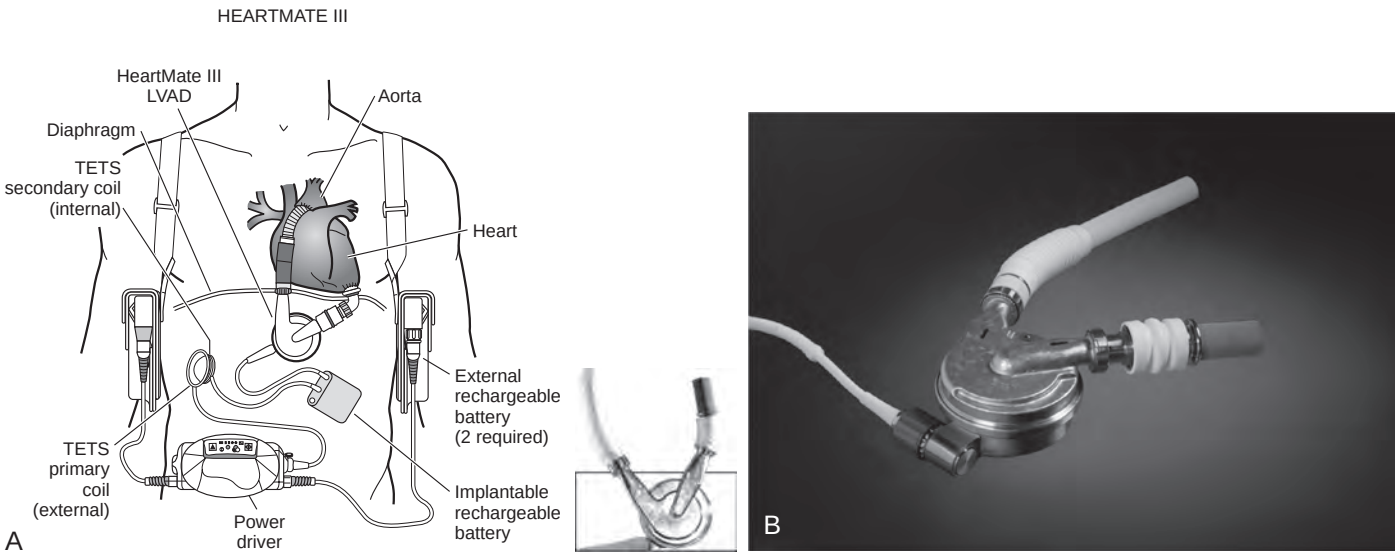


Fig. 28.14 (A) and (B) HeartMate III. *LVAD,* Left ventricular assist device; *TETS,* Transcutaneous energy transduction system. *(From Stone ME, Fischer GW. New approaches to the surgical treatment of end-stage heart failure. In: Kaplan J, Reich D, Lake C, Konstadt S, eds.* Kaplan's Cardiac Anesthesia. *5th ed. Philadelphia: Elsevier; 2006:867–890.)*

The SynCardia Temporary Total Artificial Heart

From 1991, the Jarvik-7 was known as the CardioWest TAH. Now known as the SynCardia temporary total artificial heart (TAH-t; SynCardia Systems Inc., Tucson, Ariz), the current incarnation of this device is in use today as a bridge to transplantation in more than 100 centers in North America, Europe, Asia, and Australia/New Zealand, with nearly 50 more centers currently in the process of certification worldwide.

The TAH-t is a pneumatically driven, orthotopically placed, biventricular pump weighing less than 0.5 pounds that can produce in excess of 9 LPM of pulsatile flow. Metal tilting-disk prosthetic valves within the device mandate anticoagulation during support. FDA approval of this TAH as a bridge to transplantation came in 2004, and a CE mark was granted for its use in Europe in 2006.

This device has seen a major resurgence of interest in the past few years as an implantable support device for patients with end-stage biventricular failure (instead of biventricular support with paracorporeal VADs), as a bridge to retransplantation in patients experiencing rejection and failure of a transplanted heart (instead of reimplanting an LVAD), and when there is LVAD failure (in lieu of device exchange).

According to the manufacturer, more than 1400 implantations have now been performed, with the longest duration of support at approximately 4 years. The rate of successful bridge to transplantation with this device has been reported at approximately 75% to 80% for over a decade,[68,69] but it remains to be seen if such success will continue to be manifested as the number of implants grows beyond the confines of clinical trials. As with other devices used to provide MCS, stroke and infection are encountered, but data regarding rates of these complications are not currently available from the INTERMACS database. A recent update publication in the *Texas Heart Institute Journal* reported that "most" (4%) of the strokes associated with the TAH-t occur essentially in the perioperative period, and the rate of fatal infections with this device is approximately 2%.[69] As it produces pulsatile flow, acquired von Willebrand syndrome, and bleeding complications from arteriovenous malformations (now commonly observed with continuous flow VADs) may not be seen with the TAH-t. Again, a large real-world experience with this device has just begun.

Originally powered and controlled by a massive control console ("Big Blue"), the availability of a small, wearable controller weighing less than 15 pounds (the Freedom portable driver) now allows for easy ambulation and hospital discharge. An even smaller controller will soon be available, as will a smaller version of the TAH itself (with 50-mL ventricles), for use in small adults and children. Ironically, although it was originally conceived of and used as a destination device, the TAH-t is only now currently the subject of a formal destination therapy trial.

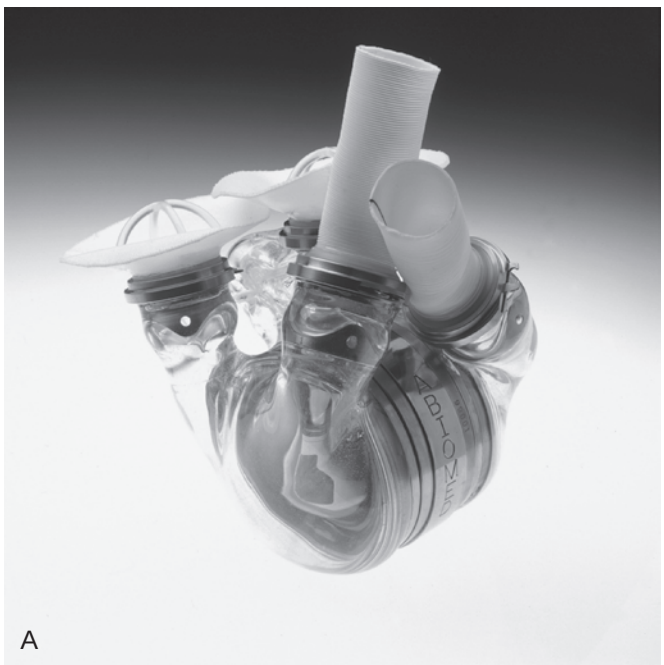
AbioCor Implantable Replacement Heart

The AbioCor implantable replacement heart (Abiomed, Danvers, Mass; Fig. 28.15) potentially represents a major advance in artificial heart technology because it is truly totally implantable; there are no percutaneous cables, conduits, or wires. The device is motor driven, so a source of compressed air to drive the pumping action is not required, allowing patients complete mobility without the need for even a portable or wearable controller. The device itself weighs approximately 2 pounds and is orthotopically implanted, as illustrated in Fig. 28.15.

The AbioCor is indicated for patients not eligible for transplant who are younger than 75 years old and have end-stage, biventricular failure. Transcutaneous energy transfer is used (in lieu of a percutaneous cable) to supply the motor-driven hydraulic pumping of the artificial ventricles with power and system control. Artificial unidirectional valves within the device mandate anticoagulation during support.

A relatively small number (14) of implantations of this device at the University of Louisville and three other centers in the early 2000s demonstrated a moderate amount of success (survival of over 1 year was achieved, but there were high rates of stroke and infection and a few device failures).[70]

The FDA initially denied application for approval of this device in 2005 citing "quality of life vs quantity of life" issues, but the AbioCor



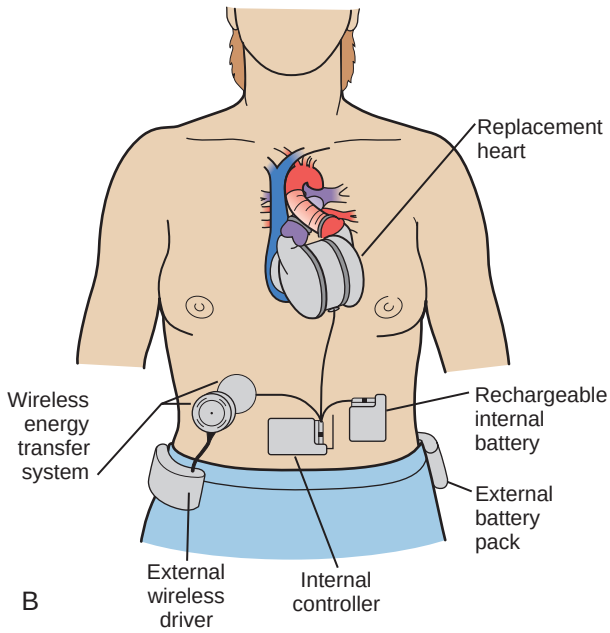


Fig. 28.15 (A) The AbioCor implantable replacement heart. (B) Orthotopic implantation of the AbioCor implantable replacement heart. The native failed heart is removed, and the AbioCor is implanted orthotopically, anastomosed to cuffs of native atria and the great vessels. Transcutaneous energy transfer technology eliminates the need for percutaneous wires. *(Courtesy of Abiomed, Inc., Danvers, Mass.)*

eventually received FDA approval in 2006 under the Humanitarian Device Exemption Program,[71] largely as a result of the testimony of patients and families of those supported regarding the ability of the supported patients to be present to "share significant life events" with their families.[72] A very small number of implants apparently followed as part of a postmarket study, but there have been no recent publications about this device, and it is essentially no longer even available.

Future of the Total Artificial Heart

As reviewed by Gerosa and associates in 2014,[73] a number of innovative TAHs with advanced technologies are under development worldwide that seek novel solutions, portending advancements in the permanent replacement of the failing human heart.[74–79]

Perioperative Anesthetic Considerations for VAD Support

The anesthetic approach to the patient requiring VAD implantation depends entirely on the urgency of the situation. Patients requiring emergent VAD support are in extremis and health professionals can do little but provide supportive care until the patient can be placed on CPB. In contrast, patients presenting for elective VAD implantation as a bridge to transplantation or as destination therapy have end-stage heart failure and, when medically optimized, can appear remarkably well despite significantly depressed cardiac function. Some patients presenting for elective LVAD insertion have suffered an acute decompensation of long-standing heart failure and will have been admitted preoperatively to an intensive care unit with pharmacologic therapy (eg, milrinone, nesiritide, dobutamine) and intraaortic balloon counterpulsation therapy in an attempt to stabilize and optimize hemodynamics.

Regardless of their outward appearance, all patients requiring VAD support decompensate easily from even the most transient of hemodynamic aberrations (eg, tachycardia, bradycardia, hypercarbia, loss of sinus rhythm, sudden alterations in volume status, hypotension) and thus must be approached with caution.

Patients Presenting for Elective LVAD Implantation

Severely depressed cardiac function is the key consideration in the management of all patients presenting for LVAD insertion. The majority will have a dilated cardiomyopathy that is accompanied by mitral regurgitation, diastolic dysfunction, a dilated tricuspid annulus with functional tricuspid regurgitation, and varying degrees of pulmonary hypertension. Renal insufficiency, cerebral vascular disease, and mild coagulopathy due to hepatic congestion are not uncommon. As coronary artery disease has become one of the most common causes of heart failure (31.8% of all patients currently listed for heart transplantation),[80] ongoing ischemia is a potential concern. Many of these patients will have undergone previous cardiac surgery (eg, coronary artery bypass grafting, valve repair/replacement, ventricular reshaping, correction of congenital heart disease), adding the attendant risks of repeat sternotomy to the anesthetic concerns. Finally, it is common for this population to have a pacemaker and/or implantable cardioverter-defibrillator that must be managed perioperatively.

Issues Related to Outpatient Medications

Patients presenting for elective LVAD implantation have generally been managed with medications that reduce afterload, promote diuresis, prevent arrhythmias, control heart rate and antagonize the adverse myocardial remodeling that accompanies chronic, progressive heart failure. Typically employed agents include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aldosterone antagonists, amiodarone, β-blockers, diuretics, and digoxin. While effective for the preoperative optimization of this population, agents with long elimination half-lives, such as ACE inhibitors and amiodarone, result in significant vasodilation that will need to be addressed and countered pharmacologically in the period after bypass. Where feasible, it is generally recommended to withhold diuretics in the immediate preoperative period in an attempt to lessen the relative hypovolemia and electrolyte depletion seen with these commonly used agents. There is currently no consensus about whether or not to withhold ACE inhibitors preoperatively.

Preoperative Nutritional Optimization

It is widely understood that preoperative malnutrition predisposes the general surgical population to an array of postoperative complications, including delayed wound healing and increased risk of infection. Nutritional status has also been established as an important determinant of survival in patients with heart failure, and in VAD patients there is growing evidence that nutrition, as measured by traditional surrogates, such as serum albumin and body mass index, is a critical determinant of postimplantation survival. In a study by Lietz and colleagues, poor preoperative nutrition status was identified as one of several predictors of poor postimplantation outcomes as part of a risk-stratification score.[7] More recently, preoperative hypoalbuminemia was reported as an independent risk factor of mortality in a large cohort of patients with nonpulsatile devices.[81] Interestingly, postoperative correction of albumin levels also correlated with a significant survival advantage in this study.

Postoperative indicators of suboptimal nutritional status, such as low prealbumin levels, have also been shown to correlate with increased mortality in this population.[82] Based on these findings, aggressive optimization of nutritional status has become an important component of patient management before and after operations. In patients refractory to conventional approaches to nutritional augmentation, enteral and/or parenteral feeding should be considered. Of note, parenteral nutrition, despite its traditional association with increased risk of infection, has been shown to be a safe and effective alternative to enteral nutrition preoperatively for VAD patients and may prove in the future to be a standard component of perioperative nutritional optimization in patients refractory to other methods.[83]

The Immediate Preoperative Period

It is prudent to provide supplemental oxygen (via nasal cannula or face mask) and monitor vital signs during the preoperative period, especially if anxiolytic medications are given. The potential for hypoventilation always exists with sedation, and this population will not generally tolerate sudden decreases in sympathetic tone, hypoxemia, and the potentially increased pulmonary vascular resistance that may accompany a sudden respiratory acidosis. Preinduction insertion of an intraarterial catheter for blood pressure monitoring is of critical importance for patients with severely depressed cardiac function.

Induction and Maintenance

The anesthetic plan must take into account the severe degree of cardiac dysfunction and potential preexisting organ insufficiency. The failing heart is at least partially compensated by a heightened adrenergic state, and anesthetic induction agents that markedly blunt sympathetic tone should be avoided as they may result in rapid cardiovascular decompensation or collapse. Additionally, management goals for patients with heart failure should also include the avoidance of anesthetic agent–induced depression of cardiac function and of hemodynamic conditions that increase myocardial demand, such as tachycardia and increased ventricular afterload. In summary, the induction strategy should aim to strike a balance between adequate depth of anesthesia and maintenance of stable hemodynamics.

Etomidate (0.2 mg/kg IV) is an ideal induction agent for patients with heart failure because it does not cause a significant reduction in SVR nor does it decrease myocardial contractility. An induction

technique based on a high-dose opioid (eg, fentanyl 50–100 μg/kg) and a neuromuscular blocking agent will likely result in several hours of hemodynamic stability. The resultant bradycardia with high doses of opioids, however, could result in further decreases in cardiac output. Additionally, amnesia is usually inadequate with narcotics alone and ventilatory support will be required for several hours after the procedure has ended. Thus, high-dose opioid techniques are less frequently used currently.

Ketamine remains an extremely useful alternative agent in patients with severely decreased ventricular function. A ketamine induction (1–2.5 mg/kg IV or 2.5–5 mg/kg IM) followed by a maintenance infusion (50–100 μg/kg/min) will usually provide excellent hemodynamic stability while ensuring adequate analgesia and amnesia. Before administering ketamine, a small dose of midazolam (eg, 1–2 mg IV) is often given to theoretically lessen the potential postemergence psychomimetic side effects that may occur in some patients and an antisialagogue (eg, glycopyrrolate 0.2 mg IV) is generally employed. Studies conducted in laboratory animals have shown ketamine to exert a relatively profound direct myocardial depressant effect, which is ordinarily balanced by its indirect sympathomimetic properties. In the setting of advanced heart failure, however, where partial compensation is achieved through chronic activation of the adrenergic system and downregulation of myocardial β-adrenergic receptors, there is a theoretical risk of unmasking and seeing primarily the direct depressant effects of ketamine on the heart with doses adequate for induction.[84,85]

Thus, a standard balanced technique consisting of small doses of midazolam, etomidate as the induction agent, moderate doses of opioid (eg, total fentanyl dose 10–20 μg/kg), a neuromuscular blocking agent, and potent volatile inhaled agents as tolerated is often used in well-optimized patients. As a general rule, however, high doses of all the potent inhaled volatile agents are poorly tolerated in this population because they all interfere with calcium handling and cyclic nucleotide secondary messengers in the myocardium. By comparison with the other currently available agents, sevoflurane appears to cause less myocardial depression and decrease in SVR, although low concentrations of isoflurane are commonly used without difficulty. In addition to direct myocardial depression and vasodilation, the inhaled anesthetic agents may also adversely affect myocardial automaticity, impulse conduction, and refractoriness, potentially resulting in reentry phenomena and dysrhythmias. Dysrhythmias are especially likely when the delivered concentration of an agent is abruptly increased.

As perioperative bleeding is a common problem following VAD implantation, an antifibrinolytic agent (eg, ε-aminocaproic acid or tranexamic acid) is used during these cases.

Monitoring

In addition to standard American Society of Anesthesiologists monitors (eg, ECG, end-tidal CO_2, temperature, pulse oximetry, and blood pressure), an intraarterial catheter, a pulmonary artery catheter, and TEE are routinely employed during LVAD implantation.

Before LVAD implantation, TEE is used to detect anatomic pathologies that will:

- impede optimal LVAD filling (eg, mitral stenosis, severe tricuspid regurgitation, severe RV dysfunction),
- decrease the potential for optimal LV decompression (eg, aortic regurgitation), and
- cause complications once the LVAD is functioning (eg, patent foramen ovale, atrial septal defect, intracardiac thrombus, ascending aortic atherosclerosis, mobile ascending aortic plaques).

During LVAD implantation, TEE is used to:

- ensure proper inflow cannula position (in the center of the left ventricle, pointing toward the mitral valve; often the midesophageal two-chamber view at a 90-degree angle best reveals the cannula position, but three-dimensional imaging can also be helpful) (Fig. 28.16), and

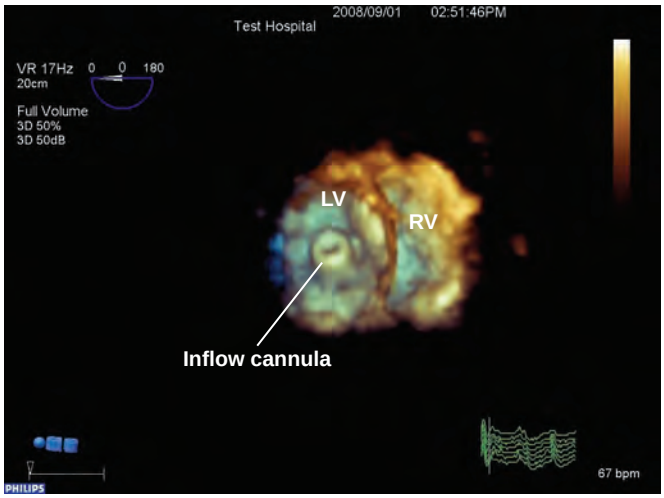


Fig. 28.16 The cannula orifice should be centrally located entering the apex of the ventricle, aligned to the left ventricular inflow tract (mitral valve orifice), not abutting any ventricular structures. *LV,* Left ventricle; *RV,* right ventricle.

- ensure adequate de-airing of the device (and the heart) before and after engagement of support.

The Postimplantation Period

Hemodynamics can initially be quite labile once LVAD support is engaged until intravascular volume is restored, vasomotor tone is reestablished in both the systemic circuit and the pulmonary beds, and RV function is optimized. Thus, despite a properly functioning device, inotropic and vasoactive agents are often required to enable separation from CPB. Certain management strategies appear to be more advantageous than others, and an understanding of the physiology of the LVAD-supported state greatly aids in decision making.

Potential Effects of LVAD Support on Right Ventricular Function

Data from the era of the pulsatile VADs consistently reported the response of the right ventricle to LV unloading by an LVAD to include an increased RV preload, increased RV compliance, decreased RV afterload, and overall decreased RV contractility.[86–92] It has also been established that preexisting or perioperative RV disorders (eg, regional ischemia, poorly compensated chronic ventricular failure, inflammatory insults) can predispose the patient to profound deterioration of RV function when LVAD support is engaged.

To understand RV decompensation in the post-LVAD implantation setting, several key physiologic principles must be appreciated, namely, ventricular interdependence, series circulatory effects, and ventriculoarterial coupling (Box 28.5). First, the concept of *ventricular interdependence* centers on the continuous nature of the muscle fibers between the free wall of the right ventricle and the left ventricle and the presence of a common interventricular septum (IVS), which results in anatomic and mechanical coupling of the ventricles.[93] Second, the concept of *series circulatory effects* holds that it is the output of the right ventricle that fills the LVAD and that the LVAD output in turn becomes the preload of the right ventricle. Third, the concept of *ventriculoarterial coupling* holds that no matter how impaired the intrinsic systolic mechanics of the ventricle are, the chamber can always function better as a pump if one reduces the afterload against which it must pump. Additionally, one must appreciate the unique anatomic and physiologic properties of the right ventricle as they relate to pump function.

BOX 28.5 KEY PHYSIOLOGIC PRINCIPLES IN VENTRICULAR ASSIST DEVICES

- Ventricular interdependence
- Series circulatory effects
- Ventriculoarterial coupling

Ejection of blood from the right ventricle is accomplished by two separate simultaneous actions: (1) compression of the chamber caused by contraction of the single layer of transverse fibers that make up the free RV wall, and (2) a twisting caused by sequential contraction of the two layers of obliquely oriented septal fibers.

In the absence of normal septal twisting, RV ejection must be produced only by contraction of the basal wall that contains a single layer of predominantly transverse fibers. This compression may not always provide enough contractile force to ensure adequate cardiac output, especially if pulmonary vascular resistance is increased. It has long been known that normal septal function can compensate for loss of the RV free wall with respect to overall RV systolic performance, but the RV free wall cannot always compensate for loss of septal function, and RV failure appears to be a problem primarily when the septum becomes dysfunctional.

Perhaps the most obvious effect of LV decompression by an LVAD is the potential shift of the IVS to the left, but bowing of the IVS to the left creates what has been called an *architectural septal disadvantage* because the distortion of the normal architecture of the IVS results in the otherwise obliquely oriented septal muscle layers assuming a more transverse orientation with respect to one another, with subsequent loss of normal septal twisting. Numerous investigators have demonstrated the critical contribution of the IVS to RV pump function,[86,94–98] and it has long been demonstrated that as long as septal function is unimpaired, contraction of the RV free wall is of little consequence where overall RV pressure development and volume outflow are concerned.[99,100]

Another consequence of deforming the septum is dysfunction of the electrical conduction system due to stretching of the conducting pathways. Intraventricular conduction delays resulting in dyssynchronous contraction of the ventricle lead to a decrease in overall systolic function. Additionally, it is clear that stunning of the IVS is common following prolonged CPB despite the best of myocardial protective efforts, and there can be residual adverse electrophysiologic effects of cardioplegia that can persist through the early period after bypass. One or both of these factors can act to increase the degree of septal dysfunction. Thus, decompression of the left ventricle plays a big role in the baseline predisposition to RV failure, because it causes septal shift leftward, which can result in septal dysfunction, but this is not the only factor predisposing to RV failure during LVAD support.

The LVAD and right ventricle exist in series, as codependent pumps in a circuit. Given that the right ventricle may be mechanically disadvantaged because of septal dysfunction of various causes when LVAD support is engaged, it may not tolerate even modestly increased preload. Potential sources of increased RV preload during LVAD support include high LVAD outputs, requisite perioperative transfusions of blood and blood products, and the potential for increased tricuspid regurgitation if the level of LV decompression results in septal displacement. Potential causes of increased tricuspid regurgitation include (1) deformation of the tricuspid annulus, and (2) distraction of the subvalvular apparatus attached to the IVS, resulting in failure of apposition of the leaflets.

Despite the predisposition to RV dysfunction based on ventricular interdependence and the potential problems that may come from the series circulatory effects, it appears that the beneficial effect of decreased RV afterload due to LVAD action still tends to outweigh any impairment of intrinsic RV systolic mechanics. An overall improvement in RV pump function is generally seen during LVAD support in patients with normal pulmonary vascular resistance. This illustrates the principle of *ventriculoarterial coupling,* in which a conceptual separation of RV systolic mechanics from overall RV pump function reveals the critical importance of RV afterload.

As discussed in detail earlier, and as might be surmised from the success of Fontan physiology, RV pumping function is probably dispensable in the LVAD-supported patient, so long as the pulmonary vascular resistance is normal.[101] Pulmonary vascular resistance, however, is not always normal after LVAD implantation. In many patients, pulmonary vascular resistance rises due to pulmonary vascular endothelial injury from inflammatory mediators resulting from prolonged exposure to extracorporeal circulation, as well as from perioperative blood and platelet transfusions. Other causes include the routine ones that are encountered in the care of critically ill patients, such as hypoxemia, hypercarbia, acidosis, hypothermia, large tidal volumes, pain, and catecholamine infusions. Fig. 28.17 demonstrates the potential consequences of increased RV afterload.

Furthermore, the potential roles of perioperative events and management cannot be discounted in the etiology of potential RV failure during LVAD support. Numerous factors potentially influence the outcome of the patient, including the timing of LVAD insertion in the course of the patient's heart failure, surgical misadventures, stunning of the right coronary artery distribution during CPB, and hypotension in the post-CPB period compromising coronary perfusion. While ischemic insults or other injuries to the RV free wall do not appear to have great influence on the development of RV failure when LVAD support is engaged, ischemic insults to the septum will likely have profoundly negative consequences.

The quality of perioperative care is also a major determinant of success in LVAD implantation, and it is imperative that staff caring for patients immediately after LVAD implantation be well versed in the relevant physiology and associated risks. While relative hypovolemia is a common issue in the LVAD-supported patient, large rapid volume loads are a potential problem for a right ventricle that is already mechanically disadvantaged, and fluid management must be approached judiciously. Perhaps the biggest concern is increased pulmonary vascular resistance. As described earlier, once the septum becomes deformed from LV decompression, the transversely oriented fibers can only generate enough pressure to eject into a low resistance pulmonary vascular bed. Thus, between the physiology of the LVAD-supported state and potential perioperative events and requisite postoperative care, there are many reasons why the right ventricle is at increased risk of failure during LVAD support.

Intravascular Volume Status

LVADs are dependent on adequate volume in the LV chamber. Most elective LVAD patients will have started out volume overloaded and with a massively dilated left ventricle. With the nonpulsatile devices, if the amount of blood removed from the ventricle by continuous VAD action exceeds the amount of blood present in the left ventricle, *suckdown* occurs; that is, the continuous flow VAD sucks the ventricle empty, which results in decreased output and hypotension. Thus, the goal for perioperative fluid management is to maintain a euvolemic, if not slightly hypervolemic, state (which may help minimize vasopressor requirements), assuming the unsupported and potentially dysfunctional right ventricle is able to handle the volume load. An empty left ventricle also shifts the IVS to the left, changing the geometry of the right ventricle, which decreases its function (septal architectural disadvantage discussed earlier) and decreased RV function is another important reason for an inadequate preload to an LVAD. Furthermore, the effect of surgical positioning and/or retractors must be monitored so as not to obstruct venous return to the right ventricle, and high intrathoracic pressures (eg, from excessively large tidal volumes) should be avoided once the chest is closed for the same reason. Overall, LVADs generally function well as long as there is sufficient intravascular volume (and RV function) to fill the pump, but management must

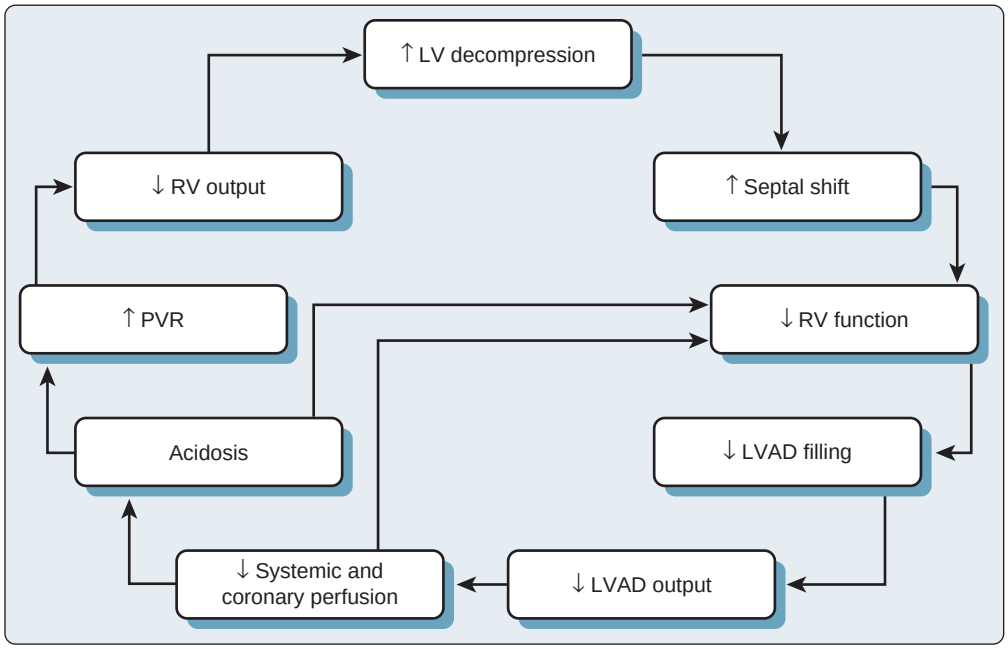


Fig. 28.17 The potential consequences of increased right ventricular *(RV)* afterload. *LV,* Left ventricular; *LVAD,* left ventricular assist device; *PVR,* pulmonary vascular resistance.

be individualized. The HM II control console (Fig. 28.18) provides several parameters that are helpful in this regard.

Afterload and Contractility

In general, the profound vasodilatation that often follows LVAD implantation requires administration of vasoconstrictors to maintain adequate perfusion pressures. A major goal following LVAD implantation is to maintain pulmonary vascular resistance as low as possible; thus, vasopressin may have advantages over norepinephrine because of vasopressin's lack of pulmonary vasoconstrictive effects.[102] Physicians must be cautious, however, because markedly increased SVR may sometimes impair forward flow from certain LVADs. The current generation of axial flow devices are not likely to be affected, but the output from the new miniaturized centrifugal devices can be sensitive to afterload. Inotropic agents are also typically required to support the function of the right ventricle. A typical pharmacologic regimen that may be required includes milrinone (0.3–0.75 µg/kg per minute), vasopressin (2.5-5 units/h), nitric oxide (20–40 parts per million) and epinephrine (0.05–0.25 µg/kg per minute). As noted earlier, norepinephrine may be disadvantageous if significant pulmonary hypertension is present due to the imperative to keep RV afterload as low as possible. Where refractory vasodilatory shock is manifest, a bolus of methylene blue (0.5–2 mg/kg IV) may be of help in restoring vasomotor tone. In severe cases, a continuous infusion of methylene blue (0.5 mg/kg per hour) may be required.

Bleeding

Anecdotally, and for a number of potential reasons, intraoperative or postoperative bleeding does not seem to be as severe with the modern devices as it once may have been with the large pulsatile devices, but coagulopathy following VAD implantation remains common despite the routine use of antifibrinolytic agents, and the transfusion of platelets, cryoprecipitate, and fresh frozen plasma (FFP) is often necessary to restore hemostatic competence. However, practitioners must be cautious, because rapid infusion of large volumes can precipitate RV failure. Moreover, significant risk of transfusion-associated lung injury (TRALI) exists with the transfusion of platelets

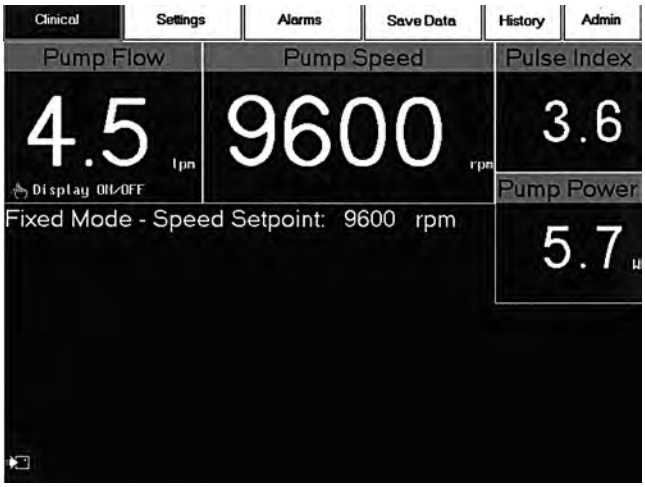


Fig. 28.18 The HeartMate II control console. *(From Reed AP, Yudkowitz FS, eds.* Clinical Cases in Anesthesia. *4th ed. Philadelphia: Elsevier; 2014.)*

and FFP. Where available, thromboelastography can be extremely useful to help guide the judicious transfusion of blood products. Factor concentrates such as prothrombin complex concentrates (PCC) represent a compelling alternative to FFP, both from the perspective of avoiding volume overload and TRALI. When compared to FFP, PCCs have been shown to restore target factors and reverse factor-dependent coagulopathy more rapidly, with negligible additional volume, and lower risk of TRALI.[103,104]

Another source of coagulopathy uniquely associated with LVAD implantation involves the dysfunction of von Willebrand factor (vWF). Sheer forces generated by some VAD devices promote cleavage of vWF multimers by the metalloprotease ADAMTS13, leading to an acquired vWF deficiency and increased tendency for gastrointestinal bleeding, wound site bleeding, and epistaxis. Recent data from a population of nearly 1000 HM II patients demonstrated an overall 38% incidence

and prevalence of bleeding, with gastrointestinal bleeding in 29% of those implanted as destination therapy and 13% of those implanted as bridge to transplantation.[105] Thus, strategies to control bleeding in these patients should ideally include the use of vWF-containing concentrates, factor VIII concentrates, antifibrinolytics, and desmopressin (DDAVP).

The Postimplantation Role of Transesophageal Echocardiography

After LVAD placement, TEE is used to:

- Ensure adequate LV decompression (but not complete obliteration of the LV cavity)
- Ensure RV function does not deteriorate (may need RVAD as well)
- Ensure tricuspid regurgitation does not worsen (may need annuloplasty)
- Reevaluate for patent foramen ovale (must be closed if detected)
- Assist with diagnosis of new patient problems that arise in the postoperative period (eg, hypovolemia, tamponade, cannula misalignment or obstruction)

Anesthetic Considerations for SynCardia Total Artificial Heart Implantation

Preoperative considerations and pre-CPB management are largely as discussed earlier for LVAD implantation. Patient receiving an elective TAH (eg, as a bridge to transplantation) generally have biventricular failure, which, if chronic, has likely resulted in hepatic pathophysiology, portending poor hemostatic potential and poor nutritional status. Patients receiving a TAH in the setting of a failing heart transplant or a malfunctioning LVAD require all of the considerations associated with reoperative cardiac surgery.

The Role of Transesophageal Echocardiography Before Cardiopulmonary Bypass for Total Artificial Heart Implantation

Given that the native ventricles and heart valves are removed during implantation, the role of the pre-CPB TEE is somewhat limited, but certain baseline findings may need to be addressed before engaging support by the device and/or may play a role in the period after implantation.

- As the native atria will remain once the device is in place (the inflow cuffs of the SynCardia device are anastomosed to the ventricular side of the mitral and tricuspid annuli), atrial septal defects must be sought (and closed).
- The inferior vena cava should be imaged and measured at the point where it enters the right atrium, and the flow profile should be noted.
- Flow profiles in all four pulmonary veins should be imaged and noted.
- Atherosclerotic burden in the aorta should be characterized and taken into account, so as to assist in guiding anastomosis of the aortic outflow graft.
- The left atrial appendage (which will be ligated during the implantation) should be imaged.
- Although the mitral and tricuspid leaflets and all of the subvalvular apparatus will be excised during the implantation, the annuli will remain, so it is reasonable to assess the annuli for vegetations and calcifications.

Post-CPB management centers on optimization of volume status and vascular resistances and restoration of hemostasis. Perfusion pressures are directly dependent on volume status and the vascular resistances, but the TAH requires appropriate optimization of the parameters of its function. Such parameters include the drive pressures, the pump rate, and the percentage of time spent in systole.

- Drive pressures should be set slightly higher than the systemic and pulmonary pressures (eg, set at 100–150 mm Hg and 60-80 mm Hg, respectively), but the pressures should not be so excessive as to cause bleeding from fresh suture lines on the great vessels. The drive pressures are adjusted to achieve full ejection. Often, the left-sided drive pressures are set relatively higher than those for the right to unload the pulmonary veins.
- Pump rate is adjusted as needed, but an initial rate of approximately 125 beats per minute is not unusual.
- Percent systole is generally initially set to 50% and then adjusted as needed to achieve complete filling.
- Vacuum is generally not used to assist filling until the chest is closed (to avoid entraining air through fresh suture lines).

To understand how to optimize the patient supported by a SynCardia TAH, familiarity is required with the waveforms on the controller for filling and ejection. The standard device ventricles can accommodate 75 mL, but the fill volume is normally set to 50 to 60 mL so the device can accommodate occasionally increased venous return. Regarding the waveforms, an abrupt drop to zero flow during diastole represents complete filling, and an abrupt end-systolic rise in pressure represents complete ejection. If the flow does not drop to zero during the diastolic phase, then filling of the ventricles is incomplete, and augmentation of intravascular volume is indicated. Alternatively, next steps are to decrease the beat rate and/or slightly decrease the percent systole (eg, 50% down to 48%). Once the chest is closed, the amount of vacuum can be increased to assist filling, but vacuum stronger than –20 mm Hg may increase hemolysis. If no abrupt rise in end-systolic pressure is noted during device systole, then ejection is incomplete, and next steps are increasing the drive pressure and/or decreasing the relevant vascular resistance with an appropriate vasodilator (eg, nicardipine or nitroprusside for the left side; nitric oxide, milrinone for the right side).

As with other RVADs, pulmonary edema has been reported with this device, sometimes requiring ECMO.[106] It should be understood that the origins of such pulmonary edema may be multifactorial; hydrostatic pressure in the pulmonary bed as a result of RVAD action certainly plays a role, but alveolar integrity may also be compromised.

Following implantation of a TAH, TEE is used to:

- Ensure adequate de-airing of the device
- Detect flow acceleration in the pulmonary veins or inferior vena cava, which may represent relative occlusion due to kinking or twisting as a result of the positioning of the device
- Visualize the proper functioning of the tilting disk mechanical valves in the device
- Visualize the outflow into the great vessels

These images and assessments should be performed again following chest closure, as the position of the device may have changed.

Following chest closure, device settings may need to be adjusted to ensure full filling and emptying.

Conclusion

This chapter has summarized the phenomenal advances realized in the past decade in the arena of MCS. As patients with heart failure comprise one of the fastest growing segments of our aging population, and as outcomes continue to improve with advancing technology and patient-care experience, MCS will undoubtedly continue to play a pivotal strategy in prolonging a high quality of life for patients who would otherwise succumb to end-stage heart failure.

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29

Reoperative Cardiac Surgery

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KEY POINTS

1. Reoperative cardiac surgery presents greater risk than first-time surgery because patients are usually older, have more comorbidities, and have more advanced cardiovascular disease. Also, resternotomy can be hazardous due to adhesions of cardiac structures to the sternum. Bypass conduits may not be unavailable due to prior use, and the frequency of valve replacement versus valve repair is higher.
2. A thorough history, clinical evaluation, and review of imaging must be performed—with particular thought to weighing the risk of surgery against the possibility of medical management with multidisciplinary expertise—before making the decision to proceed.
3. Preinduction anesthetic preparations include placement of defibrillator pads, pacemaker or defibrillator adjustments, and placement of invasive monitoring in the setting of the possibility of peripheral cannulation strategies and alternative cardiopulmonary bypass techniques such as cooling before sternotomy.
4. Coagulopathy can be strategically managed using point-of-care testing to guide blood and blood product transfusion.
5. Emergency reexploration is a high-risk situation in which expeditious surgical intervention is required, usually in the setting of bleeding with pericardial tamponade. Transfusion should be anticipated, hemodynamics supported, and heparin ready to administer in anticipation of possible cardiopulmonary bypass.

In contemporary practice, 3% to 4% of coronary artery bypass graft (CABG) operations and approximately 10% of valve surgery procedures are reoperations.[1,2] Reoperative cardiac surgery carries an incremental risk of mortality and major morbidity compared with first-time or primary cardiac surgery because patients are usually older, with additional comorbidity and more advanced cardiac disease, and because of specific technical challenges presented by prior cardiac surgery.[3] The surgical approach to incision and cannulation in coronary and valve surgery reoperations often differs significantly from the approach used in primary cases, and adverse intraoperative events that require immediate changes to the planned strategy are common and often predictable.[4–6] Preoperative assessment and planning with the surgical team is therefore particularly important because optimal patient care may require the modification of several aspects of standardized cardiac anesthetic approaches. The incidence of emergency reexploration ranges from 1% to 5% after cardiac surgery, and the primary challenges relate to effectively managing major cardiopulmonary instability and ensuring safe and efficient surgery, either in the operating room or outside the operating room setting.

This chapter deals with two different aspects of reoperations in cardiac surgery. The first is repeat cardiac surgery performed at an interval of more than 1 month after a cardiac operation, in which the presence of adhesions, prior cardiac surgery, and patient comorbidity require a highly tailored approach to anesthesia and operative intervention. The second is emergency reexploration, usually within the first few hours to days after cardiac surgery, which may occur in the operating room or in the intensive care unit (ICU).

Reoperative Cardiac Surgery

Indications for Reoperative Cardiac Surgery

The indications for reoperative cardiac surgery are based on the same principles as for primary cardiac surgery. However, the incremental hazard of resternotomy, the lack of bypass conduits, the greater age and comorbidity of this patient group, and the likelihood of valve replacement rather than repair are additional considerations. Consequently, the threshold for recommending surgery rather than medical or transcatheter approaches is higher for reoperative patients. The large majority of patients with symptomatic coronary artery or graft stenoses after CABG surgery are most effectively treated by percutaneous coronary intervention (PCI).[1] Very symptomatic patients with significant lesions to a left anterior descending graft are generally considered to gain symptomatic and prognostic benefit from reoperative coronary artery surgery. The main indications for reoperative valve surgery include prosthetic valve dysfunction (for which the results of transcatheter valve-in-valve implantation are still preliminary) and endocarditis, which is a contraindication to transcatheter valve replacement. Paravalvular leaks are increasingly addressed by percutaneous placement of occluder devices. Late reoperation for isolated severe tricuspid regurgitation is associated with particularly high mortality and major morbidity because of the high prevalence of preoperative moderate-to-severe right ventricular dysfunction, pulmonary arterial hypertension, and multiorgan dysfunction in this population.

Preoperative Assessment

History

Patients undergoing reoperative cardiac surgery are generally older have more comorbidity and more advanced cardiovascular disease than patients undergoing first-time surgery.[3] The decision to operate usually depends on correlating a precise account of the nature, timing, and severity of symptoms with the findings from diagnostic studies and balancing the benefits of intervention against the incremental risk of mortality and morbidity posed by reoperation. The presence of any significant comorbidity is a major consideration in calculating the patient's predicted risk of death or major complications.

Risk calculators, such as The Society of Thoracic Surgeons online Risk Calculator (accessible at http://riskcalc.sts.org/stswebriskcalc/#/calculate), are very helpful adjuncts. Patients who are not capable of many of the activities of daily living at baseline due to noncardiac disability may not be appropriate candidates for reoperative intervention, and a careful functional history is needed to evaluate this possibility. Additionally, the medical history should establish details of all prior cardiovascular procedures, including date and type of PCI; any previous cardiac surgery, including incisions; history of difficult intubation or adverse reaction to anesthesia, respiratory failure, or tracheostomy; coagulopathy and blood transfusions; and postoperative sepsis and organ dysfunction. All efforts should be made to obtain prior hospital records, particularly operative notes, so that the precise details of previous procedures, including cannulation sites, cardiotomies, prosthesis sizes, and any intraoperative complications can be accurately known. Although the balance of risks generally favors continuing antiplatelet medication until surgery in non-reoperative patients, this may not be the case in patients scheduled for reoperative surgery, who will be at greater risk of postoperative coagulopathy and bleeding. It may be appropriate to admit patients preoperatively in order to discontinue oral anticoagulation and transition to a shorter-acting regimen, such as a heparin infusion.

Clinical Examination

One of the most important risk factors for poor outcomes is frailty.[4] Although this is not well defined, and consequently is not included in most risk models, it is a relatively easy, albeit subjective, judgment often made by looking at a patient. Quantitative evaluation of frailty through shuttle tests, muscle mass measurements, and strength gauges has been used in clinical trials but is not commonly performed in clinical practice. Physical examination of all patients referred for cardiac surgery includes a careful inspection of the entire chest and abdomen. Patients may omit to mention distant cardiac and thoracic surgery procedures, and these may become evident only from incisions, which can be inframammary, posterior thoracotomy, or axillary. All incisions, including conduit harvest sites, pacemaker or defibrillator insertion sites, and potential sites of peripheral cannulation for cardiopulmonary bypass (CPB) in upper and lower extremities should be assessed for signs of distant or recent infection, poor healing, and vascular complications such as stenosis or aneurysm formation. Important clinical signs that may not have been documented in the history or prior investigations and are easy to elicit include chronic or paroxysmal atrial fibrillation; hypertension or hypotension; peripheral edema; sensory and motor neuropathy, particularly in elderly or diabetic patients; cognitive impairment; and poor dentition, which necessitates a dental examination in any patient for whom valve surgery is planned. Evaluation of the airway includes inspection of the suprasternal notch and trachea for evidence of prior tracheostomy.

Imaging

With the exception of young adult patients without risk factors for acquired or congenital coronary artery disease, all patients should have recent cardiac catheterization including coronary angiography to assess the patency and anatomy of native vessels and any CABG. In young patients, computed tomographic (CT) coronary angiography usually provides sufficient information about coronary anatomy. Coronary angiograms should be reviewed to determine whether grafts are close or even adherent to the sternum. The presence of patent coronary bypass grafts is a potential hazard during sternal reentry and mediastinal dissection because manipulation of them may result in embolization, occlusion, or hemorrhage that could precipitate myocardial ischemia and ventricular fibrillation. Additionally, the presence of patent bypass grafts may dictate operative choice of incision, cannulation, and myocardial protection strategies (see later discussion) (Fig. 29.1).

Cross-sectional imaging, typically CT, is particularly helpful in planning cardiac reoperation because it reveals the relationships among important structures including the aorta, right atrium, right

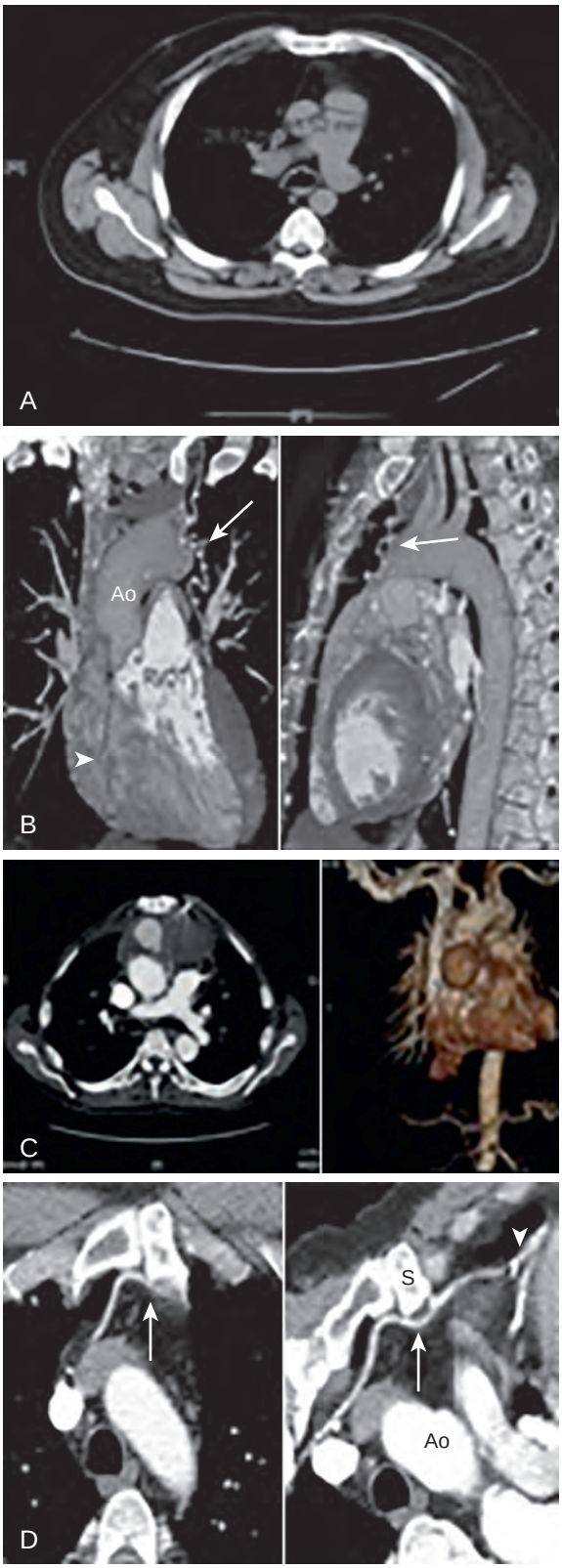

Fig. 29.1 Cross-sectional imaging of reoperative cardiac surgery patients illustrates anatomy that indicating the risk posed by resternotomy. (A) Low-risk resternotomy: Aorta and pulmonary artery are of normal caliber and well away from the sternum. (B) Moderate-risk resternotomy: Patent left internal mammary artery graft *(arrow)* is lying lateral to and distant from the sternum. There is a normal-caliber aorta *(Ao)* distant from sternum. (C) High-risk resternotomy: Right ventricle is adherent to sternum. (D) Patent left internal mammary artery graft crosses midline close to sternum *(arrow)*. *(From Akujuo A, Fischer GW, Chikwe J. Current concepts in reoperative cardiac surgery.* Semin Cardiothorac Vasc Anesth. *2009;13:206–214.)*

ventricle, pulmonary artery, innominate vein, and any bypass grafts to the planned incision. Noncontrast CT provides helpful visualization of calcification and aneurysmal segments along the entire arterial tree from aortic root to femoral vessels that may dictate choice of cannulation site. The presence of large amounts of prosthetic material indicates potentially severe adhesions. Intravenous contrast may be employed in CT angiography to demonstrate the course of bypass grafts more clearly; contrast is required to assess patency, and it provides detailed information on the presence of peripheral vascular disease, which is particularly relevant if peripheral arterial cannulation is planned or the patient is likely to need an intraaortic balloon pump.

Echocardiography is necessary to quantify right and left ventricular function, the presence of pulmonary hypertension, and the nature and grade of any valvular dysfunction. Transesophageal echocardiography (TEE) is particularly valuable in the detailed assessment of prosthetic valve endocarditis and failed valve repair or if transthoracic echocardiographic windows are poor. The presence of moderate aortic insufficiency precludes mitral valve approaches under fibrillatory or beating heart conditions without aortic cross-clamping. It also implies that antegrade cardioplegia will not be delivered reliably via the aortic root and will lead to ventricular distention if the heart fibrillates on CPB before cross-clamping or circulatory arrest, resulting in inadequate myocardial protection.

In patients for whom a thoracotomy approach is planned, preoperative lung function testing, including arterial blood gas sampling, will provide an indication of whether single-lung ventilaton will be tolerated, particularly in the post-CPB period, when lung function is worse than baseline. Preoperative evaluation of central venous access with ultrasound is helpful in patients with a history of multiple central venous catheters, transvenous pacemakers, or dilaysis shunts and in those with prothombotic disorders because they are at increased risk of stenosis or occlusion of the brachiocephalic venous circulation.

Before Induction

Days Before Induction

Reoperative patients require the same laboratory tests as patients undergoing first-time surgery. The presence of renal or hepatic dysfunction at baseline means that particular attention must be paid to maintenance of adequate systemic flows, perfusion pressure, and venous drainage on CPB. Patients with preoperative anemia and thrombocytopenia, particularly if they have low body surface areas, are more likely to require blood products than if they were undergoing first-time surgery. In reoperative patients, the hemostatic benefits of stopping antiplatelet drugs (particularly dual antiplatelet therapy) before surgery outweigh the risks of acute coronary ischemia.[5] In patients with or at high risk of acute coronary syndromes, short-acting antiplatelet drugs can be used as a bridge to surgery.[7,8] Intravenous heparin should be stopped 4 to 6 hours before the planned surgery time and eptifibatide (Integrilin) infusions at least 12 to 24 hours beforehand. Withholding long-acting vasodilators, particularly angiotensin-converting enzyme inhibitors, for 48 hours before surgery may reduce the risk of postoperative vasoplegia.

Immediately Before Induction

Adhesive external defibrillator pads must be attached to the patient before induction. It is advisable to review placement of these pads with the surgical team, who may need access to the left chest wall. The external defibrillator pads are retained throughout the case for several reasons: Internal paddles usually cannot be used because of dense adhesions; electrocautery of adhesions close to myocardium may directly induce ventricular fibrillation; and damage to patent bypass grafts during mediastinal dissection can cause severe myocardial ischemia leading to ventricular fibrillation. As in primary cases, delivery of external defibrillator energy to the heart may be enhanced by optimal lung inflation.

A significant proportion of reoperative patients have cardiovascular implantable electronic devices that should be checked preoperatively by an individual familiar with the device to ascertain its functionality and to devise a plan for intraoperative management (see Chapter 5). The defibrillator function mode of an implantable cardioverter-defibrillator should be disabled for the duration of surgery using the appropriate programming computer. Otherwise, defibrillation shocks (which can precipitate asystole or ventricular fibrillation) may be triggered by electrocautery. The devices should be interrogated again and appropriate defibrillator and pacing settings restored postoperatively, before the removal of temporary epicardial pacing wires. The external defibrillator pads should remain in place for the entire period that the permanent devices are disabled.

In reoperative cases in which CPB times may be prolonged, with associated vasoplegia or low cardiac output states, arterial pressure tracings from distal arteries are often damped and may be unreliable. The presence of two arterial catheters is particularly valuable in reoperative patients who are at increased risk of vasoplegia, low cardiac output, or malperfusion; one of these catheters should be placed in a large proximal artery (either femoral or axillary) to provide a reliable indication of central arterial pressure. Alternatively, monitoring of central arterial measurements via the aortic cannula, an aortic vent or cardioplegia cannula, or placement of a small-bore needle or catheter directly into the aorta can be performed at key intervals such as onset and weaning from CPB. The plan should be discussed with the surgical team because cannulation and the operative strategy will dictate the available location and utility of these catheters. If axillary artery cannulation is planned, the ipsilateral radial artery provides helpful assessment of distal hyperperfusion or hypoperfusion once CPB is commenced, but a catheter in the contralateral arm (radial or axillary) or a femoral catheter must be placed for assessment of the systemic arterial pressure. If femoral cannulation is planned for CPB, then an ipsilateral femoral arterial catheter should not be placed (because it will be in the way) unless the surgeon requests such a placement to facilitate percutaneous femoral cannulation. If a radial artery conduit harvest is planned, the ipsilateral radial artery should not be catheterized and venous access should be avoided in the ipsilateral arm to optimize maintenance of a sterile surgical field during radial artery harvest.

Anesthesia

Balanced and high-dose narcotic techniques can be used in the reoperative setting. Particular attention must be paid to patients who are at high risk of cardiovascular collapse during induction, such as those with unprotected critical left main (or left main equivalent) coronary artery stenosis, severe aortic stenosis, or cardiac tamponade. If these types of patients decompensate, their obstructive anatomy means that they will rarely respond well to standard cardiopulmonary resuscitation. Emergency sternotomy, internal cardiac massage, and institution of central CPB are usually not possible because of adhesions that prevent safe, rapid access to the mediastinum. Therefore, in selected reoperative patients thought to be at particularly high risk of cardiovascular decompensation during induction of anesthesia, it may be appropriate to place arterial and central lines in the awake patient and then perform preparation and draping for sternotomy and/or rapid femoral cannulation with the surgeon scrubbed before anesthesia is induced.

In view of the potential for massive hemorrhage and the difficulty in achieving rapid surgical access, large-bore venous access, such as with a 9-French (or larger) central venous introducer, is essential to guarantee the capability for rapid volume infusion. This should be obtained with superficial vascular ultrasound guidance, manometry, and/or confirmation of the wire during the Seldinger technique in the right atrium by TEE. Lung separation with a double-lumen endotracheal tube or a bronchial blocker may be indicated for thoracotomy approaches.

Once the patient has been intubated tracheally and monitoring catheters have been inserted, all prior chest and abdominal incisions, previous drain sites, extrathoracic cannulation, and conduit harvest

TABLE 29.1 Risk Stratification of Low, Medium, High, and Very High Risk Sternotomies, With a Summary of Operative Strategy Tailored to Address Risks

Preoperative Assessment of Risk		*Intraoperative Strategy*
INCREASING RISK OF MAJOR INJURY	Low-risk resternotomy: • Prior cardiac surgery without patent coronary bypass grafts • Aorta and mediastinal structures a safe distance from the sternum (Fig. 29.1A)	• Resternotomy, dissection of adhesions, standard aortocaval cannulation; initiate bypass; proceed with residual adhesiolysis and cardiac surgical procedure • Optional: Expose peripheral cannulation sites before stenotomy
	Moderate-risk resternotomy: • Patent coronary bypass grafts that lie >1 cm from the sternum, including patent left internal mammary artery (IMA) to left anterior descending coronary artery routed lateral to the sternum (*arrow* in Fig. 29.1B)	• As above • Optional: peripheral arterial cannulation, with 5000 units of heparin given and arterial line flushed intermittently by perfusion; resternotomy and division of adhesions as above • If major vascular injury occurs, venous cannulation can be performed peripherally, and centrally and after full heparinization cardiopulmonary bypass (CPB) is commenced.
	High-risk resternotomy: • Patent left IMA graft crossing midline close to sternum, right ventricle adherent to sternum (Fig. 29.1C), normal aorta in close proximity to sternum • Third- or fourth-time resternotomy	• Peripheral and arterial cannulation with full heparinization before resternotomy • Optional: Institute CPB, stop ventilation, and drain venous return into pump reservoir to decompress right side of heart
	Very-high-risk resternotomy: • Patent left IMA graft crossing midline adherent to sternum (Fig. 29.1D) and large area of myocardium at risk, aortic tube graft or aneurysm adherent to sternum	• Peripheral and arterial cannulation with full heparinization, institution of CPB, cooling before resternotomy • Optional: circulatory arrest under moderate hypothermia during sternotomy

Adapted from Akujuo A, Fischer GW, Chikwe J. Current concepts in reoperative cardiac surgery. *Semin Cardiothorac Vasc Anesth.* 2009;13:206–214.

sites should be reconfirmed by the surgical team. Femoral and axillary cannulation sites should be marked, and the patient should be prepared and draped so that extrathoracic cannulation sites (axillary and femoral), conduit harvest, and permanent pacemakers and defibrillators can be accessed from within the sterile field. An antifibrinolytic agent should be administered intravenously before incision to mitigate the incremental risk of postoperative bleeding in reoperative patients.

Before Incision

The strategy and order of sternotomy, heparinization, cannulation, and institution of bypass may be very different in a reoperation because the safest sequence of these steps is dictated by the risk posed by resternotomy (Table 29.1).[6] Many institutions mandate a surgical time-out and checklist before incision in which the patient, key personnel, and operative plans are identified. This is a useful point at which to reconfirm the planned sequence of steps. Cross-matched blood should be checked and made immediately available before incision. The CPB circuit should be fully primed, and the bypass lines should be brought up to the field before sternotomy, during which time the perfusionist, attending anesthesiologist, and circulating nurse must be present.

Incision

The sternal skin incision is usually made in the standard fashion, and then the sternal wires are untwisted, cut, and either bent to the sides or removed entirely. This can theoretically result in laceration of vascular structures in close proximity underneath, including the right ventricle. Some surgeons elect routinely to perform an initial dissection under the sternum using thoracoscopic guidance. In cases in which an aneurysmal aorta is thought to be densely adherent to the posterior sternal table, a small transverse incision may be made in the second or third left intercostal space to allow the aorta to be dissected free before median sternotomy.

The anterior sternal table is divided with an oscillating saw. Under an optional period of apnea, the posterior table is then divided along its entire length with either the oscillating saw or a heavy blunt-tipped scissors. This part of the sternotomy poses the most risk to underlying structures. Injury to these structures is particularly problematic because hemorrhage and hemodynamic instability may prevent completion of the sternotomy—in which case the surgeon will have insufficient surgical access to address the injury effectively. To minimize the risk of this scenario, surgeons commonly try to decompress the mediastinal structures by asking the anesthesiologist to hold ventilation and, in the case of patients who have been cannulated and heparinized, asking the perfusionist to exsanguinate the patient into the pump temporarily. On rare occasions, the safest option is to commence CPB using peripheral cannulation, cool the patient, and arrest the circulation before skin incision and sternotomy (see Table 29.1). This last option would usually be reserved for cases in which there is a very high risk of laceration of the ascending aorta on sternotomy.

Electrocautery is used to dissect the heart away from the left sternal edge and then the right sternal edge. Excessive retraction of the sternum before this dissection is fully completed can result in right ventricular rupture. Other possible complications during this initial dissection are ventricular arrhythmias, including fibrillation as a result of electrocautery in proximity to the myocardium and injury to a patent left internal mammary artery (IMA) graft resulting in myocardial ischemia and a high likelihood of ventricular dysfunction and/or ventricular fibrillation.

Subsequent mediastinal dissection is targeted at obtaining access to central cannulation and aortic cross-clamp sites, specifically the aorta, and the right atrium. A "no touch" technique is used for bypass grafts to avoid distal embolization and myocardial ischemia. The most common injuries during this phase of dissection are to the right atrium, which is frequently thin walled and densely adherent at sites of prior cannulation and atriotomy. Such injuries can usually be addressed with primary suture closure, but occasionally institution of CPB is mandated to effect a repair.

For patients undergoing a mitral, a tricuspid, or (occasionally) an aortic valve procedure, a right thoracotomy may be less hazardous than a median sternotomy. In these cases, after the intercostal muscles have been divided, the right lung is deflated before the pleural space is entered. This technique is used to reduce the risk of injury to structures lying adjacent to the sternum. The disadvantage with a right thoracotomy approach is that access to the lateral border of the heart, the ascending aorta, and the aortic valve is limited. Although it is effective and safe in many patients, retrograde arterial perfusion from femoral arterial cannulation has been associated with a higher risk of stroke than antegrade arterial perfusion from the ascending aortic or axillary cannulation, particularly in elderly patients and those with aortic atherosclerosis.[9,10]

Cannulation

Arterial and/or venous cannulation for CPB can be peripheral, central, or a combination of both. The choice depends on the risks posed by

sternal reentry and the presence of peripheral arterial disease (see Table 29.1), as well as the presence of multiple sites of previous and planned surgery on the aorta and right atrium, which may limit the room available for central cannulation.[10] For example, the presence of multiple patent graft anastomoses to the aorta may favor peripheral arterial cannulation. For patients who are at high risk of catastrophic injury to mediastinal structures, arterial (and in certain cases venous) cannulation may be carried out peripherally before sternotomy. The choice of cannulas should take into account the patient's body surface area: If the venous cannula is too small, the perfusionist will be unable to adequately drain the venous return, and if the arterial cannula is too small, the perfusionist will be unable to provide adequate arterial flow without excessive line pressures. Should the peripheral vessels be too small to permit adequately sized cannulas, it is usually possible to subsequently add additional cannulas centrally, if needed, to improve the adequacy of systemic perfusion.

The right or left axillary artery and vein may be exposed by a 5-cm incision in the deltopectoral groove. Use of the axillary artery for arterial cannulation offers less risk of limb ischemia and cerebrovascular events than use of the femoral artery, which is less well collateralized and provides retrograde arterial flow.[10] The most common complication of axillary artery cannulation involves trauma to the branches of the brachial plexus that are intimately involved with the artery. Injury to the artery itself, causing ischemia, dissection, and hyperperfusion, is also possible. The risks of ischemia and dissection are minimized by cannulating a T-graft sewn to the axillary artery rather than cannulating the artery directly. Institution of CPB via the T-graft may be associated with hyperperfusion of the ipsilateral arm. This can be avoided by maintaining the ipsilateral radial arterial pressure no higher than the contralateral radial or femoral arterial pressure once CPB has commenced; this is done by adjusting tension on a Silastic sling (vessel loop) placed in the surgical field around the axillary artery just distal to the cannulation site.

The femoral artery may be accessed with a modified Seldinger technique or, more commonly, under direct vision, usually via a 4-cm incision in the inguinal skin crease. The main complications of a Seldinger approach to femoral arterial cannulation are retrograde dissection and retroperitoneal bleeding. The femoral artery is more commonly affected by atherosclerotic disease than the axillary artery, and a careful check of distal pulses is mandatory after decannulation. Occasionally, the arteriotomy will require revision or patch repair to ensure distal flow.

If arterial cannulation alone is carried out peripherally, it is unnecessary to fully heparinize the patient initially. A single dose of 5000 units of heparin will be sufficient to keep the line free of thrombus if the perfusionist flushes the cannula intermittently before institution of CPB. Full heparinization to an activated coagulation time greater than 480 seconds is usually required before venous cannulation, use of pump (cardiotomy) suction, or institution of CPB, although policies may vary from institution to institution.

The main indication for peripheral venous cannulation (which mandates full heparinization) before sternotomy is the surgeon's decision to institute CPB before sternotomy. The axillary vein is sometimes used, but the larger femoral vein, which has a straighter course to the right atrium, provides the most reliable access and venous drainage. These cannulas are more safely inserted with an open technique to directly visualize the vein then with a Seldinger technique.

A major complication of femoral venous and arterial cannulation, which may not manifest until later in the case, is retroperitoneal hemorrhage caused by perforation of the femoral or iliac vessel or retrograde dissection of the aorta. A significant retroperitoneal bleed or dissection on CPB are characterized by low flows, low systemic pressures, poor venous drainage due to loss of circulating volume, and, eventually, abdominal distention from accumulating hematoma and venous stasis. Retrograde aortic dissection from femoral or axillary cannulation may occasionally occur on institution of CPB and is associated with high perfusion line pressures and low systemic perfusion pressure. To avoid these complications, a soft guidewire should be inserted in the vessel under direct vision and without force; the pointed cannula occluder should be withdrawn into the cannula as soon as the cannula is in the vessel; the cannula must not be advanced against significant resistance; and the wire must be kept under tension, checking that it can be moved easily backward and forward at all stages. Inadequate venous drainage caused by malposition, kinking, or placement of a cannula that is too small (particularly in femoral cannulation, where the length of the cannula further contributes to reduced flow) can mimic both of these scenarios with poor venous return, subsequent low flow, and eventual abdominal distention.

Cardiopulmonary Bypass

The patient can be placed on CPB before resternotomy, if indicated (see Table 29.1). Safe institution of CPB should be confirmed by the anesthesiologist, perfusionist, and surgeon. This is even more important if the patient has been placed on bypass emergently because cannula choice and placement may not be optimal. As described earlier, the anesthesiologist should be vigilant and use TEE whenever possible to rule out complications and causes of inadequate perfusion such as retrograde aortic dissection or inadequate venous drainage. Inadequate venous drainage may be signified only by a high central venous pressure and failure to adequately decompress the right side of the heart (which may be apparent only on echocardiography). If adequate flows and venous drainage cannot be established, peripheral arterial or venous cannulas must be supplemented with additional peripheral or central cannulas, with confirmation of satisfactory arterial flow and venous drainage before proceeding to clamp the aorta. Echocardiographic confirmation of correct placement of caval and coronary sinus cannulas before institution of CPB is very helpful, particularly because the surgeon cannot readily palpate these in reoperative cases owing to adhesions.

If proximity of right-sided heart structures to the sternum is a concern (particularly the right ventricle in patients with severe pulmonary hypertension), some surgeons take the precaution of temporarily draining the circulating volume into the venous reservoir of the CPB circuit before sternotomy. This has the theoretical advantage of decompressing the right side of the heart, which may reduce the risk of injury from the sternal saw. After the sternotomy is completed, the remainder of the mediastinal dissection can be carried out with the patient on or off CPB, depending on the challenges presented by adhesions and pathology. Although starting CPB early increases bypass time, it likely reduces the risk of injury to important structures and does not appear to increase morbidity, mortality, or postoperative bleeding.[3] The main reason this is not done routinely is that the patient is fully heparinized while lysis of adhesions is carried out, potentially leading to increased transfusion requirements during the procedure; red cell salvaging may minimize transfusions.

Myocardial Protection

Whereas the approach to myocardial protection for reoperative cardiac surgery follows the same basic principles as for first-time surgery (i.e., decompression of the heart, usually in cold diastolic arrest to minimize myocardial oxygen demand), there are several additional factors that commonly impact the myocardial protection strategy. Patients undergoing reoperative cardiac surgery typically have worse myocardial function and more advanced coronary and valvular heart disease than patients having first-time surgery. In most reoperations, technical challenges increase the cross-clamp time significantly. If one or more patent IMA grafts are present, they will perfuse the coronary circulation with systemic blood flow after the aorta is cross-clamped. The subsequent washing out of cardioplegic solution from the myocardium with systemic blood, which is usually warmer and normokalemic, will cause the heart to resume electrical activity. If this is not addressed, the areas of myocardium not perfused by the IMA may become ischemic. To prevent this phenomenon, there are several approaches. The traditional approach has been to clamp the IMA, but this has been

associated with increased risk of injury to the graft and adverse outcomes.[11] Increasingly, surgeons elect to avoid manipulating patent grafts altogether, cooling the patient to 25 to 27°C so that the heart is supplied continuously with cool, oxygenated blood and remains in diastolic arrest. Alternatively, cardioplegic arrest can be avoided completely, using either off-pump techniques (for coronary artery surgery) or on-CPB techniques with the heart beating and intermittent fibrillatory arrest. If there is any more than mild aortic insufficiency, fibrillatory arrest will result in ventricular distention unless the left ventricle is vented, and retrograde blood flow from the aorta can make mitral valve surgery very challenging in this scenario.

Retrograde cardioplegia is a useful adjunct, but correct placement of a coronary sinus catheter is more challenging in reoperative patients because manual palpation is usually prevented by diaphragmatic adhesions. Consequently, the surgeon is more reliant on TEE to assess coronary sinus placement, and it is crucial to continuously monitor the coronary sinus pressure during cardioplegia to confirm an appropriate pressure response (see Chapters 13 through 15). Additionally, if the aorta is open, the surgeon should see cardioplegia effluent from the left and right main coronary ostia. If necessary, the right atrium can be opened and the retrograde cardioplegia catheter can be placed directly in the coronary sinus; this requires bicaval cannulation and either vacuum-assisted venous drainage or snaring of both cavae to prevent a venous airlock.

Surgical Strategy

Reoperative surgery presents specific challenges after safe institution of CPB. Exposure of the coronary arteries for bypass grafting is usually hampered by adhesions, which must be completely divided to access the circumflex coronary distribution. Exposure of the cardiac valves can be made challenging by the presence of bypass grafts or prosthetic valves in other positions, and the size of prosthesis that can be placed may be limited by the presence of a prior prosthesis in the same or a different position. Excision of prosthetic valves may result in more extensive damage to adjacent structures, requiring more complex reconstruction; this is particularly the case if prosthetic valve endocarditis is present because extensive débridement of all infected material is required before implantation of a new prosthesis. Performing mitral valve surgery without cross-clamping may result in suboptimal exposure because the full aortic root obscures the anterolateral commissural area, and in the presence of aortic insufficiency (which may be exacerbated by the atrial retractor), the posterior mitral valve may be obscured by blood from the left ventricle. Additionally, careful attention must be paid to maintaining fibrillatory arrest and a fully pressurized aortic root as soon as the mitral valve is competent to minimize the risk of ejecting air into the ascending aorta.

Weaning From Bypass

The main difference in weaning from CPB in reoperative cases compared with first-time surgeries is the need for more extended de-airing. The pulmonary vasculature and left ventricle are fixed open by adhesions and, as a result, entrain more air than in non-reoperative cases. Even if no intracardiac air is visualized, protamine should not be given for several minutes after discontinuation of CPB because air tends to return to the heart from the pulmonary veins for several minutes, requiring continued active venting until it is all ejected. This also facilitates urgent reinstitution of CPB if needed for hemodynamic instability due to intracoronary air emboli, myocardial stunning, or right ventricular failure.

Coagulation Management

Because of the large surface area of dissection (particularly in a fully heparinized patient) and prolonged CPB time, coagulopathy is common in reoperative patients. Point-of-care testing, including platelet function assays and thrombelastography, and transfusion algorithms are useful to guide therapy toward restoration of hemostasis and minimizing transfusion requirements (see Chapters 19, 34, and 35).[12]

Intraoperative Emergency Scenarios

Intraoperative adverse events occur in 3% to 10% of reoperative cardiac procedures, with a quarter occurring before or during sternotomy and most of the remainder occurring during mediastinal dissection before institution of CPB.[3,12,13] Potentially life-threatening injuries related to sternotomy include trauma to patent bypass grafts (which are the most frequently injured structures) and injury to the aorta. Additionally, injuries to the right atrium, right ventricle, and innominate vein are common and challenging to address, especially in patients with right-sided heart failure. Rapid volume replacement via large peripheral or central venous catheters or via the arterial cannula may be required. Major injury to arterial structures is immediately life-threatening, either from hemorrhage or from myocardial ischemia, and usually mandates immediate heparinization, cannulation, and institution of CPB. In a recent series from the Cleveland Clinic, the incidence of injury to a patent IMA graft was 5.3% in 655 patients treated between 1986 and 1996, compared with 3% in a later patient cohort from the same institution. This improvement was attributed to better preoperative imaging and planning.[11] The authors concluded that lapses in preventive strategies, including inadequate preoperative imaging, were responsible for 55% of the intraoperative adverse events in their series.

In the event of major hemodynamic instability that is likely to necessitate CPB (including major bleeding), the anesthesiologist should administer a dose of heparin sufficient to institute CPB (300–400 units/kg or an in vitro titration dose calculated to exceed 2.5–3.0 units/mL of blood). Assuming no access to central cannulation sites, extrathoracic sites should be cannulated emergently and CPB initiated. When the patient is fully heparinized and an arterial cannula is in place, "suction bypass" may be initiated to allow for partial temporary CPB. In this scenario, all venous return to the CPB circuit comes from cardiotomy suction ("coronary suckers") placed into the mediastinum and/or lacerated cardiac structures until venous cannulation can be established. The patient should still be ventilated because the left side of the heart is likely to be ejecting blood returning from the pulmonary veins. The period of cardiotomy suction bypass should be as short as possible; extensive hemolysis results from the turbulent flow and mixture with air in the cardiotomy tubing.

If there is a major injury to the aorta, institution of CPB alone will not be sufficient to control the problem. The primary goal is to obtain some degree of control of the bleeding by direct compression or occlusion sufficient to allow effective CPB for several minutes. Restoration of aortic continuity often requires institution of systemic hypothermia so that the aorta may be assessed and repaired during a period of moderate hypothermic circulatory arrest.

If a patent CABG is inadvertently lacerated or transected, it is possible to reduce the risk of resultant myocardial ischemia and ventricular fibrillation by inserting an intracoronary shunt to restore flow across the injured portion. It is frequently necessary to rapidly institute CPB, however. This is clearly the case if significant ST-segment elevation, bradycardia, or ventricular fibrillation is associated with arterial bleeding in this setting. The primary aim initially is decompression of the left ventricle and restoration of adequate systemic circulation. The eventual goal is restoration of coronary perfusion by repair of the injury or replacement of the graft.

Major intraoperative adverse events can have a significant impact on the plan for surgery. Once the patient is stabilized, it is worth reviewing the need for a revised strategy with the team. For example, the surgeon may elect not to address lesions with borderline indications, so as to reduce subsequent CPB and myocardial ischemic times. Very occasionally, the procedure may be halted and the patient taken to the ICU with a plan to return to the operating room in 24 to 48 hours after a period of stabilization. If there is significant mediastinal compression from pulmonary edema and abdominal distention or if

there is severe right ventricular dysfunction, it may not be possible to close the patient's chest without significant hemodynamic compromise. If chest closure is deferred, the sternum is usually splinted open. Patients with open chests should be paralyzed and fully sedated to avoid laceration of the right ventricle by the sternal edges. Although the skin edges are usually approximated to a sterile membrane and mediastinal drains placed under an air-tight adhesive seal (often with mediastinal packing), continued bleeding from mediastinal structures and sternal edges may be substantial, and these patients may need to be returned to the operating room before planned formal chest closure for mediastinal washout.

Results of Reoperative Surgery

In an analysis from the Cleveland Clinic of adverse intraoperative events during reoperative cardiac surgery in 127 patients between 2002 and 2004, the authors found that patients with prior CABG were twice as likely to experience an adverse intraoperative event (8.2% vs 4.4%, $P = .003$), most of which resulted from injury to bypass grafts.[10] Similarly, in a retrospective analysis from the Mayo Clinic of 231 patients undergoing reoperative cardiac surgery between 1996 and 2007, damage to prior bypass grafts represented one third of all intraoperative injuries observed in the series, with an incidence of 11%.[11] This was most likely to occur before institution of CPB and was associated with higher mortality than most other cardiac injuries.

In a retrospective analysis from Mount Sinai Medical Center of 363 patients who underwent reoperative valve surgery between 2000 and 2011, the incidence of injury to bypass grafts was lower (3%), and the presence of patent bypass grafts was not found to be a significant predictor of intraoperative adverse events.[3] This may be attributed to the introduction of an individualized risk-stratified approach to reoperative surgical strategy. The approach included routine preoperative CT scans, liberal use of peripheral cannulation and CPB before sternotomy, and direct supervision of sternal reentry and mediastinal dissection by attending surgeons. Operative mortality decreased from 5% to 2% over the course of the study period. Injury to a major structure occurred in 3% ($n = 11$) of cases, including lacerations of the right ventricle ($n = 3$), aorta ($n = 1$), pulmonary artery ($n = 1$), and patent bypass grafts ($n = 2$), but the only predictor of early morbidity or mortality was severe pulmonary hypertension (odds ratio [OR] 2.7; 95% confidence interval [CI] 1.17–6.2) with higher operative risk scores. Pulmonary hypertension is an indicator of advanced valvular cardiomyopathy and is associated with pulmonary dysfunction. Strategies to address pulmonary hypertension include aggressive management with preoperative nesiritide infusion; perioperative inhaled and intravenous pulmonary inodilators; decompression of the right ventricle with CPB before sternotomy, if indicated; meticulous cardioprotection; a liberal approach to tricuspid annuloplasty to treat tricuspid annular dilatation or moderate tricuspid regurgitation; and intraaortic balloon counterpulsation in the setting of postoperative right ventricular dysfunction.

Emergency Reexploration

Indications

Emergency reexploration is needed in approximately 1% to 3% of patients in the first few hours to days after cardiac surgery. Emergency resternotomy is indicated for definitive management of cardiac tamponade and acute massive mediastinal hemorrhage. Emergency resternotomy permits internal cardiac massage (which has been shown to increase the cardiac index to 1.3 L/min per m^2 from 0.6 L/min per m^2 in the closed chest), placement of epicardial pacing wires, relief of tension pneumothorax, internal defibrillation, and management of excess mediastinal bleeding.[14] Consequently, the other main indication for emergency reexploration is cardiac arrest that does not respond satisfactorily to a few minutes of cardiopulmonary resuscitation and is likely to have a cause that can be addressed by emergency resternotomy. After cardiac surgery, 20% to 50% of cardiac arrests result in emergency sternotomy.[14]

With the exception of catastrophic surgical bleeding or acute cardiac tamponade, the timing of intervention for excess mediastinal bleeding is almost always subject to some debate. When the surgical team has specific concerns about surgical bleeding sites, the threshold for surgical reexploration may be low. It may be much higher in the setting of significant coagulopathy, particularly if an extended effort was made to secure hemostasis in the operating room. In general, indications that the patient may require reexploration for bleeding include (1) greater than 400 mL bleeding in 1 hour; (2) greater than 200 mL/hour for more than 2 hours; (3) greater than 2 L of blood loss in 24 hours; (4) increasing rate of bleeding, particularly in the absence of coagulopathy; and (5) bleeding associated with hypotension, low cardiac output, or tamponade.

General Considerations

Anesthetic and surgical considerations in patients undergoing emergency reexploration differ from those in patients undergoing reoperative cardiac surgery, including surgical revision of bypass grafts or other cardiac procedures in the early postoperative setting. In the setting of emergency reexploration, patients are characteristically hemodynamically unstable and often undergoing cardiopulmonary resuscitation with external cardiac massage. The trigger for emergency resternotomy may have been preceded by several hours of a low cardiac output state, with profound metabolic disturbances. In the case of persistent hemorrhage, the patient may be coagulopathic and may have already received massive transfusions. Emergency reexploration often takes place in the ICU if the patient is too unstable to be transferred to the operating room. Advanced preparation in the form of practice drills and team protocol development is important to help overcome the disadvantages of reduced access to operating room personnel, equipment, and space that can be major obstacles to the safe and effective resuscitation of these patients. Additionally, the longer the time between the index cardiac surgery procedure and cardiac arrest, the less likely it is that the cause of cardiac arrest can be effectively addressed by emergency resternotomy. The following recommendations are based on the excellent guidelines for resuscitation in patients with cardiac arrest after cardiac surgery produced by the European Association of Cardio-Thoracic Surgery Clinical Guidelines Committee.[14]

The identification of cardiac arrest and rapid initiation of advanced life support are essential and include external cardiac massage, defibrillation, and airway management in cardiac surgery patients. Swift and accurate confirmation of airway patency and bilateral lung auscultation are essential. Hypoxia is a cause of cardiac arrest that will not be satisfactorily addressed (i.e., effective management may be delayed) by emergency resternotomy. High airway pressures or reduced compliance on manual ventilation are most commonly caused by bronchospasm, endotracheal tube obstruction, selective bronchial intubation, or tension pneumothorax. Cardiac arrest not caused by ventricular fibrillation or ventricular tachycardia after cardiac surgery may be caused by hypoxia, tamponade, profound hypovolemia, tension pneumothorax, and complete conduction block with failure of epicardial pacing. Ventricular fibrillation and tachycardia cause approximately one third of cardiac arrests after cardiac surgery and may result from myocardial ischemia, metabolic and electrolyte disturbances (particularly acidosis and hypokalemia), or asynchronous pacing resulting in an R-on-T phenomenon whereby a pacing spike occurs on the T wave, which may cause ventricular arrhythmias (i.e., premature QRS complex interrupting the preceding T wave). In an analysis of 79 emergency resternotomies in the setting of cardiac arrest, the major determinant of survival was chest reopening within 10 minutes.[14]

Location of Resternotomy

The decision to preform reexploration in the ICU or to transfer the patient to the operating room is dictated primarily by the stability

of the patient. If the patient is hemodynamically stable enough for safe transfer to the operating room, this is almost always preferable to resternotomy in the ICU, for several reasons. First, equipment for surgical intervention in the ICU is usually limited, which is a key consideration for any patient who is likely to require reinstitution of CPB. Second, once in sterile gloves and gown, the surgeon is completely reliant on other personnel to locate instruments and equipment. The operating personnel are often unfamiliar with the location of equipment within the ICU, and ICU staff are almost invariably unfamiliar with the specific supplies required and preoccupied with the other critical aspects of patient care. Third, impediments to sterility, light, and access on the wide and relatively immobile intensive care bed hamper effective surgical interventions. Regular practice of emergency sternotomy drills and team protocols allows the whole team to overcome some of these limitations, but units where this is done regularly are the exception rather than the rule.[14]

Performing Emergency Resternotomy

The primary role of the anesthesiologist is to ensure that the patient is adequately ventilated during resternotomy, which may require emergency reintubation and should always include confirmation of airway patency and bilateral air entry as outlined earlier. The second priority is to maintain circulation by securing venous access with large-bore volume infusion, management of potentially massive transfusion requirements, and vasoactive infusions. The third priority is to administer 300 units/kg of heparin to the patient as soon as the decision is made to use CPB. The cessation of sedatives and anesthetic agents for a few minutes in the setting of cardiac arrest is unlikely to cause awareness. These medications can be reinstituted once hemodynamic stability and cerebral perfusion are achieved. Clear and focused communication with the surgical and nursing teams is vital. A dedicated nurse should be identified to remain at the bedside to assist with infusion pumps, drugs, and airway management.

If the patient is receiving chest compressions, these are continued until the surgeon is gowned and gloved. Use of an all-in-one sterile drape (with a clear adhesive window that covers the incision) is faster than preparation of the skin with antiseptic and assembly of multiple drapes. Chest compressions are then resumed by the gowned and gloved surgical team. The minimum equipment required to reopen the chest is a sterile Yankauer suction tip and tubing attached to wall suction, a blade, a wire cutter, and a heavy needle driver. The wound is incised down to the wires, which are cut and pulled out so that the sternal edges can be retracted. The process from chest compressions to open chest should take no more than 3 to 5 minutes, with minimal compromise of sterile technique. Opening of the sternum often relieves tamponade, with a large spike in the patient's blood pressure if there was a cardiac output before resternotomy. If there is no cardiac output, the surgeon's priority is to perform internal cardiac massage without disrupting any bypass grafts, followed by internal defibrillation if indicated, epicardial pacing, or control of bleeding. It is generally safest to perform internal cardiac massage with two hands, with the right hand placed so that knuckles are against the diaphragm and fingertips at the apex of the heart and the left palm placed over the right ventricle, squeezing palm to palm to generate a systolic pressure of 50 to 60 mm Hg. Emergency institution of extracorporeal membrane oxygenation or CPB may be required if cardiac output cannot be restored. The patient must be fully heparinized. If hemodynamic stability and bleeding can be achieved only temporarily, the patient may be transferred to the operating room with an open chest for definitive control. A sternotomy is indicated for reexploration in the setting of cardiac arrest after nonsternotomy cardiac surgery, such as minimally invasive direct coronary artery bypass (MIDCAB) or minithoracotomy valve surgery, in order to permit internal cardiac massage and institution of CPB; a sternal saw should be kept in the ICU for this purpose.

Approximately 40% to 50% of patients survive emergency reexploration for cardiac arrest after cardiac surgery, of whom half survive to leave the hospital. Sternal wound infections have been described in 5% of survivors. Empiric antibiotics are usually given during emergency reexploration, and antibiotic washout with a prolonged course of antibiotics postoperatively is a reasonable adjunct.

In the case of awake patients who are stable enough to transfer to the operating room, it is often appropriate to place any needed catheters and to prepare and drape the patient before induction of anesthesia because induction may precipitate acute hemodynamic decompensation. The most common scenario in which this happens is delayed tamponade. Although these patients may appear to be quite well compensated and the surgical plan may be limited to drainage via a small subxiphoid incision, these patients should be regarded as potentially requiring emergency resternotomy and should have large-bore venous access, arterial and central venous pressure monitoring, and TEE in place.

Conclusion

This chapter has discussed the risks of reoperative cardiac surgery. An evolution in management strategies at major cardiac centers appears to have decreased morbidity and mortality over time. The anesthesiologist plays a vital role in managing large-bore venous access, using TEE to monitor the adequacy of cannulation and cardiac function, managing hemostasis, among other functions. The collaboration of a cohesive team of surgeons, anesthetists, perfusionists, and nurses is key to further improvement in outcomes in this high-risk patient cohort.

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Patient Safety in the Cardiac Operating Room

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KEY POINTS

1. Cardiac surgical patients are at significant risk from preventable adverse events. These events occur through human error, by either faulty decision making (diagnosis, decision for treatment) or faulty actions (failure to implement the plan correctly).
2. Human error is ubiquitous and cannot be prevented or eliminated by trying harder or by eliminating the one who errs. Reduction in human error requires system changes that prevent errors from occurring (forcing functions) or prevent errors from reaching the patient.
3. Sleep deprivation and fatigue can render a person more likely to make an error. Although residents' hours are limited, those of other physicians in the United States are not, unlike in other countries.
4. Nontechnical skills such as leadership, communication, cooperation, and situational awareness are critical to patient safety, but they are rarely taught. Distractions, disruptions, noise, and alarms contribute to technical errors and increase mortality rates in cardiac surgery.
5. Communication is the leading root cause of sentinel events, whether through missing information or through misunderstanding. Use of structured communication protocols reduces errors. Handoffs performed without a protocol involve significant numbers of omitted items.
6. Team training reduces surgical mortality rates, but it must be done with careful preparation and with regular retraining.
7. Surgical briefings that use a checklist significantly reduce surgical mortality rates (World Health Organization Safe Surgery Saves Lives). Debriefings allow teams to identify hazards and formulate improvements.
8. Simulation is an effective means to teach both technical and nontechnical skills and to allow teams to train for rare but dangerous events.
9. Cognitive aids should be available in every operating room to provide direction during rare crisis events (eg, malignant hyperthermia, pulseless electrical activity).
10. Medication errors occur approximately in 1 in every 150 to 200 anesthetic cases. The Anesthesia Patient Safety Foundation published a set of recommendations to reduce medication errors, including standardization, use of technology such as bar codes and smart infusion pumps, having pharmacy involvement in every step of the medication process, and building a culture of safety.
11. Awareness during anesthesia occurs approximately 1 to 2 times per 1000 anesthetic cases, and it occurs more often in cardiac surgical procedures. Use of a processed electroencephalogram or achieving an end-tidal concentration of 0.7 minimum alveolar concentration is effective in reducing the incidence of awareness.
12. The culture of an organization or a unit contributes significantly to patient safety or danger. Strict hierarchical cultures typically harbor a culture of blame and shame, which inhibits identification and correction of hazards. A "Just Culture" acknowledges that human error occurs and seeks to redesign the system to prevent future errors, but also holds individual persons accountable for willful violations.

The early days of cardiac surgery saw amazing successes and crushing defeats for the pioneers such as Blalock, Gibbons, and Lillihei.[1] The knowledge that their patients were certain to die without surgical treatment drove these physicians to find ways to provide safe and effective extracorporeal circulation and oxygenation. Today, nearly half a million patients undergo coronary artery bypass graft (CABG) procedures each year, with mortality and morbidity rates that would astound those early pioneers.[2] Indeed, over the decade between 2000 and 2009, the mortality rate associated with isolated CABG decreased from 2.4% to 1.9%, representing a relative risk reduction of 24.4% (Fig. 30.1).[2]

Despite impressive advances, reports show that cardiac surgical patients each year become ill and die because of preventable adverse events.[3] In the study by Gawande and colleagues,[3] cardiac surgical patients were more likely to have adverse events than other surgical patients (12.2% vs. 3%), and 54% of these were considered to be preventable. These numbers may underestimate the true rate of adverse events. A systematic review by He and associates[4] found that 6.7% of cardiac surgical patients had hospital-acquired ventilator-associated pneumonia, a complication generally believed to be preventable.[5]

The difficulty of assessing the incidence of preventable adverse events is demonstrated by studies reporting that 99,000,[6,7] 280,000,[8] and possibly as many as 400,000[9] hospitalized patients die each year in the United States as a result of preventable adverse events. Starfield[8] postulated that preventable adverse events are the third leading cause of death in the United States. Despite significant attention and discussion, eradication of these preventable medical events has proved

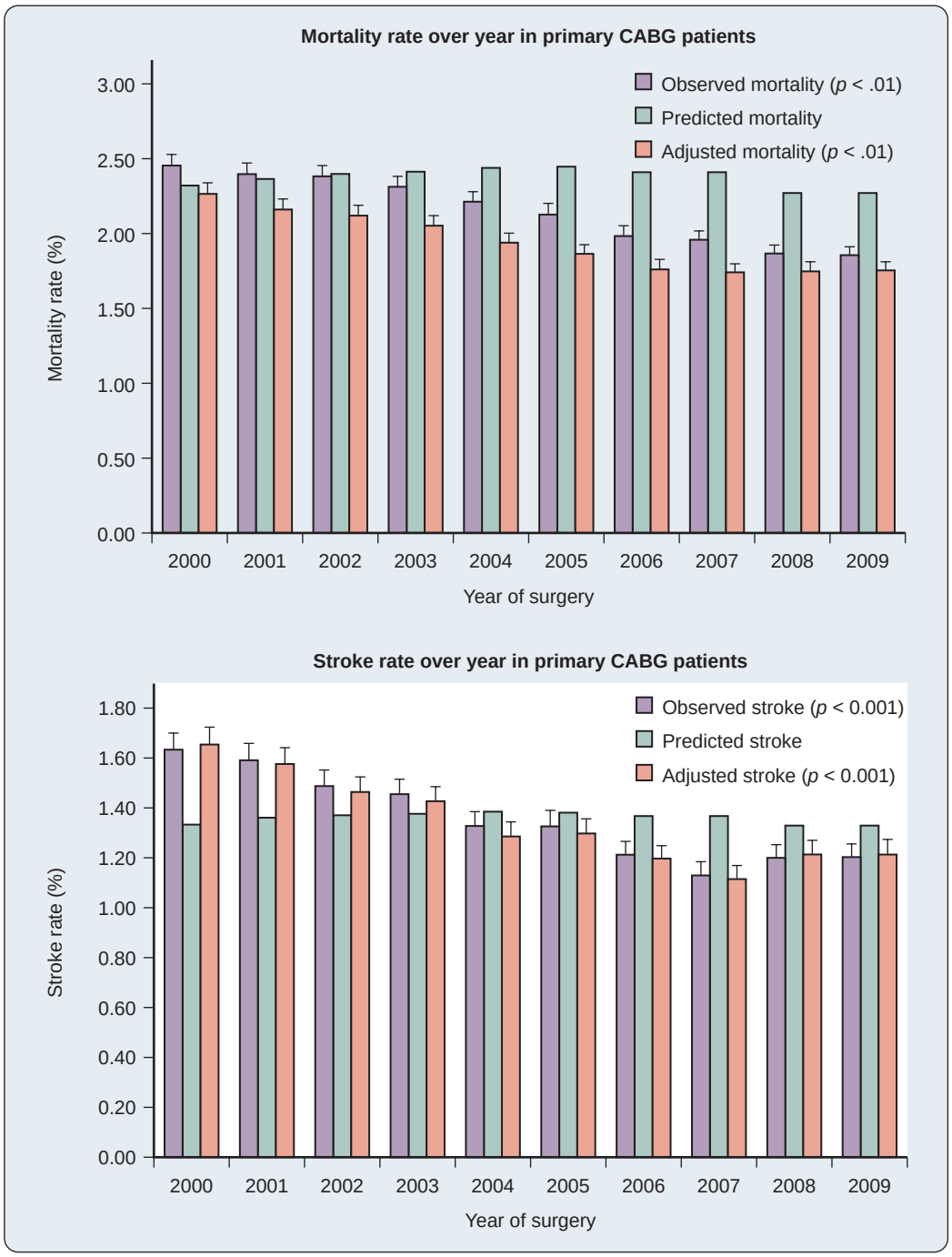


Fig. 30.1 Change in mortality and morbidity in patients with primary coronary artery bypass grafting (CABG) between 2000 and 2009. *(From ElBardissi AW, Aranki SF, Sheng S, et al. Trends in isolated coronary artery bypass grafting: an analysis of The Society of Thoracic Surgeons adult cardiac surgery database.* J Thorac Cardiovasc Surg. *2012;143:273–281.)*

difficult,[10] largely because medical education remains focused on technical rather than nontechnical aspects of medicine. Far more time is spent teaching anesthesia residents how to intubate the trachea and how to cannulate the internal jugular vein than in how to communicate clearly and without error or how to understand the complexities of human error.[11]

Patient safety involves both doing the right thing (ie, applying best practice to every situation) and doing the right thing the right way (ie, avoiding human error). Whereas most of this textbook is devoted to discussion of the right thing to do in a given circumstance, this chapter discusses both requirements for safe practice: (1) formulation of the correct plan for patient care (implementing evidence-based best practices) and (2) flawlessly carrying out the plan (preventing or correcting human error.)

The Science of Safety

In the past, efforts to reduce preventable harm focused on the individual health care professional, on trying harder, being more alert and vigilant, and "doing better." Fortunately, extensive scientific evidence

exists to inform clinicians on how teams and institutional and system culture influence safety.[12,13] Like aviation, the nuclear industry, and the military, medicine is a complex, high-stakes field in which errors can result in great harm. Although patients are not airplanes, and performing a surgical operation is not precisely analogous to flying a plane, much can be learned from other high-reliability industries. Rigorous patient safety science has improved the understanding of how errors occur and how to design safe practices, test them for efficacy, implement changes effectively, and measure the effectiveness of interventions, thus ensuring improvements.

The need for science in our efforts is exemplified by the approach to the wrong-site surgical procedure, which was recognized as a major issue in 2000. In 2004, The Joint Commission published the Universal Protocol to prevent wrong-site surgical procedures. Nonetheless, in 2013, wrong-site and wrong-patient errors occurred some 50 times a week in the United States.[14] The approach to reducing the frequency of wrong-site surgical procedures failed at many levels.[15] First, the Universal Protocol put forward by The Joint Commission did not address the complexity of wrong-site occurrences (eg, wrong-side errors on radiographs or in the medical record were not addressed). Second, the protocol was implemented from the top down rather than by involving frontline staff in designing a solution; the result was cavalier performance by many staff members.[16] Third, the proposed intervention (time out to identify the patient and the surgical site) was not tested for effectiveness before a national mandate was issued.[14]

If patient safety is to be improved, it will be through scientific study and application.[17] However, much of the descriptive, observational, or qualitative science that relates to patient safety is foreign to physicians, who are primarily familiar with rigorous quantitative experimentation.[18] In addition, traditional scientific medical journals have been reluctant to publish qualitative studies, even studies conducted with statistical and scientific rigor. Thus, most patient safety studies are found in journals of safety and quality, journals often not available in a medical library. These qualitative studies, however, hold promise for improving patient safety and will need to become part of the medical lexicon.[19]

One such comprehensive observational study of the hazards in the cardiac operating room (OR) was undertaken in the Locating Errors Through Networked Surveillance (LENS) group as part of the FOCUS project (Flawless Operative Cardiac Unified Systems).[20,21] This collaborative study involved the Society of Cardiovascular Anesthesiologists and the Johns Hopkins Armstrong Institute, and it consisted of observations of 20 cardiac operations by a team of trained observers, including human factors engineers, anesthesiologists, and organizational psychologists.[21] The analysis identified a myriad of hazards in the cardiac OR and detailed the complex interaction of organizational structure (lack of policies), teamwork behaviors (poor communication), system shortcomings (inadequate support requiring multiple workarounds), equipment and technologies (poorly designed and integrated), and individual failings (situational awareness).[21–25] The complexity of interactions among systems, providers, and processes highlights the truth that a simple solution to patient safety is not feasible. Experts from a variety of disciplines will be required to examine every aspect of perioperative cardiac surgical care and integrate proposed solutions.[19,26,27]

Evidence-Based Best Practice

Knowing is not enough; we must apply. Willing is not enough; we must do.

Johann Wolfgang von Goethe (1749–1832)

Patients are less safe when they are exposed to practices that are outmoded and substandard relative to the current best practice. For anesthesiology, some of the first "guidelines" for practice were put forward in 1986, with the adoption of formal standards of monitoring.[28] The proliferation of guidelines since that time has been significant. The National Guideline Clearinghouse houses 2300 medical guidelines and nearly 1000 surgical guidelines. Despite this proliferation, guideline development is not simple or easy. In one study, nearly half of the reviewed guidelines were based on expert opinion rather than grade A evidence; many guidelines did not grade the evidence, and many authors had conflicts of interest.[29,30]

In 2011, the Institute of Medicine published a set of eight standards to be met when developing guidelines.[31] The standards address the following:

1. Transparency
2. Management of conflicts of interest
3. Group composition
4. Systematic review
5. Establishing the evidence foundations for and rating strength of recommendations
6. Articulation of recommendations
7. External review process
8. The need and process for regular updating of guidelines

The eighth standard recognizes the Bill Kelley adage that "The great questions in medicine never change; the answers do with regularity."[32] The continual need to update and revise guidelines, and the finding that many are based on opinion, albeit expert, are often used to provide an excuse for not implementing guidelines. However, rather than waiting for the evidence to become perfect and without uncertainty, physicians should use the best evidence available to achieve consensus.[33]

Many articles have detailed improvement in outcomes after published guidelines are implemented.[34–36] However, it is clear that guidelines or best practices are not always implemented. Perhaps the most widely known historical example of resistance to adoption of best practices is the failure of Dr. Semmelweis to persuade his fellow Viennese physicians to wash their hands between patients. Despite the excellent evidence that hand washing could virtually eliminate puerperal fever, his colleagues not only rebuffed his attempts, but they also ensured that he would not be reappointed.[37] Of course, physicians now readily accept that sterile technique is mandatory in surgery and do not view it as an individual physician's choice.

In 2003, Leape and colleagues[38] reviewed CABG and angioplasty procedures and found that 24% of angioplasties and 9% of CABG procedures were inappropriate according to guidelines published by the American College of Cardiology and the American Heart Association (ACC/AHA) and by the RAND Corporation. Another example of inadequate implementation of guidelines is transfusion practice. Guidelines for transfusion in cardiac surgery have existed since the mid-1980s, but a review of institutional practice in 1998 found poor adherence to these guidelines.[39] In 2007, The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists published more formal and society-specific joint guidelines for transfusion in cardiac surgery[40]; 3 years later, 80% of surgeons, anesthesiologists, and perfusionists reported that they had read the guidelines, but only 20% had implemented any of them.[41]

Resistance to implementing guidelines either can be passive (lack of attention to guidelines, no attempt to learn the latest guidelines or best practices) or active, with a conscious decision not to implement published guidelines. Active resistance can be based on a perceived loss of a physician's clinical autonomy, a belief that implementing guidelines reduces the physician's "unregulatable art—an art that depends on our ability to build relationships with patients and families; to integrate answers to patients' questions into the content of their lives; and to heal, even when our science cannot cure."[33]

Perhaps more difficult for many physicians is that new evidence often shows previous guidelines to be incomplete at best and wrong at worst. When perioperative hyperglycemia was shown to be associated with adverse outcomes, increasingly stringent glycemic protocols and guidelines were developed, moving from a target of less than 180 mg/dL to less than 140 mg/dL to a target of 80 to 110 mg/dL.[42] A subsequent randomized, controlled trial demonstrated that tight glucose control (80–100 mg/dL) was related to hypoglycemic episodes and increased morbidity and mortality rates.[43] Similarly, guidelines

concerning the preoperative use of β-antagonists in cardiac patients changed following demonstration of benefit (atenolol)[44] and then deleterious effects (metoprolol).[45] These guidelines may change again with increasing evidence that agents with a high beta1:beta2 affinity (sotolol) are beneficial, whereas those with lower beta1:beta 2 affinities, such as metoprolol, agents are deleterious.[46] This continual change in what is "best practice" causes many clinicians to disregard excellent guidelines for fear that the recommendations subsequently may be proved to be wrong. Even though new evidence will always arise, clinicians must apply the currently available best evidence but always remain alert to the new.

Whatever the rationale, implementation of even well-supported guidelines takes significant effort. Widespread and effective implementation of the ACC/AHA guidelines regarding β-blockade following acute myocardial infarction required extensive effort on a national level.[47–49] With the increasing number of evidence-based guidelines and best practices, it is necessary to reduce the effort and resources needed to ensure implementation. Each institution or cardiac surgical unit should develop processes that address both rapid adoption of proved innovations and elimination of less effective therapies.[33] Failure to do so will cause the government or third-party payers to institute audits and penalties for care that does not meet an external quality level.

Human Error

Errare humanum est, perseverare autem diabolicum.
Lucius Annaeus Seneca, 4 BC to AD 45

Theory of Human Error

The universality of human error is well known and is accepted in virtually every walk of life, except perhaps medicine. Here it is expected that physicians and providers will be perfect, that the natural cognitive slips and trips and biases inherent in daily life will be overcome by the importance of the work being done and the fact that lives hang in the balance. Although most anesthesiologists acknowledge that they have made a medication error in the past, most also believe that they are less likely to make an error than their colleagues.[50]

The elegant exploration of the physiology and psychology of human error by Dr. James Reason[51] and research into system accidents[52] have made it clear that patient safety in the cardiac OR will not come about by identifying and eliminating error-prone individual clinicians.[51,53] In general, if the system is designed such that one person can make a given error, it is virtually guaranteed that another human will as well. For example, despite a Joint Commission Sentinel Alert in 2006 to caution care providers of the dangerous errors made possible by the use of universal connectors (Luer), hundreds of patients have died since then because intravenous fluids, pressure lines, or enteral feedings were erroneously connected to epidural catheters or arterial lines and vice versa.[54] The appropriate system change is now being implemented, with unique connectors for intravenous, arterial, enteral feeding, and pressure tubing and neuraxial catheters established by the International Standards Organization.[55]

Even in the least complex systems (eg, leaving the house to go to an interview), a trivial misstep (car door not properly latched, overhead light on, dead battery) can lead to far-reaching consequences (failure to be hired) because of concurrent defects (neighbors not available, bus strike, taxis unavailable as a result of bus strike).[52] Highly complex systems such as health care or the nuclear power industry are far more vulnerable, even though many of the worst events similarly begin with a trivial misstep (O-ring not tested in low temperatures in the space shuttle rocket). Even when the initiating event is a human error, correcting or preventing adverse outcomes nearly always requires a system change.[51,56] Reason's Swiss cheese model is now well accepted to demonstrate how system defenses must be in place to prevent or at least detect human errors before harm is done to patients (Fig. 30.2).[56]

At the individual patient level, inciting events that can culminate in a patient's harm or death typically begin with an erroneous process

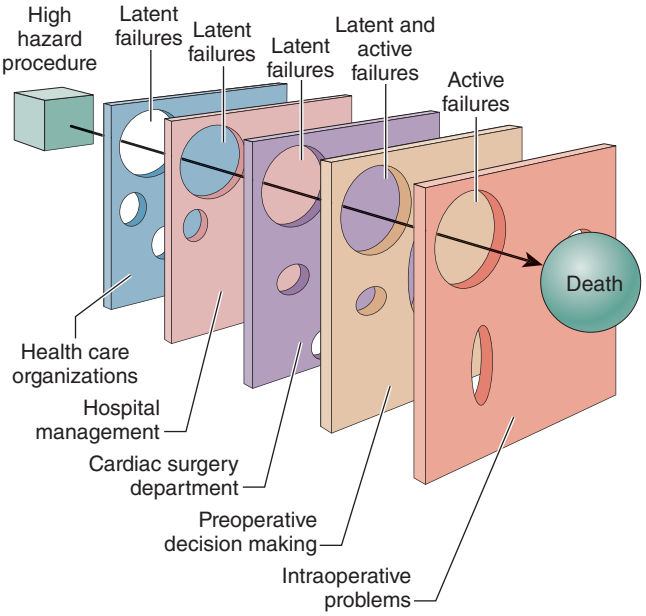


Fig. 30.2 Accident model. Active and latent failures in health care organizations, hospital management, and individual human error can all contribute to adverse events during high-risk procedures. *(From Carthey J, de Leval MR, Reason JT. The human factor in cardiac surgery: errors and near misses in a high technology medical domain.* Ann Thorac Surg. *2001;72:300–305.)*

that is part of the inherent cognitive processes (Fig. 30.3). As presented by Reason, much of what is done every day is the running of a subconscious, automatic schema.[51] Errors in the completion of automatic schema are *action errors,* such as a syringe swap, or neglecting to turn on the ventilator when terminating bypass (failure to complete a planned sequence). *Decision errors* occur when the plan or diagnosis is in error, and these errors can result from either inappropriate pattern recognition or faulty reasoning (administering atropine for bradycardia that is caused by electrocautery interference with a pacemaker). *Reasoning errors* occur when the subconscious has no preset schema or rule that applies, and decisions regarding what is happening or what to do occur through a relatively slow and methodical conscious process (hypoxemia resulting from undiagnosed large pulmonary arteriovenous malformations).[51] With time, diagnoses that were made initially through a reasoning process can become more rote and subconscious, based on learned pattern recognition (Fig. 30.4).[57,58] However, whether decisions are based on pattern recognition or conscious reasoning, a host of influences can contribute to cognitive errors (Fig. 30.5).[57,59,60]

Reasoning or cognitive errors are less common than are action errors (eg, taking a wrong turn, missing an exit), but their consequences are more serious and more difficult to uncover, and recovery is more difficult. The near nuclear meltdown at the Three Mile Island nuclear plant in Pennsylvania in 1979 was based on the incorrect assumption (cognitive error) that a lit bulb on the control panel indicated an open coolant valve when it only meant that the switch had been flipped (in reality, the valve was stuck shut). In many high-risk industries such as aviation and nuclear power, conscious decision making is rarely required because almost all processes and procedures are well defined and tested. In addition, rare scenarios that could require diagnosis or conscious thought have been planned for and rehearsed (water landing in the event of total engine failure). In medicine, however, clinicians often encounter an unexpected event (large cyst on the epiglottis) that requires conscious reasoning, frequently under time pressure. The cognitive process used to deal with unexpected events is estimated to result in erroneous diagnoses anywhere from 2% to 50% of the time.[59]

Although cognitive psychologists largely have defined the process by which humans make decisions, as well as the inherent biases that

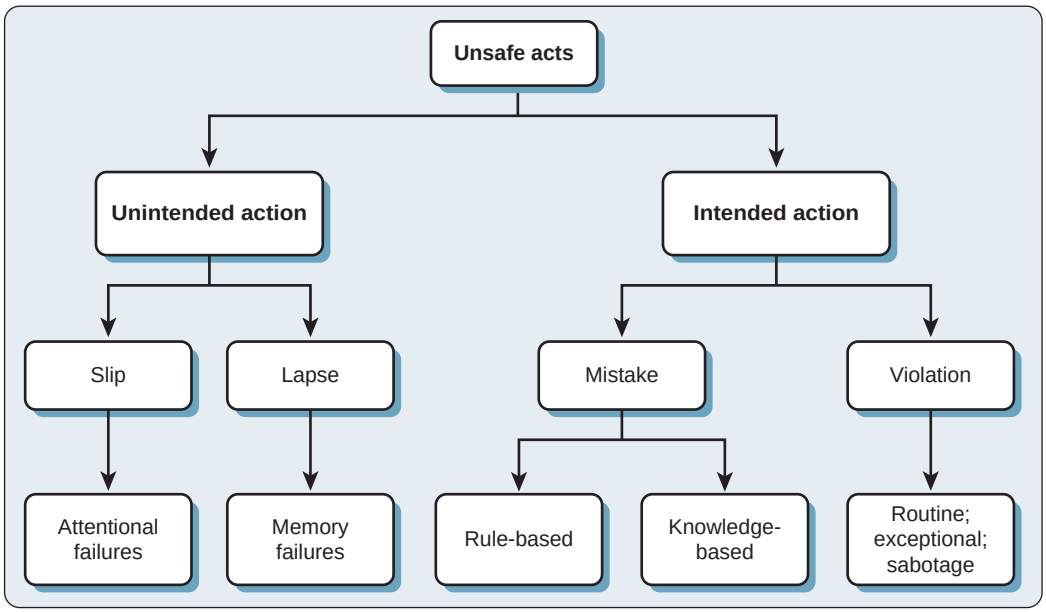


Fig. 30.3 Human error types. *(Adapted from Reason J. Human Error. New York: Cambridge University Press; 1990.)*

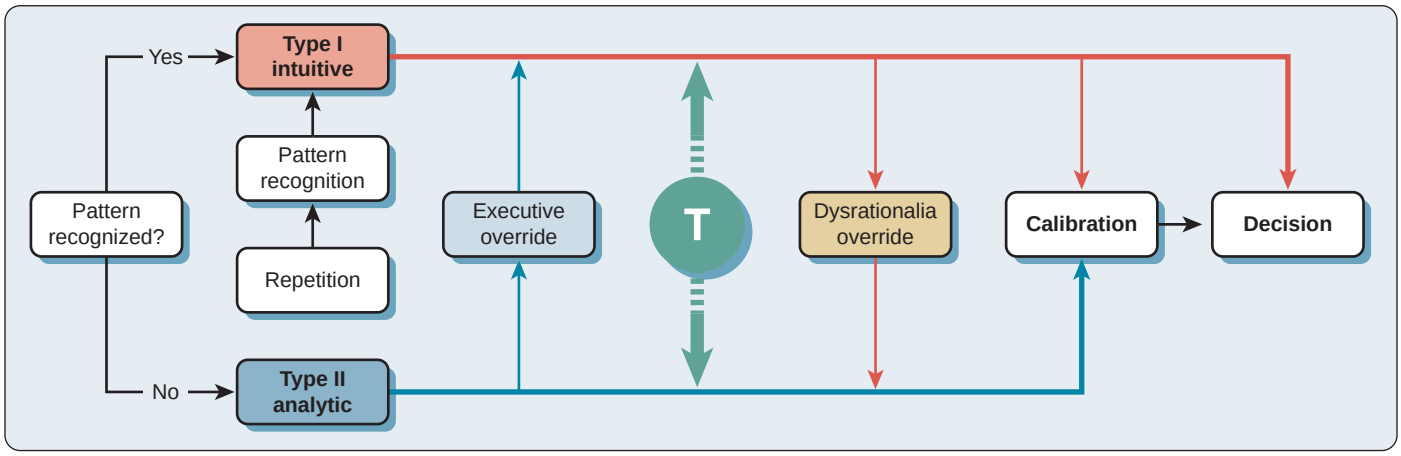


Fig. 30.4 Dual process model of reasoning: how intuitive processes (type I) and analytic processes (type II) interact to influence diagnostic thinking. Some type I processes go directly to end decisions without any overrides, toggling, or calibration and represent largely unexamined decision making. Explicit effort allows for toggling *(T)* between type I and type II processes. Repetition of analytic processes until they become automatic is the basis of skill acquisition. This model does not account for proportion of time spent in, or the superiority of, one process over another. Error may be made in either system at any point, including the starting point (ie, patterns may be "recognized" incorrectly). *(From Stiegler MP, Tung A. Cognitive processes in anesthesiology decision making.* Anesthesiology. *2014;120:204–217, as adapted with permission from Croskerry P, Singhal G, Mamede S. Cognitive debiasing 1: origins of bias and theory of debiasing.* BMJ Qual Saf. *2013;22(suppl 2):ii58–ii64.)*

can lead to cognitive errors,[57,58] little of this science is known to the average physician or is taught in medical school. Although some of the biases are better known and discussed (anchoring, availability heuristic, confirmation), others are not yet well recognized or managed (loss aversion, preference for certainty, blind-spot bias) but can significantly influence cognitive error (Table 30.1).[57] In addition, the need to make a rapid decision in a life-threatening situation results in further dependence on availability and approximation heuristics, a strategy that clearly speeds decision making, but one that is susceptible to cognitive error.[61] Although medicine is beginning to follow aviation and develop cognitive aids to assist in handling unexpected events, the use of these aids is not yet widespread.[61–64]

As noted earlier, a single adverse clinical event actually involves multiple latent risks: situations that permit an error to occur or allow an error to reach the patient (see Fig. 30.2.)[51] In a case report, Spiess and associates[65] detailed a near-catastrophic failure of oxygenation during cardiopulmonary bypass (CPB) at the point of suturing a prosthetic aortic valve in place. The inciting event occurred when a perfusionist inserted an oxygen sensor into the fresh gas line, a sensor not designed for use in the presence of anesthetic gas; the sensor cracked, allowing the fresh gas flow to escape, so that no oxygen reached the oxygenator. Although an individual clinician performed the inciting unsafe act, latent risks existed at the system level (refusal to purchase appropriate sensors), at the unit level (no process for vetting and approving such

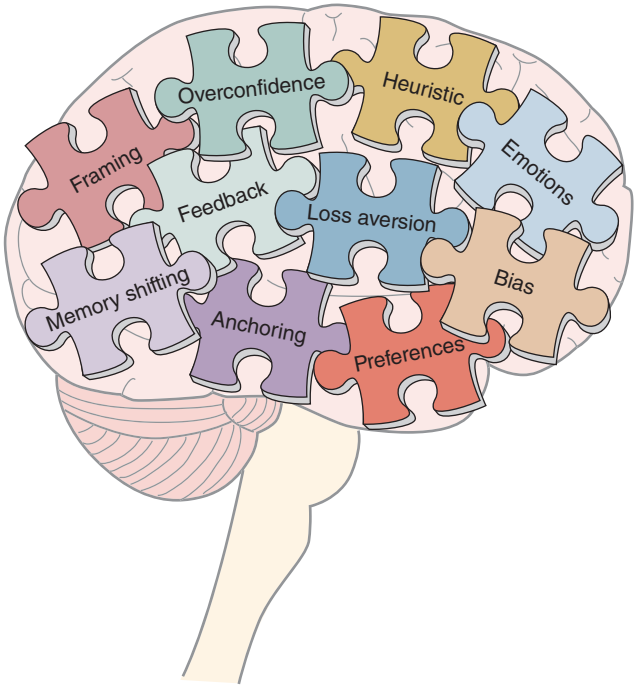


Fig. 30.5 Influences on decision making and diagnostic error. Various nonrational factors influence decisions; these factors themselves are neither good nor bad. Decisions may also use rational processes. *(From Stiegler MP, Tung A. Cognitive processes in anesthesiology decision making.* Anesthesiology. *2014;120:204–217.)*

workarounds), and at the individual level (staff members afraid to speak up because of an irascible surgeon).

Taxonomy of Errors

Analyzing adverse events and developing solutions require in-depth review of all system and organizational characteristics that may contribute to errors.[53,56,66] One such approach is the Human Factors Analysis and Classification System (HFACS) developed by Wiegmann and Shappell and their colleagues[67–69] to analyze adverse events in aviation, and it has been adapted for use in many different high-risk industries (Fig. 30.6). The HFACS taxonomy was developed from the original four categories of unsafe acts as proposed by Reason (see Fig. 30.3), and it provides a detailed framework for analysis of error and latent risk. It has been adapted for use in both cardiac surgery and health care in general, and it has been found to provide a robust analysis (Box 30.1).[26,70] Using structured interviews of cardiac surgical teams, ElBardissi and colleagues detailed the relationships and significant influences among the categories and identified significant correlations (Fig. 30.7).[26] It is obvious that personal readiness failures, such as fatigue or stress, can degrade skill and decision-making ability and result in errors. Less clear is that problems with teamwork represent equal or even greater latent risks than do individual factors.

Personal Readiness (Fatigue, Stress)

The Institute of Medicine Committee on Optimizing Graduate Medical Trainee Hours and Work Schedules to Improve Patient Safety conducted a comprehensive review of the medical and scientific literature and concluded that working for more than 16 consecutive hours is unsafe for both trainees (marked increased risk of an accident while

TABLE 30.1 Nonrational Cognitive Factors That Influence Decision Making

Cognitive Factor	*Explanation*
Representativeness heuristic	Diagnosing or identifying by the degree of resemblance to preexisting or "classic" mental models
Availability heuristic	Diagnosing or identifying by resemblance to previous, highly memorable, events; "memorableness" may be induced by an emotionally charged past experience (usually negative), a peer review "morbidity and mortality" conference, or another novelty
Anchoring, fixation, "tunnel vision"	1. Insufficient adjustment from an initial assessment of a value or a state. "Anchoring" on the starting point can bias subsequent estimates. 2. Focus on a single feature of a case or event exclusively, at the expense of considering other aspects of the case. This may include task fixation, such as troubleshooting of an alarm at the expense of maintaining situation awareness
Retrospective biases	Tendency to view events that have already occurred differently once the outcome is known 1. Hindsight bias: tendency to view events as having been more predictable, and thus actions more correct or incorrect, than was apparent as the situation was unfolding 2. Outcome bias: favorable (if the outcome is good) or unfavorable (if the outcome is bad) assessments of judgments, regardless of actual decision quality (eg, drunk driver who arrives home safely rationalizes that he made a "good choice")
Confirmation bias	A tendency toward seeking (or "seeing") only information that supports a diagnosis or hypothesis, rather than information that refutes it
Visceral (transference) bias	The tendency to allow feelings about a patient to affect care decisions, as with a "VIP patient," a victim of trauma, or a "high-maintenance" patient
Omission bias	Tendency toward inaction rather than action, out of fear of causing harm (to patient, if action failed; to self, by damaging professional reputation if wrong); may be especially likely when a significant authority gradient is perceived or real
Bias blind spot	A flawed sense of invulnerability to bias; may be more prominent among cognitively sophisticated and highly intelligent persons
Overconfidence	Inaccurately high self-assessment with regard to positive traits; can refer to medical knowledge, certainty regarding diagnosis, technical abilities, and situational assessment
Memory shifting or reconstruction	Failure to recall information accurately; occurs when meaning and verbatim information are coded differently and results in "filling in" details (sometimes misinformation) when memories are recalled; also called "memory reconstruction error"
Preference for certainty	Human preference for certainty over risk, even at the expense of sacrificing a greater expected value (ie, calculated by expected utility theory)
Framing	A schema of interpretation that changes perception without altering facts; equivalence framing refers to the interpretation of the same set of data as either a gain or loss; emphasis framing focuses on a subset of selected data to match an event or explanation
Loss aversion	Tendency for humans to view a loss as significantly more psychologically powerful than a gain of the same amount
Affect (emotion); anger; regret	Emotional influences on decision behavior; anger describes the tendency for angry or disruptive behavior to influence the decisions of oneself or others; regret describes the tendency to allow regret for previous decisions to affect future ones; anticipated regret is the desire to avoid regret from future consequences or outcomes of decision choices
Feedback bias	Significant time elapses between actions and consequences; lack of outcome data reporting
Commission bias	Tendency toward action rather than inaction, even when those actions are not indicated or founded on desperation; the "better safe than sorry" mentality of adding additional invasive monitors, central access, or liberal blood transfusion; backfires when those actions have unintended effects

From Stiegler MP, Tung A. Cognitive processes in anesthesiology decision making. *Anesthesiology.* 2014;120:204–217.

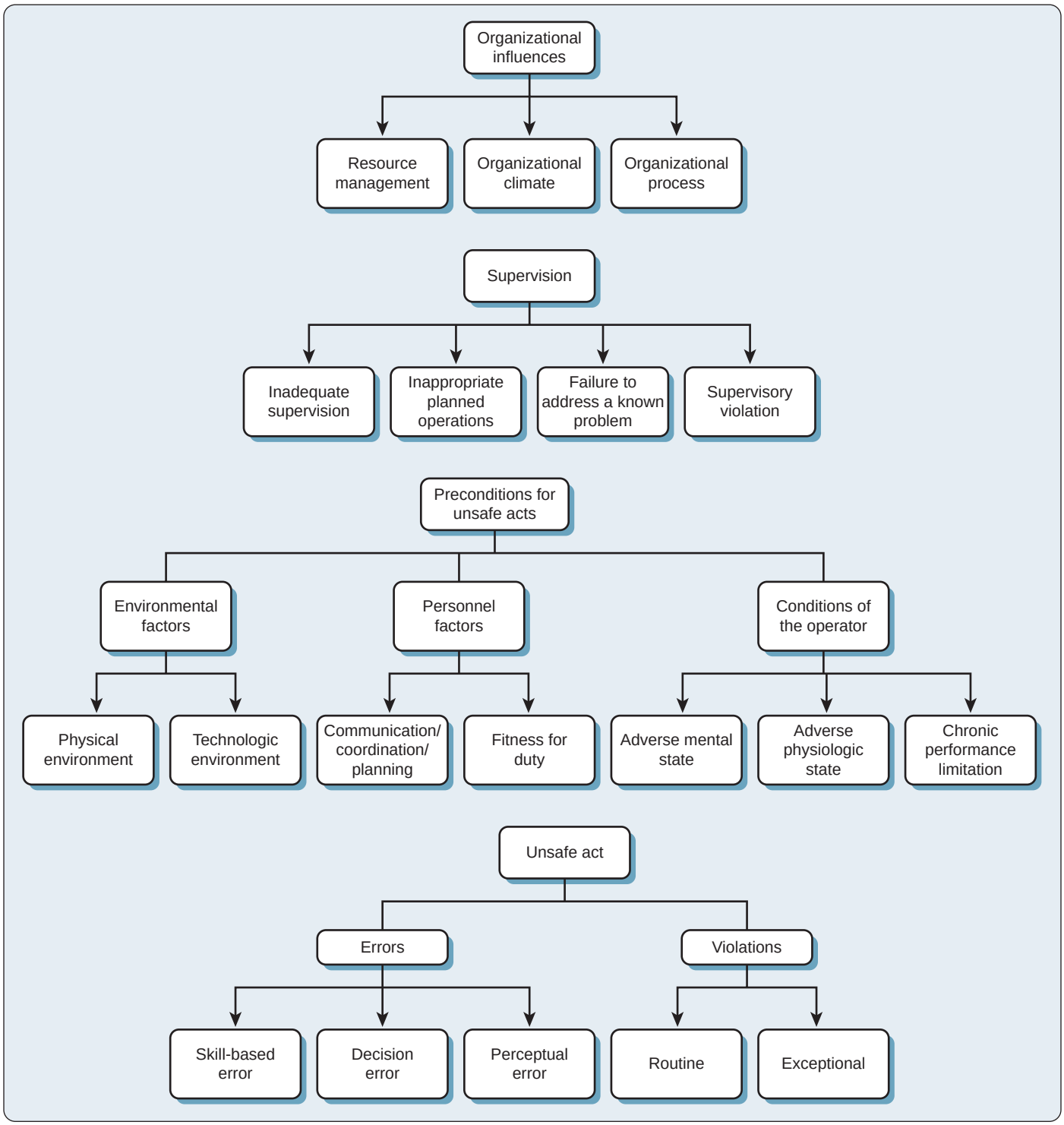


Fig. 30.6 The Human Factors Analysis and Classification System. *(Modified from Shappell S, Detwiler C, Holcomb K, et al. Human error and commercial aviation accidents: an analysis using the human factors analysis and classification system.* Hum Factors. *2007;49:227–242.)*

driving home) and for their patients (attention failure, serious errors, and diagnostic mistakes.)[71] After 24 hours of being awake, impairment of reaction time is comparable to that produced by a blood alcohol concentration of 0.10 g/dL.[72,73] Sleep-deprived persons have a poor capacity to recognize their fatigue, thus reducing their capacity to work safely.[74] A survey of resident physicians suggested that fatigue-related errors resulting in death or injury of a patient are not uncommon.[75]

Landrigan and associates[76] reported that trainees working recurrent 24-hour shifts had 36% more serious medical errors compared with trainees with 16-hour shifts, five times as many serious diagnostic errors, 61% more needlestick and sharps injuries, double the risk of a motor vehicle crash when driving home, a 1.5- to 2-standard deviation deterioration in performance, and 300% more fatigue-related medical errors leading to a patient's death.

Individual persons vary in susceptibility to the effects of sleep deprivation. Young people are more susceptible to a single night of sleep deprivation, whereas older people are more vulnerable to a sequence of night shifts.[77] Differences also exist among otherwise

BOX 30.1 DESCRIPTION OF HUMAN FACTOR LEVELS

Organizational Influences

1. Climate: vision within the organization including policy, command structure, and culture
2. Process: means by which the vision of an organization is carried out, including operations, procedures, and oversight
3. Resource management: how human, monetary, and resources necessary to carry out the organizational vision are managed

Unsafe Supervision

4. Inadequate supervision: oversight, management of personnel, and resources, including training, guidance, and leadership
5. Problem correction: instances when deficiencies among individual persons, equipment, training, or other safety areas are "known" to the supervisor yet allowed to continue
6. Inappropriate operations: management of work, including aspects of risk management, crew pairing, and operational tempo

Preconditions to Unsafe Acts

7. Environmental factors
   a. Technologic environment: design of equipment and controls, display-interface characteristics, checklist layouts, task factors, and automation
   b. Physical environment: operational setting and environment (heat, lighting)
8. Adverse mental states: psychological and/or mental conditions, such as fatigue, pernicious attitudes, and misplaced motivation that negatively affect performance
9. Adverse physiologic states: medical and/or physiologic conditions such as illness, intoxication, and abnormalities known to affect performance
10. Physical or mental limitations: physical or mental disabilities, such as poor vision; lack of skill, aptitude, or knowledge; and other mental illnesses that affect performance
11. Teamwork: communication, coordination, and other teamwork issues that affect performance
12. Personal readiness: off-duty activities, such as adhering to rest requirements, alcohol restrictions, and other mandates required to perform optimally on the job

Unsafe Acts

13. Decision errors: "thinking" errors representing intended behavior that proceeds as designed, yet the plan proves inadequate for the situation. Errors manifest as poorly executed procedures, improper choices, or simply the misinterpretation of relevant information.
14. Skill-based errors: highly practiced behavior that occurs with little thought. These errors frequently appear as breakdown in visual patterns, forgotten intentions, and omitted items during procedures. The technique with which one performs a task is included.
15. Perceptual errors: errors arising when sensory input is degraded. Faced with acting on imperfect or incomplete information, operating room staff members run the risk of misjudging procedures as well as responding incorrectly to a variety of visual-vestibular illusions.
16. Routine violations: "bending the rules," a type of violation that is habitual and often enabled by management that tolerates departures from the rules
17. Exceptional violations: departures from authority, neither typical of the individual nor condoned by management

From ElBardissi AW, Wiegmann DA, Dearani JA, et al. Application of the human factors analysis and classification system methodology to the cardiovascular surgery operating room. *Ann Thorac Surg.* 2007;83:1412–1418; discussion 8–9.

healthy young people, and these differences have been linked to particular genetic polymorphisms.[78,79] Czeisler[80] speculated that in the future it may be possible to differentiate, from a cheek swab, the genetic subset of persons who tolerate sleep deprivation relatively well from those persons who are very sensitive.

Recognition that sleep deprivation may adversely affect performance has led to policies that limit work hours, beginning with pilots in the 1950s. In the United States the Accreditation Council for Graduate Medical Education (ACGME) limits the hours of trainees in approved programs, but no work limitation exists for nontrainee physicians, including attending physicians. New Zealand attempts to limit consecutive work hours for trainees to 16 hours.[81] In the European Union, all occupations are limited to 13 consecutive work hours and 48-hour work weeks. Whether limiting trainees' work hours lessens the effectiveness of training programs has been the subject of much debate, and it has been reviewed.[82] Noncompliance with work hour limits in ACGME-accredited training programs has been widespread.[83]

An effect of sleep deprivation on overall patient morbidity and mortality rates has not been demonstrated convincingly. A retrospective cohort study of procedures performed by physicians with and without preceding overnight procedures found no difference in complication rates.[84] Complications were more likely (odds ratio, 1.72; 95% confidence interval [CI], 1.02–2.89) if sleep opportunity was less than 6 hours. In three studies that evaluated the role of fatigue in cardiac surgery, no relationship was found between sleep deprivation and major morbidity or mortality rates.[85–87] However, given the available evidence connecting sleep deprivation with impairment in performance, it seems likely that work hour limitations will become more stringent rather than less so. The unintended consequence of limiting the number of consecutive hours worked is increased risk with more frequent handovers and introduction of a new team. A retrospective review by Hudson and colleagues[88] of 14,421 cardiac surgical procedures found that 966 involved handover to a new anesthesia team. After propensity matching, handover was found to increase mortality rates (match-adjusted odds ratio, 1.425; 95% CI, 1.013–2.006; $P = .0422$) and major morbidity rates (match-adjusted odds ratio, 1.274; 95% CI, 1.037–1.564; $P = .0212$) (Fig. 30.8).[88]

Fatigue has been implicated as a contributor to impaired performance, critical incidents, and errors in anesthesia.[89,90] The work hours and schedules of anesthesiologists expose them to circadian disruption, with both acute and chronic sleep deprivation causing fatigue. Anesthesiologists may be more susceptible to even mild sleep deprivation compared with other medical specialties because of the vigilance required to provide safe anesthesia care.

In a well-designed, realistic, simulation-based trial, in both a sleep-deprived state and a rested state, 12 residents anesthetized a simulated patient for 4 hours.[91] The sleep-deprived group had a trend to poorer vigilance with slower response times. The sleep-deprived group took numerically longer (not significant) to detect and correct abnormal clinical events, and during the simulated anesthetic regimen, nearly one-third of the sleep-deprived group fell asleep at some stage. Similarly, a survey of perfusionists found that 15% reported performing CPB after 36 hours, and 50% reported experiencing microsleep during bypass.[92] Two-thirds reported fatigue-related errors, and 6.7% reported serious perfusion accidents related to fatigue.[92]

In an analysis of the first 5700 critical incidents reported to the Australian Incident Monitoring System database, 2.7% of incidents listed fatigue as a contributing factor.[90] Drug errors were more frequent, and anesthesiologists reported that haste, distraction, inattention, failure to check equipment, fault of technique, and pressure to proceed with surgical procedures were all more common with fatigue. Experience and training did not render an anesthesiologist any less likely to make a fatigue-related error. A healthy patient and a relief anesthesiologist were factors identified that minimized the critical incident. Eighty-six percent of surveyed anesthesiologists reported that they had made a fatigue-related error. Fifty percent of trainees and 27%

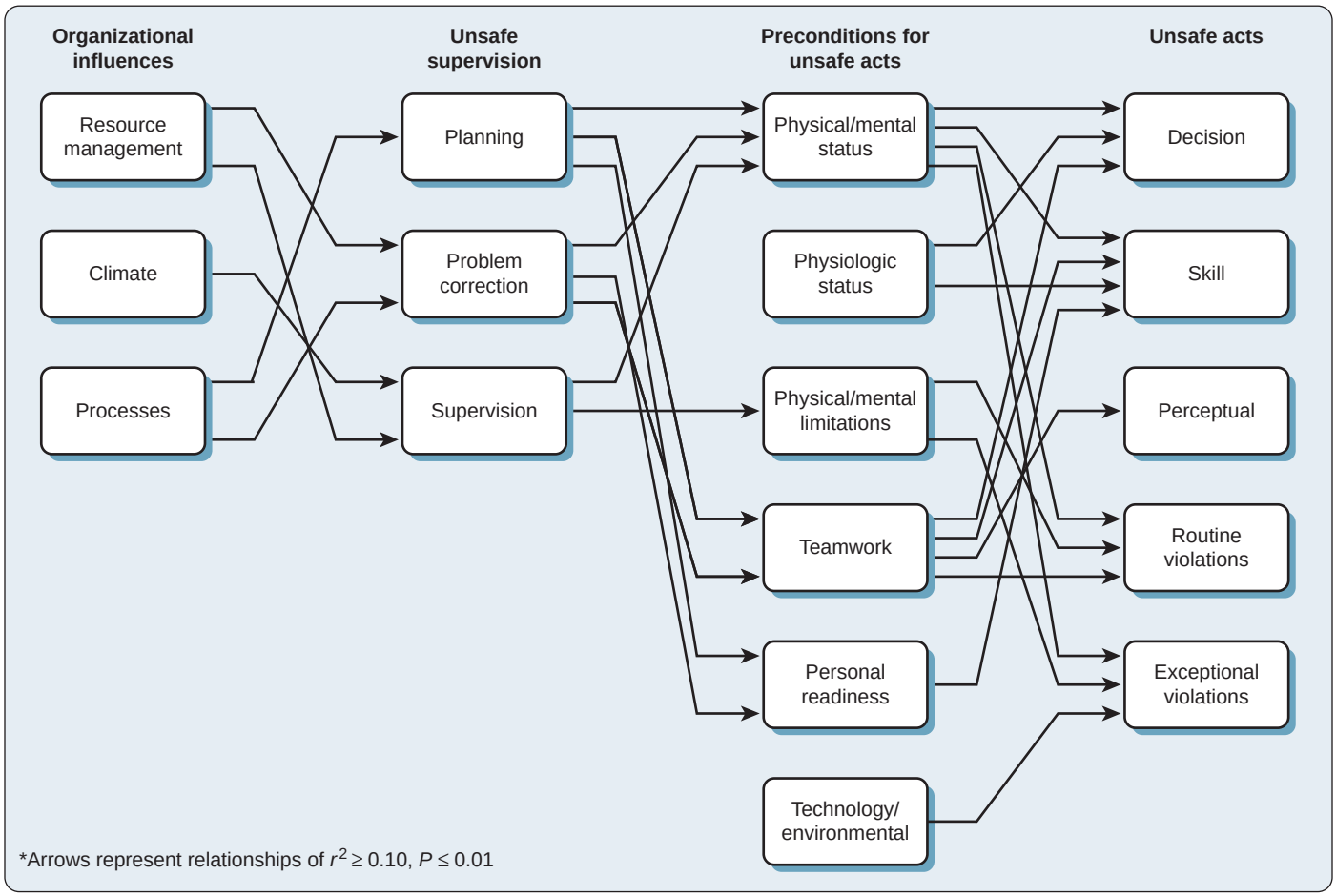


Fig. 30.7 Significant correlations among individual items of the Human Factors Analysis and Classification System taxonomy. *(From ElBardissi AW, Wiegmann DA, Dearani JA, et al. Application of the human factors analysis and classification system methodology to the cardiovascular surgery operating room.* Ann Thorac Surg. *2007;83:1412–1418; discussion 8–9.)*

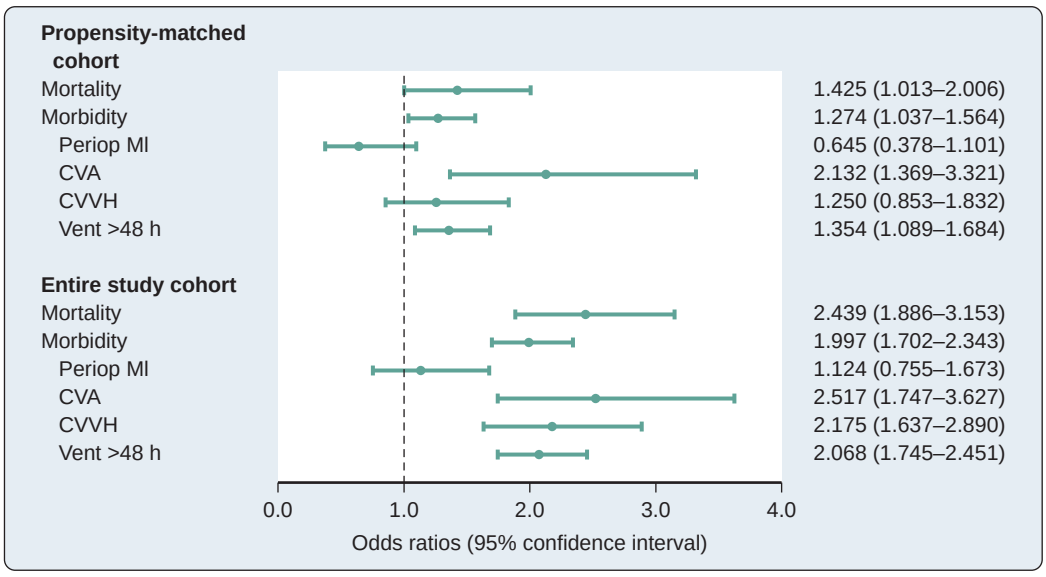


Fig. 30.8 Unadjusted and match-adjusted odds ratios for in-hospital mortality and morbidity associated with anesthetic handover among patients undergoing cardiac surgical procedures. *CVA,* Cerebrovascular accident; *CVVH,* continuous venoveno hemodialysis; *Periop MI,* perioperative myocardial infarction; *Vent >48 hr,* mechanical ventilation for longer than 48 hours postoperatively. *(From Hudson CC, McDonald B, Hudson JK, et al. Impact of anesthetic handover on mortality and morbidity in cardiac surgery: a cohort study.* J Cardiothorac Vasc Anesth. *2015;29:11–16.)*

of anesthesiologists believed that their average work week exceeded what they could do and maintain patient safety.[93] The anesthesiologists who exceeded their self-defined hourly or weekly limits were more likely to report a fatigue-related error.[93]

In a study by Gander and associates,[94] attending anesthesiologists showed a progressive decline in postduty psychomotor vigilance task performance, even with relatively small amounts of sleep loss (<1 hour/day). An analysis of incident reports in one of the hospitals found that in 23% of the reports, the anesthesiologist involved had more than 2 hours of sleep loss. Anesthesiologists who cited fatigue as a contributing factor were 7.4 times more likely to report sleep loss of more than 2 hours.[94]

Sleep quality and quantity become impaired at approximately age 50 and older.[95,96] No formal studies have assessed how these changes may affect the performance of older anesthesiologists. However, tolerance for late-night and shift work is reduced with aging.[96] Thus many of the fatigue-related performance impairments identified in residents potentially are worse in older anesthesiologists.

Despite studies showing no effect on mortality rates, the overall weight of evidence suggests that fatigue and sleep deprivation have harmful effects. Pressure exists to reduce total and consecutive work hours. The European Working Time Directive (EWTD) (also enacted into UK legislation) prescribes a maximum of 48 to 56 hours per week and only 13 consecutive work hours. The EWTD limits doctors-in-training to a maximum 48-hour week, averaged over a 6-month period, which is substantially less than allowed in the United States by the ACGME. Clearly, the implications of reduced work hours are significant at an individual level (eg, training experience with fewer work hours, importance of handover of care at shift changes) and at a departmental level (rostering changes, medicolegal and compliance issues). Given the trend to reduced work hours, more staff members may be required to fill rosters, with financial implications for hospital anesthesia departments and health services.

In addition, the nature of anesthetic work makes it difficult to avoid at least some work at night. Work patterns need to be designed to minimize the possibility of shift work– or fatigue-related error and must consider both total individual work hours and the effect of shift work on sleep and circadian rhythm. Useful overviews are available for individual practitioners on the impact of fatigue on learning and on good sleep hygiene to mitigate the impact of fatigue and for departments on the impacts of different rostering systems.[97–101]

Vigilance While Performing Transesophageal Echocardiograms

The introduction and subsequent widespread use of transesophageal echocardiography (TEE) brought about a major advance in cardiac surgery and anesthesia for both diagnosis and intraoperative monitoring. Anecdotally, we have noticed times when all attention in the OR is focused on the TEE machine rather than on the patient, especially with trainees. This seems to be more noticeable during the phase of learning TEE than with clinicians who are more experienced. Only one study has addressed this issue. During a study on task distribution, workload, and vigilance during cardiac anesthesia, Weinger and colleagues[102] found a significant increase in response time to vigilance probes (a light on the monitor screen) during the TEE examination. These investigators concluded, "use of the TEE may decrease vigilance to changes in other clinical data." Several factors limit the applicability of this study: the residents had limited anesthesia and TEE experience, the location of the TEE machine and monitors was poor, and the study involved only 20 patients. The findings of the study were questioned in a subsequent letter to the editor.[103]

In a report of four retained central venous catheter guidewires from a single institution, two of the cases involved performance of TEE by the attending anesthesiologist while the central venous catheter was being placed by a trainee.[104] This finding suggested the possibility that TEE distracted the attending anesthesiologist from noticing that the guidewire had not been removed from the patient.[104]

This area needs further investigation, but consideration should be given to where the TEE machine is placed in relation to the patient and the other monitors. The anesthesiologist working alone may be more vulnerable, given that attention can be focused on only one place at a time. Although all cardiac anesthesiologists recognize the poor ergonomics of machines and monitors,[24,105] no studies define best practices.

Violations

A significant section of the HFACS and of the original Reason taxonomy addresses "violations," when someone deliberately and consciously disobeys the existing rules or safe practices.[26,51,56,67] For a violation to occur, the following must exist: (1) a set of rules or regulations, or at least social norms; (2) an action that is contrary to those rules or guidelines; and (3) an intentional action to violate. Alper and Karsh[106] provided a categorization of violations based on Reason's original taxonomy of error (Fig. 30.9).

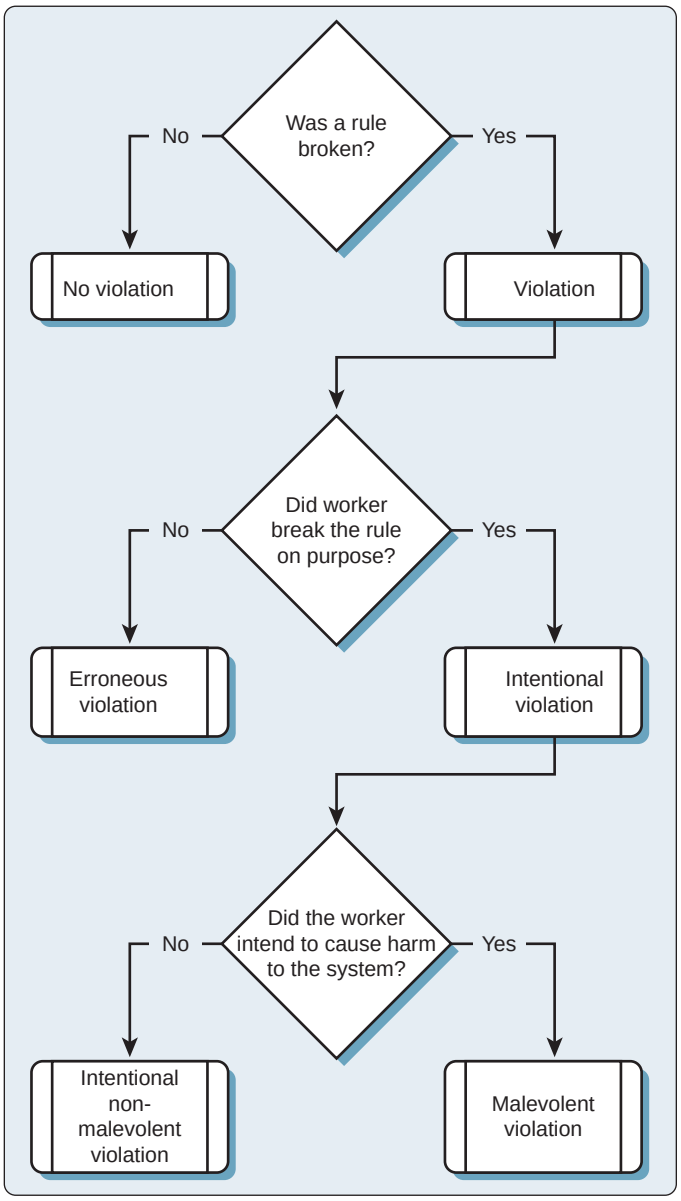
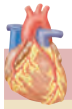


Fig. 30.9 Categorization of violations. *(From Alper SJ, Karsh BT. A systematic review of safety violations in industry.* Accid Anal Prev. *2009;41:739–754.)*



BOX 30.2 FACTORS CONTRIBUTING TO SAFETY VIOLATIONS IN HEALTH CARE

Individual Traits
- Experience (knows a better way to get it done, which may be correct)
- Attitude toward compliance (worker's beliefs about likely outcomes)
- Previous accident (no previous incident leads to belief that violation is safe)
- Previous injury
- Laziness (reported only as a contributing factor in others)

Information, Education, Training
- Level of knowledge (knowledge of rules, policies, and regulations)
- Conflict or confusion among staff members
- Level of training (lack of familiarity with regulations)
- Level of training (may increase or decrease likelihood of violation)
- Unfamiliarity with design

Design Flaws
- Poor design requiring violation (design of tool or environment makes compliance impossible)
- Changes to approved design (rules apply to previous design and do not fit the newer design)
- Required equipment not available
- Complicated design

Safety Climate
- Poor management (lack of supervision, senior workers giving advice to violate)
- Management tolerating or approving violations (management ignores or encourages violation to meet other goals)
- Subjective norm to comply (normalization of deviance)
- Perceived expectations by doctors (nurse perceives expectation is to violate)

Competing Goals
- Time pressure (quicker way of working or save time)
- Work pressure (unable to complete task unless rule is violated)
- Perceived risk (if low or no risk, more likely to violate)
- Conflicting demands (cannot achieve one goal without violating another goal)
- Physical fatigue or exhaustion

Problems with Rules
- Impossible rule to work within
- Complex rule (no one understands the rule)
- Outdated rule (violation may result in greater safety)
- Difficult rule to comply with (technically difficult to comply)

Modified from Alper SJ, Karsh BT. A systematic review of safety violations in industry. *Accid Anal Prev.* 2009;41:739–754.

As noted by Alper and Karsh[106] and Reason,[51,56] violations can be routine and at times even necessary to get the work done (workarounds), but they clearly put the patient at risk. As summarized by Alper and Karsh,[106] workers provide many reasons that they or others violate rules and regulations (Box 30.2). Although certainly some individual traits contribute to violations, many of the cited factors are system-level issues, including rules that cannot be understood or followed, outdated rules, poor management, and superiors who expect violations to enhance productivity. For example, a violation is often the result of "normalization of deviance," in which poor hand hygiene or failing to use a full-barrier drape during central line placement occurs among junior staff members because they follow the example of senior staff. The complexity of reasons that workers violate safe practices, rules, and regulations led Alper and Karsh[106] to conclude that "the conversation about violations needs to continue to evolve from one of automatically assigning blame to one that views violations as symptoms of system design problems."

Teamwork and Communication

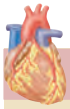
As noted earlier, preventable adverse events or human errors in the cardiac OR often are related not to technical skill or knowledge base but to cognitive, teamwork, or system failures.[107–111] With the publication of an examination of errors and near misses in pediatric cardiac surgery by de Leval and colleagues,[112,113] the role of human factors (ie, nontechnical skills) has become apparent. Skills such as communication, cooperation, and leadership are recognized to be critical components of teamwork, and deficiencies in these skills have been associated with adverse outcomes.[114] Stress levels can be determined accurately among surgical staff across the surgical case and also are related to team performance.[115] In a systematic review of the literature, Hull and colleagues[116] found that these nontechnical aspects of team performance also can affect a surgeon's technical performance. As Frankel and associates stated,[117] "we can assure our patients that their care is always provided by a team of experts, but we cannot assure our patients that their care is always provided by expert teams."

Communication failures, human factors, and leadership deficiencies have been found to be the top three causes underlying sentinel events in every review from The Joint Commission since 2004.[118] In a review of litigated surgical outcomes, a communication failure among caregivers was responsible for the adverse outcome in 87% of cases.[119] Clearly, teamwork behaviors and communication are critical to patient safety. A scientific approach requires validated measurement tools and rigorous studies of how these nontechnical skills can be strengthened in a way that improves patient outcomes.[120]

Measurement

The technical skills of a surgeon or anesthesiologist can be assessed in an objective fashion. For example, the rate of completion of critical steps in a laparoscopic cholecystectomy and the time required to complete a simulated fiberoptic intubation can be quantified.[121] The qualitative and observational assessment of nontechnical skills, although still rigorous and scientific, can seem arbitrary and subjective to physicians inculcated in quantitative science.[18,122] However, observational, qualitative research is able to capture the number and nature of adverse events in cardiac surgery.[107,123,124] Furthermore, observational research has identified team behaviors that are associated with teamwork failures and with surgical excellence.[114,123,125,126] Observational research does have limitations. Observers must be trained to be effective,[18,127] and not all observers can become proficient.[128] Moreover, the location and focus of observers in the OR determine what events are captured.[129] These limitations, however, have not precluded significant advances in the measurement of teamwork skills.

The need for objective assessment of nontechnical skill is underscored by the finding that the ability of physicians to assess their own skill level is poor. Although assessment of technical skill is similar between self and observer in simulation studies, self-assessment of nontechnical skills by both junior and senior physicians is consistently higher (more skilled) than the ratings of expert observers.[130,131] Observers also are able to assess disruptions, communication failures, environmental issues, and the impact of those factors on outcome



BOX 30.3 TEAMWORK ASSESSMENT TOOLS

OTAS (Observational Teamwork Assessment for Surgery)[127,128,136–139]	Procedural task checklist centered on patient, equipment, and communications tasks ratings • Communication • Cooperation • Coordination • Shared leadership • Shared monitoring
NOTECHS (Oxford Non-technical Skills)[126,128,141–144]	Adapted from the aviation NOTECHS scale used in Europe • Cooperation and teamwork • Leadership and management • Situational awareness • Problem solving and decision making • ± Communication and interaction
ANTS (Anaesthetists' Non-technical Skills)[148,149]	Based on aviation crew resource management principles, developed by industrial psychologists and anesthesiologists • Task management • Teamworking • Situation awareness • Decision making
SPLINTS (Scrub Practitioners' List of Non-technical Skills)[151,152]	Psychologist-facilitated focus groups identified key nontechnical skills for scrub practitioners • Situation awareness • Communication and teamwork • Task management

From Wahr JA, Prager RL, Abernathy JH 3rd, et al. Patient safety in the cardiac operating room: human factors and teamwork: a scientific statement from the American Heart Association. *Circulation.* 2013;128:1139–1169.[4]

more accurately than the involved clinicians.[115,130] OR personnel rate disruptions as affecting others more than themselves, whereas trained observers find the disruptions affect all team members equally.[132] Finally, nontechnical skills must be explicitly taught and monitored because senior physicians do not demonstrate higher nontechnical skill levels than juniors unless the senior physicians are specifically trained in these skills.[130,133,134] Unfortunately, although most physicians agree that nontechnical skills are important, not all physicians agree that they can be taught.[135]

The nontechnical skill measurement tools in current use have been developed primarily from established and validated aviation tools (Box 30.3). Five instruments have been designed for surgical teams and subteams: the Observational Teamwork Assessment for Surgery (OTAS),[127,128,136–140] the Oxford Non-technical Skills (NOTECHS),[116,126,141–144] the Non-technical Skills for Surgeons (NOTSS),[128,130,145,146] the Anesthetists' Nontechnical Skills (ANTS),[147–149] and the Scrub Practitioners List of Non-Technical Skills (SPLINTS).[150–152] Specific tools also have been developed to measure individual skills, such as leadership by the Surgeons' Leadership Inventory.[153,154] Most measurement tools assess skill in multiple domains, including communication, cooperation and teamwork, leadership (shared, coordination), situational awareness (shared monitoring), and problem solving and decision making. These tools have been proved to be valid (ie, they measure what they purport to measure), reliable (ie, they have high interobserver correlation), feasible, and sensitive.[128] NOTECHS, which is specifically designed to evaluate skills across the team, has been used to evaluate the effect of teamwork training, and it shows a significant inverse relationship between nontechnical score and number of technical errors.[126,143]

Scientific development of patient safety interventions also requires measuring effectiveness, with the gold standard being changes in morbidity and mortality rates after implementation. Although such interventions have been successfully implemented,[155–165] demonstration of a further reduction in the already low rate of death among surgical patients (2–3%) requires a large sample size. For this reason, many studies of interventions in patient safety use surrogate outcomes, such as a change in the effect of disruptions (the Disruptions in Surgery Index,[132,166] the Surgical Flow Disruption Tool[167]), or changes in the safety climate.[168] Many safety climate surveys exist and are considered reliable. However, most studies using these surveys have described the existing culture,[168–172] as well as changes in climate after teamwork training.[173,174] Only rarely have studies attempted to demonstrate a relationship between the measured safety climate and patient outcome.[175,176]

Disruptions, Distractions, Major and Minor Events

The cardiac OR is a highly complex setting where professionals from multiple disciplines interact with complicated and often poorly designed equipment to complete hazardous interventions—typically under significant time constraints—in patients with challenging cardiac disease and other comorbidities.. Despite the apparent need for quiet concentration, distractions and disruptions rule the day.[111,132,166] In cardiac surgical cases, door openings average 19.2/hour, 22.8/hour if prosthetic devices are involved.[177] OR traffic, door openings, conversations, alarms, and even music can result in an excessive noise level.[178] It is no wonder that failures of teamwork resulting in surgical flow disruptions occurred at a rate of 11.7/hour in one study,[124] and at 11/case in another.[111]

Team members perceive disruptions and distractions, as well as team behaviors, in discipline-specific ways. Surgeons tend to downplay disruptions and report them as having a lesser effect on performance than do nurses or trained observers.[166] All too often, significant disruptions and distractions simply are treated as annoyances and part of the daily work. Data show, however, that technical errors and adverse patient outcomes increase as disruptions accumulate.[179,180] Moorthy and colleagues[181] found that OR noise reaching 80 dB is associated with a significant increase in surgical technical errors.

A landmark study of pediatric cardiac found that even minor events (ie, those not expected to affect outcome) reduced the team's ability to compensate for or recover from a major event (Fig. 30.10).[113,122] In observing 250 arterial switch operations, de Leval and associates[112,113] and Solis-Trapala and colleagues[122] reported that, for every 3 minor problems above the mean of 10 per case, intraoperative performance diminished and operative duration increased. As noted, "little things matter."[123,182]

Equipment and Alarms

As noted earlier, distractions and disruptions are rife in the cardiac OR. In addition, the quantity and complexity of the equipment required for cardiac operations are significant. Equipment-related problems are responsible for 10% to 12% of flow disruptions.[111,183,184] Even though ergonomic design is known to be an important factor in patient safety, it has been suboptimal, both for OR room design and layout and for equipment design.[24,185,186] ORs built years or decades ago are now necessarily cluttered with equipment, each device requiring electrical cords and communication tethers. Cesarano and Piergeorge[187] describe the "spaghetti syndrome": how cluttered equipment and tangled lines limit access to the patient, thereby putting both patients and staff at risk. Slips, trips, and falls cause workplace injuries and are related to cords and cables, low-profile equipment, and protective and absorptive mats.[188]

In a study of disruptions observed in 10 cardiac operations, 33% of flow disruptions were related to OR design and physical layout.[105] The investigators developed a taxonomy that can be used to categorize flow disruptions and design flaws that can guide further research and improvements. Using observations drawn from 20 cardiac operations, Pennathur and colleagues[24] identified many unique technology-related hazards and demonstrated how these hazards negatively affected the

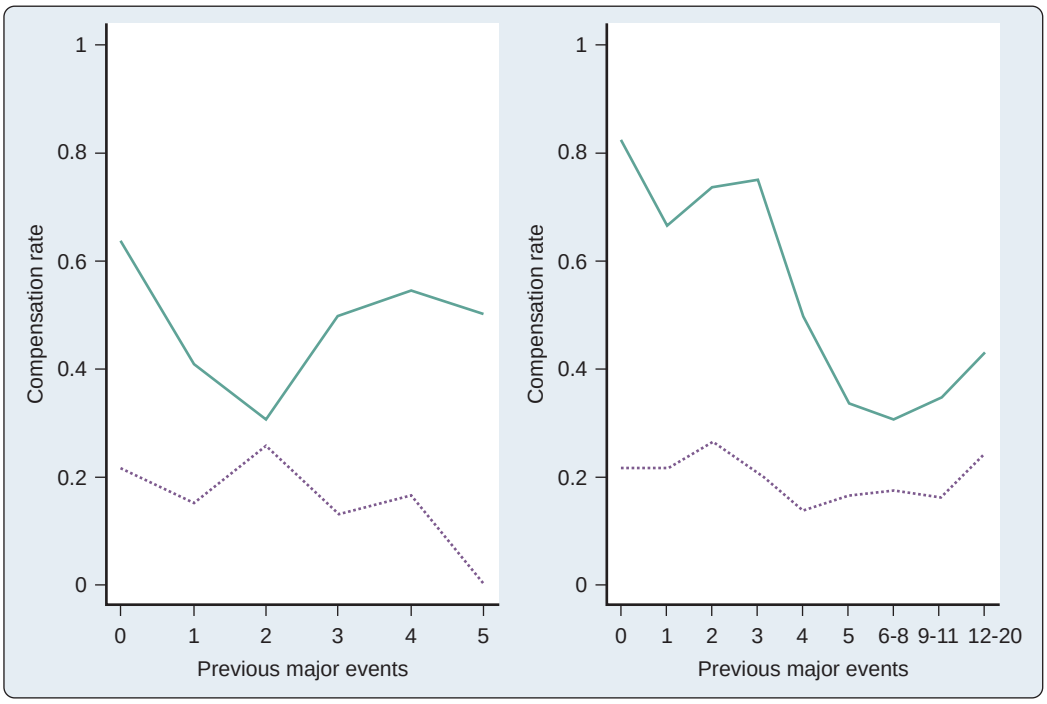


Fig. 30.10 Effect of major *(solid line)* and minor *(dotted line)* events on a team's ability to compensate for subsequent events. *(Solis-Trapala IL, Carthey J, Farewell VT, de Leval MR. Dynamic modelling in a study of surgical error management.* Stat Med. *2007;26:5189–5202.)*

cognitive processes of the team. As the investigators stated, "the interaction of poorly designed spaces, organizational constraints, and functional capability has the potential to multiply latent risks inherent in [cardiovascular] OR technologies."[24]

In a literature review regarding hazards associated with cardiac surgery, Martinez and colleagues[185] identified four ways in which equipment harms the patient: (1) poor design and ergonomics, (2) poor training or negligence with use, (3) poor maintenance and upkeep, and (4) risk inherent in use of the device (eg, the risk that a TEE probe will cause esophageal injury). Medical devices and equipment typically are designed by engineers who spend little time in the environment in which the devices will be used. Even rarer is the participation of human factors engineers in the pre-purchase evaluation of equipment for device-specific form and function, as well as for integration of the equipment into the existing physical layout out of a typical OR. As a result, the interaction between people and technologies in the OR is suboptimal.[186,189,190] Wiegmann and colleagues[191] studied the design and function of CPB machines and found significant deficiencies. Information displays were poorly placed and difficult to read, components were poorly integrated and not well positioned, and alarms were either too quiet or had inappropriate tonality.

Indeed, one of the most problematic factors in cardiac surgery is the sheer volume of noise in the OR. Beepers, ringing telephones, ancillary conversations, and alarms often raise OR noise levels to those considered hazardous by the US Occupational Safety and Health Administration.[178,192–195] Noise, including music, can adversely affect auditory processing in the cardiac OR, and the impact of noise is particularly great when the listener is intent on a task.[196] Furthermore, unexpected sentences (low predictability) were significantly less well processed than those that were expected and predictable.[196] This finding has serious implications for conversations that carry critical information that is not expected ("I'm having difficulty oxygenating").[196] Some experts have advocated for the "sterile cockpit" concept that is common in aviation, in which no conversation occurs except for the task at hand during takeoff and landing. In a surgical operation, however, it is difficult to identify which periods are critical versus noncritical. Wadhera and associates[197] pointed out that the critical time

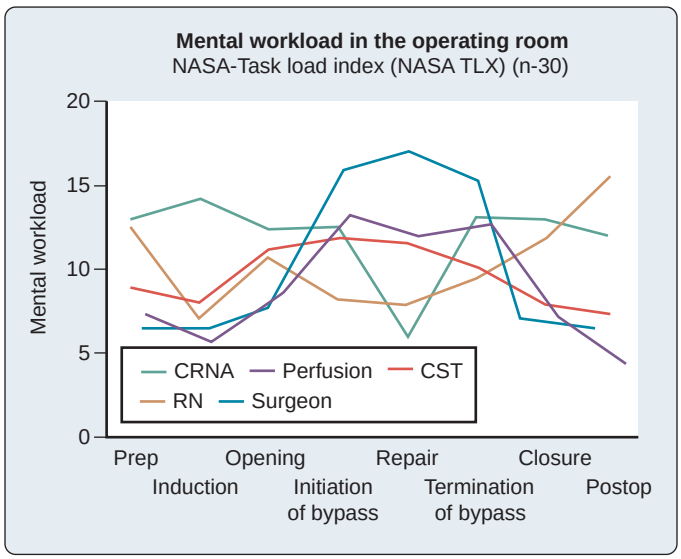


Fig. 30.11 Varying level of mental workload in the cardiovascular operating room by role. *CRNA,* certified registered nurse anesthetist; *CST,* certified surgical technologist; *NASA,* National Aeronautics and Space Administration; *Prep,* preparation; *RN,* registered nurse; *TLX,* Task Load Index. *(From Wadhera RK, Parker SH, Burkhart HM, et al. Is the "sterile cockpit" concept applicable to cardiovascular surgery critical intervals or critical events? The impact of protocol-driven communication during cardiopulmonary bypass.* J Thorac Cardiovasc Surg. *2010;139:312–319.)*

for the surgeon may be noncritical for an anesthesiologist. Thus level of concentration and workload vary by discipline across the surgical procedure such that every moment is critical to one discipline or another (Fig. 30.11).[197]

Perhaps the most distressing single contribution to OR noise is the frequency of alarms. Alarms clearly are designed to alert to parameters

outside the norm, but a typical cardiac OR has some 18 alarms, each with manufacturer-chosen visual and audio alerts.[198] Unfortunately, the volume or tonality of the alarm has no rhyme or reason. A "not ventilating" alarm can be quiet and nearly undetectable, whereas a circuit humidifier alarm can be hair-raising. Schmid and colleagues[199] reported that 359 alarms occurred per cardiac operation, for a rate of 1.2/*minute*. In one study, 90% of alarms were found to be false-positive events, often resulting in alarms being turned off or ignored.[200] In a study of 731 alarm warnings, only 7% were found to be useful, and 13% were triggered by a planned intervention.[198] As concerning as the noise and disruption are, even more concerning is the tendency to tune out the alarms or even turn off the alarms when they become too annoying, potentially resulting in a serious preventable adverse event. The Joint Commission made alarm management a goal in 2012, but true correction will require a comprehensive national (or international) approach to standardize the volume and tonality of alarms by system (eg, ventilation, cardiac) and by urgency and then to require all manufacturers to meet these standards.

Teamwork

In the highly complex world of cardiac surgery, teamwork and communication are critical to outcome. As already noted, communication and teamwork failures are common in significant preventable adverse events.[201] As described earlier, these issues are not trivial. Poor nontechnical skills and teamwork directly affect patient outcomes. System failures,[119] communication failures,[175,202] poor teamwork behaviors,[114] unfamiliarity among team members,[180,203] and the number of minor events[122] are all associated with increased technical errors, morbidity, and mortality.

In other studies, the quality of teamwork behaviors has been linked to surgical duration,[179] number of technical errors,[116,126,142,180] and number of major events.[204] Mishra and colleagues[126] found zero to six technical errors per operation (mean, 2.62 errors) and observed an inverse correlation between errors and the surgeon's situational awareness score. Poor teamwork has been found to directly increase stress levels among surgeons,[166,205] and stressful situations degrade teamwork behaviors.[206] At a systems level, Meterko and colleagues[207] found a significant and positive correlation between institutional teamwork culture and patient satisfaction scores and a significant and negative correlation between bureaucratic culture and satisfaction scores. In this analysis of data from 125 Veterans Affairs (VA) hospitals, a full standard deviation in patient satisfaction scores was noted between hospitals that ranked in the top third and those ranked in the bottom third for teamwork culture.

Conversely, teams with high levels of teamwork suffer less interference from observed distractions and interruptions.[124,208] ElBardissi and colleagues[209] examined the relative influence of attending surgeons' experience (years since fellowship) versus the number of previous collaborations with a given cardiac fellow on CPB duration and cross-clamp time. A multivariate model for cross-clamp time showed that the cumulative experience of the attending surgeon with a fellow mattered much more than the years of experience of the attending surgeon (Fig. 30.12). In another analysis, teams that were familiar with the operating surgeon had significantly fewer event failures (8.6 versus 22) and teamwork failures (5.6 vs 15.4) than teams in which most members were not familiar with the surgeon.[180] Operations conducted with the "day" team had shorter length of stay, duration of ventilation, and duration of surgical procedure, whereas operations that had a change in teams were associated with an increase in incidence of septicemia.[203] As noted earlier, transfer of a case to a new anesthesia team (handover) increased morbidity and mortality rates.[88,210] Teams engaged in more complex operations tend to demonstrate better teamwork performance, but even in these cases, the presence of nonroutine events is associated with more complications postoperatively.[211]

As noted earlier, team members (especially physicians) are poor at assessing their own teamwork and communication skill level. In multiple studies, surgeons' and anesthesiologists' teamwork and

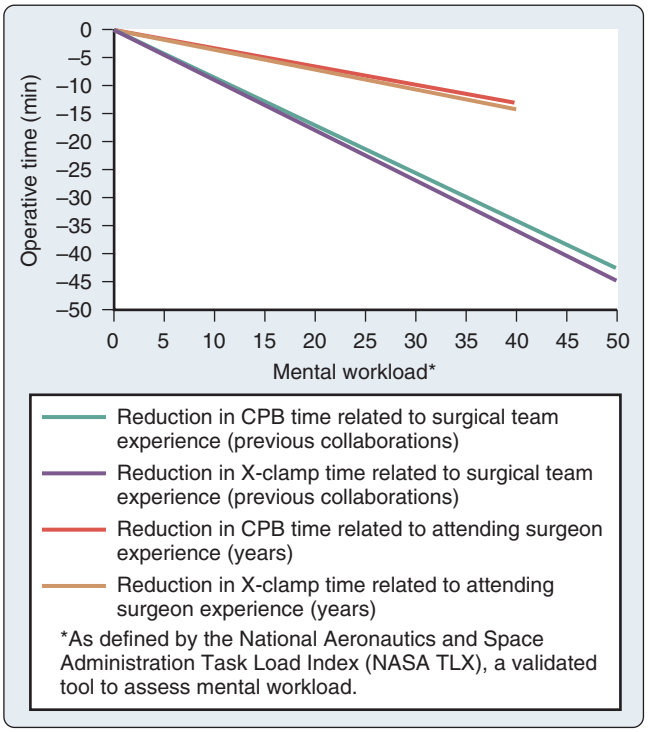


Fig. 30.12 Relative influence of attending surgeons' experience and cumulative experience on cardiopulmonary bypass *(CPB)* and cross-clamp *(X-clamp)* times. *(From ElBardissi AW, Duclos A, Rawn JD, et al. Cumulative team experience matters more than individual surgeon experience in cardiac surgery.* J Thorac Cardiovasc Surg. *2013;145: 328–333.)*

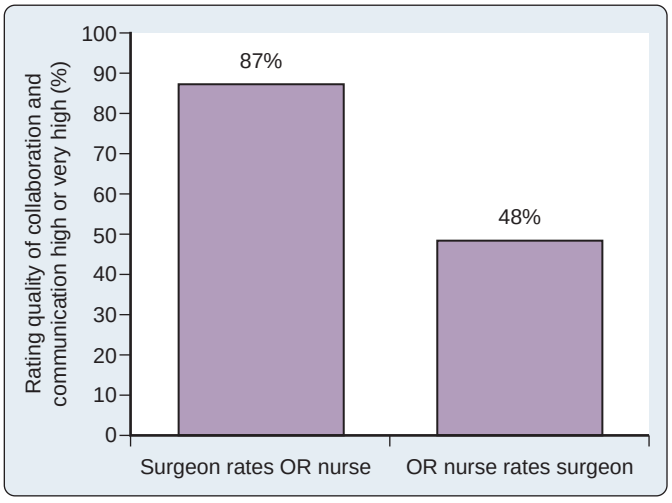


Fig. 30.13 Differences in perceptions of teamwork between surgeons and operating room *(OR)* nurses. *(From Makary MA, Sexton JB, Freischlag JA, et al. Operating room teamwork among physicians and nurses: teamwork in the eye of the beholder.* J Am Coll Surg. *2006;202: 746–752.)*

communication skills were rated much more highly by themselves than by nurses and perfusion staff members.[212,213] In one study, surgeons rated the quality of other surgeons' teamwork as high or very high 85% of the time, whereas nurses rated the collaboration with surgeons as high or very high only 48% of the time (Fig. 30.13).[214]

In a study of attitudes about teamwork among OR teams, surgeons and anesthesiologists reported that they understood the staff members' roles, whereas staff members did not appear to believe that their roles were understood.[215] In that study, the physicians perceived the team

TABLE 30.2 Definitions of Types of Communication Failure With Illustrative Examples and Notes

Failure	*Definition*	*Illustrative Example*
Occasion failures	Problem in the situation or context of the communication event	The staff surgeon asks the anesthesiologist whether the antibiotics have been administered. At the point of this question, the procedure has been under way for more than an hour. Because antibiotics are optimally given within 30 minutes of incision, the timing of this inquiry is ineffective both as a prompt and as a safety redundancy measure
Content failures	Insufficiency or inaccuracy apparent in the information being transferred	As the case is set up, the anesthesia fellow asks the staff surgeon whether the patient has an ICU bed. The staff surgeon replies that the "bed is probably not needed, and there isn't likely one available anyway, so we'll just go ahead." Relevant information is missing, and questions are left unresolved: has an ICU bed been requested, and what will the plan be if the patient does need critical care and an ICU bed is not available?
Audience failures	Gaps in the composition of the group engaged in the communication	The nurses and anesthesiologist discuss how the patient should be positioned for operation without the participation of a surgical representative. Surgeons have particular positioning needs, so they should be participants in this discussion. Decisions made in their absence occasionally lead to renewed discussions and repositioning of the patient on their arrival
Purpose failures	Communication events in which the purpose is unclear, not achieved, or inappropriate	During a living donor liver resection, the nurses discuss whether ice is needed in the basin they are preparing for the liver. Neither knows. No further discussion ensues. The purpose of this communication—to find out whether ice is required—is not achieved

ICU, Intensive care unit.
From Lingard L, Espin S, Whyte S, et al. Communication failures in the operating room: an observational classification of recurrent types and effects. *Qual Saf Health Care.* 2004;13:330–334.

structure to be that of separate subteams, whereas nurses viewed the team as unitary.[215] In a survey of adequacy of communication, teamwork, and situational awareness, surgeons rated both communication and establishing a shared understanding as "adequate," whereas anesthesiologists and nurses rated both as inadequate ($P < .01$ for both). Coordination of team activities and performance of briefings were similarly rated as inadequate by all team members but the surgeons.[213] In a survey of 90 physicians and 230 nurses working in intensive care units (ICUs), only 33% of nurses rated the quality of collaboration and communication between nurses and physicians as high or very high, compared with 73% of physicians.[216] Surgeons also perceive the organizational culture of safety and teamwork to be stronger than do anesthesiologists and nurses.[212] Finally, perceptions of teamwork climates are not just different among types of caregivers, but they also are distinctly different among institutions.[217]

In a survey of attitudes toward error, stress, and teamwork, Sexton and colleagues[218] compared the responses of 1033 doctors, nurses, fellows, and residents working in ORs and ICUs with the responses of more than 30,000 airline cockpit crew members (captains, first officers, and second officers). Only one-fourth of pilots denied that fatigue affected their performance, whereas 70% of surgeons and 47% of anesthesiologists did. Similarly, most pilots (97%) rejected hierarchies in which senior members resisted input from junior members, but only 55% of surgeons rejected such hierarchies. Nearly two-thirds of medical staff reported that errors were handled inappropriately by their hospital; one-third of ICU staff did not acknowledge that they make errors, and more than one-half of ICU staff stated that it is difficult for them to report or discuss errors.[218] Similarly, Flin and associates[219] found that all team members had a positive attitude toward behaviors associated with safety and teamwork, but that both nurses and surgeons expressed a belief in their invulnerability to stress or fatigue. Surgeons viewed surgical team leadership and communication more positively than did nurses on the same team.[219]

In a study using a survey of pediatric cardiac surgical teams, most team members believed that open communication channels were maintained during surgical procedures; nonetheless, 29% reported having trouble speaking up if they perceived a problem with patient care.[169] Fewer than half (45%) reported that morale was high, and 60% reported having trouble discussing mistakes, even though 83% reported they had made errors with the potential to harm patients. Only 30% stated that debriefings occurred after mistakes are made.[169]

Communication

One specific aspect of teamwork is communication, defined as the exchange of information between a sender and a receiver.[220] Systematic literature reviews indicate that effective communication is a hallmark of successful teams and is critical to providing high-quality patient care.[220,221] In cardiac surgery, an enormous amount of information is continuously exchanged among multiple providers. Studies have shown that communication failures are common,[139,184,222,223] and such failures represent the most frequent root cause of adverse events.[180,224,225] Breakdowns in communication contribute significantly to failures in patient safety.* In an observational study of 48 cardiac surgical procedures, a total of 421 communication events occurred during 90 hours of observed procedures; 129 of these events were classified as failures (ie, one-third of all communications failed, at a rate of 1.43/hour).[223] In 45.7% of events, the timing was poor; 35.7% involved missing or inaccurate content; 24% occurred when issues raised were not resolved; and 20.9% involved "audience," in which key persons were missing (Table 30.2). More than one-third of these failures had a visibly deleterious effect on system processes.[223] As seen in other teamwork skills, providers tend to rate their own profession as being less responsible for the effects of poor communication.[231]

One very specific aspect of communication is that required during a transition of care from one provider to another (relief during surgical procedures) or between teams (OR to ICU), termed "the handoff" (also known as the handover). A handoff is essentially a contemporaneous process of passing patient-specific information from one caregiver to another to ensure continuity and safety of patient care. Standardized handoff communication was a safety goal of The Joint Commission for 2006 (Goal 2E).[232] Handoffs occur multiple times during surgical procedures as staff members are relieved, and multiple handoffs occur among teams: from cardiology to cardiac surgery, from the preoperative team to the intraoperative team, even from anesthesia to perfusion at the initiation of bypass, from the OR to the ICU, from the ICU to the ward, and, finally, from the hospital back to the primary care provider or cardiologist. Greenberg and associates[201] and Rogers and colleagues[233] reviewed 258 surgical malpractice cases in which error led to injury of a patient; 60 cases involved communication failures. Forty-three percent of the failures occurred during a handoff, and 19% occurred across departments. Most of the communication failures (92%) were verbal, involved a single transmitter and receiver, and were equally the result of omission of critical information (49%) and misinterpretation (44%).[201,233]

These errors are understandable, given the complexity of cardiac surgical procedures, the nuances of patients' physiology (often understood as much at a subconscious level as at a conscious one), and the frequent distractions that arise during patient care.[88,228,229,234–236] Handoffs rarely occur in a quiet setting, and distractions are common. Occasionally, no handoff occurs at all.[235,237] A review of the literature portrays handoffs as being highly variable, unstructured, and

*References 113, 118, 119, 175, 180, 223, 224, 226 to 230.

performed under pressure from competing tasks.[238] In one study of pediatric cardiac surgical handoffs, important content items were reported only 53% of the time, and distractions occurred at a rate of 2.3/minute of reporting.[239] Handoffs from OR to postanesthesia care unit (PACU) personnel are nonstandardized and depend on the staff involved; typically, no specific point occurs at which responsibility is transferred.[240]

In a process that first rigorously defined critical information items in the handoff from the OR to the recovery room, Nagpal and colleagues[134,236] found a median of 9 omissions out of 29 elements; they noted that one-third of critical tasks were not performed and that critical team members often were not present. Furthermore, information degraded as the patient progressed through sequential handoffs.[229] Only 56% of essential information was transmitted from OR to recovery and only 44% from recovery to the ward. At least one critical event associated with these omissions occurred in 75% of patients.[229]

Interventions to Improve Patient Safety

It is clear from the preceding discussion that nontechnical aspects of cardiac surgical procedures play a vital role in patient outcomes. Efforts to improve these aspects of cardiac operations are required to decrease the number of patients who suffer preventable harm. Key areas of focus include the following: standardizing care as much as possible, including implementing evidence-based best practices; undertaking formal training and practice in teamwork behaviors and skills; implementing pre-surgery briefings, and the use of cognitive aids such as checklists; using regular debriefings to identify areas in which improvement is needed; strengthening structured communication protocols both during surgical procedures and during transitions of care; and using simulation to provide directed practice both for nontechnical skills and for the technical aspects of crisis management.

Although these interventions have been shown to increase patient and staff satisfaction and to reduce mortality rates,[162,176,241–244] interventions are often met with ambivalence at best and hostility at worst.[141,245] As noted, this response can have several causes: overestimation of skill level; discounting of the effects of stress, fatigue, and disruptions; and a view that imposition of external guidelines limits individualized patient care or is insulting to staff members' intelligence and dedication.[†] In short, "patient safety is hard."[247]

In addition, even in the best of circumstances, fully implemented protocols and teamwork skills do not totally eliminate errors or accidents; they only lengthen the period between accidents.[52] Continual external changes to a system (ie, new equipment, change of personnel or roles) introduce new complexities, each with new opportunities for error. Although Duncan and colleagues[248] described how development of a training program for elimination of retained guidewires during central line insertion reduced the incidence of this error, Vannucci and colleagues[104] reported a different result. After two guidewires were retained, a comprehensive training program was instituted; in a short time, another two events occurred. The two persons associated with the last two events had completed the training. Whether they truly embraced the education and implemented the policy is unclear.[104] It is clear that patient safety requires a multifaceted, multidisciplinary, and continual process involving a broad range of tools and techniques.[249]

Teamwork Training

The evidence presented earlier (ie, that poor teamwork skill is directly linked to technical errors and adverse patient outcomes) indicates that specific teamwork training should improve outcomes. Many investigators and experts have pointed to the aviation industry's use of Crew Resource Management (CRM) to achieve excellent teamwork and reduce errors and accidents and have suggested that medical teams adopt CRM.[141–143,173,250–259] Key components of effective teamwork are similar between aviation and medicine: leadership and management, situational awareness, shared decision making, cooperation, and coordination.[141–144] However, the effect of teaching CRM to surgical teams has been mixed. When pilots were brought in to teach surgical staff how to perform effective briefings, no change in safety attitudes occurred among faculty physicians, and only a modest change occurred among junior physicians.[173] France and colleagues[253,260] instituted an 8-hour, aviation-style CRM training and found that, after training, compliance with the CRM practices was only 60%.

An experienced patient safety research team in Oxford, United Kingdom developed a 9-hour educational program based on aviation-style CRM, followed by 3 months of twice weekly coaching from CRM experts. In the 55 procedures studied after this training, nonprocedural errors were reduced (8.5 to 5.16 per procedure), operational technical errors were reduced (1.73 to 0.98) and the Safety Attitudes Questionnaire teamwork climate increased from 64 to 69. These improvements were, however, modest, and the investigators noted, "Non-technical skills training improved technical performance in theatre, but the effects varied between teams. Considerable cultural resistance to adoption was encountered, particularly among medical staff. Debriefing and challenging authority seemed more difficult to introduce than other parts of the training."[142] However, more recent reviews demonstrated that CRM-based team training consistently increases team effectiveness,[261] and it improves teamwork practices and complication rates.[262]

Teamwork training appears to improve patient safety, but positive effects are not achieved by simply implementing aviation-style CRM. Team training must be developed that specifically addresses surgical team issues and acknowledges the significant differences between aviation and medicine. The largest study of the effect of team training of surgical teams was performed in Veteran's Health Administration hospitals, led by a former astronaut and physician, Jim Bagian. The Medical Team Training program consisted of 2 months of preparation, a full-day interactive session facilitated by health care clinical peers, and (perhaps most significant) quarterly coaching activities with discussions of lessons learned.[163,252] In a comparison of surgical mortality rates for the year before and the year after training, the 74 participating facilities had a 18% reduction in annual mortality rate (rate ratio [RR], 0.82; 95% CI 0.76–0.91) compared with a 7% decrease in the 34 facilities that were not participating.[163] Propensity matching showed that the decrease in risk-adjusted surgical mortality rate was 50% greater in the training facilities. In addition, a "dose effect" occurred: for every quarter of training, a reduction of 0.5 deaths/1000 procedures performed was reported (95% CI, 0.2–1.0; $P = .001$).[163]

The Agency for Healthcare Research and Quality (AHRQ) has developed a similar team training program, called TeamSTEPPS. Although it is used more widely than the VA Medical Team Training, no large-scale study of the effect on mortality rates has been conducted. However, multiple studies have shown improved teamwork climate measures and improved compliance with quality measures (eg, time of antibiotic administration),[125,263,264] clinical care,[263] and teamwork skills.[125] One of the most detailed studies undertook a 2-month training program for all members of the OR teams.[125] Significant improvements were reported in overall OR teamwork score and communication score, as well as improvements in first case starts, quality measures, and patient satisfaction. More importantly, surgical mortality rates decreased from 2.7% to 1.0%, and morbidity rates decreased from 20.2% to 11.0%. However, 1 year later surgical mortality rates had increased slightly from 1% to 1.5%, and morbidity rates had increased from 11% to 13%, thus indicating a deterioration in gains, although rates were still better than before the intervention.[125] The investigators concluded that team training can improve OR team performance and improve patient outcomes, but continued efforts are required to sustain these gains.[125]

Although all currently tested team training methods are built on aviation-style or well-recognized team training methods, few data are available to support which elements are required. Training sessions range from a few hours with little coaching or follow-up[171,265] to several days with regular coaching sessions over at least a 12-month

[†]References 115, 130, 142, 169, 205, 206, 213, 216, 246, 247.

Fig. 30.14 World Health Organization surgical safety checklist. *(Copyright 2009, World Health Organization. Available at: <http://www.who.int/patientsafety/safesurgery/checklist/en/>.)*

period.[163,212,252] The content is variable, and sustaining improvement is challenging.[125,265] From the current data, it appears that teams must be trained as a team and not by roles,[266] simulation is particularly effective in defining hazards and creating team coordination,[266–268] both executive leadership[269,270] and frontline managers are key for effective implementation,[271] and the impact wanes after a few months without continual coaching and training.[125,260,265]

Checklists and Briefings

Checklists and briefings can improve team communication and reduce errors of omission. A checklist is a simple listing of specific tasks or information that is verified as completed or as being correct, and it serves to ensure that no steps are omitted. A briefing is an open-ended discussion and review of the salient points of the plan at hand, and it typically uses a checklist to ensure that all pertinent details are addressed. A checklist is the *tool* that defines the pertinent details, whereas a *briefing* is the process a team goes through to review these details.[272] Checklists do not vary in content between uses because each item represents critical steps not to be missed; in contrast, each briefing is defined by the unique aspects of the case. Briefings open a dialogue among team members and encourage each member to agree to the details of the plan, exchange information, raise critical points or questions, and identify concerns.[245]

Checklists are simple cognitive aids that can improve performance of simple tasks (shopping) or complex endeavors (landing a fighter plane on an aircraft carrier deck), and they serve as reminders of routine tasks that may otherwise be missed.[273,274] Checklists successfully have been used to ensure completion of critical steps in a variety of surgical procedures,[258,275,276] as well as in preparation for anesthesia.[277]

Two of the best-known patient safety efforts, the World Health Organization (WHO) Safe Surgery Saves Lives[162,176] and the Surgical Patient Safety System (SURPASS),[160,278] are termed checklists but are actually guided briefings that use a checklist (Fig. 30.14). They are discussed later in this section.

Checklists have been developed to provide direction in rare, crisis situations such as malignant hyperthermia or pulseless electrical activity. Ziewacz and colleagues[64] identified 12 of the most frequently occurring OR crises and developed evidence-based essential care steps for each (Fig. 30.15). In simulations of crisis situations, access to and use of the checklist resulted in a sixfold reduction in missed critical steps. Arriaga and colleagues[63] then tested the checklist in hundreds of simulations with 17 different surgical teams and demonstrated a significant reduction in steps missed (6% of critical steps missed with checklist vs 23% without). Harrison and Gaba and their team at Stanford University in California[279] similarly designed cognitive aids that use checklists for a variety of anesthesia-related emergencies.

Checklists can help drive implementation of best practices, often by reducing voluminous guidelines to a simple set of the most critical evidence-based best practices.[274,280] The Keystone Project implemented a list of five key evidence-based elements to prevent central line–associated bloodstream infections (CLABSI).[280] In the 108 ICUs participating, the median rate of CLABSI fell from 2.7 per 1000 catheter-days to 0 at 3 months, and the mean rate decreased from

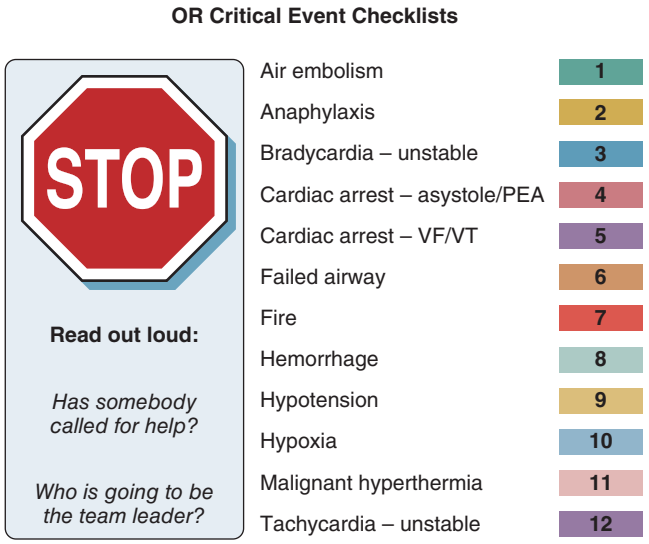


Fig. 30.15 Front cover of the operating room *(OR)* crisis manual. *PEA,* Pulseless electrical activity; *VF/VT,* ventricular fibrillation/ventricular tachycardia. *(From Ziewacz JE, Arriaga AF, Bader AM, et al. Crisis checklists for the operating room: development and pilot testing.* J Am Coll Surg. *2011;213:212 e10–217 e10.)*

7.7 per 1000 catheter-days to 1.4 at 18 months.[280] The reduction in CLABSI is sustainable,[281] and it can be replicated in other settings.[282] Similar evidence-based checklists have reduced ventilator-associated pneumonia and mortality rates.[5,283] Effective development and implementation of checklists are not, however, as simple as the checklist itself.[284,285] Efforts have been made to identify how effective checklists should be designed and implemented.[284,286–288]

Although the value of the checklist itself has been widely touted,[273] experts argue that it is the adaptive work of the team that results in improved patient safety rather than the technical use of a checklist.[289] When a checklist is imposed by management without the willingness of the team to embrace a change in attitudes and behaviors, the checklist can be seen as undermining clinicians' autonomy and authority, as infantilizing, and it actually may delay improvement.[247,286,288,290] In 2008, the Dutch Health Authority mandated implementation of the WHO checklist; compliance with all three phases of the checklist occurred in only 39% of the 11,151 cases.[165] Although overall mortality rates decreased from 3.13% to 2.85%, the reduction was strongly associated with the degree of compliance (Fig. 30.16). The effectiveness of the Michigan Keystone project was ascribed by the leaders to the creation of a "densely networked community" with a shared mission, as well as a willingness to use data to create discipline, rather than the mere existence of a checklist.[291]

Briefings are reviews of the salient points of the plan, and they allow teams to develop a closely shared mental model of the operation to be performed. In aviation, even training runs that have been performed countless times before by the same team begin with an extensive brief. During a brief, all members of the team assume equal hierarchy in

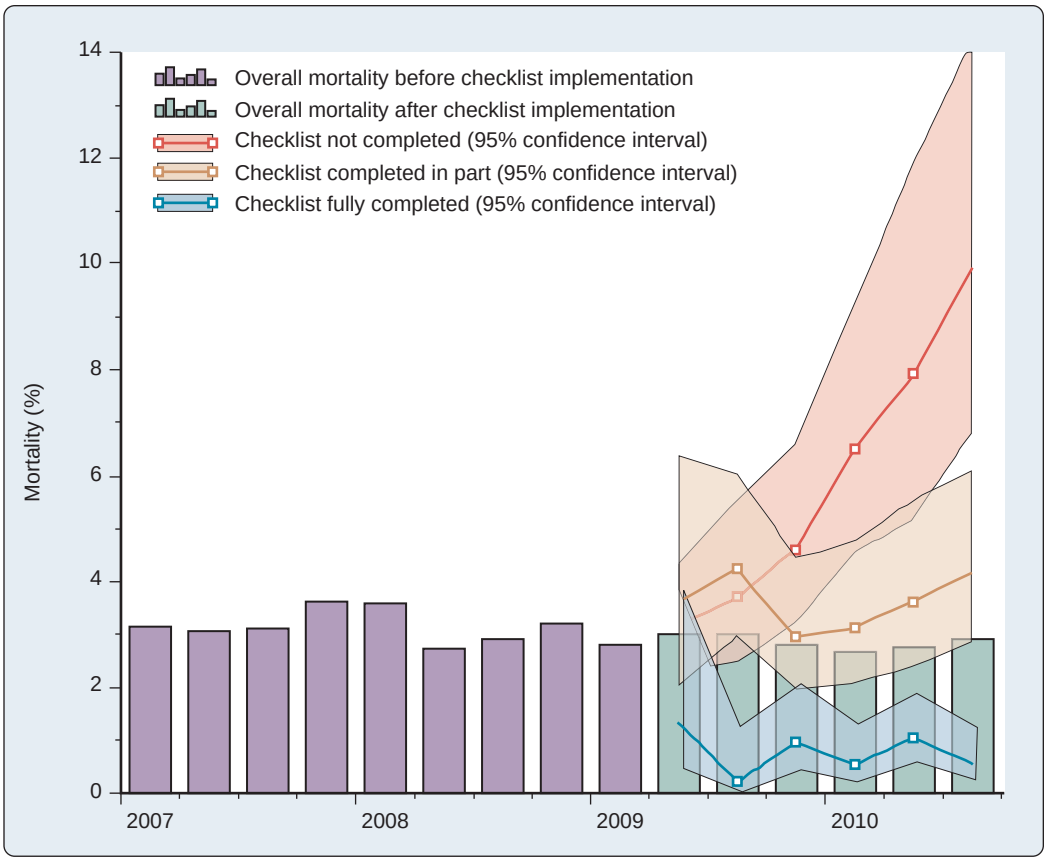


Fig. 30.16 In-hospital 30-day mortality during the study period. *Bars* show the overall mortality rate per trimester; *lines* show mortality rates with 95% confidence interval per trimester for the three compliance groups (completed, completed in part, and noncompleted checklists) after checklist implementation at April 1, 2009. *(From van Klei WA, Hoff RG, van Aarnhem EE, et al. Effects of the introduction of the WHO "Surgical Safety Checklist" on in-hospital mortality: a cohort study.* Ann Surg. *2012;255:44–49.)*

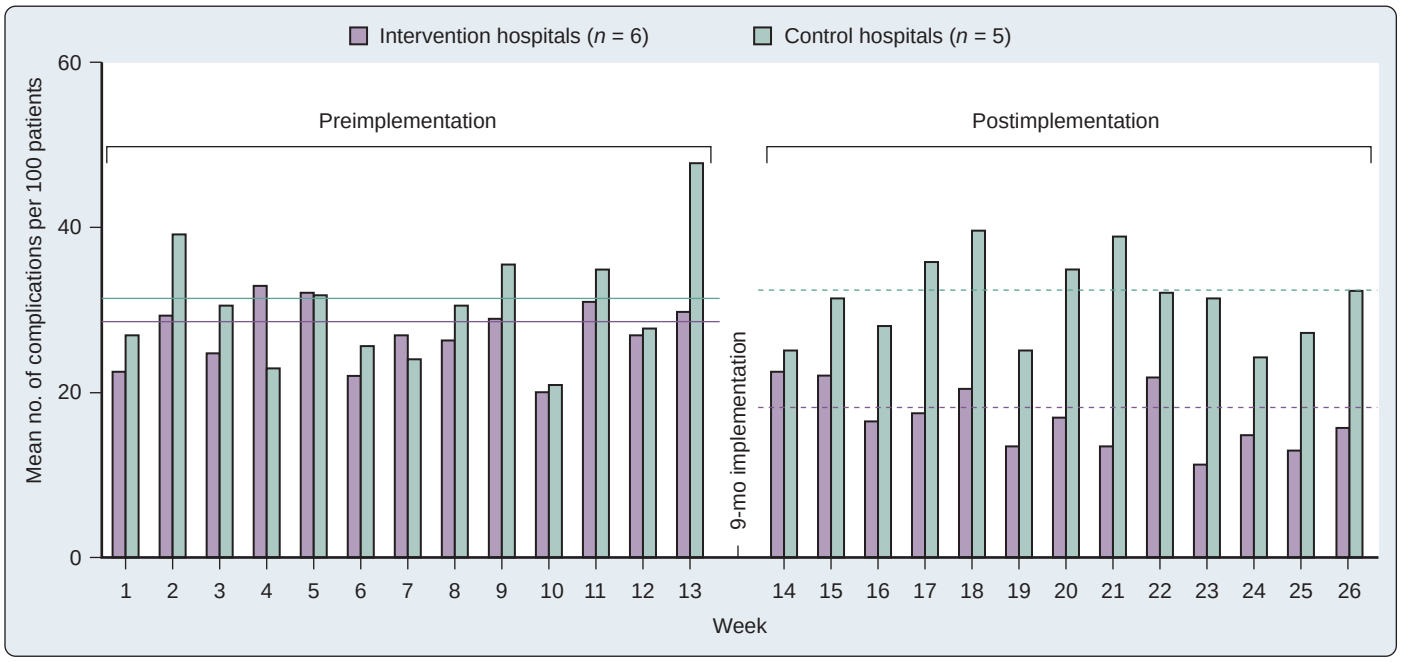


Fig. 30.17 Mean number of complications in hospitals after implementation and in control hospitals. *(From de Vries EN, Prins HA, Crolla RM, et al. Effect of a comprehensive surgical safety system on patient outcomes.* N Engl J Med. *2010;363:1928–1937.)*

terms of raising concerns and identifying vulnerabilities. In surgery, as was common in aviation before implementation of CRM, strict hierarchies inhibit trainees and low-status staff from raising concerns or questioning the plan. Many OR personnel report that they would have trouble speaking up, even if they believed that patient safety was compromised.[169] Without formal intervention or team training, few if any briefings are performed, and poor agreement exists about what constitutes a briefing.[246,292,293] Although 39% of surgeons in a UK survey stated that they performed a brief for every surgical procedure, 96% of the nurses disagreed.[246] The WHO Safe Surgery study found that few briefings occurred among the 3733 procedures performed before implementation of the checklist or briefing.[162]

As mentioned earlier, the WHO Surgical Safety Checklist (see Fig. 30.14) contains the elements of a brief in the section termed "Anticipated Critical Items," by inviting the surgeon, the anesthesiologist, and the nursing staff to review the critical or nonroutine steps and voice any concerns.[162] Implementation of this tool in eight hospitals in eight cities, representing a wide range of economic circumstances and a diverse population, reduced the mortality rate from 1.5% to 0.8% and the complication rate from 11% to 7%.[162] A second global study found that use of this checklist in urgent surgical cases had the same effect, by reducing the mortality rate from 3.7% to 1.4%.[244] In a follow-up national study of 25,513 patients, a reduction of the in-hospital 30-day mortality rate from 3.15% to 2.85% was demonstrated (odds ratio, 0.85; 95% CI, 0.98.)[165] This effect was, however, dependent on compliance: the odds ratio in cases with full implementation was 0.44 (95% CI, 0.28–0.70) versus 1.09 (95% CI, 0.78–1.52) for partial compliance and 1.16 (95% CI, 0.86–1.56) for noncompliance,[165] respectively (see Fig. 30.16).

The SURPASS is a checklist that covers the entire continuum of cardiac surgery and includes a presurgical briefing as well as a postsurgical debriefing.[278] Implementation of the SURPASS tool reduced the complication rate from 27.3% to 16.7% and decreased the mortality rate from 1.5% to 0.8% (Fig. 30.17) in one series.[160] A closed claim review of adverse events that occurred before implementation found that some 40% of the events would have been prevented with use of the SURPASS tool.[294]

Briefings enhance team performance and require little time. In an analysis of 37,133 briefings, Berenholtz and colleagues[295] found that briefings averaged 2.9 minutes and debriefings averaged 2.5 minutes. Implementing briefings reduced the number of nonroutine events in cardiac surgical procedures by 25%,[293] and it increased the perception that wrong-site operations would be prevented.[296] After briefings were instituted at 16 cardiac surgical centers, surgical flow disruptions decreased from 5.4 per case to 2.8 ($P = .004$), disruptions resulting from inadequate procedural knowledge decreased from 4.1 to 2.2, and miscommunication events fell from 2.5 per case to 1.2.[297] Nurses made fewer trips to the core and spent less time there. Briefings improved communication; they reduced the number of communication failures per case from 3.95 to 1.31 and identified new problems or knowledge gaps.[298]

Briefings improve the teamwork climate and teamwork behaviors and are associated with greater satisfaction within the team.[‡] In one study of perceptions after briefings were instituted, respondents commented, "Your opinions seem to matter. You feel more valued," and "People are willing to say when they are not happy. They are not worried about backlash."[300] In an Israeli study, team members reported feeling more valued for their work, teamwork, and safety climate.[293] In a UK study, teams reported that the team culture was better and that potential problems had been identified after briefings were instituted.[241] Preoperative briefings reduced unexpected delays in surgical procedures by 31% in one study.[301] Implementation of briefings improved compliance with best practices, including antibiotic dosing, venous thromboembolism prophylaxis, and maintenance of normothermia and normoglycemia.[302–304]

Despite the evidence demonstrating the value of briefings, certain institutional, interpersonal, and psychological factors "constrain safety."[290] Resistance to or acceptance of briefings varies by team roles, and the attitude of and participation by key team members influences compliance, with significant latent failures (ie, those not grasped by the participants) reducing the effect of briefings and training.[141] In the VA team training effort, effective institution of briefings and debriefings was entirely dependent on executive leadership.[305] In an analysis of 756 briefings, Whyte and colleagues[245] found that the response to briefings depended on the institutional and social milieu in which the briefings

[‡]References 141, 173, 241, 292, 293, 295, 299, 300.

occurred and on individual perceptions of the purpose of the briefing. Surgeons randomly assigned to an intervention group demonstrated better team behaviors than did the control surgeons, but they reported lower levels of comfort, communication, and team efficiency, thus indicating that adoption of briefings or checklists may be uncomfortable at first.[286] Even with effective executive leadership and local champions, a wide range of attitudes and physiologic responses can hinder implementation. Identifying and understanding potential obstacles and resistances are necessary for effective implementation.[213,245,246,292]

Debriefings and Learning From Defects

As noted earlier, critical parts of any safety program include identifying latent hazards and formulating system changes to decrease the chance that patients will be harmed. Identifying these hazards can involve an institutional quality improvement process, as discussed later or, at the team level, by continually asking "Did anything happen today that we don't want to see happen again?"

Regular team debriefings at the end of surgical procedures can serve as a means to identify hazards and formulate improvements. Although debriefings are often discussed in conjunction with briefings and occur in the same context as briefings, they differ in timing, content, purpose, and practice. Debriefings should occur at the end of each surgical procedure and provide an opportunity for the team to reflect on the procedure and verbalize lessons learned or deficiencies identified.[306] It can be as simple as asking "Did everything go as well as we wanted it to (or as we expected) today?" Debriefings allow the team to come together to rectify problems and to find ways to improve performance in the next case.[241,295,302,305] They give the teams a chance to identify latent hazards and vulnerabilities, develop and implement system improvements, address areas of teamwork weakness, and formulate future plans.[306–308] Like briefings, debriefings are associated with enhanced team behaviors, climate, and performance. Unfortunately, like briefings, they are difficult to implement and are viewed with resistance by some staff.[241]

Learning from defects (LFD) is one of many ways for teams continually to identify and mitigate hazards. The LFD tool, developed by Pronovost and colleagues[309] at Johns Hopkins University in Baltimore, is a simplified and streamlined root cause analysis that provides a structured approach to identifying the elements that contribute to the hazard or defect and developing safety improvements. When used as a part of a comprehensive unit safety program (CUSP) developed by the Johns Hopkins researchers, it promotes team cohesion and enhances perceptions of the local safety climate.[310]

Structured Communication Protocols (Closed Loop, Handoff Protocols)

As noted in multiple studies, communication failures underlie the majority of serious adverse events that harm patients.[§] In the cardiac OR, messages are continually sent and received. Failure occurs when messages are not encoded clearly or decoded correctly, when the appropriate audience is not reached, and when critical information is omitted.[223,313] Closed-loop communication can address many of these failures, by requiring the sender to identify the intended recipient, who then repeats the message as heard, after which the sender verifies the accuracy.[110] This type of communication is especially important in stressful situations and when the potential audience is large.[314] Structured communication ensures that the team has a shared mental model, with shared goals, expectations, and plan execution.[315] Unfortunately, only perfusionists routinely practice closed-loop communication in the cardiac OR.[110]

Structured communication techniques include both standardized word use (eg, words for letters such as in the North Atlantic Treaty Organization [NATO] phonetic alphabet) and protocols for stating numbers (1-1 instead of 11, which can sound like 7). Using such techniques can reduce ambiguity, enhance clarity, and eliminate many potential errors.[316] The armed forces and aviation teams have used techniques such as read-backs, Situation-Background-Assessment-Recommendation (SBAR), advocacy and inquiry, and critical assertions to improve information transfer, reduce omission of information, and facilitate communication across ranks. Despite many recommendations to adopt these techniques,[317] few surgical teams have done so; consequently, few data exist to demonstrate efficacy in reducing harm in the OR.

Structured communication protocols have been studied extensively in information transfer during handoffs of a patient from one caregiver or team to another. As noted earlier, handoff failures represent a significant source of medical errors and harm to patients, both between and within teams.[134,229,233,235,236] The complexity of the information to be transmitted and the chaotic settings in which handoffs occur, with frequent interruptions and disruptions, virtually guarantee loss of critical information.[228,236,238] Nagpal and colleagues[134] undertook a systematic modified Delphi process to identify the critical elements of a handover from OR to PACU and then structured a protocol to ensure that all elements were included. Use of this tool reduced critical omissions from 9 to 3 per handover and task errors from 2.8 to 0.8 (Fig. 30.18).[318] In a study of handovers in pediatric cardiac surgical procedures, use of a teamwork-driven process and use of a protocol reduced critical information omissions from 6.33 to 2.38.[319] In another study, implementing a process based on a Formula-1 pit stop that specified preparation before handoff (phase 1), tasks to be completed before information transfer (phase 2), and specific information to be transmitted (phase 3) reduced the number of information omissions and shortened the handover process (Fig. 30.19).[320]

Zavalkoff and colleagues[321] found that implementing a simple fill-in-the-blank tool improved total handover scores as well as information subscores, and it did not prolong the process. These results were echoed by Craig and associates,[322] who reported that implementing a handover tool improved attentiveness, organization, and information flow and reduced interruptions. Petrovic and colleagues[323] used a standardized handoff protocol from the cardiac OR to the cardiac ICU and found that information omissions decreased from 26% to 19%, the presence of all critical personnel increased from 0% to 68% of handovers, and satisfaction scores increased. The finding that information omissions still occurred 19% of the time may indicate a need for a better protocol, a lack of participation by personnel, or simply the complexity of the problem.

The use of electronic technology in handover protocols has been proposed, but it has not been tested widely. One such system developed and implemented at Columbia University, (Multimedia Abstract Generation of Intensive Care, MAGIC) generates an automated briefing from the patient's electronic record; these briefings have been found to be accurate and better than a physician-generated handover because the information is available earlier to the receiving team.[324–326] The use of a dedicated Internet connection between catheterization centers and a cardiac surgical center shortened the time between cardiac catheterization and surgical decision from 36 hours to 1 hour and the time interval between diagnosis and operation from 56 to 18 hours.[327] The widespread use of electronic patient records and information-sharing systems, such as that provided by the Epic Care Everywhere (Epic, Verona, WI) system, certainly will increase the accuracy of patient information that is immediately available and will hopefully reduce errors.[328]

Simulation

Simulation in medicine is growing rapidly and has been used to train individual clinicians in specific skills, assess the technical and nontechnical skills of individual clinicians and teams, understand how and why errors occur, and devise means of preventing them. Simulation is, first and foremost, changing the face of medicine from "see one, do one, teach one to an approach in which students and residents practice on

[§]References 201, 213, 222, 223, 228, 262, 311, 312.

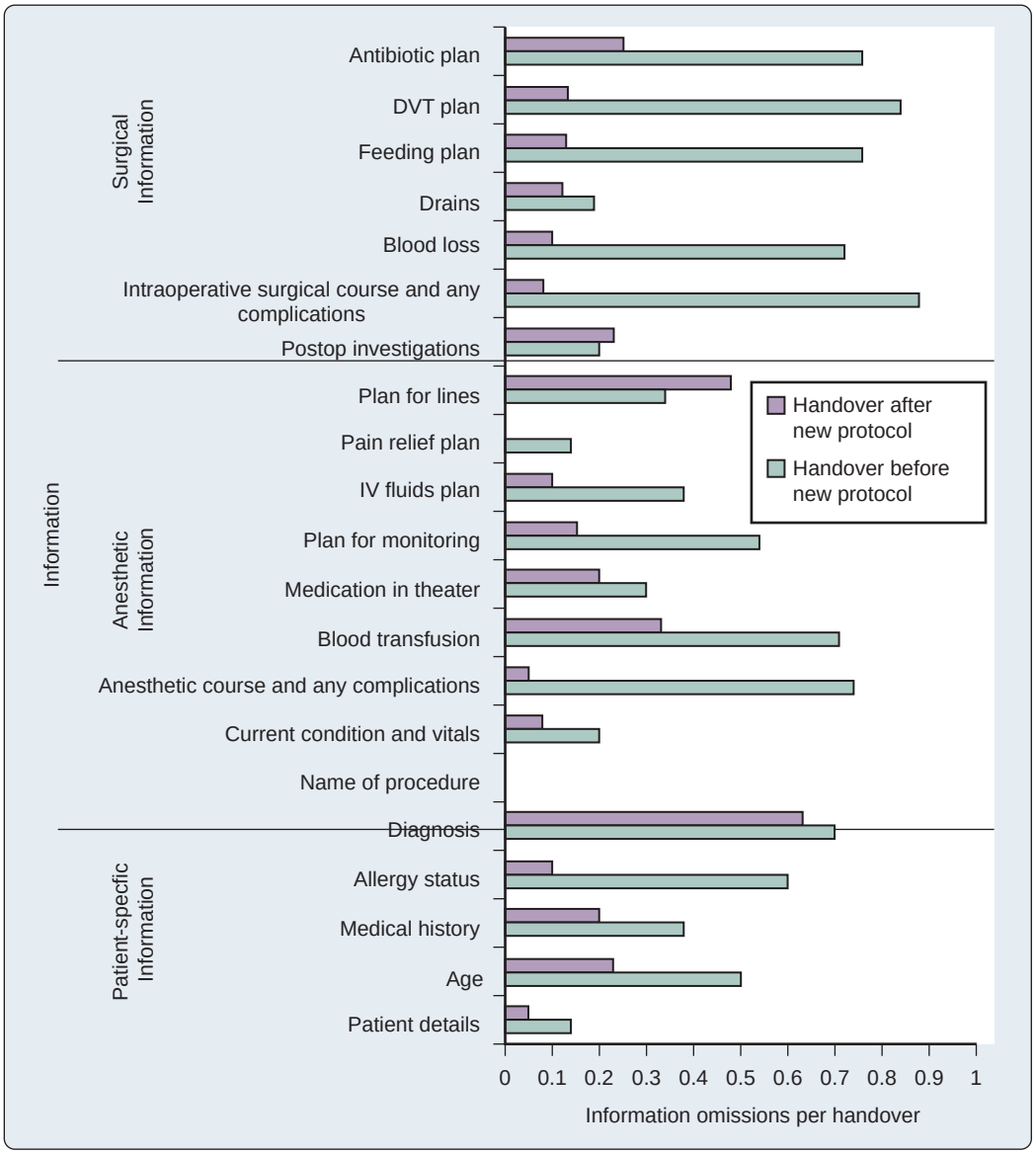


Fig. 30.18 Omissions of information per handover from the operating room to the postanesthesia care unit before and after implementing a protocol. *DVT,* Deep vein thrombosis; *IV,* intravenous; *Postop,* postoperative. *(From Nagpal K, Abboudi M, Manchanda C, et al. Improving postoperative handover: a prospective observational study.* Am J Surg. *2013;206:494–501.)*

simulators, not actual patients. Using simulation, procedures such as intubation, laparoscopic operations, and bronchoscopy are learned and, hopefully, perfected before attempted in patients.[329–335] The technical skill of trainees can be assessed before they perform procedures on patients.[133,336–339]

Simulation is an effective tool both to teach[263,340–343] and to assess nontechnical skills and teamwork.[130,131,144,181,344,345] In one study, simulation using crisis situations resulted in better teamwork attitudes than did specific teamwork training.[267] In addition, simulation is especially valuable in teaching the management of rare crisis situations,[63,330,346–350] as well as investigating successful ways to manage crises.[63,64,279,351] Simulation is an effective way to test the effects of stress, caffeine, fatigue, and other factors on performance[140,352–354] and to test the ability of certain interventions to reduce errors.[355–357] Simulation is such an effective tool that it is now used in some institutions as the primary method for teaching perfusionists management of CPB (E. Darling, SUNY Upstate, Syracuse, NY; personal communication as presented at the CREF 35th Annual Meeting, Long Beach CA, 2015). Finally, adequate performance in simulated events is a part of medical and nursing licensure.[358,359]

Medication Safety

Drug Errors

Substantial evidence indicates that drug administration errors are common in anesthetic practice. In 1993, the Australian Incident Monitoring Study (AIMS) identified 144 instances of a wrong drug being given or nearly given to a patient out of the first 2000 incidents reported.[360] In 1995, Merry and Peck[50] reported a survey of 75 anesthesiologists in New Zealand, 89% of whom indicated that they had made at least one error of drug administration, with 12.5% indicating that they had harmed a patient by a drug-related error. In a voluntary survey of 10,806 anesthetic cases in 2 hospitals in New Zealand,[361] the overall rate of drug error was 1 in 133 anesthetic cases (0.75%). Drug errors resulted in 1 case of intraoperative awareness, 2 cases of

Summary of the new handover protocol

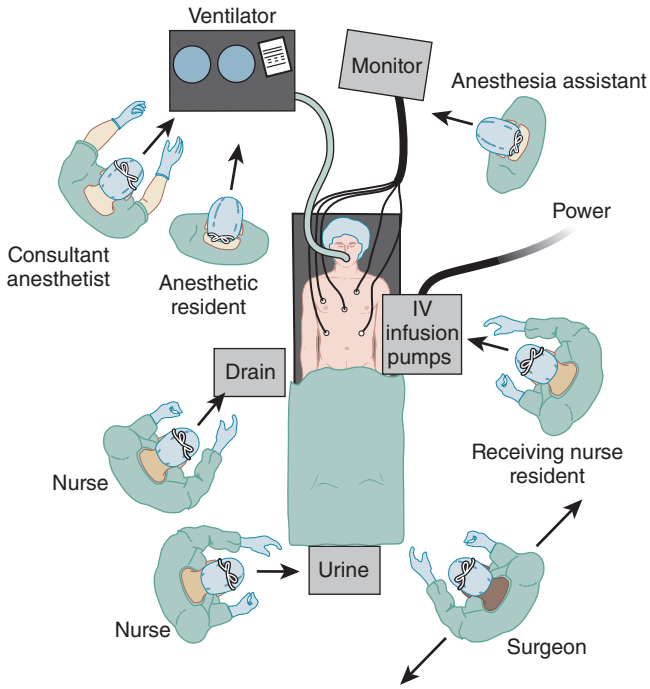
Phase 0: Prehandover	The Patient Transfer Form is completed by the anesthetist and is collected from the operating room at least 30 min before the patient is transferred to the ICU. The receiving nurse ensures the bed space is set up according to the monitoring, ventilation, and other requirements specified on the Patient Transfer Form. The receiving doctor ensures that all appropriate paperwork is ready.
Phase 1: Equipment and technology handover	On arrival the team transfers the patient ventilation, monitoring, and support from portable systems used during the transfer to the ICU systems.  Safety check: the anesthetist checks the equipment and that the patient is appropriately ventilated and monitored and is stable. The receiving nurse and doctor are identified and confirm their readiness.
Phase 2: Information handover	The anesthetist, then the surgeon, speak alone and uninterrupted, providing the relevant information about the case, using the Information Transfer Aid Memoir. Safety check: the receiving nurse and doctor should use the Information Transfer Aid Memoir to check that all necessary information has been obtained and ask appropriate questions.
Phase 3: Discussion and plan	The surgeon, anesthetist, and receiving team discuss the case as a group. The receiving physician manages the discussions and identifies anticipated problems, and anticipated recovery is discussed. The ICU team now has responsibility for patient care and confirms the plans for the patient.

Fig. 30.19 Phases of a handover protocol as developed from Formula-1 pit stop concepts. *ICU,* Intensive care unit; *ODA,* operating department assistant. *(Modified from Catchpole KR, de Leval MR, McEwan A, et al. Patient handover from surgery to intensive care: using Formula 1 pit-stop and aviation models to improve safety and quality.* Paediatr Anaesth. *2007;17:470–478.)*

prolonged neuromuscular blockade, and 47 cases of transient physiologic effects. A similar survey in Canada found that 85% of anesthesiologists reported that they had made at least 1 drug error or "near miss," with 4 deaths in the 1038 reported errors.[362] A report based on annual surveys conducted by the Japanese Society of Anesthesiologists between 1999 and 2002, reflecting 4,201,925 anesthetic cases,[363] found an incidence of "critical events" caused by drug administration error of 0.02%. The incidence of death resulting from drug error was 0.00044%. Additional reports from Australia,[364] Japan,[365,366] and South Africa[367] suggest that anesthetic drug error continues to be a significant problem around the world. The incidence of drug administration errors in an academic practice in the United States appears to be similar to that reported from elsewhere in the world. In a self-reporting study performed in a single center in the United States, Cooper and associates[368] found a rate of error of 0.40% (35 in 8777, or 1 in 203 anesthetic cases) and a rate of pre-error of 0.19% (17 in 8777).

The majority of reported drug errors can be classified as Webster and colleagues[361] proposed (Table 30.3). In the study by Abeysekera

and associates,[364] nearly 50% of the errors were syringe and drug preparation errors, with 18.9% being swaps of correctly labeled syringes and 20.8% caused by selection of the wrong ampoule or vial, thus resulting in an incorrectly labeled syringe. Equipment misuse or failure accounted for 26%, incorrect route for 14%, and communication error for 4%. Administration of a drug in the OR is a complex procedure, with up to 41 steps involved in the first-time administration of a drug.[364,369] Human factors experts classify 36 of these steps as automatic behavior with muscle memory (susceptible to skill based or action errors), whereas 5 steps require conscious attention, decision, and judgment (decision errors, susceptible to cognitive errors).[369] Traditionally, the anesthesiologist performs all the steps alone, eliminating the opportunity for a double-check that is common elsewhere in medicine, in which a pharmacist checks the physician's prescription and a nurse checks both.

In addition, cardiac surgical procedures requiring CPB present the relatively unusual situation in which the anesthesiologist and the perfusionists may be administering drugs intravenously. Perfusionists frequently administer anesthetic drugs during CPB, and they may administer a variety of other drugs as well. Rarely, the perfusionist also may be an anesthesiologist (particularly in Australia), but whether the anesthesiologist even supervises the perfusionist in the administration of drugs varies depending on the particular practice setting. In some practice settings the anesthesiologist may leave the OR during CPB.

In a voluntary survey of incidents during perfusion, 29% of perfusionists in Australia and New Zealand reported related incidents during bypass.[370] In a similar survey of US perfusionists, 524 respondents reported a total of 5023 incidents, of which only 78 were medication errors.[371] The respondents also reported 11 cases of incorrect units of blood given, with 2 deaths. An updated survey by the same researchers found a total of 4882 events that occurred over 2 years; 63 events were related to medication errors, and 10 were related to incorrect units of blood.[372]

Surveys and voluntarily reported incidents may underestimate the true incidence of medication error in the operating room. In one of the only prospective, observational studies of medication errors in the operating room, Nanji and colleagues[372a] reported that 193 of 3671 (5.3%) medication administrations during 277 operations involved a medication error and/or an adverse drug error; 79.3% were preventable. The voluntarily reported errors typically have a low harm rate, but analysis of the American Society of Anesthesiologists (ASA) Closed Claims Project database provides a different view of the same problem because this database contains only errors that resulted in substantial harm and thus malpractice litigation.[373] As of 2003, 205 drug errors were recorded in the database, representing 4% of 5803 cases of litigated malpractice claims in anesthesiology. In these cases of serious harm, succinylcholine was the primary drug in 17% of the cases and epinephrine in 8%. In 12 of 35 cases succinylcholine was given inappropriately. Drug administration errors involving epinephrine were particularly dangerous, with death or major morbidity resulting in 11 of the 17 epinephrine-related cases. Six of the 17 cases involving epinephrine were caused by ampoule swaps. An informative case report describing the nearly fatal results of inadvertent epinephrine administration resulting from an ampoule swap has been published.[374]

Among the Closed Claims were 19 cases of intraoperative awareness (9%), 14 of which involved inadvertent administration of muscle relaxant to awake patients; the remaining cases were caused by inadequate or omission of anesthetic agents. ASA Closed Claims Project reviewers judged the care to be "less than appropriate" in 84% of the drug error claims, compared with 35% in non–drug error claims. Payments were made to plaintiffs in 72% of the drug error claims compared with 52% of the non–drug error claims. An analysis of litigation against the National Health Service in England related to anesthetic drug errors found a spectrum of errors that were similar to those found by the ASA Closed Claims Project.[375]

Wrong-route errors are particularly problematic and are caused in large part by the universality of the Luer connector.[376] In a notable case, bupivacaine solution intended for epidural use was administered free flowing into an intravenous infusion; although the baby was saved, the young parturient died.[377] Case reports abound: aminophylline[378] and tranexamic acid[379] given by the subarachnoid route; vecuronium,[380] ondansetron,[381] potassium chloride,[382] and rocuronium[383] given through epidural catheters; and vecuronium nearly given into an intraventricular (intracerebral) port. Human ingenuity has found a way to place a catheter into virtually every location in the body; human error has found a way to make every possible misconnection between infusion type and access line, often with disastrous outcomes (Table 30.4).[384] Erroneous injection of drugs into the intrathecal space has devastating outcomes. Accidental injection of vincristine into the subarachnoid space was first reported in 1968; since then at least 58 deaths have occurred worldwide, despite extensive publicity of the danger.[385] Enteral feedings (death, meningitis), formaldehyde (death), and chlorhexidine (parturient death) have all been given into the subarachnoid space.[384]

TABLE 30.3 Types of Drug Errors

Error Type	*Definition*
Incorrect dose	Wrong dose of an intended drug
Substitution	Incorrect drug instead of the desired drug; a syringe or vial swap
Omission	Intended drug not given (eg, missed antibiotic redosing)
Repetition	Extra dose of an intended drug
Incorrect route	Intended drug erroneously given by an unintended route
Other	Patient allergic to drug; rapid infusion of drug intended to be given slowly; wrong selection of antibiotic

From Webster CS, Merry AF, Larsson L, et al. The frequency and nature of drug administration error during anaesthesia. *Anaesth Intensive Care.* 2001;29:494–500

TABLE 30.4 Types of Misconnections (JC Sentinel Event Alert 36)

Misconnection Type			*Notes*
Enteral feeding solution	to	IV line, central line, hemodialysis line	116 reports, 21 deaths known, underreported
Epidural infusion	to	IV line	Bupivacaine deaths
Blood pressure cuff	to	IV line	Air embolism, multiple deaths
IV solution	to	Nasogastric tube	—
IV solution	to	Epidural route	Dopamine, epinephrine
Syringe bolus	to	Epidural route	Antibiotics, NMBs, narcotics, sedatives
IV solution	to	Arterial line	Relatively easy to detect
Syringe	to	Arterial line	Wide variety of drugs
IV solutions	to	Foley catheter, dialysis lines, ventriculostomy port, tracheal cuff	—
Capnography sampling	to	IV line	—
Oxygen tubing	to	Needleless IV port	Potential air embolus
Pneumatic stockings insufflation line	to	Piggy-back port of IV line	Air embolus

IV, Intravenous; *NMBs,* neuromuscular blocking agents.
Reprinted from AIRS Committee, with permission.[32]

Infusion pumps have become increasingly prevalent in the cardiac OR, and they offer significant advantages, including the ability to deliver very small volumes of fluids or drugs at precisely programmed rates. They are not, however, a panacea for medication errors. From 2005 through 2009, the US Food and Drug Administration (FDA) received approximately 56,000 reports of adverse events associated with the use of infusion pumps, including numerous injuries and deaths.[386] Adverse events were related to hardware issues (battery failures, sparking, and fires), as well as software issues (error messages, double recording a single key strike such that 10 becomes 100). However, as any anesthesiologist can attest, many were related to poor user interface design or human factors issues.[386] In addition to issues with the pumps, user error is common. Compliance with the drug library is critical for prevention of error, but a systematic review found numerous studies showing high rates of user override of soft alerts, as well as a variable compliance rate with drug library use.[387]

Prevention of Drug Administration Errors

Although drug administration errors clearly are very important, few studies have tested the effectiveness of interventions to reduce error in randomized controlled trials. A review evaluated the evidence for various measures for reducing drug administration errors in anesthetic practice and made recommendations. [388] However, most of the evidence available for review was anecdotal, and it was based on the opinions of clinician experts without input from human factors engineers.[388] Recommendations included carefully reading the label on any ampoule or syringe, optimizing legibility and contents of labels, labeling syringes, formally organizing drug drawers and workspaces, and double-checking drugs with another person or a device.

In 2010, the Anesthesia Patient Safety Foundation convened a consensus conference of more than 100 participants to develop strategies to improve medication safety in the OR.[369] The consensus statements focused on four key areas: standardization, technology, pharmacy involvement, and culture (Box 30.4). Standardization focused primarily on having a single concentration of a drug available in the OR, but it also involved using standardized drug trays across all anesthetizing locations and having a single concentration of infusions that are administered by infusion devices with drug libraries. Pharmacy involvement was believed to be critical to reducing errors, from educational duties to managing the entire dispensing process from ordering of drugs to providing them to the anesthesiologists. Cultivating a culture of safety, as addressed later, was believed to be critical to improving safety, but "The fact that anesthesia professionals are 'fiercely independent' and thus reluctant to change their individual practice habits (as related to medication preparation and delivery) to fit a standardized protocol was noted."[369]

Bar code reading devices represent an underused technology, and bar coding drugs at the point of care to verify the correctness of the drug and the dose is widely regarded as a technologic solution that could improve the accuracy of drug administration.[369,389–394] The FDA issued a rule in February 2004 (updated in April 2014) that requires bar codes on most prescription drugs, certain over-the-counter drugs, and blood products.[395] The FDA believes that effective bar code use could

BOX 30.4 CONSENSUS RECOMMENDATIONS FOR IMPROVING MEDICATION SAFETY IN THE OPERATING ROOM

Standardization

1. High-alert drugs (eg, phenylephrine and epinephrine) should be available in standardized concentrations or diluents prepared by the pharmacy in a ready-to-use (bolus or infusion) form that is appropriate for both adult and pediatric patients. Infusions should be delivered by an electronically controlled smart device containing a drug library.
2. Ready-to-use syringes and infusions should have standardized, fully compliant, machine-readable labels.
3. *Additional ideas*
   a. Interdisciplinary and uniform curriculum for medication administration safety to be available to all training programs and facilities
   b. No concentrated versions of any potentially lethal agents in the operating room
   c. Required read-back in an environment for extremely high-alert drugs such as heparin
   d. Standardized placement of drugs within all anesthesia workstations in an institution
   e. Convenient required method to save all used syringes and drug containers until the case is concluded
   f. Standardized infusion libraries and protocols throughout an institution
   g. Standardized route-specific connectors for tubing (intravenous, arterial, epidural, enteral)

Technology

1. Every anesthetizing location should have a mechanism to identify medications before drawing up or administering them (bar code reader) and a mechanism to provide feedback, decision support, and documentation (automated information system).
2. *Additional ideas*
   a. Technology training and device education for all users, possibly requiring formal certification
   b. Improved and standardized user interfaces on infusion pumps
   c. Mandatory safety checklists incorporated into all operating room systems

Pharmacy/Prefilled/Premixed

1. Routine provider-prepared medications should be discontinued whenever possible.
2. Clinical pharmacists should be part of the perioperative and operating room team.
3. Standardized pre-prepared medication kits by case type should be used whenever possible.
4. *Additional ideas*
   a. Interdisciplinary and uniform curriculum for medication administration safety for all anesthesia professionals and pharmacists
   b. Enhanced training of operating room pharmacists specifically as perioperative consultants
   c. Deployment of ubiquitous automated dispensing machines in the operating room suite (with communication to central pharmacy and its information management system)

Culture

1. Establish a "just culture" for reporting errors (including near misses) and discussion of lessons learned.
2. Establish a culture of education, understanding, and accountability through a required curriculum and continuing medical education and through dissemination of dramatic stories in the *APSF Newsletter* and educational videos.
3. Establish a culture of cooperation and recognition of the benefits of the STPC paradigm (standardization, technology, pharmacy/prefilled/premixed, and culture) within and among institutions, professional organizations, and accreditation agencies.

From Reprinted from Eichhorn JH. APSF hosts medication safety conference: consensus group defines challenges and opportunities for improved practice. *APSF Newslett.* 2010;25:1–8.

result in a 50% reduction in medication errors, thereby preventing 500,000 adverse events and transfusion errors while saving $93 billion over 20 years.

Several studies of the use of bar code scanning systems in hospital nursing units suggested that errors may be reduced.[396–399,400] The VA Health Care System was an early adopter of bar code technology, but centers experienced some significant difficulties with point-of-care bar coding.[397] Some of the most common problems were simple but critically important, such as nonreadable bar codes on patients' wristbands and drug containers. According to Mills and colleagues,[397] "The VA discovered that introducing new technology to complex medical systems, while beneficial, also presents new challenges."

The federal code mandating bar-coded drugs is imperfect. Only approximately 90% of drugs arrive at a pharmacy with a bar code; the linear bar codes mandated are easily rendered illegible, the locations of bar codes on inhalers render them unreadable when inserted in the administration device, and so on.[401,402] In addition, between 2015 and 2017, manufacturers are mandated to follow the more stringent labeling required by some states and countries, requiring many more details about the drug. These new requirements may increase the price of many drugs but could improve patient safety—but only if hospitals fully implement bar code scanning across the delivery process.

Several commercially available systems allow bar code scanning of drugs in the anesthesia clinical environment, including the SAFERsleep system (SAFERSleep LLC, Nashville, TN), BD Intelliport (BD Medical, Franklin Lakes, NJ), and the Plexus Information System (Plexus Technology Group, Jackson, MI). The SAFERSleep system devised by Merry and associates[403] is the only one that has been tested in a randomized prospective clinical trial. No significant differences in errors occurred when the system was used compared with conventional methods, primarily because of sample size but also due to user error or violation. In a subset analysis, significantly fewer errors occurred when the system was used as intended, including that users scanned the bar code of each drug before administration and kept the voice prompt active (a computer voice speaks the name of the drug after the bar code is scanned).[403] A drug safety system has been described combining the Codonics printer (Codonics, Middleburg Heights, OH), which scans the bar code on drug vials and prints corresponding syringe labels, with a syringe label bar code scanner driven by Smart Anesthesia Manager software; as with SAFERSleep, the Smart Anesthesia Manager system includes a voice prompt that speaks the name of the drug when the syringe is scanned.[404,405] A study to determine whether this system reduces errors is ongoing.

Although no comprehensive assessment of the incidence and nature of errors related to infusion pumps has been made, it is clear from the available evidence that programming errors are significant sources of error.[387] Infusion pumps play a major role in drug administration in cardiac surgical patients, so errors related to infusion pumps are of significant concern to cardiac anesthesiologists.

Some infusion pumps use drug libraries with predefined dosing limits and warn the practitioner if the dosing parameters entered will result in a dose that is outside the predefined dosing limits. Smart infusion pumps, although not perfect, repeatedly have been shown to intercept and prevent errors, primarily wrong rate and dose.[387] A smart pump can potentially intercept errors during multiple steps in the medication delivery process (Fig. 30.20).[387] Most intercepted errors represented a low level of harm, but some studies included examples of many-fold errors of high-alert drugs (100 times the intended dose of norepinephrine) or more than 100-fold underdoses.

However, the evidence for the effectiveness of pumps with drug libraries is mixed, with some studies suggesting benefit and others not.[406] Lack of compliance with "soft alerts" that warn users but do not prevent drug administration may limit effectiveness.[387] Pumps that allow for bar code identification of medications and that interact with the electronic medical record or anesthesia information system may prove more effective.

A prospective, randomized trial of smart infusion pumps in a cardiac surgical ICU found approximately 2 serious medication errors per 100 patient-pump-days.[407] No significant improvement occurred with the use of smart pumps, although the pumps frequently were not used as intended. The drug library intended to prevent programming errors was bypassed 25% of the time. This study demonstrated that technology alone may not solve a problem; close attention to the details of implementing the technology and making it work properly are essential. Nuckols and colleagues[408] found that the smart pumps they tested could prevent only 4% of the adverse drug events in the ICU. Many errors were related to bolus dosing and failure to monitor and respond to drug-related problems adequately. These investigators did not conclude that smart pumps should be abandoned, but they advocated for smarter and more capable pumps.

Although smart pumps can alert to programming errors that may result in an incorrect dose, they do not recognize that a wrong drug has been placed in the pump or that the drug is being administered to the wrong patient. Bar coding may be a solution to this problem. A bar code on a medication bag can be scanned, along with the patient's bar-coded identification, to prompt the pump electronically with the appropriate drug and drug concentration, thus preventing misidentification of the drug or the patient, as well as preventing pump programming errors. Furthermore, if the pump is connected to the electronic medical record, the dosing information from the pump can be automatically documented in the record. Application of bar code scanning to infusion pumps is a relatively new and evolving technology.

Transfusion Safety

Although bar coding of drugs has received greater publicity, bar coding of blood units and the use of bar coding to ensure accurate matching of blood component to recipient comprise a promising technology. A study of transfusion errors in New York State estimated the incidence of ABO mismatched transfusion at 1 per 12,000 to 1 per 33,000.[409] A report from a hospital in Japan specializing in cardiovascular disease described a computer-assisted transfusion management system with bar coding at the bedside.[410] Nearly 60,000 blood components were transfused without error, and 1 human error was prevented. The system also improved the efficiency of blood component management and reduced the outdate rate on red blood cells from 3.9% to 0.32%.[410] Studies of bar code–based blood safety systems in the United States also suggest efficacy.[411,412] Blood components currently are tracked and managed with the FDA-mandated bar codes from the time of donation through release to the ordering team, but bar codes are infrequently used during the transfusion process. Using the existing bar coding on blood components could contribute to both efficiency and accuracy in the OR, especially if the bar code data were electronically linked to the blood bank record (ie, the crossmatch) and to the electronic medical record and anesthesia information system.

Prevention of Intraoperative Awareness

An early report of patients who had experienced awareness during anesthesia was made in 1961 by Meyer,[413] who described the patients as "Expressionless and staring … blank and stunned … having suffered a catastrophic reaction." Since then, intraoperative awareness has become a dreaded complication associated with a significant rate of posttraumatic stress disorder.[414,415] The incidence of intraoperative awareness varied in early published reports; more recently, three large prospective multicenter studies reported similar overall rates of approximately 0.1% to 0.2%.[416–418] A report from China found an larger incidence of approximately 0.4% in that country.[419] Prospective studies of pediatric patients found rates of 0.8% to 1.1%.[420,421] Retrospective studies that rely on self-reporting or quality assurance data tend to find lower rates. Pollard and associates found an incidence of intraoperative awareness of 0.007%[422]; the Fifth National Audit Project (NAP5) from the United Kingdom found an incidence of 0.004%, based on self-reporting.[423] In many studies, the incidence increased if neuromuscular blocking drugs were used.

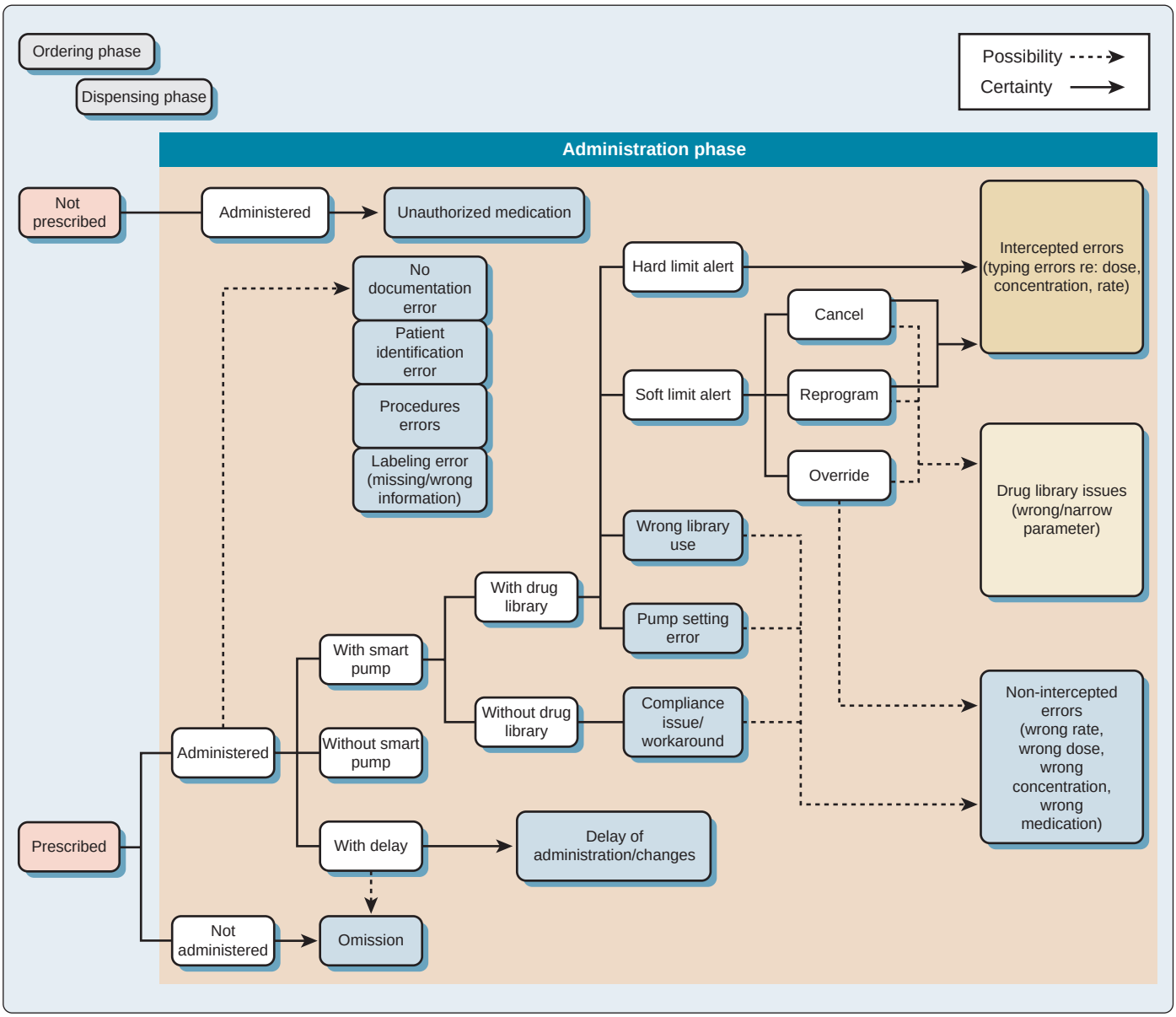


Fig. 30.20 Processes of intravenous medication administration with smart pumps and potential errors or intercepted errors in the prescribing phase to the administration phase. *(From Ohashi K, Dalleur O, Dykes PC, Bates DW. Benefits and risks of using smart pumps to reduce medication error rates: a systematic review.* Drug Saf. *2014;37:1011–1120.)*

Patients experiencing intraoperative awareness report a range of experiences, from isolated auditory perceptions (class 1) to paralysis and pain (class 5), with the additional modifier of D for distress (ie, fear, anxiety, suffocation, impending doom, or imminent death).[424] The sequelae of such an experience are variable, but as many as 70% of patients report sequelae of posttraumatic stress disorder.[414,415,425,426]

The variable rates of occurrence of intraoperative awareness relate in large part to the character of this experience. Patients often are reticent to speak of the experience and frequently do not report it unless specifically queried, and they may not be able to verbalize the experience for days or weeks. Sandin and colleagues[417] interviewed 11,785 patients in the PACU, and then at 6 days, and again at 7 to 14 days following general anesthesia. Only 6 patients reported recall in the PACU, whereas 12 reported it at 6 days and 17 at 7 to 14 days. This delay in the appearance of explicit memory has led many anesthesiologists to be skeptical about an incidence of 0.1% to 1%, because few patients will have had the opportunity to relate the experience to their anesthesiologist.[427,428]

Intraoperative awareness may be caused by specific, identifiable errors in anesthetic drug administration, such as administration of a muscle relaxant instead of a hypnotic agent during induction of anesthesia, unrecognized failure of an infusion pump, or an unrecognized empty vaporizer. However, most cases of awareness cannot be traced to such obvious events,[429] but they are likely related to complex differences among patients in response to anesthetic drugs.[430–434] Current theory, as summarized by Mashour and colleagues,[434] is that intraoperative awareness requires both consciousness, including both arousal and subjective experience, and explicit recall (memory).[434] Arousal, subjective experience, and memory occur at different neural loci and respond to anesthetic agents in different ways. Consciousness appears to be mediated by the coordinated activity of the frontal, higher-order areas, which are disrupted by various anesthetic agents, whereas sensory input and processing appear to be unchanged (Fig. 30.21).[431,432] It is likely that mechanisms of unconsciousness relate to the effect of anesthetics on cortical processing rather than alteration of sensory input.

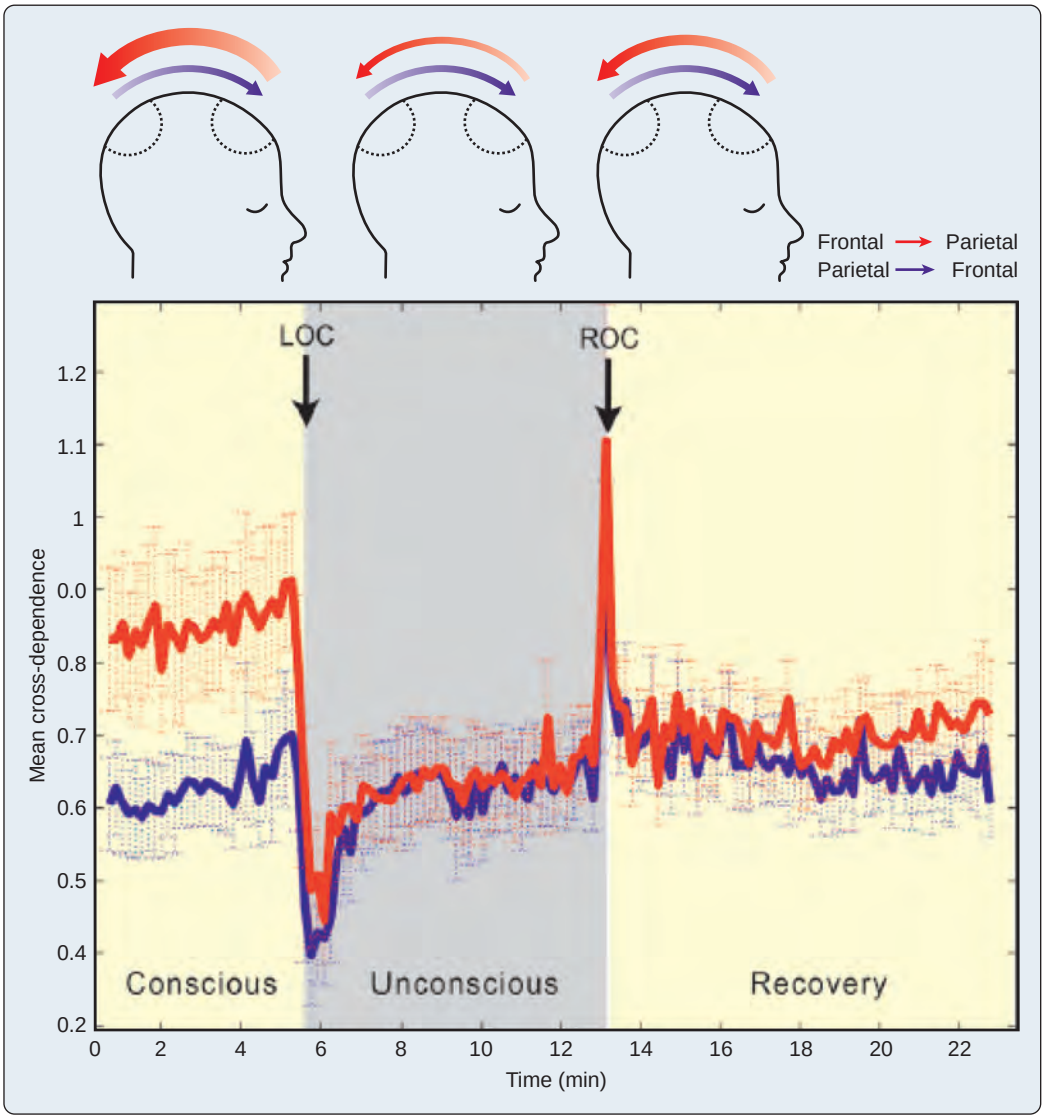


Fig. 30.21 Selective inhibition of frontoparietal feedback activity after induction of general anesthesia with propofol in humans. *LOC,* Loss of consciousness; *ROC,* return of consciousness. *(From Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: from neurobiology to clinical practice.* Anesthesiology. *2011;114:1218–1233; adapted with permission from Lee U, Kim S, Noh GJ, et al. The directionality and functional organization of frontoparietal connectivity during consciousness and anesthesia in humans.* Conscious Cogn. *2009;18:1069–1078.)*

Recall under anesthesia also requires the formation of explicit memory.[434–436] Although it is beyond the purview of this chapter, the neurobiology of memory appears to be closely linked to the γ-aminobutyric acid A ($GABA_A$) receptor, long familiar to anesthesiologists. The specific subtypes of $GABA_A$ receptors modulated by anesthetics are being identified. At least 19 genes code for the various $GABA_A$ subunits, and this finding may indicate a genetic foundation for awareness. Certain subtypes confer resistance to the memory inhibition of isoflurane while not changing the immobilization or hypnotic effects.[437] Indeed, one of the strongest predictors of intraoperative awareness is a previous episode of awareness, thus supporting the view that genetic differences in GABA subunits may be related to awareness.[438] Auditory input is relatively resistant to inhaled anesthetic agents, a possible explanation for the finding that auditory perceptions are some of the events more commonly recalled.[424,435] In addition, large interindividual variations exist in anesthetic drug effect or anesthetic drug clearance.[439]

Genetic and physiologic factors possibly explain why some patients have intraoperative awareness despite apparent appropriate anesthetic management. Specific types of surgical procedures also increase the risk: cardiac surgical procedures increase the risk of intraoperative awareness from the overall level of approximately 0.1% to 0.2%[417,418] to approximately 0.4% to 1%,[418,440–446] a 10-fold increase. Ghoneim and Block and their colleagues[445,446] confirmed that cardiac surgical procedures are associated with an increased risk. The report of NAP5 from the United Kingdom found that cardiothoracic surgical procedures were associated with a threefold increase in the risk, from an overall rate of 0.004% to 0.012%.[417,447] Likely causes for this increased risk include deliberately light anesthesia during periods of hemodynamic instability and gaps in anesthetic delivery during separation from CPB. Administration of neuromuscular blocking drugs, ubiquitous in cardiac surgical patients, also increases the risk for intraoperative awareness.[417,423]

The difficulty of identifying awareness in a paralyzed patient has encouraged the use of processed electroencephalograms (EEGs) to potentially estimate the depth of anesthesia; several commercial products are available for this purpose. The processed EEG monitor known as BIS (bispectral index; Medtronic, Minneapolis, MN) is by far the

most prevalent, and it has been studied the most. In multiple studies, a BIS value lower than 60 has been associated with an extremely low probability of awareness during anesthesia.[448,449] Detailed reviews of BIS monitoring are available (see Chapter 18).[450,451]

Two published studies demonstrated that the use of BIS monitoring can decrease the rate of intraoperative awareness when compared with "usual practice."[444,452] In a multicenter retrospective case comparison study, 5057 consecutive BIS-monitored patients were compared with 7826 non–BIS-monitored patients from the same institution.[452] Two cases of intraoperative awareness occurred in the BIS-monitored series compared with 14 in the non–BIS-monitored series ($P < .039$). In a prospective, randomized multicenter trial (B Aware), 2503 "high-risk" patients were randomized to BIS or non-BIS monitoring.[444] The protocol provided no suggested care for the non-BIS group other than "usual practice." Two cases of intraoperative awareness occurred in the BIS-monitored group compared with 11 in the non–BIS-monitored group (odds ratio, 0.18; 95% adjusted CI, 0.02–0.84; $P = .022$).

Avidan and colleagues[453,454] performed two prospective, randomized trials comparing BIS monitoring with a "targeted end-tidal anesthetic gas analysis (ETAC)" (target range, 0.7 to 1.3 minimum alveolar concentration [MAC], with gas analyzers audibly alarmed for these limits).[453,454] In the B-Unaware trial, 2 of 967 and 2 of 974 patients from the BIS and ETAC groups experienced recall.[454] In the Bag-RECALL trial, 7 of 2861 patients (0.24%) in the BIS group experienced recall, as compared with 2 of 2852 (0.07%) in the ETAC group.[453] This finding suggests that the use of BIS or an inhalation anesthetic protocol with alarmed gas analyzers was similarly effective in reducing awareness.

Mashour and associates[455] performed another prospective trial comparing BIS and ETAC in 21,601 unselected patients. No difference was reported in the incidence of intraoperative awareness in the two groups. However, in post hoc analysis, significantly less awareness was noted in the BIS group (0.08%) compared with the patients assigned to BIS but who received no monitoring and did not use ETAC (0.38%; $P = .001$). This analysis supports the fact that explicit attention to anesthetic level, whether through use of a specific target for end-tidal anesthesia concentration or by BIS monitoring, reduces the incidence of awareness.

A Cochrane Collaboration review of BIS monitoring in 2014 concluded that BIS-guided anesthesia reduced intraoperative awareness in high-risk patients when compared with patients who received only standard monitoring.[456] However, no superiority of BIS was seen in preventing awareness when compared with achieving a targeted anesthetic concentration. A more comprehensive evaluation examined BIS, E-Entropy (GE Healthcare, Chicago, IL), and Narcotrend (MonitorTechnik, Bad Bramstedt, Germany) and found that BIS reduced the risk of intraoperative awareness, at a quality-adjusted life-year cost of $22,339 to $44,198. Data were insufficient to evaluate the effectiveness of Narcotrend or E-Entropy.[457]

Several important caveats for BIS or other processed EEG monitoring should be familiar to clinicians.

- Using processed EEG to evaluate anesthetic depth depends on similarities in the effects of anesthetic drugs on the EEG. Ketamine and nitrous oxide[458] have distinct effects on the EEG that are not taken into account by the BIS algorithm.
- Signals on the EEG are of very low amplitude and are subject to interference by high-frequency devices such as cautery, electromyographic activity, and temporary external pacemakers (all tend to elevate the BIS). Small doses of muscle relaxant usually obliterate high-frequency artifact caused by muscle activity, but not that associated with electrocautery.
- Processing and smoothing of the EEG occurs over 15 or 30 seconds, so the BIS number lags slightly behind clinical events, such as induction, when a patient clearly is asleep before the BIS changes. Similarly, changes from unconscious to conscious state can occur rapidly such that the patient is awake before a change in the BIS.
- BIS numbers reflect the state of the brain on the EEG, but they do not reveal how the brain arrived at that state. For example, BIS declines during sleep,[459] yet clearly, natural sleep is not the same as anesthesia.
- Changes in surgical stimulation can change the BIS rapidly. The propensity of response to a surgical stimulus is more likely with inhaled agents and less likely if opioids are present.[460] The BIS number does not distinguish among the various possible combinations of opioid and hypnotic drugs.[461]
- During thoracic aortic surgical procedures with partial left-sided heart bypass, drugs administered into a vein below the clamp have a lower than expected cerebral concentration, whereas those administered above the clamp may have a higher concentration. These variations in concentration are reflected in the BIS, which may increase if the drugs are administered below the cross-clamp or decrease if the drugs are administered above the cross-clamp.[462,463]
- BIS values should be viewed as providing one more value for use in conducting the anesthetic protocol, but they definitely do not substitute for the conventional judgments that anesthesiologists make in the absence in BIS.

Although BIS monitoring remains controversial, the currently available evidence suggests that cardiac anesthesiologists should seriously consider using BIS or achieve a targeted end-tidal anesthetic concentration, given the high rate of intraoperative awareness demonstrated in patients undergoing cardiac surgical procedures. The ETAC specified in the trials conducted by Aviden and colleagues and Mashour and associates was 0.7 MAC, a level that may not be tolerated in compromised cardiac surgical patients. Mashour and colleagues[434] suggested that the threshold of inhaled anesthetic agent to prevent awareness lies between the point at which 50% of patients do not move with incision (1 MAC) and the concentration at which 50% of patients regain consciousness, typically 0.3 to 0.5 MAC.

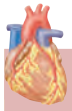
No single foolproof method to avoid all instances of intraoperative awareness exists, but multiple elements that must be considered and managed (Box 30.5). However, given the variations in patients' responses to anesthesia, even the best of attempts is unlikely to reduce the incidence much below 1 to 2 in 1000. Anesthesia providers should also therefore be alert to and elicit any experience of awareness from patients, by using a modified Brice interview.[464] When such patients are identified, evidence demonstrates that early intervention can enhance recovery from posttraumatic stress disorder.[465]

Reducing System Vulnerability

Single Center Interventions

The preceding section focused on individual interventions designed to improve teamwork and communication and to avoid certain common errors in the cardiac OR. However, most quality improvement initiatives in cardiac surgery represent comprehensive, multidisciplinary, and multiunit approaches. Doran and colleagues[466] used the Institute for Healthcare Improvement Breakthrough model of rapid cycle improvements in a community cardiac surgical program and found significant improvements in length of stay, ventilator time, patient satisfaction, and cost. Stanford and associates[467] used a total quality management approach that implemented perioperative checklists, nursing-led progress tracking, morbidity and mortality conferences focused on "fix the problem, not the blame," and multidisciplinary consultations.[467,468]

The Geisinger Health System in Danville, Pennsylvania asked surgeons to develop a care bundle for patients undergoing CABG that would be evidence based and hard-wired into the care processes. A continual improvement approach was used to improve the implementation of the bundle. Significant improvements were seen in ICU readmissions, hospital readmissions, blood product use, and overall costs.[157] Developed in 2006, this program has grown into a true "pay-for-performance" program, in which surgeons receive a base salary with incentives that are based on benchmarks of patient satisfaction and outcomes.



BOX 30.5 RECOMMENDATIONS FOR PREVENTION OF INTRAOPERATIVE AWARENESS

- Check all equipment drugs and doses; ensure that the anesthetic agent is reaching the patient.
- Consider amnestic premedication.
- Use a peripheral nerve stimulator to titrate neuromuscular blockade; minimize it as much as possible.
- If intense paralysis is required, consider using a tourniquet on the forearm to allow movement of that hand if the patient is aware.
- Administer at least 0.5 to 0.7 minimum alveolar concentration of an inhaled agent; set the alarm for an end-tidal concentration lower than this level.
- Monitor the inhaled anesthetic concentration on cardiopulmonary bypass.
- Consider vasoactive agents to manage hypotension rather than lowering the anesthetic concentration.
- If the anesthetic level cannot be maintained because of hemodynamic compromise, consider hypnotic or amnestic agents.
- Supplement hypnotic agents with analgesic agents such as opioids to decrease the experience of pain in the event of awareness.
- Consider use of a processed electroencephalogram such as a bispectral index monitor, particularly if using total intravenous anesthesia; do not seek to lower the anesthetic concentration based solely on a bispectral index number.
- Evaluate known risk factors for awareness; explicitly ask about previous episodes of awareness. In patients with a previous history, consider increasing anesthetic concentrations and using sufficient opioids.
- Redose intravenous anesthetic agents during periods when inhaled anesthesia cannot be used (during long intubation attempt or during rigid bronchoscopy).
- When planning for sedation, explicitly discuss with the patient expectations for recall.

Modified from Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: from neurobiology to clinical practice. *Anesthesiology*. 2011;114:1218–1233.

Culig and colleagues[159] use an operational excellence model based on the Toyota Production System to design and establish a new community cardiac surgical program. The investigators described shifting the culture from a hierarchical "defects are punished" model to a collaborative "Just Culture" model. This change was accomplished with disciplined 10-minute daily meetings, including a formal problem-solving process. Over 2 years, the risk-adjusted complication rate was 60% lower than that observed in their region.[159]

Multicenter Collaboratives

Multicenter collaboratives in cardiac surgery have been developed for the purpose of sharing site-specific and physician-specific data, as well as identifying best practices; these collaboratives have improved quality and safety over the past 2 decades. The first collaborative model began in 1987 with the formation of the Northern New England Cardiovascular Disease Study Group.[469–471] Five hospitals in New England agreed to share patients' demographic, process, and outcome data and developed risk-adjusted methods to create predictive models. Variability in actual versus predicted mortality rates led to round-robin site visits and frequent face-to-face meetings to understand how differences in practices affected outcomes. The teams met to share practices and to develop, test, and implement standardized protocols.[472] This model of shared learning led to reductions in overall mortality rates,[164,471] lower mortality rates in women undergoing cardiac operations,[473] reduced rates of re-exploration for significant bleeding,[474] and more appropriate use of aspirin in patients undergoing CABG.[475]

Other multicenter collaboratives have demonstrated similar success. The Virginia Cardiac Surgery Quality Initiative was initiated in 1996, and it currently includes 17 hospitals and 10 cardiac and thoracic surgical teams.[476] This collaborative has resulted in reductions in the incidence of postoperative atrial fibrillation, decreased blood transfusions,[34] and better glucose management.[477] The Michigan Society of Thoracic and Cardiovascular Surgeons formed a quality initiative that has been funded by a statewide health plan. Their efforts have increased internal mammary artery use and decreased the incidence of prolonged ventilation.[158,478,479] Additional collaborative efforts include the Minnesota Cardiac Surgery Database, the Alabama Coronary Artery Bypass Grafting Project, the California Local/Regional Cardiac Surgery Database, and the Washington Clinical Outcomes Assessment Program.[480]

Culture of Safety

Organizational Culture

Most of the preceding discussion has focused on safety at the individual and team levels. Although there is much that individuals and teams can and must do, individual efforts will fall short unless a well-developed organizational safety culture is present.[290] Deficits in safety culture were cited in the abnormally high death rates in pediatric cardiac hospitals in both Bristol, England (Fig. 30.22)[481–483] and Winnipeg, Canada.[484–486] In both instances, frontline providers had raised concerns about poor outcomes, but they were unheeded. Existing quality assurance programs were woefully ill-equipped to identify and address sentinel events, and both hospitals had an institutional unwillingness to challenge the perceived autonomy of physicians.[487,488] Most concerning was the unwillingness of the hierarchy in Winnipeg to consider or even acknowledge the concerns of nurses and anesthesiologists, who eventually refused to provide anesthesia services for these cases.[487] In both Winnipeg and Bristol, a strong hierarchical culture existed that emphasized deference and power differences, so much so that nurses were judged to be incapable of recognizing substandard surgical care.[487] Few nurses would disagree, even years after those inquiries, that the hierarchical culture that existed in Winnipeg and Bristol is still common in health care settings around the world.

Although the terms *safety culture* and *safety climate* may be used interchangeably, they represent different aspects of the same concept. An organization's safety culture refers to the collective behaviors and values that influence its ability to identify and mitigate hazards and systemic unsafe conditions.[489] Safety climate refers to the commitment that workers bring to carrying out the organization's mission and adhering to the established policy and procedures. Safety culture would include an organization setting policies for briefings and debriefings; safety climate would be the willingness of the surgical team to embrace the value of the process deeply rather than perfunctorily checking a box. Even when institutions appear outwardly similar, quite different cultures and subcultures can exist. Local culture drives behavior: institutions with strong hierarchical cultures have low safety climate levels, whereas those with a group orientation and entrepreneurial efforts have higher safety levels.[170,490] The evidence that a hierarchical culture can affect safety highlights the need for a shift in education and training to a paradigm in health care that is more collaborative and multidisciplinary.[487,491,492]

Although overall organizational culture and climate are critical, those of smaller units, such as the cardiac OR and ICU, are often distinctly different from (albeit influenced by) those of the organization.[493] Numerous studies have investigated the attitudes and beliefs of OR personnel and have raised interesting and potentially actionable issues.[169,171,214,265,494] One large multicenter survey found that the safety climate scores differed widely by hospital, *but not by position*, a finding indicating that nurses nationwide tend to have more concerns about safety climate than do physicians.[493] In a similar study, nurses reported having a more negative view of their work unit's support of and attention to safety than did physicians, who expressed more concern about

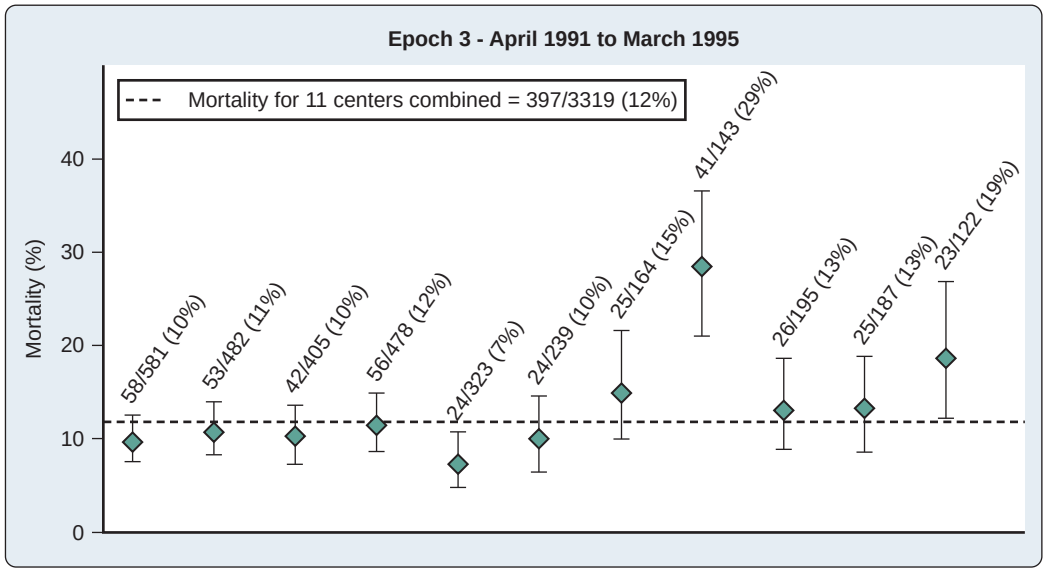


Fig. 30.22 Mortality rates at Bristol (29%) versus other pediatric cardiac hospitals in England. *(From Aylin P, Bottle A, Jarman B, Elliott P. Paediatric cardiac surgical mortality in England after Bristol: descriptive analysis of hospital episode statistics 1991–2002. BMJ. 2004;329:825.)*

being shamed if they commit an error.[494] In another study, a survey of ICU teams found that, "relative to physicians, nurses reported that it is difficult to speak up, disagreements are not appropriately resolved, more input into decision making is needed, and nurse input is not well received."[216]

Fleming and colleagues[495] investigated the leadership, structure, and safety climate of an OR team, as well as their views on stress and fatigue, teamwork, work values, and error and procedural compliance. Respondents reported that procedures and protocols often were not followed, and only 43% stated that they would feel comfortable speaking up if they perceived a threat to patient safety.[495] Although the data are meager, and culture measurement tools have inherent limitations, the detailed findings from Winnipeg and Bristol indicate that these attitudes and climates are deeply embedded in health care and can directly affect patient outcomes.

Effect of Organizational Culture on Outcome

Unfortunately, few studies have formally assessed the effect of organizational culture and characteristics on patient outcomes.[185] One study attempted to link outcomes after CABG with the organization's culture and total quality management scores. The investigators found a fourfold difference between institutions in patient outcomes for CABG (eg, length of stay, length of intubation), but neither the quality management score nor a high supportive organizational culture score was associated with the differences in patient outcome.[496] Several studies investigated the relationship between local climate and culture and threats to patient outcomes or actual outcomes; these studies found that more threats to patient safety occurred in less functional climates.[171]

Data do exist regarding the effect of a strong or rigid hierarchical culture on safety. Organizations with this type of culture place a high premium on stability and are characterized by rigid coordination, uniformity, strict limits on individual authority or innovation, and strong adherence to rules and regulations.[497] These characteristics are not inherently bad. In surgery, as in the military, clear lines of authority and roles as well as adherence to protocols are necessary for excellent performance. However, when a hierarchical culture leads to significant power distance, status asymmetry, or disruptive behavior, team members will be reluctant to speak up or to challenge authority even when threats to patient safety exist.[169,217,493] More distressing is that rigid hierarchical cultures in both Bristol and Winnipeg resulted in a leadership that that discounted and ignored multiple reports of concern.[481,482,486–488] Centralized authority typically causes frontline workers to feel less empowered to speak up or take action when facing safety issues.[490,498] Entities with a rigid hierarchical culture have inferior scores on performance measures and overall safety climate.[207,499,500]

Hierarchical organizations, as noted, are typically rule oriented and bureaucratic. When failures occur, hierarchical organizations focus on identifying someone to blame and holding that person accountable, even if the failure occurred at the system level.[501] These organizations unintentionally establish a culture of blame and shame in which individual persons are often silent about their own mistakes, or about vulnerabilities in the system, in large part because they fear criticism or even retribution. The Joint Commission and the Institute of Healthcare Improvement have emphasized using adverse event reporting to identify and rectify system vulnerabilities. Nonetheless, surveys demonstrate that less than half of staff members report that their hospital has a nonpunitive reporting system.[502]

A hierarchical culture also may foster disruptive behavior, an element of teamwork that may be linked to errors and adverse events. A survey done in 102 hospitals found that, of the respondents (2846 nurses, 944 physicians, 40 executives, and 700 other), 77% had witnessed disruptive behavior in physicians, and 65% reported seeing disruptive behavior in nurses.[503] Disruptive behavior was linked to medical errors by 71% of respondents and to death by 27% of respondents. In a different survey, more than 80% of personnel reported that disruptive behavior had led to reduced focus, reduced communication and collaboration, and poor relationships among the team.[504] Thus, frontline staff members believe that these behaviors affect patient safety and outcomes.[503–506] The Joint Commission implemented leadership standards in 2009 that required creating and maintaining a culture of safety and required having a policy in place to address disruptive behavior.[507] In the 2009 standard, specific types of behavior were enumerated, whereas the newer, revised definitions refer simply to "behaviors that undermine a culture of safety."

As a stressful, intense and complex milieu, the cardiac surgical setting is particularly susceptible to disruptive or bullying behavior.[508] Disruptive behaviors are perpetuated by a hierarchical culture dominated by physicians and a perceived code of silence.[509] The decision not to speak up for fear of retaliation erodes teamwork and a safety culture.[503,509] Vanderbilt University in Nashville, Tennessee studied the effect of a program designed to address professionalism and unprofessional behaviors. The program includes discussions around leadership, a model for intervention, policies, surveillance tools, training,

and accountability.[510] These efforts have led to reduced malpractice claims, better team communications, and behavior changes among physicians.[511]

The best evidence to support the concept that organizational culture and climate affect patient outcome is the work done in the VA Medical Team Training effort. The implementation of Medical Team Training, as reported earlier, reduced operative mortality rates across 108 VA hospitals and significantly improved staff perceptions of the safety climate at their institution.[512,513] Whether the safety climate or culture actually changed at an institution or only the perception of it changed is not clear. Certainly, having executives assigned to a unit or performing executive walkarounds improves safety attitudes.[270,514] It is also possible that the executives carry back to the executive suite knowledge that subtly changes the culture and climate among the leadership.

Improving Organizational Culture

As noted earlier, few studies directly link organizational culture to patient outcomes. Similarly, interventions to change organizational culture, whether at the hospital or unit level, are in their infancy. One such intervention that has been associated with improved patient outcomes is the Comprehensive Unit-Based Safety Program (CUSP), developed during the Keystone project to eliminate central line infections.[280] The CUSP program includes four elements: (1) educating staff on safety science, (2) assigning executives to work with staff to promote safety, (3) identifying and then learning from defects in care, and (4) using teamwork and improvement tools together with quantitative assessments of culture.[515] To date, CUSP primarily has been implemented in ICUs, where it has significantly reduced central line infections, cases of ventilator-associated pneumonia, and surgical site infections.[5,516,517] Implementing the CUSP program improves teamwork climates.[310,518] One of the key elements of CUSP is empowering staff to identify, investigate, and rectify defects in care, within an environment that focuses on vulnerabilities in the system rather than on erring individual members of the system.[310,515,517]

Developing a Just Culture

As noted earlier, health care organizations typically have investigated significant adverse events with great vigor, but all too often they did so to identify someone to blame rather than find out how the system failed. Once identified, that person is shamed at best or prosecuted and jailed at worst.[50,519–521] This culture of blame results in staff members who maintain silence in the presence of performance problems, near misses, and violations because they fear they will be blamed or suffer retaliation.[522]

Although health care organizations typically voice support of a just culture, establishing a climate in which employees feel safe when voicing concerns or identifying vulnerabilities within their own unit requires moving from the ubiquitous control-based management style to a commitment-based style in which employees continually learn from errors and continually eliminate system vulnerabilities.[523] Commitment-based management is believed to be essential to creating a just culture in which individual members are held accountable only when they knowingly and unnecessarily increase risk,[117,501] and in which organizations learn and improve by openly identifying vulnerabilities and correcting them.

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31 Cardiopulmonary Bypass Management and Organ Protection

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KEY POINTS

1. Cardiopulmonary bypass (CPB) provides the extracorporeal maintenance of respiration and circulation and permits the surgeon to operate on a quiet, nonbeating heart.
2. CPB is associated with a number of profound physiologic perturbations. The central nervous system, kidneys, gut, and heart are especially vulnerable to ischemic events associated with extracorporeal circulation.
3. Advanced age is the most important risk factor for stroke and neurocognitive dysfunction after CPB.
4. Acute renal injury from CPB can contribute directly to poor outcomes.
5. Drugs such as dopamine and diuretics do not prevent renal failure after CPB.
6. Myocardial stunning represents injury caused by short periods of myocardial ischemia that can occur during CPB.
7. Blood cardioplegia has the potential advantage of delivering oxygen to ischemic myocardium, whereas crystalloid cardioplegia does not carry much oxygen.
8. Gastrointestinal complications after CPB include pancreatitis, gastrointestinal bleeding, bowel infarction, and cholecystitis.
9. Pulmonary complications such as atelectasis and pleural effusions are common after cardiac surgery with CPB.
10. Embolization, hypoperfusion, and inflammatory processes are central common pathophysiologic mechanisms responsible for organ dysfunction after CPB.
11. Controversy regarding the optimal management of blood flow, pressure, and temperature during CPB remains. Perfusion should be adequate to support ongoing oxygen requirements; mean arterial pressures of more than 70 mm Hg may benefit patients with cerebral and/or diffuse arthrosclerosis. Arterial blood temperatures should never exceed 37.5°C.
12. The initiation and termination of CPB are key phases of a cardiac surgery procedure, but the anesthesiologist must remain vigilant throughout the entire bypass period.
13. Total CPB can be tailored to allow deep hypothermic circulatory arrest or partial bypass. These special techniques require sophisticated monitoring and care.
14. Organ dysfunction cannot definitively be prevented during cardiac surgery with off-pump techniques.

An anesthesiologist-in-training once posed the question, "Why is my presence necessary during cardiopulmonary bypass? The perfusionist has direct control of the patient's blood pressure and respiration. The inhalation anesthetic is attached to the bypass circuit. Drugs are administered into the venous reservoir. What is my role?"[1] The resident's answer was incomplete but more robust than that argued by many clinicians, who suggest that the presence of a member of the anesthesia care team (eg, anesthesiologist, nurse anesthetist, credentialed anesthesia assistant) during cardiopulmonary bypass (CPB) is not essential. The American Society of Anesthesiologists (ASA) states that the absence of anesthesia personnel during the conduct of a general anesthetic violates the first of the ASA Standards for Basic Anesthetic Monitoring.[2] The absence of a member of the anesthesia care team during CPB is below the accepted standard of care. At a minimum, the anesthesiologist's role during CPB is to maintain the anesthetic state—a more challenging task than the usual case when the patient's blood pressure, heart rate, and movement provide information regarding the depth of anesthesia. The complexities of CPB and the necessary integration of risk factors with the nuances of cardiac surgery warrant constant thinking and rethinking of how the conduct of CPB and surgery modulates the risks and what protective strategies need implementation. This chapter outlines the tasks, challenges, and responsibilities of the cardiovascular anesthesiologist that extend beyond the maintenance of the anesthetic state, focusing on overall organ protection.

Historical Perspective on Cardiopulmonary Bypass

On May 6, 1953, John Gibbon, Jr., MD, surgically treated a young woman with an atrial septal defect using CPB, and the long-elusive goal of extracorporeal circulation was achieved (Fig. 31.1). The 60th anniversary of the first successful use of CPB was celebrated in 2013. Ten years prior, a number of insightful perspectives on this important medical landmark accompanied the 50th anniversary of this achievement.[3–5] The fundamental importance of this early achievement continues to be recognized today.

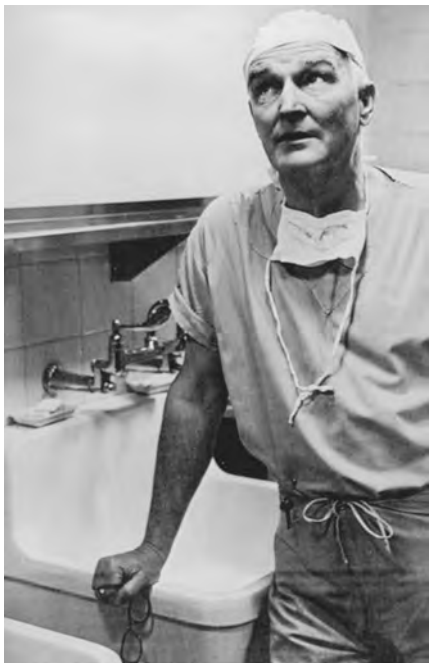


Fig. 31.1 Dr. John Gibbon, Jr., before the first successful application of total extracorporeal circulation for cardiac surgery in humans.

Modern cardiac surgery continues to be challenged by the risk of organ dysfunction and the morbidity and mortality that accompany it. Catastrophic organ system failure was common in the early days of CPB, but advances in perfusion, surgical techniques, and anesthesia have allowed most patients to undergo surgery without major morbidity or mortality. However, organ dysfunction ranging in severity from the most subtle to the most severe still occurs, manifesting most frequently in patients with decreased functional reserves or extensive comorbidities. With more than 1,000,000 patients worldwide undergoing various cardiac operations annually, understanding organ dysfunction and developing perioperative organ protective strategies are paramount.

This chapter briefly describes modern bypass circuits and highlights the many current controversies regarding the management of patients during CPB. It also deals with perfusion accidents that can be life-threatening events. It is critical that all members of the cardiac surgery team anticipate and respond appropriately to mishaps during CPB. More common than the rare catastrophe that can occur are the injurious end-organ effects that can result from the inherent nature of CPB. The multiple pathophysiologic perturbations precipitated by the process of extracorporeal circulation and the putative effects of these phenomena on end-organ function are discussed in detail.

Goals and Mechanics of Cardiopulmonary Bypass

The CPB circuit is designed to perform four major functions: oxygenation and carbon dioxide elimination, circulation of blood, systemic cooling and rewarming, and diversion of blood from the heart to provide a bloodless surgical field.[6] Typically, venous blood is drained by gravity from the right side of the heart into a reservoir that serves as a large mixing chamber for all blood return, additional fluids, and drugs. Because (in most instances) negative pressure is not employed, the amount of venous drainage is determined by the central venous pressure, the column height between the patient and reservoir, and resistance to flow in the venous circuitry. Negative pressure will enhance venous drainage and is used in some bypass approaches, including port-access CPB. Venous return may be decreased deliberately (as is done when restoring the patient's blood volume before coming off bypass) by application of a venous clamp. From the reservoir, blood is pumped to an oxygenator and heat exchanger unit before passing through an arterial filter and returning to the patient. Additional components of the circuit generally include pumps and tubing for cardiotomy suction, venting, and cardioplegia delivery and recirculation, as well as in-line blood gas monitors, bubble detectors, pressure monitors, and blood sampling ports. A schematic representation of a typical bypass circuit is depicted in Fig. 31.2 (see Chapter 32).

The cannulation sites and type of CPB circuit used are dependent on the type of operation planned.[7] Most cardiac procedures use full CPB, in which the blood is drained from the right side of the heart and returned to the systemic circulation through the aorta. The CPB circuit performs the function of the heart and lungs. Aorto-atriocaval cannulation is the preferred method of cannulation for CPB, although femoral arteriovenous cannulation may be the technique of choice for emergency access, "redo" sternotomy, and other clinical settings in which aortic or atrial cannulation is not feasible. Procedures involving the thoracic aorta are often performed using partial bypass in which a portion of oxygenated blood is removed from the left side of the heart and returned to the femoral artery. Perfusion of the head and upper extremity vessels is performed by the beating heart, and distal perfusion is provided below the level of the cross-clamp by retrograde flow by the femoral artery. All blood passes through the pulmonary circulation, eliminating the need for an oxygenator (see Chapter 23).

Physiologic Parameters of Cardiopulmonary Bypass

The primary objective of CPB is maintenance of systemic perfusion and respiration. Controversy arises with the question of whether systemic oxygenation and perfusion should be "optimal or maximal" or "adequate or sufficient." Remarkably, after more than 60 years of CPB, there is continued disagreement regarding many fundamental management issues of extracorporeal circulation. Clinicians and investigators disagree on what the best strategies are for arterial blood pressure goals, pump flow, hematocrit, temperature, blood gas management, or mode of perfusion (pulsatile vs nonpulsatile). Whereas each of these physiologic parameters used to be taken into account individually, the application of each has organ-specific effects. As a result, the ensuing discussions deal with these parameters on an organ-specific basis.

End-Organ Effects of Cardiopulmonary Bypass

Modern cardiac surgery continues to be challenged by the risk of organ dysfunction and the morbidity and mortality that accompany it. A number of injurious common pathways may account for the organ dysfunction typically associated with cardiac surgery. CPB itself initiates a whole-body inflammatory response with the release of various injurious inflammatory mediators. Add to this the various preexisting patient comorbidities and the potential for organ ischemic injury caused by embolization and hypoperfusion, and it becomes clear why organ injury can occur. Most cardiac surgery, because of its very nature, causes some degree of myocardial injury. Other body systems can be affected by the perioperative insults associated with cardiac surgery (particularly CPB), including the kidneys, lungs, gastrointestinal tract, and central nervous system.

Understanding the fundamentals of organ dysfunction, including the incidence, significance, associated risk factors, causes, and pathophysiology, provides a framework for discussing various organ-specific protective strategies. The following section describes the various organ dysfunction syndromes that can occur in patients undergoing cardiac

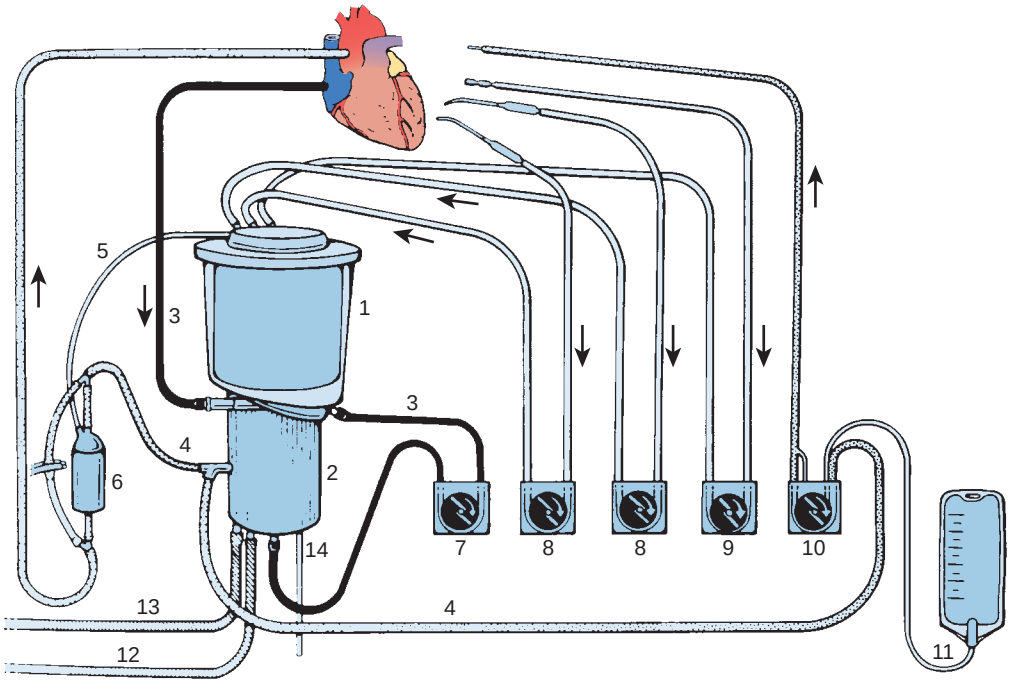


Fig. 31.2 Components of the extracorporeal circuit. *1,* Integral cardiotomy reservoir; *2,* membrane oxygenator bundle; *3,* venous blood line; *4,* arterial blood line; *5,* arterial filter purge line; *6,* arterial line filter; *7,* venous blood pump (also called the arterial pump head; this pump forces venous blood through the membrane oxygenator and arterialized blood to the patient's aortic root); *8,* cardiotomy suction pump; *9,* ventricular vent pump; *10,* cardioplegia pump; *11,* crystalloid cardioplegia; *12,* water inlet line; *13,* water outlet line; and *14,* gas inlet line. *(From Davis RB, Kauffman JN, Cobbs TL, Mick SL.* Cardiopulmonary Bypass. *New York: Springer-Verlag; 1995:239.)*

surgical procedures, with particular emphasis directed at strategies for reducing these injuries.

Central Nervous System Injury

Incidence and Significance of Injury

Central nervous system dysfunction after CPB represents a spectrum of clinical entities ranging from neurocognitive deficits, occurring in approximately 25% to 80% of patients, to overt stroke, occurring in 1% to 5% of patients.[8–11] The significant disparity among studies in the incidence of these adverse cerebral outcomes relates in part to their definition and to numerous methodologic differences in the determination of neurologic and neurocognitive outcomes. Retrospective versus prospective assessments of neurologic deficits account for a significant portion of this inconsistency, as do the experience and expertise of the examiner. The timing of postoperative testing also affects determinations of outcome. For example, the rate of cognitive deficits can be as high as 80% for patients at discharge, between 10% and 35% at approximately 6 weeks after coronary artery bypass grafting (CABG), and 10% to 15% more than a year after surgery. Higher rates of cognitive deficits have been reported 5 years after surgery, when as many as 43% of patients have documented deficits.[9] The issue of whether cardiac surgery causes cognitive loss has been greatly debated. Some have questioned if long-term deficits result as a consequence of surgery,[12] yet, even if only present in the short term, deficits are meaningful to patients and families (see Chapter 40).[13]

Although the incidence of these deficits varies greatly, the significance of these injuries cannot be overemphasized. Cerebral injury is a most disturbing outcome of cardiac surgery. To have a patient's heart successfully treated by the planned operation but discover that the patient no longer functions as well cognitively or is immobilized from a stroke can be devastating. There are enormous personal, family, and financial consequences of extending a patient's life with surgery, only to have the quality of the life significantly diminished.[11,14] Death after CABG, although having reached relatively low levels in the past decade (generally less than 1% overall), is increasingly attributable to cerebral injury.[11]

Risk Factors for Central Nervous System Injury

Successful strategies for perioperative cerebral and other organ protection begin with a thorough understanding of the risk factors, causation, and pathophysiology involved. Risk factors for central nervous system injury can be considered from several different perspectives. Most studies outlining risk factors take into account only stroke. Few describe risk factors for neurocognitive dysfunction. Although it is often assumed that their respective risk factors are similar, few studies have consistently reported the preoperative risks of cognitive loss after cardiac surgery. Factors such as a poor baseline (preoperative) cognitive state, years of education (ie, more advanced education is protective), age, diabetes, and CPB time are frequently described.[15,16]

Stroke is better characterized with respect to risk factors. Although studies differ somewhat as to all the risk factors, certain patient characteristics consistently correlate with an increased risk for cardiac surgery–associated neurologic injury. In a study conducted by the Multicenter Study of Perioperative Ischemia of 2108 patients from 24 centers, incidence of adverse cerebral outcome after CABG surgery was determined and the risk factors were analyzed.[15] Two types of adverse cerebral outcomes were defined. Type I included nonfatal stroke, transient ischemic attack, stupor or coma at time of discharge, and death caused by stroke or hypoxic encephalopathy. Type II included new deterioration in intellectual function, confusion, agitation, disorientation, and memory deficit without evidence of focal injury. A total of 129 (6.1%) of the 2108 patients had an adverse cerebral outcome in the perioperative period. Type I outcomes occurred in 66 (3.1%) of

TABLE 31.1 Risk Factors for Adverse Cerebral Outcomes After Cardiac Surgery

Risk Factor	*Type I Outcomes*	*Type II Outcomes*
Proximal aortic atherosclerosis	4.52 (2.52–8.09)[a]	
History of neurologic disease	3.19 (1.65–6.15)	
Use of IABP	2.60 (1.21–5.58)	
Diabetes mellitus	2.59 (1.46–4.60)	
History of hypertension	2.31 (1.20–4.47)	
History of pulmonary disease	2.09 (1.14–3.85)	2.37 (1.34–4.18)
History of unstable angina	1.83 (1.03–3.27)	
Age (per additional decade)	1.75 (1.27–2.43)	2.20 (1.60–3.02)
Admission systolic BP > 180 mm Hg		3.47 (1.41–8.55)
History of excessive alcohol intake		2.64 (1.27–5.47)
History of CABG		2.18 (1.14–4.17)
Arrhythmia on day of surgery		1.97 (1.12–3.46)
Antihypertensive therapy		1.78 (1.02–3.10)

[a]Adjusted odds ratio (95% confidence intervals) for type I and type II cerebral outcomes associated with selected risk factors from the Multicenter Study of Perioperative Ischemia.

BP, Blood pressure; *CABG,* coronary artery bypass graft surgery; *IABP,* intraaortic balloon pump.

From Arrowsmith JE, Grocott HP, Reves JG, Newman MF. Central nervous system complications of cardiac surgery. *Br J Anaesth* 2000;84:378–393.

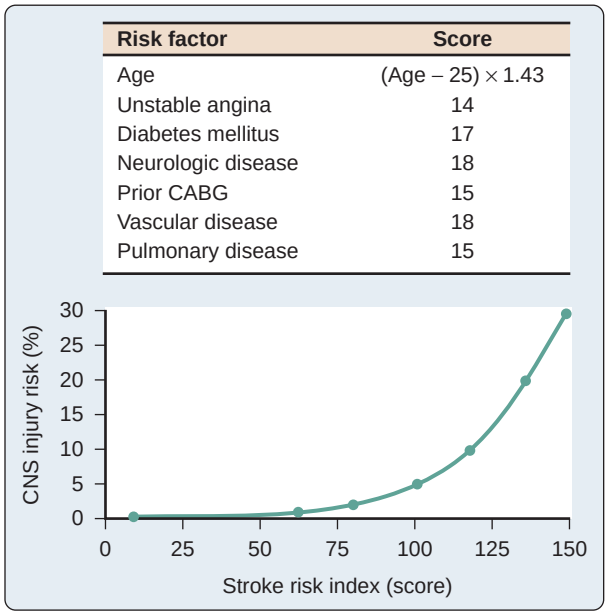


Fig. 31.3 Preoperative stroke risk for patients undergoing CABG surgery. The individual patient's stroke risk can be determined from the corresponding cumulative risk index score in the nomogram. *CABG,* Coronary artery bypass graft; *CNS,* central nervous system. *(Modified from Arrowsmith JE, Grocott HP, Reves JG, Newman MF. Central nervous system complications of cardiac surgery.* Br J Anaesth *2000;84:378–393.)*

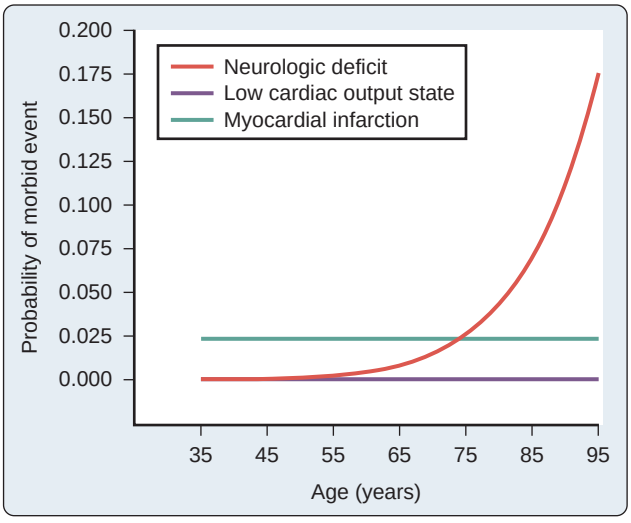


Fig. 31.4 The relative effect of age on the predicted probability of neurologic and cardiac morbidity after cardiac surgery. *(Modified from Tuman KJ, McCarthy RJ, Najafi H, Ivankovich AD. Differential effects of advanced age on neurologic and cardiac risks of coronary artery operations.* J Thorac Cardiovasc Surg *1992;104:1510–1517.)*

2108 patients, with type II outcomes occurring in 63 (3.0%) of 2108 patients. Stepwise logistic regression analysis identified eight independent predictors of type I outcomes and seven independent predictors of type II outcomes (Table 31.1).

In a subsequent analysis of the same study database, a stroke risk index using preoperative factors was developed (Fig. 31.3). This risk index allowed for the preoperative calculation of the stroke risk based on the weighted combination of the preoperative factors, including age, unstable angina, diabetes mellitus, neurologic disease, previous coronary artery or other cardiac surgery, vascular disease, and pulmonary disease.[14] Of all the factors in the Multicenter Study of Perioperative Ischemia analysis and in multiple other analyses,[11,17–21] age appears to be the most overwhelmingly robust predictor of stroke and of neurocognitive dysfunction after cardiac surgery.[8,9] Tuman and colleagues[21] described that age has a greater impact on neurologic outcome than it does on perioperative myocardial infarction (MI) or low cardiac output states (LCOSs) after cardiac surgery (Fig. 31.4).

The influence of gender on adverse perioperative cerebral outcomes after cardiac surgery has been evaluated. Women appear to be at higher risk for stroke after cardiac surgery than men.[19,22] Hogue and coworkers[23] found that women appear more likely to suffer deficits in the visuospatial cognitive domain after cardiac surgery, although the frequency of cognitive dysfunction after cardiac surgery is similar for women and men.

Another consistent risk factor for stroke after cardiac surgery is the presence of cerebrovascular disease and atheromatous disease of the aorta. With respect to cerebrovascular disease, patients who have had a prior stroke or transient ischemic attack are more likely to suffer a perioperative stroke.[22,24–26] Even in the absence of symptomatic cerebrovascular disease, such as the presence of a carotid bruit, the risk of stroke increases with the severity of the carotid disease. Breslau and associates[27] reported that Doppler-detected carotid disease increased the risk of stroke after cardiac surgery by threefold. Similarly, Brener and colleagues[28] described that a carotid stenosis greater than 50% increased the risk of stroke from 1.9% to 6.3%.

Although the presence of cerebrovascular disease is a risk factor for perioperative stroke, it does not always correlate well with the presence of significant aortic atherosclerosis.[29] Atheromatous disease of the ascending aorta, aortic arch, and descending thoracic aorta has been consistently implicated as a risk factor for stroke in cardiac surgical patients.[30–33] The widespread use of transesophageal echocardiography (TEE) and epiaortic ultrasonography has added new dimensions to the detection of aortic atheromatous disease and the understanding of its relation to stroke risk. These imaging modalities have allowed the diagnosis of atheromatous disease to be made in a more sensitive and detailed manner, contributing greatly to the information regarding potential stroke risk. The risk of cerebral embolism from aortic atheroma was described early in the history of cardiac surgery[34] and has been described repeatedly and in detail since then.[11,35–37] For example, Katz and coworkers[38] found that the incidence of stroke was 25% in patients with a mobile atheromatous plaque in the aortic arch, compared with a stroke rate of 2% in those with limited atheromatous disease. Studies have consistently reported higher stroke rates for

patients with increasing atheromatous aortic involvement (particularly the ascending and arch segments).[39] This relationship is outlined in Fig. 31.5.

Causes of Perioperative Central Nervous System Injury

Because central nervous system dysfunction represents a wide range of injuries, differentiating the individual causes of these various types of injuries becomes somewhat difficult (Box 31.1). They are frequently grouped together and superficially discussed as representing different severities on a continuum of brain injury. This likely misrepresents the different causes of these injuries. The following section addresses stroke and cognitive injury (Table 31.2), and their respective causes are differentiated when appropriate.

Cerebral Embolization

Macroemboli (eg, atheromatous plaque) and microemboli (ie, gaseous and particulate) are generated during CPB, and many emboli find their way to the cerebral vasculature.[40] Macroemboli are responsible for stroke with microemboli being implicated in the development of less severe encephalopathies. Sources for the microemboli are numerous and include those generated de novo from the interactions of blood within the CPB apparatus (eg, platelet-fibrin aggregates) and those generated within the body by the production and mobilization of atheromatous material or entrainment of air from the operative field. Other sources for emboli include lipid-laden debris that can be added by cardiotomy suction.[41] Other gaseous emboli may be generated though injections into the venous reservoir of the CPB apparatus itself.[42,43]

Numerous studies outline the relationship between emboli and cognitive decline after cardiac surgery.[44–46] However, one of the major limitations in understanding this relationship has been the relative inability to discern between gaseous and particulate microemboli.[47] Typically, Doppler ultrasonography has been used to measure cerebral embolic signals, but Doppler cannot reliably distinguish between gaseous and particulate emboli.[48] In addition to using Doppler evidence, Moody and associates[40] performed histologic analyses on brains from cardiac surgical patients and described the presence of millions of cerebral emboli represented as small capillary arteriolar dilations. More recently, the relationship between emboli and cognitive changes has been questioned.[47,49,50]

The impact of aortic atheroma on cognitive decline is incompletely understood. It is widely known from nonsurgical as well as cardiac surgical studies that there is a clear relationship between aortic atheroma and stroke,[30,51–53] but the relationship between cognitive outcome and cerebral atheroma is much less uncertain. Several studies describe different results.[54,55] Whereas some data suggest that cerebral emboli are more likely with a higher degree of atheroma in the ascending aorta,[56] there are no data to demonstrate that these atheroma correspond to cognitive decline.[54] Part of the discordance between these two findings may reflect the limitation of Doppler technology to discriminate between gaseous and particulate emboli, thereby possibly misrepresenting the true cerebral embolic load.[57]

Global Cerebral Hypoperfusion

The concept that global cerebral hypoperfusion during CPB may lead to neurologic and neurocognitive complications originates from the earliest days of cardiac surgery, when significant (in degree and duration) systemic hypotension was a relatively common event. Although

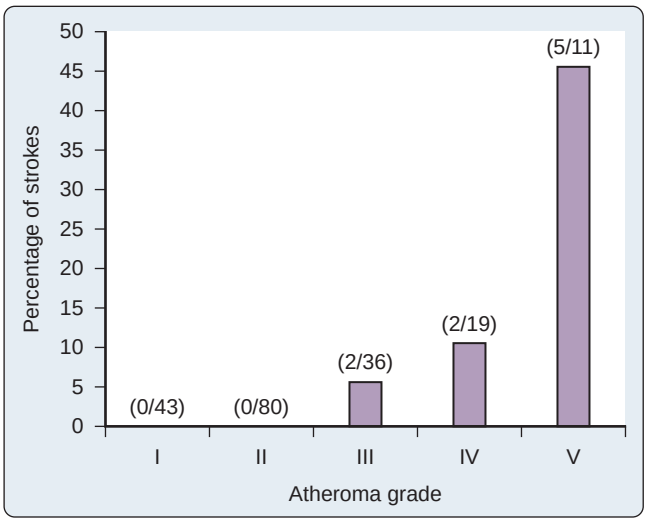


Fig. 31.5 Stroke rate 1 week after cardiac surgery as a function of atheroma severity. Atheroma was graded by transesophageal echocardiography as follows: I, normal; II, intimal thickening; III, plaque < 5 mm thick; IV, plaque > 5 mm thick; V, any plaque with a mobile segment. *(From Hartman GS, Yao FS, Bruefach M 3rd, et al. Severity of aortic atheromatous disease diagnosed by transesophageal echocardiography predicts stroke and other outcomes associated with coronary artery surgery: a prospective study.* Anesth Analg *1996;83:701–708.)*

BOX 31.1 POTENTIAL CONTRIBUTORS TO CENTRAL NERVOUS SYSTEM COMPLICATIONS AFTER CARDIOPULMONARY BYPASS

- Cerebral emboli
- Global hypoperfusion
- Inflammation
- Cerebral hyperthermia
- Cerebral edema
- Blood-brain barrier dysfunction
- Genetics

TABLE 31.2 Potential Contributors to Causes of Cognitive Dysfunction After Cardiac Surgery

Cause	*Possible Settings*
Cerebral microemboli	Generated during cardiopulmonary bypass (CPB); mobilization of atheromatous material or entrainment of air from the operative field; gas injections into the venous reservoir of the CPB apparatus
Global cerebral hypoperfusion	Hypotension, occlusion by an atheromatous embolus leading to stroke
Inflammation (systemic and cerebral)	Injurious effects of CPB, such as blood interacting with the foreign surfaces of pump-oxygenator; upregulation of proinflammatory cyclooxygenase mRNA
Cerebral hyperthermia	Hypothermia during CPB; hyperthermia during and after cardiac surgery, such as aggressive rewarming
Cerebral edema	Edema from global cerebral hypoperfusion or increased cerebral venous pressure from cannula misplacement
Blood-brain barrier dysfunction	Diffuse cerebral inflammation; ischemia from cerebral microembolization
Genetic influences	Effects of single nucleotide polymorphisms on risk for Alzheimer disease or for acute coronary syndromes and other thrombotic disorders

this concept (ie, that hypotension would lead to global cerebral hypoperfusion) makes intuitive sense, studies that have examined the relationship between mean arterial pressure (MAP) and cognitive decline after cardiac surgery have generally failed to show any significant relationship.[16,58,59]

This is not the case for stroke, for which Hartman and investigators[37] and Gold and coworkers[60] demonstrated a link between hypotension and the presence of a significantly atheromatous aorta with an increased risk of stroke (see Fig. 31.5). This is not a clear relationship, however, and likely represents an interaction between macroembolism and global cerebral hypoperfusion. It is likely, for example, that if an area of the brain that is being perfused by a cerebral vessel becomes occluded by an atheromatous embolus, it may be more susceptible to hypoperfusion if collateral perfusion is compromised by concomitant systemic hypotension.[61] Other evidence for global cerebral hypoperfusion comes from Mutch and associates,[62] who examined magnetic resonance imaging (MRI) assessments of cerebral blood flow (CBF) showing progressive decreases in CBF during the course of experimental CPB in pigs. However, clinical demonstrations of a reduction in CBF during lengthy CPB have not been shown.[63]

Temperature-Related Factors

The various trials of hypothermia during CPB with detailed temperature monitoring have also shown that *hyperthermia* can occur during and after cardiac surgery. During rewarming from hypothermic CPB, there can be an overshoot in cerebral temperature due to aggressive rewarming generally aimed at decreasing time on CPB and overall operating room time. This cerebral hyperthermia may well be responsible for some of the injury that occurs in the brain.[64]

The postoperative period is also a critical time in which hyperthermia can contribute to brain injury.[65,66] Grocott and colleagues[65] demonstrated that the peak temperature in the postoperative period (24 hours after surgery) was related to cognitive decline 6 weeks after cardiac surgery. It is not clear whether this hyperthermia causes de novo injury or exacerbates injury that has already occurred (eg, injury that might be induced by cerebral microembolization or global cerebral hypoperfusion). It is necessary to be cautious in concluding whether these relationships are temporal or causal. However, it is assumed that the brain is injured during CPB, and because experimental brain injury is known to cause hyperthermia (resulting from hypothalamic injury[67]), the hyperthermia that is demonstrated in the postoperative period may be caused by the occurrence or extent of brain injury. However, if hyperthermia results from the inflammatory response to CPB, the hyperthermia itself may induce or exacerbate cerebral injury.

Inflammation

Although it is well known that blood interacts with the foreign surfaces of the pump-oxygenator to stimulate a profound inflammatory response,[68] the systemic end-organ effects of this inflammatory response are less clearly defined. Much of the data relating organ dysfunction in the central nervous system to the inflammatory response in the cardiac surgical patient are based on indirect experimental and clinical evidence. It is not clear whether a cerebral inflammatory response occurs as a result of CPB in humans. Hindman and coworkers[69] reported that cyclooxygenase mRNA was upregulated after CPB, suggesting that on the molecular biologic level, CPB induces overexpression of this proinflammatory gene in the brain. What is not clear is whether this was a primary event (ie, as a direct result of the proinflammatory effects of CPB) or a secondary event as a result of other injurious effects of CPB (eg, microembolization). In settings other than cardiac surgery, inflammation has been demonstrated to directly injure the brain (eg, sepsis-mediated encephalopathy),[70] but it is also known to result as a response to various cerebral injuries (eg, ischemic stroke).[71]

There is no direct evidence that inflammation causes cardiac surgery-associated adverse cerebral outcome; however, there is some supportive indirect evidence. For example, Mathew and investigators[72] demonstrated a relationship between poor cognitive outcome and an impaired immune response to circulating endotoxin, which inevitably translocates from the gut into the bloodstream as a result of alterations in splanchnic blood flow during CPB. Having a low antibody response to circulating endotoxin is paradoxically associated with an overstimulated inflammatory response,[73] thus demonstrating that the relationship between low endotoxin antibodies and poor cognitive outcome may be mediated by an augmented inflammatory response. There is increasing genetic evidence linking inflammation to adverse cerebral outcomes, both stroke and cognitive loss (see "Genetic Influences").

Cerebral Edema

Cerebral edema after CPB has been reported in several studies.[74,75] The explanation for why cerebral edema may occur early in the period after bypass is not clear. It may be caused by cytotoxic edema resulting from global cerebral hypoperfusion or possibly by hyponatremia-induced cerebral edema. Generalized cerebral edema due to increases in cerebral venous pressure caused by cannula misplacement, which frequently occurs during CPB, is another reason.[76] Specifically, use of a dual-stage venous cannula can often lead to cerebral venous congestion during the vertical displacement of the heart during access to the lateral and posterior epicardial coronary arteries. It is not clear from these studies whether the edema results because of injury that occurs during CPB, leading to cognitive decline, or whether the edema itself directly causes the injury by consequent increases in intracranial pressure with global or regional decreases in CBF and resulting ischemia. As both technology for CPB and our understanding of physiologic management improve, the occurrence of CPB-related cerebral edema becomes less likely. [77]

Blood-Brain Barrier Dysfunction

The function of the blood-brain barrier (BBB) is to aid in maintaining the homeostasis of the extracellular cerebral milieu protecting the brain against fluctuations in various ion concentrations, neurotransmitters, and growth factors that are present in the serum.[78] The impact of CPB on the function and integrity of the BBB is not clearly known. Gillinov and colleagues[79] were unable to show any changes in BBB dysfunction 2 hours after CPB in piglets as assessed using carbon 14–aminoisobutyric acid tracer techniques in post-bypass brain homogenates. However, Cavaglia and coworkers,[80] measuring the leakage of fluorescent albumin from blood vessels in brain slices after CPB, were able to demonstrate significant breaches in the BBB. Both studies looked at a single time point (ie, immediately after CPB), and it is not known whether there are temporal changes in the BBB integrity.

It is difficult to determine whether the changes in BBB integrity, if present at all, are a primary cause of brain dysfunction or simply a result of other initiating events such as ischemia (ie, from cerebral microembolization) or a diffuse cerebral inflammatory event. Changes in the BBB could cause some of the cerebral edema that has been demonstrated, or it could result from cerebral edema if the edema resulted in ischemic injury (from increases in intracranial pressure).[75]

Possible Pharmacologic Influences

Anesthetics have been demonstrated to affect cognitive loss after surgery. Experimental studies of cognitive outcome in young rats exposed to anesthetics have demonstrated that relatively brief (several hours) exposure to isoflurane can lead to long-term cognitive changes in the animals.[81,82] Coupled with the demonstration in other experimental models of necrosis in neonatal brains exposed to certain anesthetic agents (eg, isoflurane, midazolam, nitrous oxide),[83] these data suggest that corresponding proteomic changes can occur in the brain after exposure to anesthetics,[84] and the investigators highlighted this as a potential area for further research.

Genetic Influences

Genetics may play a role in modifying the degree of central nervous system injury or in the ability of the brain to recover after an injury has occurred. Several investigations have assessed the genetic influences

on cerebral outcome after CPB. The most commonly explored gene variant, or single nucleotide polymorphism (SNP), has been the ε4 allele of the apolipoprotein gene. This gene has been reported to be responsible for increasing the risk of sporadic and late-onset Alzheimer disease (as well as complicating outcome after a variety of other head injuries).[85] Although early reports suggested that this may be an important influence,[86] later reports shed some doubt on how robust this effect is.[87] A second SNP examined relates to the PLA2 receptor polymorphism. This platelet integrin receptor polymorphism is important in the cause of acute coronary syndromes and other thrombotic disorders.[88,89] A small study of patients undergoing cardiac surgery demonstrated worse impairments in the mini–mental state examination in the PLA2-positive patients compared with PLA2-negative patients.[90]

With the multitude of genes that may play a role in injury, it is important to go beyond examining the impact of single SNPs and explore the impact of multiple SNPs, alone or in combination. In a study of 2140 patients examining 26 different SNPs, the presence of the minor alleles of C-reactive protein (CRP) and interleukin (IL)-6 had a threefold increase in the risk of stroke after cardiac surgery.[91] Of note, no single (or combination of) prothrombotic genes were associated with stroke, suggesting that inflammatory, as opposed to thrombotic, mechanisms may be more important to the risk of a stroke.

With respect to cognitive dysfunction after cardiac surgery, a study by Mathew and associates[92] outlined the impact of genetics on outcome after cardiac surgery. In this study of 513 patients who were extensively genotyped (30 SNPs) and had cognitive testing after cardiac surgery, a link between SNPs of CRP and P-selectin (CRP1059G4/C and SELP1087G/A) and a reduction in cognitive deficit were found. The incidence of cognitive deficit was 16.7% in carriers of the minor alleles of both of these genes compared to 42.9% of the patients possessing these major alleles. Unique in this study was the mechanism-based genetic effect where these polymorphisms were also associated with reductions in both CRP and platelet activation, suggesting that an attenuation of perioperative inflammatory and prothrombotic states may be beneficial with respect to reducing cognitive deficits after cardiac surgery.[93]

Neuroprotective Strategies

Emboli Reduction

There are multiple sources of particulate and gaseous emboli during cardiac surgery. Within the CPB circuit itself, particulate emboli in the form of platelet-fibrin aggregates and other debris are generated. Gaseous emboli can be created in the circuit or augmented if already present by factors such as turbulence-related cavitation and potentially even by vacuum-assisted venous drainage.[94] Air in the venous return tubing is variably handled by the bypass circuit (ie, reservoir, oxygenator, and arterial filters). The ability of the circuit to prevent the transit of gaseous emboli through the oxygenator varies considerably between manufacturers and remains a significant source of emboli. The impact of perfusionist interventions on cerebral embolic load has also been studied. Borger and colleagues[43] found that after drug injections into the venous reservoir, gaseous emboli can make a rapid passage through to the arterial outflow. Reducing these perfusionist interventions reduced emboli generation and neurocognitive impairment.

Significant quantities of air can be entrained from the surgical field into the heart itself; flooding the field with carbon dioxide has been proposed as being effective in reducing this embolic source.[95] Its ability to specifically reduce cerebral injury has not been rigorously evaluated although it has been demonstrated to significantly reduce the amount of TEE-detectable bubbles in the heart after cardiac surgery.[96] Even with the use of carbon dioxide in the surgical field, significant amounts of entrained air can be present. Although the oxygenator-venous reservoir design attempts to purge this air before reaching the inflow cannula, the arterial line filter handles a great deal of what is left. The capacity of the arterial filter to remove all sources of emboli (gaseous or particulate) has significant limitations, and, despite its use, emboli can easily pass through and on into the aortic root.

The aortic cannula may be very important to reduce cerebral emboli production. Placement of the cannula into an area of the aorta with a large atheroma burden may cause the direct generation of emboli from the "sandblasting" of atherosclerotic material in the aorta.[97] The use of a long aortic cannula, where the tip of the cannula lies beyond the origin of the cerebral vessels has also been found to reduce emboli load.[98] The type of cannula itself may be an important factor. Various designs have allowed the reduction of various sandblasting-type jets emanating from the aortic cannula. Baffled cannulas and cannulas that allow the incorporation of regional brain hypothermia and diversion of emboli away from the cerebral vessels have been investigated.[99] A cannula that has a basket-like extension that can be inserted just before cross-clamp removal has also been studied.[100] However, in a large (N = 1289) study, this Embol-X cannula was unable to reduce the incidence of central nervous system dysfunction.[101] A smaller (N = 24) study paradoxically showed an increase in embolic signals with its deployment in the aorta.[102] This has been because of air bubbles trapped within the basket or abrasion of the atheromatous aortic wall. Few other emboli-reducing strategies have been studied sufficiently to determine their impact on cognitive loss after cardiac surgery. The safety of introducing new techniques also has not been thoroughly studied; the additional risk assumed when significantly altering a standard of practice to use a new device must be considered.

Blood that is returned from the surgical field though the use of the cardiotomy suction may significantly contribute to the particulate load in the CPB circuit and subsequently in the brain. The use of cell-salvage devices to process shed blood before returning it to the venous reservoir may minimize the amount of particulate- or lipid-laden material that contributes to embolization.[41,42] Most of this material is small enough or so significantly deformable (because of its high lipid content) that it can pass through standard 40-μm arterial filters. There are several issues with the cell saver, however. One is the cost that is incurred with its use, and the other is its side effects of reducing platelet and coagulation factors through its intrinsic washing processes. Modest use of cell salvage up to a certain, although as yet undefined, volume of blood is likely prudent. Despite this rationale, the results from studies examining neurologic outcome have shown variable effects of cell-saver use on cognitive outcome. A study by Djaiani and colleagues[103] demonstrated a benefit whereas a study by Rubens and coworkers[104] did not. This may have been because of differences in cell savers used that likely varied in their ability to remove lipid emboli.

Management of Aortic Atherosclerosis

The previous section dealt with issues related to reduction of emboli, many of which are likely spawned from atheromatous plaque in the aorta. Further specific management of the atheromatous aorta, particularly as it relates to stroke risk, requires special attention. The widespread use of TEE and complementary (and preferably routine) epiaortic scanning has contributed greatly to the understanding of the risks involved in managing patients with a severely atheromatous aorta. There is indisputable evidence linking stroke to atheroma.[30,51–53] However, the strength of association between atheroma and cognitive decline seen after cardiac surgery is less clear.

A small study used a combination of epiaortic scanning and atheroma avoidance techniques (with respect to cannulation, clamping, and vein graft anastomosis placement) to attempt to reduce neurocognitive deficits.[55] In that study, the incidence of cognitive decline was lower in patients who had an avoidance technique guided by epiaortic scanning compared with no epiaortic scanning. It was limited by its small size, but it identified an area that requires more investigation. Others have examined this issue and found the relationship between cognitive decline and atheroma to be doubtful.[105] Regardless of whether atheroma causes cognitive dysfunction, their contribution to cardiac surgery-associated stroke is enough to warrant specific strategies for management.

One of the difficulties in interpreting studies that have evaluated atheroma avoidance strategies is the absence of any form of blinding of the investigators. For the most part, a strategy is chosen based on

TABLE 31.3 Comparison of Studies Investigating Pulsatile Flow During Cardiopulmonary Bypass

Proposed Beneficial Effect of Pulsatile Flow	References	
	Yes	*No*
Reduced systemic vascular resistance	108–114	115–123
Changes in systemic blood flow distribution	108, 124	110, 115, 116, 121
Improved microcirculatory flow/ aerobic metabolism	108, 109, 111, 123, 125, 126	110, 115, 116, 121–123
Attenuation of Hormonal Responses		
Catecholamines	127	109, 119
Renin/angiotensin	114, 119, 122	115, 116, 127, 128
Antidiuretic hormone	113, 127	117
Cortisol		117, 128
Thromboxane/prostacyclin	120	
Improved renal blood flow or urine output	111, 113, 115, 124, 126	110, 116–118, 123, 129, 136
Improved pancreatic blood flow	124, 129	
Improved cerebral blood flow, metabolism, or outcome	112, 125, 130–132, 140	137–139

the presence of known atheroma, and the results of these patients are compared with historic controls. What constitutes the best strategy is unclear. Multiple techniques can be used to minimize atheromatous material liberated from the aortic wall from getting into the cerebral circulation. These range from optimizing placement of the aortic cannula in the aorta to an area relatively devoid of plaque to the use of specialized cannulas that reduce the sandblasting of the aortic wall. The use of alternative aortic cannulas and different locations may decrease embolization of atheromatous plaque. The avoidance of partial occlusion clamping for proximal vein graft placement by performing all of the anastomoses in a single application of an aortic cross-clamp has demonstrated a benefit.[106] Specialized cannulas that contain filtering technologies[100] and other means to deflect emboli to more distal sites have been developed and studied.[107] Technology is advancing rapidly, and proximal (and distal) coronary artery anastomotic devices are becoming increasingly available and focus on minimizing manipulation of the ascending aorta. None of these aortic manipulations has yet yielded significant neuroprotective results in large, prospective, randomized trials, but their potential holds promise.

Pulsatile Perfusion

A large body of literature has accumulated comparing the physiology of pulsatile with nonpulsatile perfusion.[108,109] Nevertheless, it remains uncertain whether pulsatile CPB has shown substantive clinical improvement in any outcome measure compared with standard, nonpulsatile CPB. Table 31.3, although by no means complete, represents this highly contradictory body of literature.[110–139] Claims of advantages to pulsatile flow are effectively offset by conflicting studies of similar design.

Nonpulsatile CPB is the most commonly practiced form of artificial perfusion. As intuitive as it may seem that this type of nonphysiologic, nonpulsatile pump flow could be injurious, there is an overall lack of data to suggest that using pulsatile flow during clinical CPB has a neurologic benefit. In a large (N = 316), double-blind, randomized investigation by Murkin and coworkers[140] examining the effect of pulsatile versus nonpulsatile CPB on neurologic and neuropsychologic outcomes, no significant benefit was demonstrated. One study of balloon pump–induced pulsatile perfusion during CPB failed to show any improvements in jugular venous oxygen saturation of regional brain oxygenation.[141] A significant limitation to most pulsatility studies is that, because of technical limitations, true "physiologic" pulsatility is almost never accomplished. Instead, variations of sinusoidal pulse waveforms are produced that do not replicate the kinetics and hydrodynamics of normal physiologic pulsation. A somewhat dated review by Hickey and associates,[109] published in 1983, offered important criticism and insight into this controversy and remains germane to recent reports. A fundamental difference between pulsatile and nonpulsatile flow is that additional hydraulic energy is required and applied to move blood when pulsatile flow is used. This extra kinetic energy is known to improve red blood cell transit, capillary perfusion, and lymphatic function.[135] The hydraulic power of pulsatile flow is the sum over time of the product of instantaneous pressure and instantaneous flow. CPB may influence many of the properties of the blood (viscosity) and the vasculature itself (arterial tone, size, and geometry) as a result of hemodilution, hypothermia, alteration of red blood cell deformability, and redistribution of flow. As a result of these changes, generation of what appears to be a normal pulsatile *pressure* waveform may not result in a normal pulsatile *flow* waveform. Simply reproducing pulsatile pressure is not sufficient to ensure reproduction of pulsatile flow, nor does it allow quantification of energetics.

Virtually no study has quantified the energetics of the pulsatile or nonpulsatile perfusion used. Few studies report representative pressure waveforms.[110–115] Even fewer give flow waveforms.[136,137] When pulsatile flow is not quantified, critical features such as vascular impedance and the hydraulic power delivered cannot be evaluated (ie, whether the pulsatile perfusion used in a particular study was really delivering more hydraulic power than the nonpulsatile perfusion with which it is compared). Grossi and investigators[137] developed two indices of pulsatility: the pulsatility index (PI), which quantitates the relative sharpness of a given waveform with respect to its mean flow, and the pulse power index (PPI), which quantifies the power of a pulsatile waveform compared with nonpulsatile equal flow. They found that despite use of a computer-controlled pulsatile pump, in every case PI or PPI was considerably less than control (non-bypass pulsatility). Only with specific combinations of pulse rate and pulsatile flow contours (which had high PI or PPI) was lactate production lower than the nonpulsatile perfusion at the same minute flow during pulsatile CPB. This study indicates that not all pulsatile perfusion is the same and that pulsatile modes are not necessarily capable of improved perfusion relative to nonpulsatile systems.

It is therefore not surprising that such a wide disparity of results should occur. We are unaware of any human study in which pulsatility has been quantitated in terms other than pulse pressures. Consequently, whether the generated pressure waveform is a sine wave or some other pattern cannot be ascertained.[115,116,119,121–125,128–130] The comparatively small size of the arterial inflow cannula can effectively filter out a large component of the pulsatile kinetic energy. Consequently, as achieved clinically, pulsatile flow may be quite similar energetically to nonpulsatile flow.

Newer pulsatile technologies may better reproduce the normal biologic state of cardiac pulsatility. Computer technologies that allow creating a more physiologic pulsatile perfusion pattern have demonstrated, at least experimentally, preservation of cerebral oxygenation. This approach showed some promise in a pig model of CPB in which pulsatile flow controlled by a computer to replicate the normal biologic variability in pulsatility was associated with significantly lower jugular venous oxygen desaturation during rewarming after hypothermic CPB.[142] However, most studies do not present convincing evidence to suggest that routine pulsatile flow during CPB, as can be achieved by widely available technology, is warranted.

Acid-Base Management: Alpha-Stat Versus pH-Stat

Optimal acid-base management during CPB has long been debated. Theoretically, alpha-stat management maintains normal CBF autoregulation with the coupling of cerebral metabolism ($CMRO_2$) to CBF, allowing adequate oxygen delivery while minimizing the potential for emboli. Although early studies[140] were unable to document a difference in neurologic or neuropsychologic outcome between the two techniques, later studies showed reductions in cognitive performance when pH-stat management was used, particularly in cases with prolonged CPB times.[143] pH-Stat management (ie, CO_2 is added to the oxygenator fresh gas flow) results in a higher CBF than is needed for the brain's metabolic requirements. This luxury perfusion risks

excessive delivery of emboli to the brain. Except for congenital heart surgery, for which most outcome data support the use of pH-stat management[144,145] because of its improvement in homogenous brain cooling before circulatory arrest, adult outcome data support the use of only alpha-stat management.

Temperature and Rewarming Strategies

The use of some hypothermia remains a mainstay of perioperative management in the cardiac surgical patient. Its widespread use relates to its putative, although not definitively proved, global organ protective effects. Although hypothermia has a measurable effect on suppressing cerebral metabolism (approximately 6% to 7% decline per 1°C),[146] it is likely that its other neuroprotective effects may be mediated by nonmetabolic actions. In the ischemic brain, for example, moderate hypothermia has multimodal effects, including blocking the release of glutamate,[147] reducing calcium influx,[148] hastening recovery of protein synthesis,[149] diminishing membrane-bound protein kinase C activity,[150] slowing the time to onset of depolarization,[151] reducing formation of reactive oxygen species,[152] and suppressing nitric oxide synthase activity.[153] Some or all of these effects in combination may convey some of the neuroprotective effects of hypothermia. Although experimental demonstrations of this are abundant, clinical examples of hypothermia neuroprotection have been elusive.[154–159]

Some of the most meaningful data on CPB temperature and cerebral outcome came from work that had its origins in the late 1980s and early 1990s. It was at that time the judicious use of warm CPB was tried because of its putative myocardial salvaging effects when used with continuous warm cardioplegia.[160–163] However, because CPB was being carried out at higher temperatures than what were considered conventional, the implications on the brain were also studied. Several large studies have been undertaken to elucidate the effects of temperature management on cerebral outcome after cardiac surgery. The Warm Heart Investigators trial,[160] a trial performed at Emory University,[164] and a later trial at Duke University,[165] although having several methodologic differences, had very similar results with respect to neurocognitive outcome[166,167] but some very divergent results with respect to stroke. None of the studies, or studies performed since, demonstrated any neuroprotective effect of hypothermia on neurocognitive outcome after cardiac surgery. However, the Emory trial did demonstrate an apparent injurious effect (as manifest by a worse stroke outcome) of what was most likely mild degrees of hyperthermia during CPB. Neither the Warm Heart Investigators trial nor the Duke trial showed any effect of temperature on stroke per se. These data suggest that active warming to maintain temperatures at (or greater than) 37°C may pose an unnecessary risk of stroke.

Just as hypothermia has some likely protective effects on the brain, hyperthermia, in an opposite and disproportionate fashion, has some injurious effects. Although the studies referred to previously[160,164,165] demonstrated no neuroprotective effect, there is emerging evidence that if some degree of neuroprotection is afforded by hypothermia, it may be negated by the obligatory rewarming period that must ensue.[64] Grigore and colleagues[64] demonstrated in a prospective trial that compared with conventional "fast" rewarming, slower rewarming resulted in a lower incidence of neurocognitive dysfunction 6 weeks after cardiac surgery. These lower rewarming rates led to lower peak cerebral temperatures during rewarming, consistent with past observations that rapid rewarming can lead to an overshoot in cerebral temperature resulting in inadvertent cerebral hyperthermia.[168] By reducing this rewarming rate, it reduces the overshoot in temperature and prevents the negative effects of cerebral hyperthermia. Consistent with the concept that preventing some of the rewarming may be protective was a study by Nathan and coworkers[169] that demonstrated an intermediate-term (3 months) neurocognitive benefit for patients who were maintained between 34°C and 36°C for a prolonged (12 hours) period postoperatively. That trial may have had its beneficial effect by the avoidance of cerebral hyperthermia during rewarming rather than the prolonged hypothermia.[169] However, the 5-year follow-up rate did not show a sustained benefit.[170]

Although there are numerous sites for monitoring temperature during cardiac surgery, several warrant special consideration. One of the lessons learned from the three warm versus cold trials, as well as from other information regarding temperature gradients between the CPB circuit, nasopharynx, and brain,[168] is that it is important to monitor (and use as a target) a temperature site relevant to the organ of interest. If it is the body, a core temperature measured in the bladder, rectum, pulmonary artery, or esophagus is appropriate. However, if the temperature of the brain is desired, barring implantation of a thermistor directly into the brain (which has been done),[171] it is important to look at surrogates of brain temperature. These include nasopharyngeal temperature and tympanic membrane temperature. More invasive surrogates of brain temperature have been obtained using a jugular bulb thermistor.[168,172] Testing these different temperature sites has demonstrated that vast temperature gradients appear across the body and across the brain. It is likely that during periods of rapid flux (eg, during rewarming), these temperature gradients are maximal.

The previous discussion is reflected in the latest guidelines on cardiac surgery–related temperature management that have been jointly published by The Society for Thoracic Surgeons and the Society for Cardiovascular Anesthesiologists.[173]

Mean Arterial Pressure Management During Cardiopulmonary Bypass

The relationship between blood pressure during CPB and CBF is pertinent to understanding whether MAP can be optimized to reduce neurologic injury. Tables 31.4 and 31.5 outline some of the pertinent studies regarding the relationship (or lack thereof) between blood pressure and neurologic outcome. Plochl and associates[174] examined the

TABLE 31.4 Studies Supporting Relationship Between Intraoperative Hypotension and Postoperative Neurologic Dysfunction

First Author	*Year*	*Number of Patients*
Gilman[763]	1965	35
Javid[764]	1969	100
Tufo[765]	1970	100
Lee[766]	1971	71
Stockard[767]	1973	25
Stockard[768]	1974	75
Branthwaite[769]	1975	538
Savageau[770]	1982	227
Gardner[771]	1985	168
Gold[60]	1995	248

TABLE 31.5 Studies Not Supporting Relationship Between Intraoperative Hypotension and Postoperative Neurologic Dysfunction

First Author	*Year*	*Number of Patients*
Kolkka[772]	1980	204
Ellis[773]	1980	30
Sotaniemi[774]	1981	49
Slogoff[775]	1982	204
Govier[175]	1984	67
Nussmeier[58]	1986	182
Fish[776]	1987	100
Townes[777]	1989	90
Slogoff[561]	1990	504
Bashein[778]	1990	86
Stanley[779]	1990	19
Kramer[780]	1994	230
McKhann[781]	1997	456

lower threshold of the autoregulatory curve in dogs whereby further lowering blood pressure would result in inadequate CBF and oxygen delivery during CPB. In that study, the brain became perfusion pressure dependent below 50 mm Hg. The investigators also demonstrated that hypothermia did not shift this threshold leftward. Clinically, the available data suggest that in an otherwise normal patient, CBF during nonpulsatile hypothermic CPB using alpha-stat blood gas management is largely independent of MAP as long as that MAP is within or near the autoregulatory range for the patient (ie, 50–100 mm Hg).[175] Although the autoregulatory curve is traditionally considered a horizontal plateau, this plateau has a slightly positive slope, but this slight upward slope is unlikely to have a significant clinically meaningful effect. For example, Newman and investigators[16] demonstrated that under hypothermic conditions, CBF changes only 0.86 mL/100 g per minute for every 10–mm Hg change in MAP. Although this change (1.78 mL/100 g per min) was greater with normothermia,[176] these changes represent a relatively small fraction of the normal CBF of approximately 50 mL/100 g per minute. Underlying essential hypertension as a comorbidity, however, likely includes a rightward shift in the autoregulatory curve. The degree to which this rightward shift occurs, is not clear, but it would be reasonable to expect that it is at least 10 mm Hg, suggesting that the lower range of autoregulatory blood flow is more likely to be 60 than 50 mm Hg.[177] In addition, diabetes may lead to autoregulatory disturbances that make CBF more pressure passive than nondiabetics.[178,179]

Although the data relating MAP to neurologic and neurocognitive outcome after CABG surgery are inconclusive, most data suggest that MAP during CPB is not the primary predictor of cognitive decline or stroke after cardiac surgery. However, with increasing age, MAP during CPB may play a role in improving cerebral collateral perfusion to regions embolized, improving neurologic and cognitive outcome.[16]

Gold and colleagues[60] added significantly to the understanding of the influence of perfusion pressure on outcome after cardiac surgery in a study of 248 patients randomized to low (50–60 mm Hg) or high (80–100 mm Hg) MAP during CPB. Although a difference was demonstrated in their composite end point of combined adverse cardiac and neurologic outcome (4.8% high vs 12.9% low; $P = .026$), when the individual outcomes were compared, there were similar trends but no statistical differences. A secondary analysis of the same data performed by Hartman and coworkers[37] found interesting interactions among pressure, aortic atheroma, and stroke; patients who were at risk of cerebral embolic stroke (from having severely atheromatous aortas) were more likely to manifest a stroke if MAP was maintained in the lower range than in the higher range. Intuitively, this is logical. Some experimental data in the noncardiac surgical setting suggest that collateral perfusion to penumbral areas of brain suffering from ischemic injury are relatively protected by higher perfusion pressure.[61] Overall, it appears that MAP (in the normal range) has little effect on cognitive outcome, but in those with significant aortic atheroma, it may be prudent to modestly increase blood pressure.

Rather than choosing a specific or fixed (and arguably arbitrary) blood pressure threshold based on the conflicting preceding data, a more prudent approach may be to individualize the blood pressure targets based on the emerging concept of cerebral oximetry–based real-time physiologic feedback. Technologies such as near-infrared spectroscopy-based cerebral oximetry have played an important role in guiding this approach. This may allow for the determination of individual autoregulatory-driven blood pressure targets. For example, Ono and associates recently reported that the magnitude and duration of blood pressure below an individual's autoregulatory threshold was associated with major postoperative morbidity after cardiac surgery.[180] In a similar manner, managing blood pressures below an individual's lower cerebral autoregulatory limits were shown to be associated with an increased incidence of acute kidney injury,[181] as were blood pressures above the upper autoregulatory threshold with delirium.[182] This also highlights the ability of cerebral oximetry to potentially inform surgeons about noncerebral outcomes.

Glucose Management

Hyperglycemia is a common occurrence during the course of cardiac surgery. Administration of cardioplegia containing glucose and stress response–induced alterations in insulin secretion and resistance increase the potential for significant hyperglycemia.[183] Hyperglycemia has been repeatedly demonstrated to impair neurologic outcome after experimental focal and global cerebral ischemia.[184–186] The explanation for this adverse effect likely relates to the effects that hyperglycemia has on anaerobic conversion of glucose to lactate, which ultimately causes intracellular acidosis and impairs intracellular homeostasis and metabolism.[187] A second injurious mechanism relates to an increase in the release of excitotoxic amino acids in response to hyperglycemia in the setting of cerebral ischemia.[185] If hyperglycemia is injurious to the brain, the threshold for making injuries worse appears to be 180 to 200 mg/dL.[188,189]

Despite much experimental data, the role of glucose management on cerebral outcome after clinical CPB is not clear. Although Hindman and others[190] caution about the use of glucose-containing prime for CPB, Metz and Keats[191] did not find a difference in neurologic outcome in patients undergoing CPB with a glucose prime (blood glucose during CPB of 600–800 mg/dL) versus no glucose prime (blood glucose level of 200–300 mg/dL). This finding was supported by Nussmeier and colleagues,[192] who reported that use of a glucose-containing prime was not a risk factor for cerebral injury in nondiabetic or diabetic patients undergoing CABG procedures. In the largest retrospective review, outcome data from 2862 CABG patients showed no association between the intraoperative maximum glucose concentration and major adverse neurologic outcome or in-hospital mortality.[193,194]

The appropriate type of perioperative serum glucose management and whether it adversely affects neurologic outcome in patients undergoing CPB remain unclear. The major difficulty in hyperglycemia treatment is the relative ineffectiveness of insulin therapy. Using excessive amounts of insulin during hypothermic periods may lead to rebound hypoglycemia after CPB. Chaney and coworkers[195] attempted to maintain normoglycemia during cardiac surgery with the use of an insulin protocol and came to the conclusion that even with aggressive insulin treatment, hyperglycemia is often resistant and may actually predispose patients to postoperative hypoglycemia. This concern over potentially increasing adverse effects by exerting tight glycemic controls has reportedly been supported.[196,197] Attempting to mediate injury may predispose patients to additional injury.

Off-Pump Cardiac Surgery

Off-pump coronary artery bypass (OPCAB) surgery is frequently used for the operative treatment of coronary artery disease (see Chapter 20). Although its ability to optimally treat coronary disease (through the demonstration of long-term graft patency) has not yet been shown in a long-term, prospective, randomized, controlled fashion, it is clear that OPCAB and similar operations (eg, minimally invasive direct coronary artery bypass) will continue to be mainstays of cardiac surgery, although in an evolving fashion. Their impact on adverse cerebral outcomes after cardiac surgery has been variably reported.[198]

Although early data suggested less cognitive decline after OPCAB procedures, most studies have not seen it eliminated altogether. The reasons for this are unclear but likely reflect the complex pathophysiology involved. For example, if inflammatory processes play a role in initiating or propagating cerebral injury, OPCAB, with its continued use of sternotomy, heparin administration, and wide hemodynamic swings, all of which may contribute to a stress and inflammatory response, may be a significant reason why cognitive dysfunction is still seen. Ascending aortic manipulation, with its ensuing particulate embolization, is also still commonly used.

The results of the largest OPCAB study by Van Dijk and associates[199] to examine cognitive dysfunction showed that although there was a reduction in cognitive decline in the early months after surgery, at 1 year,[200] and even at 5 years,[170] there were no differences between groups. In a subset of patients from this study, jugular bulb saturation was examined. More desaturation (indicative of ischemia risk to the

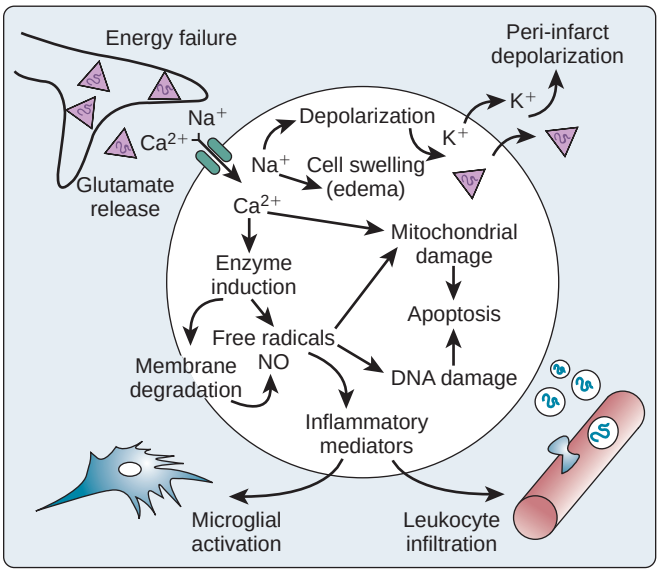


Fig. 31.6 Cerebral ischemic cascade. A simplified overview of central nervous system events that occur after energy failure in the ischemic brain. *(From Dirnagl U, Iadecola C, Moskowitz M. Pathobiology of ischemic stroke: an integrated review.* Trends Neurosci *1999;22:391–397.)*

brain) was seen in the OPCAB group. This may have been due to the low cardiac output that can be seen during manipulation of the heart, as well as jugular venous hypertension.[201] The effects of OPCAB on stroke risk have not been sufficiently analyzed, but one meta-analysis showed no beneficial effect on the incidence of stroke.[198]

Pharmacologic Neuroprotection

In addition to the improvements in CPB technology, knowledge of the molecular workings of the brain has improved significantly, revealing potential pharmacologic neuroprotective targets. The oversimplified concept that depletion of high-energy phosphates and destruction of brain tissue rapidly follow ischemia has been replaced by a considerably more complex temporal, topographic, and biochemical picture. Advanced imaging techniques have discovered spatial gradations of residual CBF in the downstream territory of an occluded cerebral vessel producing an ischemic penumbra, where CBF is critically reduced but still sufficient to prevent immediate cell death. There is a marked difference in the temporal association between the ischemic insult and eventual cell death, resulting in a therapeutic window in which intervention (particularly pharmacologic) may attenuate infarct size. This window differs between the profoundly ischemic core and the penumbra. In the ischemic core, restoration of oxygen and glucose supplies is essential where high-energy phosphates have been severely depleted. In contrast, in the penumbra, the decrease in oxygen and glucose delivery is insufficient to kill cells directly. In these regions, pharmacologic agents with little or no ability to modify CBF have been shown experimentally to effectively reduce cerebral infarct volume, even if administered after the onset of permanent focal ischemia.

The central nervous system ischemic cascade (Fig. 31.6) is triggered by reductions in CBF, globally or regionally, to the point at which the demands of cerebral metabolism can no longer be met.[202] This depletion in cerebral energy stores leads to membrane ionic pump failure, resulting in a number of injurious events mediated by the influx of sodium, the opening of voltage-dependent calcium gates, a release of stored intracellular calcium, and overall membrane depolarization. Membrane depolarization results in the release of excitatory amino acids (eg, glutamate, aspartate), with subsequent dramatic increases in intracellular calcium. This increase in cytoplasmic calcium propagates the cascade through the activation of a number of calcium-dependent enzymes, including endonucleases, nitric oxide synthase, various proteases, protein kinases, and phospholipases. If left unabated, these enzymes will result in neuronal death.

Although some of these events are potentially reversible if reperfusion is quickly reestablished, reperfusion itself initiates a number of other destructive pathways. The reestablishment of oxygen delivery provides substrate for the production of reactive oxygen species, so-called free radicals. Reperfusion initiates a number of other damaging extracellular events, including BBB breakdown, endothelial swelling, and localized thrombosis that together may culminate in microvascular occlusion and further ischemia. Each of these pathways in the ischemic cascade represents discrete groups of potential targets for neuroprotection. The ischemic cascade has formed the basis for the initiation of pharmacologic neuroprotective strategies in the setting of overt stroke and of cardiac surgery–related cerebral injury.

No pharmacologic therapies have been approved by the US Food and Drug Administration or foreign regulatory agencies for the prevention or treatment of cardiac surgery–associated cerebral injury, despite numerous previous investigations of specific pharmacologic agents in this setting (Table 31.6). The failure to discern any single compound that might protect the brain is not unique to cardiac surgery. With the exception of thrombolysis, there are no other therapies in the general medical field either.[203] However, understanding these failures is as important as any successes as it can refocus attention to pathways incompletely investigated.

The following discussion addresses many of the principal drugs that have been investigated in the setting of cardiac surgery.

TABLE 31.6 Agents Studied as Pharmacologic Neuroprotectants During Cardiac Surgery

Agent	*Study Reference*
Thiopental	57
Propofol	200
Acadesine	205
Aprotinin	209, 210
Nimodipine	220–222
GM_1 ganglioside	223
Dextromethorphan	225
Remacemide	225
Lidocaine	230
β-Blockers	232
Pegorgotein	235
C5 complement inhibitor (pexelizumab)	237
Lexiphant (platelet-activating factor antagonist)	239
Clomethiazole	244
Ketamine	251

Thiopental

Thiopental was one of the first agents investigated as a potential neuroprotective agent for patients undergoing cardiac surgery. In a study by Nussmeier and colleagues,[58] thiopental was administered (until electroencephalographic [EEG] isoelectricity was obtained) before cannulation and continued until separation from CPB. In this study, neurologic complications on postoperative day 10 were significantly reduced in the thiopental group versus controls. Based on the encouraging results of this trial, high-dose thiopental was frequently used for valvular and other open ventricular procedures. The proposed mechanism of this effect related to the suppressive effects of barbiturates on cerebral metabolism. This mechanism, along with experimental data reporting the beneficial effects of the barbiturates,[204] made it a logical choice for cardiac surgery. However, results of additional investigations of the use of thiopental were not as positive. A study by Pascoe and coworkers[205] and one by Zaidan and coworkers[206] failed to support a beneficial effect of thiopental on neurologic outcome after cardiac surgery. These negative trials and the side effects of prolonged sedation with barbiturates served to quell the optimism for barbiturates. Retrospectively examining the initial Nussmeier study,

the beneficial effects of the thiopental might not have been related to a direct neuroprotective effect but to an indirect effect on reducing emboli. The well-known cerebral vasoconstricting effects of thiopental (matching CBF with a barbiturate-induced reduction in $CMRO_2$) may have resulted in a reduction in embolic load to the brain during CPB and as a result, a beneficial effect on neurologic outcome. It has subsequently been shown that isoelectricity itself is not necessary to incur a neuroprotective benefit from barbiturates.[207] Evaluations of sub-isoelectric doses of thiopental have not been performed.

Propofol

Propofol has effects similar to those of thiopental on $CMRO_2$ and CBF and has some antioxidant and calcium channel antagonist properties.[208] Along with supportive data from experimental cerebral ischemia studies,[209–211] propofol has been evaluated as a neuroprotectant in the setting of cardiac surgery. A prospective, randomized clinical trial was conducted to determine whether propofol-induced EEG burst suppression would reduce the incidence or severity of cerebral injury during valvular surgery.[212] In a randomized trial ($N = 215$) of burst-suppression doses of propofol, there was no beneficial effect on cognitive outcome at 2 months. The investigators concluded that EEG burst-suppression doses of propofol provided no neuroprotection during valvular cardiac surgery. No other studies in nonvalve cardiac surgery have assessed the effects of propofol on the brain.

Acadesine

The adenosine-regulating agent acadesine was studied in the early 1990s with the aim of improving myocardial outcome; stroke was examined as a secondary outcome.[213] Compared with placebo, high- and low-dose infusions of acadesine resulted in a lower stroke rate ($P = .016$). Other adenosine-like agents also have provided neuroprotection in preclinical experimental settings.[214,215] Despite this positive, albeit indirect, clinical data and supportive experimental data, no further clinical neuroprotection indication for acadesine has been pursued.[216] However, studies of this drug have recently been renewed, though they have not had any beneficial effect on neurologic outcome.[217]

Aprotinin

In a large, multicenter trial of aprotinin for primary or redo CABG and valvular surgery evaluating its blood loss–reducing effects, the high-dose aprotinin group also had a lower stroke rate compared with placebo ($P = .032$).[218,219] Similarly, Frumento and investigators[220] retrospectively examined patients at high risk for stroke (because of the presence of significant aortic atheroma), and those who received aprotinin had a significantly lower stroke rate. In a small ($N = 36$) study examining the effect of aprotinin on cognitive deficit after CABG surgery, the incidence of cognitive deficit was reduced in the aprotinin group (58% aprotinin vs 94% placebo; $P = .01$).[221] However, the high rate in the placebo group, the small size of the study, and methodologic concerns limit the applicability of these results to broader populations.[222] Animal investigations in the setting of cerebral ischemia failed to show any direct benefit on functional or neurohistologic outcome after cerebral ischemia.[223]

There has been considerable investigation of the potential mechanism for aprotinin-derived neuroprotection. Initial enthusiasm focused on its antiinflammatory effects potentially preventing some of the adverse inflammatory sequelae of cerebral ischemia. However, aprotinin may have beneficial effects independent of any direct neuroprotective effect through an indirect effect of modulating cerebral emboli. Brooker and colleagues[41] identified the cardiotomy suction as a major source of cerebral emboli during CPB. By extrapolation, if a drug reduces the amount of particulate-containing blood returning from the operative field to the cardiotomy reservoir (by decreasing overall blood loss), cerebral emboli and the resulting neurologic consequences may also be decreased.

More recently, the potential adverse effects of aprotinin were reported by Mangano and coworkers in their observational study of 4374 patients.[224] In that study, patients having received aprotinin had a significantly higher rate of cerebrovascular complications ($P < .001$). The Blood Conservation Using Antifibrinolytics: A Randomized Trial (BART) reported a significant reduction in bleeding but an overall mortality risk with aprotinin compared with other antifibrinolytics.[225] However, there were no differences in the stroke rate with aprotinin compared with tranexamic acid (2.5% aprotinin vs 3.7% tranexamic acid; odds ratio [OR], 0.78; 95% confidence interval [CI], 0.45–1.35). Although the Mangano study and the BART trial contributed to the market withdrawal of aprotinin, the relevance of the potential neurologic effects of kallikrein inhibition remains. There are at least two other highly potent kallikrein inhibitors (CU-2010 and ecallantide) that have undergone clinical development, but their neurologic effects are unknown.[226–228]

Nimodipine

Calcium plays a central role in propagating cerebral ischemic injury. For this reason, as well as a demonstrated beneficial effect of the calcium channel blocker nimodipine in subarachnoid hemorrhage and experimental cerebral ischemia, a randomized, double-blind, placebo-controlled, single-center trial was undertaken to assess the effect of nimodipine on neurologic, neuro-ophthalmologic, and neuropsychologic outcomes after valvular surgery.[229–231] The trial was not completed after safety concerns regarding an increased bleeding and death rate in the nimodipine group prompted an external review board to suspend the study after enrolling 150 of 400 patients planned to be studied. There was also no neuropsychologic deficit difference between the placebo or nimodipine groups at this interim review. As a result, the true effect of this drug or similar calcium trial blockers may never be fully known in this setting.

GM_1 Ganglioside

The monosialoganglioside GM_1 ganglioside has been investigated as a potential neuroprotectant during cardiac surgery.[232] In addition to the potential beneficial effects of this type of compound on preserving neuronal membranes, some data suggest that it has a potential beneficial effect on reducing excitatory amino acid transmission.[233] In a preliminary (but underpowered) cardiac surgery study, there was no beneficial effect demonstrated. However, the study investigators used this pilot trial to describe useful statistical methodology needed to measure differences in neurocognitive outcome, thereby constituting a template for later trials. This trial highlights one of the biggest difficulties in this investigative field—the interpretation of negative but underpowered studies.

Dextromethorphan

The *N*-methyl-D-aspartate (NMDA) receptor plays a major role in cerebral ischemic injury.[202] Although human stroke trials have been limited by distressing psychomimetic side effects, a wealth of experimental data point to NMDA-receptor antagonists as being robust neuroprotective agents with a potential role in CPB-associated cerebral injury.[234] Dextromethorphan, known for its antitussive activity, has some nonspecific NMDA antagonistic properties. A small ($N = 12$) pilot study examined dextromethorphan in the setting of pediatric cardiac surgery using EEG and MRI end points to determine a difference between treatment groups, but no difference was found, probably because of the small size of the study.[235] There have been no other studies examining NMDA-receptor antagonism in the setting of pediatric cardiac surgery.

Remacemide

A second NMDA-receptor antagonist that has been evaluated for neuroprotection during CABG surgery is remacemide. In a well-designed and well-executed study by Arrowsmith and coworkers,[234] remacemide was given orally for 4 days before CABG. A neurocognitive battery was performed 1 week before and 8 weeks after CABG. A deficit was defined as a decrease in 1 standard deviation in 2 or more of the 12 tests within the neurocognitive battery. The patients were evaluated for their learning ability by subtracting the postoperative neurocognitive score

from the preoperative score (formulating a Z score). Although there was no difference between groups with respect to the dichotomous outcome of cognitive deficit (P = .6), examination of a continuous measure of learning ability showed there was a beneficial cognitive effect in the patients who received remacemide (P = .028). Despite these apparently beneficial results, because of the length of time that it took to perform this single-center trial, initial nonbeneficial preliminary results, and a prolonged period of data analysis and review for publication, this drug was not further pursued for this indication. It has highlighted, however, the potential utility of this class of drugs for this indication and ongoing investigations examining other NMDA-receptor antagonists continue.[236–238]

Lidocaine

Intravenous lidocaine, because of its properties as a sodium channel blocking agent and potential antiinflammatory effects, has been investigated as a neuroprotectant in cardiac surgery. In a study of 55 patients undergoing valvular surgery, a lidocaine infusion (in an antiarrhythmic dose of 1 mg/min) was begun preinduction and maintained for 48 hours after surgery.[239] Neurocognitive testing was performed preoperatively and 8 days, 2 months, and 6 months postoperatively. Compared with placebo, neurocognitive outcome 8 days after surgery was significantly better in the lidocaine group (P = .025). However, a much larger double-blind, randomized trial in cardiac surgery failed to replicate the finding. Mathew and associates,[240] in a study of 241 patients, found no difference in the incidence of cognitive loss with the perioperative administration of lidocaine. Interestingly, they found that in patients with diabetes, and in those receiving high doses of lidocaine, outcome was worse and may have confounded any potential benefit in the overall cohort receiving it. Lidocaine cannot be recommended at this time as a clinical neuroprotective agent in cardiac surgery, but it continues to be investigated.

β-Blockers

Although the use of β-blockers in patients with cardiac disease has been predominantly directed toward the prevention of adverse myocardial events, in a study of neurologic outcomes after cardiac surgery, β-blockers have been demonstrated to have mixed effects in neurologic outcomes. In a retrospective study of almost 3000 patients, stroke and encephalopathy were studied.[241] Patients receiving β-blocker therapy had a significantly lower incidence of neurologic deficit versus those not receiving β-blockers. Although the reasons for this potential benefit are not clear, there are several potential reasons why β-blockers may be efficacious, including the modulation of cerebrovascular tone and CPB-related inflammatory events. Support for a potential neuroprotective effect from β-blockers has come from a study of carvedilol, which is known to have mixed adrenergic antagonist effects, as well as acting as an antioxidant and inhibitor of apoptosis[242] (see Chapter 11). Any potential benefit to β-blocker therapy needs to be tempered by recent data in the non–cardiac surgery population that demonstrated neurologic harm. The POISE trial, although demonstrating a reduction in MI, demonstrated an increase in stroke rate in patients randomized to receive metoprolol perioperatively.[243] It is unclear how this information pertains to the cardiac surgical population.

Pegorgotein

The generation of reactive oxygen species is a well-described pathophysiologic mechanism of ischemic reperfusion injury. Combined with the whole-body inflammatory response associated with CPB and its own generation of reactive oxygen species, this mechanism has opened the field of neuroprotection and cardiac surgery to antioxidant therapies. Superoxide dismutase is involved in the catabolism of free radicals, and its mimetics have had beneficial results in the setting of experimental ischemia. Pegorgotein, a monomethyoxypolyethyleneglycol covalently linked to superoxide dismutase, is protective against reperfusion-mediated cardiac and neuronal injury in animal studies.[244] One study was initiated to examine whether pegorgotein would be associated with a reduced number of neurocognitive deficits after cardiac surgery.[245] In this study of 67 patients undergoing primary elective CABG surgery (n = 22 to 23 in each of three groups: placebo, 200 IU/kg of pegorgotein, or 5000 IU/kg of pegorgotein), no difference in neurocognitive outcome was found.

C5 Complement Inhibitor: Pexelizumab

The activation of complement is central to the inflammatory response seen as a response to CPB.[246] In a small (N = 18) study using a simple assessment of cognitive function, patients receiving an inhibitor to C5 (h5G1.1-scFv, pexelizumab), demonstrated fewer visuospatial deficits at hospital discharge.[247] Additional large-scale (phase III) investigations of this compound to more adequately delineate any potential longer-term neuroprotective effects from this drug in this setting have been performed. Mathew and collegues[247] assessed pexelizumab in a 914-patient study aimed at evaluating its effect on myocardial outcome and mortality. A secondary end point of neurocognitive outcome demonstrated that pexelizumab, although having no effect on global measures of cognition, appeared to have a benefit with respect to the visuospatial domain.

Platelet-Activating Factor Antagonist: Lexiphant

Platelet-activating factor antagonists have demonstrated neuroprotective effects in experimental models of cerebral ischemia.[248] Platelet-activating factor is thought to modulate postischemic injury by the release of cerebral cellular lipids and free fatty acids that may result in cellular injury and cerebral edema.[249] In an investigation of 150 cardiac surgery patients receiving placebo or one of two different doses of lexiphant, no protective effects were found in neurocognitive outcome 3 months after cardiac surgery. This study was significantly underpowered, which is a recurring and troublesome feature of many studies in this field.[250]

Clomethiazole

Clomethiazole, which enhances γ-aminobutyric acid (GABA) receptor activity, has been evaluated in CABG surgery. GABA has repeatedly been shown to be an important neuroprotective target in focal and global experimental ischemia.[251,252] However, in a relatively large, well-designed, and well-conducted study, it failed to decrease neurocognitive dysfunction in patients after cardiac surgery.[253]

Steroids

Corticosteroids have long been considered as potential cerebroprotective agents in part because of their ability to reduce the inflammatory response. Inflammation is considered an important factor in propagating ischemia-mediated brain injury.[254,255] However, with the exception of spinal cord injury,[256] steroids have never been demonstrated to possess any significant clinical neuroprotective properties. Furthermore, the administration of steroids has actually worsened cerebral outcome in a large trial (N = 10,000). The Corticosteroid Randomization after Significant Head Injury (CRASH) trial demonstrated an increased relative risk (RR) of death (RR, 1.18; 95% CI, 1.09–1.27; P = .0001) in those receiving high-dose steroids within 8 hours of injury.[257,258] Part of their lack of effect may result from the hyperglycemia that generally follows their administration. Hyperglycemia in animal models and several human studies of cerebral injury has been associated with worsened neurologic outcome.[188,259] The use of high-dose dexamethasone (1 mg/kg) in cardiac surgery was recently studied by Dieleman and colleagues.[260] In the largest ever trial of a potentially neuroprotective agent (though the trial was powered to a composite end point that included other outcomes in addition to neurologic outcome) in cardiac surgery, they were unable to show any beneficial effort in stroke, cognitive outcome, or delirium.[261,262] The administration of steroids with the intent of conferring some degree of neuroprotection during cardiac surgery cannot be recommended.

Ketamine

The neuroprotective effects of S(+D)-ketamine, a frequently used anesthetic that is also an NMDA-receptor antagonist, was evaluated in a

small ($N = 106$) study enrolling cardiac surgery patients.[263] The incidence of neurocognitive dysfunction 10 weeks after surgery trended toward being lower in the ketamine group (20% for ketamine vs 25% for controls; $P = .54$), but because the study was underpowered, it was not a significant change. There has been renewed interest in ketamine for its potential to reduce the incidence of delirium.[264] This drug awaits further large trials to determine its potential benefit. Although there is some experimental evidence supporting its role as a neuroprotectant, there is insufficient clinical evidence to support its use for this specific indication.[265]

Acute Kidney Injury

Despite concern for almost half a century over the seriousness of renal dysfunction as a complication after cardiac surgery,[266–269] acute kidney injury (AKI) persists as a prevalent and important predictor of early death.[270] Even during procedures where there is no evidence of AKI based on serum creatinine levels, more subtle markers often demonstrate renal tubular injury.[271] Increasing degrees of AKI after cardiac surgery are associated with poorer outcome, greater costs, and more short- and long-term resource utilization.[267,272–274] The degree of AKI also predicts poorer long-term survival in patients returning home.[275–277] Notably, long-term outcome is just as strongly linked to the success of renal recovery as the magnitude of the injury, incomplete return of renal function occurring in up to a third of the patients.[275–277] While some of the harm associated with AKI simply reflects its accompaniment of other serious complications as an "epiphenomenon" (eg, sepsis), there is also compelling evidence that AKI itself contributes to adverse outcome.[278–283] Accumulation of "uremic toxins" beyond creatinine has widespread adverse effects on most organ systems,[278,279,284] and where it is best studied in chronic renal disease, inadequate clearance of uremic toxins adversely affects survival.[285]

Even when postoperative dialysis is avoided, the strong relationship of AKI with adverse outcome continues to fuel the search for therapies to protect the kidney. Although practicing avoidance of the numerous recognized renal insults is a well-established approach to reducing AKI rates, the search for renoprotective strategies has otherwise been extremely disappointing. More recently, lack of progress has fueled a strategic reexamination of AKI with agreement that, compared to other conditions such as acute myocardial infarction (AMI) where advances have been made, progress in AKI therapy has been hampered by its obligate delay in diagnosis (serum creatinine accumulation takes 48 to 72 hours) and poor agreement on its definition.[286,287] Thus, strategic policies have reframed AKI along the lines of AMI, viewing it as a condition with threshold criteria, whose treatment demands prompt diagnosis and acute intervention.[286] On a positive note, consensus serum creatinine thresholds are already available to diagnose AKI and are becoming widely embraced, while tools allowing earlier diagnosis of AKI—equivalent to the ST-segment, creatine kinase MB (CK-MB), and troponin tests to diagnose AMI—may be clinically available soon.[286–290]

Clinical Course, Incidence, and Significance

The specific surgical procedure is important when considering postoperative AKI. The incidence varies widely by operation (Fig. 31.7), each

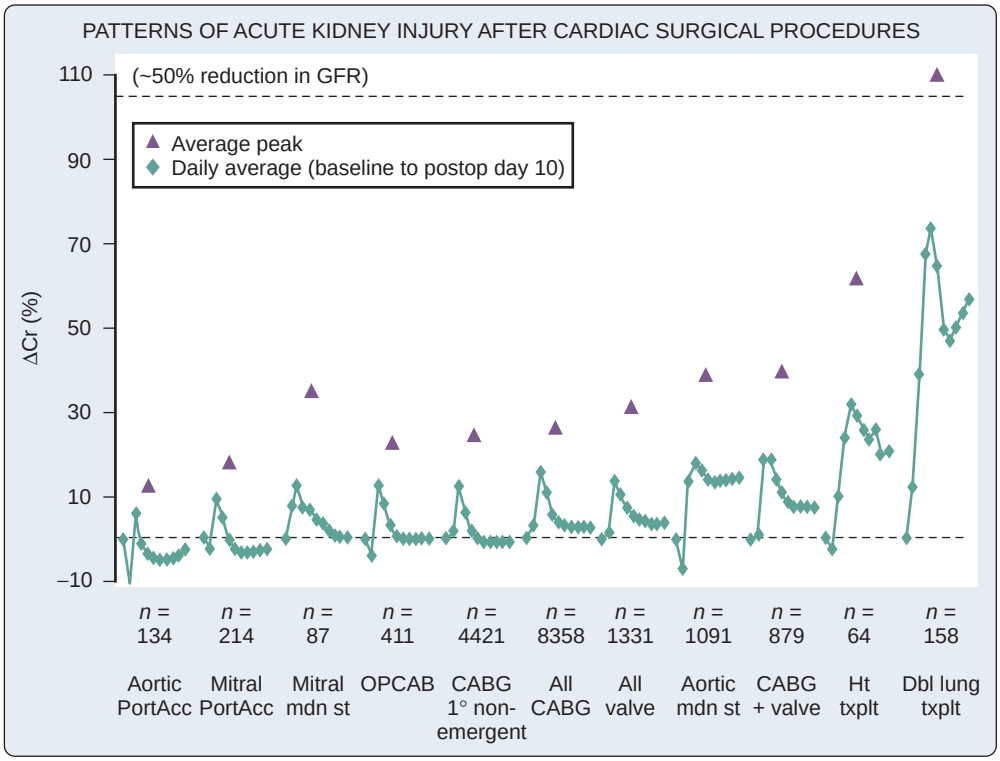


Fig. 31.7 Different cardiac surgical procedures are associated with characteristic patterns of acute kidney injury. Average daily *(diamonds)* and unadjusted average peak *(triangles)* serum creatinine values are presented. *aortic mdn st,* Median sternotomy aortic valve replacement; *aortic PortAcc,* minimally invasive parasternotomy aortic valve replacement; *CABG,* coronary artery bypass graft surgery; *dbl lung txplt,* double lung transplantation; *GFR,* glomerular filtration rate; *ht txplt,* heart transplantation; *mdn st,* median sternotomy mitral valve surgery; *1°,* nonemergent; *%ΔCr,* peak fractional serum creatinine rise; *OPCAB,* off-pump coronary artery bypass surgery; *PortAcc,* port access mitral valve surgery; *postop,* postoperative. *(Used with permission from Stafford-Smith M, Patel UD, Phillips-Bute BG, et al. Acute kidney injury and chronic kidney disease after cardiac surgery.* Adv Chronic Kidney Dis *2008;15:257–277.)*

cardiac surgery having its own characteristic renal insult and pattern of serum creatinine change. For example, creatinine often drops immediately after CABG surgery (presumably as a result of hemodilution), but then rises, typically peaking on postoperative day 2, then returning toward or even below baseline values in subsequent days. Up to 30% of CABG patients sustain sufficient insult to meet threshold AKI criteria (eg, RIFLE–injury[286]/AKIN criteria[291]: a creatinine rise > 0.3 mg/dL or 50% within the first 48 hours).[267,272,292,293] The reported incidence thus varies according to the definition of kidney injury, as well as by the institution reporting their results (Fig. 31.8). The previously mentioned RIFLE and AKIN criteria for AKI are consistent with the definitions that adhere to the KDIGO (Kidney Disease Improving Global Outcomes) criteria that also includes a urine volume definition (ie, urine volume < 0.5 mL/kg per hour).[294–296] Even among patients with similar risk factors undergoing the same procedure, however, current models poorly predict the likelihood of AKI. AKI has also been linked to accelerated long-term renal decline that may lead to end-stage disease requiring chronic dialysis.[297–302]

Of the 1% to 3% of patients sustaining AKI severe enough to require dialysis following CABG, up to 60% will die before being discharged from the hospital, and many of the survivors will require continuing dialysis or be left with chronic kidney disease.[303] Up to 20% of individuals presenting for nonemergent CABG surgery have chronic kidney disease.[304,305] While dialysis after cardiac surgery is always important, when this is associated with poor preoperative renal function, postoperative mortality rates more closely resemble those of similar patients who avoid dialysis.[306] The rate of "renal recovery" after AKI is also difficult to predict, but emerging evidence suggests it is highly associated with outcome and apparently independent of AKI.[276,307]

Risk Factors and Surgery-Related Acute Kidney Injury Pathophysiology

Numerous studies have characterized risk factors for nephropathy after cardiac surgery (Fig. 31.9).[308] Despite an increasing understanding of perioperative renal dysfunction, known risk factors account for only one-third of the observed variability in creatinine rise after cardiac surgery. Procedure-related risk factors include emergent and redo operations,[309,310] valvular procedures,[309,311,312] and operations requiring a period of circulatory arrest[310] or extended durations of CPB.[267,272,313–315] Infection and sepsis,[310,313,316] atrial fibrillation,[317] and indicators of LCOS, including need for inotropic agents and insertion of an intraaortic balloon pump during surgery, also have been associated with renal impairment.[272,309,310,313,318]

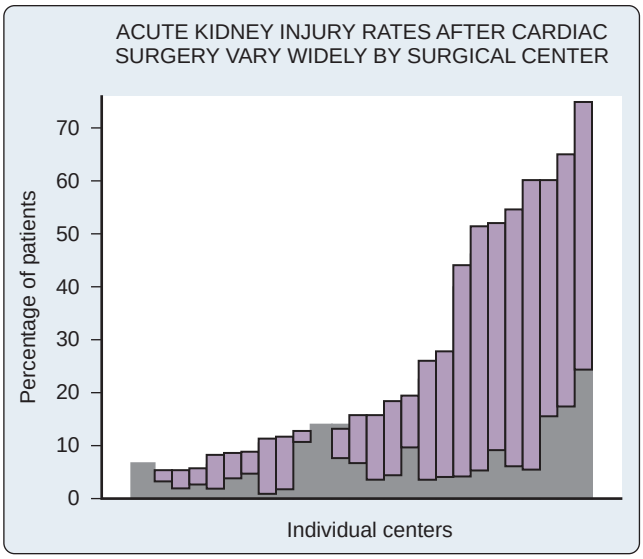


Fig. 31.8 Even after adjusting for case complexity, among institutions there is wide variation in acute kidney injury (*shaded bar* represents risk, injury, or failure according to the ADQI-RIFLE system)[286] and dialysis *(dark bar)* rates, as exemplified by Heringlake and colleagues[366] in a study of 2003 data from 26 German heart centers. *(Modified with permission from Heringlake M, Knappe M, Vargas Hein O, et al. Renal dysfunction according to the ADQI-RIFLE system and clinical practice patterns after cardiac surgery in Germany.* Minerva Anestesiol *2006;72:645–654.)*

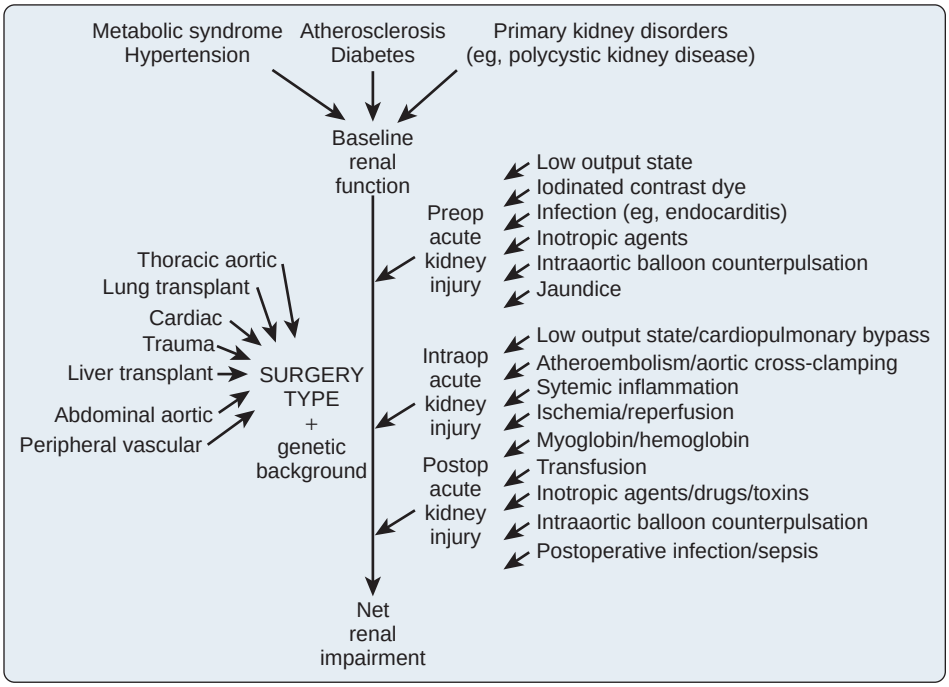


Fig. 31.9 Numerous sources of kidney insult play a variably important role for each patient during the perioperative period. *(Used with permission and modified from Stafford-Smith M, Patel UD, Phillips-Bute BG, et al. Acute kidney injury and chronic kidney disease after cardiac surgery.* Adv Chronic Kidney Dis *2008;15:257–277.)*

Preoperative demographic risk factors identified include advanced age,[267,272,310,312,318,319] increased body weight,[267] African American ethnicity,[267,320] hypertension and wide pulse pressure,[309,321,322] baseline anemia,[323] peripheral or carotid atherosclerotic disease,[267,309] diabetes, preoperative hyperglycemia, and/or elevated hemoglobin A1c in nondiabetics,[267,272,321,324,325] reduced left ventricular (LV) function, and obstructive pulmonary disease.[267,309,310,313,314] Interestingly, baseline chronic kidney disease is not a risk factor for AKI, but since even small amounts of additional renal impairment may lead to dialysis when severe renal disease is present at baseline, these individuals are at greatest risk for dialysis.

A genetic predisposition to AKI exists and explains more variation in AKI after cardiac surgery than conventional clinical risk factors alone.[326,327] A handful of candidate polymorphisms known to affect inflammation and vasoconstriction have been studied, and several, alone or in combination, demonstrate strong associations with AKI following cardiac surgery.[326,327] For example, copossession of the IL-6-572C and angiotensinogen 842C polymorphisms in Caucasians (6% of patients) predicts an approximately fourfold greater than average creatinine rise (121%) after CABG.[327] These data add credence to the idea that much of the variability in postoperative AKI may result from genetic influences[327] and suggest that wider genetic profiling and future whole genome studies may lead to useful preoperative risk prediction tools and may even provide a roadmap in the search for useful renoprotective strategies.

The development of AKI in an individual patient after cardiac surgery reflects the actual net injury from numerous potential perioperative sources known to be capable of inflicting insult (see Fig. 31.9). Many markers of renal risk hint at causes of perioperative AKI in individuals. Thus, perioperative AKI contrasts with single-insult renal injuries such as contrast nephropathy. Nonetheless, a common pathway mediates the consequences of AKI, including tubular and vascular cell dysfunction, necrosis, and apoptosis.[328] Although details of the trigger mechanisms for this reflexive component of AKI remain elusive, there is better understanding of the direct renal consequences of some insults specific to cardiac surgery. Although the physiology of perioperative renal recovery is as yet less studied, emerging data suggest this is also likely to be important. A brief overview of AKI pathophysiology focused on cardiac surgery is pertinent.

Using intraoperative epiaortic scanning, Davila-Roman and coworkers found ascending aortic atheroma burden correlates with AKI.[329] Sreeram and associates noted that postoperative AKI correlates with arterial emboli load.[330] Conlon and colleagues, however, did not see a relationship between renal artery stenosis and AKI.[331] Renal atheroembolism is sometimes a dominant source of cardiac surgical AKI[332] and often observed at autopsy.[30] Filter devices deployed before cross-clamp removal often capture macroscopic atheroemboli.[100] Plaque disruption caused by balloon pump counterpulsation is also likely a contributor to AKI.[310,333] Antiembolism strategies have been widely adopted into the conduct of cardiac surgery,[334–337] but evidence that they lead to decreased incidence of AKI is lacking. One randomized filter device trial in a post hoc analysis found less incidence of AKI in higher-risk patients.[101]

Other emboli sources may be relevant to AKI in some circumstances. Fat droplets, particulates, and bubbles are common during cardiac surgery. Renal embolic infarcts from any source are pizza wedge–shaped and involve adjacent cortex and medulla, highlighting the vascular arrangement and lack of redundancy of kidney perfusion. Incriminated particulates other than atheroma include thrombus, platelet fibrin debris, septic vegetations, and even normal vessel wall.[100,338] One-third of patients who have undergone endocarditis surgery suffer significant AKI.[339] Although sternal marrow lipid droplet reinfusion with red cell salvage is common[340] and may have effects on renal cortical blood flow,[341] its importance is unknown. Air bubbles have rarely been associated with AKI.[342] Surgical field insufflation of CO_2 reduces intravascular emboli,[343] but whether this reduces AKI rates has not been assessed.

Many cardiac surgery patients meet the criteria for systemic inflammatory response syndrome (SIRS) in the early postoperative period. AKI is a major consequence of SIRS.[344] Sepsis is a strong predictor of postoperative AKI, likely mediated through the effects of renal inflammation.[286,310,313,345] A surge of circulating proinflammatory cytokines is typical after trauma, major surgery, and CPB.[346] Local cytokine release also occurs in response to ischemia-reperfusion–mediated renal nuclear factor-κB (NF-κB) activation.[347] Finally, impaired renal filtration affects the course of any inflammatory response by influencing the primary clearance mechanism for many cytokines (eg, IL-6, IL-1β, tumor necrosis factor-α).[348]

Many elements of cardiac surgery contribute to the risk of hypoperfusion and ischemia-reperfusion–mediated AKI. Embolism, LCOS, and exogenous catecholamines can all contribute,[310,330,349] leading to cellular high-energy phosphate depletion, calcium accumulation, oxygen free radical generation, local leukocyte activation, and NF-κB activation.[350] These changes can cause apoptotic cell death through caspase activation (executioner enzymes) and/or tissue necrosis.[351] Apoptosis instigates more local inflammation and injury,[352,353] and, experimentally, inhibition of caspase or NF-κB attenuates ischemia-reperfusion AKI.

Femoral artery cannulation can be complicated by leg ischemia and has been blamed for myoglobinuric AKI.[354] Although statins can cause myopathy, these agents have not been associated with increased renal risk in vascular and major non–cardiac surgery patients.[355] Myoglobin and hemoglobin avidly bind nitric oxide and are believed to cause AKI through vasoconstrictor effects but also direct cytotoxicity and frank tubular obstruction.[356]

Withdrawal of the antifibrinolytic agent aprotinin from the market eliminates one concern of perioperative renal toxicity for cardiac surgery patients.[357] In contrast, the lysine analogue antifibrinolytics ε aminocaproic acid and tranexamic acid can raise concern because of their renal effects of small protein spillage into the urine (tubular proteinuria).[358,359] A single retrospective analysis of 1502 patients involving the introduction of ε aminocaproic acid therapy did not show an increase in AKI.[304] While tubular proteinuria often heralds tubular injury, with lysine analogue antifibrinolytics this is completely resolved within 15 minutes after the agent is discontinued.[358,359]

Other perioperative nephrotoxins include some antibiotics,[360] α-adrenergic agonist agents,[361] cyclosporine,[362] and nonsteroidal antiinflammatory agents.[363] However, the net effect on post–cardiac surgery AKI of α_1-mediated vasoconstriction and dopaminergic and α_2-mediated renal vasodilation with hemodynamic compromise is unknown. Although experimentally, even short periods of high-dose norepinephrine cause long-lasting AKI,[364] and catecholamines during cardiac surgery also predict AKI,[310,365] disentangling cause and association for these agents is problematic as they are rarely used in the absence of other major risk factors (eg, LCOS). Interestingly, in a survey of German intensive care units (ICUs) involving more than 29,000 cardiac surgery patients, centers with worse AKI rates were more likely to prefer dopamine over other inotropes and avoid norepinephrine as a vasopressor.[366]

Intravenous contrast is known to have nephrotoxic effects. Contrast-associated nephropathy is usually heralded by a significant rise in serum creatinine within 5 days after intravascular contrast injection and occurs in approximately 2% to 7% of patients.[367,368] The pathophysiology primarily results from vasoconstriction and direct renal tubular cell injury. Those at greatest risk typically have preprocedure renal impairment.[369] In a study of 27 CABG patients, Garwood and associates[370] found indicators of tubular injury to be elevated in those presenting for surgery within 5 days of cardiac catheterization relative to those further separated from an intravenous contrast injection. Use of low-osmolar contrast media and aggressive prestudy hydration have significantly reduced the risk of contrast-associated nephropathy for patients with diabetic nephropathy and other causes of chronic renal disease.

Considerable evidence has emerged with respect to the potential for colloid solutions, particularly hydroxyethyl starches, to contribute

BOX 31.2 CONTRIBUTORS TO RENAL INJURY DURING CARDIOPULMONARY BYPASS

- Emboli
- Renal ischemia
- Reperfusion injury
- Pigments
- Contrast agents
- Hydroxyethyl starches

to AKI in a number of settings (Box 31.2).[371] Cardiac surgery is no different and several studies have provided evidence suggesting that hydroxyethyl starches are one of the factors associated with renal dysfunction. For example, in a recent prospective study of 6478 cardiac surgery patients, use of a hydroxyethyl starch 134/0.4 was associated with an increased requirement for renal replacement therapy (OR, 1.46; 95% CI, 1.09–1.97).[372] When added to additional data from a meta-analysis of 15 randomized trials that evaluated hydroxyethyl starch administration in the perioperative setting, including 5 of the 15 studies being in cardiac surgery, the need for renal replacement therapy was significantly increased with the use of hydroxyethyl starch solutions (RR, 1.44; 95% CI, 1.04–2.01).[373] This was true for all the hydroxyethyl starch solutions as a class, but in particular with a hydroxyethyl starch 130/0.4 (RR, 1.47; 95% CI, 1.02–2.12).[373] As a result of these cardiac surgery studies, as well as the mounting evidence against the use of starches in other critical care settings, the avoidance of hydroxyethyl starch solutions is recommended.[374]

Strategies for Renal Protection

The sluggish serum creatinine rise consequent to sudden drops in glomerular filtration is now considered inadequate to be the signal for acute renoprotection, much as Q waves are too late to be useful for cardioprotection. When serum creatinine is employed, the obligatory delay in AKI recognition has even been suggested to explain some of the disappointing results from past renoprotection studies. Developing and validating tools for more prompt AKI diagnosis has become a priority. The hope is that early AKI biomarkers can be identified that can play a role in renal protection much like CK-MB and troponin currently serve for myocardial protection.

Nonetheless, despite its limitations as an early biomarker, serum creatinine remains an important clinical tool because of its many other uses. Indisputably, creatinine accumulation serves as a prognostic gold standard heralding AKI that is highly predictive of other major adverse outcomes, including death.[267] Validation for even the most promising of newer early AKI biomarkers is very limited or lacking in comparison. In addition to injury, serum creatinine characterizes renal recovery unlike most AKI biomarkers. Renal recovery as reflected by declining creatinine levels is highly predictive of short- and long-term outcomes beyond the magnitude of kidney insult.[276] Finally, the generalizability across studies and settings of creatinine-based consensus definitions for AKI, such as RIFLE and AKIN,[291] are gaining popularity.

Unfortunately, the lack of success in developing effective renoprotective responses and the renal monitoring challenges outlined earlier dictate that any review of renal protection still remains limited primarily to strategies to minimize or avoid AKI risk factors. Few to no interventions have consistently proven effective once AKI is established. However, there is hope that the new paradigm, viewing AKI as a threshold diagnosis much like AMI, whose recognition must be swift and intervention immediate if tissue salvage is to occur, will lead to progress in this field.

Early Acute Kidney Injury Biomarkers

Beyond serum creatinine, the race is on to identify one or more "early biomarkers" for AKI. As a condition whose treatment paradigm demands prompt intervention, AKI currently has no equivalents to CK-MB, troponin, and the ST segment for the heart.

BOX 31.3 EARLY ACUTE KIDNEY INJURY BIOMARKERS[a]

- **Serum accumulation markers:** reflect acute kidney injury (AKI) much like creatinine, serum accumulation, and decreased clearance with drop in glomerular filtration (Note: also useful to monitor renal recovery)
  Cystatin C
  Proatrial natriuretic peptide (1–98)
  Tryptophan glycoconjugate
- **Tubular enzymuria markers:** reflect AKI through leakage of cell contents into urine after tubular cell damage
  α-Glutathione S-transferase
  π-Glutathione S-transferase
  β-*N*-acetyl-β-d-glucosaminidase
  γ-Glutamyl transpeptidase
  Alkaline phosphatase
  Lactate dehydrogenase
  Ala-(leu-gly)-aminopeptidase
  Proximal renal tubular epithelial antigen
  Urinary sodium hydrogen exchanger isoform 3
- **Tubular proteinuria markers:** reflect AKI through appearance of small proteins in urine that would normally be taken up by tubular cells, reflecting tubular cell dysfunction (Note: not useful if using lysine analog antifibrinolytic agents)
  α_1-Microglobulin
  β_2-Microglobulin
  Albumin
  Adenosine deaminase binding protein
  Renal tubular epithelial antigen-1
  Retinol binding protein
  Lysozyme
  Ribonuclease
  Immunoglobulin G
  Transferrin
  Ceruloplasmin
  Lambda and kappa light chains
  Urinary total protein
- **Renal stress markers:** reflect AKI through various pathophysiologies reflecting or triggered by acute stress
  Neutrophil gelatinase-associated lipocalin
  Urinary interleukin-18
  Platelet activating factor
  Kidney injury molecule-1
  Cysteine rich protein 61
  Urinary P_{O_2}

[a]Early AKI biomarkers reflect renal insult through diverse mechanisms. Understanding of the physiology underpinning each marker can aid in understanding their potential value to improve the diagnosis of AKI.

The search for better early AKI biomarkers currently involves several contenders involving numerous physiologic mechanisms (Box 31.3). Markers such as creatinine and cystatin C that accumulate to diagnostic levels because of decreased clearance are further challenged during the perioperative period because of signal-to-noise confounders, such as hemodilution, that complicate early AKI recognition by disrupting steady state assumptions. While only a few new early biomarker candidates involve a substitute "ideal" creatinine, most involve one of three other early consequences of AKI: tubular cell damage, tubular cell dysfunction, and the adaptive stress response of the kidney. For example, damaged renal cells leak contents directly into urine; this strategy underpins tubular enzymuria AKI biomarkers, including ß-*N*-acetyl-ß-D-glucosaminidase and at least eight other candidates. Monitoring markers of the kidney's stress response provides another strategy for AKI recognition, including some frontrunners; these include neutrophil gelatinase-associated lipocalcin, urinary IL-18, and at least three other candidates. Simple urinary partial pressure of

oxygen (P_{O_2}) monitoring correlates with changes in renal medullary oxygen levels and predicts subsequent AKI in cardiac surgery patients.

Some early biomarker candidates are poorly suited specifically to perioperative AKI. So-called tubular proteinuria biomarkers, including urine α_1- and α_2-microglobulin and at least 12 other markers, manifest AKI through spillage into the urine of small filtered proteins due to impaired reuptake by the kidney. As outlined earlier, commonly used lysine analogue antifibrinolytics (ε aminocaproic acid and tranexamic acid) mimic this abnormality by selectively blocking kidney tubule receptors, causing a reversible form of this same proteinuria with apparently benign consequences; these biomarkers are considered of little value in most cardiac surgery settings.

Several large prospective observational studies are currently under way that may help identify the winner(s) of the early AKI biomarker race. It will be important for surgical and anesthesia advocates to highlight AKI biomarker issues unique to cardiac surgery lest these be overlooked in the broader pursuit of consensus AKI definitions.

Cardiopulmonary Bypass Management and the Kidney

Basic issues in the management of CPB that relate to the kidney involve the balance between oxygen supply and oxygen demand, particularly to the renal medulla. Perfusion pressure (ie, MAP during CPB) and oxygen-carrying capacity (as related to hemodilution and transfusion) address the supply issues, with the use of hypothermia being directed at modulating renal oxygen demand.

Profound hypothermia is a highly effective component of the protective strategy used during renal transplantation. Mild hypothermia during CPB would, therefore, seem to be a logical component of a perioperative renal protective strategy.[375] However, three separate studies have not found any protective benefit of mild hypothermia during CPB.[376–378] In the largest study, including 298 elective CABG patients who were randomly assigned to normothermic (35.5–36.5°C) or hypothermic (28–30°C) CPB, there was no association between normothermic (as compared with hypothermic) bypass and increased renal dysfunction after cardiac surgery.[378]

Low CPB blood pressure is typically not associated with the hypoperfusion characteristic of hypovolemic shock and LCOS, conditions that are highly associated with AKI. Studies addressing the role of perfusion pressure have not shown an association with AKI.[319,324,379,380] A retrospective, multivariable analysis of minute-to-minute CPB blood pressure data from 1404 CABG surgery procedures, including an assessment of a degree-duration integral index of MAP below 50 mm Hg, found no links between acute or extended episodes of hypotension during CPB and AKI.[324] Interestingly, some data are emerging on the interrelationship between cerebral autoregulatory limits (ie, defining individual blood pressure targets) and AKI after cardiac surgery. For example, in an observational study of patients being monitored with cerebral oximetry to determine the lower limit of cerebral autoregulation, Ono and investigators found that the duration and magnitude of blood pressure below this cerebral threshold was associated with AKI.[181]

Moderate hemodilution is thought to reduce the risk of kidney injury during cardiac surgery through blood viscosity–related improvement in regional blood flow.[381,382] However, the practice of extreme hemodilution (hematocrit < 20%) during CPB has been linked to adverse renal outcome after cardiac surgery.[383,384] Accounting for perfusion pressure, in the study of 1404 CABG patients cited in the previous paragraph,[324] independent associations were noted for both lowest hematocrit during CPB and transfusion with postoperative AKI. Other studies have reported similar patterns and suggest that profound hematocrit change (eg, >50% drop) may be even less well tolerated, highlighting the importance of a clinical strategy including transfusion only after all measures of hemodilution avoidance have been taken.[385–388]

Glycemic control during CPB has been identified as a potential opportunity to attenuate AKI. However, recent evidence has called into question the influential findings of Van den Berghe and colleagues, who reported reduced AKI and dialysis rates with postoperative therapy targeting tight serum glucose control (63% of study patients were post cardiac surgery).[389] Despite widespread adoption of these intensive insulin protocols, numerous subsequent studies have failed to reproduce Van den Berghe's findings of benefit. Wiener and coworkers performed a meta-analysis of the available randomized ICU studies involving over 3500 patients and found no reduction in AKI, dialysis rates, or mortality.[390] In a study combining Van den Berghe–like postoperative management of 400 cardiac surgery patients randomized to intensive intraoperative insulin therapy (target 80–100 mg/dL) versus usual management, Gandhi and associates found no benefit and similar dialysis rates (6/199 vs 4/201; $P = .54$), even noting an unexpected increase in 30-day mortality and stroke with tight control.[196]

Pharmacologic Intervention

There is very little in terms of interventions available to the clinician to pharmacologically prevent or treat established perioperative AKI as evidenced by a Cochrane database review.[391] Proposed changes to improve the likelihood of success in finding renoprotective strategies have included increasing the size of studies designed to see benefit should it be present and, as outlined earlier, improving timely AKI detection to allow earlier intervention. Researchers have performed meta-analyses for many prevalent therapies by combining data from their randomized clinical trials. In some cases, these reports indicate study size concerns may have been warranted. Potential optimism comes from a finding of reduced AKI in a meta-analysis of trials involving 934 cardiac surgery patients comparing various natriuretic peptides with placebo (urodilatin [two studies], brain natriuretic peptide [three studies], atrial natriuretic peptide [nine studies])[392]; however, combined evaluation of the most studied single agent, atrial natriuretic peptide, still remained inconclusive.[393] Another meta-analysis involving 20 studies assessing various methods to guide fluid and inotrope therapy to achieve hemodynamic optimization targets, involving 4220 patients, found reduced AKI and a trend toward reduced mortality.[394] Although they provide hope, neither of these meta-analyses has sufficient evidence to make practical recommendations for changes in clinical practice.

Other systematic reviews and meta-analyses of collected AKI cardiac surgery studies have been reported. For example, several meta-analyses found *N*-acetylcysteine not to have renal benefit even in large cardiac surgery populations.[395–398] A meta-analysis limited to randomized cardiac surgery trials of fenoldopam (20 studies, more than 1400 patients) concluded that a larger trial (1700–2300 patients) was needed to reconcile promising but conflicting evidence.[399] Another, less rigorous analysis of trials and observational studies of the use of fenoldopam in patients who have undergone cardiovascular surgery (1059 patients, 13 studies), by Landoni and investigators suggested reduced dialysis and death after cardiac surgery.[400]

A meta-analysis of statin therapy preceding cardiac surgery including 3 randomized and 16 observational studies (over 30,000 patients) found a reduced incidence of renal failure with this therapy.[401] A meta-analysis of 61 studies comparing "renal-dose" dopamine to placebo (3359 patients) found extremely modest benefit on day 1—with increased urine output, slight serum creatinine decline (4%), and glomerular filtration rate rise (6%).[402] However, by day 2 these gains were lost, and there was no effect on mortality, need for dialysis, or adverse events. Meta-analyses of loop diuretics trials and controlled studies in critically ill patients describe improvements in markers of renal function (urine output, oliguric period), and reduced need for dialysis but also concerning trends toward increased mortality and poorer renal recovery.[403–405] Unfortunately, because of the limitations of current research tools, most potential renoprotective therapies have not been subjected to the rigor of a large randomized trial or even meta-analysis, and none has been given the opportunity to be used immediately after the onset of AKI. Additional data, including rationale and existing studies for a number of these therapies, is outlined next.

Dopamine

Mesenteric dopamine$_1$ (D_1) receptor agonists increase renal blood flow, decrease renal vascular resistance, and enhance natriuresis and

diuresis. Despite the absence of clinical evidence of renoprotection, this rationale has been used to justify the use of low-dose ("renal-dose") dopamine (<5 μg/kg per min) for decades. However, numerous double-blind, randomized studies in several surgical and nonsurgical settings have failed to demonstrate any renal benefits.[406–408] Concerns have been raised that dopamine in cardiac surgery is not benign, including evidence suggesting impairment of hepatosplanchnic metabolism despite an increase in regional perfusion[409] and increased postoperative arrhythmias.[410] Despite the lack of benefit and accumulating concerns regarding the use of low-dose dopamine, many centers continue to use this agent for renoprotection.

Fenoldopam

Fenoldopam mesylate, a derivative of benzazepine, is a selective D_1-receptor agonist. Although first approved as an antihypertensive agent, fenoldopam has shown promise in the prevention of contrast-induced nephropathy.[411–413] There is, however, very little in the way of randomized, controlled studies to evaluate the agent as a therapy for postoperative renal dysfunction. In one prospective, randomized study involving 160 patients with preoperative renal dysfunction, improved renal function with fenoldopam versus placebo was reported after cardiac surgery; however, no long-term benefit was evaluated.[414] Other prospective, randomized, double-blind studies enrolling patients with established postoperative renal injury have proved inconclusive or even indicated possible adverse outcomes in patients with diabetes.[415] More systematic study is needed before this agent can be recommended for renoprotection in cardiac surgery.

Diuretic Agents

Diuretics increase urine generation by reducing reuptake of tubular contents. This can be achieved by numerous mechanisms, including inhibiting active mechanisms that lead to solute reuptake (eg, loop diuretics), altering the osmotic gradient in the tubular contents to favor solute remaining in the tubule (eg, mannitol), or hormonal influences that affect the balance of activities of the tubule to increase urine generation (eg, atrial natriuretic peptide). The general renoprotective principle of diuretic agents is that increasing tubular solute flow through injured renal tubules will maintain tubular patency, avoiding some of the adverse consequences of tubular obstruction, including oliguria or anuria and possibly the need for dialysis. Other agent-specific properties (eg, antioxidant effects, reduced active transport) have also been proposed to have beneficial effects in the setting of ischemic renal injury.

Loop diuretics, such as furosemide, produce renal cortical vasodilation and inhibit reabsorptive transport in the medullary thick ascending limb, causing more solute to remain in the renal tubule and increasing urine generation. In animal models, administration of furosemide and other loop diuretics has been shown to raise oxygen levels in the renal medulla,[416] presumably by reducing oxygen consumption by tubular active transport, but it also results in distal tubular hypertrophy.[417] In experimental models, loop diuretics have provided protection from renal tubular damage after ischemia-reperfusion and nephrotoxic injuries.[418–420] In contrast to evidence from animal experiments, several clinical studies have shown no benefit and possibly even harm from perioperative diuretic therapy in cardiac surgery patients.[421–423] In a double-blind, randomized, controlled trial comparing infusions of furosemide, low-dose dopamine, or placebo administered during and for 48 hours after surgery in 126 cardiac surgery patients, Lassnigg and coworkers[424] found no benefit of dopamine and a greater postoperative rise in serum creatinine in the group receiving furosemide. Although they may facilitate avoidance of dialysis in responsive patients by maintaining fluid balance, there is insufficient evidence to support the routine use of loop diuretics as specific renoprotective agents. However, in situations of severe hemoglobinuria, they may facilitate urine production and tubular clearance of this nephrotoxin.

Mannitol, an osmotic diuretic, has been evaluated in several studies of cardiac surgical patients.[376,425,426] Although an increased diuresis has been documented, very few studies have carefully assessed postoperative renal dysfunction in these patients. In an animal model of thoracic aortic clamping, mannitol did not provide evidence of improved renal function after unclamping.[427] In addition to the lack of beneficial effect on the kidney, several studies have identified a nephrotoxic potential of high-dose mannitol, especially in patients with preexisting renal insufficiency.[428]

Several studies have addressed the potential for renoprotection with natriuretic peptides. Three natriuretic peptides have received most of the attention in human trials: atrial natriuretic peptide (ANP; anaritide), urodilatin (ularitide), and brain natriuretic peptide (BNP; nesiritide).[429] Natriuretic peptides have primary effects, including receptor-mediated natriuresis and vasodilation, and are normally secreted in response to volume expansion. ANP increases glomerular filtration and urinary output by constricting efferent and dilating afferent renal arterioles.[430] In a secondary analysis of randomized data from an ICU study of 504 patients with established AKI, Allgren and colleagues noted a 24-hour intravenous infusion of ANP (0.2 μg/kg per min) was associated with improved dialysis-free survival in oliguric patients (8 vs 27%; $P = .008$) but not in nonoliguric patients (59 vs 48%; $P = .03$).[431] Unfortunately, a repeat study designed to reproduce these favorable findings did not see any benefit.[432] Few studies have evaluated urodilatin, and these have all provided inconclusive results.[433] BNP has potent vasodilating properties and is generated in response to ventricular dilatation. Evidence from cardiology studies suggest that BNP treatment may worsen renal function in patients with heart failure.[434,435] However, two randomized studies in cardiac surgery patients suggest renoprotective benefit from this agent.[436,437]

N-Acetylcysteine

N-Acetylcysteine is an antioxidant that enhances the endogenous glutathione scavenging system and has shown promise as a renoprotective agent by attenuating intravenous contrast-induced nephropathy. The weight of evidence, including four meta-analyses, suggests that potential benefits that may exist with contrast nephropathy are not pertinent to perioperative patients.[395–398,438,439]

Adrenergic Agonists

The α_1- and α_2-adrenergic receptors in the kidney modulate vasoconstrictor and vasodilatory effects, respectively. Agents that attenuate renal vasoconstriction may have potential as renoprotective drugs because vasoconstriction most likely contributes to the pathophysiology of AKI. Clonidine, an α_2-agonist, has been shown experimentally to inhibit renin release and cause diuresis, and it has been evaluated in an experimental AKI model confirming its potential as a renoprotective agent.[440–444] Similarly, two clinical trials have demonstrated some promise. A prospective, double-blind, randomized, placebo-controlled clinical trial evaluating preoperative clonidine in 48 CABG patients found that creatinine clearance decreased over the first postoperative night from 98 ± 18 (preoperatively) to 68 ± 19 mL/min ($P < .05$) in the placebo-treated group, but it remained unchanged in clonidine-treated patients (90 ± 1 to 92 ± 17 mL/min; $P < .05$).[445] The effect was transient, however, with creatinine clearance in both groups being no different at postoperative day 3. Despite being positively supported in a second trial,[446] clonidine has not gained popular acceptance as a renoprotective agent. Notably, decreased afferent α_1-adrenergic receptor–mediated vasoconstriction has been suggested as an explanation for the renal protective benefit of thoracic epidural blockade in cardiac surgery patients.[447]

Calcium Channel Blockers

Diltiazem is the calcium channel blocker that has been most evaluated as a renoprotective agent in cardiac surgery, with its ability to antagonize vasoconstricting signals and reports of beneficial effects in experimental models of toxic and ischemic acute renal failure.[448,449] However, in humans, numerous small randomized trials and a retrospective study combine to provide a confusing picture, including

evidence suggesting diltiazem therapy in cardiac surgery patients may have minor renal benefits, no benefit, or even potential harm.[450–455]

Sodium Bicarbonate

The perioperative infusion of sodium bicarbonate has recently attracted attention because of reduced AKI compared to a placebo saline infusion in 100 post–cardiac surgery patients.[456] Despite evidence that sodium bicarbonate–based hydration appears to be of benefit in other settings such as contrast-induced nephropathy, the considerable additional fluid and sodium load required with this therapy has raised concern for some clinicians.[457]

Angiotensin-Converting Enzyme Inhibitor and Angiotensin I Receptor Blockers

The renin-angiotensin-aldosterone system mediates vasoconstriction and is important in the paracrine regulation of the renal microcirculation. Angiotensin-converting enzyme (ACE) inhibitor and angiotensin I receptor blocker agents act by inhibiting steps in activation of the renin-angiotensin-aldosterone system. Although ACE inhibitor and angiotensin receptor blocker agents have demonstrated effects at slowing the progression of most chronic renal diseases,[458] their role in AKI has not been well studied.[459,460] In a study of 249 aortic surgery patients, Cittanova and coworkers[461] reported an increased risk of postoperative renal dysfunction in patients receiving preoperative ACE inhibitor therapy. Animal studies suggest that both groups of drugs have protective properties in experimental AKI.[462] In a small ($N = 18$), double-blind, placebo-controlled clinical trial enrolling CABG patients, preservation of renal plasma flow intraoperatively in patients receiving the ACE inhibitor captopril relative to placebo was demonstrated.[463] A similar study assessing perioperative enalaprilat (an angiotensin receptor blocker) therapy in 14 CABG patients demonstrated greater renal plasma flow in the enalaprilat group before CPB and on postoperative day 7, as well as greater creatinine clearance after CPB.[464,465]

Insulin-Like Growth Factor

The concept of combining AKI prevention with enhanced renal recovery is appealing given the emerging evidence; insulin-like growth factor offers the potential for the importance of the latter, with promising findings from animal AKI studies and reports in humans with chronic kidney disease of improved renal function and delayed need for dialysis.[466–468] However, unfortunately the only randomized controlled trial in 72 patients with acute renal failure found no renal benefit and a significant side effect profile.[469]

Alternate Perioperative Renoprotective Strategies

In a survey involving over 29,000 cardiac surgery patients from 26 German heart programs, Heringlake and associates reported extremely wide variation in AKI rates by center, ranging from 3.1 to 75% (mean 15.4%; see Fig. 31.9).[366] Although programs were unaware of their AKI ranking when responding to a questionnaire, centers were asked to provide case mix data and answer questions on their standard practice in patients with elevated renal risk. Groups of centers with higher and lower AKI rates had similar case mix and urgency/emergency rates, but several differences existed in their responses to standard management questions. Centers with high and low rates of AKI used loop diuretics at about the same rates but selected norepinephrine in preference to epinephrine or dopamine as a vasopressor and were less likely to prefer dopamine for either inotropy or renal prophylaxis. Using monitoring of AKI rates among centers as a tool to identify outliers and alter practice patterns was a useful strategy to improve outcomes in one study.[273]

Myocardial Injury

From the earliest days of modern cardiac surgery, perioperative myocardial dysfunction, with its associated morbidity and mortality, has been reported.[470] Evidence, including substantial subendocardial cellular necrosis, led to the conclusion that this injury resulted from an inadequate substrate supply to the metabolically active myocardium.[471] Optimizing myocardial protection during cardiac surgery involves several compromises inherent in allowing surgery to be performed in a relatively immobile, bloodless field, while preserving postoperative myocardial function. The fundamental tenets of this protection center on the judicious use of hypothermia along with the induction and maintenance of chemically induced electromechanical diastolic cardiac arrest. Bigelow and investigators[472] were the first to describe the use of hypothermia for this purpose, and this was complemented by subsequent work by Melrose and colleagues,[473] who first reported the electromechanical arrest of the heart by the administration of potassium-containing cardioplegia. Despite continued efforts directed at myocardial protection, it is clear that myocardial injury, although reduced, still remains a problem, and with it, the representative phenotype of postoperative myocardial dysfunction.

Incidence and Significance of Myocardial Dysfunction After Cardiopulmonary Bypass

Unlike other organs at risk of damage during cardiac surgery, it is assumed, because of the very nature of the target of the operation being performed, that all patients having cardiac surgery will suffer some degree of myocardial injury. Although the injury can be subclinical, represented only by otherwise asymptomatic elevations in cardiac enzymes (eg, myocardial creatine kinase isoenzyme [CK-MB]), it frequently manifests more overtly. The degree to which these enzymes are released by injured myocardium, frequently to levels sufficiently high to satisfy criteria for MI, have been related to perioperative outcome after cardiac surgery.[474–476] Chaitman[475] reported CK-MB results from the Guard During Ischemia Against Necrosis (GUARDIAN) trial in 11,950 patients with acute coronary syndromes or undergoing high-risk percutaneous intervention or CABG surgery. CK-MB values more than 10 times the upper limit of normal during the initial 48 hours after CABG were significantly associated with 6-month mortality ($P < .001$).[475]

Risk Factors for Myocardial Injury

With an increasingly sicker cohort of patients presenting for cardiac surgery,[477] many with acute ischemic syndromes (eg, often with evolving MIs) or significant LV dysfunction, the need has never been greater for optimizing myocardial protection to minimize the myocardial dysfunction consequent to aortic cross-clamping and cardioplegia.[478] The continued increase in cardiac transplantation and other complex surgeries in the heart failure patient has served to fuel the search for better myocardial protection strategies.

Pathophysiology of Myocardial Injury

Myocardial stunning represents the myocardial dysfunction that follows a brief ischemic event. It is differentiated from the reversible dysfunction associated with chronic ischemia, which is called hibernation.[479] Myocardial stunning typically resolves over the 48 to 72 hours after the ischemic event and is frequently observed after aortic cross-clamping with cardioplegic arrest.[480,481] Important factors that contribute to stunning include not only the metabolic consequences of oxygen deprivation but also the premorbid condition of the myocardium, reperfusion injury, acute alterations in signal transduction systems, and the effects of circulating inflammatory mediators.

The metabolic consequences of oxygen deprivation become apparent within seconds of coronary artery occlusion. With the rapid depletion of high-energy phosphates, accumulation of lactate and intracellular acidosis in the myocytes soon follows, with the subsequent development of contractile dysfunction. When myocyte adenosine triphosphate (ATP) levels decline to a critical level, the subsequent inability to maintain electrolyte gradients requiring active transport (eg, Na^+, K^+, Ca^{2+}) leads to cellular edema, intracellular Ca^{2+} overload, and loss of membrane integrity.

Predictably with the release of the aortic cross-clamp and the restoration of blood flow, myocardial reperfusion occurs. With reperfusion the paradox, represented by the balance of substrate delivery restoration needed for normal metabolism that also can serve as the substrate for injurious free radical production, becomes a significant issue for consideration. Reperfusion causes a rapid increase in free radical production within minutes, and it plays a major role initiating myocardial stunning. Bolli[482] identified the importance of this effect by demonstrating that antioxidants administered just before reperfusion significantly diminished myocardial stunning, an effect not observed if the same substance were introduced after reperfusion. Sun and associates[483] and Sekili and colleagues[484] subsequently demonstrated the significance of the free radical effect by demonstrating that up to 80% of myocardial stunning could be avoided with an appropriately timed regimen of free radical scavengers.

Free radical insults during myocardial reperfusion result in the near-immediate dysfunction of proteins involved in ion transport and excitation-contraction coupling, as well as injury to membranes through damage mediated through lipid peroxidation.[485] Free radical–mediated myocardial dysfunction is related to a myofilament defect manifest by an impairment in Ca-activated excitation-contraction coupling.[485] Although free radicals can directly injure these myofilament components, injury to other proteins related to ion transport and membrane integrity serve to increase intracellular calcium. Several mechanisms have been proposed to explain this impairment of myofilament function, although the most likely explanation includes physiologic downregulation of excitation-contraction coupling in response to cellular Ca^{2+} overload. The mechanisms underlying Ca^{2+} overload are not well understood, but they are thought to involve free radical–related and free radical–independent abnormalities in Ca^{2+} homeostasis. Whatever the cause, the rapid calcium influx during myocardial reperfusion can quickly overload the myocyte with Ca^{2+}.[486] The importance of Ca^{2+} overload is demonstrated by the substantial protection from reperfusion injury obtained by pretreatment with traditional Ca^{2+} blocking agents.[487]

A free radical–independent mechanism for Ca^{2+} overload involves activation of the Na^+/H^+ exchanger during reperfusion in an attempt by the cell to correct intracellular pH.[488] The resultant increase in intracellular Na^+ from activation of the Na^+/H^+ exchanger further activates the Na^+/Ca^{2+} exchanger, increasing Ca^{2+} influx.[489] Evidence for the activation of Na^+/H^+ exchangers being responsible for some of the harmful effects of reperfusion is shown by the benefits that Na^+/H^+ exchanger inhibitors have had on myocardial stunning with reductions in arrhythmias, improvement in systolic and diastolic function, and reductions in myocyte injury.[490] In addition to its role in Ca^{2+} overload, activation of the Na^+/H^+ exchanger has been linked to increased phospholipase activity, generation of prostaglandins and other eicosanoids, and activation of platelets and neutrophils—all potentially injurious processes.[488,490]

In addition to free radical upregulation, myocardial reperfusion associated with acute myocardial ischemic injury induces inflammation mediated by neutrophils and an array of humoral inflammatory components.[488,491,492] Several studies using novel neutrophil inhibitors have demonstrated a cardioprotective effect in models of myocardial stunning.[492,493] Prostaglandins are also generated during reperfusion and their adverse effects appear to be synergistic with increases in intracellular calcium. The relationship of leukotriene and cytokine release to reperfusion injury is less clear.[488,491] Consistent with a role for prostaglandins in this injury is the demonstration that inhibition of prostaglandins by nonsteroidal antiinflammatory agents can significantly diminish myocardial stunning.[494]

A potential additional mechanism for myocardial dysfunction specific to the setting of CPB relates to proposed acute alterations in β-adrenergic signal transduction.[495] Acute desensitization and downregulation of myocardial β-adrenergic receptors during CPB has been demonstrated after cardiac surgery.[495,496] Although the role of the large elevations in circulating catecholamines seen with CPB on β-adrenergic malfunction is unclear, it has been proposed that an increased incidence of post-CPB LCOS and reduced responsiveness to inotropic agents may be attributed in part to this effect.[497,498]

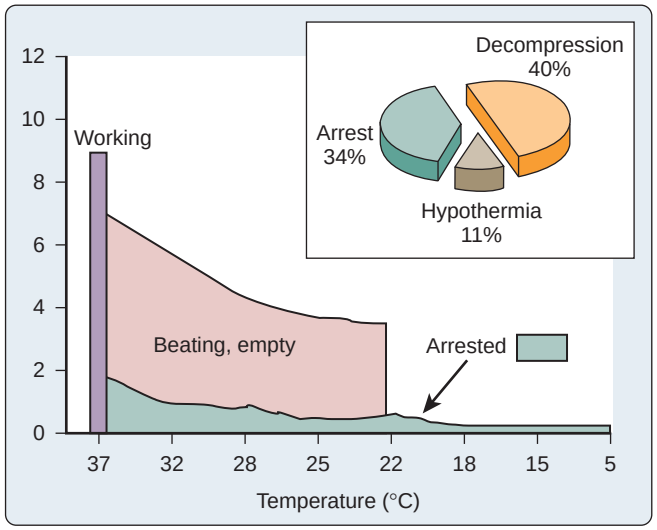


Fig. 31.10 Myocardial oxygen uptake (reflecting oxygen demand) versus temperature. Compared with the oxygen uptake of a normally beating heart, eliminating cardiac work by venting the beating heart during bypass reduces oxygen demand by 30% to 60%. Arresting the heart reduces demands by another 50%, producing a total reduction of approximately 90%. Hypothermia extends the reductions in oxygen demand. *(From Vinten-Johansen J, Thourani VH. Myocardial protection: an overview.* J Extra Corpor Technol *2000;32:38–48.)*

Myocardial Protection During Cardiac Surgery: Cardioplegia

Optimizing the metabolic state of the myocardium is fundamental to preserving its integrity. The major effects of temperature and functional activity (ie, contractile and electrical work) on the metabolic rate of the myocardium have been extensively described.[471,489,499] With the institution of CPB, the emptying of the heart significantly reduces contractile work and myocardial oxygen consumption (MvO_2). Nullifying this cardiac work reduces the MvO_2 by 30% to 60%. With subsequent reductions in temperature, the MvO_2 further decreases, and with induction of cardiac arrest and hypothermia, 90% of the metabolic requirements of the heart can be reduced (Fig. 31.10). Temperature reductions diminish metabolic rate for all electromechanical states (ie, beating or fibrillating) of the myocardium (Table 31.7).

Although cardiac surgery on the empty beating heart or under conditions of hypothermic fibrillation (both with the support of CPB) is sometimes performed, aortic cross-clamping with cardioplegic arrest remains the most prevalent method of myocardial preservation. Based on the principle of reducing metabolic requirements, the introduction of selective myocardial hypothermia and cardioplegia (ie, diastolic arrest) marked a major clinical advance in myocardial protection.[500,501] With the various additives in cardioplegia solutions (designed to optimize the myocardium during arrest and attenuate reperfusion injury) and the use of warm cardioplegia, the idea of delivering metabolic substrates (as opposed to solely reducing metabolic requirements) is also commonplace. Several effective approaches to chemical cardioplegia are employed. The clinical success of a cardioplegia strategy may be judged by its ability to achieve and maintain prompt continuous arrest in all regions of the myocardium, early return of function after cross-clamp removal, and minimal inotropic requirements for successful separation from CPB. Composition, temperature, and route of delivery constitute the fundamentals of cardioplegia-derived myocardial protection (see Chapter 32).

Composition of Cardioplegia Solutions

The composition of the various cardioplegia solutions used during cardiac surgery varies as much between institutions as it does between individual surgeons. In very general terms, cardioplegia can be classified into blood-containing and nonblood-containing (ie, crystalloid) solutions. Whereas crystalloid cardioplegia has fallen out of favor, blood cardioplegia in various combinations of temperatures and routes of delivery is the most used solution. However, even within the category of blood cardioplegia, the individual chemical constituents of the solution vary considerably with respect to the addition of numerous additives. Table 31.8 outlines the various additives to cardioplegia solutions along with their corresponding rationale for use. Although all cardioplegia solutions contain higher than physiologic levels of potassium, solutions used for the induction of diastolic arrest contain the highest concentrations of potassium as opposed to solutions used for the maintenance of cardioplegia. In addition to adjustment of electrolytes, manipulation of buffers (eg, bicarbonate, tromethamine), osmotic agents (eg, glucose, mannitol, potassium), and metabolic substrates (eg, glucose, glutamate, and aspartate) constitute the most common variations in cardioplegia content. Oxygenation of crystalloid cardioplegia before infusion is aimed at increasing aerobic metabolism, but the limited oxygen-carrying capacity of crystalloid makes a rapid decline in metabolic rate through immediate and sustained diastolic arrest critical to effective cardioprotection with this technique.

Blood cardioplegia has the potential advantage of delivering sufficient oxygen to ischemic myocardium to sustain basal metabolism or even augment high-energy phosphate stores, as well as possessing free radical scavenging properties.[502] The introduction of blood cardioplegia in the late 1970s followed recognition of the clinical utility of this technique.[503] Although low-risk cardiac surgical patients appear to do equally well with crystalloid or blood cardioplegic protection, evidence is compelling that more critically ill patients, including those with "energy-depleted" hearts (eg, cardiogenic shock, AMI before CPB), have improved outcomes using blood cardioplegia.[504,505] Patients at high risk also appear to have better recovery after a combination of antegrade and retrograde blood cardioplegia delivery, when compared with antegrade administration alone.[505]

Because an infusion of oxygenated blood cardioplegia is in many ways similar to myocardial reperfusion, it is not surprising that the composition of blood cardioplegia is based on reperfusate parameters known to minimize myocardial stunning.[506,507] These parameters include maintenance of Ca^{2+} at 1.0 mEq/L (by chelating Ca^{2+} from perfusate blood) to diminish myocyte Ca^{2+} uptake; pH between 7.6 and 7.8 (the pH of water in the hypothermic temperature range used); osmolality between 340 and 360 mOsm to minimize edema-related myocardial dysfunction after reperfusion; and hyperkalemia between 10 and 25 mEq/L to safely sustain electromechanical arrest. To create blood cardioplegia with these characteristics, blood is mixed in a ratio of 4:1 with a prepared crystalloid solution.

Infusion of a single, warm (37°C) reperfusion dose of cardioplegia (so-called hot shot) containing metabolic substrates (ie, glucose, glutamate, and aspartate) just before aortic cross-clamp removal is preferred by some clinicians. The rationale for this is evidence that normothermia maximally enhances myocardial aerobic metabolism and recovery after an ischemic period. Although, some have advocated continuous infusion of hyperkalemic warm cardioplegia throughout the period of aortic cross-clamping,[508] this technique has not gained wide popularity for CABG because of the technical challenges of grafting vessels perfused in this way and the threat of ischemia to nonperfused (warm) myocardium during grafting.

Numerous other cardioplegia additives continue to be assessed involving various buffers, osmotic agents, metabolites, ATP and precursors, enzymes controlling ATP synthesis and catabolism, oxygen radical scavengers, and antioxidants. Protection of myocardial β-adrenergic receptor function using intracoronary administration of esmolol appears to hold promise as an alternate cardioprotective method.[509] Alternative cardioplegia strategies potentially extending safe ischemic periods for heart transplantation to up to 24 hours are also being evaluated.[510–512]

Cardioplegia Temperature

The composition of cardioplegia solutions varies considerably; in contrast, myocardial temperature during cardioplegia is almost uniformly reduced to between 10°C and 12°C or less by the infusion of refrigerated cardioplegia and external topical cooling with ice slush. However, the introduction of warm cardioplegia has challenged this once universally considered necessity of hypothermia for successful myocardial protection.[160] Although hypothermic cardioplegia is the most commonly used temperature, numerous investigations have examined tepid (27–30°C) and warm (37–38°C) temperature ranges for the administration of cardioplegia. Much of the work aimed at determining the optimum temperature of the cardioplegia solution

TABLE 31.7 Influence of Temperature on Myocardial Oxygen Consumption for Different Work and Electrical Conditions

	Myocardial Oxygen Consumption (mL/100 mg per min)			
Cardiac Conditions	*37°C*	*32°C*	*28°C*	*22°C*
Beating, empty	5.5	5.0	4.0	2.9
Fibrillating, empty	6.5	3.8	3.0	2.0
K^+ cardioplegia	1.8	0.8	0.6	0.3
Beating, full	9.0	—	—	—

Data from Buckberg G. Left ventricular subendocardial necrosis. *Ann Thorac Surg.* 1977;24:379–393; and Sarnoff S, Braunwald E, Welch G. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol.* 1958;192:148–156.

TABLE 31.8 Strategies for the Reduction of Ischemic Injury With Cardioplegia

Principle	*Mechanism*	*Component*
Reduce O_2 demand	Hypothermia	Blood, crystalloid, ice slush, lavage
	Perfusion	
	Topical/lavage	
	Asystole	KCl, adenosine (?), hyperpolarizing agents
Substrate supply and use	Oxygen	Blood, perfluorocarbons, crystalloid (?)
	Glucose	Blood, glucose, citrate-phosphate-dextrose
	Amino acids	Glutamate, aspartate
	Buffer acidosis	Hypothermia (Rosenthal factor), intermittent infusions
	Buffers	Blood, tromethamine, histidine, bicarbonate, phosphate
	Optimize metabolism	Warm induction (37°C), warm reperfusion
Reduce Ca^{2+} overload	Hypocalcemia	Citrate, Ca^{2+} channel blockers, K channel openers (?)
Reduce edema	Hyperosmolarity	Glucose, KCl, mannitol
	Moderate infusion pressure	50 mm Hg

From Vinten-Johansen J, Thourani VH. Myocardial protection: an overview. *J Extra Corpor Technol.* 2000;32:38–48.

centered on the fact that although hypothermia clearly offered some advantages to the myocardium in suppressing metabolism (particularly when intermittent cardioplegia was delivered), it may have some detrimental effects.

The deleterious effects of hypothermia include the increased risk of myocardial edema (through ion pump activity inhibition) and the impaired function of various membrane receptors on which some pharmacologic therapy depends (such as the various additives to the cardioplegia solutions). The other disadvantages of hypothermic cardioplegia, in addition to the production of the metabolic inhibition in the myocardium, are an increase in plasma viscosity and a decrease in red blood cell deformability.[161,499,513] As a result, investigations aimed at using warmer cardioplegia temperatures have been explored.[160,514] During the initial phase of cardioplegia delivery, hypothermic temperatures, in addition to inhibiting some of the needed drug-receptor interactions, fail to optimize the metabolic rate in the myocardium. Hypothermia results in a leftward shift in the oxygen hemoglobin dissociation curve, inhibiting the release of oxygen into tissues. The myocardium is relatively ischemic during this initial induction phase of cardioplegia, with the uptake of the oxygen to this tissue being low, and, as a result, significant oxygen debt occurs.

The adverse effects of hypothermia spawned interest in using warm cardioplegia. With the warm induction of cardiac arrest, metabolic activity is maintained, ion exchanges through cellular membranes are maintained, intracellular acidosis occurring with hypothermia is eliminated, oxygen delivery is optimized by maintaining a near-normal hemoglobin-oxygen dissociation curve, hypothermia-induced changes in viscosity and blood rheology are avoided, and red blood cell deformability and resulting flow through the myocardial microvasculature are maintained. The principal differences in cold versus warm cardioplegia result from the timing and route of delivery. If the myocardium is maintained at normothermic temperature, continuous cardioplegia must be delivered to adequately supply substrate to the metabolically active myocardium. In most cases, this is done using continuous retrograde cardioplegia (discussed later).

A compromise temperature (tepid, 27–30°C) has also been proposed.[514] Ikonomidis and associates[514] compared outcomes for patients receiving warm, tepid, or cold cardioplegia. Although numerous differences were found between the various groups, the recovery of LV stroke work at 1 and 4 hours after surgery was optimal in the tepid group. The researchers concluded that tepid cardioplegia provided better overall protection with superior functional recovery.[515] Hayashida and colleagues[515] conducted a randomized trial comparing the effects of cold (9°C), tepid (29°C), and warm (37°C) cardioplegia in 42 patients undergoing CABG surgery. Overall, the investigators found that $M\dot{V}O_2$ and lactate production were greatest in the warm group, intermediate in the tepid group, and least in the cold cardioplegia group. However, early postoperative LV function was optimized in the tepid cardioplegia group.[515]

Cardioplegia Delivery Routes

If using tepid or warm cardioplegia administration, the continuous administration of this cardioplegia needs to be ensured. Retrograde cardioplegia, where a cardioplegia catheter is introduced into the coronary sinus, allows for almost continuous cardioplegia administration. Retrograde delivery is also useful in settings where antegrade cardioplegia is problematic such as with severe aortic insufficiency or during aortic root or aortic valve (and frequently, mitral) surgery (Box 31.4). It also allows the distribution of cardioplegia to areas of myocardium supplied by significantly stenosed coronary vessels. Retrograde cardioplegia has proved safe and effective in patients with coronary artery disease and in those undergoing valve surgery.[516,517] With the administration of retrograde cardioplegia, certain provisos should be considered. The acceptable perfusion pressure to limit perivascular edema and hemorrhage needs to be limited to less than 40 mm Hg.[518]

Two trials added information about cardioplegia routes of delivery. The CABG patch trial[519] enrolled high-risk CABG patients with impaired LV function and demonstrated the superiority of the combined antegrade and retrograde delivery of blood cardioplegia compared with antegrade cardioplegia alone. The limitation of this trial was that the antegrade group received crystalloid cardioplegia (as opposed to blood cardioplegia in the antegrade-retrograde group), raising questions about whether the differences in the groups were seen because of the route of administration or the constituents of the cardioplegia itself. A second trial failed to demonstrate any differences when the administration of intermittent antegrade cold blood cardioplegia was compared with a group receiving antegrade cold blood cardioplegia induction followed by retrograde cold blood maintenance in valve surgery.[520] They did find that the antegrade-retrograde approach was technically more convenient, allowing for shorter aortic cross-clamp times.

BOX 31.4 USES FOR RETROGRADE CARDIOPLEGIA

- Along with anterograde cardioplegia
- In the presence of aortic insufficiency
- For aortic (and mitral) valve surgery
- To perfuse severely diseased coronary arteries

Retrograde cardioplegia does have some limitations. Although the retrograde approach has been shown to effectively deliver cardioplegia adequately to the left ventricle, because of shunting and blood flowing into the atrium and ventricles by the thebesian veins and various arteriosinusoidal connections, the right ventricle and septum frequently receive inadequate delivery of cardioplegia. Difficulties with retrograde delivery can also occur if the coronary sinus catheter is placed beyond the great cardiac vein, or if anatomic variants occur that communicate with systemic veins, such as a persistent left superior vena cava (SVC).[518,521,522] Because retrograde cardioplegia is inefficient in producing arrest of the beating heart, induction of arrest with this technique must be achieved by a single antegrade infusion of cardioplegia before its institution.

Ischemic Preconditioning

Myocardial stunning during cardiac surgery is affected by several parameters. The preischemic state of the myocardium can influence the degree of stunning that follows an ischemic event. Ischemic preconditioning (IPC) is endogenous myocardial protection triggered by exposure to brief periods of (5–15 min) ischemia. IPC is a natural defense mechanism that permits the heart to better tolerate myocardial ischemia. Although brief ischemic episodes in themselves result in stunning, they also build up a temporary resistance to the adverse effects of subsequent, more prolonged ischemia.[523,524] IPC has been well described experimentally.[525–527] Several proposed mechanisms are responsible for IPC, including the activation of several myocardial G protein–coupled receptors, most notably A_1 adenosine and α_1-adrenergic receptors.[528] Protein kinase C appears to be a key cellular mediator of IPC, in part through activation of ATP-sensitive potassium channels.[529]

Myocardial protection strategies continue to be an active area of investigation, including assessment of IPC. Attempts to induce IPC by brief ischemia or pharmacologic means before CPB have been assessed in human cardiac surgical patients. Sevoflurane, and other frequently used volatile anesthetics, have been demonstrated to pharmacologically replicate IPC.[530] Administration of adenosine, before bypass or in cardioplegic solutions, has been studied as a pharmacologic means to induce IPC. It has been associated with reduced postoperative myocardial injury, reduced inotropic requirements, and improved myocardial recovery.[531,532] The potential for myocardial stunning after beating heart OPCAB has not been fully assessed. Intermittent coronary occlusion before beating heart OPCAB to induce IPC, although unclear as

to its effect, has had some clinical assessment,[533] but it is not usually used. See the discussion of anesthetic preconditioning in Chapters 10 and 20 for more details on OPCAB management.

Gastrointestinal Complications

Incidence and Significance

Gastrointestinal (GI) complications after cardiac surgery, although occurring relatively infrequently (0.5–5.5%), portend a significantly increased risk of overall adverse patient outcome. The variability in the reported incidence of GI complications is partly a reflection of how they are defined as well as the variable patient and operative risk factors in the studied cohorts.[534–545] As devastating as they are, because of the relative low incidence, studies of GI complications are few. Although the most commonly considered GI complications include pancreatitis, GI bleeding, cholecystitis, and bowel perforation or infarction, hyperbilirubinemia (total bilirubinemia > 3.0 mL/dL) has also been described as an important complication after cardiac surgery. In one of the largest prospective studies examining these complications after CPB, McSweeney and associates[542] studied 2417 patients undergoing CABG (with or without concurrent intracardiac procedures) in a multicenter study in the United States. The overall incidence of GI complications in this study was 5.5%, ranging from 3.7% for hyperbilirubinemia to 0.1% for major bowel perforation or infarction (Table 31.9).

In addition to their association with other morbid events, adverse GI complications are significantly associated with increased mortality after cardiac surgery.[542,546–548] The average mortality rate among subtypes of GI complications in the study by McSweeney was 19.6%, and in other reports, the mortality rate ranges from 13% to 87%, with an overall average mortality rate of 33%. Even the seemingly insignificant complication of having an increased laboratory measurement of total bilirubin was associated with a 6.6 odds ratio of death in the McSweeney study, compared with a death odds ratio of 8.4 for all adverse GI outcomes combined. Apart from the significant effect on mortality, the occurrence of an adverse GI outcome also significantly increases the incidence of perioperative MI, renal failure, and stroke, as well as significantly prolonging ICU and hospital lengths of stay.[542]

TABLE 31.9 Adverse Gastrointestinal Outcomes

	No. of Patients	*Percentage of Patients With a Gastrointestinal Event (N = 133)*	*Percentage of Total Patients (N = 2417)*
Hyperbilirubinemia, total[a]	90	67.7	3.7
3.1–5.0 mg/dL	54	40.6	2.2
5.1–9.0 mg/dL	19	14.2	0.8
>9.0 (mg/dL)	17	12.8	0.7
Gastrointestinal bleeding	28	21.0	1.2
Pancreatitis	19	14.3	0.8
Cholecystitis	7	5.3	0.3
Bowel perforation	2	1.5	0.1
Bowel infarction	2	1.5	0.1

[a]Hyperbilirubinemia was defined as maximum total bilirubin after surgery of 3.0 mg/dL.
From McSweeney ME, Garwood S, Levin J, et al. Adverse gastrointestinal complications after cardiopulmonary bypass: can outcome be predicted from preoperative risk factors? *Anesth Analg.* 2004;98:1610–1617.

Risk Factors

A long list of preoperative, intraoperative, and postoperative risk factors for GI complications have been identified in a number of studies.[540,542,549–555] As many factors are associated with one another, it is only when these risk factors are examined in multivariable analyses that a more accurate understanding of what the most significant risk factors for visceral complications after cardiac surgery are. Table 31.10 represents the most consistently reported risk factors for GI complications after cardiac surgery. Preoperatively, age (>75 years), history of congestive heart failure, presence of hyperbilirubinemia (>1.2 mg/dL), combined cardiac procedures (eg, CABG plus valve), repeat cardiac operation, preoperative ejection fraction less than 40%, preoperative elevations in partial thromboplastin time, emergency operations; intraoperatively, prolonged CPB, use of TEE, and blood transfusion; and postoperatively, requirements for prolonged inotropic or vasopressor support, IABP use for the treatment of LCOS; and prolonged ventilatory support are all risk factors. These factors identify patients at high risk, and they lend some credence to the overall pathophysiology and suspected causes of these adverse events. If there is a common link among all these risks, it is that many of these factors would be associated with impairment in oxygen delivery to the splanchnic bed.

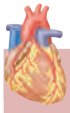
Pathophysiology and Causative Factors

Impairments in splanchnic perfusion commonly occur during even the normal conduct of cardiac surgery. When this is superimposed on an already depressed preoperative cardiac output or is associated with prolonged postoperative LCOS, the impairment in splanchnic blood flow is further perpetuated. The systemic inflammatory response to CPB itself can be initiated by splanchnic hypoperfusion by means of translocation of endotoxin from the gut into the circulation. De novo splanchnic hypoperfusion can be a result of the humoral vasoactive substances that are released by inflammation remote from the gut.[555–557] Another causative factor for GI complications directly related to splanchnic hypoperfusion is atheroembolism. Several studies have directly attributed atheroembolism to splanchnic hypoperfusion and gut infarction.[549,553,558] Prolonged ventilator support is another causative factor for GI complications, with several lines of investigation having described a relationship between prolonged ventilation and GI

TABLE 31.10 Commonly Identified Risk Factors for Visceral Complications After Cardiac Surgery

Preoperative Risk Factors	*Type of Cardiac Surgery*	*Cardiopulmonary Bypass Factors*	*Postoperative Risk Factors*
Age	Emergency surgery	Duration of CPB	Low cardiac output, use of inotropes, vasopressors, or IABP
History of CHF or low EF	Reoperations	Cross-clamp duration	Reoperation for bleeding
Renal insufficiency	Valve or combined procedures		Loss of normal sinus rhythm
Peptic ulcer disease, chronic lung disease, recent acute myocardial infarction, diabetes mellitus, peripheral vascular disease, use of IABP[a]	Cardiac transplantation		Renal failure
			Ventilation > 24 hours
			ICU stay > 1 day
			Increased bilirubin or lactate level, mediastinitis[a]

[a]Less commonly mentioned risk factors.
CHF, Congestive heart failure; *CPB,* cardiopulmonary bypass; *EF,* ejection fraction; *IABP,* intraaortic balloon bump; *ICU,* intensive care unit.
From Hessel EA 2nd. Abdominal organ injury after cardiac surgery. *Semin Cardiothorac Vasc Anesth.* 2004;8:243–263.



BOX 31.5 PROTECTING THE GASTROINTESTINAL TRACT DURING CARDIOPULMONARY BYPASS

- Avoiding high doses of vasopressors
- Maintaining a high perfusion flow
- Reducing emboli-producing maneuvers

adverse events; this likely results from a direct effect of positive pressure ventilation impairing cardiac output and subsequently splanchnic perfusion.[538,540,552,559] Lung volume reduction surgery and lung transplantation also produce (approximately 9%) GI complications.[560,561]

Protecting the Gastrointestinal Tract During Cardiac Surgery

As with other aspects of organ protection, critical causative factors need to be addressed with specific targeted therapies (Box 31.5). Unfortunately, as with most other organ-protective strategies, the major limitation in making definitive recommendations is an overall lack of large, well-controlled, prospectively randomized studies to provide supportive data for any one particular technique. However, some recommendations can be made, and attention can be focused on a number of other less well-studied but potentially valid strategies.

Cardiopulmonary Bypass Management

Because CPB itself has been shown to impair splanchnic blood flow, modifications in how it is conducted may have some salutary effects on GI tract integrity. Several studies have focused on the issue of the relative importance of pressure versus flow during CPB, demonstrating that it is likely more beneficial to maintain an adequate bypass flow rate than only maintaining pressure during bypass.[562–564] The addition of significant vasoconstrictors to artificially maintain an adequate MAP in the presence of inadequate flow on CPB may lead to further compromise of splanchnic blood flow. Few definitive data offer guidance about pulsatility. Some studies have shown improvements with pulsatility by indirect measurements (ie, gastric mucosal intracellular pH [pHi]), but no studies have found definitive differences in clinical outcomes. Similarly, the optimal CPB temperature to protect the gut is also unknown. Just as aggressive rewarming can be injurious to the brain,[64] there is some evidence that rewarming can cause increases in visceral metabolism, making any overshoot in temperature suspect by adversely altering the balance of gut oxygen consumption and delivery.[565]

Emboli Reduction

Whereas microembolization and macroembolization to the splanchnic bed clearly occur during CPB and possibly even during the period after bypass, there are few data to determine whether emboli reduction strategies can alter GI outcome. Mythen and Webb[566] found a relationship between transcranial Doppler–detected emboli (used as a surrogate for overall microembolic load within the body) and adverse changes in gastric mucosal pHi. However, with respect to microembolization, a trial that used an intraaortic filter to reduce atheroemboli failed to have any influence on the rate of GI complications.[101] It remains prudent to avoid maneuvers (ie, aortic cannulation and cross-clamping) in areas of high atheroma burden, which is an overall tenet of cardiac surgery for the prevention of all complications.

Drugs

Various vasoactive drugs have been used to enhance splanchnic blood flow during CPB. It is likely that most of these drugs, such as the phosphodiesterase III inhibitors, dobutamine, and other inotropic agents, maintain or enhance splanchnic blood flow, not because of a direct effect on the vasculature but by the inherent enhancement in cardiac output. Dobutamine and dopamine have had a paradoxical detrimental effect on the splanchnic vasculature, with some evidence that they cause further mucosal ischemia.[567,568] Dopexamine has also been studied in a small group that showed an improvement in mucosal blood flow (using laser Doppler flowmetry), but there was no beneficial effect on gastric mucosal pHi.[569] An increasingly common drug in the setting of cardiac surgery is vasopressin. Although vasopressin can clearly augment systemic MAP, it does so at the cost of severe impairments to splanchnic blood flow.[570] Although there are always trade-offs when choosing which vasoactive agent to use, if having a very low MAP is going to be detrimental to other organ systems, the choice to use vasopressin should at least be made with the knowledge that it can have an adverse effect on splanchnic blood flow.

Selective Gastrointestinal Decontamination

Addressing the concept that gut translocation of endotoxin plays a role in inflammation and other organ injuries, one interesting therapy that has been tried in the setting of cardiac surgery involves the administration of oral antibiotics to selectively decontaminate the GI tract preoperatively.[571] Although examined in a small ($N = 100$) study, a combination of oral polymyxin, tobramycin, and amphotericin preoperatively for 3 days reduced the degree of endotoxemia; it was not associated with a beneficial effect on patient outcomes. One possible explanation is that there is such an overwhelmingly large depot of gram-negative organisms in the GI tract that the elimination of even a large population of these by oral antibiotics still leaves significant repositories of endotoxin in the gut. Killing these bacteria may in itself cause the release of the endotoxin, which can then be absorbed into the systemic circulation by impairment of mucosal blood flow inherent in the non-physiologic flow during CPB.

Off-Pump Cardiac Surgery

There is little evidence that the use of off-pump cardiac surgery is in any way beneficial to the GI tract. Three retrospective studies[542,550,572] have shown no differences in GI complications. One reason for this lack of apparent difference between on-pump and off-pump cardiac surgery may again be related to the common denominator of splanchnic perfusion. OPCAB surgery is fraught with hemodynamic compromise that may lead to prolonged periods of splanchnic hypoperfusion by itself or as a result of the concurrent administration of vasopressors to maintain normal hemodynamics during the frequent manipulations of the heart.

Antiinflammatory Therapies

Although the inflammatory response to CPB has been implicated as a causative factor in GI complications after cardiac surgery, few data are available to assess the ability of various antiinflammatory therapies (eg, corticosteroids, aprotinin, complement inhibitors) to reduce these types of complications (see Chapter 9).

Lung Injury During Cardiac Surgery

Incidence and Significance

Pulmonary dysfunction was one of the earliest recognized complications of cardiac surgery employing CPB.[573] However, as improvements in operative technique and CPB perfusion technologies occurred, the overall frequency and severity of this complication decreased. Juxtaposed to the improvements in cardiac surgery, which led to an overall reduction in complications, is an evolving patient population that now comprises a higher-risk group with a higher degree of pulmonary comorbidities, increasing their risks of postoperative pulmonary dysfunction. With the advent of fast-track techniques,[574] even minor degrees of pulmonary dysfunction have reemerged as significant contributors to patient morbidity and the potential need for extended postoperative ventilation. As with most postoperative organ dysfunction, there is a range of dysfunction severity. Arguably, some

degree of pulmonary dysfunction occurs in most patients after cardiac surgery; however, it manifests clinically only when the degree of dysfunction is particularly severe or the pulmonary reserve is significantly impaired.[575,576] As a result, even minor CPB-related pulmonary dysfunction can cause significant problems in some patients.

The full range of reported pulmonary complications includes simple atelectasis, pleural effusions, pneumonia, cardiogenic pulmonary edema, pulmonary embolism, and various degrees of acute lung injury ranging from the mild to the most severe (ie, acute respiratory distress syndrome [ARDS]). Although the final common pathway in all of these forms of pulmonary dysfunction complications is the occurrence of hypoxemia, these complications vary widely in their incidence, cause, and clinical significance. Understanding that the changes that occur after CPB represent a continuum, it becomes necessary to define what constitutes pulmonary dysfunction and injury.

Definitions have varied. One commonly accepted definition that was used in a large study ($N = 1461$ patients) performed in the setting of cardiac surgery defined acute pulmonary dysfunction as a patient requiring mechanical ventilation with an arterial partial pressure of oxygen (Pa_{O_2}) to fraction of inspired oxygen (F_{IO_2}) ratio of less than 150, irrespective of positive end-expiratory pressure, coupled with a chest radiograph that indicated the development of bilateral pulmonary infiltrates, assuming that other causes of hypoxia such as pneumothorax could be excluded. Using this definition, approximately 12% of patients on admission to the cardiovascular ICU after cardiac surgery met the criteria of early acute pulmonary dysfunction.[577,578] Early acute pulmonary dysfunction should be differentiated from the more severe but less common ARDS that occurs in 1% to 2% of patients.[577,579] Although these two forms likely represent similar processes with different degrees of severity, ARDS differs particularly in its timing. The definition of ARDS in the setting of cardiac surgery generally requires the presence of refractory hypoxemia, diffuse bilateral pulmonary infiltrates on chest radiograph, the requirement for mechanical ventilation with an F_{IO_2} of more than 0.40, and, most important, a duration of at least 3 days (as opposed to on admission to the ICU). This must be in the presence of a low pulmonary artery wedge pressure (PCWP < 18 mm Hg). In a study by Welsby and colleagues[580] of 2609 consecutive adult cardiac surgery patients, 7.5% of whom had pulmonary complications, the overall mortality rate was 21%, with 64% of these patients remaining in the hospital more than 10 days. In another study, the most significantly affected patients (ie, those with ARDS) had a mortality rate upward of 80%.[581] These significant morbidity and mortality rates lend credence to pulmonary complications remaining as significant and relevant today as in the early days of cardiac surgery.

Atelectasis and pleural effusions are the most common pulmonary abnormalities seen after cardiac surgery, presenting in more than 60% of patients.[582,583] Atelectasis is commonly attributed to a number of intraoperative and postoperative events. With the induction of general anesthesia, physical compression of the left lower lobe to aid exposure of the heart and facilitate in the dissection of the internal mammary artery, as well as the apnea occurring during the conduct of CPB have all been implicated.[584,585] Postoperative causes include the poor respiratory efforts by patients with impaired coughing, lack of deep inspirations, and pleural effusions.[586] Despite a high incidence of these radiographically recognized complications, the clinical significance is relatively low.[587,588]

Similar to atelectasis, pleural effusions, despite occurring commonly after cardiac surgery (40–50%), rarely cause significant perioperative morbidity. More common in the left thorax, likely as a consequence of the bleeding from the dissection of the internal mammary artery, other causes of pleural effusions relate to continued postoperative bleeding, pulmonary edema from cardiogenic and noncardiogenic causes, and pneumonia. Surgical trauma can also disrupt the normal pleural lymphatic flow through the thorax and, very rarely, direct damage to the internal thoracic duct can lead to the development of a chylothorax. Small effusions tend to resolve over time (a few months postoperatively) and rarely require any specific treatment. However, large pleural effusions that compromise the underlying lung respond well to thoracentesis and temporary chest tube placement, but if persistent, they may require decortication.

Pneumonia after cardiac surgery also has a variable incidence but a much higher significance to overall patient outcome. Reported rates of pneumonia range widely from 2% to 22%.[589–592] Pneumonia occurring early after cardiac surgery portends a very poor outcome, illustrated in one study by a mortality rate of 27%.[593] Factors that increase the risk for postoperative pneumonia include smoking, the presence of chronic obstructive pulmonary disease, other pulmonary complications requiring prolonged intubation, significant heart failure, and the transfusion of large volumes of blood products.

Risk Factors for Pulmonary Dysfunction

Rady and coworkers[577] defined preoperative, operative, and postoperative variables that represent risk factors for early pulmonary dysfunction after cardiac surgery. Although it is not entirely clear whether any of these risk factors can be modified, identifying their presence raises the level of vigilance for the subsequent development of pulmonary dysfunction.[578–593] The risk factors for the most severe ARDS syndrome as defined by Christenson and associates[579] include hypertension, current smoking, emergency surgery, heart failure (New York Heart Association classes III and IV), postoperative LCOS, and a LV ejection fraction of less than 40%. More recently, Filsoufi and investigators reported the risk factors for respiratory failure focusing on valve surgery patients.[594] They studied 2808 patients, reporting risk factors of preoperative renal failure, female gender, ejection fraction less than 30%, double valve procedures, active endocarditis, advanced age (>70 years), heart failure, reoperation, emergent procedures, previous MI, and prolonged (>180 min) CPB time.

Pathophysiology and Causative Factors

Studies have demonstrated CPB-induced changes in the mechanical properties (ie, elastance or compliance and resistance) of the pulmonary apparatus (particularly the lung as opposed to the chest wall) and changes in pulmonary capillary permeability. Impairment in gas exchange has been demonstrated to be a result of atelectasis with concomitant overall loss of lung volume.[573,595–599] Most research has focused on the development of increases in pulmonary vascular permeability (leading to various degrees of pulmonary edema) as the principal cause of the impaired gas exchange that occurs during cardiac surgery and results in a high alveolar-arterial (A-a) gradient.

The cause of pulmonary dysfunction and ARDS after cardiac surgery is complex, but largely revolves around the CPB-induced systemic inflammatory response with its associated increase in pulmonary endothelial permeability.[600,601] A central causative theme is a significant upregulation in the inflammation induced because of the interaction between the blood and foreign surfaces of the heart-lung machine or the inflammation related to the consequences of splanchnic hypoperfusion with the subsequent translocation of significant amounts of endotoxin into the circulation. Endotoxin is proinflammatory, and it has direct effects on the pulmonary vasculature.[602] Clinical studies have demonstrated an increase in circulating intracellular adhesion molecules after CPB in patients with development of acute lung injury.[603] Pathologic examination of the lungs of patients manifesting ARDS has shown extensive injury to the tissue, including swelling and necrosis of endothelial cells and type I and II pneumocytes.[604] In addition to CPB-mediated inflammation, inflammation mediated by endotoxemia has been reported. Several studies have identified transfusion of packed red blood cells (>4 units) as a risk factor for ARDS in cardiac surgical patients (see Chapter 34).[605,606]

Pulmonary Thromboembolism

Although not an injury to the lungs occurring as a direct result of CPB itself, deep vein thrombosis (DVT) and pulmonary embolism

occur with regular frequency in the cardiac surgical population. The incidence of pulmonary embolism after cardiac surgery ranges from 0.3% to 9.5%, with a mortality rate approaching 20%.[339,607,608] The incidence of pulmonary embolism appears to be lower after valve surgery compared with CABG, which may be due to the anticoagulation that is started soon after valve surgery.[608,609]

The incidence of DVT is 17% to 46%, with most cases being asymptomatic.[339,608] The higher incidences were reported from series that used lower extremity ultrasound to more comprehensively examine populations.[339] DVT has been reported for the leg from which the saphenous vein grafts were harvested and from the contralateral leg.[608,610] In a study of post-CABG patients ($N = 270$) admitted to a rehabilitation unit who underwent lower extremity ultrasound examinations, DVT was detected in 17%, with two patients subsequently developing pulmonary emboli.[611] In a postmortem study in 147 patients after cardiac surgery, pulmonary embolism was the cause of death for 4%.

The recommendations for DVT prophylaxis in cardiac surgery are aspirin and elastic gradient compression stockings in patients who ambulate within 2 to 3 days after surgery and low-molecular-weight heparin and sequential compression stockings in nonambulatory patients.[339] These recommendations are based on a randomized trial in which prophylaxis with sequential pneumatic compression stockings provided no added protection against DVT in ambulating CABG patients treated with aspirin and elastic gradient compression stockings.[612]

Pulmonary Protection

Ventilatory Strategies

Several studies have examined the use of continuous positive airway pressure (CPAP) during CPB as a means to minimize the decrement in the A-a gradient that can occur after surgery. In a small study by Gilbert and colleagues,[613] the effect of CPAP was examined in a randomized trial of 18 patients undergoing CABG surgery with CPB. CPAP did not appear to make any difference with respect to changes in measured lung resistance and elastance. In a larger ($N = 61$) study by Berry and coworkers,[614] CPAP did appear to have some transient beneficial effects on A-a gradient; however, these minor differences dissipated 4 hours after bypass. Overall, it is unlikely that CPAP plays any major role in preventing or treating the pulmonary dysfunction that occurs in the setting of cardiac surgery.

The inspired oxygen content of the gases that the lungs see during the period of apnea during CPB may have an effect on the A-a gradient, probably because of the enhanced effect of higher FIO_2 on the ability of atelectasis (so-called absorption atelectasis) on these gradients. With these findings in mind, it would be prudent to reduce the FIO_2 to room air levels during CPB. Several simple therapies can be introduced before separation from CPB, including adequate tracheobronchial toilet and the delivery of several vital capacity breaths that may reduce the amount of atelectasis that has occurred during bypass[585] (Box 31.6).

Ventilatory support of patients with acute lung injury (including ARDS) has undergone changes (see Chapter 39).[615,616] Although not studied specifically in the setting of cardiac surgery, a study authored by the Acute Respiratory Distress Syndrome Network highlighted the avoidance of ventilator-associated pulmonary mechanotrauma.[616] Delivery of repeated large tidal volumes may damage the alveoli and other small lung structures, and these mechanical stresses may activate a pulmonary inflammatory response with a local release of cytokines, further enhancing injury to the lungs. As a result, these groups of investigators randomized patients to small (approximately 6 mL/kg) or traditional tidal volumes (12 mL/kg). They demonstrated in this multicenter trial that the low tidal volume ventilation strategy could reduce mortality in patients with ARDS by up to 25%. Although this has not been specifically studied in the setting of cardiac surgery, it would be prudent to employ this beneficial ventilator strategy in cardiac surgical patients who have significant acute lung injury.

BOX 31.6 STRATEGIES TO PROTECT THE LUNGS

- Reduced fraction of inspired oxygen (FIO_2) during bypass
- Low postoperative tidal volume
- Vital capacity breath before bypass separation

Pharmacologic Pulmonary Protection

Steroids

Antiinflammatory therapies may play a role in moderating the effects of the more significant forms of pulmonary dysfunction that occur after cardiac surgery and that have inflammation as a central causative factor. However, with the exception of corticosteroids, few antiinflammatory therapies are available for routine use. Corticosteroid use can reduce the amount of systemic inflammation as measured by circulating cytokines.[617–619] However, this has not been coupled with a reduction in pulmonary dysfunction. Chaney and colleagues, in two separate studies,[195,620] demonstrated that relatively high doses of methylprednisolone actually had a detrimental effect on post-CPB pulmonary function. Both studies demonstrated no improvement or worsening in lung compliance, shunt, A-a gradient, and delays in extubation. It was speculated that the A-a gradient deterioration and delayed pulmonary extubation associated with steroid administration was attributable to steroid-induced sodium retention and vasodilation resulting in increased shunt and increased lung water content with pulmonary edema. Steroid administration led to significant hyperglycemia, which is difficult to treat during CPB.[620] In a similar study by Oliver and coworkers[619] comparing placebo to steroids or hemofiltration, the steroid-treated patients had larger increases in postoperative A-a gradients. Using a preset mechanical ventilation protocol to guide ventilation weaning, steroids again failed to reduce the time to tracheal extubation (519 ± 293 vs 618 ± 405 min; $P = .21$), confirming the findings of Chaney and colleagues.[620] However, the latest information on steroid use in cardiac surgery comes from the high-dose (1 mg/lg) dexamethasone in cardiac surgery trial.[260] The high-dose dexamethasone group, in contrast to previous studies, had a shorter duration of mechanical ventilation and pulmonary infections suggesting that if not overtly protective, then at the very least, there was no increased pulmonary risk to steroid use.

Aprotinin

The nonspecific serum protease inhibitor aprotinin was once used to reduce blood loss and transfusion after cardiac surgery, and there is some evidence that it reduced CPB-related systemic inflammation.[621–623] Aprotinin was first investigated for use in the setting of cardiac surgery as a means to protect the lungs from the whole-body inflammatory response initiated as a result of the contact activation of blood with the foreign surfaces of the CPB apparatus.[624,625] These studies serendipitously discovered aprotinin's salutary effect on preventing blood loss and transfusion in cardiac surgery.[626] After these studies, aprotinin was extensively evaluated for its blood loss and transfusion-sparing effects, with little further work focused on the pulmonary effects. Despite being a robust inhibitor of CPB-related inflammatory response, any ability to prevent the pulmonary complications of CPB has not yet been demonstrated.

Nitric Oxide

One of the consistent sequelae of pulmonary dysfunction is the development of variable degrees of elevated pulmonary vascular resistance and pulmonary hypertension. As a result, several pulmonary vasodilators have been used, most notably inhaled nitric oxide, in an attempt to reduce the pulmonary artery pressures and with it the workload of the right ventricle (see Chapter 26).[627–629]

BOX 31.7 MANAGEMENT BEFORE CARDIOPULMONARY BYPASS

- Anticoagulation
- Cannulation of the heart
- Careful monitoring to minimize organ dysfunction
- Protection of the heart
- Preparation for cardiopulmonary bypass

Nitric oxide has been used in cardiac surgery and in heart and lung transplantation as a selective pulmonary vasodilator.[630] However, there are no trials demonstrating any beneficial use for its prophylactic administration in the setting of cardiac surgery. Although it has statistically significantly reduced pulmonary artery pressures in cardiac surgery, it is unclear whether these reductions are reflected in improvements in overall outcome.

Management of Bypass

The Prebypass Period

An important objective of this phase is to prepare the patient for CPB (Box 31.7). This phase invariably involves two key steps: anticoagulation and vascular cannulation. With rare exception,[631] heparin is still the anticoagulant clinically used for CPB. Dose, method of administration, and opinions as to what constitutes adequate anticoagulation vary. Heparin must be administered before cannulation for CPB, even if cannulation must be done emergently. Failure to do so is to risk thrombosis in both the patient and extracorporeal circuit. Chapters 19, 34, and 35 offer a complete discussion of hemostasis management of cardiac surgery patients. After heparin has been administered, a period of at least 3 minutes is customarily allowed for systemic circulation and onset of effect; an activated coagulation time or heparin concentration measurement demonstrating actual achievement of adequate anticoagulation is then performed.

Vascular Cannulation

The next major step in the prebypass phase is vascular cannulation. The goal of vascular cannulation is to provide access whereby the CPB pump may divert all systemic venous blood to the pump-oxygenator at the lowest possible venous pressures and deliver oxygenated blood to the arterial circulation at pressure and flow sufficient to maintain systemic homeostasis (see Chapter 32).

Arterial Cannulation

Arterial cannulation is generally established before venous cannulation to allow volume resuscitation of the patient, should it be necessary. The ascending aorta is the preferred site for aortic cannulation because it is easily accessible, does not require an additional incision, accommodates a larger cannula to provide greater flow at a reduced pressure, and carries a lower risk of aortic dissection compared with other arterial cannulation sites (femoral or iliac arteries). Because hypertension increases the risk of aortic dissection during cannulation, the aortic pressure may be temporarily lowered (MAP < 70 mm Hg) during aortotomy and cannula insertion. Several potential complications are associated with aortic cannulation, including embolization of air or atheromatous debris, inadvertent cannulation of aortic arch vessels, aortic dissection, and other vessel wall injury.[632–637]

Reviews and clinical reports emphasize the importance of embolization as the major mechanism of focal cerebral injury in cardiac surgery patients. Barzilai and coworkers[638] and Wareing and associates[633] reported intraoperative use of two-dimensional epiaortic ultrasound imaging as a guide to selection of cross-clamping and cannulation sites. In 24% and 33% of the patients in the Barzilai and Wareing studies, respectively, ultrasonic findings led to selection of alternate cannulation sites. A femoral or axillary artery, rather than the ascending aorta, can be cannulated for systemic perfusion. These alternate sites can be used when ascending aortic cannulation is considered relatively contraindicated, as in severe aortic atherosclerosis, aortic aneurysm or dissection, or known cystic medical necrosis.[7,120,639,640] Historically, the anesthesiologist sought evidence of cannula malposition by looking for unilateral blanching of the face, gently palpating carotid pulses and checking for new unilateral diminution, and by measuring blood pressure in both arms and to check for new asymmetries. However, robust assessments of CBF symmetry can more reliably be made with the use of near-infrared spectroscopy cerebral oximetry (see Chapter 18).

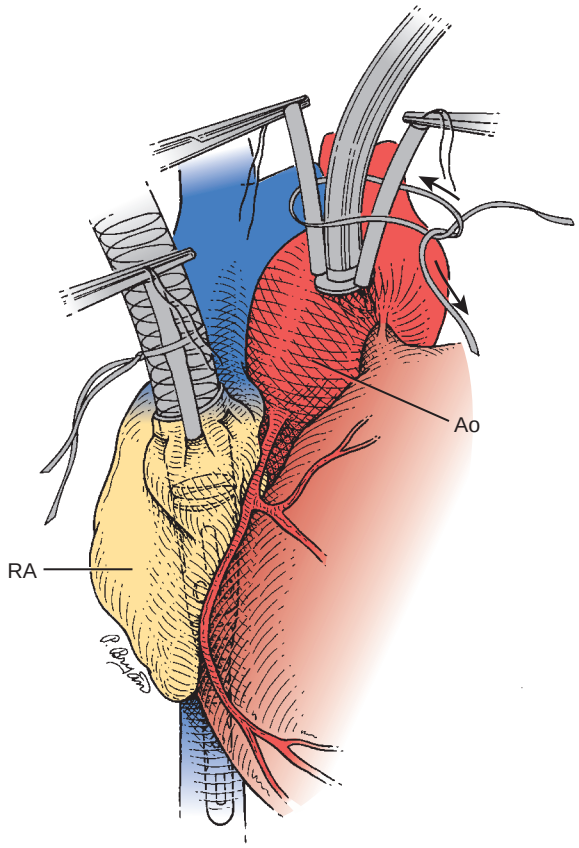


Fig. 31.11 Aortic *(Ao)* and single, double-staged, right atrial *(RA)* cannulation. Notice the drainage holes of venous cannula in right atrium and inferior vena cava. *(From Connolly MW.* Cardiopulmonary Bypass. *New York: Springer-Verlag; 1995:59.)*

Venous Cannulation

Venous cannulation can be achieved using a single atrial cannula that is inserted into the right atrium and directed inferiorly (Fig. 31.11). Drainage holes in this multistage cannula are located in the inferior vena cava (IVC) and right atrium to drain blood returning from the lower extremities and the SVC and coronary sinus, respectively. This technique has the advantage of being simpler, faster, and requiring only one incision; however, the quality of drainage can be easily compromised when the heart is lifted for surgical exposure.[641] The bicaval cannulation technique, required in cases in which right atrial access is needed, involves separately cannulating the SVC and IVC (Fig. 31.12). Loops placed around the vessels can be tightened to divert all caval blood flow away from the heart. Blood returning to the right atrium from the coronary sinus will not be drained using this technique, so an additional vent or atriotomy is necessary.

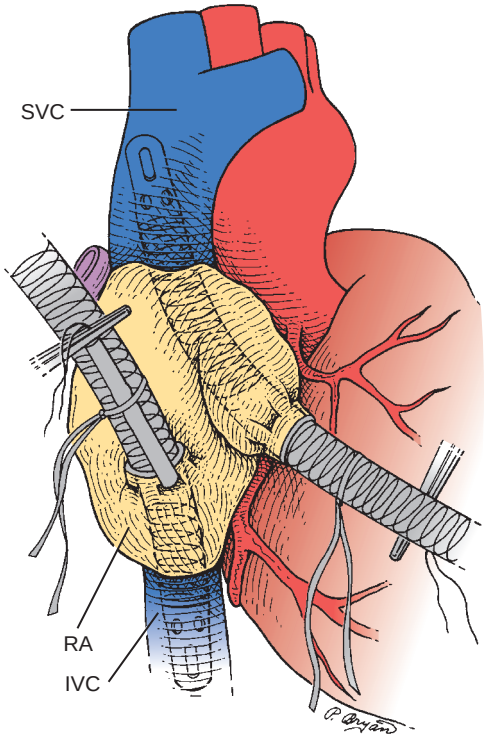


Fig. 31.12 Position of two-vessel cannulation of right atrium *(RA)* with placement of drainage holes into superior vena cava *(SVC)* and inferior vena cava *(IVC)*. The aortic cannula is not shown. *(From Connolly MW. Cardiopulmonary Bypass. New York: Springer-Verlag; 1995:59.)*

BOX 31.8 BYPASS PREPARATION CHECKLIST

1. Anticoagulation
   a. Heparin administered
   b. Desired level of anticoagulation achieved
2. Arterial cannulation
   a. Absence of bubbles in arterial line
   b. Evidence of dissection or malposition?
3. Venous cannulation
   a. Evidence of superior vena cava obstruction?
   b. Evidence of inferior vena cava obstruction?
4. Pulmonary artery catheter (if used) pulled back
5. Are all monitoring and/or access catheters functional?
6. Transesophageal echocardiograph (if used)
   a. In "freeze" mode
   b. Scope in neutral or unlocked position
7. Supplemental medications
   a. Neuromuscular blockers
   b. Anesthetics, analgesics, amnestics
8. Inspection of head and neck
   a. Color
   b. Symmetry
   c. Venous drainage
   d. Pupils

During CPB, blood will continue to return to the left ventricle from a variety of sources, including the bronchial and thebesian veins, as well as blood that traverses the pulmonary circulation. Abnormal sources of venous blood include a persistent left SVC, systemic-to-pulmonary shunts, and aortic regurgitation. It is important to avoid LV filling and distention during CPB to prevent myocardial rewarming, minimize LV wall tension, and limit myocardial oxygen demand.[642] This can be accomplished with the use of a vent placed in the left ventricle via the left superior pulmonary vein. Alternate sites include the pulmonary artery, the aortic root, or directly in the left ventricle via the ventricular apex.

Venous cannulas, using a multistage or bicaval cannula, are large and can impair venous return from the IVC or SVC. Superior vena caval obstruction is detected by venous engorgement of the head and neck, conjunctival edema, and elevated SVC pressure. Inferior vena caval obstruction is far more insidious, presenting only as decreased filling pressures because of lowered venous return.

Femoral venous cannulation is sometimes used for CPB without, or before, sternotomy or right atrial cannulation (eg, redos, ascending aortic aneurysms). Because of the femoral venous cannula's comparatively small size and long length, venous return can be impaired but is optimized when the tip of the cannula is advanced (under TEE guidance) until it is placed at the level of the SVC–right atrium junction. Kinetic or vacuum-assisted negative pressure can be applied to further enhance drainage.

Other Preparations

Once anticoagulation and cannulation are complete, CPB can be instituted. Because there usually is redundant pulmonary artery catheter length in the right ventricle, and the heart is manipulated during CPB, there is a tendency for distal migration of the catheter into pulmonary artery branches.[643] This distal migration of the catheter increases the risks of "overwedging" and pulmonary artery damage. During the prebypass phase it is advisable to withdraw the pulmonary artery catheter 3 to 5 cm to decrease the likelihood of these untoward events. It is also advisable to check the integrity of all vascular access and monitoring devices. A pulmonary artery catheter placed through an external jugular[644,645] or subclavian vein[646] can become kinked or occluded on full opening of the sternal retractor. If TEE is being used, the probe should be placed in the "freeze" mode and the tip of the scope placed in the neutral and unlocked position. Leaving the electronic scanning emitter turned on during hypothermic CPB adds heat (in some TEE models) to the esophagus and posterior wall of the ventricle.

Before initiating CPB, the anesthesiologist should assess the depth of anesthesia and adequacy of muscle relaxation. It is important to maintain paralysis to prevent patient movement that could result in dislodgment of bypass-circuit cannulas and prevent shivering as hypothermia is induced (with the attendant increases in oxygen consumption).[647] It is often difficult to determine the depth of anesthesia during the various stages of CPB. Because blood pressure, heart rate, pupil diameter, and the autonomic nervous system are profoundly affected by extracorporeal circulation (eg, the heart is asystolic, blood pressure is greatly influenced by circuit blood flow, and sweating occurs with rewarming), these variables do not reliably reflect the anesthetic state. Although hypothermia decreases anesthetic requirements, it is necessary to provide analgesia, hypnosis, and muscle relaxation during CPB. Useful adjuncts to assessing depth of anesthesia are available in the form of processed EEG devices. For example, the bispectral index has proven useful in preventing awareness during cardiac surgery.[648] With the initiation of CPB and hemodilution, blood levels of anesthetics and muscle relaxants acutely decrease. However, plasma protein concentrations also decrease, which increases the free-fraction and active drug concentrations. Every drug has a specific kinetic profile during CPB, and kinetics and pharmacodynamics during CPB vary greatly among patients. Many clinicians administer additional muscle relaxants and opioids at the initiation of CPB. A vaporizer for potent inhalation drugs may be included in the bypass circuit. Hall and investigators[649] offer an extended discussion of pharmacokinetics and bypass. A final inspection of the head and neck for color, symmetry, adequacy of venous drainage (neck vein and conjunctiva engorgement), and pupil equality is reasonable to serve as a baseline for the anesthetic state. A summary of preparatory steps to be accomplished during the prebypass phase is given in Box 31.8.

Initiation and Discontinuation of Bypass Support: An Overview

Initiation of Cardiopulmonary Bypass

Uncomplicated Initiation

Once all preparatory steps have been taken, the perfusionist progressively increases delivery of oxygenated blood to the patient's arterial system, as systemic venous blood is diverted from the patient's right side of the heart, maintaining the pump's venous reservoir volume. After full flow is achieved, all systemic venous blood is (ideally) draining from the patient to the pump reservoir. An on-bypass checklist of issues to address shortly after initiation of bypass can serve as a valuable safety tool (Box 31.9). The central venous pressure (CVP) and pulmonary arterial pressure should decrease to near zero (2–5 mm Hg), whereas systemic flow, arterial pressure, and oxygenation are maintained at desired values.

Hypotension With Onset of Bypass

Systemic arterial hypotension (MAP, 30–40 mm Hg) is relatively common on initiation of CPB. Gordon and colleagues[650] proposed that much of this could be explained by the acute reduction of blood viscosity that results from hemodilution with nonblood priming solutions. These investigators proposed systemic vascular resistance (SVR = MAP − CVP/CO) to be the product of blood viscosity (η) and inherent systemic vascular hindrance: SVR = η × SVH. MAP increases with initiation of hypothermia-induced vasoconstriction, along with levels of endogenous catecholamines and angiotensin. The hemodilution also results in the loss of nitric oxide binding by hemoglobin[651]; the excess free nitric oxide can lead to further vasodilation. Treatment with α-agonists is *usually* not necessary if the hypotension is brief (<60 s). Of concern is the potential for myocardial and cerebral ischemia because hypothermia has not yet been achieved.

Until the aortic cross-clamp is applied, the coronary arteries are perfused with hemodiluted, nonpulsatile blood. Schaff and coworkers[652] showed that subendocardial ischemia occurred in the distribution of critical coronary stenosis when MAP was less than 80 mm Hg in the normothermic empty beating heart. If placement of the aortic cross-clamp is delayed, MAP should be maintained in the range of 60 to 80 mm Hg to support myocardial perfusion, especially in the presence of known coronary stenosis or ventricular hypertrophy. This arterial pressure is likely adequate to maintain CBF until hypothermia is induced.

Unless pulsatile perfusion is used, once at full flow, the arterial pressure waveform should be nonpulsatile except for small (5–10 mm Hg) sinusoidal deflections created by the roller pump heads. Continued pulsatile arterial pressure indicates that the left ventricle is receiving blood from some source.

Pump Flow and Pressure During Bypass

Pump flow during CPB represents a careful balance between the conflicting demands of surgical visualization and adequate oxygen delivery. Two theoretical approaches exist. The first is to maintain oxygen delivery during CPB at normal levels for a given core temperature. Although this may limit hypoperfusion, it increases the delivered embolic load. The second approach is to use the lowest flows that do not result in end-organ injury. This approach offers the potential advantage of less embolic delivery as well as potential improved myocardial protection and surgical visualization.[653,654] However, some of these advantages are not seen when the left ventricle is vented during CPB.[655]

During CPB, pump flow and pressure are related through overall arterial impedance, a product of hemodilution, temperature, and arterial cross-sectional area. This is important because the first two factors, hemodilution and temperature, are critical determinants of pump flow requirements. Pump flows of 1.2 L/min per m^2 perfuse most of the microcirculation when the hematocrit is near 22% and hypothermic CPB is being employed.[656] However, at lower hematocrits or periods of higher oxygen consumption, these flows become inadequate.[657–659] Because of changes in oxygen demand with temperature and the plateauing of oxygen consumption with increasing flow, a series of nomograms have been developed for pump flow selection (Fig. 31.13).

In addition to use of these nomograms, most perfusion teams also monitor mixed venous oxygen saturation, targeting levels of 70% or greater. Unfortunately, this level does not guarantee adequate perfusion of all tissue beds, because some (muscle, subcutaneous fat) may be functionally removed from the circulation during CPB.[659] Hypothermic

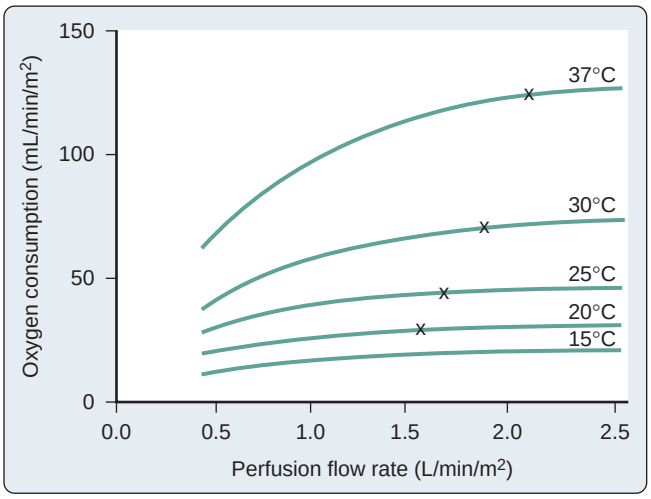


Fig. 31.13 Nomogram depicting the relationship of oxygen consumption (VO_2) to perfusion flow rate and temperature. The *x* on the curves represents common clinically used flow rates at the various temperatures. *(From Kirklin JW, Barratt-Boyes BG. Cardiac Surgery. New York: Wiley; 1986:35.)*

BOX 31.9 BYPASS PROCEDURE CHECKLIST

1. Assess arterial inflow.
   a. Is arterial perfusate oxygenated?
   b. Is direction of arterial inflow appropriate?
   c. Evidence of arterial dissection?
   d. Patient's arterial pressure persistently low?
   e. Inflow line pressure high?
   f. Pump/oxygenator reservoir level falling?
   g. Evidence of atrial cannula malposition?
   h. Patient's arterial pressure persistently high or low?
   i. Unilateral facial swelling, discoloration?
   j. Symmetrical cerebral oximetry?
2. Assess venous outflow.
   a. Is blood draining to the pump/oxygenator's venous reservoir?
   b. Evidence of SVC obstruction?
   c. Facial venous engorgement or congestion, CVP elevated?
3. Is bypass complete?
   a. High CVP/low PA pressure?
   b. Impaired venous drainage?
   c. Low CVP/high PA pressure?
   d. Large bronchial venous blood flow?
   e. Aortic insufficiency?
   f. Arterial and PA pressure nonpulsatile?
   g. Desired pump flow established?
4. Discontinue drug and fluid administration.
5. Discontinue ventilation and inhalation drugs to patient's lungs.

CVP, Central venous pressure; *PA*, pulmonary artery; *SVC*, superior vena cava.

venous saturation may overestimate end-organ reserves.[660] Slater and associates[564] characterized the hierarchy of regional blood flows during CPB at 27°C. Animals were perfused at pump blood flows of 1.9, 1.6, 1.3, and 1.0 L/min per m^2. Regional perfusion of various end-organs (brain, kidney, small intestine, pancreas, and muscle) was quantified with a fluorescent microsphere technique. CBF was unchanged at the three greatest pump flows. Renal perfusion was maintained at flows of 1.9 and 1.6 L/min per m^2. Perfusion to the pancreas was constant at all flows studied, and small bowel perfusion varied linearly with pump flow. Muscle bed flows were decreased at all flows. This study confirmed previous work regarding end-organ perfusion during CPB and highlighted the vulnerability of the kidneys to reduced flows at moderate hypothermia.

During CPB, most of the outcomes studied in relation to pump flow are those related to the organs at high risk for ischemic injury (ie, kidney and brain). Much work has been applied to examining the relationship between renal dysfunction and pump flow.[314,319,661,662] Preexisting renal disease is a consistent predictor of postoperative renal dysfunction, the incidence of which ranges between 3% and 5%. Renal function appears unaltered when pump flows greater than 1.6 L/min per m^2 are employed,[661] but whether this management will affect outcomes in patients with preexisting renal dysfunction is less clear.[662] Because of autoregulation, most studies,[175,663] but not all,[664] suggest that CBF is unaltered by variation in pump flow. At low-flow states, CBF is probably more dependent on perfusion pressure.[665–667] Discussion regarding organ-specific relationships of pressure to organ dysfunction are included in the previous section on end-organ effects of CPB.

Preparation for Separation

Before discontinuation of CPB, conditions that optimize cardiac and pulmonary function must be restored. To a great extent this is achieved by reversing the processes and techniques used to initiate and maintain CPB (Box 31.10).

BOX 31.10 PREPARATION FOR SEPARATION FROM BYPASS CHECKLIST

1. Air clearance maneuvers completed
2. Rewarming completed
   a. Nasopharyngeal temperature 36–37°C
   b. Rectal/bladder temperature ≥35°C, but ≤37°C
3. Address issue of adequacy of anesthesia and muscle relaxation
4. Obtain stable cardiac rate and rhythm (use pacing if necessary)
5. Pump flow and systemic arterial pressure
   a. Pump flow to maintain mixed venous saturation ≥70%
   b. Systemic pressure restored to normothermic levels
6. Metabolic parameters
   a. Arterial pH, P_{O_2}, P_{CO_2} within normal limits
   b. Hct: 20–25%
   c. K^+: 4.0–5.0 mEq/L
   d. Possibly ionized calcium
7. Ensuring all monitoring/access catheters are functional
   a. Transducers re-zeroed
   b. TEE (if used) out of freeze mode
8. Respiratory management
   a. Atelectasis cleared/lungs reexpanded
   b. Evidence of pneumothorax?
   c. Residual fluid in thoracic cavities drained
   d. Ventilation reinstituted
9. Intravenous fluids restarted
10. Inotropes/vasopressors/vasodilators prepared

Hct, Hematocrit; *TEE*, transesophageal echocardiography.

Potential for Patient Awareness

It is not uncommon for patients to sweat during rewarming. This is almost certainly caused by perfusion of the hypothalamus (ie, the thermoregulatory site) with blood that is warmer than the latter organ's set-point (37°C). The brain is a high-flow organ and can be assumed to equilibrate fairly quickly (10 to 15 minutes) with cerebral perfusate temperature (ie, nasopharyngeal temperature). A less likely, but more disturbing, possibility is that restoration of brain normothermia with decreased anesthetic concentration may result in an inadequate depth of anesthesia and the potential for awareness. It is estimated that awareness occurs during cardiac surgery in approximately 0.1% of patients.[648]

The following suggestions are made to attempt to limit the possibility and sequelae of awareness during cardiac surgery with CPB. During the preoperative evaluation, the possibility of awareness and why it could occur should be discussed with the patient. Use of volatile agents for their amnestic properties should be considered. During the postoperative visit, a mechanism whereby the patient can freely communicate perioperative experiences should be provided. Necessary support, including counseling, to minimize potential long-term psychologic problems should awareness be reported should be provided.

Patient movement before discontinuation of CPB is, at the least, extremely disruptive and may be genuinely life-threatening if it results in cannula dislodgment or disruption of the procedure. Additional muscle relaxant should be administered. If awareness is suspected, supplemental amnestics or anesthetics should be administered during rewarming. Because sweating stops almost immediately on discontinuation of CPB, continued sweating after emergence from CPB may be a sign of awareness. Neurologic monitors such as the bispectral index can be used to help judge the depth of anesthesia during and after weaning from CPB.[668]

Rewarming

When systemic hypothermia is used, body temperature is restored to normothermia by gradually increasing perfusate temperature with the heat exchanger. Time required for rewarming (ie, heat transfer) varies with arterial perfusate temperature, patient temperature, and systemic flow. Excessive perfusate heating is not advisable for at least three key reasons: possible denaturation of plasma proteins, possible cerebral hyperthermia, and the fact that dissolved gas can come out of solution and coalesce into bubbles if the temperature gradient is too great. Because small increases (0.5°C) in cerebral temperature exacerbate ischemic injury in the brain, it is critical to perfuse the patient with blood temperatures at or below 37°C. Although this will increase the duration of rewarming, the risk of hyperthermic brain injury is greatly increased with hyperthermic blood temperatures. Most centers now employ mild hypothermia (ie, systemic temperature 32–35°C) instead of moderate hypothermia (26–28°C), reducing the amount of heat transfer required to achieve normothermia during rewarming.

Rewarming may be enhanced by increasing pump flow, which thereby increases heat input. At levels of hypothermia routinely used (25–30°C), the patient behaves as if vasoconstricted (calculated SVR is relatively high). Increasing pump flow in this setting may result in unacceptable hypertension. There are two approaches to this problem: wait out the vasoconstriction or pharmacologically induce patient vasodilation. When rectal or bladder temperature approaches 30 to 32°C, patients appear to rapidly vasodilate. This is probably the result of decreasing blood viscosity or relaxation of cold-induced vasoconstriction with warming. Increasing pump flow at this point serves several purposes: increased heat transfer, support of systemic arterial pressure, and increased oxygen delivery in the face of increasing oxygen consumption. Often, waiting for the patient to spontaneously vasodilate is sufficient, and with subsequent increased pump flows, rewarming will be adequate at separation from CPB support. Circumstances in which more aggressive rewarming may be needed include profound hypothermia with a large hypoperfused "heat sink" and late initiation of warming by accident or design.

Skeletal muscle and subcutaneous fat are relatively hypoperfused during CPB. These tissues cool slowly and are also slow to warm. Temperatures at high-flow regions (eg, esophagus, nasopharynx) do not reflect the temperature of these tissues. Davis and investigators[669] reported that restoration of normothermia (as monitored at high-flow sites) led to a net heat deficit after CPB, with subsequent recooling after emergence (ie, afterdrop). Pharmacologic vasodilation allows an earlier increase in pump flow and delivery of warmed arterial blood to low-flow beds, making the rewarming process more uniform. Noback and Tinker[670] used sodium nitroprusside (3.5 ± 0.8 μg/kg per min) to permit increased pump flows during warming, from 4.0 to 4.5 L/min, keeping MAP at approximately 70 mm Hg. Compared with a group who were warmed without sodium nitroprusside for an equivalent period of time, the sodium nitroprusside group had much greater peripheral warming and a much smaller decline in postbypass temperature. Arteriolar vasodilators (eg, nicardipine, sodium nitroprusside) are much more likely to be effective in this process than venodilators (eg, nitroglycerin). Other aids to warming during or after CPB are sterile forced-air rewarming devices and servoregulated systems,[671] as well as heating blankets, warmed fluids,[672] heated humidified gases,[673] and increased room temperature. The issue of afterdrop is less of a concern during routine cardiac surgery but manifests frequently in patients following deep hypothermic circulatory arrest (DHCA).

Unfortunately, there is a very narrow range for acceptable systemic temperatures at the end of CPB. Just as temperatures that are "too hot" increase the risk of cerebral injury, those that are "too cool" may lead to inadequate rewarming and the problem of shivering, increased oxygen consumption and carbon dioxide production, and coagulopathies. It is imperative to prevent cerebral hyperthermia in patients undergoing CPB. Additional heat may be added to the patient *after* discontinuation of CPB with the use of external heating devices. This approach can prevent the complications of hypothermia without the use of hyperthermic blood.

Targets for rectal or bladder temperature before separation from CPB vary among institutions. Nathan and Polis[674] surveyed 28 Canadian centers regarding temperature monitoring practices during cardiac surgery and found the use of a variety of monitoring sites (Fig. 31.14). Many centers failed to use monitors likely to reflect cerebral temperatures routinely: not one center studied routinely monitored tympanic membrane temperature, and only slightly more than one-half monitored nasopharyngeal temperatures. The investigators were unable to discern any uniformity of practice regarding monitors or rewarming temperature end points. In general, temperatures measured at highly perfused tissues exceeded 37°C in most centers at the end of bypass.

Cook and colleagues[675] reported that cerebral hyperthermia occurs with rewarming. They studied 10 cardiac surgery patients requiring hypothermic CPB and measured nasopharyngeal and cerebral venous temperature (monitored at the jugular bulb). Ten minutes after the onset of rewarming from 27°C, cerebral venous temperature was 37°C, but nasopharyngeal temperature was only 34°C ± 2.9°C. After 18 minutes of rewarming, nasopharyngeal temperature reached 37°C and cerebral venous temperature was 38.2°C ± 1.1°C. Peak central venous temperature exceeded 39°C for an average of 15 minutes in all 10 patients before the termination of CPB.

Nathan and Polis[674] found a substantial difference between tympanic membrane and urinary bladder temperature in 11 patients rewarmed after hypothermic CPB (Fig. 31.15). The peak temperature for each patient was aligned at minute 0; temperatures were displayed for 30 minutes before (–30 to 0 min) and after (0 to 30 min) the peak temperature. There was a smooth increase in bladder temperature from 31.4 to 36°C, but an "overshoot" in peak tympanic membrane temperature to a mean of 38.6°C (range, 37.7–39.7°C). Because tympanic membrane temperature better reflects cerebral temperature than does bladder temperature, it is likely that all 11 patients were exposed to hyperthermic cerebral temperatures.

Restoration of Systemic Arterial Pressure to Normothermic Value

After aortic cross-clamp release, the heart is again perfused through the native coronary arteries. Until the proximal anastomoses are made, myocardial perfusion may be compromised in the presence of a low MAP. Consequently, it is advisable to gradually increase MAP during rewarming to levels of approximately 70 to 80 mm Hg.

With discontinuation of CPB, a marked discrepancy often exists between blood pressure readings measured from the radial artery and the central aorta. Radial arterial catheters may underestimate central

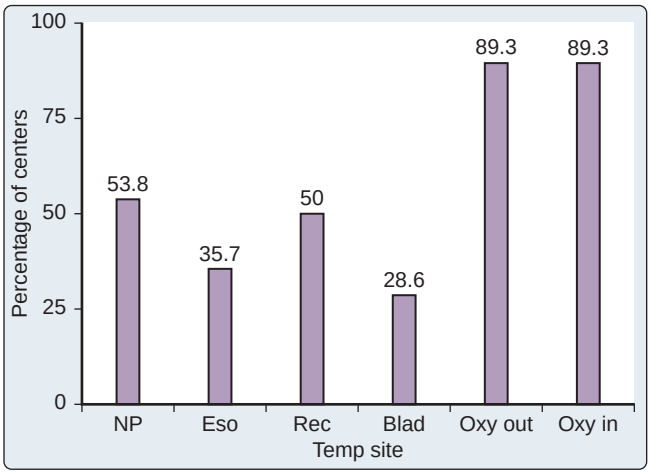


Fig. 31.14 Temperature monitoring sites in 30 adult cardiac surgery centers in Canada. *Blad,* Bladder; *Eso,* esophageal; *NP,* nasopharyngeal; *Oxy in,* oxygenator inlet; *Oxy out,* oxygenator outlet; *Rec,* rectal; *Temp,* temperature. *(From Nathan HJ, Lavallée G. The management of temperature during hypothermic cardiopulmonary bypass: I. Canadian survey.* Can J Anaesth *42:669–671, 1995.)*

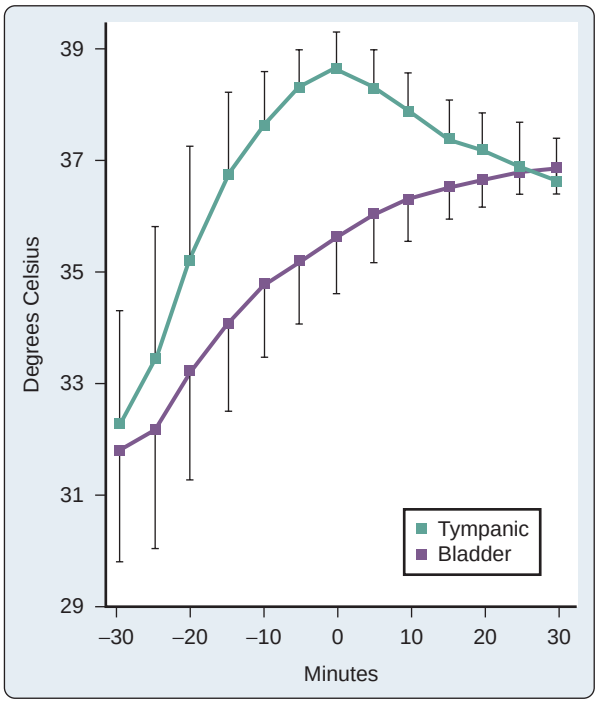


Fig. 31.15 Tympanic and bladder temperatures during rewarming. Time 0 represents the maximum temperature achieved. Mean ± standard deviation are shown. *(From Nathan HJ, Lavallée G. The management of temperature during hypothermic cardiopulmonary bypass: I. Canadian survey.* Can J Anaesth *1995;42:669–671.)*

aortic systolic pressures by 10 to 40 mm Hg. Discrepancies in MAP tend to be of a lesser magnitude (5–15 mm Hg). Such a discrepancy is not present before CPB, nor is it present after CPB in all patients. Mechanisms are undefined, but evidence supports vasodilatory and arteriovenous shunting phenomena in the forearm and hand.[676] Gravlee and coworkers[677] found that systolic pressure differences after CPB were not significantly influenced by duration of CPB, use of sodium nitroprusside or phenylephrine during the final 15 minutes of CPB, SVR, minimum CPB temperature, CPB separation temperature, or duration of rewarming. Blood pressure readings from brachial or femoral arterial catheters tend to more accurately reflect central aortic pressure. It is unknown at what point during CPB radial artery–central aortic blood pressure discrepancies develop, but most investigators report their resolution 20 to 90 minutes after discontinuation of CPB (see Chapter 13).

If measured radial arterial pressure is suspected to be low in relation to central aortic pressure, several actions can be taken. The surgeon can estimate central aortic pressure by palpation of the ascending aorta, place a small needle in the aortic lumen, use an aortic cannula to allow temporary monitoring of aortic pressure, or place a femoral arterial catheter.

Removal of Intracardiac Air

At the end of the procedure, intracardiac air is present in virtually all cases that require opening the heart (ie, valve repair or replacement, aneurysmectomy, septal defect repair, repair of congenital lesions).[678] In such cases, it is important to remove as much air as possible before resumption of ejection. Surgical techniques differ. With the aortic cross-clamp still applied, the surgeon or perfusionist can partially limit venous return and LV vent flow, causing the left atrium and left ventricle to fill with blood. Through a transventricular approach, the left ventricle can then be aspirated. The left atrium and left ventricle are balloted to dislodge bubbles, and the cycle is repeated. The operating table can be rotated from side to side and the lungs ventilated to promote clearance of air from the pulmonary veins. Rather than using transventricular aspiration, some surgeons vent air through the cardioplegia cannula or a needle vent in the ascending aorta. Before removal of the aortic cross-clamp, the patient is placed head down, so that bubbles will float away from the dependent carotid arteries. Some surgeons favor temporary manual carotid occlusion before cross-clamp removal, but safety and efficacy of this potentially dangerous maneuver are undocumented. A venting cannula is often left in the aorta at a location that should allow air pickup after resumption of ejection.

Oka and associates,[678] using TEE, showed that routine air clearance techniques are not completely effective. Transcranial Doppler studies document a high incidence of intracranial gas emboli on release of the aortic cross-clamp or resumption of ejection. Oka and associates[678] described three essential elements of air removal: mobilization of air by positive chamber filling, stretching of the atrial wall, and repeated chamber ballottement; removal of mobilized air by continuous ascending aortic venting; and proof of elimination by TEE. The investigators contended that using these techniques could completely eliminate intracardiac air. Carbon dioxide gas insufflated by gravity into open cardiac chambers during CPB helps replace nitrogen in the bubbles with a more soluble gas. Accordingly, the persistence of gas bubbles observed by TEE after release of the aortic cross-clamp was lower in patients exposed to CO_2 in the chest wound than in the controls. However, CO_2 insufflation should be used in addition to, rather than instead of, other de-airing maneuvers.[679]

Intracardiac air may be present in 10% to 30% of closed cardiac cases as well (eg, CABG).[678] Robicsek and Duncan[680] demonstrated that during aortic cross-clamping, air may enter the aorta and left ventricle retrograde through native coronary arteries opened in the course of CABG surgery, particularly when suction is applied to vent the left side of the heart or aortic root. They suggest that efforts to expel air from the left ventricle and aortic root should be routine before unclamping the aorta. It is unclear to what extent gas emboli originating from the heart and aorta contribute to neurologic injury. Oka and associates[678] found that most patients in whom LV microbubbles were detected were free of major neurologic injury. This result is in agreement with the findings of several investigators who detected LV and cerebral microbubbles for various periods after CPB without apparent neurologic sequelae. However, microembolic load correlates with magnitude of cognitive dysfunction.[681] Other studies report that air ejected from the left ventricle can also travel to the coronary arteries, resulting in sudden and sometimes extreme myocardial ischemia and failure after separation from bypass (see Chapter 36).

Defibrillation

Before discontinuation of CPB, the heart must have an organized rhythm that is spontaneous or pacer induced. Ventricular fibrillation, common after cross-clamp release and warming, will often spontaneously convert to some other rhythm. Prolonged ventricular fibrillation is undesirable during rewarming for at least three reasons: subendocardial perfusion is compromised in the presence of normothermic ventricular fibrillation; myocardial oxygen consumption is greater with ventricular fibrillation compared with a beating heart at normothermia; and, if the left ventricle receives a large amount of blood (aortic insufficiency or bronchial return) in the absence of mechanical contraction, the left ventricle may distend. LV distention increases wall tension and further compromises subendocardial perfusion. On the other hand, early resumption of mechanical contraction may make some surgical procedures difficult (eg, modification of distal anastomoses).

Defibrillation, when necessary, is accomplished with internal paddles at much lower energies than would be used for external cardioversion. In the adult, starting energies of 5 to 10 J are routine. Defibrillation is less effective when the heart has not fully rewarmed, and it is rarely successful if myocardial (perfusate) temperature is less than 30°C.[682] Repeated attempts at defibrillation, particularly with escalating energy levels, can lead to myocardial injury. If defibrillation is not successful after two to four attempts, options include further warming, correction of blood gas and electrolyte abnormalities if present (high P_{O_2} and high normal serum potassium [K^+] seem favorable), increased MAP, and antiarrhythmic therapy. Bolus administration of 100 mg of lidocaine before the release of the cross-clamp significantly lowers the incidence of reperfusion ventricular fibrillation.[683] Increasing coronary perfusion by increased MAP is believed to result in myocardial reperfusion and recovery of the energy state. Larger loading doses of antiarrhythmics will be needed to achieve therapeutic concentrations, because of the larger CPB volume of distribution.

Restoration of Ventilation

With discontinuation of CPB, the venous outflow line is gradually occluded and pulmonary arterial blood flow restored. Researchers disagree as to the nature and magnitude of pulmonary dysfunction after CPB, and various aspects of this problem were discussed earlier. Some studies have found evidence of increased dead space–to–tidal volume ratio (V_d/V_t) after CPB, whereas others have not.[684] Increased V_d/V_t would result in less effective alveolar ventilation than prebypass, which would result in elevated $PaCO_2$. Other studies report modest increases in pulmonary shunt fraction after CPB, which leads to less effective oxygenation and decreased PaO_2. Catastrophic bypass-induced pulmonary injury with severe hypoxemia immediately on discontinuation of CPB is exceedingly uncommon in adults.

Before discontinuation of CPB, the lungs must be reinflated. Positive pressure (20–40 cm H_2O) is repeatedly applied until all areas of atelectasis are visually reinflated. Attention is specifically directed at the left lower lobe, which seems more difficult to reexpand. Fluid that has collected in the thoracic cavities during CPB is removed by the surgeon, and if the pleural cavity has not been opened, evidence of pneumothorax is also sought. The ventilatory rate can be increased 10% to 20% above prebypass values to compensate for increased V_d/V_t if present. Ventilation is resumed with 100% oxygen and subsequent adjustments in F_{IO_2} are made based on arterial blood gas analysis and pulse oximetry.

Correction of Metabolic Abnormalities and Arterial Oxygen Saturation

When rewarming is nearly complete and separation from CPB is anticipated to occur in 10 to 15 minutes, an arterial blood sample is taken and analyzed for acid-base status, P_{O_2}, partial pressure of carbon dioxide (P_{CO_2}), hemoglobin or hematocrit, potassium, and ionized calcium.

Oxygen-Carrying Capacity

Generally, a hematocrit of at least 20% to 25% is sought before bypass is discontinued. The primary compensatory mechanism to ensure adequate systemic oxygen delivery in the presence of normovolemic anemia is increased CO. Increased CO results in an increased myocardial oxygen need, which is met by increased coronary oxygen delivery by coronary vasodilation. The lower limit of the hematocrit, below which increased CO can no longer support systemic oxygen needs, is reported to be 17% to 20% in dogs with completely healthy hearts.[685] With increases in systemic V_{O_2}, such as occur with exercise, fever, or shivering, higher values of the hematocrit are required. Patients with good ventricular function and good coronary reserve (or good revascularization) might be expected to tolerate hematocrit values in the 20s. When ventricular function is impaired or revascularization is incomplete, hematocrit above 25% may aid in support of the systemic circulation and concomitantly lower myocardial oxygen requirements on discontinuation of bypass.

When pump or oxygenator reservoir volume is in excess, the hematocrit can be increased by use of hemofiltration. As described by Klineberg and colleagues,[686] application of a hydrostatic pressure gradient across a porous membrane results in transport of water and low-molecular-weight solutes (molecular weight, 500–50,000). Ultrafiltrate composition is similar to glomerular filtrate with solute concentrations identical to that of plasma water (see Chapter 32).

Arterial pH

Considerable debate has centered on the extent to which acidemia affects myocardial performance and whether correction of arterial pH with sodium bicarbonate is advantageous or deleterious to the heart.[687] Studies have challenged long-held beliefs that acidemia impairs myocardial performance. Nevertheless, most in vivo and clinical studies have found metabolic acidosis impairs contractility and alters responses to exogenous catecholamines.[688] Hemodynamic deterioration is usually mild above pH 7.2 because of compensatory increases in sympathetic nervous system activity.[688] Attenuation of sympathetic nervous system responses by ß-blockade or ganglionic blockade increases the detrimental effect of acidosis. The ischemic myocardium has been found to be particularly vulnerable to detrimental effects of acidosis. Patients with poor contractile function or reduction of myocardial sympathetic responsiveness (eg, chronic LV failure), those treated with β-blockers, or those with myocardial ischemia are especially susceptible to the adverse effects of acidosis. For these reasons arterial pH is corrected to near-normal levels before discontinuation of CPB, using sodium bicarbonate. Concerns regarding carbon dioxide generation and acidification of the intracellular space can be obviated by slow administration and appropriate adjustment of ventilation, both of which are easily achieved during CPB.

Electrolytes

Electrolytes most commonly of concern before discontinuation of CPB are potassium and calcium. Serum potassium concentration may be acutely low because of hemodilution with nonpotassium priming solutions, large-volume diuresis during CPB, or the use of insulin to treat hyperglycemia. More commonly, potassium concentration is elevated as a result of systemic uptake of potassium-containing cardioplegic solution; values exceeding 6 mEq/L are not uncommon. Other potential causes of hyperkalemia that must be considered are hemolysis, tissue ischemia or necrosis, and acidemia. Hypokalemia can be rapidly corrected during CPB with relative safety because the heart and systemic circulation are supported. Increments of 5 to 10 mEq of KCl over 1- to 2-minute intervals can be given directly into the oxygenator by the perfusionist, and potassium subsequently is rechecked. Depending on severity and urgency of correction, elevated potassium can be treated or reduced by any of several standard means: alkali therapy, diuresis, calcium administration, or insulin and glucose. Alternatively, hemofiltration can be used to lower serum potassium. While the patient is still on CPB, potassium-containing extracellular fluid is removed and replaced with fluid not containing potassium.

Ionized calcium is involved in the maintenance of normal excitation-contraction coupling and therefore in maintaining cardiac contractility and peripheral vascular tone. Low concentrations of ionized calcium lead to impaired cardiac contractility and lowered vascular tone. Concerns have been raised about the contribution of calcium administration to myocardial reperfusion injury and to the action of various inotropes.[689] Some investigators argue in favor of measuring ionized calcium before discontinuation of CPB and to administer calcium in patients with low concentrations to optimize cardiac performance.[690] Although they routinely measure ionized calcium before discontinuation of bypass, calcium salts are not routinely administered. When confronted with poor myocardial or peripheral vascular responsiveness to inotropes or vasopressors after bypass in the presence of a low level of ionized calcium, calcium salts should be administered to restore ionized calcium to normal (not elevated) levels in the hope of restoring responsiveness. The same strategy can be used for measuring and administering magnesium.

Other Final Preparations

Before the patient is separated from CPB, all monitoring and access catheters should be checked and calibrated. The zero-pressure calibration points of the pressure transducers are routinely checked. Not uncommonly, finger pulse oximeter probes do not have a good signal after CPB. In those cases, a nasal or ear probe is placed to obtain reliable oximetry. Intravenous infusions are restarted before separation from CPB, and their flow characteristics are assessed for evidence of obstruction or disconnection.

During warming and preparation for separation, an assessment should be made of the functional status of the heart and peripheral vasculature based on visual inspection, hemodynamic indices, and metabolic parameters. Based on this assessment, inotropes, vasodilators, and vasopressors thought likely to be necessary for successful separation from CPB should be prepared and readied for administration.

Separation From Bypass

After all preparatory steps are taken (see Box 31.10), CPB can be discontinued. Venous outflow to the pump or oxygenator is impeded by slowly clamping the venous line, and the patient's intravascular volume and ventricular loading conditions are restored by transfusion of perfusate through the aortic inflow line. When loading conditions are optimal, the aortic inflow line is clamped, and the patient is separated from CPB.

At this juncture it must be determined whether oxygenation, ventilation, and, more commonly, myocardial performance (systemic perfusion) are adequate. A discussion of these issues no longer involves CPB per se, but rather applied cardiopulmonary physiology. Consequently, a discussion of this extremely important topic is detailed in Chapters 36 and 38. Should separation fail for any reason, CPB can simply be reinstituted by unclamping the venous outflow and arterial inflow lines and restoring pump flow. This allows for support of systemic oxygenation and perfusion while steps are taken to diagnose and treat those problems that precluded successful separation.

Perfusion Emergencies

Accidents or mishaps occurring during CPB can quickly evolve into life-threatening emergencies (Box 31.11). Many of the necessary conditions of CPB (cardiac arrest, hypothermia, volume depletion) preclude the ability to resume normal cardiorespiratory function if an accident

TABLE 31.11 Comparison of the Five Most Common Accidents From the Three Perfusion Surveys

	Stoney 1972–1977[703]		Wheeldon 1974–1979[782]		Kurusz 1982–1985[783]	
Complication[a]	*Incidents*	*PI/D*	*Incidents*	*PI/D*	*Incidents*	*PI/D*
Air embolism	(2) 1.14	0.41	(2) 0.79	0.18	(6) 0.80	0.12
Coagulopathy	(1) 1.26	0.51	(6) 0.26	0.09	(8) 0.21	0.05
Electrical failure	(3) 0.67	0.01	(1) 1.00	0.06	(4) 0.84	0.003
Mechanical failure	(4) 0.38	0.02	(5) 0.27	0	(7) 0.30	0.007
Inadequate oxygenation	(5) 0.33	0.02	(3) 0.59	0	(3) 0.88	0.07
Hypoperfusion	—	—	(4) 0.30	0.18	(2) 0.96	0.15
Protamine reaction	—	—	—	—	(1) 2.80	0.22
Drug error	—	—	—	—	(5) 0.82	0.08

[a]The five most common complications for each study are listed as incidence per 1000 perfusions and the number of permanent injuries and mortalities as incidence per 1000 perfusions. The numbers in parentheses are the rank of each complication from most to least.

PI/D, Permanent injury or death.

Data from Stoney WS, Alford WC Jr, Burrus GR, et al. Air embolism and other accidents using pump oxygenators. *Ann Thorac Surg.* 1980;29:336; Wheeldon DR. Can cardiopulmonary bypass be a safe procedure? In: Longmore DB, ed. *Towards Safer Cardiac Surgery.* Lancaster, UK: MTP Press; 1981:427–446; Kurusz M, Conti VR, Arens JF, et al. Perfusion accident survey. *Proc Am Acad Cardiovasc Perf.* 1986;7:57.

BOX 31.11 PERFUSION EMERGENCIES

- Arterial cannula malposition
- Aortic dissection
- Massive air embolism
- Venous air lock
- Reversed cannulation

threatens the integrity of the extracorporeal circuit. Fortunately, major perfusion accidents occur infrequently and are rarely associated with permanent injury or death (Table 31.11). However, all members of the cardiac surgery team must be able to respond to perfusion emergencies to limit the likelihood of perfusion-related disasters. Some of the most common emergencies are discussed in the subsequent sections.

Arterial Cannula Malposition

Ascending aortic cannulas can be malpositioned such that the outflow jet is directed primarily into the innominate artery,[691–693] the left common carotid artery (rare),[694,695] or the left subclavian artery (rare).[696] The latter two can occur with the use of long arch-type cannulas. In the first two circumstances, unilateral cerebral *hyperperfusion*, usually with systemic hypoperfusion, occurs, whereas flow directed to the subclavian artery results in global cerebral *hypoperfusion*. Despite the fact that not all combinations of arterial pressure monitoring site and cannula malposition produce systemic hypotension, it is commonly regarded as a cardinal sign of cannula malposition. For example, right arm blood pressure monitoring and innominate artery cannulation,[691] or left arm monitoring and left subclavian artery cannulation,[696] may result in *high* arterial pressure on initiation of bypass. With other positioning and monitoring combinations, investigators report persistently low systemic arterial pressure (MAP, 25–35 mm Hg), which is poorly responsive to increasing pump flow or vasoconstrictors. Over time (minutes), signs of systemic hypoperfusion (eg, acidemia, oliguria) develop.[694] Because a variable period of systemic hypotension with CPB initiation is nearly always seen with hemodilution, hypotension alone is not significant evidence to establish a diagnosis of arterial cannula malposition. Ross and coworkers[694] described a case of accidental left common carotid cannulation with unilateral facial and conjunctival edema accompanied by rhinorrhea, otorrhea, and signs of systemic hypoperfusion. In a similar case, Sudhaman[695] found left facial congestion, whereas the right side was pale. Watson[691] described a case of innominate artery cannulation. On initiation of CPB, the skin over the carotid vessels on the right was colder than on the left. Three cases of innominate cannulation produced dramatic unilateral facial blanching with onset of CPB due to perfusion with nonblood-containing priming solution.[692,693] On initiation of CPB and periodically thereafter, it is advisable to inspect the face for color change and edema, rhinorrhea, or otorrhea and to palpate the neck with onset of cooling for temperature asymmetry. EEG monitoring was first advocated as a method of detecting cannula malposition. In one study, cannula malposition, detected by EEG asymmetry, occurred in 3 (3.5%) of 84 patients.[697] However, transcranial Doppler, and more commonly available cerebral oximetry, is the monitor of choice to detect malperfusion secondary to cannula complications (see Chapter 18).

Two other arterial cannula malpositions are possible: abutment of the cannula tip against the aortic intima, which results in high line pressure, poor perfusion, or even acute dissection when CPB is initiated, and the cannula tip directed caudally toward the aortic valve. This may result in acute aortic insufficiency, with sudden LV distention and systemic hypoperfusion on bypass. If the aortic inflow cannula is soft, aortic cross-clamping will occlude the arterial perfusion line, which can rupture the aortic inflow line. Suspicion of any cannula malposition must immediately be brought to the attention of the surgeon.

Aortic or Arterial Dissection

Signs of arterial dissection, often similar to those of cannula malposition, must also be sought continuously, especially on initiation of CPB. Dissection may originate at the cannulation site, aortic cross-clamp site, proximal vein graft anastomotic site, or partial occlusion (side-biting) clamp site. Dissections are due to intimal disruption or, more distally, to fracture of atherosclerotic plaque. In either case, some systemic arterial blood flow becomes extraluminal, being forced into the arterial wall. The dissection propagates mostly but not exclusively in the direction of the systemic flow. Extraluminal blood compresses the luminal origins (take-offs) of major arterial branches such that vital organs (heart, brain, kidney, intestinal tract, spinal cord) may become ischemic. Because systemic perfusion may be low, and origins of the innominate and subclavian arteries may be compressed, probably the best sign of arterial dissection is persistently low systemic arterial pressure.[698] Venous drainage to the pump decreases (blood is sequestered), and arterial inflow "line pressure" is usually inappropriately high. The surgeon may see the dissection if it involves the anterior or lateral ascending aorta (bluish discoloration), or both.[698,699] It is possible the surgeon may *not* see any sign of dissection, because the dissection is out of view (eg, posterior ascending aorta, aortic arch, descending aorta). A careful TEE examination at this time may show the dissection and its extent. Dissection can occur at any time before, during, or after CPB. As with cannula malposition, a suspicion of arterial dissection must be brought to the attention of the surgeon. The anesthesiologist must not assume that something is suddenly wrong with the arterial pressure transducer but should "think dissection."

After a dissection of the ascending aorta is diagnosed, immediate steps to minimize propagation must be taken. If it has occurred before CPB, the anesthesiologist should take steps to reduce MAP and the rate of rise of aortic pressure (dP/dt). If it occurs during CPB, pump flow and MAP are reduced to the lowest acceptable levels. Arterial perfusate is frequently cooled to profound levels (14–19°C) as rapidly as possible to decrease metabolic demand and protect vital organs.[699] A different arterial cannulation site is prepared (eg, the femoral artery is cannulated or the true aortic lumen is cannulated at a site more distal on the aortic arch). Arterial inflow is shifted to that new site with the intent that perfusing the true aortic lumen will reperfuse vital organs.[699] The ascending aorta is cross-clamped just below the innominate artery, and cardioplegia is administered (into the coronary ostia or coronary sinus). The aorta is opened to expose the site of disruption, which is then resected and replaced. Reimplantation of the coronary arteries or aortic valve replacement, or both, may be necessary. The false lumina at both ends of the aorta are obliterated with Teflon buttresses, and the graft is inserted by end-to-end suture.[639] With small dissections it is sometimes possible to avoid open repair by application of a partial occlusion clamp with plication of the dissection and exclusion of the intimal disruption.[699] Troianos and associates[700] described three cases of arterial dissection during CPB in which TEE was found useful. Although provisional diagnoses were made on the basis of traditional signs, TEE allowed assessment of the origin and extent of dissection. Diagnosis of arterial dissection has also been assisted by presence of EEG[701] and cerebral oximetry asymmetry.[702]

Arterial dissections originating from femoral cannulation also necessitate reductions in arterial pressure, systemic flow, and temperature. If the operation is near completion, the heart may be transfused and CPB discontinued; otherwise, the aortic arch must be cannulated and adequate systemic perfusion restored to allow completion of the operation.[698]

Massive Arterial Gas Embolus

Macroscopic gas embolus is a rare but disastrous CPB complication. Two independent studies in 1980 reported incidences of recognized massive arterial gas embolism of 0.1% to 0.2%.[703,704] The current incidence is probably lower because of the widespread use of reservoir-level alarms and other bubble detection devices. Between 20% and 30% of affected patients died immediately, with another 30% having transient or nondebilitating neurologic deficits, or both. Circumstances that most commonly contributed to these events were inattention to oxygenator blood level, reversal of LV vent flow, or unexpected resumption of cardiac ejection in a previously opened heart. Rupture of a pulsatile assist device[705] or intraaortic balloon pump[706] may also introduce large volumes of gas into the arterial circulation.

The pathophysiology of cerebral gas embolism (macroscopic and microscopic) is not well understood. Tissue damage after gas embolization is initiated from simple mechanical blockage of blood vessels by bubbles.[707,708] Although gas emboli may be absorbed or pass through the circulation within 1 to 5 minutes,[707–710] the local reaction of platelets and proteins to the blood gas interface or endothelial damage is thought to potentiate microvascular stasis,[710–715] prolonging cerebral ischemia to the point of infarction. Areas of marginal perfusion, such as arterial boundary zones, do not clear gas emboli as rapidly as well-perfused zones,[707] producing patterns of ischemia or infarction difficult to distinguish from those due to hypotension or particulate emboli.

Recommended treatment for massive arterial gas embolism includes immediate cessation of CPB with aspiration of as much gas as possible from the aorta and heart, assumption of steep Trendelenburg position, and clearance of air from the arterial perfusion line. After resumption of CPB, treatment continues with implementation or deepening of hypothermia (18–27°C) during completion of the operation and clearance of gas from the coronary circulation before emergence from CPB.[704,705,716,717] In many reports of patients suffering massive arterial gas embolus, seizures occurred postoperatively and were treated with anticonvulsants.[128,717–719] Because seizures after ischemic insults are associated with poor outcomes, perhaps because of hypermetabolic effects, prophylactic phenytoin seems reasonable. Hypotension has been shown to lengthen the residence time of cerebral air emboli and worsen the severity of resulting ischemia.[720] Maintenance of moderate hypertension therefore is reasonable and clinically attainable to hasten clearance of emboli from the circulation and, hopefully, improve neurologic outcome.

Many clinicians have reported dramatic neurologic recovery when hyperbaric therapy was used for arterial gas embolism, even if delayed up to 26 hours after the event.[705,715,716,721] Spontaneous recovery from air emboli has also been reported,[712,717,719,721] and no prospective study of hyperbaric therapy in the cardiac surgery setting has been performed.[722] Few institutions that do cardiac surgery have an appropriately equipped and staffed hyperbaric chamber to allow expeditious and safe initiation of hyperbaric therapy. Nonetheless, immediate transfer by air is often possible and should seriously be considered. It seems reasonable to expect that institutions that perform cardiac surgery should have policies regarding catastrophic air embolism.

In 1980, Mills and Ochsner[704] suggested venoarterial perfusion as an alternative to hyperbaric therapy. Retrograde perfusion through the SVC cannula at 1.2 L/min at 20°C for 1 to 2 minutes was used in five of their eight patients with massive gas embolism. The goal was to flush air from the cerebral arterial circulation. None of the patients so treated had evidence of neurologic injury. Other reports using this technique have followed.[723,724] Hendriks and investigators,[725] in a porcine model of venoarterial perfusion, found that only 50% of injected gas (nitrogen) could be recovered from the aorta. Ninety-eight percent of the removable gas was collected from the aorta in the first 7 to 10 minutes of retrograde perfusion. Although no animal (clinically or pathologically) appeared to sustain neurologic injury, the investigators concluded that venoarterial perfusion did not adequately remove embolized gas, and hyperbaric therapy remained the treatment of choice. The timing of the embolism is also a major consideration. For example, if massive air embolism occurs during connection, serious consideration should be given to abandoning the procedure in order to allow immediate therapy and awakening the patient to assess neurologic status. Air embolism and its subsequent cerebral ischemia are likely worsened by the nonphysiologic nature of CPB as well as its inherent inflammatory processes.

Venous Air Lock

Air entering the venous outflow line can result in complete cessation of flow to the venous reservoir, and this is called *air lock*. Loss of venous outflow necessitates immediate slowing, even cessation of pump flow, to prevent emptying the reservoir and subsequent delivery of air to the patient's arterial circulation. After an air lock is recognized, a search for the source of venous outflow line air must be undertaken (eg, loose atrial purse-string suture, atrial tear, open intravenous access) and repaired before reestablishing full bypass.

Reversed Cannulation

In reversed cannulation, the venous outflow limb of the CPB circuit is incorrectly connected to the arterial inflow cannula, and the arterial perfusion limb of the circuit is attached to the venous cannula. On initiation of CPB, blood is removed from the arterial circulation and returned to the venous circulation at high pressure. Arterial pressure is found to be extremely low by palpation and arterial pressure monitoring. Very low arterial pressures can also (more commonly) be due to dissection in the arterial tree. In the latter case, the perfusionist will rapidly lose volume, whereas with reversed cannulation, the perfusionist will have an immediate gross excess of volume. If high pump flow is established, venous or atrial rupture may occur. The CVP will be dramatically elevated, with evidence of facial venous engorgement.

Line pressure is the pressure in the arterial limb of the CPB circuit. Because arterial cannulas are much smaller than the aorta, there is always a pressure drop across the aortic cannula. Arterial inflow line

pressure will always be considerably higher than systemic (patient) arterial pressure. The magnitude of the pressure drop depends on cannula size and systemic flow; small cannulas and higher flows result in greater gradients. The CPB pump must generate a pressure that overcomes this gradient to provide adequate systemic arterial pressure. For a typical adult (ie, MAP of about 60 mm Hg, systemic flow of about 2.4 L/min/m^2, and a 24-Fr aortic cannula), line pressure in an uncomplicated case usually ranges from 150 to 250 mm Hg. The fittings on the arterial inflow line are plastic; the fittings and the line itself can rupture. Perfusionists typically do not want a line pressure in excess of 300 mm Hg.

CPB must be discontinued and the cannula disconnected and inspected for air. If air is found in the arterial circulation, an air embolus protocol is initiated. Once arterial air is cleared, the circuit is correctly reconnected and CPB restarted. In adults, the venous outflow limb of the CPB circuit is a larger-diameter tubing than the arterial inflow tubing, precisely to eliminate reversed cannulation. This is why reversed cannulation is rare in adults—but it has happened. In pediatric cases, the arterial inflow and venous outflow limbs of the CPB circuit are close or equal in size.

Special Patient Populations

Care of the Gravid Patient During Bypass

Studies assessing the effects of cardiac surgery and CPB on obstetric physiology and fetal well-being are lacking. However, several reviews and many case reports describe individual experience in caring for the gravid patient and fetus during cardiac surgery and extracorporeal circulation.[726–731] These surveys and anecdotal reports, along with an understanding of the well-documented physiology of pregnancy and the effects of cardiac therapeutics on fetal physiology, can serve as a basis for a rational approach to care for the pregnant patient and fetus during cardiac surgery (Box 31.12).

Several groups have published reports detailing their individual experiences or survey data on maternal and fetal outcomes after cardiac surgery and CPB.[726–731] Jacobs and colleagues[727] reported their experience with three first-trimester gravid patients. All recovered from their operative procedures and delivered normal term infants. The first survey data on pregnancy and cardiac surgery were reported in 1969 by Zitnik and coworkers[728] from the Mayo Clinic. Among the 20 patients, there was only one maternal death, but seven fetuses died before term. The study authors concluded that cardiac surgery does not increase the likelihood of death in the pregnant patient with heart disease, but it is associated with substantial fetal mortality. Lapiedra and associates[730] and Becker[729] individually published reports in the 1980s on gravid patients undergoing heart surgery. Lapiedra and associates[730] reviewed their own experiences and found only one fetal death and no instance of maternal death in their review of 23 cases. Becker[729] surveyed members of The Society of Thoracic Surgeons on their experiences with pregnant patients requiring cardiac surgery. Of the 600 surgeons responding, 119 reported on a total of 169 gravid patients undergoing cardiac surgery, 68 of whom were managed with CPB. Pomini and investigators[731] reviewed 69 case reports of gravid patients undergoing cardiac procedures and CPB. Overall, the embryo-fetal mortality rate was 20.2%, but fetal loss was reduced to 12.5% in the last 40 cases. The reported experience on maternal and fetal outcomes after cardiac procedures with CPB suggests that cardiac surgery is well tolerated by the mother, but poses a significant risk to the fetus.

Although most physicians advocate providing perioperative care that can ensure maternal well-being, appropriate investigation would enable clinicians to care optimally for mother and fetus. This section outlines recommendations for perioperative management of the gravid patient requiring cardiac surgery and CPB. The basic principles for the perioperative management of the gravid patient requiring any type of surgery are outlined by Levinson and Shnider[732]: maternal safety, avoidance of teratogenic drugs, avoidance of intrauterine asphyxia, and prevention of preterm labor (see Chapter 50).

BOX 31.12 SPECIAL PATIENTS WHO MAY NEED CARDIOPULMONARY BYPASS

- Pregnant women
- Accidental hypothermia victims
- Neurosurgical patient with an intracranial aneurysm

Considerations Before Bypass

Premedication and Patient Positioning

Premedication should be appropriate for the specific cardiac lesion and physical status of the patient. Teratogenic drugs should be avoided, especially in the first trimester of pregnancy. After the 34th week of gestation, stomach emptying is delayed and patients are at increased risk for pulmonary aspiration. Although it is not possible to ensure gastric emptying before anesthesia induction, sodium citrate and an H_2-receptor antagonist may provide some protection against aspiration pneumonia. The gravid uterus obstructs aortic flow and IVC blood return to the heart. Gravid patients should never be supine; they must be positioned with left uterine displacement throughout the perioperative period.

Maternal and Fetal Monitor Information

The pregnant patient undergoing cardiac surgery requires the usual monitors employed during cardiac surgery, as well as monitors that can assess fetal well-being. Monitors that help assess the adequacy of maternal cardiovascular performance and oxygen delivery to the fetus are of paramount importance. Little is known about the effects of cardiovascular drugs and other therapeutic measures on the pregnant cardiac patient undergoing CPB. Appropriate monitors permit the assessment of an individual therapy on maternal and fetal oxygen delivery.

Monitors for cardiac surgery and CPB are discussed in detail in other chapters. A two-lead (II, V_5) electrocardiogram (ECG), peripheral pulse oximeter, and blood pressure cuff should be placed first. These monitors provide information concerning cardiorespiratory function as other, more invasive monitors are placed. Before the induction of anesthesia, a radial artery and pulmonary artery catheter should be placed. These monitors provide beat-to-beat systemic and pulmonary artery pressure information and the ability to measure CO and arterial and mixed-venous blood gases. An oximetry pulmonary artery catheter provides continuous information on venous oxygen saturation, and an indirect, approximate measure of the adequacy of maternal tissue oxygen delivery.

Uterine activity should be monitored with a tocodynamometer applied to the maternal abdomen. This monitor transduces the tightening of the abdomen during uterine contractions. As is the case with other types of major surgery, the tocodynamometer should not interfere with the conduct of cardiac surgery; if necessary, the monitor may be intermittently displaced by the operating surgeon. The use of an intraamniotic catheter to monitor uterine activity and pressure may be inadvisable in a patient who is fully heparinized. Intraoperative uterine contractions may have a deleterious effect on fetal oxygen delivery (by causing an increase in uterine venous pressure and decrease in uterine blood flow) and signal the onset of preterm labor. Use of the tocodynamometer is imperative, as it provides important information about the state of the uterus and allows intervention if necessary. Various reports have documented the common occurrence of uterine contractions during cardiac surgery and CPB. Uterine contractions may appear at any time during the perioperative period but occur most frequently immediately after the discontinuation of CPB and in the early ICU period.[733] It is therefore important to leave the tocodynamometer in place after the completion of surgery. Although uterine contractions

occur frequently in the perioperative course, they usually are effectively treated with magnesium sulfate, ritodrine, or ethanol infusions, and they do not result in preterm labor or fetal demise.[734]

Fetal heart rate (FHR) monitors should be used in all gravid patients after 20 weeks gestation because one of the primary perioperative goals is to avoid fetal loss. Use of an FHR monitor permits recognition of fetal distress and allows the clinician to institute measures to improve fetal oxygen delivery. The FHR monitor recognizes and records the FHR, FHR variability, and uterine contractions. A spinal electrode placed in the fetal scalp gives the most reliable fetal ECG and therefore the best FHR information. However, this method may be undesirable in the presence of maternal anticoagulation. External FHR monitoring—using ultrasound, phonocardiography, or external abdominal ECG—is less exact but preferable in this clinical setting.

The cardiac surgeon, perfusionist, and cardiac anesthesiologist may not be familiar with uterine and FHR monitors. As a result, having a perinatologist or an obstetrician present during cardiac surgery is desirable to assess for preoperative fetal distress and the anticipated need for emergency cesarean section during cardiac surgery.

FHR is usually normal in the prebypass period, but decreases precipitously with the initiation of CPB and remains below normal for the entire bypass period. There are many potential causes of this observed decrease in FHR. Persistent fetal bradycardia is a classic sign of acute fetal hypoxia. However, in the CPB setting, especially when hypothermia is employed, it is difficult to ascribe fetal bradycardia to hypoxia or to decreased fetal oxygen demand. Fetal tachycardia typically occurs after the discontinuation of CPB. This tachycardia may represent a compensatory mechanism for the oxygen debt incurred during CPB. The FHR usually returns to normal by the end of the operative period.

Interventions optimizing maternal blood oxygen content, correcting any acid-base imbalance, and replenishing fetal glycogen stores may alleviate signs of fetal hypoxia. Some clinicians recommend an increase in CPB pump flow to improve fetal oxygen delivery.[729,731]

After anesthesia induction, a urinary bladder catheter with a temperature probe and TEE probe should be placed. The former provides information on fluid balance and core temperature. TEE is always helpful, but is especially important in the patient undergoing valvular or congenital heart surgery, because it can document pathologic changes and help assess the adequacy of repair.

Conducting the Bypass Procedure

The conditions of extracorporeal circulation—nonpulsatile blood flow, hypothermia, anemia, and anticoagulation—will likely have a negative impact on fetal well-being during CPB. There are no studies that recommend a particular CPB management strategy in gravid patients. Recommendations are summarized (Table 31.12) for the management of CPB in pregnant patients, based on the survey and anecdotal reports in the literature (Table 31.13).

Blood Flow

Optimal CPB blood flow in the gravid patient is unknown. However, the increase in CO associated with pregnancy is well defined, and it might be argued that high blood flows during CPB are more physiologic in the gravid patient. Becker[729] suggested that flow during CPB in the pregnant patient be maintained at a minimum of 3.0 L/min per m^2. A few reports demonstrate that increasing CPB circuit blood flow improves FHR, suggesting improvement in fetal oxygen delivery. In a report by Koh and colleagues,[735] FHR improved when pump flow was increased from 3100 to 3600 mL/min. Similarly, Werch and Lambert[736] reported an improvement in FHR when blood flow was increased from 2800 to 4600 mL/min. In another case, flow was increased from 2.3 to 2.9 L/min per m^2, with a brief, unsustained apparent improvement in fetal oxygen delivery.[736]

Blood Pressure

Under normal conditions, uterine blood flow is determined solely by maternal blood pressure, as the placental vasculature is maximally dilated. However, it is not known what factors determine uterine blood flow during the very abnormal condition of CPB. For example, catecholamine levels increase by several times during CPB; therefore, uterine vascular resistance may increase during extracorporeal circulation in response to increased levels of norepinephrine and epinephrine. However, regardless of the state of uterine vascular resistance during CPB, maternal blood pressure will be an important determinant of uterine blood flow and fetal oxygen delivery. Moderately high pressure (MAP ≥ 65 mm Hg) should be employed during perfusion in the gravid patient.[729]

There are no reports demonstrating that increasing blood pressure during CPB improves FHR or fetal oxygen delivery. Most case reports on CPB in the gravid patient do not include information on blood pressure during CPB. The few blood pressure values reported in gravid perfusion cases ranged from 55 to 95 mm Hg.[734,737]

In theory, the use of short-acting vasodilators, such as nitroglycerin or sodium nitroprusside, may counteract the effects of CPB and norepinephrine- or epinephrine-induced increases in uterine vasculature resistance. If maternal blood pressure is maintained by increasing extracorporeal circuit pump flow, uterine blood flow and fetal oxygen delivery may be increased with vasodilators. Monitoring should be conducted to assess the effect of a given therapeutic on fetal oxygen delivery during CPB.

Temperature

Controversy exists regarding temperature management during CPB in the nongravid patient, although most perfusions are conducted

TABLE 31.12 Recommendations for the Conduct of Extracorporeal Circulation in the Gravid Patient

Variable	*Recommended Value/ Characteristic*	*Rationale*
Blood flow	3.0 L/min/m^2	Cardiac index normally is increased during pregnancy.
Blood pressure (MAP)	60–70 mm Hg	Uterine blood flow depends on maternal MAP.
Temperature	32–34°C	Mild hypothermia decreases fetal oxygen requirements and is less likely to cause fetal arrhythmia.
Oxygenator type	Membrane	Membrane oxygenators are associated with fewer embolic phenomena than bubblers.
Hematocrit	25–27%	The quantity of oxygen carried in maternal blood (and therefore the oxygen available to the fetus) greatly depends on hemoglobin concentration.
Duration of perfusion	Minimized	The duration of bypass is dictated by the complexity of the operative procedure.
Cardioplegia	?	No data
Pulsatile perfusion	?	No data

MAP, Mean arterial pressure.

TABLE 31.13 Prevalence of Maternal and Fetal Mortality Following Cardiac Surgery and Cardiopulmonary Bypass in Gravid Patients

Study	*Maternal Death*	*Fetal Death*
Jacobs et al. (1965)	0/3 (0%)	0/3 (0%)
Zitnik et al. (1968)	1/20 (5%)	7/20 (35%)
Becker (1983)	1/68 (1.5%)	11/68 (16%)
Lapiedra et al. (1986)	0/23 (0%)	1/23 (4.3%)
Pomini et al. (1996)[a]	2/69 (2.9%)	8/69 (20.2%)
Pomini et al. (1996)[b]	0/40 (0%)	5/40 (12.5%)
Arnoni et al. (2003)	5/58 (8.6%)	11/58 (18.6%)

[a]All patients from 1958 to 1992.
[b]Last 40 patients in series only.

under hypothermic conditions. Similarly, there are few data and no consensus regarding temperature management in the gravid patient undergoing CPB.

There are theoretical advantages and disadvantages for normothermic and hypothermic CPB in the gravid patient. Hypothermia can cause fetal bradycardia and may lead to fetal ventricular arrhythmias, resulting in fetal wastage. Rewarming after hypothermic CPB may precipitate uterine contractions and preterm labor.[729] However, others reported the onset of uterine contractions at the time of discontinuation of CPB in spite of normothermic perfusion. Uterine contractions also occur at various times in the postbypass and postoperative periods. The association of uterine contractions with rewarming after hypothermic bypass is unclear.

Hypothermia may be protective to the fetus during extracorporeal circulation by decreasing fetal oxygen requirements. Assali and Westin[738] demonstrated that hypothermia to 28°C in gravid dogs caused an increase in uterine vascular resistance but did not result in a decrease in uterine blood flow. Hypothermia did not affect fetal survival. Pardi and colleagues,[739] using a fetal lamb model, reported that temperatures above 18°C were well tolerated. More profound hypothermia caused irreversible fetal acidosis and hypoxia. Several reports discuss the effects of deliberately induced and septicemia-associated hypothermia in gravid patients. The investigators observed that FHR decreased with maternal hypothermia but improved with maternal rewarming.[740]

Perfusion temperatures of 25 to 37°C have been used in gravid patients undergoing CPB.[729,734,737,741] Because Pomini and coworkers[731] found an apparent decrease in fetal loss when CPB temperatures were maintained at or above 36°C, they recommend normothermic temperatures during bypass. However, they acknowledge the lack of follow-up in many of the case reports they reviewed. The authors reported a case in which hypothermic CPB at 25°C was required for 2 hours 40 minutes and in which the patient underwent two periods of rewarming. Uterine contractions occurring in the early postoperative period were successfully treated with magnesium sulfate. Despite the magnitude and duration of hypothermia and two periods of rewarming, a normal infant was delivered 10 days postoperatively.[734]

In conclusion, the optimal gravida temperature during CPB has not been established. There are no data that suggest hypothermia is harmful to the mother or fetus undergoing bypass.

Accidental Hypothermia

In the early 1950s, Bigelow and colleagues demonstrated a direct relationship between metabolic rate and temperature and postulated that DHCA could facilitate cardiac surgery.[472] Although extracorporeal circulation was not used in these early cardiac cases (a tub of ice and warming coils were used to induce hypothermia and rewarm the patient), the notion that a patient could survive hypothermic arrest was established. With the introduction of CPB in the mid-1950s,[742] the induction of profound hypothermia with circulatory arrest, followed by resuscitation, was greatly facilitated by the extracorporeal circuit. It was a short leap to consider the use of CPB to resuscitate the victim suffering accidental hypothermia.

Patients with core temperatures below 32°C, and without a perfusing cardiac rhythm, are best managed with some type of extracorporeal support.[743] This section discusses the management of hypothermic patients who are optimally managed with CPB for rewarming. Danzl and Pozos[744] outlined treatment algorithms for hypothermic patients who do not require extracorporeal circulation for resuscitation (eg, patients with preserved circulation and suffering only moderate hypothermia [temperature ≥ 32°C]).

Patient Selection

Clinicians lack consensus regarding the absolute indications or contraindications for the use of CPB in the treatment of accidental deep hypothermia.[745] However, there are theoretical considerations and some data to help guide the decision-making process regarding the rewarming of accidental hypothermia patients. Phenomena that greatly limit the likelihood of successful resuscitation include the presence of asphyxia before the initiation of hypothermia, as occurs commonly in avalanche and drowning victims. Similarly, patients with severe traumatic injury, or extremely elevated potassium levels (≥10 mmol/L) are unlikely to benefit from resuscitative efforts.

One report suggests that several factors may increase the likelihood of a desirable patient outcome after accidental hypothermia managed with CPB.[746] Victims suffering profound hypothermia (without prior asphyxia), as opposed to moderate hypothermia, benefit from the substantial slowing of metabolic processes and are less likely to have severe end-organ damage. Young patients in good health are more likely to survive resuscitative efforts than are older, debilitated victims. Patients who have multiple preexisting medical problems are less likely to have a desirable outcome. Initial rescue treatment algorithms may influence the likelihood of surviving profound hypothermia. The maintenance of profound hypothermia in the rescued patient before the initiation of extracorporeal warming may greatly enhance the likelihood of successful recovery. Rewarming with CPB is the most efficient method to resuscitate the hypothermic patient. Tissue perfusion is enhanced by hemodilution, and metabolic perturbations can be easily corrected.

Caring for the Accidental Hypothermia Victim

After the decision is made to resuscitate an accidental hypothermia victim, the patient should be maintained at the hypothermic temperature and rapidly transferred to a facility that can provide extracorporeal rewarming. In the operating room, various vascular sites may be cannulated to initiate rewarming. Femoral vessels or mediastinal vasculature may serve as conduits for rewarming. Because the ventricle is noncompliant at temperatures below 32°C, sternotomy or thoracotomy may be preferable to facilitate direct cardiac massage and defibrillation. Although hypothermia reduces anesthetic requirements, the prudent use of anesthetics, analgesics, sedative-hypnotics, and volatile drugs is recommended. These agents should be administered through the extracorporeal circuit.

To treat an asystolic patient, the extracorporeal circuit must include a pump, oxygenator, and heat exchange waterbath. At flow rates of 2 to 3 L/min, with the waterbath at 37°, the patient's core temperature can increase by as much as 1 to 2°C every 3 to 5 minutes. Slowly, the flow rate can be increased as determined by venous return. Given the data regarding the adverse effects of mildly hyperthermic blood on ischemic cerebral damage, the accidental hypothermia patient should not be perfused with blood warmed to temperatures in excess of 37°C. If the victim has a perfusing cardiac rhythm, venovenous rewarming may be used. Indeed, strong arguments can be made for limiting the rewarming to only 32 to 33°C and then adhering to cardiac arrest protocols that use prolonged mild hypothermia to optimize cerebral outcomes.

One study suggests that under certain circumstances (eg, profound hypothermia before asphyxia; young, healthy patients; maintenance of hypothermia before bypass-supported rewarming) accidental hypothermia patients have an almost even chance of surviving and not suffering significant end-organ (including cerebral) deficits. Walpoth and associates[746] reviewed the hospital records of 234 patients suffering accidental hypothermia. Forty-six of these patients had core temperatures below 28°C and had circulatory arrest. Of the 32 patients rewarmed with CPB support, 15 were long-term survivors. These 15 patients were reexamined and studied an average of 7 years after their resuscitation from accidental hypothermia. The survivors were uniformly young (25.2 ± 9.9 years) and were resuscitated with CPB 141 ± 15 minutes after discovery. Although neurologic and neuropsychologic deficits were observed in all the victims in the early postresuscitation period, all patients had fully or almost completely recovered at the long-term follow-up. The investigators concluded that otherwise healthy individuals can survive accidental deep hypothermia with a preserved good quality of life.

Intracranial Aneurysm Surgery

Surgery for intracranial aneurysm represents a major challenge for the surgeon and anesthesiologist.[747] For a small number of these cases, DHCA has been applied to improve surgical access and cerebral protection. Like many areas, significant evolution in technique and application has occurred over time. Initial enthusiasm for DHCA in intracranial aneurysm surgery was tempered by the unfortunate occurrence of coagulopathies. Its use was further restricted by advances in neurosurgical microscopic techniques (aneurysm wrapping, parent vessel ligation, and use of temporary clips). Improvements in perioperative monitoring and neuroanesthesia have reserved a use for DHCA in the approach to giant aneurysms that might otherwise be inoperable.

DHCA for intracranial aneurysm requires precise integration of a remarkably large and diverse team, which includes anesthesiologists, nurses, perfusionists, cardiac surgeons, and neurosurgeons. All components and demands of the operation should be thoroughly familiar to all participants. The anesthesiologist is primarily occupied by five areas. The first area is patient selection and consent, which needs to include a careful assessment for preexisting coagulation problems or contraindications to TEE. The second area entails careful premedication and induction. This is undertaken to blunt hemodynamic responses to invasive monitor placement and intubation and to avoid respiratory depression in that subgroup of patients with elevated intracranial pressure. The third area of focus for the anesthesiologist is maintenance and monitoring. This includes TEE, EEG, and placement of defibrillator pads in addition to the routine anesthetic monitors. Next, the anesthesiologist prepares for initiation of CPB and arrest. Lastly, the anesthesiologist manages rewarming, resumption of native circulation, and correction of coagulation abnormalities. Depending on the length of arrest and adequacy of cardiac protection, these steps may proceed smoothly or be complicated by significant hemodynamic embarrassment.

DHCA has been used for intracranial aneurysm surgery with good success at a number of centers.[748–753] The high percentage of patients surviving is probably the best indicator of the value of this technique, although the relatively small number of cases performed on an annual basis make controlled outcome trials difficult to complete. Silverberg and investigators[748] reported nine operative cases with no operative deaths, although six modest perioperative complications occurred (ie, small stroke, transient cranial nerve palsy, frontal lobe hematoma, and pulmonary embolus). Baumgartner and colleagues[749] also had no reported deaths in their series, and all patients went on to live independently. Like Silverberg's series, a fair number of patients experienced modest perioperative complications (ie, four thromboembolic episodes, three strokes, three transient neurologic palsies). The other reported series[750–753] were similar in the respect that most patients went on to live independently and modest perioperative complications were in the range of 50%. Given that the overall numbers involved are small, it is very difficult to develop precise estimates for morbidity and mortality rates. However, given that DHCA in intracranial aneurysm surgery has been reserved for only the most difficult cases, the results seen are encouraging. As in most areas of cardiac surgery, continued developments have led to an evolution in neurosurgery as well and in how these intracranial aneurysms are being addressed. For example, many more are now being addressed with neurovascular radiologic coiling than are being treated open under DHCA. It is likely that this will be a continuing trend in the declining use of DHCA to treat intracranial aneurysms.

Minimally Invasive Surgery and Cardiopulmonary Bypass

In the mid-1990s, interest in minimally invasive techniques for cardiac surgery emerged. Today, coronary revascularization and mitral and aortic valvular surgery are being performed in some centers with minimally invasive approaches. The proponents of port-access cardiac surgery (PACS) suggest that this technique permits minimally invasive cardiac surgery while providing the support of CPB. This section describes the current technology and expertise with port-access CPB. Minimally invasive procedures and off-pump cardiac surgery are discussed further in Chapters 20, 21, 27, 29, 32, 33, and 37.

Port-Access Bypass Circuit

The port-access system consists of a series of catheters that are introduced through various puncture sites, including the femoral artery and vein, and threaded through the aorta and venous system to the heart. The perfusion is usually set up from the femoral vein to the oxygenator and then returned via the femoral artery. An inflatable balloon on the end of an endoaortic clamp (EAC) catheter can be used to arrest the blood flow in the aorta, and other catheters help drain and reroute the blood flow to the heart-lung machine. Through two of the catheters, cardioplegia solution can be administered to the heart (Fig. 31.16).[754,755]

The EAC is an occlusion balloon that functions as an aortic cross-clamp and permits antegrade cardioplegia infusion into the aortic root and coronary arteries. The lumen used to administer cardioplegia can also function as an aortic root–venting catheter. Some surgeons prefer to use a direct modified aortic cross-clamp inserted through a port in the right side of the chest instead of using the EAC; they depend on administration of cardioplegia in a retrograde fashion via the coronary sinus. Retrograde cardioplegia can be delivered through an endocoronary sinus catheter (ECSC) that is placed with a percutaneous approach (Fig. 31.17).

Blood returns to the CPB through the femoral venous catheter that is advanced to the level of the IVC–right atrium junction. Because extrathoracic gravity drainage is usually insufficient in providing adequate blood flow for complete CPB support, kinetic-assisted venous drainage, with controlled suction, is used to augment the drainage of blood to the heart-lung machine (see Chapter 32). Removing all air from the system at the end of surgery is challenging and must be done carefully.

Port-access CPB demands an expanded role of the anesthesiologist during CPB. The anesthesiologist is responsible for inserting the ECSC (and the even endopulmonary vent [EPV]) through introducer sheaths placed in the right internal jugular vein. The ECSC should be placed first with the assistance of both fluoroscopy and TEE. The technique was described in detail by Lebon and coworkers[756] and Miller and associates,[757] who have a combined experience of more than 600 insertions. TEE guidance is used for engaging the coronary sinus and fluoroscopy for advancing the catheter in the coronary sinus. Proper placement is judged by attaining a pressure in the coronary sinus greater than 30 mm Hg during cardioplegia administration at a rate of 150 to 200 mL/min. The mean total procedure time in the series by Lebon and coworkers was 16 ± 14 minutes. Failure can occur for a number of reasons, but the most common reason is displacement of the catheter from the coronary sinus during surgical manipulations. Complications, including perforation and dissections, have been reported in a small percentage of patients (see Chapters 13 and 15).

As with any new procedure or technology, the anesthesiologist should expect a learning curve regarding the skill of placing an ECSC and EPV. A side benefit of port-access bypass is the necessity of increased communication among members of the health care team.

Monitoring for Endovascular Clamp Bypass

Measures of venous drainage, arterial blood flow, ventricular venting, cardioplegic delivery, regional perfusion, and aortic occlusion must be carefully monitored to ensure safe and adequate CPB and myocardial protection. Although the surgical staff is positioned to assess cardioplegia delivery and LV venting, and the perfusionist monitors arterial flow and venous drainage to and from the CPB circuit, the anesthesiologist is responsible for determining the proper placement of the EAC and adequacy of CBF.[758]

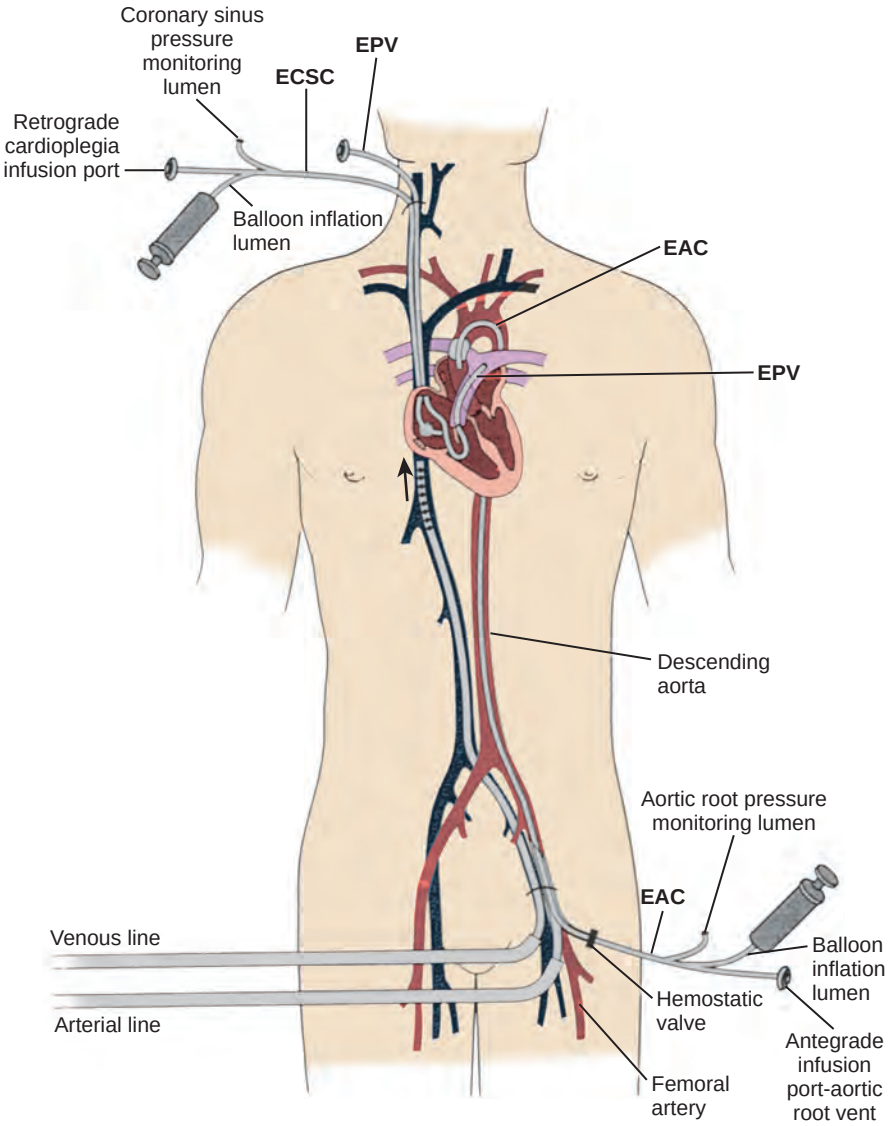


Fig. 31.16 Positioning of endovascular catheters. The femoral venous drainage catheter tip is positioned at the right atrium–superior vena cava junction by fluoroscopy and transesophageal echocardiography. *EAC,* Endoaortic clamp; *ECSC,* endocoronary sinus catheter; *EPV,* endopulmonary vent. *(From Toomasian JM, Peters SP, Siegel LC, Stevens JH. Extracorporeal circulation for port-access cardiac surgery.* Perfusion *1997;12:83–91.)*

The aorta catheter with the EAC should be positioned in the ascending aorta 2 to 4 cm distal to the aortic valve. Because cephalad migration of the endovascular aortic root clamp may compromise CBF, it is imperative to monitor endovascular clamp position continuously. There are several proposed methods to achieve this essential goal (Table 31.14). TEE and color-flow Doppler aid in visualizing the placement of the EAC balloon in the ascending aorta and in detecting any leakage of blood around the balloon. Right radial artery pressure will decrease acutely if the EAC migrates and obstructs the brachiocephalic artery. Some clinicians choose to measure blood pressure in the left and right radial arteries. The occurrence of acute difference in radial artery pressures may indicate cephalad migration of the EAC. Pulse-wave Doppler of the right carotid artery can verify cerebral perfusion but is frequently difficult to assess under the conditions of nonpulsatile blood flow. The ability of transcranial Doppler monitoring of the middle cerebral artery and cerebral oximetry techniques to determine the adequacy of CBF requires further evaluation. The TEE probe may be useful in visualizing the ascending aorta and location of the balloon; however, many clinicians report the inadequacy of this technique.

Port-Access Cardiac Surgery Outcome Data

Early advocates of PACS hoped that this new approach would provide the benefits of minimally invasive surgery with the advantage of extracorporeal support and myocardial preservation during procedures on the heart. A relatively slow learning curve exists, and multiple, unexpected complications have been reported (eg, inadequate de-airing of the ventricle before discontinuation of CPB support, aortic or femoral artery dissection, malposition of the endovascular clamp).

Coronary artery surgery can be done using PACS, but it has not become a popular technique compared with OPCAB and other minimally invasive revascularization procedures. Mohr and investigators[759] reported a 9.8% mortality rate in their series of 51 patients undergoing elective mitral valve replacement or repair with PACS. Two patients suffered femoral artery dissections (requiring conversion to conventional techniques), and three patients required second operations for repair of postoperative perivalvular leaks. Patients in the port-access group reported the same amount of pain as those undergoing sternal splitting (as measured by a visual analog pain scale), challenging the

TABLE 31.14 Potential Strategies to Monitor Cerebral Blood Flow During Port-Access Bypass

Monitor	*Limitations*	*Observation With Cephalad Migration of Endoaortic Clamp*[a]
Fluoroscopy	1. Must interrupt surgery to use monitor	EAC occluding great vessels
Transesophageal echocardiography	1. May be difficult to visualize EAC position during cardiopulmonary bypass	EAC in area of great vessels
Carotid ultrasound	1. Difficult to monitor signal continuously—depends on index of suspicion 2. Difficult to obtain signal with nonpulsatile blood flow	Sudden loss of blood flow signal
Transcranial Doppler	1. Difficult to monitor MCA blood flow continuously—depends on index of suspicion 2. Difficult to insonate MCA during nonpulsatile blood flow 3. Poor sensitivity/specificity	1. Loss of MCA blood flow velocity signal 2. Change in ratio of RMCA vs LMCA blood flow velocity 3. Change in RMCA or LMCA blood flow direction
Cerebral oximetry (R vs L signal)	1. Sensitivity/specificity?	Decrease in cerebral venous blood oxygen saturation; change in R vs L signal[b]
Electroencephalography	1. Hypothermia, anesthetics, and roller pump artifacts limit interpretation of EEG signals	EEG slowing/change in right vs left EEG signal
Right and left radial arterial pressures	1. Requires cannulation of both radial arteries; increased risk for hand ischemia 2. Left radial arterial free graft conduit not possible	Change in the ratio of right and left radial arteries measured MAP

EAC, Endoaortic clamp; *EEG,* electroencephalographic; *L,* left; *MAP,* mean arterial pressure; *MCA,* middle cerebral artery; *R,* right.
[a]Hypothetical observation; the sensitivity and specificity of these monitors in this clinical setting have not been evaluated.
[b]The rate and magnitude of change depend on many factors, including the patient's cerebral temperature, magnitude of obstruction, and collateral blood flow.

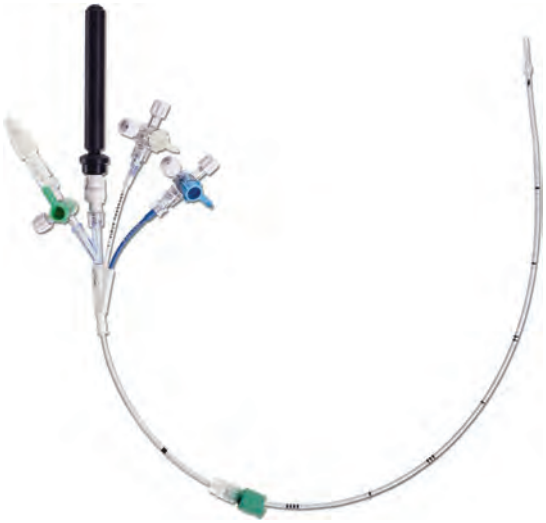


Fig. 31.17 Steerable coronary catheter for port-access surgery. *(Courtesy Edwards Lifesciences, Irvine, CA.)*

hypothesis that minimally invasive procedures result in less pain than conventional approaches (see Chapter 42). Two other large series of mitral valve surgery via right thoracotomies with PACS found the outcomes to be similar to the standard operations done via a sternotomy.[760,761] The use of robotic assistance for mitral valve repairs performed via a thoracotomy using PACS has gained popularity in some centers; results have shown good success rates, less transfusion need, and shorter hospital stays.[762]

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32

Extracorporeal Devices and Related Technologies

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KEY POINTS

1. Cardiopulmonary bypass (CPB) has been described as one of the boldest and most successful feats of medicine.
2. CPB has progressed from experimental to a commonly practiced invasive high-risk procedure as evidenced by randomized trials of off-pump versus on-pump surgery that showed significantly better composite outcomes with on-pump surgery.
3. Two predominant methods of blood propulsion are used: positive displacement roller pumps and constrained vortex or centrifugal-type pumps.
4. Modern heart-lung machines are equipped with a number of alarm systems and redundant backup systems to overcome primary system failures.
5. Blood gas exchange devices have improved over time in terms of reduced blood-surface interface, improved efficiency, and improved blood device-related inflammatory response.
6. Gaseous and particulate microemboli enter the CPB circuit from entrainment in the venous inflow to the circuit and also through the cardiotomy suction system. None of the currently available CPB systems remove all of the emboli.
7. Gaseous emboli may be reduced by correcting air entrainment around venous cannulation sites, avoiding the use of excessive vacuum-assisted venous drainage (≥20 mm Hg), use of an arterial line filter, minimizing use of vent and cardiotomy suction flow, and use of a venous reservoir with a screen filter of 40 µm or less pore size.
8. Coating technology for CPB tubing and circuit components reduces inflammation and thrombus formation.
9. There is growing concern about plasticizers such as di(2-ethylhexyl) phthalate (DEHP) in polyvinyl chloride tubing. New plasticizers such as dioctyl adipate (DOA) that have less leaching are under investigation.
10. Cardioplegia delivery must be delivered accurately to prevent myocardial damage, and new pump delivery systems provide a better operator-interface for effective delivery.
11. Blood conservation is paramount, and an effective system involves proper equipment selection for the size of the patient, careful coagulation management, and the use of advanced techniques such as acute normovolemic hemodilution, retrograde and antegrade priming, ultrafiltration, and autotransfusion.
12. Numerous studies have demonstrated efficacy of techniques using miniaturized CPB circuits for coronary artery bypass and valve procedures; adoption of these techniques has been limited.
13. Despite the growing evidence regarding the efficacy of pulsatile flow during CPB, particularly in high-risk coronary artery bypass graft (CABG) patients, clinical use remains low.
14. Numerous techniques to continuously perfuse the cerebral circulation have been developed, reducing the use of deep hypothermic circulatory arrest.
15. Communication and teamwork are of paramount importance during cardiac surgery.
16. Automated perfusion recording systems that capture physiologic patient data from patient monitors and from the heart-lung machine provide a single source for collecting, recording, and displaying essential data for the perfusionist at the point of care that enhances patient safety.
17. The use of simulation and the study of human factor science are emerging areas of research that will help teams to become effective in responding to routine and nonroutine events that may occur during CPB.

The development of surgical interventions for the treatment of cardiovascular disease has resulted in enhancements in the quality of life for an indeterminate number of patients. One of the most influential areas that has aided in the evolution of this discipline has been the development of devices and techniques for extracorporeal circulation (ECC). Indeed, the sheer complexity of how blood behaves in an extravascular environment and the influence of synthetic materials on biologic processes have provided rich areas for research.

The first reported successful use of the heart-lung machine was on May 6, 1953, when John H. Gibbon, Jr., closed an atrial septal defect with the use of a heart-lung machine, the culmination of more than 20 years of his own research.[1,2] What may not be fully appreciated is the fact that at least 17 other cases were performed in the early 1950s using some form of ECC, yet only Dr. Gibbon's patient survived.[1] By the early 1950s, Gibbon had completed an extensive series of animal experiments with the heart-lung machine with survival rates of greater

than 90%. However, his first attempt in human patients was not successful. On his second attempt, the patient's circulation was supported for 27 minutes while the atrial septal defect was repaired. According to Dr. Bernard J. Miller, "Near the termination of the operation, the machine suddenly shut down—reason being, clotting of the blood on the oxygenator took place, and the automatic arterial control sensed the sudden fall in the pool at the bottom and shut the entire machine down."[3,4] However, the patient survived and was discharged from the hospital in 9 days and lived until age 65 years, when she died in 2000. Gibbon's five subsequent procedures at Jefferson Hospital were not successful, and he abandoned the use of ECC. However, his one successful case served to inspire others, including John Kirklin at The Mayo Clinic, C. Walton Lillihei at the University of Minnesota, and Denis Melrose at Hammersmith Hospital in London, to continue the further development of ECC and cardiopulmonary bypass (CPB) in the laboratory and ultimately in the clinical arena. The accomplishments of these early pioneers in cardiac surgery have been described as being "the boldest and most successful feats of man's mind."[4]

Since the 1950s, CPB has undergone a dramatic metamorphosis from a lifesaving, yet life-threatening, technique to a procedure practiced nearly 1 million times a year throughout the world. It is uncommon in today's medical environment to encounter such an invasive procedure, with such significant risk and inherent morbidity, being practiced as routine. The goal of all techniques of CPB has always been to design an integrated system that could provide nutritive solutions with appropriate hemodynamic driving force to maintain whole-body homeostasis, without causing inherent injury. A recent randomized clinical trial, the Randomized Off-Pump or on Bypass (ROOBY) trial, involving 2203 elective or urgent coronary artery bypass grafting (CABG) patients randomized to either off- or on-pump surgery is a testament to the efficacy and safety of CPB as currently practiced. At 1 year, the on-pump group had significantly better composite outcomes (death, myocardial infarction [MI], or repeat revascularization) than the off-pump group (9.9% vs 7.4%; $P = 0.04$). The overall rate of graft patency was lower in the off-pump group than in the on-pump group as well (82.6% vs 87.8%; $P< 0.01$).[5] Concordant with the ROOBY trial's overall findings, a study examining off-pump CABG for diabetic patients reported no advantage in clinical outcomes and cost over on-pump CABG.[6] A metaanalysis that included 12 randomized controlled trials (RCTs) reported a 38% increased rate of early revascularization with off-pump surgery.[7] A systematic review by Moller and colleagues that included over 15,000 subjects found no clinical benefit to off-pump CABG regarding mortality, stroke, or MI and an increased survival benefit with on-pump CABG.[8]

This chapter is a compilation of information on extracorporeal devices and techniques used in the conduct of cardiovascular perfusion. No attempt is made to chronicle or list the multitude of components and perfusion devices currently manufactured. Rather, examples have been chosen to best represent current technology. Similarly, the techniques described under perfusion practices were chosen because of the current clinical interest, with specific protocols taken from referenced sources.

Mechanical Devices

Blood Pumps

All extracorporeal flow occurs through processes that incorporate a transfer of energy from mechanical forces to a perfusate and, ultimately, to the tissue. Methods of achieving this transfer of energy include using gravitational and mechanical forces or a combination of the two. It is through the transfer of energy from an electrical power source to the motor of a pumping mechanism and on to the fluid (blood) that causes tissue perfusion.[4,9] Most extracorporeal pumps fall into one of the following categories: positive displacement (PD), centrifugal or constrained vortex, passive filling, pneumatic and electrical pulsation, and axial flow (the latter pumps are used primarily as cardiac assist or replacement devices)[10–12] and are described in Chapter 25.

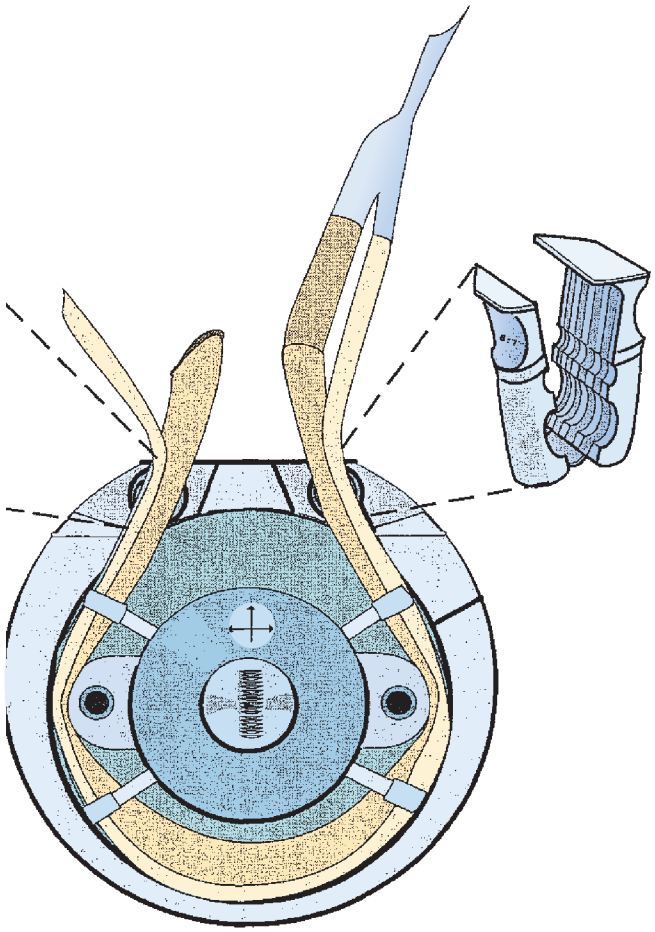


Fig. 32.1 Stockert S-3 twin roller pump diagram. A positive displacement pump with a stationary raceway and rotating twin roller pumps. *(Courtesy Sorin Group, Arvada, CO.)*

Positive Displacement Pumps

The PD pump operates by occluding tubing between a stationary raceway and rotating roller(s) or occluder(s) (Fig. 32.1). The pumping mechanism is also referred to as the *pump head*, and the tubing that traverses the raceway is referred to as the *pump header*. PD pumps were first proposed for use in cardiovascular medicine in the 1930s by Gibbon.[2] In 1935, an adaptation to the PD pump was described that included tube bushings at the head of the raceway on both inlet and outlet locations to prevent tubing creepage around the roller head.[12] Melrose[13] later modified the pump to include a grooved raceway, which further reduced tubing shimmy. Both of these adaptations were important in reducing the mobility of tubing during the operation of the pump, which decreased the potential for tubing rupture in the pump head. In a PD pump, fluid is displaced in a progressive fashion from suction to discharge, with the capacity of the displacement dependent both on the volume of the tubing occluded by the rollers and on the number of revolutions per minute (rpm) of the roller. All PD roller pumps (RPs) use the volume in the pump header, which is referred to as a *flow constant* and is specific to each size of tubing referred to by the internal diameter of tubing, for calculating the flow of the pump. This is displayed on a digital readout and is referred to as the *output* (flow) of the pump. It is measured in liters per minute. Although many types of RPs have been used for CPB, the most common PD pump in use today is the twin-RP.

There are currently at least five manufacturers of PD pumps used in ECC, with each device consisting of minor variations of the twin-RP design (Box 32.1). A modern heart-lung machine consists of between

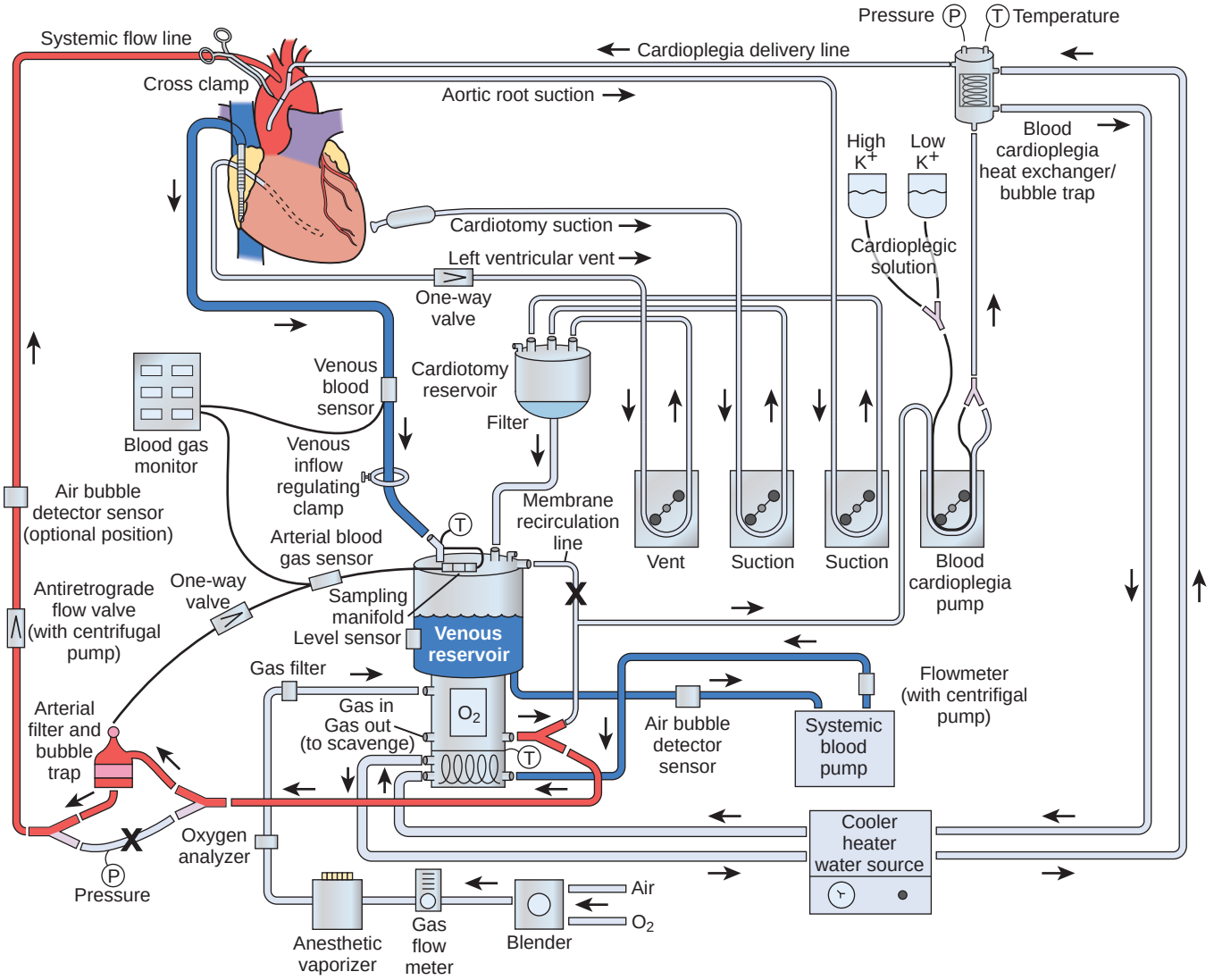


Fig. 32.2 Schematic diagram of cardiopulmonary bypass circuit, including four roller pumps (one vent pump, two suction pumps, and a cardioplegia deliver pump). A centrifugal blood pump for systemic blood propulsion is shown on the lower right. *(From Hensley FA, Martin DE, Gravlee GP.* A Practical Approach to Cardiac Anesthesia, *4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008: Fig. 18.1.)*

BOX 32.1 ROLLER PUMPS

- Composed of twin rollers.
- Deliver flow using positive displacement of the fluid in the tubing.
- Blood flow is calculated using tubing stroke volume and pump revolutions per minute.
- An underocclusive roller pump may result in retrograde flow in the patient and in the cardiopulmonary bypass circuit.
- An overocclusive roller pump may increase hemolysis and produce spallation of the perfusion tubing.

four and five of these RPs positioned on a base console (Figs. 32.2 and 32.3). Most machines are modular in design, permitting the rapid change-out of a defective unit in the case of single-pump failure. It is standard practice of perfusionists to rotate the pumps along the base console in different positions so that mechanical wear is distributed evenly while maintaining equitable time utilization. Each pump is independently controlled by a rheostat that functions to regulate the rpm of the rollers. Each pump is calibrated according to specific flow constants that are calculated from the internal diameter of tubing, as well as the tubing length, placed in the pump raceway. Periodically, PD pumps are calibrated by performing a timed collection of pumped fluid to verify that after proper calibration the pump delivers the volume indicated on the pump flow display. The internal diameters for ECC tubing ranges between 1/8 and 5/8 inch/minute. For this reason, a single console can be used to perfuse a wide range of patients whose size may vary from a few kilograms to more than one hundred. This is accomplished simply by changing the raceway tubing and the shims that hold the tubing in place. The larger the internal diameter of the tubing, the lower the rpm necessary to achieve a desired pump flow. This is especially important because there is a positive correlation between red blood cell (RBC) hemolysis and the rpm of the pump rotation. The magnitude of hemolysis is related to both the time and exposure of the blood to shear forces generated by the pump. However, most of the hemolysis generated during a routine CPB procedure is not related to the occlusiveness of the arterial pump

Fig. 32.3 HL20 heart-lung machine console. *(Courtesy Maquet Cardiovascular, Wayne, NJ.)*

Fig. 32.4 Rotaflow centrifugal pump disposable with low-friction one-point bearing (sapphire ball and PE calotte). *(Courtesy Maquet Cardiovascular, Wayne, NJ.)*

head but rather to the air-surface interface interaction occurring with the use of suction and "vent" line components of the circuit.[14–16] An underocclusive arterial pump head will result in retrograde flow. This, in turn, will require increased rpms to ensure adequate forward flow.[17] A region of high pressure and shear force is created at the leading edge of the roller where the tubing is compressed, which is followed by a period of negative pressure as the tubing expands behind the roller. This momentary negative pressure under certain conditions may induce the cavitation of air dissolved in the solution. A further related concern is particulate emboli that may be generated by microfragmentation, so-called spallation, of the inner surface of the tubing where the roller contacts the tubing and where the fold at the edges of the tubing occurs.[14] Studies of tubing wear over time have shown that polyvinylchloride fragments generated from RPs are numerous, frequently less than 20 µm in diameter, and begin to occur during the first hour of use.[15] Overocclusive adjustment of the RP results in both hemolysis of RBCs and spallation (particulate fragmentation from the inner walls of tubing), which continues with PD pumps.[18] Kurusz[14] identified the erosive and fatiguing action of the RP as a major source for generating tubing particles in CPB circuits.

The setting of occlusion in the pump head is extremely important and varies among the pumps used on the heart-lung machine console. The arterial pump head occlusion should be set by a water-drop method that incorporates a "30-and-1" rule for setting occlusion. In this method, the occlusion of the arterial pump is set by displacing a column of water (perfusate) 30 cm above the highest water level in the venous or cardiotomy reservoir (whichever is highest) and allowing the perfusate to drop 1 cm/min. Of note, if cardioplegic solution is to be delivered through a separate RP, and/or a left ventricular drainage line (left ventricular vent) placed in a roller head, occlusion for these pumps should be set at 100% (full occlusion) with no drop in fluid movement. This ensures that during the time when cardioplegic solution is not delivered, or the left ventricular vent is turned off, the risk for negative pressure in the ascending aorta or coronary sinus, created by a slowly falling column of fluid, does not create a siphon that causes cavitation or the entrainment of air into the infusion lines. Such aspirated air could be infused directly into the patient by restarting the pump. The heart is vented during CPB to facilitate the removal of ventricular blood that accumulates from noncoronary mediastinal collateral vessels, arteriovenous sinusoids, and thebesian veins, all of which drain directly into the left atrium (LA) or left ventricle. Other anatomic locations of venting the heart include the pulmonary artery and the ascending aorta, with the latter usually drained through an antegrade cardioplegia cannula. The remaining pumps usually are referred to as "pump suctions and vents" and aspirate shed blood from the operative field (see Fig. 32.2). Additional PD pumps may be used to carry out ultrafiltration (UF) or dialysis, for topical myocardial cooling devices, or for removing air from collapsible venous reservoirs.

BOX 32.2 CENTRIFUGAL PUMPS

- Operate on the constrained vortex principle.
- Blood flow is inversely related to downstream resistance.
- Flow rate is determined using an ultrasonic flow meter.
- Increase in centrifugal pump revolutions per minute may result in heat generation and hemolysis.
- If the centrifugal pump is stopped, the line must be clamped to prevent retrograde flow.

Centrifugal Pumps

The second type of extracorporeal pump is a resistance-dependent pump termed a *centrifugal* pump (CP) or *constrained vortex* pump.[19–21] The CP conducts fluid movement by the addition of kinetic energy to a fluid through the forced centrifugal rotation of an impeller or cone in a constrained housing (Box 32.2). The greatest force, highest energy, is found at a point most distal to the center axis of rotation (Figs. 32.4–32.6). CPs operate as pressure-sensitive pumps, with blood flow directly related to downstream resistance. Blood flow is, therefore, related to both the rpm of the cones or impellers and the total resistance. This represents an important safety feature in coupling blood flow with resistance. During unexpected increases in resistance, the total energy transfer from the CP to blood will not generate forces

Fig. 32.5 Revolution centrifugal pump disposable. *(Courtesy Sorin Group, Arvada, CO.)*

Fig. 32.7 CentriMag blood pump. Thoratec CentriMag magnetically levitated bearingless blood pump. *(Reprinted with permission from Thoratec Corporation.)*

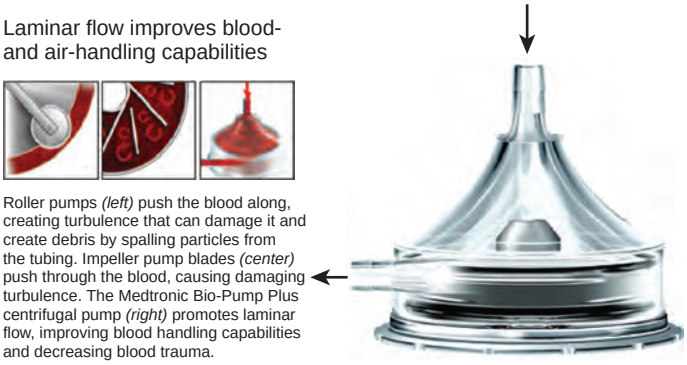


Fig. 32.6 Medtronic Bio-Pump Plus centrifugal pump. The manufacturer states that the Bio-Pump laminar flow design is superior to roller pump and impeller pump designs with inherently more turbulent flow characteristics. *(Courtesy Medtronic Cardiovascular, Eden Prarie, MN.)*

sufficient to cause arterial line separation. However, when downstream occlusion occurs, either through increases in afterload or through the placement of line clamps, the fluid in the pump head will be heated because of hydrodynamic processes in the magnetic coupling. This increase in temperature could result in increased blood trauma and coagulation defects.[21]

The acceptance of these devices in routine CPB has increased tremendously since first being introduced into clinical practice in 1969,[22] and it is the pump of choice during emergency bypass procedures. The CP also has been used as a ventricular assist device (VAD) because of its inherent safety features and pressure sensitivity, as well as relatively low cost. These pumps have been used extensively off-label for VADs; none of the CPs has received US Food and Drug Administration (FDA) clearance for use as systemic circulatory support for more than 6 hours. CP pumps have been used extensively off-label as VADs or in extracorporeal membrane oxygenation (ECMO) circuits. The afterload and preload sensitivity of these pumps make them particularly amenable for use for ECMO in the treatment of reversible respiratory dysfunction and postcardiotomy dysfunction.[23] The CentriMag Blood Pumping System (Thoratec Corporation, Pleasanton, CA) has a novel magnetically levitated *bearingless motor* technology designed to minimize friction and heat generation in the blood path (Fig. 32.7), which reduces stasis and minimizes blood trauma. The CentriMag is approved for use for up to 6 hours of support and is undergoing further investigation for prolonged use for patients with heart failure (HF). This device also recently received approval by the FDA for use as a right ventricular support device, for use up to 30 days to treat patients with right-HF—the first approval of this class of pump for use beyond 6 hours. The CentriMag received Conformité Européene Mark for use in patients as a ventricular support pump for days to weeks. In an in vitro study, Guan and colleagues[24] compared mechanical performance characteristics of the CentriMag pump with a conventional CP, the Rotaflow Centrifugal Pump (Maquet, Wayne, NJ) and reported better mechanical performance characteristics with the Rotaflow pump in terms of higher shutoff flow rate, maximal flow, and propensity for retrograde flow.[24] These findings deserve further study given the magnitude of cost for the CentriMag pump system's disposable components (CentriMag costs 20 to 30 times more than other CP disposable components).

When air is introduced into the CP, as in emptying of the venous reservoir, the pump head will deprime, stopping forward flow, which reduces the risk for gas embolization. However, when small quantities of air are aspirated into the pump head, these bubbles will coalesce and be passed into the outlet stream of fluid movement and potentially into the patient. Although the CP has been described as exerting less trauma to the cellular elements of blood,[25] variability in individual pump hemolytic potential has been reported.[26,27] Tamari and associates[28] have reported that the degree of hemolysis in CP is related to the hemodynamic conditions under which the pump is operated, with lower flows and higher pressure resulting in more hemolysis than similarly operated RPs. There have been reports of thrombus formation when these pumps are used with low anticoagulation or for prolonged periods.[29] Later designs possess fins and channels that prevent these areas of stasis. Improved designs have addressed issues of stasis, heat generation, and bearing wear. One contemporary design has minimal contact area for the cone and the outer housing and incorporates a series of magnets to suspend the moving rotor within the pump housing.[30] Additional advantages of CP over PD RPs include reduced mechanical trauma to extracorporeal tubing and the generation of high-volume output with moderate pressure development. A potential complication associated with nonocclusive-type pumps involves retrograde flow through the aortic cannula when the pressure in the central aorta exceeds that generated by the pump.[31] This may occur during times of power disruption or pump failure when there is an increased risk for drawing air into the arterial line via purse-string sutures placed to secure the arterial cannula (see Safety Mechanisms for Extracorporeal Flow section later in this chapter). Other uses of CPs include supported

Fig. 32.8 E-Clamp electronic line clamp works in conjunction with the Revolution centrifugal pump. The clamp is automatically deployed to clamp the line when retrograde flow is detected or if the air detector or level detector is triggered. *(Courtesy Sorin Group, Arvada, CO.)*

CPB in high-risk angioplasty patients, left-heart bypass (LHB) during repair of descending thoracic aortic aneurysms or dissections, and venovenous bypass during hepatic transplantation. Use of CPs to assist venous return for minimally invasive cardiac surgery is described as kinetic-assisted venous return.[32,33]

Currently, six manufacturers produce CPs for extracorporeal use: Biomedicus (Biomedicus-Medtronics, Minneapolis, MN), Delphin (3M Health Care, Ann Arbor, MI), Revolution Pump (Sorin Group, Arvanda, CO), Capiox-SP (Terumo Medical Corporation, Somerset, NJ), Rotoflow Maquet (Wayne, NJ), and the CentriMag Pump (Thoratec Corporation Pleasanton, CA). The operational characteristics are similar among the various systems in which the internal smooth cones or vaned impellers are connected to a central magnet (isolated from contact with blood by encasement in a polycarbonate housing), which couples with a motor by magnetic force. The centrifugal console usually is placed in the arterial pump head position on the heart-lung machine, replacing the main drive. All of the consoles currently available include their own battery backup systems in the event of power failure and a manually operated motor in case of drive motor or console failure. The Revolution pump is equipped with an electronic tubing clamp that may be programmed to deploy automatically if low, zero, or retrograde flow is sensed; if the level sensor in the venous reservoir senses a low level; if a high arterial line pressure is sensed; or if the air detector on the arterial line senses air in the circuit (Fig. 32.8). Each manufacturer markets the disposable component that is used with their pump; furthermore, some of the manufacturers have developed adaptor plates so that their disposable component may be used on another manufacturer's pump console.

A number of investigators have conducted in vitro studies comparing CPs and RPs in terms of blood handling during short-term and long-term use. Oku and colleagues,[34] Jakob and associates,[35] Englehardt and others,[36] and Hoerr and coworkers[37] reported less hemolysis with the CP when tested in vitro. Kress and associates[38] showed no difference between the two pump types in a rabbit ECMO model. Tamari and colleagues[39] examined hemolysis under various flow and pressure conditions in an in vitro model using porcine blood and concluded that the hemolysis index was related to the duration of blood exposure to shear, the ratio of pump pressure difference between the inflow and outflow, and the flow rate of the pump. From this work they provided guidelines related to pump selection based on the pressure/flow ratio likely to occur in a given application. Rawn and others[40] compared an underocclusive RP with a CP and found a significantly higher index of hemolysis in the CP (3.38 to 14.65 vs 29.58 g/100 L pumped). In a randomized trial, Salo and coworkers[41] examined inflammatory response mediators in 16 CABG patients with CPB times of less than 2 hours. These mediators included interleukin-1 beta (IL-1β), IL-2, IL-6, phospholipase A_2, endotoxin, fibronectin, and serum C Group II phospholipase A_2. These researchers found no differences in the levels of these inflammatory markers immediately post-CPB and at 24 hours after surgery. Other randomized clinical trials have been conducted to compare emboli generation, neurocognitive outcome, blood trauma, and patient charges. Wheeldon and colleagues[42] conducted a randomized, controlled trial in 16 patients, in which the only difference in equipment and technique was the type of pump used, and found significantly fewer microemboli, less complement activation, and better preservation of platelet count. Parault and Conrad[43] reported a similar significant improvement in platelet preservation in a retrospective review of 785 cases and further reported that the differences were more profound in patients older than 70 years with CPB times of longer than 2 hours. Klein and associates[44] conducted a randomized, prospective clinical study in 1000 adult cardiac patients comparing RPs with the Biomedicus CP (Medtronic, Eden Prairie, MN), using risk stratification methodology, and reported clinical benefits to the CP including blood loss, renal function, and neurologic outcomes, but no significant difference in mortality. Ashraf and others[45] examined S100 beta levels relative to pump type in a randomized, controlled trial that included 32 patients who had CABG and found no significant difference in S100 beta levels between the groups at 2 and 24 hours after bypass. Dickinson and colleagues[46] conducted a retrospective review of 102 patients examining length of stay, total patient charges, reimbursement, mortality, and major complications but could not identify a single difference. A more recent randomized control trial by Scott and others[47] subjected 103 patients to a battery of six standardized tests and found a trend toward fewer abnormal tests in the CP group; however, it failed to reach statistical significance. DeBois and coworkers[48] conducted a trial in 200 elective CABG surgery patients who were randomized to either an RP or CP and found similar patient characteristics including platelet counts, hematocrit, transfusion rate, and mortality; however, they observed differences favoring the CP with regard to weight gain, length of stay, and net hospital financial balance. Alamanni and colleaugues[49] evaluated the prevalence of major neurologic complications in 3438 consecutive patients and found the occurrence of injury to be associated with age and a history of a previous neurologic event. The authors further reported that use of the CP provided a risk reduction for the considered events ranging from 23% to 84%. Babin-Ebell[50] and associates conducted a randomized trial of CABG patients and found a significant reduction in tissue factor in the group supported with a CP; however, this did not translate into a measurable reduction in thrombin formation or other apparent clinical benefit. Baufreton and others[51] examined cytokine production (tumor necrosis factor-α, IL-6, IL-8) and circulating adhesion molecules (soluble endothelial-leukocyte adhesion molecule-1 and intercellular adhesion molecule-1) in a randomized, controlled trial of 29 CABG patients. They reported greater SC5b-9 and elastase levels in the CP group, suggesting more favorable performance from the RP with regard to complement and neutrophil activation.

Although nearly all of the randomized trials show significant benefit to systems designed with CPs, it is difficult to separate the improved performance conferred from other characteristics, such as lower prime volume, surface coating, more limited surface area, and reduced air-to-blood contact. A metaanalysis that included 18 RCTs comparing CP and RP in adult cardiac surgery suggests no significant difference for hematologic variables, postoperative blood loss, transfusions, neurologic outcomes, or mortality.[52]

CPs produce less blood damage; however, this improvement may be inconsequential given the blood trauma and inflammation related to contact activation of the blood related to cardiotomy suction, the introduction of gaseous and particulate emboli, and related factors. According to the recently published *Guidelines on Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery,* jointly endorsed by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists, *"It is not unreasonable to select a CP rather than a RP but more so for safety reasons rather than blood conservation"* (American Heart Association (AHA)/American College of Cardiology (ACC) class IIb level of evidence B).[53,54] In 2000, approximately 50% of the cardiac centers in the United States routinely used CPs for adult

CPB.[55] Exclusive use of CPs for pediatric cardiac surgery is about 5%; however, one-third of centers report occasional use of CPs.[56] The lower maximum pressure generated by CPs represents a noteworthy advantage because the likelihood of disruption of a tubing connection with the CP is negligible compared with that of an RP.

Electromagnetic transducers and Doppler ultrasonic flowmeters are the two methods of measuring CP flow, as compared with the calculated flow display of the PD pumps, which is the product of a flow constant and the rpms. Some have argued that separate flow meters should be used with PD pumps to directly measure the flow to avoid errors that may occur related to an unocclusive roller head or selection of the wrong flow constant.[57] Electromagnetic flowmeters operate under Faraday's principle, that an electric current can be produced in a wire moved through a magnetic field. Voltage is generated when an electrical conductor moves through a magnetic field if the movement is perpendicular to the magnetic lines between the poles of the magnet. Because blood is an electrical conductor, voltage is generated when it passes through a magnetic field and the voltage is directly proportional to the velocity of blood movement. The Doppler technology uses digital signal processing to transform the Doppler analog signal received from the flowmeter into digital format. Fast Fourier transformation then matches the incoming signal to recognizable patterns, which are displayed as flow rates.

Safety Mechanisms for Extracorporeal Flow

Some of the most recent advances in pump design have been a result of a heightened awareness of increasing safety associated with complex operating systems. The PD pumps are pressure independent, which means they will continue to pump regardless of downstream resistance. In a CPB circuit, the summation of resistances against which a pump must function includes the total tubing length, the oxygenator, the heat exchanger, the arterial line filter, the cannula, and the patient's systemic vascular resistance (SVR). Additional factors that influence SVR include the viscosity of the perfusate, related to the total formed element concentration, which primarily is dependent on the formed elements of blood and the temperature of the solution. According to Poiseuille's law, the greatest resistance to flow is created at the arterial cannula, where the change in the caliber of the tubing lumen declines the most. Perfusionists routinely monitor the summation of all resistances and record this value as the arterial line, or system, pressure. This always will be greater than the pressure measured at the distal end of the circuit terminating at the cannula tip because the pressure drop across each component in the series circuit will be subtracted from the summation of resistance (resistors) in the entire circuit. Bypass circuitry and components have been designed to incorporate minimal pressure drops; therefore, in routine adult perfusion, the resistance becomes a function of the patient's SVR and the pump flow rate. Establishing a normal value for arterial line resistance is difficult, although normal limits range between 100 and 350 mm Hg. Any acute change in resistance, such as unexpected clamping or kinking of the arterial line, results in an abrupt increase in arterial line pressure, which can lead to catastrophic line separation or circuit fracture anywhere on the high-pressure side of the circuit. A life-threatening event could occur on the initiation of CPB if the tip of the arterial cannula lodges against the wall of the aorta, undermining the intima of the vessel. Under these conditions, aortic dissection can occur as the vessel intima separates from the media, directing blood flow into a newly created false lumen. This dissection can extend throughout the entire length of the aorta. For this reason, perfusionists routinely check the line pressure after cannulation before the onset of CPB to ensure the presence of a pulsatile waveform, indicating proper cannula placement in the central lumen of the aorta. Either the absence of pulsatile pressure in the outflow portion of the perfusion circuit or an extremely high line pressure (>400 mm Hg when CPB is initiated) should immediately be investigated (see Chapter 31).

All heart-lung machines include a microprocessor-controlled safety interface with their pump consoles. These systems monitor and control pump function and serve as the primary mechanical safety control system for regulating extracorporeal flow. Pressure limits are set by the perfusionist and are determined by patient characteristics and the type of intervention performed. These units consist of early-warning alarms that alert the user to abrupt changes in pressure and will automatically turn off a pump when preset limits are exceeded. These safety devices have been used in both the main arterial pump and the cardioplegia pump; the latter become more important with the utilization of retrograde cardioplegia administration into the coronary sinus.[58,59] Currently, the incorporation of a safety monitor for negative pressure sensing, located on the inflow side of the arterial pump head and during pulsatile perfusion when intermittent occlusion is created, still is lacking.

Electrical failure in the operating room (OR) can be especially catastrophic in the conduct of ECC when the native heart and lungs are unable to function. When such an event occurs during CPB, it is imperative that instantaneous actions be instituted to minimize the risk for whole-body hypoperfusion. The perfusionist should be mindful of the power limitations of the electrical outlet used in the cardiac OR and also be aware of the location of the circuit breaker panel for the room and the specific number of the breaker in the panel for the outlet used for the heart-lung machine and other support equipment. Methods to ensure the safe conduct of CPB involve the incorporation of an emergency power source in the extracorporeal circuit that provides a secondary power source in the event of electrical interruption. Electrical failure during CPB was reported by 42.3% of respondents in a survey on perfusion accidents.[60] Although hospitals are equipped with emergency generators for such events, their availability may be limited to certain electrical circuits within the operating suite. Furthermore, these emergency power systems require a brief interruption in power before a generator or backup source of power is initiated. Most heart-lung machines are equipped with uninterrupted backup power, sometimes referred to as the *uninterrupted power source,* whereby there is a seamless transfer from the wall power source to an internal battery within the pump should the wall power fail. Thus with this system, there is no loss of flow from the pumps that could result in retrograde flow and entrainment of air or disruption of settings and timers. Cases of primary power failure with concurrent emergency backup failure also have been reported.[61] As a tertiary fallback measure, emergency hand cranks for CPB pumps are standard features in extracorporeal circuitry, which enable pump operation in the event of total power failure and when emergency systems fail to operate. However, care should be taken to ensure that the direction of blood flow is ascertained because hand cranking in the reverse direction of fluid flow could result in serious patient injury related to exsanguination and the entrainment of air around purse-string sutures at cannulation sites. The Retroguard valve (Quest Medical Incorporated, Allen, TX), a mechanical circuit component to prevent retrograde flow in the arterial outflow of the circuit, is available to prevent retrograde flow in the arterial line and possible entrainment of air into the circuit and into the patient's arterial circulation. It is composed of a simple duck-billed valve that adds minimal resistance to forward flow in the circuit and will close when downstream pressure is greater (Fig. 32.9).

Although the chance of infusing massive air boluses to patients has been reduced dramatically since the early days of CPB,[60] this remains a serious potential event during surgery (Box 32.3). Cannulation of the heart with aortic and venting catheters has been identified as the primary cause for air embolization during ECC.[62] Methods of air-bubble detection have improved tremendously, and the sensitivity for detecting small amounts of air has increased in modern heart-lung machines.[63] Ultrasonic and capacitance air-detection systems, used for both level sensing and air detection in arterial and cardioplegia circuit lines, represent dramatic improvements over less sensitive (photoelectric) methods.[64] Reliable level-sensing devices alert the perfusionist to rapid changes in venous reservoir levels with the ability to servoregulate blood flow, stop the arterial blood pump, or engage an electronic line clamp (see Fig. 32.9). The American Society of Extracorporeal Technology's International Consortium for Evidence-Based Practice

Fig. 32.9 Quest Medical RetroGard Valve. Blood enters from the 3/8-inch inlet, passes through a duck-billed valve, and exits through a 3/8-inch outlet. This valve prevents retrograde flow. This valve may also be placed on an inlet port of the venous reservoir to prevent pressurization of the hard shell venous reservoir. *(Courtesy Quest Medical, Allen, TX.)*

BOX 32.3 SAFETY MASSIVE AIR EMBOLISM

- Cannulation of the heart with aortic and venting catheters is a primary source of massive air embolism (MAE).
- Air detection and level-sensing safety devices should be used in the cardiopulmonary bypass circuit.
- One-way vent valves, positive pressure release valves, and filter purge line valves may prevent MAE related to reversed vent tubing or a pressurized venous reservoir.

has stated that both air-bubble detection and level-sensing devices must be used in all extracorporeal circuits.[65]

Electronic Perfusion Records

Health care providers and patients alike have benefitted from the influence of computer technology on improving the tools and techniques in the cardiovascular OR.[66] Since the first reported use of a digital computer to calculate indices of cardiopulmonary function in 1966, microprocessor-driven technologies have emerged to offer tremendous advantages in surgical device function and reliability.[67] Such systems are able to function without interruption through all processes of the procedure, with minimal downtime ensured with proper use and maintenance. The ability to transmit and store vast amounts of data confers significant advantages in decreasing delays in both clinical communication and treatment. [68]

The practice of ECC is represented by a multitude of physiologic and mechanical events, which are closely interrelated and constantly changing. The continuous generation of information during these events provides a perfect situation for data capture and processing, optimizing the conduct of perfusion.[69–71] Microprocessor connectivity between devices allows for real-time data to be quickly transmitted to a central processing system. As such, output data from the heart-lung machine (as well as information from peripheral equipment such as in-line blood gas analyzers, coagulation devices, cooler/heater units, and regional oximetry monitors) can be easily integrated into a single perioperative data management system. Electronic medical records (EMRs), when used in conjunction with physiologic patient data from the anesthesia-monitoring device, provide a single source for collecting, recording, and displaying essential data for the perfusionist at the point of care.

EMRs do not simply transmit information; they quickly compute values specific to the needs of the patient. Formulas using the patient's body surface area provide the clinician with immediate feedback on perfusion and oxygen requirements during ECC. Continuous real-time monitoring of both arterial and venous saturation values is used to calculate oxygen delivery and consumption ratios. Tracking fluid inputs (crystalloids, colloids, and blood products) and outputs (ultrafiltrate, urine output, and blood loss) provides trends on the overall fluid balance of the patient. ECC prime constituents and medications can be used to predict dilutional patient hematocrit values. At the conclusion of the surgical procedure, automated and manually inputted data collected during ECC are incorporated into the official perfusion perioperative record. These data may also be uploaded to a secure server to be used for retrospective quality assurance and improvement activities.[72] By electronically automating the generation of quality indicators for CPB, Baker and colleagues demonstrated an improved adherence to process of care guidelines and reduced practice variation when compared with a control group of clinicians that did not receive quality improvement (QI) data feedback.[73] Similar benefits have been reported at national and regional levels, as clinical registries help cardiac surgical programs benchmark and compare discrete perfusion variables to other institutions.[74,75] Clinical registry findings can then be "translated" back to key stakeholders to increase the speed at which new and effective treatments reach patients. In 2010, the Centers for Medicare and Medicaid Services (CMS) established provisions of the American Recovery and Reinvestment Act of 2009 that provide financial incentives to hospitals that successfully demonstrate meaningful use of electronic health records (EHRs).[76] These standards require CMS-eligible institutions to record and report clinical quality measures aimed to quantify health care processes and outcome. The perceived benefits of the meaningful use of EMR data will result in better clinical outcomes, increased transparency and efficiency of services, empowered individuals, and more robust research data on health systems.[76]

The newest generation of perfusion EMRs is now capable of providing real-time safety alerts to potentially dangerous events during extracorporeal support. Through the advent of continuous monitoring of critical care parameters, computer-generated notifications can alert the clinician when various physiologic parameters fall outside of the desired level of compliance. Similar to the aviation industry, these computer-guided early warning systems help perfusionists quickly diagnose potentially adverse conditions before they manifest into significant complications.[77] The Viper EMR data acquisition system (Spectrum Medical, Fort Hunt, SC) is a clinical software application that collects and interprets data in real-time by incorporating compliance threshold limits (Figs. 32.10 and 32.11). Clinicians can activate high and low threshold alarms for a multitude of physiologic parameters during ECC support. When a clinical variable falls outside the preset compliance limit, a pop-up banner alert message immediately notifies the clinician. Beck and colleagues demonstrated nearly a 10-fold decrease in perfusionist response time (3.6 vs 30 seconds) for critical values occurring for clinicians assigned to the Viper and non-alert groups, respectively.[78] The authors concluded that the use of this type of technology not only improved operator performance, but also had the ability to translate into improved patient safety and outcome. Another unique feature of the Viper system is the ability to broadcast clinical information to locations across the medical center campus.

Fig. 32.10 Viper display with table and graphical display of data. *(Courtesy of Spectrum Medical, Fort Mill, SC.)*

When coupled with compliance alert thresholds, remote monitoring can enable the perfusionist to be notified of suboptimal clinical parameters when they are not immediately available at the bedside. Fung and colleagues demonstrated the effective use of remote monitoring to diagnose and troubleshoot complications for patients on ECMO support.[79] The continued support and growth of such telehealth services could extend the clinical reach of health care providers to patients that can benefit from their expertise.

Most major perfusion hardware manufacturers offer EMR solutions for intraoperative data management and reporting. However, there is significant variation with each technology in its ability to interface with other OR devices and software applications. This limits the amount of data that can be collected and stored for QI tools. Further, the lack of device connectivity requires significant levels of manual data entry, which not only focuses the attention of the clinician away from the patient, but also limits information that can be used to make informed clinical decisions at the point of care. The Sorin CONNECT Perfusion EMR (Sorin Group, Milan, Italy) incorporates an intuitive goal-directed perfusion (GDP) technology that quantifies the adequacy of modifiable factors during ECC (Fig. 32.12). CONNECT features real-time calculations of oxygen delivery, oxygen consumption, and venous CO_2 values. Similar GDP management strategies have been shown to be associated with reductions in the incidence of postoperative acute kidney injury following cardiac surgery.[80]

As the use of EHRs continue to grow in the health information technology ecosystem, all perfusion-based patient care activities will

Fig. 32.11 Viper tablet for display and data entry. *(Courtesy of Spectrum Medical, Fort Mill, SC.)*

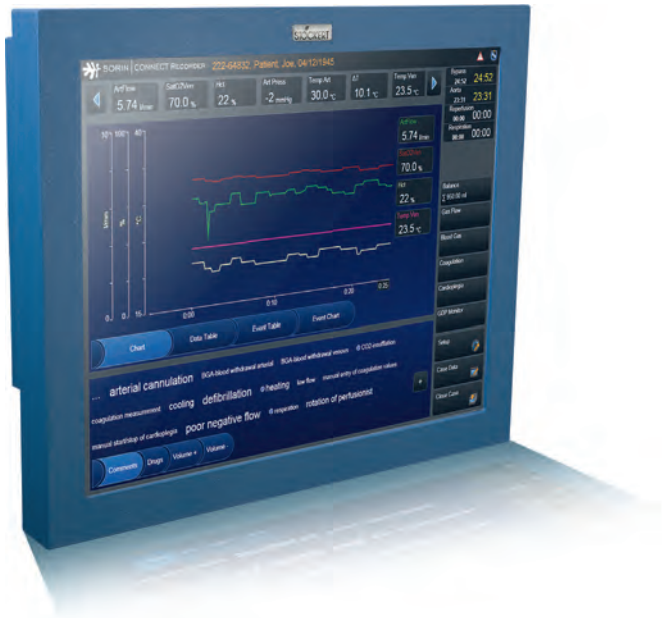


Fig. 32.12 Sorin Connect perfusion electronic medical record with goal-directed perfusion display. *(Courtesy of The Sorin Group, Arvada, CO.)*

eventfully transition away from paper to electronic data entry. However, the overall impact on positive patient care and outcome will rely on the EMR's ability to integrate with other health care systems to make the data meaningful. Choosing the right EMR solution, as opposed to the "one size fits all" platform, may offer a level of data granularity that best meets the unique needs of the cardiac surgical patient. Although a significant investment of time, money, and training is associated with implementing many EMR systems, the observed benefits of translational medicine from the bench to the bedside cannot be understated. The digital age in medicine is transforming the delivery and coordination of patient care and outcome.

BOX 32.4 MEMBRANE OXYGENATORS

- Hollow-fiber membrane oxygenators are commonly used for cardiopulmonary bypass.
- An oxygen gas mixture flows through microporous polypropylene hollow fibers.
- Blood flow is directed over the microporous hollow fibers.
- Recently nonporous polymethylpentene (PMP) hollow fibers have been developed.
- PMP fibers provided a more durable surface for prolonged oxygenation such as extracorporeal membrane oxygenation.
- PMP fibers do not permit the passage of volatile anesthetics such as isoflurane.

Extracorporeal Circuitry

Blood Gas Exchange Devices

The ECC of blood incorporating total heart-lung bypass could not be accomplished were it not for the development of devices that could replace the function of the lungs in pulmonary gas exchange. The technology of pumps to replace the mechanical action of the heart was developed well before their incorporation in ECC. Therefore the limiting factor hindering the progression of CPB was the development of an artificial lung, or BGED, commonly referred to as a *membrane oxygenator* (Box 32.4). The term *membrane* denotes the separation of blood and gas phases by a semipermeable barrier, whereas *oxygenator* refers to the change in oxygen partial pressure that occurs by the arterialization of venous blood. However, "oxygenator" is a misrepresentation of the functional ability of these systems to perform ventilatory control of carbon dioxide. Numerous engineering challenges hindered the development of BGEDs, but two of the most pressing were the design of high-capacity units for gas exchange with low rates of bioreactivity. The latter requirement, also termed *biocompatibility,* was imperative to reduce both RBC trauma and activation of the formed elements of blood.

In the 1940s, the first dialyzer membranes were made of cellulose acetate, and although intended for use in dialysis, they also had gas exchange characteristics.[1] In the 1950s, several membrane materials (including polyethylene and ethyl cellulose) were used in a flat sheet or plate configuration. At the same time, rotating disk oxygenators were introduced whereby gas exchange was accomplished by spreading venous blood in a thin film over a rotating disk, which was exposed to an oxygen-rich environment. In the 1960s, the first disposable membrane oxygenators were introduced and were made primarily of silicone rubber in either a plate or spiral wound design. Silicone offered the distinct advantage of separating both the blood and gas phases, facilitating gas exchange through a semipermeable barrier by diffusion. Teflon was introduced in the 1970s as a membrane material, together with microporous polypropylene (PPL), which first appeared in Travenol membrane devices. Today, the majority of commercially available oxygenators are made of PPL in either a pleated or folded configuration, or as capillary hollow fibers. In the United States, manufacturers develop oxygenators that meet federal regulatory guidelines for performance and biocompatibility. Those devices meeting these requirements are "cleared," approved for use for up to 6 hours of CPB, and represent the majority of oxygenators. Currently, only one oxygenator that utilizes silicone membranes is approved for long-term support such as that occurring for ECMO. However, the "off-label" use of more durable, lower prime, hollow-fiber technology membrane oxygenators and newer polymethylpentane fiber oxygenators is widely reported in the literature.

Historically, oxygenators were divided into three broad classes based on the method of gas exchange: film oxygenators, bubble devices, and membrane systems. The stationary 0.7-mm screen oxygenator used by Gibbon is an example of a film oxygenator. Blood was distributed over a screen producing a film that increases the surface area of the blood and its exposure to oxygen allowing gas to transfer by diffusion.[81] Bubble-type devices have been shown to denature plasma proteins, increase RBC fragility,[82] activate platelets,[83] and generate substantial gaseous microemboli (GME).[84–86] For these reasons, they are no longer used in most countries and are infrequently encountered in all but a few remaining places throughout the world. Bubbler systems use a direct gas-blood interface, with gas exchange occurring by the dispersion of gas, either 100% oxygen or a mixture of oxygen and carbon dioxide (carbogen), through a column of desaturated blood. Bubble devices are made of two separate compartments: an oxygenating column and a defoaming chamber. The dispersion of gas in a bubbler occurs through a sparger plate, where a thin film of blood comes in direct contact with gas. This direct blood-gas interface results in the production of foam, where gas exchange occurs. Coalescence of the foam is achieved in the defoaming chamber both through the presence of surface tension–reducing substances and by filtration. Gas exchange is affected by several factors, including the quantity of gas and the size of bubbles produced in the gas sparger.[87] Small bubbles are extremely efficient at oxygen exchange but poor at carbon dioxide exchange, whereas large bubbles are poor in oxygen but good in carbon dioxide exchange.

Membrane oxygenators are made of three distinct compartments: gas, blood, and water (see Fig. 32.10). The latter phase is also termed the *heat exchange compartment* and is used for temperature control. Gas and blood are partitioned into separate compartments with either a limited or absent gas-blood interface. Microporous membrane oxygenators initially have a blood- gas interface that becomes diminished only after the inner blood contact surface has been exposed to plasma; and a protein layer is deposited, acting as a diffusible barrier to gas exchange. The most common material in use today in membrane oxygenators is microporous PPL, which has excellent capacity for gas exchange and good biocompatibility. Membrane devices made of silicone materials transfer gas directly by diffusion across the semipermeable membrane and effectively never have a blood-gas interface.[88] Despite the improvements made to extracorporeal devices over the past several decades, once blood is exposed to synthetic surfaces, hematologic changes result. Initially, complement is activated mainly through alternative pathways, resulting in the liberation of toxic mediators such as C3a and C5a.[89,90] Both platelets and leukocytes that elicit a complex series of inflammatory and hemostatic reactions that ultimately increase the risk for postoperative complications are activated.[87]

Gas transfer in membrane oxygenators is a function of several factors that include surface area, the partial pressures of venous oxygen and carbon dioxide, blood flow, ventilation flow (called *sweep rate*), and gas flow composition. Membrane devices independently control arterial oxygen and carbon dioxide tensions (PaO_2 and $PaCO_2$). Pao_2 is a function of the FIO_2, whereas $PaCO_2$ is determined by the sweep rate of the ventilating gas. This independent control of ventilating gas results in arterial blood gas values more closely resembling normal physiologic blood gas status. However, it is common for perfusionists to maintain PaO_2 levels in the 150- to 250-mm Hg range during CPB because of the limited reserve capacity of membrane oxygenators.

A multitude of factors must be considered in the design of a membrane BGED, including total surface area, blood film thickness, diffusion residence time, gas diffusion rate, blood flow rate, blood flow geometrics, and gas flow characteristics. The most influential factors that affect blood trauma in an oxygenator are related to how blood traverses the device and are termed *shear stress* and *stasis*.[91] Design characteristics that minimize these effects by optimizing flow pattern geometry through extracorporeal devices have been generated through mathematical models termed *computational fluid dynamics*.[92] Two of the most important considerations in designing a membrane device are determining the type of membrane material and the handling of water vapor produced in the gas phase of the device. This water vapor would be synonymous with pulmonary exudate and, when excessive, mimics pulmonary edema associated with permeability changes of the alveolar capillary membrane. Another important membrane feature is how blood flows through the membrane. As fluid moves through a conduit, laminae are established, with the highest velocity of flow achieved in the center of the tube. At the same time, the outermost layers, nearest the walls of the conduit, effectively have no velocity because of the drag coefficient of the inside surface. This occurs in both the gas phase and the blood phase of membrane oxygenators. The laminar effect can be disrupted by several techniques that produce a "secondary flow," facilitating increased gas exchange.[93] In hollow-fiber membrane oxygenators, incorporating blood flow outside of the fibers, mixing is achieved by winding of the fibers, creating a crossing pattern, increasing blood exposure to the membrane surface. Laminar flow is reduced in hollow-fiber oxygenators with blood flow through the fibers by the expansion and contraction of the capillaries via the movement of blood through them, gently disrupting the boundary layers.

Estimating the total surface area of material necessary for gas exchange is a function of the predicted oxygen demands of the patient, the pattern of flow within the device. As the surface area of an oxygenator increases, the volume of solution necessary to prime the system increases. Early microporous PPL hollow-fiber membrane devices used a pattern of blood flow through the fiber. Contemporary designs have blood flow around hollow fibers with gas flowing through the fibers. Oxygenators with longer blood flow paths may require less fiber surface area. Those with shorter blood flow paths require more fiber surface area to achieve a similar oxygen transfer. Systems that use the latter design require a lower membrane surface area for gas exchange and hence result in lower prime volumes. Microporous PPL membranes have the distinct advantage of a greater gas transfer rate per surface area of membrane than that of silicone membranes.

The oxygenator represents the largest source of nonendothelialized surface area in the extracorporeal circuit, ranging in size between 0.5 and 2.5 M^2. As a consequence, it is imperative that the device is meticulously primed to remove all residual air before establishing CPB. Oxygenators have been shown to possess different abilities to remove gaseous emboli that vary according to the physical CPB conditions including temperature and pressure decline.[94–97] In an effort to reduce surface exposure and prime volume, several membrane oxygenators are now manufactured that either possess integrated arterial line filters (CAPIOX FX Oxygenator; Terumo Cardiovascular Group, Ann Arbor, MI [Fig. 32.13] and Affinity Fusion; Medtronic, Minneapolis, MN [Figs. 32.14 and 32.15]) or have an arterial line filter that is sequenced in the oxygenator (Inspire; Sorin Group, Arvada, CO [Fig. 32.16]). Some studies suggest that these devices may result in a reduction in GME.[98,99]

Numerous studies have identified the occurrence of GME during cardiac surgery with CPB.[100] Weitkemper and colleagues[101] have shown

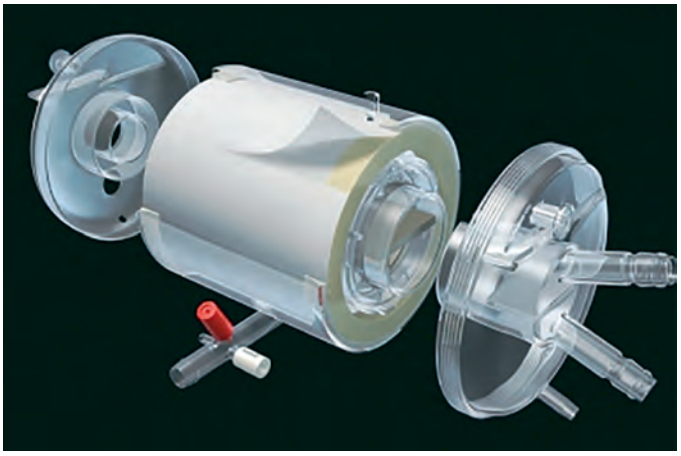


Fig. 32.13 Terumo FX Oxygenator with integral 32-micron screen filter surrounding the fiber bundle. *(Courtesy Terumo Cardiovascular Group, Ann Arbor, MI.)*

that currently used microporous membrane oxygenators have widely variable characteristics related to how they handle gas. Furthermore, the design characteristics in some cases cause partial removal of GME, as well as a change in size and numbers of microbubbles. Dickinson and associates[102] conducted an in vitro analysis that showed significant air-handling differences between the oxygenators from four different manufacturers. They demonstrated how a sonar-based system, the Embolus Detection and Classification (EDAC; Lunar Technology, Blacksburg, VA) system, could be used to evaluate perfusion systems with regard to their ability to handle gas entrained in the circuit.

A new nonporous membrane surface composed of polymethylpentene (PMP) fibers has shown improved diffusion compared with the conventional PPL hollow fibers. PPL affords improved durability and biocompatibility when used for long-term support[103,104] and for routine CPB.[105] Although oxygen and carbon dioxide gas exchange are comparable between PPL hollow fibers and the PMP nonporous fibers, it is important to note that the transfer of volatile anesthetic agents do not readily cross this membrane. Wiesenack and colleagues[106] demonstrated that the PMP fibers allow only minimal transfer of isoflurane compared with the currently used PPL microporous hollow-fiber oxygenators. A recent systematic review on anesthetic management during CPB reported the common use of volatile anesthetics through the heart-lung machine in the United States.[107] However, Europeans favor intravenous anesthetics during bypass, and European Council Directive 93/42/EEC bans the use of a vaporizer with a heart-lung machine.[108,109] During long-term support, it is not uncommon for PMP oxygenators to develop breaches in the surface that lead to plasma leaks after 40 to 90 hours of use, whereas the PPL fibers tend to be more robust, are not prone to plasma leaks, and continue to transfer oxygen and carbon dioxide after many days of use.

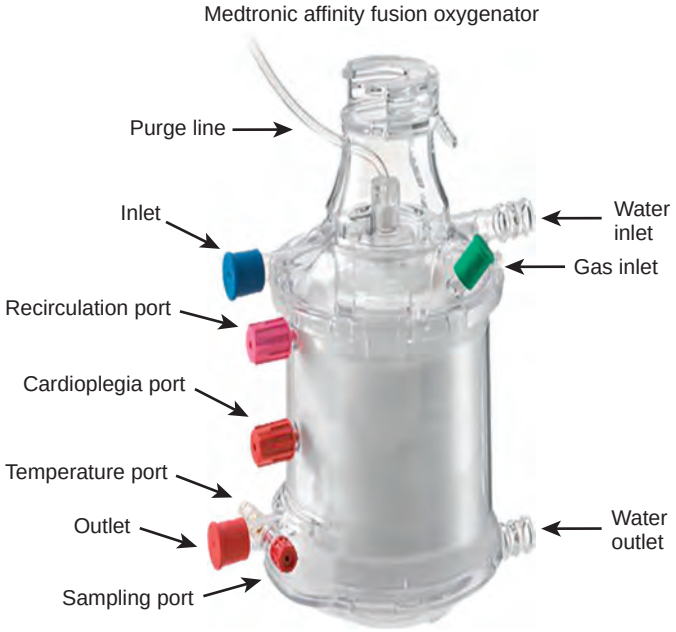
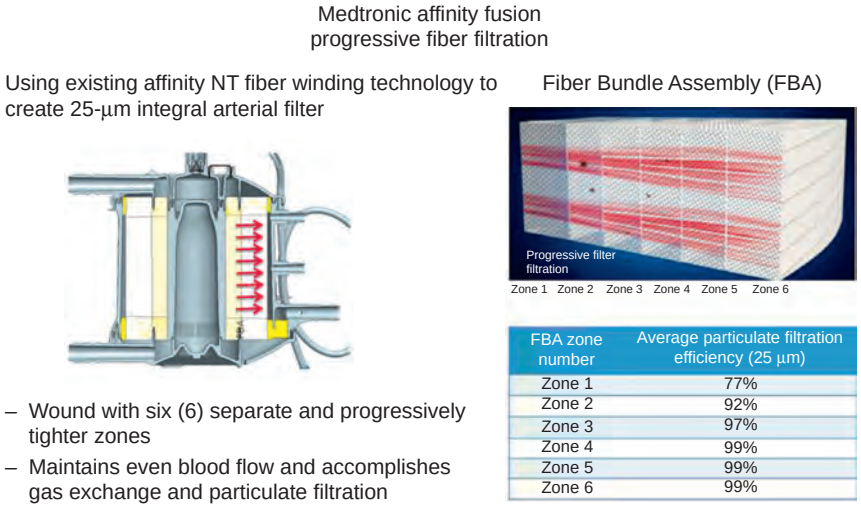


Fig. 32.14 Medtronic Affinity Fusion oxygenator. *(Courtesy of Medtronic Cardiovascular, Minneapolis, MN.)*

Fig. 32.16 Sorin Inspire oxygenator with an integrated arterial line filter. *(Courtesy Sorin Group, Arvada, CO.)*



FBA zone number	Average particulate filtration efficiency (25 µm)
Zone 1	77%
Zone 2	92%
Zone 3	97%
Zone 4	99%
Zone 5	99%
Zone 6	99%

Fig. 32.15 Medtronic Affinity Fusion oxygenator. Filtration is accomplished by six progressively tighter zones of fiber winding. Effective filtration is 25 microns.

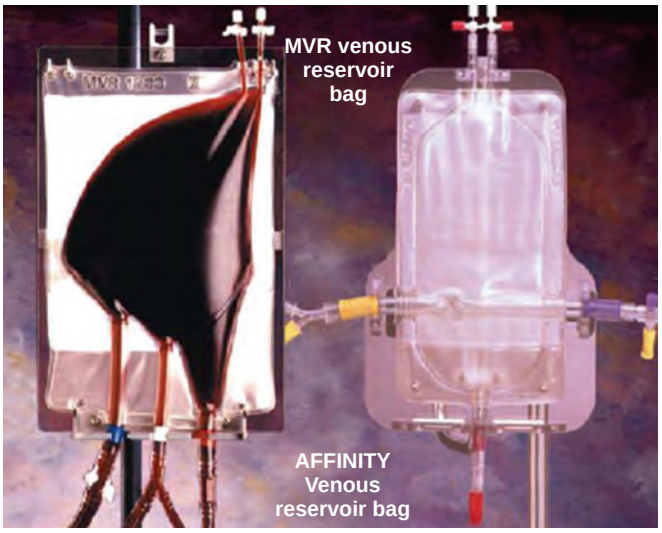


Fig. 32.17 Example of a closed system. Oxygenator with a collapsible polyvinyl chloride venous reservoir. *(Courtesy Medtronic Cardiovascular, Minneapolis, MN.)*

BOX 32.5 VENOUS RESERVOIRS

Open Systems

- Open systems have polycarbonate hard-shell reservoirs and are usually equipped with an integral cardiotomy reservoir.
- With open systems, venous return may be improved by applying regulated suction to the reservoir (vacuum-assisted venous drainage).
- With open systems, buoyant air bubbles escape to the atmosphere at the top of the reservoir.

Closed Systems

- Closed systems consist of collapsible polyvinylchloride bags.
- Closed systems require a separate cardiotomy reservoir.
- Buoyant air from the venous line accumulates in the bag and must be actively aspirated.
- Closed systems have a reduced contact surface of the blood with air or plastic.
- A separate centrifugal pump may be used to increase venous return (kinetic-assisted venous drainage).

Venous and Cardiotomy Reservoirs

There are two general categories for venous reservoirs: open and closed systems (Box 32.5). Open systems have a hard polycarbonate venous reservoir and usually incorporate a cardiotomy reservoir and defoaming compartment (see Fig. 32.13). Closed systems are collapsible polyvinylchloride bags that have a minimal surface area and often a thin single-layer screen filter, and they require a separate external cardiotomy reservoir for cardiotomy suction (Fig. 32.17). Filters and defoaming compartments in the venous reservoir and air-trapping ports located at the highest level of the blood flow path within the oxygenator are areas designed to allow passive removal of air. Studies that have examined the air-handling capabilities of oxygenators have shown that all of the currently available oxygenators do not sufficiently remove GME when challenged with air in the inflow.[102,103] The use of an open system offers several distinct advantages. Unlike collapsible reservoirs, it is not necessary to actively aspirate air, which may be entrained in the venous line during CPB. The large buoyant air migrates to the top of the reservoir and escapes through strategically placed vents on the reservoir cover. An additional benefit of the use of "open" hard-shell reservoir systems incorporates the capability of vacuum-assisted venous drainage (VAVD), although alternative methods have been implemented augmenting venous drainage to closed "bag" systems using CPs or creative vacuum applications applied to the venous line to enhance natural gravity drainage. Furthermore, a number of studies have reported a greater incidence of GME caused by air entrained in the venous line and furthermore that VAVD further increases GME counts.[105,110–114] Willcox has raised concern that VAVD has been used clinically without any significant redesign of the components of the CPB circuit to improve the gas handling performance in negative pressure conditions.[113] The prime volume may be reduced slightly because the integration of the venous reservoir with the cardiotomy eliminates connecting circuitry and may permit a smaller-bore venous line with use of VAVD. With open systems, the circulating blood is exposed to a larger and more complex surface that contains defoaming sponges and antifoam agents. Air can traverse the oxygenator into the arterial outflow of the CPB circuit and into the patient's arterial circulation, including the cerebral circulation, producing contact activation of the vascular endothelium or obstruction at the microcapillary level. Thousands of GMEs can be introduced into the patient's arterial circulation with these circuits if air becomes continuously entrained into the venous inflow, a condition that could not be tolerated with a collapsible reservoir.

VAVD also carries a risk of an accidental massive air embolism. It has been reported that occlusion of the vacuum source line can cause pressurization of the venous reservoir and introduction of a gas embolism to the patient through the venous line.[115–118] Thus it is important to monitor the reservoir pressure if vacuum-assisted venous draining is used.

Recently, several randomized clinical trials have found superior clinical outcomes with a system equipped with a closed reservoir and a centrifugal arterial pump.[119,120] Schonberger and colleagues[121] prospectively studied differences in inflammatory and coagulation activation of blood in CABG patients treated with open and closed reservoir systems. Levels of complement 3a, thromboxane B_2, fibrin degradation products, and elastase were significantly greater in open reservoir patients. Furthermore, the largest ($P < 0.001$) amount of shed blood loss, greatest ($P < 0.05$) need for colloid-crystalloid infusion, and largest (not significant) need for donor blood (0.8 ± 0.4 vs 0.2 ± 0.2 units of packed cells) were observed in the patient supported with open reservoir systems.

Aldea and associates[122] conducted a randomized, controlled trial to evaluate the effects of cardiotomy suction in CABG patients. Use of cardiotomy suction resulted in significant increases in thrombin, neutrophil, and platelet activation, as well as the release of neuron-specific enolase, after CPB. The authors suggested that limiting increases in these markers would be best accomplished by eliminating cardiotomy suction and routinely using heparin-bonded circuits whenever possible.

Miniaturized Cardiopulmonary Bypass

The principal drawbacks to the conventional CPB circuit include activation of the systemic inflammatory response, aberration in coagulation function, CPB-related gaseous embolism, and excessive hemodilution requiring blood transfusions. A principal design approach to overcome some of these problems has been the introduction of "miniaturized CPB circuits" that reduce the blood–foreign surface contact, blood-air interface, and hemodilution (Figs. 32.18 to 32.19). The currently available "mini" systems consist of either an adaptation of standard CPB components or the introduction of new devices by manufacturers that have a striking resemblance to existing devices.[123–157] The manufacturers' minisystems all use a single CP to provide kinetic venous drainage and arterial blood propulsion. All have eliminated or isolated the venous reservoir to reduce blood foreign surface contact, and all eliminated the introduction of activated blood from a cardiotomy suction system. Field shed blood is recaptured and washed by an

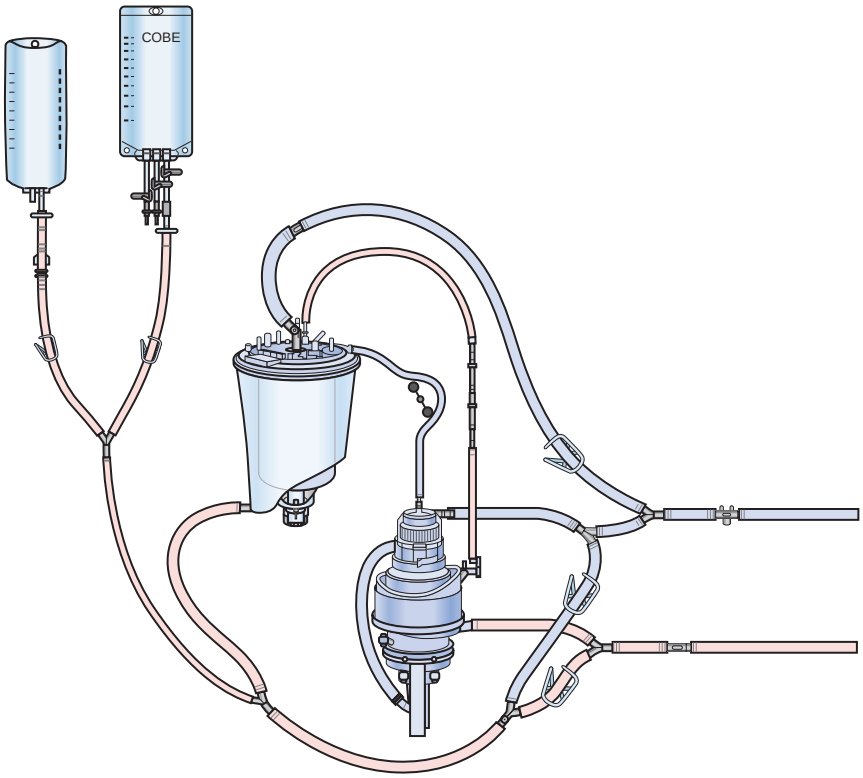


Fig. 32.18 Sorin Group Synthesis mini-bypass system. The oxygenator has an integral air detection and evacuation system and a single integral revolution centrifugal pump (providing both kinetic-assisted venous drainage and arterial blood propulsion). An integrated arterial line filter surrounds the oxygenator fiber bundle. A separate cardiotomy reservoir is incorporated into the circuit. The system may be converted to an open system by repositioning clamps and redirecting blood flow to the reservoir. *(Courtesy Sorin Group, Arvada, CO.)*

autotransfuser before reintroduction to the minisystems. Many of the systems have incorporated multisite bubble detection and innovative air removal systems to automatically remove and isolate micro and macro air entrained in the CPB circuit.

These systems lack several of the characteristics of the old standard CPB systems that made CPB simple. For example, the entrainment of air into the old systems was of little operational consequence because air could escape to the top of open reservoir systems or be aspirated by a vacuum or an RP from closed reservoir systems. Furthermore, shed blood at the surgical field could be readily collected and reintroduced into the circulation with conventional systems using the cardiotomy suction system without the use of an autotransfuser. In other words, variable venous return or excessive suction return can be easily accommodated with regular CPB systems, with minimal or no addition to the basic circuit as opposed to the minisystems currently on the market.

With most of the minisystems, minor changes in the circuit or complete major reconfiguration of the minisystem may be necessary if excessive bleeding occurs at the surgical field (addition of a venous reservoir, addition of a cardiotomy reservoir, and transfer of a massive amount of blood from the autotransfuser collection reservoir back to the minisystem). Minisystems do not facilitate emptying of the cardiac chambers as well as do conventional systems. With conventional CPB systems, the cardiac chambers can be passively emptied into a capacitance reservoir, whereas in the usual configuration, the capacity of the venous system in the presence of a minisystem is quite fixed. In minisystems, the capacitance reservoir is the patient's venous bed. To empty the heart, blood must be actively diverted to a separate reservoir or to the patient's capacitance reservoir with manipulation of the venous capacitance. Safe use of these systems requires good communication among the surgeon, anesthesiologist, and the perfusion team, together with careful monitoring. These major differences have made some centers reluctant to change to these new systems.

A metaanalysis of RCTs conducted by Zangrillo and colleagues[158] sought to determine whether the use of miniaturized CPB translates into decreased morbidity, including blood transfusion, neurologic events, and blood loss, in patients having cardiac surgery. Sixteen trials met inclusion criteria, with 1619 patients (803 to miniaturized CPB and 816 undergoing standard cardiac surgery). Miniaturized CPB proved to be beneficial in terms of decreased transfusion rate and decreased cardiac and neurologic injury. These findings are summarized in Fig. 32.20. Current use of such systems is limited. Further studies are necessary to substantiate the benefit of such systems and will likely increase the adoption of this new technology. Similarly, Harling and colleagues conducted a metaanalysis composed of 29 studies and 2355 patients, which showed no difference in mortality and neurovascular compromise and a significant favorable trend of blood loss, transfusions, and fewer arrhythmias with MECC.[159] Surprisingly, despite the preponderance of evidence, use of MECC is not widely used in the United States.

Portable Cardiopulmonary Support Systems

There has been a surge in the use of ECMO therapy for both cardiac and pulmonary support. Between 2006 and 2011 outcomes for patients supported with ECMO improved and the use of ECMO support in the United States increased by 433% [160] A variety of platforms composed of conventional CPs or RPs have been used. Maquet has designed a new system aimed to improve the safety and ease of transporting patients supported with an extracorporeal live support.[161] The Cardiohelp portable life support system (Maquet Cardiovascular, Bridgewater, NJ) is a system with a fully integrated pump and oxygenator disposable

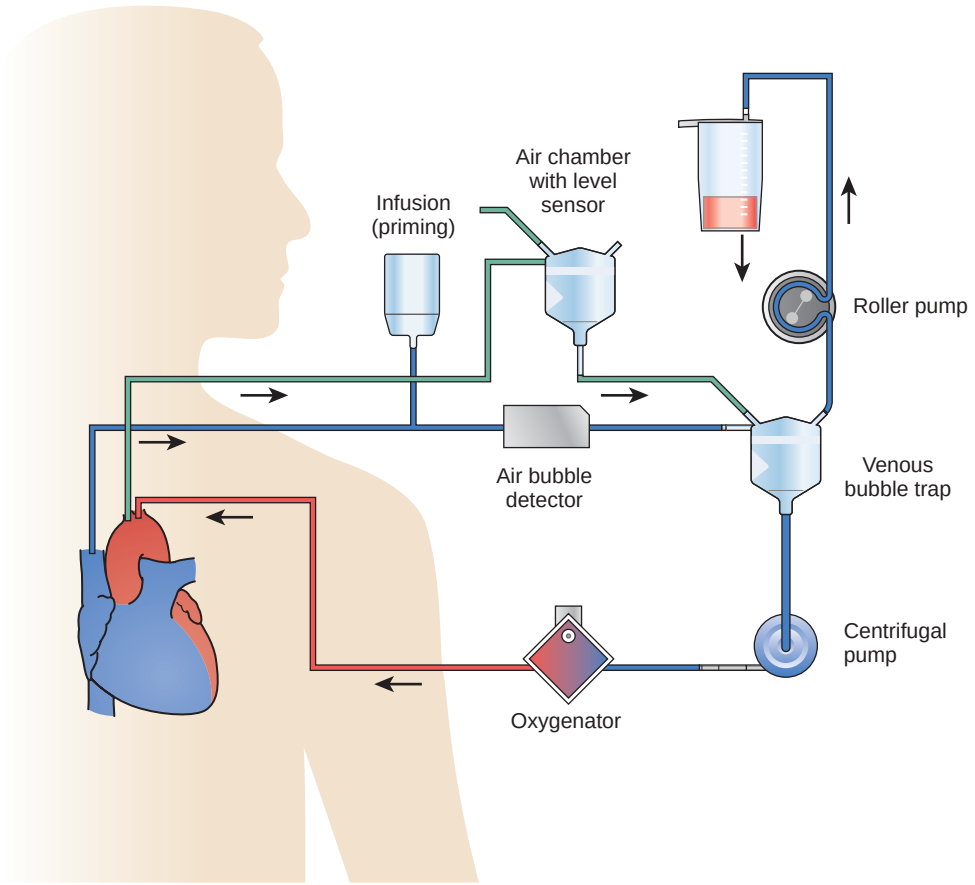


Fig. 32.19 Maquet Minimal ExtraCorporeal Circulation. The system includes venous air bubble detection and venous bubble trap, a single integral pump (providing both kinetic-assisted venous drainage and arterial blood propulsion), and quadrox oxygenator. *(Courtesy Maquet Cardiovascular, Wayne, NJ.)*

cassette with a lightweight (22-lb) pump drive and control mechanism that may be used for extracorporeal perfusion resuscitation anywhere in the hospital, for ECMO support in critical care units, or for transport within or across health care facilities (Fig. 32.21). The system has a unique console design that eliminates the use of a stator motor. The system interface plate consists of a surface with a moving magnetic field that drives the integrated CP. The Cardiohelp system is an important departure from the traditional "homemade" ECMO circuits and consists of a standardized circuit and built-in pressure alarms, temperature alarms, and hemoglobin and saturation sensors. Early reported experience with this system has been favorable in terms of ease of set up, performance, and portability.[162–164]

Heat Exchangers

Patients who are exposed to ECC will become hypothermic in the absence of an external source of heat to regulate body temperature. Most CPB systems use some form of heat exchanger in the circuit to warm and/or cool the patient's blood. The majority of oxygenators contain integral heat exchangers through which blood passes before undergoing gas exchange (see Fig. 32.15). Heat exchangers may be absent from circuits used for ventricular assist or certain types of LHB. However, in either of these scenarios, external warming blankets and ambient room temperature are controlled to restrict declines in patient temperature. Heat exchangers can be made from a variety of materials, although the most often used are aluminum (anodized or silicone-coated anodized), stainless steel, and PPL. Stainless steel is the most durable and chemically inert of all commercially used heat exchangers.

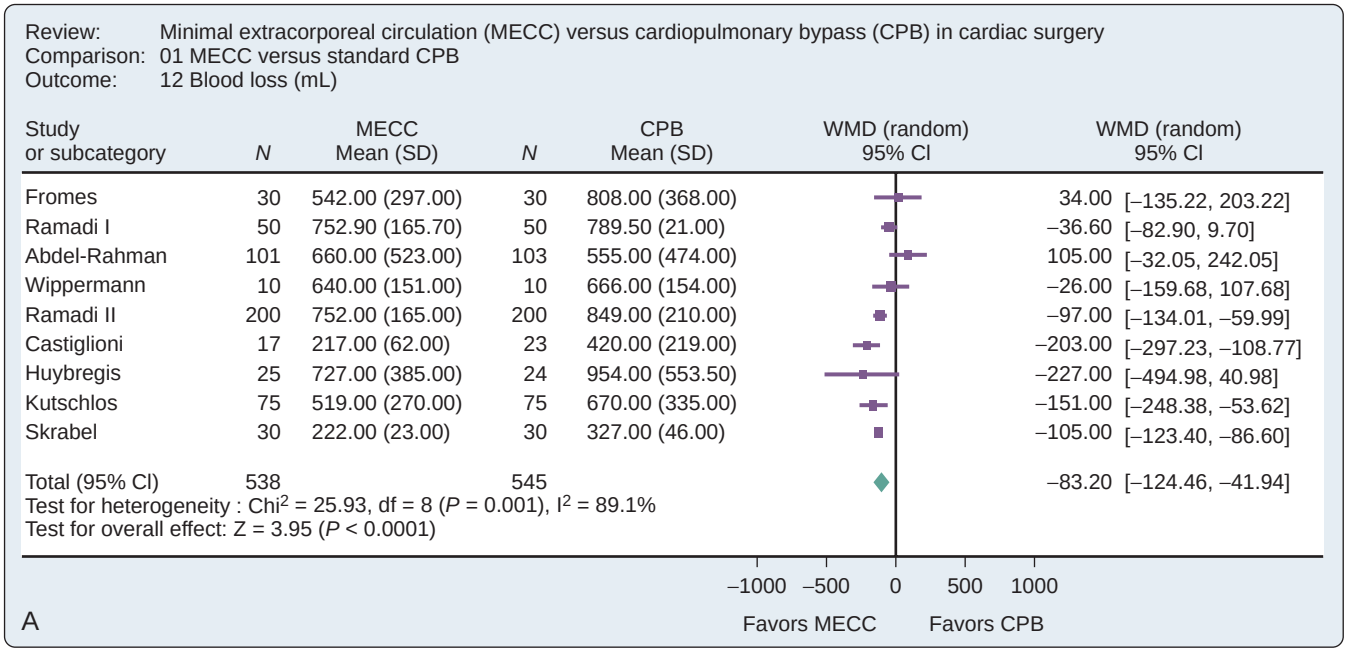
Some of the basic performance features that all heat exchangers for extracorporeal blood should possess include a high degree of chemical inertness, high resistance to corrosion, smooth surfaces, and a low-energy surface where RBC and plasmatic residues do not adhere. The ideal heat exchanger must possess the following characteristics: low resistance to blood flow, freedom from defects in material that could facilitate the mixture of blood and water, low priming volume, and disposability. The effectiveness of a heat exchanger depends on several factors, including total surface area, thickness of the conductor walls, thermal conductivity, and the residence time of blood through the device. As fluid flow through a heat exchanger is increased, the performance characteristics decline, primarily as a function of decreased residence time in the device.

Heat exchanger basic design consists of two separate phases, with water passing on one side and blood, or perfusate, on the other. The direction of blood flow is routinely countercurrent to the flow of water, optimizing heat transfer. The temperature of the water entering the heat exchanger is controlled by either an external cooler/heater device or a wall source, with a temperature range from 4°C to 42°C. The majority of heat transfer occurs by the process of conduction, in which thermal energy is passed from water to blood.

Heat exchangers can be placed in the circuit in a variety of locations, although the most common location is on the proximal side of the oxygenator, often termed an *integral heat exchanger*. It is hypothesized that with proximal, or venous-side, heat exchange, there is less chance of "outgassing of solution" caused by rapid rewarming of blood after hypothermic CPB, which could generate GME. Of similar concern is the effect of rapid cooling and warming of an organ or tissue, during which temperature fluctuations would create an environment in which

the solubility of gas in blood would abruptly decline, increasing the partial pressure so that GME could be generated. Increased risk would be directly proportional to the oxygen tension of blood, which would enhance the rate solubility shifts.

Other potential risks of heat exchangers are associated with the type of material used for construction. Because stainless steel is relatively expensive, aluminum has been used most often as the material for heat exchangers. Aluminum, however, has a high toxicity in humans; when blood levels exceed 100 mg/L, careful patient monitoring is imperative and levels greater than 200 mg/L are toxic.[165] Aluminum oxide concretions were found recently in organs of neonatal patients having undergone ECMO; these concretions most likely formed from aluminum leached from the anodized aluminum heat exchangers used in the circuit.[166] In the late 1990s, Medtronic manufactured the Forte oxygenator, the first oxygenator with a PPL heat exchanger. This change in materials was considered to reduce manufacturing costs and aid in the disposal of used oxygenators. It was discovered that the oxygenator would build up a static charge of 2200 volts because the PPL would not dissipate the charge between the water and blood side of the oxygenator. Occasionally, this oxygenator would develop blood-to-water leaks



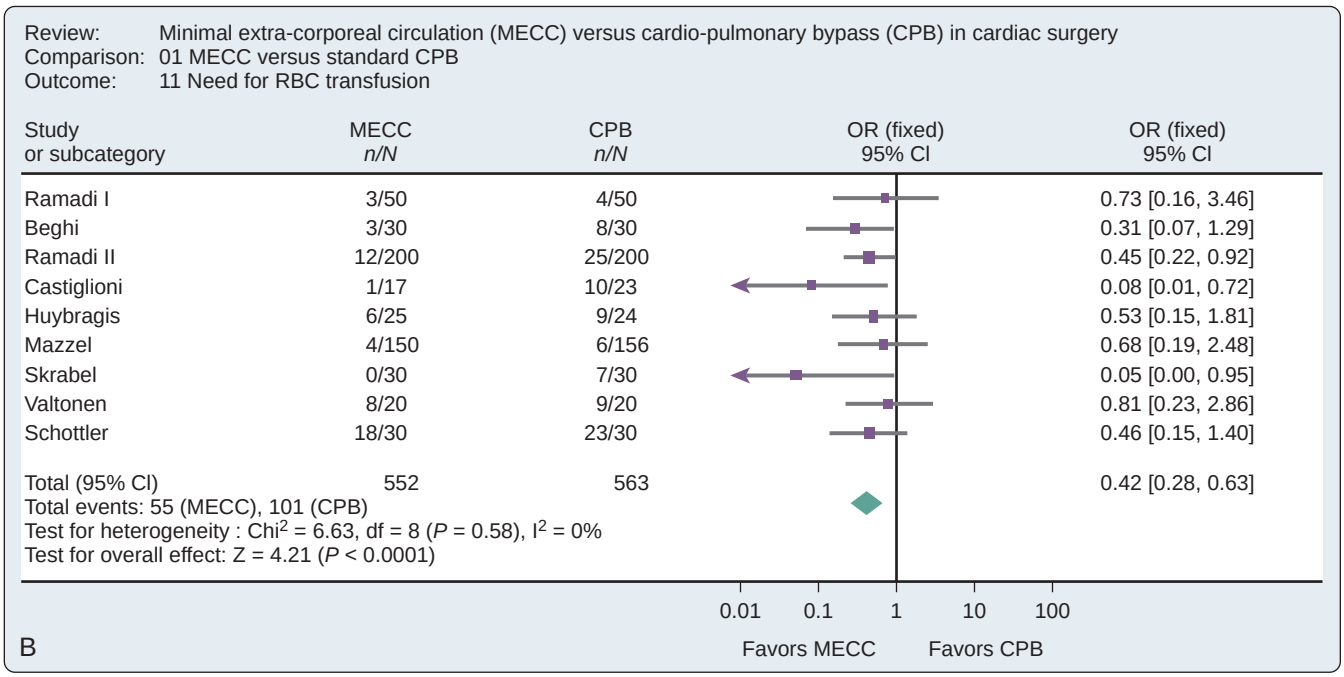


Fig. 32.20 A–C, Forest plot for the risk for neurologic events comparing miniaturized cardiopulmonary bypass versus control from nine randomized, controlled trials. *CI,* Confidence interval; *df,* degrees of freedom; *OR,* odds ratio pooled estimates of neurologic events; *SD,* standard deviation. *(From Zangrillo A, Garozzo AF, Biondi-Zoccai G, et al. Miniaturized cardiopulmonary bypass improves short-term outcome in cardiac surgery: a meta-analysis of randomized controlled studies.* J Thorac Cardiovasc Surg. *2010;139:1162–1169.)*

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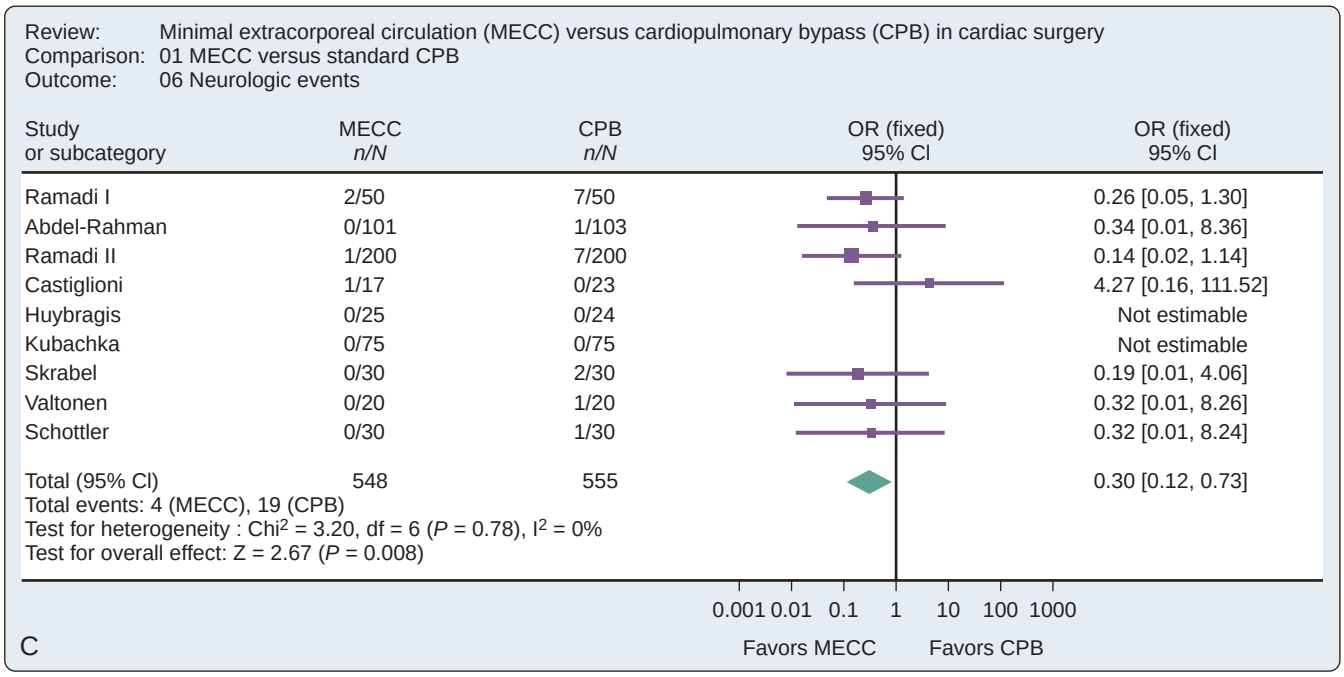


Fig. 32.20, cont'd

Fig. 32.21 The Cardiohelp portable life support system (Maquet Cardiovascular, Bridgewater, NJ) is a system with a fully integrated pump and oxygenator disposable cassette with a lightweight (22-lb) pump drive and control mechanism that is may be used for; extracorporeal perfusion resuscitation anywhere in the hospital. *(Courtesy Maquet Cardiovascular.)*

when a spark would arc across a fiber. Eventually, a grounding cable was added to prevent such leaks, but the Forte oxygenator was taken off the market because clinicians had no confidence in it.[167] However, more recently, a resurgence in the use of PPL tubes for heat exchangers has occurred. Regardless of the material used and despite careful manufacturing, heat exchangers must be tested before use. Leaks between the blood and water compartments have been reported.[168]

Heat exchanger performance standards were established in the 1982 American Association of Medical Instruments draft report.[169] Performance testing is conducted by the simultaneous measurement of three temperatures: blood inlet temperature, blood outlet temperature, and water inlet temperature. Heat exchanger performance is reflected through a coefficient for heat transfer calculated by the following equation (where a coefficient of 1 is equal to 100% efficiency):

$$HEC = (TBI - TBO)/(TWI - TBO)$$

where HEC = heat exchanger coefficient, TBI = temperature of blood inlet, TBO = temperature of blood outlet, and TWI = temperature of water inlet. The heat exchange coefficient can be calculated for various devices over steady-state conditions, which would provide comparative analysis data on heat exchanger efficiency.

Cooler/Heater Units

Cooler/heater units consist of a system that provides a thermoregulated water supply and can circulate water between 4^0 to 42^0C to the heater exchanger through a ½ -inch internal diameter water tube. The method of water delivery is a critical feature of these devices. Some systems pump water out to the heat exchanger, whereas others pull water from the cooler/heater's reservoir through the heat exchanger. The latter design is preferable in that the pressure on the water side of the oxygenator heat exchanger will then always be lower than the pressure in blood side. Should a leak be present in the oxygenator, the leak will likely be a blood-to-water leak instead of a water-to-blood leak, the latter of which would result in contamination of the patient's circulation with water and crenation and hemolysis of RBCs.[168]

Careful maintenance of the cooler/heater is critical. There have been numerous reports of mycobacterium contamination from cooler/heater unit water supplied to the oxygenator heat exchanger or to the cardioplegia delivery heat exchanger, resulting in endocarditis or death.[170–172] Mycobacterium has been detected in the water systems of cooler/heaters and in OR air samples dispersed by the air circulation from the cooling system compressor.[172] These systems require frequent maintenance, including drainage of the water supply and sanitation of the internal pump, conduits, and internal surfaces of the water tank to prevent microbial growth. Manufacturers instructions must be strictly followed to reduce patient risk.

Arterial Line Filters

Arterial line filters significantly reduce the load of gaseous and particulate emboli and should be used in CPB circuits[173,174] (Fig. 32.22). Some studies suggest that 20-µm screen filtration is superior to 40-µm filtration in the reduction of cerebral embolic counts.[174] A dose-response relation between GME and subtle neurologic injury has been reported, and some studies have demonstrated a protective effect of arterial line filtration on neurologic outcomes.[175–177] Whitaker and Stanton's[178] clinical trial showed that the use of a leukocyte-depleting arterial line filter reduced cerebral embolic count and demonstrated a trend (not statistically significant) toward improved postoperative psychometric test scores. The GME separation performance of 10 different arterial line filters in clinical use was recently evaluated.[179] All were found to be moderately effective, and rated pore size did not predict performance. A systematic review of the data related to arterial line filtration reported that the level of evidence supporting this practice was high (class I level of evidence A).[180] Filter design has been of two principal types: microporous screen filters and depth filters composed of dense fiber material packed in a polycarbonate housing patented by Swank. Screen filters are the predominant type in current use. Screen filters trap particulate and gaseous emboli that are of larger diameter than their effective pore size. The filter material is accordion pleated to provide a larger surface area within a lower prime housing. Two contemporary filter designs consist of a larger flat screen surface that is located concentrically around the oxygenator fiber bundle. The Terumo F series filter incorporates the screen material concentrically surrounding the fiber bundle. This design reduces CPB circuit prime volume because the filter media is incorporated into the oxygenator housing, eliminating the prime volume of the separate arterial filter housing.[181] Preston and colleagues[182] found that the F05 series oxygenator released more emboli than a similar model oxygenator used in combination with a separate 32-µm arterial filter, although the difference was not statistically significant. Sorin Group has incorporated a concentric filter design that surrounds the fiber bundle. The screen forms an envelope around the fiber bundle (see Fig. 32.16). This design does not effectively reduce prime volume; however, the larger housing provides an effective bubble trap (Box 32.6).

Fig. 32.22 Arterial line blood filters for use during extracorporeal circulation.

BOX 32.6 ARTERIAL LINE FILTERS

- Have been shown to reduce the rate of neurocognitive dysfunction.
- Reduce the load of gaseous and particulate microemboli to the patient.
- Typical pore size ranges between 20 and 40 µm.
- There is a trend towards integration of the arterial filter into the oxygenator.

Cannulae and Tubing

The major devices of CPB are those that replace the systems from which the heart-lung machine has derived its name. However, as with most technologic advances, it is the combination of all component parts that function to ensure success. Besides the pump and oxygenator, a seamless array of tubing is required to connect the patient to the heart-lung machine. Monitoring lines are necessary not only to ensure patient hemodynamic management but also to assess the proper function of the pump. Manufacturers of tubing and circuit packs can attest to the large number of variations in combinations and configurations of circuit assemblies requested by different institutions, as well as by individual clinicians within the same institution. The following discussion of an "ideal" tubing circuit has been generated

from the experiences of the authors and may differ somewhat among cardiac centers (Fig. 32.23).

The majority of cardiac procedures using CPB through a median sternotomy are performed with venous cannulation of the right atrium (RA) and arterial return into the ascending aorta. Numerous cannulae are available for all types of cardiac surgery, which may reflect the developmental philosophy that if a vessel could conceivably be perfused or drained, then a cannula could be made to facilitate insertion. The key principles of cannulae design include minimizing turbulence, reducing cannulae exit velocity, and avoiding areas of stagnant flow so that blood trauma and thrombus formation are minimal (Fig. 32.24). In the past, cannulae were constructed of stainless steel or tapered polyvinylchloride. Subsequently, thin-walled stainless steel was used to increase effective orifice diameter and reduce cannulae pressure drop across the cannulae. Currently, most cannulae are fabricated from polyvinylchloride with composite polycarbonate thin-walled tips. The ends of the cannulae are formed to permit easy vascular entry while maintaining maximum lumen (caliber) size. According to Poiseuille mechanics, the greatest resistance, measured as pressure drop in a circuit, is found at the smallest opening for fluid flow and has an inverse exponential relation to the fourth power of the radius of the lumen. Therefore to reduce pressure drops across the circuit, cannulae are selected to facilitate the greatest flow with the least injury to the vessel because of mechanical abrasion. Several arterial cannulae designs have incorporated multiple openings and dispersion tips to reduce velocity at the tip of the cannulae and reduce the likelihood of disruption of atheromatous debris from the intimal surface of the aorta.[183,184] Most cannulae have a wire reinforcement body to prevent kinking when the cannula is curved to accommodate placement in the surgical field and to maintain cannula rigidity. Several new designs of venous cannulas have recently emerged that incorporate a malleable, wire-reinforced backbone to allow for bending of the catheter without kinking the lumen. Cannulae could then be positioned out of the surgical field to provide an unobstructed view for the surgeon. Although cannulation of the ascending aorta is preferred for most procedures, femoral arterial cannulation often is selected for reoperations or minimally invasive surgical procedures (Fig. 32.25). The axillary or subclavian artery often is selected for arterial return for patients with severe atherosclerosis of the ascending aorta. This site offers the advantage of providing antegrade flow to the arch vessels, protection of the arm and hand, and avoidance of inadvertent cannulation of the false lumen in cases in which type A aortic dissection has occurred. The axillary artery is accessed through a subclavicular incision.[185] Although the vessel may be cannulated directly with a long thin-walled 7- or 8-mm cannula, the most reported technique is to sew a 10- or 12-mm Dacron graft to the right axillary artery and insert a 20- to 24-Fr cannula directly into the lumen of the graft. Alternatively, the arterial tubing line can be connected directly to the Dacron graft with the aid of a tubing connector. This technique provides uninterrupted flow to the right arm and hand. Transapical aortic cannulation through a 1-cm incision on the anterior wall of the left ventricle also has been described for patients with type A dissection. A 7.0-mm aortic cannula may be placed into the left ventricle and advanced across the aortic valve (Box 32.7).

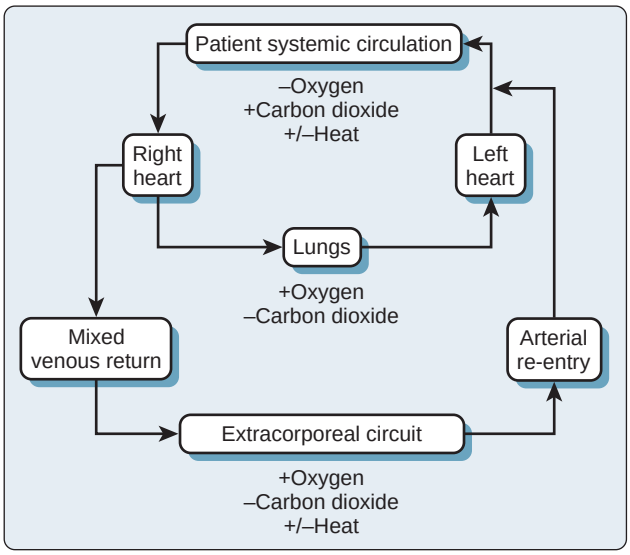


Fig. 32.23 Schematic of an "ideal" tubing circuit used during extracorporeal circulation.

Venous cannulae come in two broad classifications: single or dual stage. Single-stage cannulae are used during most open-heart situations, in which either bicaval cannulation or femoral cannulation will be performed, whereas dual-stage cannulae are used for most closed-heart procedures, in which a single cannula is placed into the RA.

Although both silicone (Silastic) and polyurethane tubing have been used in extracorporeal circuits, plasticized polyvinylchloride is exclusively used in CPB circuits. Plasticizers impart flexibility into tubing and account for as much as 40% of the polymer. The most commonly used plasticizer for medical-grade tubing is DEHP. There is growing concern about the migration (leaching) of DEHP from tubing into the blood because DEHP has been shown to cause inflammation and is potentially a carcinogen and a toxic agent.[186–189] Numerous studies since the 1970s have shown that DEHP and its metabolites are present in blood products[190–193] and tissues,[194,195] as well as intravenous solutions[196] and pharmaceuticals.[197] Recently, the release properties of various plasticized polyvinylchloride tubing exposed to electrolyte solutions for up to 28 days were evaluated. Tubing formulations with one DOA stored in 0.9% sodium chloride solution had significantly

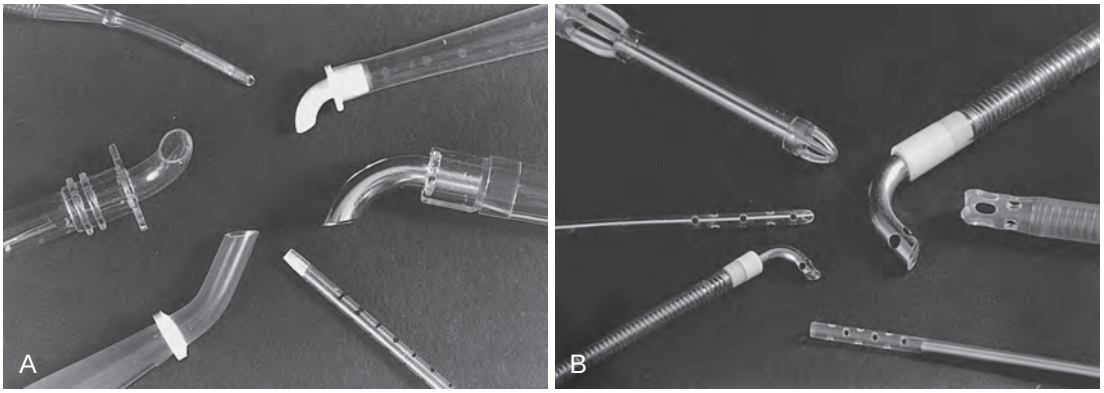


Fig. 32.24 Various commercially available cannulae for extracorporeal circulation. (A) Arterial cannulae. (B) Venous cannulae.

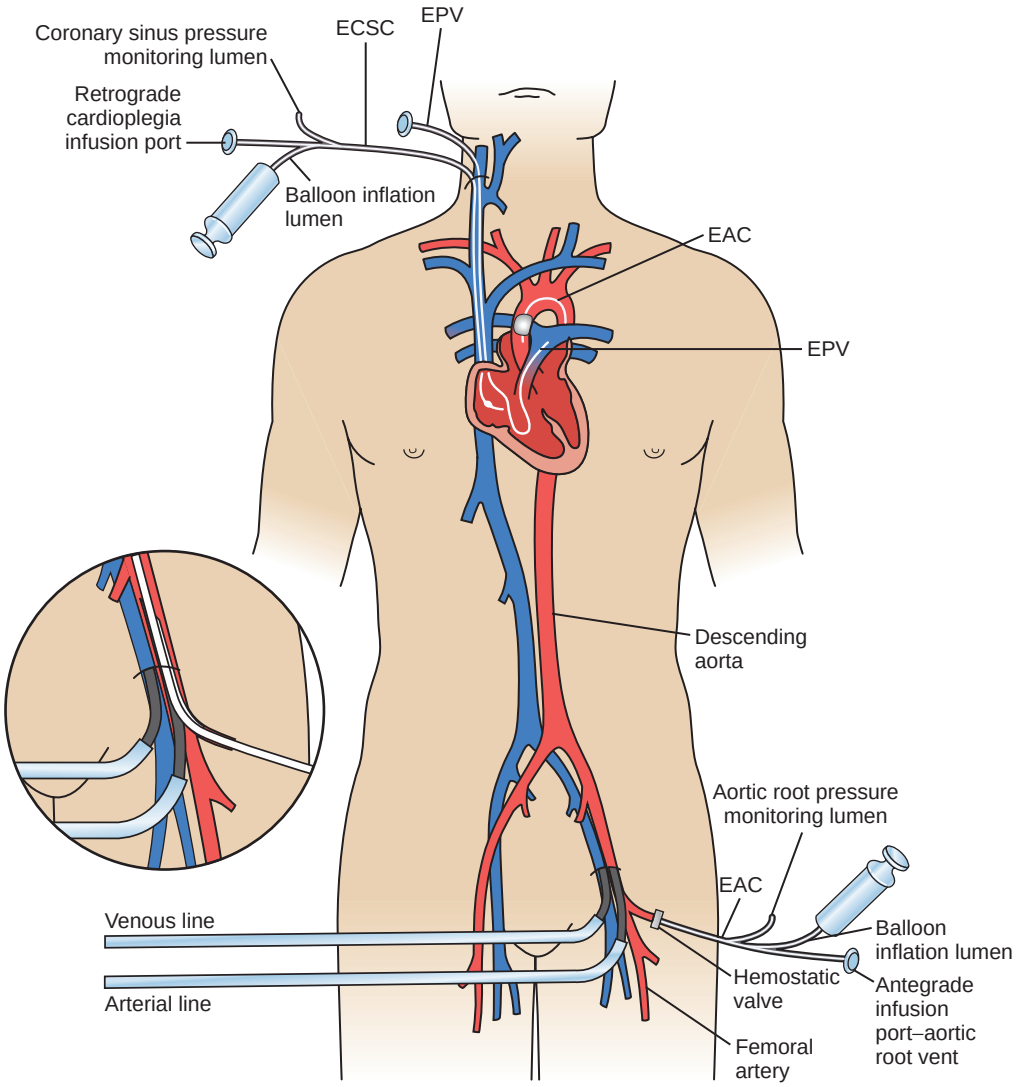
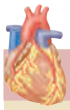


Fig. 32.25 Diagram of cannulation used for minimally invasive surgery. *EAC,* Endoaortic occlusion balloon; *ECSC,* endocoronary sinus catheter; *EPV,* endopulmonary vent. *(From Toomasian JM, Williams DL, Colvin SB, et al. Perfusion during coronary and mitral valve surgery utilizing minimally invasive port-access technology.* J Extra Corpor Technol. *1997;29:66–72.)*



BOX 32.7 ARTERIAL CANNULAE

- The arterial cannulae tip is the point of highest blood flow velocity in the cardiopulmonary bypass circuit.
- Some arterial cannulae have flow-dispersing tips to reduce exit velocity and reduce the risk for atheroma dislodgement from the wall of the aorta.
- Cannula placement should be assessed by a test infusion from the pump and observation of a pulsatile pressure excursion.

less leaching than either DEHP plasticizer or tri(2-ethylhexyl) trimellitate (TOTM). Currently, tubing pack manufacturers are able to offer select sizes and durometer tubing without DEHP additives. However, because removing DEHP reduces the overall durability of the tubing, high-pressure segments of the CPB circuit, such as the roller head raceways, would still require this additive. Several published laboratory studies suggest that the use of covalently bonded heparin coatings significantly reduces the leaching of DEHP from the tubing into the circulation.[198,199]

Blood flows out of the RA cannula and into the venous reservoir when CPB is initiated. The venous line connects the cannula to the venous reservoir. Mixed venous oxygen saturation is measured by optical or chemical fluorescence by flow through cells placed in the venous line. A stopcock is placed in the venous line to facilitate the delivery of medications and for venous sampling. Blood then enters the venous reservoir, which serves as a volume chamber for settling and acts as a safety feature, providing additional response time to the perfusionist. Venous reservoirs come in two broad categories: hard shell (see Fig. 32.16) and soft shell (see Fig. 32.17), terms that refer to the rigidity of the device and its ability to collapse on itself. Hard-shell reservoirs are open to the atmosphere (open systems) through a ventilation port on top of the reservoir and are effective in handling gross quantities of air that may return through the venous or cardiotomy line.[200] Most hard-shell reservoirs include a positive pressure relief valve that prevents overpressurization during patient support. An external vacuum source can also be applied to the ventilation port at the top of the hard-shell reservoir to use VAVD. In VAVD, gravity drainage is improved by connecting a vacuum source to the venous

reservoir.[201] Soft-shell reservoirs are called *closed systems* and will collapse on themselves with the inadvertent emptying of the reservoir. The venous reservoir also has an inlet line that drains blood from a cardiotomy reservoir.

A cardiotomy reservoir is simply a second chamber used for collecting and filtering blood aspirated from the surgical field via suction lines. Vented blood from the left ventricle, pulmonary artery, or aortic root also is returned to the venous reservoir through the cardiotomy device. These are hard-shell devices made of polycarbonate housing material with polyurethane and polyester filters and defoamers to reduce the risk for gas embolism into the venous reservoir. Some venous reservoirs also serve as integral cardiotomy reservoirs, obviating the need for a separate unit.

From the venous reservoir, blood is pumped into the heat exchanger of a membrane oxygenator by the actions of the arterial pump. The heat exchanger is connected to an external water source that maintains the perfusate temperature according to the temperature of the water pumped from the cooler/heater. The heat exchanger housing is typically composed of stainless steel, PPL, or aluminum alloy and uses a counter-current water/blood mechanism for indirect thermal conduction. Blood then passes directly to the oxygenator, where gas exchange occurs in accordance with the operation of a gas blender that controls the FIO_2 by mixing oxygen with medical-grade air, along with a flowmeter that regulates the ventilation rate. The gas blender is attached to the inlet gas port of the oxygenator via a section of 1/4-inch tubing and a bacteriostatic (0.2-μm) filter. Gas exchange across the blood and gas phases of the fiber occurs through the process of simple diffusion. Levels of high gas molecule concentration are permitted to diffuse through tiny slit pores of the oxygenator fiber strands to lower levels of gas concentration. During CPB support, this typically results in the addition of O_2 to the blood phase and the uptake of CO_2 to the gas phase. Many circuits also have a vaporizer for the delivery of volatile, inhaled anesthetic gases placed in-line between the gas blender and the oxygenator.

The oxygenator has two ports on the outflow side by which arterialized blood is accessed: a recirculation port and an arterial outlet port. The recirculation port is used both to provide a safety line for relieving overpressurization and to facilitate easy replacement in the event of device failure. It also is used as an exit port of arterialized blood for sanguineous cardioplegia or in the separate perfusion of a second arterial cannula. In traditional CPB circuits, arterial blood would leave the oxygenator outlet port and flow to the arterial line filter. However, the use of integrated oxygenators has become more common in CPB circuits. An integrated oxygenator incorporates the oxygenator bundle and arterial filter units together in one apparatus (CAPIO FX; Terumo Cardiovascular Group, Ann Arbor, MI [see Fig. 32.13] and Inspire; Sorin Group, Arvada, CO [see Fig. 32.16]). By incorporating both components together, the use of most integrated oxygenators results in a significant decrease in foreign surface area and resultant prime volume. The arterial filter is a screen device constructed of synthetic material, with a specific pore size effectively blocking particles greater in size than the rating of the filter (20 and 40 μm). Microembolic particles originate from many sources in the extracorporeal circuit, including the BGED, tubing, and heat exchanger, and include various substances including polycarbonate, filter material fibers, silicone, and polyvinylchloride particles.[202,203] Although there is considerable variability in terms of where arterial line pressure is monitored, the most common access point is located between the outlet port of the oxygenator and the arterial line filter.[204] An arterial monitoring device can be placed in-line to reflect arterial oxygen saturations and as a trending device for pH, PaO_2, and $PaCO_2$. Just distal to the arterial line filter is a bubble detector that is an essential feature for the conduct of safe perfusion. This device is controlled by a microprocessor and is used to detect microgaseous and macrogaseous emboli. This is the last safety feature in the line before blood returns to the patient through the arterial cannula. When the ascending aorta is the site for arterial perfusion, an aortic cannula is placed through a purse-string suture with positioning of the cannula tip so that flow is directed cephalad toward the brachiocephalic vessels. The location of the aortic cannula and the direction of arterial blood flow emphasize the importance of assuring safe, continuous flow of filtered perfusate devoid of embolic particles.

Cardioplegia Delivery

In the previous section, the main tubing circuit for CPB was described and the devices for bypassing the pulmonary and systemic circulation were identified. Methods of decoupling electromechanical function of the heart have been developed to achieve a safe surgical field during cardiac surgery. During aortic cross-clamping, the heart is rendered globally ischemic by the cessation of coronary blood flow. Some myocardial perfusion undoubtedly occurs through the involvement of noncoronary collateral circulation from mediastinal sources and the bronchial circulation. There are numerous methods of achieving mechanical arrest, and the combination of these techniques is referred to as *myocardial preservation*. Myocardial preservation encompasses both the pharmacologic manipulation of the solutions (cardioplegia) used to protect the heart and methods of mechanical delivery. Potassium-containing solutions arrest the cardiac muscle in a depolarized state by disruption of the myocardial action potential. Other solutions containing lidocaine and magnesium, such as del Nido and custodial cardioplegia solutions, arrest the heart in a polarized state by blocking the calcium channels. This section is devoted to methods of cardioplegia delivery to provide myocardial protection.

Melrose and colleagues[205] were the first to describe chemical arrest of the heart with potassium citrate solution. The arresting solution was delivered with a syringe directly into the aortic root after the application of the aortic cross-clamp.[205] Similarly, others described delivery of various formulations of arresting solutions contained in collapsible intravenous bags using a sterile intravenous tubing set that was passed off the surgical field and attached to an inflatable infusion pump bag. This system was replaced by the use of recirculating circuits where the cardioplegia solution was recirculated in a system that consisted of a polycarbonate-filtered reservoir and cooling of tubing that was placed in a bucket of ice (Fig. 32.26). These recirculating systems provided filtration of the solution and improved control of delivery pressure and temperature. A single-pass system for delivery of blood cardioplegia in a predetermined ratio, which subsequently became the most widely used cardioplegia delivery system, was described in 1978 by Buckberg and colleagues[206,207] (Fig. 32.27). The ratio of blood to cardioplegia could be adjusted by changing the internal diameter of the tubing in the custom delivery set. The blood and crystalloid components were delivered to a miniaturized heat exchanger bubble trap before delivery at the surgical field. With this system, the temperature of the cardioplegia could be regulated from 4°C to 37°C with the use of a cooler/heater device. Menasché[208] described a microplegia system in which arresting additives are added directly to tepid blood from the CPB circuit with a standard infusion pump to arrest the heart. This greatly decreased the volume of crystalloid solutions delivered in a typical CPB procedure and avoided the detrimental consequences of volume overload and subsequent hemodilution. The authors also cited a few particular advantages of minicardioplegia, including improved oxygenation and improved control of blood volume, not to mention reduced cost.

Adjunct means of cooling and protecting the myocardium during aortic cross-clamping include the use of topical application of cold solutions to prevent early transmural myocardial rewarming. A common method for cooling the myocardium is achieved by the surgeon creating a "pericardial well" in the chest by suspending the pericardium with stay sutures to the chest retractor. Cold (4°C) topical saline solution is then applied to the pericardium, bathing the heart in cold solution while a sucker line is placed in the well to evacuate the saline solution. Topical saline has been shown to cool the epicardium and diminish transmural gradients,[209,210] but it also has resulted in phrenic nerve paresis and myocardial damage.[211,212] An alternate technique involves a topical cooling device, which consists of a coolant flow pad in which

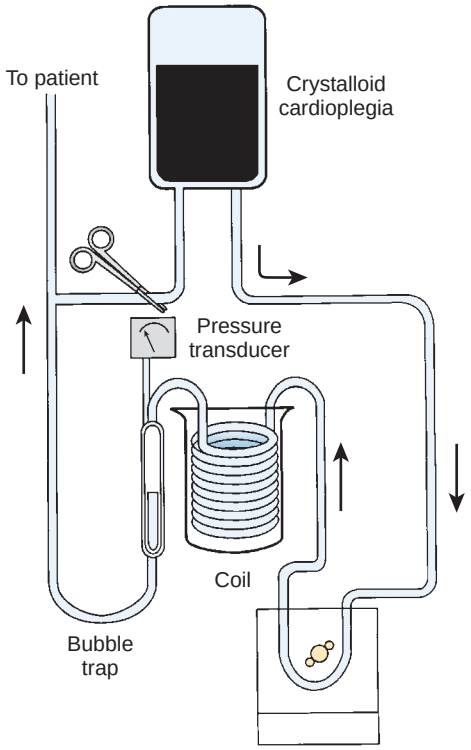


Fig. 32.26 Coil-type cardioplegia delivery system. This can be used for sanguineous or asanguineous cardioplegia solution.

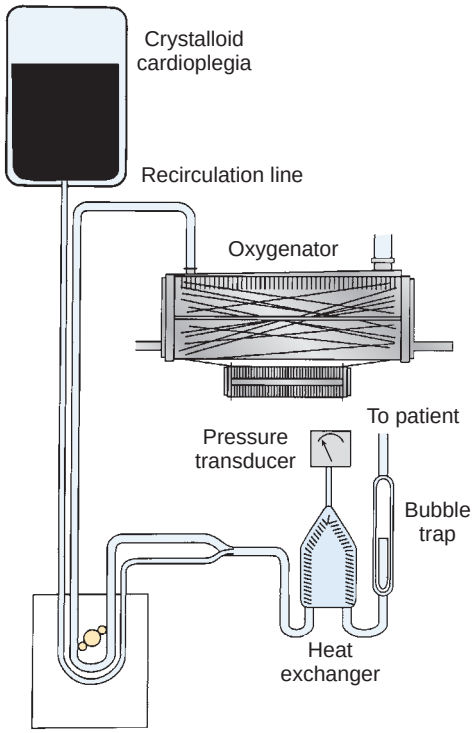


Fig. 32.27 Nonrecirculating cardioplegia delivery system for use in blood to crystalloid mixed solutions of various ratios (1:1, 4:1, or 8:1 crystalloid to blood).

cold (4°C) saline flows, separated from the body by a metal skeleton and polyurethane insulator, which protects the posterior mediastinum and phrenic nerve from hypothermic injury.[213] The benefits of a topical cooling device over topical cold saline include a reduction in total hemodilution, procurement of a drier operative field, reduced blood loss in waste suction, and more uniform distribution of cooling.[213–215] However, these devices are costly, require a separate RP for delivery, and may not be applicable for all procedures in which the heart will be lifted and elevated away from the posterior pericardium.

Disposable Cardioplegia Circuits

All cardioplegia delivery systems consist of two distinct components classified as either disposable or nondisposable devices.[216] Effective myocardial protection is ensured only through the precise interface of both disposable and nondisposable components of the cardioplegia delivery system, which function to ensure safe, precise, and accurate administration of cardioplegic solutions. The disposable items that make up a standard cardioplegic circuit consist of three basic parts: a heat exchanger, a bubble trap with an incorporated filter, and various delivery cannulae. The disposable devices are used on a single-use basis and, because of their consumptive nature, represent the most significant cost associated with mechanical myocardial protection.

Early methods of cardioplegia delivery consisted of infusions of pharmacologic agents directly into the aortic root, or left ventricle, via handheld syringes. Unfortunately, such methods caused a heterogenous distribution of solution and led to the need for more precise delivery techniques. Many clinicians turned to a pressurized bag method in which a bag of crystalloid solution was placed in a pressure bag and cardioplegia was infused at a semicontrolled rate dependent on the degree of pressure and the bore of the cardioplegic needle.[217,218] Although the results were better than those previously obtained, there was a profound lack of safety features such as pressure monitoring and control systems, as well as inadequate air-handling capacity and a lack of temperature control. Vertrees and colleagues[219] described a simple circuit that used a coronary perfusion reservoir, a coil submerged in iced water, and an RP. This system was a significant improvement over previous techniques insomuch because it included a means to trap air and to measure pressure within the circuit.

There are two major disposable circuit configurations for cardioplegia delivery: a recirculating system with a coil (polyvinylchloride or stainless steel heat exchanger) for asanguineous delivery and a sanguineous cardioplegia system for nonrecirculating delivery. In asanguineous systems, crystalloid cardioplegic solution is kept constantly recirculating throughout the cardioplegia circuit and is delivered to the patient by the movement of a clamp, directing flow away from the recirculation line and into the infusion line.[219a,220] These systems generally are the most economic in that they incorporate a coil of polyvinylchloride tubing as the heat-exchanging element, obviating the need for both a metal transfer unit and a separate cooler/heater device to regulate the temperature of the cardioplegic solution. Instead, the coil sits in a container filled with ice. The heat-exchange efficiency of coil systems has been shown to be superior to that of metal units in single-pass trials. These systems also can be used for sanguineous cardioplegia with minor adaptations to the circuit. However, with the increased use of warm sanguineous cardioplegia and the administration of warm reperfusate at the end of aortic cross-clamping, these units are not ideally suitable because of their inability to accurately control delivery temperatures.

Another type of cardioplegia delivery system is termed a *blood cardioplegia system,* which involves the shunting of arterialized blood from the oxygenator into the cardioplegia circuit, where it is mixed with a crystalloid base solution, usually of high potassium concentration, before it is delivered into the coronary circulation. The most frequently used port for obtaining saturated blood from the oxygenator is the recirculation port, although some institutions directly shunt blood from the arterial line filter. Most sanguineous cardioplegia systems are nonrecirculating and only make a single pass through a heat exchanger

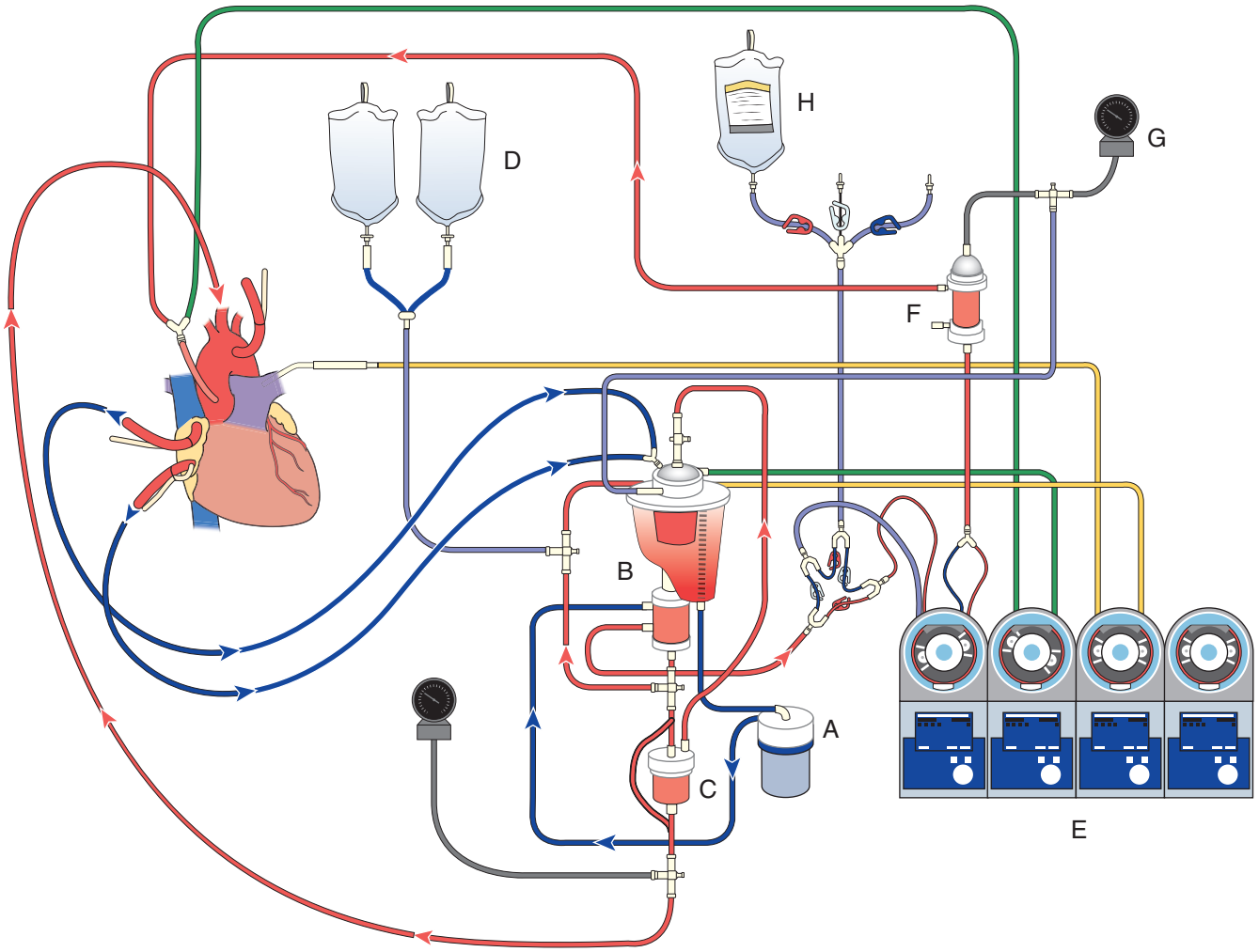


Fig. 32.28 Cleveland Clinic dual cardioplegia circuit for the del Nido cardioplegia delivery. *(A)* Centrifugal pump, *(B)* reservoir and oxygenator, *(C)* leukocyte filter, *(D)* Plasma-Lyte A solution, *(E)* heart-lung machine, *(F)* cardioplegia heat exchanger, *(G)* manometer for the cardioplegia system, *(H)* del Nido cardioplegia solution. *(Reprinted with permission Kim K, Ball C, Grady P, Mick, S. Use of del Nido cardioplegia for adult cardiac surgery at the Cleveland Clinic: perfusion implications.* J Extra Corp Tech. *2014;46[4]:317–323.)*

before passing to the heart. For this reason, these systems must have a high efficiency rating for caloric exchange between the cardioplegic solution and the cooling, or warming, source. These devices can deliver varying ratios of blood-to-crystalloid base, ranging from a 1:1 to a 1:20 ratio of crystalloid to blood. Most are equipped with temperature monitoring ports and pressure-measuring sites to monitor delivery pressures. Cleveland Clinic has reported on a single-delivery system that can be easily adapted for delivery of 4:1 blood cardioplegia or del Nido 1:4 cardioplegia solution (Figs. 32.28 and 32.29). An important consideration of sanguineous cardioplegia delivery systems is that the main arterial pump can never be turned lower than the flow rate of the cardioplegic solution pump (ie, delivering a higher volume of cardioplegic solution to the circuit than is flowing to the patient). If this were to occur, excessive negative pressures would be created in the recirculation line from the oxygenator, increasing the risk for cavitation (outgassing of solution).

Cardioplegic Delivery Catheters

Antegrade Aortic Root Cardioplegia

The delivery of cardioplegia is made possible through special cannulae that are placed within the ascending aorta or directly into the coronary ostia. These have been specifically designed to minimize pressure drop across the tip of the cannula, which has a relatively small bore (12 to 18 gauge). When cardioplegia is administered into the aorta, it is termed *antegrade cardioplegia*. The most common flow rates achieved in adult cardiac surgery are between 200 and 300 mL/min, with corresponding aortic root pressures usually between 60 and 100 mm Hg. In addition, the cardioplegic needle can be used as a "vent" by which residual air in the aortic root is removed by connecting the needle either to an RP or siphon drain. The final point of attachment is the cardiotomy reservoir.

The distribution of cardioplegia to the myocardium with antegrade cardioplegia techniques is hindered in patients with atherosclerotic lesions, where distal perfusion is lost because of vascular obstruction. Furthermore, impaired delivery of cardioplegia may occur because of the retrograde escape of cardioplegia across the aortic valve. This commonly occurs if the patient has aortic insufficiency. However, it may occur in patients with a competent aortic valve that becomes distorted by the placement of the aortic cross-clamp.[220a] Some antegrade cardioplegia cannulae have an integrated pressure monitoring lumen that allows measurement and display of the antegrade cardioplegia infusion pressure. It also is common to measure the cardioplegia delivery system pressure from a site distal to the cardioplegia delivery pump. A high system pressure alerts the team to an obstruction or malplacement

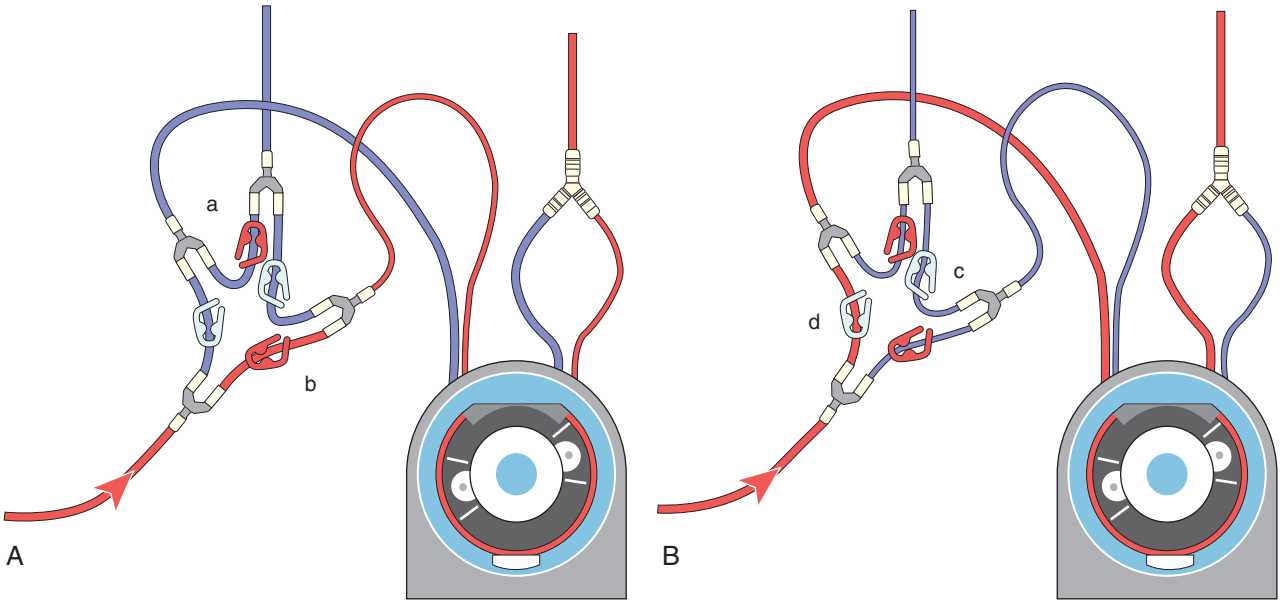


Fig. 32.29 Cleveland Clinic dual cardioplegia circuit changing from Buckberg to del Nido. (A) A set of Robert clamps (*[a]* and *[b]*) is open for del Nido cardioplegia delivery. Clamp *(a)* is open and del Nido cardioplegia is delivered through a 1/4 line. Clamp *(b)* is open and blood is delivered through a 3/16 line (blood : crystalloid ratio is 1 : 4). (B) A set of Robert clamps (*[c]* and *[d]*) is open for the Buckberg cardioplegia delivery. Clamp *(c)* is open and Buckberg cardioplegia is delivered through a 3/16 line. Clamp *(d)* is open and blood is delivered through a 1/4 line (blood : crystalloid ratio is 4 : 1). *(Reprinted with permission Kim K, Ball C, Grady P, Mick, S. Use of del Nido cardioplegia for adult cardiac surgery at the Cleveland Clinic: perfusion implications.* J Extra Corp Tech. *2014;46[4]:317–323.)*

of the cardioplegia delivery cannula. A low system pressure would occur from aortic insufficiency or from some breach of the delivery system. Conditions such as aneurysmal deformation of the ascending aorta and aortic valvular lesions both compromise the delivery of cardioplegia when administered via the antegrade direction. This concern has led to the search for alternative administration techniques for cardioplegic delivery.

Retrograde Coronary Sinus Cardioplegia

Retrograde delivery of blood to the heart via the coronary sinus and venous circulation was first proposed by C. Walton Lillehei. In 1982, Menasche and colleagues[221] revisited the application of retrograde coronary sinus cardioplegia (RCSC), and with this technique they found superior maintenance of left ventricular function when compared with direct coronary artery perfusion in patients with coronary artery disease. Initially, this technique was proposed as a means of delivering cardioplegia as a replacement for direct coronary artery cannulation in procedures involving the aortic valve or root. However, the utility of RCSC quickly expanded as a means of delivering nutritive flow to the distal myocardium in patients with severe coronary artery disease.[222,223] The delivery of RCSC, provided catheter position in the sinus and seal of the sinus by the balloon are optimal, results in a more uniform distribution of cardioplegia than antegrade and causes minimal disturbance of the operative field during administration.

Coronary sinus cardioplegia cannulae come in numerous configurations varying in catheter size, balloon configuration, stylet characteristics, and inflation mode (Fig. 32.30). Various cannula designs are available incorporating geometric design to promote better fit into the sinus. The terminal end of the cannula is fitted with a balloon, which serves the function of seating the cannula in the coronary sinus so that cardioplegia is delivered into the coronary venous system, minimizing the amount of cardioplegia leakage into the RA. Some have textured balloon surfaces to minimize dislodgement of the catheter from the coronary sinus but result in leakage of the cardioplegia solution into the RA. Some designs have balloons that automatically inflate when flow is initiated through the catheter. Others require manual filling

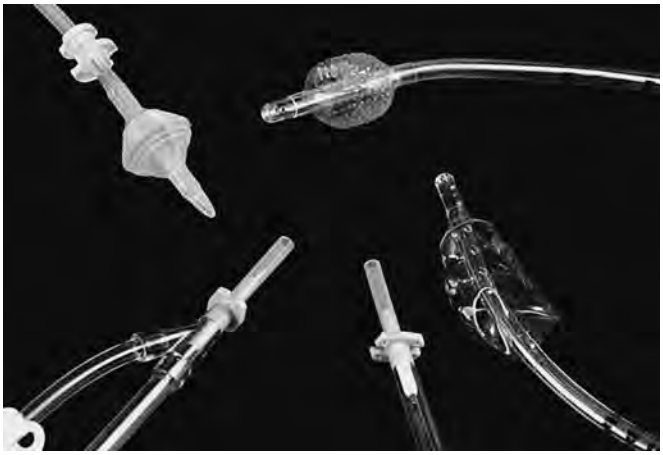


Fig. 32.30 Antegrade and retrograde cardioplegia cannulae.

of the balloon with a syringe. In an animal model, Menasche and colleagues[224] have shown that autoinflated retrograde catheters leak as much as 22% of cardioplegic flow, whereas manually inflated catheters had a leakage rate less than 1%. Several authors have described the efficacy of combining both antegrade and retrograde cardioplegic delivery methods in a single integrated system.[225,226] These authors believe that the delivery of both antegrade and retrograde cardioplegia concomitantly supplies better perfusion to all regions of the myocardium despite the degree of coronary occlusive disease. Drainage is ensured through both thebesian and arteriosinusoidal vessels. Ihnken and colleagues[227] found in a large series of high-risk patients (New York Heart Association class III and IV) that simultaneous delivery of warm cardioplegia directly into the bypass grafts and the coronary sinus was both safe and efficacious in ensuring myocardial protection. A major disadvantage of this multisite simultaneous delivery method is that

most of the flow will be directed down the path of least resistance and not necessarily uniformly to all segments of the heart muscle.

Despite the excellent results achieved with RCSC, complications resulting from cannulation and excessive pressurization of the coronary sinus occasionally are reported. These include rupture of the coronary sinus, poor perfusion of the right ventricle and posterior septum, and nonhomogenous flow patterns.[228,229] In addition, controversy exists concerning the optimal delivery flow rate of RCSC. In one study of 62 patients, retrograde flow rates less than 100 mL/min resulted in reduced coronary venous effluent pH, with the authors recommending that maintenance of a minimum flow rate of 200 mL/min be considered whenever RCSC is used.[230] The optimal delivery pressure also is controversial. Most centers use a guideline of 20 to 40 mm Hg pressure measured in the delivery catheter at a point distal to the balloon. It has been suggested by one researcher that pressures as high as 50 mm Hg are safe.[231]

Cardioplegia Delivery Systems

The currently used nondisposable devices consist of two major components: the mechanical pump and the temperature control unit. The PD twin RP is the most commonly used mechanical pump for cardioplegia. The temperature control module also is termed a *cooler/heater* and serves the function of the caloric transfer of heat by convective means between the circulating water of the cooler/heater and the cardioplegic perfusate.

Historically, commercial delivery systems for blood cardioplegia used a fixed-ratio delivery system of blood-to-crystalloid components. Cardioplegia solution mixing was achieved via a two-line RP system that combined arterialized blood and a crystalloid base solution on the distal side of the occlusive pump in a dual-lumen outlet. The ratio of blood to crystalloid was determined by the lumen size of the tubing within the raceway of the pump. Although these systems are considered as industry standards, they offered little flexibility in altering the ratio of blood or crystalloid components, and the only means of changing ionic or substrate concentration was to make up several base crystalloid bags that contained varying concentrations of solute. Several devices address these shortcomings: the Jostra HL20 Hl30 systems, the Sorin Group S-3 and S-5 Console (Sorin Group, Irvine, CA), Terumo System 1 (Terumo Cardiovascular Group, Tustin, CA), and the Myocardial Protection System (MPS; Quest Medical, Allen, TX).

The Sorin Group S-3 and S-5 heart-lung machines have an integrated cardioplegia delivery system that consists of twin RPs, monitoring and control systems, and an internal cooler/heater for temperature regulation. Two 3-inch RPs are used, containing hybrid direct-drive systems with optical encoders, which permit accurate solution delivery at low-flow delivery rates. The two-RP system was designed to allow the user to select variable ratios of blood-to-crystalloid solutions. Available ratios include 1:1 through 16:1, all blood, and all crystalloid. The system may be stop-linked to a pressure monitor, bubble detector, or to the arterial pump. The system has temperature monitors, automatic dose and ischemic time interval timers, and displays of infused blood, crystalloid, and cardioplegic solution volumes.

The Quest MPS consists of a microprocessor-controlled electromechanical instrument and disposable delivery set that is integral to the device (Fig. 32.31). There is a main pumping mechanism and a pumping subsystem that operates by a set of four pistons, each driven by a stepper motor, that align with several pouches in the disposable cartridge to mechanically displace the pouch contents. The subsystem pouches contain an arresting agent and one additional additive if required. The main pumping mechanism consists of two motor-driven piston pumps and valved pouches that alternately fill and pump extracorporealized blood and crystalloid solutions, providing constant cardioplegia flow. A number of sensors become activated when the cartridge is placed into the console, and the system software completes a series of self-checks before operation. The cardioplegic solution passes through a stainless-steel heat exchanger, which controls the caloric transfer of heat in congruence with the integral cooler/heater. There

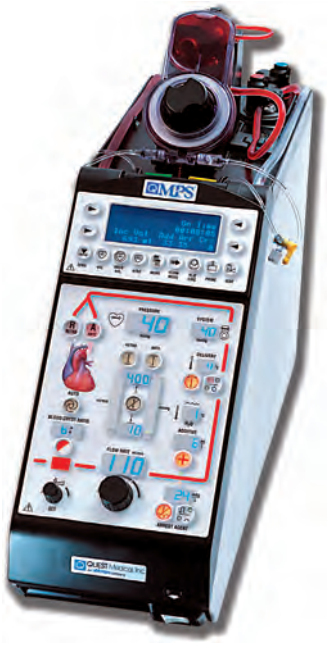


Fig. 32.31 Quest Myocardial Protection System (MPS). Cardioplegia is pumped by a system actuated by a stepper motor. Arrest solution and additive solutions are contained in 50-mL pouches and may be precisely added to the delivery solution. The disposable heat exchanger component is attached to the top of the console. The MPS has system and delivery pressure sensors, as well as an air detection and elimination system. Blood-to-crystalloid ratio, temperature, and additive drug concentrations may be adjusted in real time during delivery. *(Courtesy Quest Medical, Allen, TX.)*

are four temperature sensors to provide temperature-controlled cardioplegia delivery, and the inlet water and cardioplegia temperatures are continuously displayed.

The MPS provides the selection of variable blood-to-crystalloid ratios that range from 1:1 to 20:1, as well as the capability to deliver all blood or all crystalloid solutions. However, the MPS allows variable ratio control, which is accomplished without changing the arresting agent concentration. This independent control of cardioplegic additive and total blood delivery is an attractive feature when optimizing oxygen-carrying capacity and enhancing aerobiosis, while ensuring chemical arrest. Likewise, the MPS allows the user to change the arresting agent concentration without altering the ratio of blood to crystalloid solution. The MPS has an auto-flow mode that will vary infusion flow to maintain a set delivery pressure. The MPS is capable of pulsatile cardioplegia delivery, although few studies have demonstrated the efficacy of this delivery feature.

The Heart-Lung Machine Priming Solutions

Before ECC can be attempted, the patient must be connected to the CPB machine, necessitating the creation of a fluid-filled circuit to ensure continuity with the patient. Not only is it important that the circuit be "primed," but it also must be completely devoid of any gaseous bubbles or particulate matter that potentially could embolize. For this reason, perfusionists often perform painstaking maneuvers to rid the circuit of bubbles before bypass. Historically, early priming solutions were formulated to closely match the patient's own rheologic characteristics, which necessitated the use of fresh whole blood.[232] Priming the early oxygenating circuits required vast quantities of blood and balanced electrolyte solutions, and cardiac operations often were scheduled around the availability of blood donors. Eight to 10 units of

heparinized blood were required to prime the average CPB circuit,[233] and the risk for contracting viral hepatitis was substantial. The addition of blood to priming solutions also induced the capillary leak syndrome,[234] which may implicate histamine as a contributing factor in leading to postpump pulmonary dysfunction. As a result of the excellent work on hemodilution by Messmer and colleagues,[235,236] as well as others,[237] it is now the rare adult patient who receives any blood in the circuit before the initiation of CPB. Instead, balanced electrolyte solutions are the first choice in priming bypass circuits. In pediatric circuits, however, where the circuit volume often exceeds the patient's circulating blood volume, allogeneic blood products often are added to the prime to reduce the risk for anemia and hypoproteinemia (see Chapters 31, 34, and 35).

When nonhemic primes are used during CPB, a concomitant reduction in SVR occurs at the onset of ECC as a result of the reduced viscosity of the blood.[238] Although the oxygen-carrying capacity of the pump perfusate is reduced by hemodilution, overall oxygen delivery may not be significantly affected because the reduced viscosity enhances perfusion. Safe levels of hemodilution are dependent on multiple factors that include the patient's metabolic rate, cardiovascular function and reserve, degree of atherosclerotic disease and resultant tissue perfusion, and core temperature. Although an absolute value for the degree of hemodilution tolerated will vary among individual patients, the studies of Kessler and Messmer supported a minimal hematocrit value of 20% to ensure oxygen delivery and tissue extraction.[239,240] More recently, several large retrospective studies have described a trend towards increased morbidity and mortality with nadir hematocrits less than 23%.[241–243] Moreover, postoperative complications from anemia were compounded in patients who were transfused with homologous RBCs.[244] Progress continues to be made in better understanding absolute tolerances of hemodilution through treating patients of certain religious groups who refuse the transfusion of allogeneic blood products.[245–247]

For years controversy has raged over the inclusion of colloids in pump primes, with specific emphasis placed on the value of albumin as a routine prime constituent.[248,249] The nonphysiologic effects of CPB, with both nonpulsatile and pulsatile perfusion, are known to alter various hemodynamic and physiologic forces affecting the extravascularization of plasma water, especially in the lungs, which leads to respiratory dysfunction.[250] Total body water is increased after CPB, leading to tissue edema and altered organ function.[251] Total body fluid shifts may take several days after CPB to correct because of the degree of hypotonicity created during bypass.[252] Although the pathophysiology related to tissue edema is appreciated, the influence of factors such as total bypass time and pressure gradients during CPB remains to be elucidated. Priming of the CPB circuit with crystalloid solutions alone reduces colloid oncotic pressure, and this reduction is directly related to the total volume of prime solution and the overall level of hemodilution. Hypo-oncotic primes promote tissue edema through interstitial expansion with plasma water.[248] A significant decline in plasma albumin occurs after CPB in patients who have been exposed to crystalloid-only primes.[253] Albumin and various high-molecular-weight colloid solutions are added by some groups to the prime to offset these changes, although the benefits associated with each practice remain controversial.[254]

Both high- and low-molecular-weight hydroxyethyl starch (HES), synthetic colloids that are derived from amylopectin, have been previously used as volume-expanding adjuncts to crystalloid primes.[255,256] HES is a colloid oncotic increasing agent that has colloidal properties similar to that of 5% albumin and is relatively inexpensive.[257] However, recent evidence in critical care arenas suggest that these synthetic colloids may be harmful in some patients.[258] In 2012, a metaanalysis conducted by Navickis and colleagues concluded that the use of HES significantly increased postoperative blood loss, reoperation for bleeding, and homologous blood transfusions when compared with albumin fluid replacement therapy.[259] The FDA issued a Safety Communication in 2013 recommending against the use of HES in CPB surgery because of the increased risks of renal injury and excessive bleeding.[260] The use of hypertonic saline solutions (7.2% NaCl) in combination with hetastarch was recently shown to result in better patient hemodynamics with lower fluid requirements during CPB.[261]

The addition of glucose to prime solutions remains an area of controversy because of the relation between high glucose concentrations on CPB and neurologic dysfunction.[262,263] Metz and Keats[264] reported that when glucose was included in prime solutions of 107 patients undergoing CPB, there was a lower fluid balance as evidenced by significant reductions in crystalloid administration and there was no increased neurologic dysfunction. Although there is a paucity of prospective studies on the neurologic outcome of cardiac patients after perioperative glucose administration, evidence exists that glucose administration is associated with greater morbidity after cerebral ischemia.[265,266] The hypothesis for this pathophysiologic phenomenon is related to a shift in glycolysis from aerobic to anaerobic pathways during ischemia, which results in a metabolic end-product accumulation of lactate and decline in intracellular pH.[267] Until further work is done in which tightly controlled preoperative and postoperative neurologic examinations are performed, it may be advantageous to manage glucose conservatively, restricting glucose-containing solutions in cardiac patients.[268] Prolonged periods of perioperative hyperglycemia have also been associated with increases in inflammatory response, renal impairment, infections, and myocardial dysfunction.[269,270] The growing body of evidence advocating for tight glucose management led to the establishment of clinical practice guidelines recommending blood glucose levels to be kept below < 180 g/dL during cardiac surgery.[271]

Marelli and colleagues studied perioperative fluid balance in 100 adult patients divided into two groups who either did or did not receive albumin (50 g) in the bypass prime.[272] They were unable to show any improvement in more than 40 clinical parameters affecting patient outcome when albumin was included in the prime. It is known that, within the first few seconds of CPB, a proteinaceous film is deposited on the surface of all extracorporeal circuit surfaces.[273] Priming the pump circuitry with albumin is thought to decrease the initial adsorption of protein components, which would increase biocompatibility. However, the use of albumin for circuit coating may no longer be efficacious, as commercially available biopassive surface additives can promote CPB biocompatibility. Bonser and colleagues[274] examined complement activation in 36 patients who received priming solutions of either crystalloid, crystalloid plus albumin, or crystalloid plus the plasma expander polygeline. They measured products of both the alternate and common complement pathways and found a significantly greater level of activation in both the crystalloid and crystalloid plus albumin groups when compared with the polygeline patients. A similar study examined both plasma and dextran 70 in priming solutions and their effects on complement activation.[275] When plasma was added to the prime, a significant increase in the plasma concentration of C3 activation products (C3c and C3dg) was observed, which was not present in the dextran 70 group. A study of the effects of postbypass hypoalbuminemia demonstrated that this reduction was well tolerated except in patients with poor left ventricular function.[128]

Further important considerations in choosing a priming solution for CPB circuits include alterations induced by changes in electrolyte activity. Balanced electrolyte solutions are the first-choice base solutions of most prime solution "cocktails" used by perfusionists. Lactated Ringer's solution, Normosol-A, and Plasmalyte are used frequently because of their electrolyte compositions and isotonicity. One potential concern with the latter solutions focuses on the absence of calcium and potential for hypocalcemia. Calcium concentration varies depending on the type of prime constituents, as well as the presence of citrate in allogeneic blood products. Hysing and colleagues[276] reported substantial differences in the calcium concentrations among five different prime solutions throughout the bypass period. They reported an initial decline in ionized calcium with the initiation of CPB followed by a normalization over the first 30 minutes of ECC and emphasized the importance of frequent monitoring of this cation. In pediatric ECC and in certain adult patients who have preoperative deficiencies

in either hemoglobin or coagulation proteins, it may be necessary to prime the heart-lung machine with allogeneic blood products. When calcium-containing prime solutions, such as lactated Ringer's, are used, additional anticoagulation is necessary to prevent circuit thrombus from forming before the initiation of CPB. The most frequently used ratio of heparinization for CPB is 2500 IU of heparin for each liter of prime solution, which would ensure adequate anticoagulation for both sanguineous and asanguineous prime solutions.

Perioperative Methods of Red Blood Cell Conservation

Homologous blood is a precious resource, the transfusion of which confers both benefits and risks. The practice of transfusion began in the 1930s with the Nobel Prize–winning work of Landsteiner.[277] Transfusion medicine expanded through experience gained in battlefield medicine and the development of cardiac surgery, vascular surgery, and oncology. Of the 29 million transfusions administered each year, it is estimated that one-third to one-half are not administered in accordance with evidence-based indications.[278] Cardiac surgery programs are one of the leading consumers of blood and blood products. More than 80% of the blood used in cardiac surgery is transfused in 15% to 20% of the patients undergoing surgery.[279] In the late 1970s and early 1980s, there was concern about transfusion-related hepatitis B and C, HIV, and bacterial infections. With modern blood bank processes and screening, these risks have become extremely low; however, other associated risks, including transfusion-related lung injury, leukocyte-related target organ injury, transfusion errors, and bacterial infections are comparatively common. Furthermore, there is a growing confirmation of the relation between transfusion and reduced short- and long-term survival and increased HF in cardiac surgery patients.[280–286] Transfusion of stored blood and blood products is related to a host of adverse effects, including release of bioactive compounds that cause inflammation, reduced oxygen availability to tissues, and other immunomodulatory effects, all of which contribute to increased morbidity and mortality[287] (see Chapters 34 and 35).

Transfusion practice varies widely, and this variation is based largely on individual physician practice.[288] The administration of allogeneic blood products during cardiac surgery continues to be a major concern for both patients and clinicians. The changing population of patients undergoing cardiac surgery has presented new transfusion-related challenges that are being addressed through both pharmacologic and mechanical means. A combination of increasing age of patients undergoing cardiac surgery and a greater percentage of patients undergoing resternotomy procedures has increased the challenge of bloodless cardiac surgery. Although the safety of receiving allogeneic blood has increased dramatically, risks remain and need to be understood when considering patient transfusion. These risks include both hemolytic and nonhemolytic reactions, disease transmission, graft-versus-host disease, recipient alloimmunization, and hypervolemia.[289] Meticulous attention to bleeding and adherence to restrictive blood transfusion protocols have significantly improved patient care and outcome.[290,291] However, the diversity in surgical practices, anesthesia management, and postoperative care all represent a multifactorial process rendering reproducibility difficult from center to center.[292] An international multidisciplinary consensus panel of experts concluded that over 88% of the published RBC transfusions reviewed in the literature were either harmful or showed no benefit to patients.[293,294] Additionally, one out of three RBC transfusions are administered without a corresponding hemoglobin value.

Isovolumic hemodilution combined with hypotensive anesthesia is an effective strategy for limiting allogeneic transfusions. Intraoperative phlebotomy before ECC is performed easily with volume replacement consisting of either colloid or crystalloid solutions ranging, respectively, from 1 to 3 mL for every milliliter of phlebotomized blood. Relative contraindications to performing intraoperative donation may be left main stenosis, unstable angina, critical aortic stenosis, hemodynamic instability, and a history of cerebrovascular disease.[174] The increased risks associated with allogeneic blood are well known. Although the dangers of receiving contaminated blood vary among geographic regions, it is accepted that the incidence of posttransfusion hepatitis C has decreased markedly,[295] whereas the risk for HIV transmission has been reported to be as high as 1 in 100,000 transfusions. The emphasis on reducing the risks associated with blood exposure has long been evident within hospitals. Standing blood utilization committees are charged with the responsibility of reviewing transfusion practices within hospitals. Some states have enacted laws that protect the rights of patients undergoing elective surgical procedures in regard to blood transfusions. Legislative actions in California have established specific mandates for physician involvement in ensuring that patients at risk for transfusion are informed of the availability of alternate techniques for reducing the risk for allogeneic blood exposure. Professional medical societies have established evidence-based recommendations supporting cardiac surgical blood conservation programs.[296] Clearly, the impetus directing specific blood replacement practices associated with cardiovascular surgery will come under intense scrutiny from both internal and external sources of review.

The term *autotransfusion* has been used generically to represent the process of reinfusing blood collected from a patient at some time before infusion. Autotransfusion can be broken down into three distinct categories delineated by both the time of collection and the methods used to collect the blood. Preoperative donation, intraoperative salvage, and postoperative collection are techniques used in varying degrees at most cardiac centers. Each category is further subdivided according to the techniques used; however, the underlying goal that firmly links all processes together is the reduction in exposure of patients to allogeneic blood.

Preoperative Donation

Predonation before surgery would seem to be a plausible means of obtaining blood and avoiding homologous transfusion, particularly in this era of heightened awareness of the dangers associated with receiving allogeneic blood products. Not only is the use of autologous blood nonimmunogenic, but it also reduces the hospital's dependence on blood banks. However, this technique has had limited success in treating the cardiac surgery patient.[297] From a blood bank perspective, predonation of blood is a logistic nightmare. Furthermore, there are many contraindications to autologous blood collection in cardiac patients, including aortic stenosis, left main coronary artery disease, idiopathic hypertrophic subaortic stenosis, unstable angina, cardiac failure, recent MI, ventricular arrhythmia, symptoms on the day of donation, and the emergency need for surgery. Only 10% of transfusion recipients may be eligible for self-donation[298]; therefore the majority of surgical candidates require alternative measures to reduce exposure to the general blood supply.

Plasmapheresis

Plasmapheresis is the separation of whole blood into plasma (which may be platelet poor or platelet rich), platelets, and RBCs. The first clinical utilization of plasmapheresis in thoracic surgery was reported by Ferrari and colleagues[299] in 1987. The benefits of plasmapheresis in the cardiac surgical patient are derived from the production of autologous blood products that, because of their separation into isolated components, can be administered to treat specific deficiencies related to the patient's hemostatic needs. One of the perceived advantages involves the treatment of patients who would otherwise not be candidates for predonation of blood. The logistic difficulties are overcome when this method is used in the OR with the patient under the direct care of the anesthesiologist.

As with any new treatment, potential disadvantages do exist and are related to exsanguination phenomena. Plasmapheresis reduces circulating albumin and total protein levels before surgery, which when combined with noncolloidal fluid replacement, may lead to extravascularization of plasma water. In addition, there may exist select patients who cannot tolerate the anemia associated with use of this technique before CPB. The expenses associated with plasmapheresis

are minimal because most cardiac centers have purchased cell-washing autotransfusion devices for alternate reasons, and these machines easily can perform intraoperative plasmapheresis. The technique of plasmapheresis uses technology similar to that of cell-washing autotransfusion devices. Both systems use centrifuges, peristaltic pumps, and collection reservoirs. The process for plasmapheresis is unique in several ways, including its processing of whole blood collected using protocols for isovolumic hemodilution, before heparinization. During plasmapheresis the clinician has the ability to alter the collection process to obtain either platelet-poor or platelet-rich plasma (PRP). The platelet-poor plasma is collected at greater centrifuge speeds (5200 to 5600 rpm), resulting in tighter packing of the RBC layer, restricting the separation of platelets into a buffy coat layer. At slower centrifuge speeds (2400 to 3600 rpm), the platelet fraction is sequestered in the buffy coat layer that is then collected, together with a small volume of RBCs, as PRP.

Although it seems reasonable to sequester platelets and plasma from the CPB circulation and the stresses of surgery, an evidence-based review of the literature questions the routine use intraoperative plasmaphersis as a recommended blood conservation strategy. According to both the 2007 and 2011 Society of Thoracic Surgeons Blood Conservation Guidelines, 20 RCTs and one pooled metaanalysis failed to collectively show a clear clinical benefit in transfusion-related rates and outcome.[53,54] Similar studies suggest that the labor intensity and technical mistakes that could occur during sequestration may inadvertently increase the patient's risks of transfusions. Moreover, the patients that would most benefit from this technique are the poorest candidates for the procedure, because of clinical instability during harvest or low platelet concentrations in the systemic circulation.[54] As such, plasma and platelet pheresis may be considered only when large volumes of platelets can be sequestered.

Autologous Priming Techniques

The process of displacing crystalloid prime solution with the patient's own blood to reduce hemodilution during the onset of CPB, known as autologous priming (AP), has become a widely adopted method of reducing the burden of hemodilution that occurs at the initiation of CPB. The process involves slowly removing the clear prime from the pump with the patient's own blood through both the arterial and venous limbs of the perfusion circuit, once the patient has been given heparin and the activated coagulation time is adequately prolonged. It is necessary to position the patient in Trendelenburg position to improve right atrial filling pressure and maintain arterial blood pressure during this process. It often is necessary to also infuse phenylephrine to maintain an acceptable arterial blood pressure during this process.

Rosengart and colleagues'[300] prospective trial led the way for other investigators. Their study, conducted on 60 first-time CABG patients, established that AP limits hemodilution and reduces the number of patients needing RBC transfusions. Since their report, other randomized and observational trials have reported similar benefits.[301–305] A literature review and metaanalysis in 2009 concluded that AP significantly reduced the number of patients receiving RBC transfusions in both the OR theater and the entire length of hospital stay.[306] Trowbridge and colleagues[307] designed a prospective study aimed at identifying optimal characteristics of the AP process and found that when used effectively, defined as removal of at least 1300 mL or when less than 10% of AP volume was returned to the patient, greater hematocrit values were obtained and fewer patients received transfusions. Furthermore, they reported that the amount of removed prime returned to the patient was related to the patient's urinary output and the amount of blood loss during the procedure.[307]

Perioperative Salvage and Autotransfusion

Cardiotomy Suction

Shed blood from the surgical field and blood vented from the LA, left ventricle, pulmonary artery, or the aorta is collected and reinfused into the CPB circuit through the cardiotomy suction system. This system is composed of tubing usually ¼-inch internal diameter directed through an RP into a filtered reservoir. Cardiotomy suction blood contains fat, bone, lipids, and other debris from the surgical field. This blood is also exposed to air, shear forces, and artificial surfaces that cause exacerbation of the systemic inflammatory response and result in microcirculatory dysfunction. These substances may traverse the CPB circuit, enter into the arterial line, and ultimately obstruct the microcapillary circulation of the patient. Brown and colleagues[308] identified thousands of embolic lesions in the brains of patients who died within 3 weeks of cardiac surgery and reported an association between embolic lesions and duration of CPB. For each 1-hour increase in the duration of CPB, the embolic load increased by 90.5%. Cardiotomy suction blood has been identified as a major source of lipid emboli in several studies.[309–311] For this reason, some have advocated eliminating the use of cardiotomy suction, which is returned directly to the ECC. Several clinical studies have examined the effects of eliminating cardiotomy suction. In a randomized trial enrolling CABG patients, use of cardiotomy suction resulted in significant increases in thrombin generation, neutrophil and platelet activation, as well as the release of neuron-specific enolase.[312] Nuttall and colleagues,[313] in a study of patients in whom an open venous reservoir was used, compared the return of cardiotomy suction directly to the ECC, versus sequestration and processing of cardiotomy blood to a cell saver. Numerous blood tests were performed to evaluate platelet function, and no significant difference in any of the tests or in blood transfusion requirements was observed.

Cell Salvaging Through Centrifugation and Washing Techniques

One of the simplest forms of autotransfusion is the use of a cell-salvaging system that uses aspiration and anticoagulation to collect shed blood and return it to the patient. The simplest products to perform this function include collection sets consisting of double-lumen tubes through which an anticoagulant (usually heparin or citrate-phosphate-dextrose) is mixed with shed operative blood, aspirated by negative pressure through a vacuum source, collected in a reservoir, and directly reinfused to the patient through a filter. Inherent problems with this technique include questionable quality of reinfused blood because of contamination with particulate matter aspirated from the field that includes bone fragments, fat particles, and suture materials. In addition, the anticoagulant remains present in the reinfusate. However, this technique is a relatively easy and quick means of returning lost blood in the event of unexpected acute blood loss.

Another form of autotransfusion uses specific machines that salvage and process shed blood and include a cell-washing step. The term *cell saving* has come to denote the process of autotransfusion that involves centrifugation of collected operative blood and processing with a wash solution, 0.9% NaCl, and reinfusing the product back to the patient. The basic operating principles found in autotransfusion include aspiration, anticoagulation, centrifugation, washing, and reinfusion. The ensuing discussion focuses specifically on the processes of cell washing and separation by centrifugation as autotransfusion methods.

The major components of any automated or manual device used for cell processing in autotransfusion are listed in Box 32.8. The process begins with the aspiration of blood from the surgical site together with an anticoagulant via a double-lumen line. The blood, together with other operative contaminants, including bone chips and adipose tissue, is then collected in a cardiotomy reservoir, functioning as the first filtration, with depth and screen filters ranging in size from 40 to 120 μm. A peristaltic pump then transfers the contents from the cardiotomy reservoir into a centrifuge bowl that has been specifically designed to separate blood according to specific particulate density. Centrifugation necessary for this separation process generally is between 4800 and 5600 rpm (Fig. 32.32). The volume of the bowl is an important characteristic of these devices because this capacity has a role in the minimum amount of shed blood required to obtain an acceptable hematocrit in the returned product. Some systems come with 125-mL bowls for use

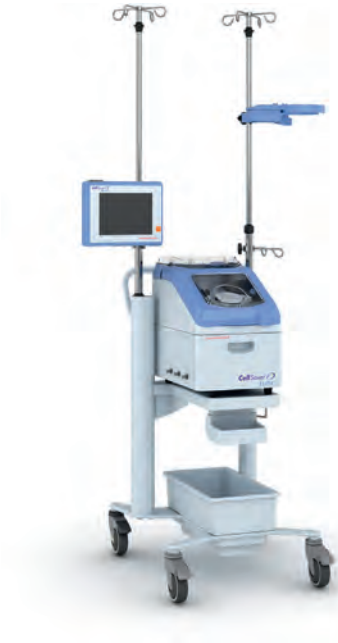


Fig. 32.32 Elite cell saver. Autotransfusion cell processing device using a peristaltic pump and centrifuge for processing of shed blood. *(Courtesy Haemonetics Corporation, Braintree, MA.)*

Fig. 32.33 Continuous Autotransfusion System (CATS). *(Courtesy Terumo Cardiovascular Group, Ann Arbor, MI.)*

BOX 32.8 BASIC COMPONENTS OF A TYPICAL AUTOTRANSFUSION DEVICE

- Centrifuge
- Centrifugal bowl
- Aspiration set
- Anticoagulant cardiotomy reservoir
- Wash fluid
- Waste bag
- Reinfusion bag

with small patients or when smaller amounts of shed blood are anticipated. The heavier RBCs are packed farthest from the axis of rotation, whereas the lighter plasma and crystalloid fractions remain closest to the center of the bowl. A wash mode is initiated when the centrifuge bowl has reached its optimal packed RBC level, with sterile physiologic saline pumped through the RBC layer, removing plasma-free hemoglobin, clotting factors, anticoagulant, and nonautogenous particles.

After the wash cycle, the washed product is pumped out of the centrifuge bowl into a collection reservoir and then transferred to a reinfusion bag for administration to the patient. The quality of the finished product is affected by several operating parameters, including the absolute aspiration pressure, the fill speed of the bowl, the wash rate, and the quantity of wash volume used. The percent of hematocrit of the processed blood also is dependent on filling rate and wash rate, and when these are kept within the manufacturer's recommendations, the final product should have a hematocrit between 45% and 60%.

One unique cell-saver design, the Continuous Autotransfusion System (CATS; Terumo Cardiovascular Group, Tustin, CA), does not have a Latham bowl and functions in a continuous manner such that the packed RBC product is harvested during centrifugation (Figs. 32.33 and 32.34). This approach has several advantages: a lower minimum amount of shed blood is required before packed RBCs may be harvested, a greater RBC concentration of resultant product is obtained, and, most important, the separated lipid layer remains suspended

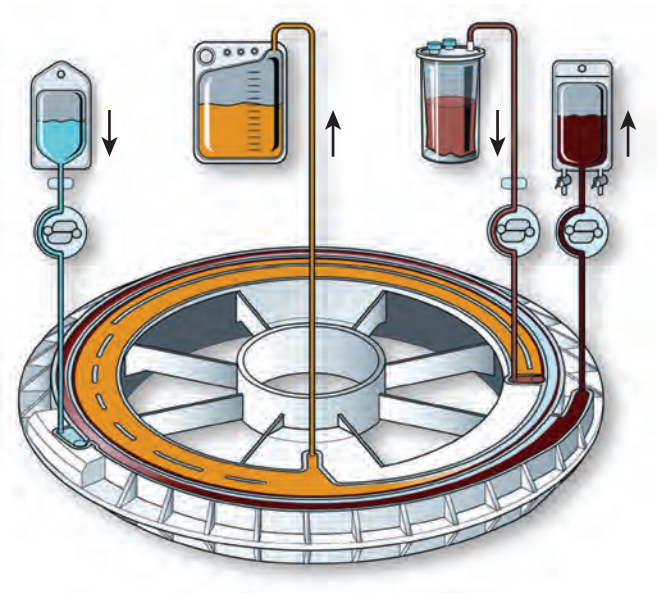


Fig. 32.34 Continuous Autotransfusion System Cell processing cassette. *(Courtesy Terumo Cardiovascular Group, Ann Arbor, MI.)*

during the process. With the traditional Latham bowl systems in which the centrifugation is stopped between cycles, lipids may remix with the final RBC product and be returned to the patient. Several recent studies have shown that the use of a continuous processing system is superior to the Latham bowl-type systems in terms of lipid removal and neurocognitive outcomes.[314,315] Kincaid and colleagues[316] studied effects of blood processing technique on production of lipid emboli in the brain (small capillary arterial dilations) in a canine model. Two recent randomized trials were designed to determine whether use of a cell saver reduced neurocognitive dysfunction after CPB. In Rubens

and colleagues' study,[317] 266 patients undergoing CABG surgery were randomized to two groups: an unprocessed cardiotomy suction blood group (control) and that processed by centrifugal cell washing (treatment group). Greater blood product administration and blood loss were observed in the treatment group. No differences in microemboli generation, neurocognitive dysfunction, or other adverse events were demonstrated between groups. In another study by Djaiani and colleagues,[314] patients randomized to cell processing with a continuous autotransfusion system had reduced transfusion requirements and improved neurocognitive function. The latter study used a continuous cell processing system that has been shown to reduce blood lipid content. The former study used a Latham bowl intermittent system, which previously has been shown to be ineffective at lipid removal. Further studies are necessary to define the impact of cardiotomy suction on clinical outcomes.

All currently manufactured machines contain microprocessors and operate in either manual or automated modes. In the manual mode, the operator has control over the processing cycle and must be present during each stage of the process. The machines that contain automatic mode capabilities also provide the user with the option of completing several cycles of blood processing without operator dedication. Some models also permit online programming at the user site, which enables the perfusionist to modify the processing program according to the level of aspirated blood contamination, producing an optimal quality product.

The safety features available on autotransfusion machines vary according to the manufacturer. Some of the more prominent features include air-sensing capabilities, level detectors, air and foam detectors, hand-cranking capabilities, two-bag reinfusion systems, and waste bag overfill automatic shutoff. The reinfusion bag from an autotransfusion device should never be directly connected to a patient through an infusion line. The peristaltic pump of the autotransfusion device is connected to the cardiotomy reservoir, which is often emptied during the filling process. The potential, therefore, is that air could be pumped into the reinfusion bag, which could then be passed on to the patient, especially in the situation in which the reinfusion bag is placed under pressure. A second transfer collection bag should be filled from the reinfusion bag and separated from the autotransfusion machine, to reduce the risks for air embolization.

Several large systematic reviews and metaanalyses have demonstrated the efficacy of routine autotransfusion usage in CPB surgery.[318,319] Cost-effectiveness always has been a concern, with the prevailing belief that autotransfusion should be considered only when anticipated blood loss would result in a reinfusion of 1 to 2 units of processed RBCs.[320] However, the active interest in minimizing patient exposure, combined with the use of smaller-volume centrifuge bowls, have prompted increased use of autotransfusion during cardiac surgery. Young and colleagues[321] reported a reduction in allogeneic RBC transfusion from 4.2 to 1.5 units/patient when autotransfusion was used in cardiac patients. The quality of RBCs processed via autotransfusion during cardiac surgery also has been compared with fresh autologous blood, with RBCs collected from the operative field having an in vivo survival comparable with that of phlebotomized blood.[322] Schwieger and colleagues'[323] study examined autotransfusion-collected blood for risk for infection and found that patients who had blood salvaged and processed by cell-washing equipment had no higher rate of infection than patients who had no autotransfusion but received banked blood.

In addition to aspirating shed blood from cardiac patients, the autotransfusion device can be used to concentrate the pump perfusate at the termination of CPB. Although this process is known to reduce the protein concentration of the perfusate when compared with reinfusion of the unprocessed pump contents, this method significantly reduced allogeneic banked blood exposure.[54,324] Many centers will infuse the blood contained in the CPB circuit at the termination of bypass. The blood in the CPB circuit is displaced with a balanced electrolyte solution so that the pump remains primed should it be necessary to return to bypass. Sometimes vasodilators are administered to the patient to increase capacitance and allow this blood to be reinfused. It is common practice in neonate and pediatric cardiac surgery to use a technique referred to as "modified ultrafiltration" (MUF). With this technique, UF is conducted to remove plasma water, while at the same time the blood remaining in the CPB circuit is slowly infused into the patient. Similarly, this technique may be performed using a device called a *Hemobag,* where the contents of the CPB circuit are infused into a collection bag and the contents of the bag are then ultrafiltered and returned to the patient.[325–327] The product returned to the patient has a lower water content and greater concentration of RBCs, platelets, white blood cells, and plasma proteins.

Dilutional coagulopathy is a potential problem with overuse of autotransfusion. When large quantities of blood are processed, the washout of clotting factors may induce bleeding purely from a dilutional effect. However, the use of waste or wall suction would result in a similar reduction in clotting factors, as well as the loss of RBCs. Autotransfusion also is used to treat patients with rare blood types or who are sensitized to donor blood and respond poorly to transfusion. In addition, certain religious beliefs will not allow the acceptance of allogeneic blood but will consider the use of autotransfusion on an individual basis.

The contraindications to the use of autotransfusion are relative and are evaluated on a per-case basis. Therefore the relative contraindications include contaminated wound sites and/or septic procedures, malignancy, aspiration during caesarean sections, and concurrent use when microfibular collagen agents are present. The risks assumed with using cell salvaging and reinfusion techniques in these patients must be weighed against the inherent benefits of autologous versus allogeneic transfusion. Hemoglobinemia resulting from RBC destruction caused by exposure of blood to disposable autotransfusion circuitry and trauma caused by aspiration and mechanical treatment has been reported.[328] The reinfusion of packed RBCs may also lead to pulmonary insufficiency if inadequate filtering of the product results in microaggregate embolization in the pulmonary vasculature. The risk for air embolism also is increased whenever extracorporeal devices are used; therefore proper precautions with operator vigilance are paramount in ensuring patient safety.

Postoperative Shed Mediastinal Blood Collection

The collection and reinfusion of postoperative mediastinal blood after cardiac surgery have been described as postoperative autotransfusion (PAT)[329,330] and have been used in cardiac surgery since 1978.[331] This process consists of connecting either a dedicated collection device or a cardiotomy reservoir from the extracorporeal circuit directly to mediastinal chest tubes and a negative pressure source. Blood flows from the mediastinal tubes into the collection reservoir, where it undergoes gross filtration (40 to 120 μm). The collected product then is reinfused back to the patient via an infusion pump and through an additional 20-μm filter. The volume collected after the operation varies from center to center and according to procedure but may range from 400 to 1200 mL over the first 24 hours. Shed mediastinal blood is defibrinogenated; therefore levels of fibrin(ogen) split products are increased after reinfusion.[332]

Morris and Tan[333] commented on the use of PAT in 155 consecutive cardiac patients. These authors found a substantial and significant reduction of approximately 30% in the use of allogeneic blood products in patients undergoing cardiac surgery with PAT. Other authors have found that when the postoperative blood loss was less than 500 mL, PAT conferred no benefit in reducing banked blood requirements.[334,335] In a prospective, randomized study of cardiac patients undergoing CABG surgery, Bouboulis and colleagues[336] found no benefit to the use of PAT, and patients receiving autotransfusion had greater incidences of febrile reactions. These authors and others have advocated the concurrent use of a cell-washing device to process the PAT product before reinfusion.[337] A portable cell-washing device, the CardioPAT, has been commercially available for processing shed blood from thoracic and pleural drainage. This device functions similarly to the centrifugal

cell-washing systems. The major differences are a smaller footprint and a slower rate of processing than the traditional cell-saver systems. The processing of this blood removes activated white blood cells and fibrinolytic mediators, which may be associated with hemolytic reactions found when unwashed blood is reinfused. Schmidt and colleagues[338] have shown that the reinfusion of PAT blood in CABG patients caused an increase in levels of cardiac enzymes including creatine kinase-MB activity. These increases may result in a compromised assessment of myocardial injury in patients undergoing cardiac surgery with PAT. Current blood conservation clinical practice guidelines indicate that although the reinfusion of washed mediastinal blood is not unreasonable in circumstances of excessive postoperative bleeding, the usefulness and efficacy of this procedure are not well-established[53]

Ultrafiltration

UF is a process in which plasma water is filtered from whole blood via a semipermeable membrane. Although primarily a method of removing plasma water, it is also an effective means of blood conservation in that it indirectly increases the volume of RBCs, platelets, and coagulation factors. The technology used in UF was initially developed as a treatment for dialysis patients who became volume overloaded.[339] UF is used synonymously with hemofiltration and diafiltration and uses similar devices and principles to those seen in continuous arteriovenous hemofiltration and slow continuous UF. Continuous arteriovenous hemodiafiltration uses a dialysate that flows countercurrent to the direction of blood flow around the fibers, removing plasma solutes and electrolytes by diffusion. When UF is used exclusively to remove excessive fluid from CPB circuits, it has been referred to as *hemoconcentration*.

Cardiac patients are particularly susceptible to volume overloading via crystalloid administration for hemodynamic maintenance and prime solution of the heart-lung machine. Priming of the extracorporeal circuit with nonhemic solutions results in hemodilution that ranges from 33% to 200% of the patient's volume. After cardiac surgery, the amount of extravascular fluid load may increase by greater than one-third of the adult patient's prebypass blood volume,[340] whereas in pediatric perfusion, the total volume of hemodilution may far exceed the patient's preoperative blood volume.[341] It is well-known that the body responds to hemodilution by increasing cardiac index as a result of reduced SVR.[342] In sick or compromised hearts, however, there is less myocardial reserve, which may result in inadequate oxygen delivery and hypoperfusion because of decreased output. UF not only reduces the risk for volume overload in these patients, but it can be used to correct electrolyte and acid-base imbalances.

UF is a hemoconcentration technique by which plasma water and certain low-molecular-weight plasma solutes are separated from circulating whole blood by free convective transport. A semipermeable hollow-fiber membrane operates on the principle of a hydrostatic pressure differential generated across the membrane to separate an ultrafiltrate from blood (Fig. 32.35).[343] The composition of the ultrafiltrate is similar to that of glomerular filtrate.[344] Uremic toxins also are selectively removed from the circulating perfusate,[345] which may decrease the incidence of acute tubular necrosis as a result of CPB. Sieving coefficients that are based on the molecular weight of plasma solutes and the porosity of the UF device have been established by the various manufacturers. These are determined by dividing the concentration of the solute in the filtrate by the concentration in the plasma. Generally, solutes greater than 50,000 Daltons do not pass through the membrane pores (albumin has a molecular mass of 65,000 Daltons).

The advantages of UF in the cardiac patient are:

1. Hemoconcentration without removing the protein segment of whole blood maintains plasma constituents including albumin and clotting factors.
2. The concentration of the albumin fraction increases colloid oncotic pressure and reduces edema by drawing fluid out of the extravascular area.

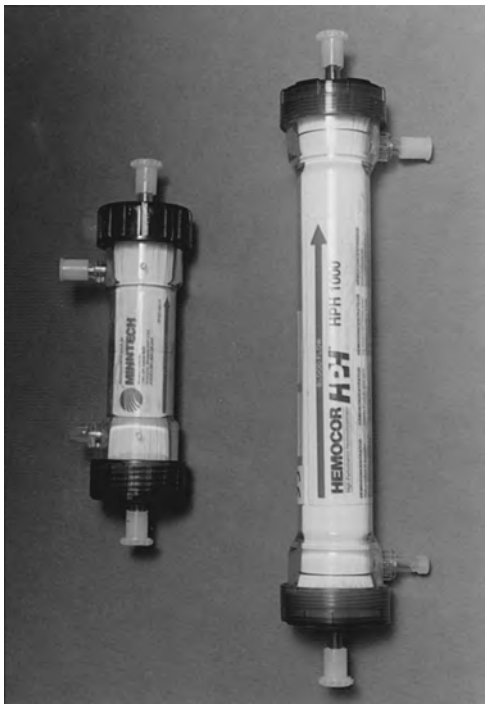


Fig. 32.35 Ultrafiltration device. *(Courtesy Minntech Corp., Minneapolis, MN.)*

3. Pulmonary dysfunction is reduced after CPB by decreasing the amount of extravascular lung fluid.[346]
4. In patients with renal impairment, its concomitant use with dialysis before surgery may prepare the patient for anesthetic induction by optimizing the electrolyte and blood urea nitrogen levels.[347]

UF differs from dialysis in that dialysis is the diffusion of solutes through a semipermeable membrane via a concentration gradient into a dialysate solution. UF uses the hydrostatic pressure gradient in removing plasma water without an osmotic gradient. The principle of operation involves a transmembrane pressure (TMP) gradient, which is the force by which solutes are separated from the solution. The calculation of TMP uses the arterial inlet pressure (P_a), venous outlet pressure (P_v), ultrafiltrate pressure of outlet (P_n), and oncotic pressure at the inlet (P_i) and the outlet (P_o):

$$TMP = P_a/2 + P_v + P_n - P_i/2 + P_o$$

The UF rate is the rate at which plasma volume is removed from the blood passing through the ultrafiltrator and is dependent on TMP and the surface area of the hemoconcentrator.[348]

Ultrafiltrators traditionally have been designed in either parallel-plate or hollow-fiber configuration. The hollow-fiber types are used in hemoconcentration and are manufactured out of cellulose, polyacrylonitrile, or polysulfone materials. Blood passes along the inside of the hollow fiber, with the outside of the hollow fiber open to siphon drainage or negative pressure created by a vacuum suction. The TMP forces created by the movement of blood through the fibers and UF pressure force plasma water and dissolved solutes through the pores in the synthetic material. The pore size of hollow-fiber ultrafiltrators varies among manufacturers but is generally between 30 and 40 angstroms. The wall thickness of the hollow fiber is around 40 μm, and the diameter of the fiber reaches 200 μm. Other factors that influence UF rates include the rate of blood flow through the device, the RBC and protein concentrations, and the temperature of the perfusate passing through the device.

There are few contraindications to hemoconcentration with an ultrafiltrator. As with any nonendothelialized material, biocompatibility becomes an important issue. Leukopenia and complement

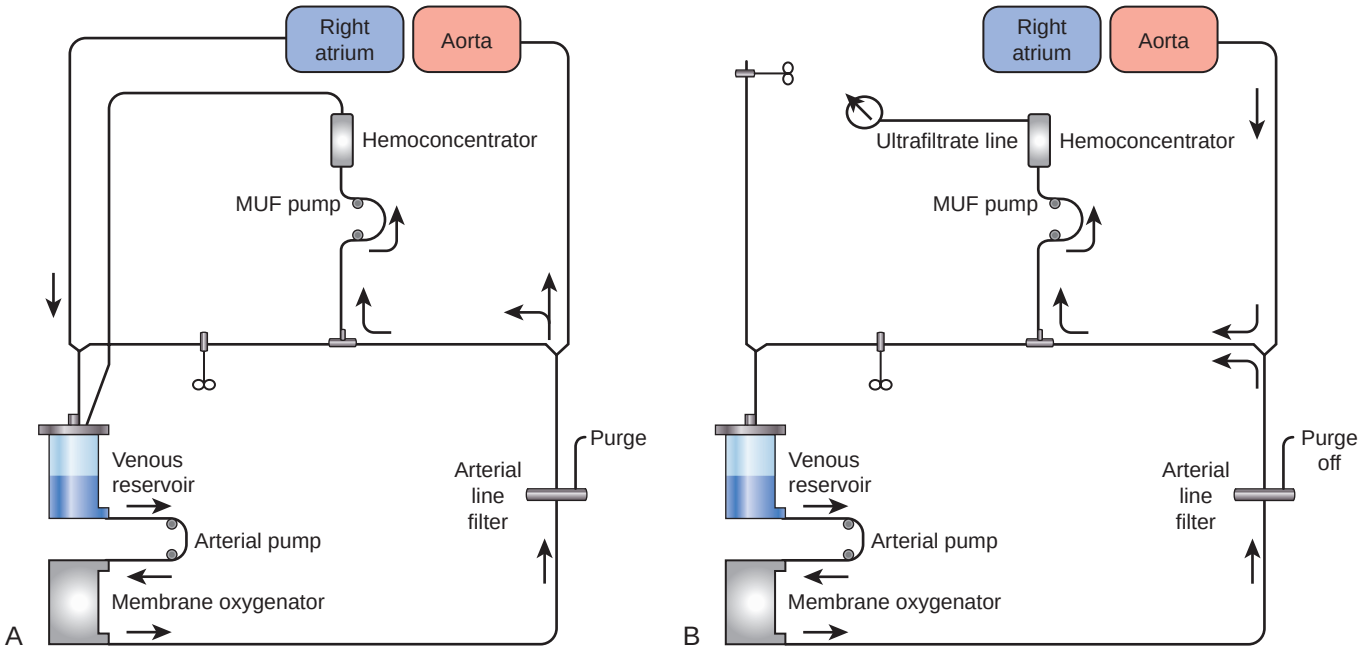


Fig. 32.36 Modified ultrafiltration *(MUF)* circuit used for pediatric cardiac surgery. (A) Conventional ultrafiltration. (B) MUF. *(From Darling EM, Shearer IR, Nanry C, et al. Modified ultrafiltration in pediatric cardiopulmonary bypass.* J Extra Corpor Technol. *1994;26:205.)*

activation have both been reported when blood is exposed to cellulosic membrane material.[349,350] Excessive TMP may lead to increased RBC trauma and release of plasma-free hemoglobin. When concentrating the pump contents, care must be taken during reinfusion because of the retention of heparin in the hemoconcentrated product. The heterogenous molecular size of heparin varies the amount of heparin retained in the hemoconcentrate. Strict cost analysis during routine cardiac surgery is difficult to quantify because patients are known to tolerate positive fluid balances of up to 4 L without adverse pathologic effects.[222] Therefore the benefits of UF in these patients have yet to be established.

Modified Ultrafiltration

In 1991, Naik and colleagues[351] described a modification to the technique of UF that has since been extensively applied to pediatric patients undergoing cardiac surgery. An international survey of pediatric perfusion practices in 2011 indicated that 71% of all respondents employed MUF for neonate, infant, and pediatric cardiac surgery.[352] Pediatric patients are thought to be more susceptible to the injurious effects of fluid overloading and may benefit from this technique because of the greater reoperation rate and use of profound and deep hypothermia seen in pediatric cardiac surgery. The technique is applied after CPB and allows the UF of both the circuit contents and the patient. The timing of MUF is critical and permits a rapid increase in patient hematocrit by the removal of plasma water.[353] The results associated with MUF have been very encouraging and have included reductions in postoperative morbidity,[354] reduced blood loss and blood utilization,[351,355] reduced inflammatory mediators,[356,357] and improvements in myocardial function[358] and cerebral oxygenation.[355] Similar benefits have been observed in adults, as several RCTs and a metaanalysis demonstrate an association with MUF and reduced postoperative bleeding and blood transfusions.[359–361]

MUF generally is performed shortly after termination of CPB and is completed with a typical ultrafiltrator. In pediatric operations, these devices are routinely set up and primed together with the entire ECC. The ultrafiltrator is placed in-line at a point distal to the membrane oxygenator with the inlet of the device connected to the arterial line and the outlet connected to the venous return line (Fig. 32.36). An RP controls the flow rate through the MUF circuit and is located in a parallel circuit between the arterial and venous cannulae. Such a configuration allows conventional UF to take place during the CPB procedure. On separation from CPB, the patient becomes the source for blood for MUF by clamping both the arterial and venous lines proximal to the MUF circuit, draining from the arterial cannula, and reinfusing directly into the venous cannula. The remaining pump contents also are concentrated during MUF and serve as a volume replacement for the removed plasma water. Blood flows during MUF vary with patient size and hemodynamic stability.

During MUF, there is an increase in mean arterial pressure (MAP) that may be related to changes in SVR associated with increasing blood viscosity and via the removal of vasoactive substances.[355,362] The obvious benefit of MUF is the removal of plasma water and the concentration of cellular and acellular elements of blood. However, a number of investigators have shown that UF reduces the production of other potential harmful substances, including cytokines and endogenous pyrogens.[357,363] This reduction in number is independent of the effects of hemoconcentration and is instead related to a reduction in the whole-body inflammatory response associated with CPB.[357] The benefits of MUF are accentuated when aggressive UF is used during the rewarming period of CPB. This is more than likely a result of the removal of the activated complement fragment C3a, which is easily sieved in the ultrafiltrate.[357] Patients treated with MUF have been shown to have a significantly faster rate of pulmonary function recovery than nonultrafiltrated patients, which may be because of a leukocyte stability and a reduced degranulation of polymorphonuclear neutrophils in the pulmonary capillaries.[357,363]

The use of MUF in adults has been well studied. In 2001, a randomized controlled trial by Luciani and colleagues reported significant reduction in early morbidity and lower blood transfusion requirements.[364] Other studies investigated transfusion requirements, blood loss, antithrombin III levels, systolic blood pressure, and cytokine levels.[360] Boodhwani and colleagues conducted a metaanalysis from 132 studies involving 1004 patients to examine the effectiveness of MUF patents on blood transfusions and reported a 0.72 unit reduction in transfusions and a significant reduction in post operative blood

loss.[361] The 2011 Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines state: *Use of modified UF is indicated for blood conservation and reducing postoperative blood loss in adult and pediatric cardiac operations using CPB. American Heart Association class I level of evidence A.*[53]

Coated Circuits

Bypass-induced coagulopathy represents one of the most prevalent pathophysiologic events associated with the exposure of blood to foreign surfaces.[365] Identifying patients at risk for development of postoperative coagulopathies has long challenged clinicians involved with cardiac surgery. Abnormal postoperative bleeding usually is classified as resulting from a preexisting coagulopathy, acquired hemostatic deficiencies, or inadequate surgical hemostasis (although a single patient can suffer from all of the above maladies). The activation of various humoral and cellular systems is associated with the exposure of blood to negatively charged foreign surfaces, with arguably the primary causative factor related to platelet dysfunction.[366–369] It has long been thought that, during ECC, thrombin formation is initiated through contact activation with factor XII (Hageman factor), with subsequent activation of the intrinsic pathway of coagulation.[370] However, recent research has shown that activation of tissue factor pathway and the extrinsic limb play an important role in the stimulation of thrombin during CPB.[371] The bypass circuit is composed of various synthetic materials, including PPL, polyvinylchloride, stainless steel and/or anodized aluminum, Dacron, and various plasticizers, all of which evoke contact activation of platelets, granulocytes, and proteins associated with the intrinsic pathway. The pathologic events associated with ECC-induced complement activation are poorly understood,[372] although potent mediators such as C3a, C4a, and C5a are thought to play a major role in postbypass whole-body inflammation[373,374] (see Chapter 35).

Surface coatings play a role in the interface between the blood and the circuit components. Attenuation of the inflammatory and coagulation pathways should translate into decreased postoperative morbidity directly related to platelet dysfunction, bleeding complications, and end-organ damage. The desire to avoid anticoagulation of patients undergoing extensive thoracic aortic surgery led to the first reported use of a shunt with a graphite-benzalkonium-heparin coating by Gott and colleagues.[375] Heparin-coating of the CPB circuit was originally intended to supplant systemic anticoagulation with heparin. Subsequently, this concept of eliminating systemic heparin was dismissed, and a strategy combining the use of low-dose systemic heparin with a heparin-coated CPB circuit was introduced.[376–380] In vitro and in vivo studies of these surfaces demonstrated reductions in coagulation and systemic inflammatory processes. Numerous studies have been conducted to evaluate the effectiveness of heparin-treated surfaces compared with circuits without heparin coatings.[381–406] Most studies have shown evidence of reduced platelet activation,[385–388] reductions in inflammation characterized by complement activation,[389–396] and improvements in clinical outcomes including bleeding and transfusions,[397–399] pulmonary function,[400,401] and cognitive function.[402–404] One randomized trial in patients undergoing redo CABG surgery showed no differences in biomarkers of inflammation or differences in blood loss and transfusion.[405] A larger randomized trial from the same center, which included redo valve patients, suggested that heparin-coated circuits imparted benefits including a trend of fewer reoperations for bleeding (0% vs 4.0%; $P = 0.058$) in CABG patients, significantly fewer major bleeding episodes (1.2% vs 5.4%; $P = 0.035$), and significantly lower blood transfusion requirements in the intensive care unit ($P = 0.013$).[406] The authors further commented that the material-independent blood activation (e.g., blood-air interface and cardiotomy suction) may have blunted the total effect of the heparin-coated surface (HCS).

Unfortunately, most of these studies were small and substantially different in anticoagulation management with heparin, the use of a partially or completely coated circuits, the method by which cardiotomy blood was managed, the use of different heparin coatings, and variations in measuring different end points across studies. The heterogeneity of the randomized trials related to heparin coatings precludes the use of metaanalysis as a method of summarizing the effectiveness of these circuits.[53,381] Stammers and colleagues[381] used weighted means in an effort to summarize the effects of 27 RCTs of heparin-coated circuits that included 1515 patients. The authors concluded that heparin-coated circuits have shown statistically better results than similar noncoated circuits by decreasing hospital costs attributable to shorter intensive care unit length of stay and bleeding-related complications; they also concluded that immunologic factors were maintained better with the use of the Carmeda-coated circuits, whereas hematologic factors, excluding platelet count, favored the Duraflo II heparin coating. Two new heparin coatings have been developed: hyaluronan-coated heparin coating (GBSTM Coating; Gish Biomedical, Rancho Santa Margarita, CA) and Bioline (Maquet, Wayne, NJ); however, comparative studies of these surfaces are promising but limited.[407]

Numerous surface modifications rendering the CPB surfaces more thromboresistant and biologically inert are commercially available. These include Xcoating PMEA (poly-2-methoxyethyl acrylate; Terumo Cardiovascular Group, Ann Arbor, MI), SMARxT (Sorin Group, Arvada, CO), *P.h.i.s.i.o.* phosphorylcholine inert surface (Sorin Group), Softline heparin-free synthetic polymer (Maquet, Wayne, NJ), and Safeline synthetic-immobilized albumin (Maquet). Preliminary findings indicate that these surfaces provide some improvements, including reduction of platelet activation, leukocyte activation, bradykinin release, and to some extent, reduction in the release of cytokines compared with noncoated surfaces.[408–412] Gu and colleagues[413] compared circuits with the SMA coating with noncoated circuits and reported improved platelet preservation and function, but no difference in complement activation. Ereth and associates[414] compared hematocrit, leukocyte count, platelet count, terminal complement complex, complement activation, myeloperoxidase, β-thromboglobulin, prothrombin fragment 1.2, plasmin-antiplasmin, heparin concentration, activated coagulation time, fibrinogen, blood loss, and blood-product usage in 36 cardiac surgery patients randomized to a trillium-coated circuit or an uncoated circuit. No significant differences were observed between the trillium-coated and uncoated group. Ferraris and associates[53] concluded that "heparin-coated bypass circuits (oxygenator alone or the entire circuit) are not unreasonable for blood conservation (class IIb, level of evidence B)." Similarly, Shann and colleagues[415] have stated, "Reduction of circuit surface and the use of biocompatible surface-modified circuits might be useful; effective in reducing the systemic inflammatory response (class IIA, level of evidence B)."

Heparin coating, or bonding, of extracorporeal circuit surfaces increases the hemocompatibility of nonendothelialized substances.[367,416,417] The specific benefits of HCS center on a reduction in the activation of humoral protein systems involved in hemostasis and complement systems, together with a benign deposition of platelets and protein on the extracorporeal surface.[418] Bound heparin inhibits the binding of factors Xa, IIa, and XII, inhibiting thrombus formation by restricting the initiation of coagulation.[419,420] Several authors have shown a reduction in granulocyte activation by reduced liberation of primary granule proteins (myeloperoxidase, lactoferrin) during in vitro whole-blood circulation in HCS circuits.[367,421] The amelioration of blood-surface interactions through the use of HCS may reflect similar responses seen in vivo at the endothelial lining of the vasculature.[417] Palatianos and colleagues[422] examined the effect of HCS on platelet preservation in a pig model of ECC, finding no reduction in platelet consumption or platelet count when HCS were used during CPB periods of 3 hours. However, their model did not include functional studies of the residual platelets, nor did they report results of hemostatic differences after ECC. In a similar animal model using calves during CPB with HCS, Tong and associates[423] were able to show superior platelet preservation and function compared with noncoated bypass circuits. Fibrinopeptide levels were reduced in the HCS group, and there was no evidence of thrombus formation in any of the coated circuits.

Once blood comes in contact with HCS, AT III attaches to the bound heparin in an accelerated fashion. Thrombin then combines with AT III, forming an inactivated complex that leaves the HCS, enabling the process to be repeated.[424] HCSs have been evaluated in various clinical settings that have included ECMO,[424] hepatic transplantation,[425] aortic aneurysm repair,[426] pulmonary artery catheters,[427] and during routine cardiac surgery. The efficacy of heparinless bypass may be especially evident when used to treat patients suffering from hypothermic exposure or in trauma patients suffering from head or severe soft-tissue injuries.

The use of HCS may result in the reevaluation of heparin therapy necessary for systemic anticoagulation during certain ECC procedures.[428–430] Reducing heparin levels has the desired effect of limiting the potential for postoperative coagulopathy that is due to heparin-related platelet defects and heparin reappearance after protamine administration (heparin-rebound effect). This may be especially attractive in patients at increased risk for adverse sequelae of heparin exposure (ie, heparin-induced thrombocytopenia, neurosurgical procedures, protamine intolerances). In some studies, the reduced level of heparinization resulted in lower postoperative blood loss.[428,430] Aldea and associates[431] have shown in patients undergoing CABG surgery that when HCSs were used in conjunction with lower heparinization protocols, there was a marked improvement in hemostasis, as well as reduced blood loss and transfusion rates. These benefits were accentuated in patients who were at a greater risk because of the urgent need for care.

Because heparin is the primary means of anticoagulation during CPB, any method that suggests reducing circulating levels must be critically evaluated.[432] Kuitunen and colleagues[433] prospectively evaluated HCS in patients undergoing CPB who received either a reduced heparinization protocol (100 IU/kg) or a full heparinization dose (300 IU/kg). These authors found that thrombin was formed during CPB, and that there was an increased risk for microembolic, intravascular, and circuit clotting with low heparin levels. This was also confirmed in an in vitro model in which whole blood exposed to an extracorporeal heparin-coated circuit with low heparin concentrations demonstrated evidence of contact activation after 120 minutes of simulated bypass.[434] In a retrospective analysis of patients undergoing first-time valve surgery, Shapira and associates[435] compared patients with HCS who had received low (100 IU/kg) heparinization with patients with normal (300 IU/kg) heparinization and non-HCS circuits. The heparin-coated group had significantly better clinical outcomes and lower allogeneic blood transfusions than the conventional group but also had an increased risk for early valve thrombosis. For this reason, the authors recommended using full-dose heparinization protocols in patients undergoing valve surgery with HCS.

One of the major difficulties in developing HCS was the bonding technique used to attach heparin to the various components used during bypass. An early technique for heparin bonding was described by Gott[436] and involved the substance tridodecylmethylammonium chloride. This method of ionic bonding is currently used in the production of shunts for aneurysm surgery and hepatic transplantation (Gott shunts; Sherwood Medical, St. Louis, MO).[425]

The difficulty in bonding heparin to extracorporeal circuits is compounded by both the diversity of synthetic compounds used during bypass and the geometric variations of cardiovascular devices that may produce areas of stagnation and flow stasis. In addition, the benefits associated with HCS are dependent on heparin being minimally eluted from the surface after contact with blood. The quantity of surface-bound heparin necessary to inhibit clot formation generally is greater than 1.0 mg/cm^2 of circuit surface area but is dependent on the distribution of heparin on the surface. It is well known that heparin is not a single unique compound, but rather is a heterogenous class of mucopolysaccharides, which also may influence binding characteristics.

Quaternary ammonium salts have been used to bond heparin ionically to synthetic surfaces, because heparin forms a highly nondissociable complex with quaternary ammonium salt. One manufacturer of HCS (Bentley Duraflow II; Baxter Health Care Corporation, Irvine, CA) uses a water-insoluble complex between heparin (porcine intestinal mucosa) and alkylbenzyldimethylammonium chloride. When ionically bound heparin surfaces are exposed to blood, there is an initial early 5% elution of bound heparin when blood first contacts the surface, but the remaining concentration stays stable for many hours. Synthetic materials that have been used successfully in covalent bonding include silicone and natural rubber, PPL, and polyethylene.

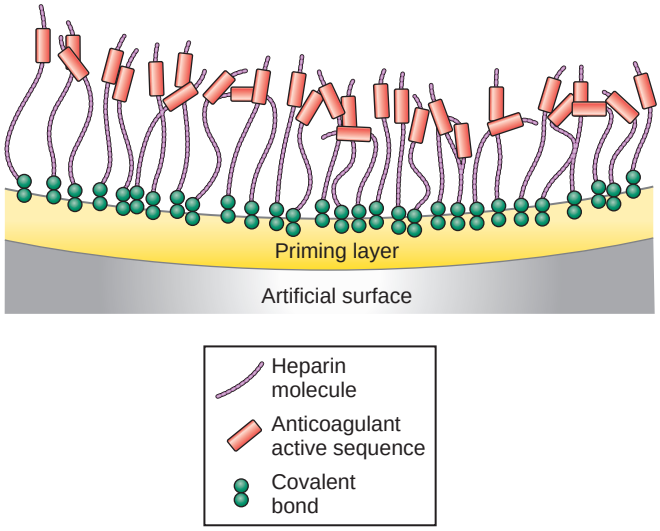


Fig. 32.37 Carmeda Bio-Active Surface. Covalent bonded heparin coating. *(Copyright Medtronic, 2016.)*

Heparin contains a hydroxyl group, carboxylic acid, and an amino group, which are all suited for covalent attachment to artificial surfaces. Covalent bonding of heparin has also been termed *end-point attachment of heparin,* in which an intermediate layer of substrate is first deposited onto the surface to which heparin is affixed by binding to a primary amine.[424] Partially degraded heparin is covalently end-point attached to extracorporeal circuits by a process developed by engineers from the Carmeda Corporation (Carmeda Bio-Active Surface; Carmeda, Stockholm, Sweden; Fig. 32.37).[424,426]

The effectiveness of HCSs is dependent on blood flow dynamics within the circuit, with thrombus inhibition related to the ratio of circuit surface area to blood volume.[437,438] HCSs are effective only when exposed to blood; therefore blood must be kept in constant circulation. Systemic heparinization still would be necessary to decrease clot formation in stagnant or low-flow capillary beds within the body, such as occurs in the pulmonary circulation. Therefore it is not likely that HCS will totally supplant the use of systemic heparinization. However, the use of heparin bonding to these circuits may necessitate the reevaluation of the total concentration of heparin necessary for systemic heparinization and may result in the identification of a more controlled protocol for the administration of heparin.[439]

Perfusion Practices

Minimally Invasive Cardiac Surgery

The changing economics of health care have forced the reevaluation of how techniques and technologies are utilized in the delivery of care. Despite the proven benefits of the heart-lung machine as a resource that enabled cardiac surgery to evolve, the morbidity associated with its use continues to plague clinicians. In a recent survey of cardiac surgeons, the question of which procedure would be preferable to eliminate, median sternotomy or CPB, more than 80% responded with the latter.[440] The development of endoscopic instruments and high-resolution video equipment has shaped the conduct of minimally invasive surgery and changed the conventional wisdom by which surgical practice is directed. The most promising results in applying

these techniques in cardiac surgery have been seen in patients requiring CABG surgery. When the procedure is performed through a left anterior minithoracotomy, it is designated as minimally invasive direct coronary artery bypass grafting. The major benefit to patients who undergo this procedure has been described as being cosmetic, at least when comparing single-vessel disease patients with those undergoing conventional therapy.[441] Although one of the primary goals of minimal invasion is the avoidance of the heart-lung machine, there are situations in which ECC is used to support the patient. This is true in patients with decreased ventricular function or in whom it is necessary to manipulate the heart for posterior access. The degree of involvement will vary from institution to institution, but in general these processes involve specialized cannulae that are most often placed transfemorally, with venous drainage accomplished with a CP kinetically assisted venous drainage (KVAD).[32,33]

When cardiac surgery is performed in patients without the use of a conventional midline sternotomy, it is referred to as *keyhole surgery*. When this technique is combined with CPB, it is referred to as port-access cardiac surgery and has been used for both CABG and valve surgery.[442,443] The success of this operative technique is dependent on a number of factors including surgical expertise and the correct utilization of specialty instruments and cannulae (Heartport EndoCPB; Heartport, Redwood City, CA; Fig. 32.38). The primary cannula, termed an *endoaortic clamp*, has been specifically designed to occlude the aorta, deliver cardioplegia, and vent the ascending aorta. In this way, myocardial protection can be achieved while enabling the surgeon to work in a quiescent, flaccid heart. The endoaortic clamp is positioned under fluoroscopic and echocardiographic guidance. Improper positioning can result in inadequate myocardial protection, left ventricular distention, or occlusion of the arch vessels.[443] A pulmonary artery venting catheter is placed through the jugular vein and used to assist ventricular unloading. The final cannula is a coronary sinus cardioplegia cannula that is used for retrograde cardioplegia administration (see Chapter 31).

The venous return is augmented by the use of KVAD and a CP. Negative pressure is measured at the inlet port to the CP and is regulated by controlling pump inertia.[32] The KVAD pressure is maintained between −50 and −80 mm Hg, which ensures adequate flow rates. The outlet of the CP is connected directly to an integrated cardiotomy/venous reservoir, which in turn, is connected to an arterial pump and the oxygenator (see Fig. 32.38). Patient management during port-access cardiac surgery is performed using similar protocols to those of conventional bypass. Additional monitoring is necessary for the CP and various cannulae that are used to vent the heart and to administer cardioplegia. Once the endoaortic clamp is correctly positioned, the balloon is inflated with a mixture of contrast media and saline, and cardioplegia solution is infused. During antegrade cardioplegia administration, the aortic root pressure will increase to between 60 and 90 mm Hg, and a pressure gradient of 20 to 40 mm Hg will be seen with the MAP. After cardioplegia administration, the aortic root vent is started and a −80 mm Hg pressure relief valve ensures that excessive negative pressure does not occur.

Weaning from CPB is accomplished in a normal fashion with the KVAD siphon gradually reduced, which diverts blood from the heart-lung machine into the patient. The aortic root and endopulmonary vents are removed, the femoral vessels repaired, and the thoracic incision sites are closed in a standard fashion. Although limited data have thus far been collected to assess this technology, it offers the surgeon a unique ability to perform minimally invasive surgery in a controlled environment with high-resolution stereoscopic visualization.

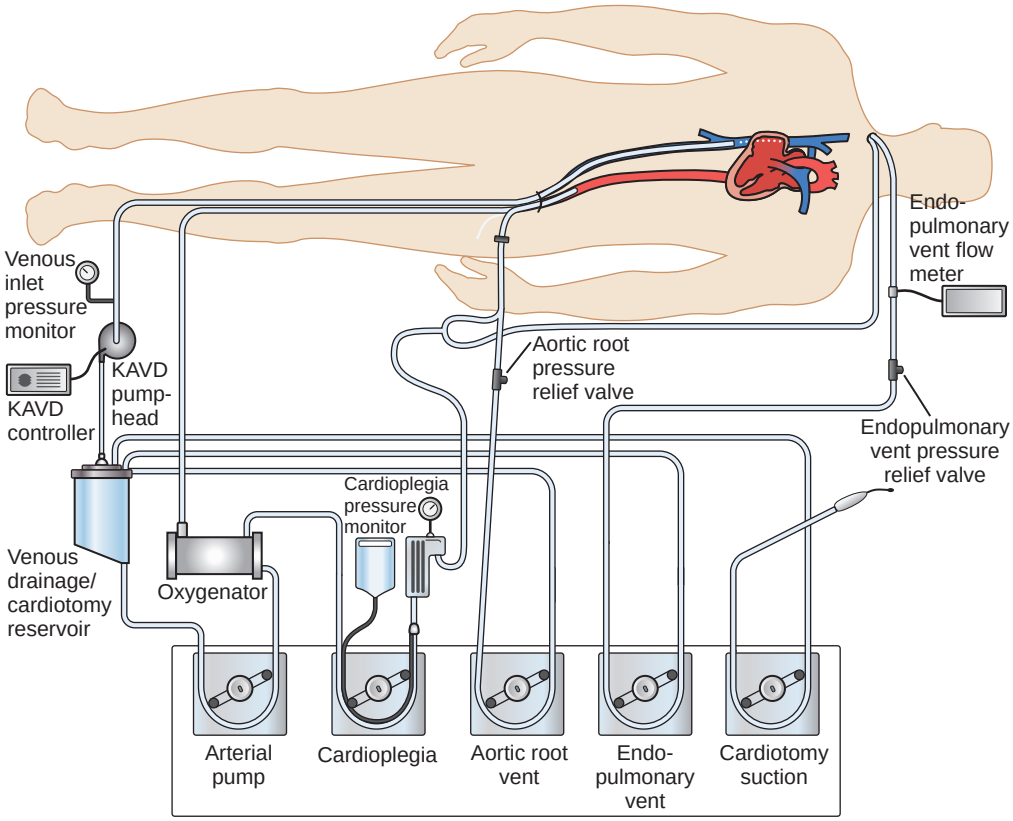


Fig. 32.38 Circuit diagram for the endovascular port-access cardiopulmonary bypass system. *KVAD*, Kinetically assisted venous drainage. *(From Toomasian JM, Williams DL, Colvin SB, et al. Perfusion during coronary and mitral valve surgery utilizing minimally invasive port-access technology.* J Extra Corpor Technol. *1997;29:66.)*

Monitoring During Cardiopulmonary Bypass

Technologic advancements in physiologic monitoring have made the process of CPB safe, comprehensive, and reliable. Monitoring devices measure both physiologic and mechanical functions of the patient-device interface. From a historic perspective, perfusionists had few devices that functioned as monitors relaying information other than hemodynamic data. Technologic advancement has generated new classes of devices for monitoring that at one time either were cost-prohibitive or viewed by perfusionists as superfluous. However, two developments occurred in the field that have greatly increased the safe conduct of CPB. First, the quantity and quality of information produced during a typical procedure increased and became more specific and sensitive in reflecting patient status. Second, the tremendous resurgence in research on the pathophysiologic events associated with CPB shifted the performance of perfusionists from relying primarily on instinctive reasoning to relying on deduction. This could only be accomplished through stricter methods of monitoring and analyzing both the patient's and machine's response to CPB. This section highlights the major variables monitored in the operation of the heart-lung machine.

After ensuring that an appropriate level of anticoagulation has been achieved, the perfusionist initiates CPB. Undoubtedly, the most important assessment of CPB after initiation of perfusion is the function of the oxygenator. This can be compared with establishing an airway in a patient before initiating basic life support. Without the proper delivery of oxygen to the venous blood and the removal of carbon dioxide, the arterial pump serves no purpose. Traditionally, isolated blood analysis was performed at a distant site from the OR and provided the clinician with a historic marker of oxygenator and patient performance. Unfortunately, this event is only a "snapshot" of one point during CPB and will not reflect ongoing changes or trends in the operation. Routine sampling of blood gases normally occurs every 15 to 30 minutes on bypass, and in the event of oxygenator failure, periods of hypoxemia and/or hypercapnia could result during those intervals. For this reason, the use of in-line blood gas monitoring is imperative and should not be considered a "luxury" because of its added cost.[444] Indeed, in this litigious society, it is questionable not to use readily available technologies that may reduce unnecessary patient risk.

Optical fluorescence technology has made reliable in-line blood gas and electrolyte monitoring a reality, providing minute-to-minute accurate surveillance of these parameters during CPB.[445,446] In-line blood gas monitoring allows for real-time monitoring of the "adequacy of perfusion," and one device currently available for use in CPB is the CDI500 (Terumo Cardiovascular Group, Ann Arbor, MI; Figs. 32.39 and 32.40). The CDI500 provides continuous real-time blood gas and electrolyte measurements for Po_2, Pco_2, pH, HCO_3^-, and K^+. The enhanced safety conferred by the use of this technology has been documented in the literature.[447] A survey of anesthesiologists in the United Kingdom and Ireland in 1994 concerning monitoring device utilization revealed that 98% of the 42 hospitals surveyed intermittently monitored blood gas tensions during cardiac surgery, and 33% used continuous blood gas monitoring.[448] In the United States, it has been estimated that approximately 40% of institutions use continuous blood gas monitoring during CPB.[444,449,450] Practice surveys indicate that the use of inline monitoring is increasingly widespread.[451–453] However, approximately two-thirds of the cardiac surgical centers worldwide do not use this technology. Ottens and colleagues[454] suggested that this may be attributed to the lack of scientific evidence and cost associated with the use of this technology.

Arterial blood oxygen saturation always should be maintained at greater than 99%, with PO_2 tensions between 150 and 250 mm Hg. Arterial PCO_2 levels will vary depending on whether alpha-stat or pH-stat blood gas management is used (see Chapter 31). Currently, there are several devices for measuring oxygenator gas exchange performance, including in-line continuous monitors. These monitors must meet basic criteria before they can be viewed as safe and accurate (Box 32.9). They must possess a rapid response time, be as accurate as standard blood gas analysis methods, be unaffected by hemodilution and temperature, and be easy to use. Alpha-stat blood gas management is achieved by maintaining electrochemical neutrality of blood as temperature declines, by keeping the pH alkalotic during hypothermic perfusion. During alpha-stat management, the rule of thumb for controlling carbon dioxide is to maintain PCO_2 levels equal to the temperature of arterial blood. For pH-stat management, the Pco_2 is kept constant at 40 mm Hg, and the pH at 7.4 at all temperatures. Therefore, when blood gases are temperature-uncorrected, a respiratory acidosis is seen. The venous oxygen saturation (SvO_2) will vary during the operative procedure depending on the metabolic state of the patient but is generally maintained at around 80%.

Clinical decisions for using in-line blood gas monitors ultimately must be determined by the ability of these devices to improve patient outcomes with a value that exceeds that of the total costs associated

Fig. 32.39 CDI500 continuous blood gas and saturation monitor. Measures arterial and venous pH, Pco_2, Po_2, potassium, hemoglobin saturation, hematocrit, and hemoglobin. *(Courtesy Terumo Cardiovascular Group, Ann Arbor, MI.)*

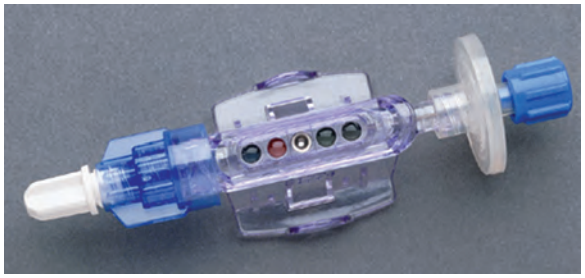


Fig. 32.40 CDI500 sensor. Blood flows through the sensor so that continuous monitoring may be accomplished. *(Courtesy Terumo Cardiovascular Group, Ann Arbor, MI.)*

BOX 32.9 CHARACTERISTICS OF AN IDEAL POINT-OF-CARE MONITORING SYSTEM FOR CARDIOPULMONARY BYPASS

- High degree of accuracy, precision, and reliability
- Rapid response time
- Minimally affected by hemodynamic conditions
- Wide parameter measurement range
- Easy calibration and alignment processes
- Stable measurement ranges (low drift) over 6 hours
- Self-contained instrumentation with minimal disposable use
- High degree of biocompatibility
- Cost-effective
- Input and output data-handling capabilities

BOX 32.10 REASONS FOR MONITORING DURING CARDIOPULMONARY BYPASS

- Assessment of oxygenator and/or device performance
- Calculation of patient conditions
- Oxygen delivery
- Oxygen extraction
- Oxygen consumption
- Carbon dioxide production
- Analysis of therapeutic interventions
- Quality assurance

BOX 32.11 POINT-OF-CARE MONITORING DEVICES

- Online monitors or analyzers
- In-line monitors
- Intra-arterial monitors
- Exhaust gas monitoring (capnography)
- Transcutaneous monitors (pulse oximetry)

with use. Complications arising from the cardiac surgical procedure remain significant in terms of the expense associated with their management.[455,456] The improvement in patient outcomes by the incorporation of a technology assumes that the intended problem is significant enough to warrant an intervention, a fact not always clear in the manufacturing and marketing of medical devices. For a practice to qualify as a standard of care, there must be some evidence that failure to incorporate the technique potentially could result in patient harm. Some of the reasons for monitoring during CPB are listed in Box 32.10.

Although overall mortality associated with CPB has declined over the past several decades, an increase in death (7.2% to 19.6%) resulting from neurologic injury has been shown.[457] Gill and Murkin[458] reported on post-CPB neuropsychologic dysfunction and have implicated cerebral microemboli generated from the bypass circuit as a major source of morbidity. These authors emphasized that microembolic phenomena are generated secondarily to alterations in bypass temperature, oxygenator type, pH management, and the use of arterial line filtration, and that modifications of these parameters reduce the overall incidence of neurologic dysfunction.

Acid-base alterations during CPB have been studied intensely both in animal and in human models, and the results are equivocal. Neurologic dysfunction has been reported in patients maintained using the pH-stat blood gas regimen, which more than likely resulted from the ensuing cerebral hyperemia consistent with the respiratory acidosis created during this condition.[459] This was confirmed by a clinical study in which 70 CABG patients were randomized either to an alpha-stat or pH-stat protocol and evaluated via neuropsychologic assessment at a mean of 42 days after the procedure.[460] The authors found that patients maintained by the pH-stat strategy had significantly impaired cerebral autoregulation and neuropsychologic impairment, when compared with their alpha-stat counterparts. Nevin and colleagues[461] have shown that hypocapnia during CPB also results in neurologic injury, whereas others have been unable to confirm that either acid-base strategy for hypothermic perfusion resulted in significant differences.[462] Fullerton and associates[463] have shown that respiratory acidemia in patients with pulmonary hypertension from mitral stenosis results in exacerbation of pulmonary hypertension and that a hypocarbic state may benefit these patients.

The effects of CPB-induced hyperoxia have been thought to exacerbate the pathophysiologic events associated with free oxygen radical formation and GME. In vivo animal studies have further confirmed that hyperoxia induces a reduction in functional capillary density caused by perturbations in leukocyte adherence to the vascular endothelium.[464] In a prospective, randomized study of 48 patients, half of whom had oxygen tensions maintained during CPB between 190 and 300 mm Hg, and half between 75 and 112 mm Hg, patient outcomes were significantly affected by the hyperoxic condition.[465] The patients in the hyperoxic group had decreased RBC rheology, increased bleeding diathesis that required greater transfusion rates, longer ventilator times, and a greater post-CPB complication rate when compared with the normoxic group. Hyperoxemia also has been shown to alter microcirculatory response during both normothermic and hypothermic CPB but was most pronounced during normothermia with increased vascular resistance and a decline in oxygen consumption.[466] A recent randomized, controlled trial involving 67 cyanotic infants found that low-to-normal oxygen tension at the onset of CPB is associated with reduced myocardial damage, reduced oxidative stress, and reduced cerebral and hepatic injury compared with hyperoxic CPB.[467]

The benefits of venous blood gas monitoring have been well accepted in cardiovascular medicine, and the information gained from such assessment has been used to guide therapeutic interventions in numerous clinical situations including critical and intensive care, internal medicine, and surgical services. Changes in both venous P_{CO_2} and P_{O_2} levels have been shown to correlate well with changes in global tissue perfusion.[468] During CPB, the importance of mixed venous oxygen saturation monitoring cannot be overemphasized. This parameter has global utility and is the one parameter universally monitored during most extracorporeal procedures. The mixed venous oxygen saturation is used to calculate whole-body oxygen consumption when, according to the Fick equation, perfusion flow and the oxygen content of arterial blood are also known. As a cautionary note, the interpretation of the mixed venous oxygen saturation must be made with a sound knowledge of any patient conditions that could overestimate or underestimate oxygen delivery and uptake, such as in the presence of anatomic or physiologic shunts, or concentrations of abnormal hemoglobin types. It is beyond the scope of this chapter to review all the currently available in-line blood gas monitors. Readers are referred elsewhere for this information (Box 32.11).[469]

The simplest device for measuring oxygen saturation of blood is an optically coupled dual-wavelength (660 and 900 nm) oximeter that reflects oxygen saturation in flowing blood (Bentley Oxysat Meter; Baxter Health Care Corporation, Irvine, CA).[470,471] The device consists of an optical transmission cell that can be placed in both the arterial and venous lines and uses light-emitting diodes and a photosensitive transistor to measure saturations. Limitations of online saturation monitoring are seen when blood flow is less than 100 mL/min, at which the accuracy greatly declines and the oximeter reads falsely high. Also, simultaneous display of arterial and venous values cannot be performed with this device.

A second type of blood gas monitor uses a microprocessor coupled via two fiberoptic cables with disposable flow-through cells and sensors that have both arterial and venous monitoring capabilities (CDI; Cardiovascular Devices Inc., 3M Health Care, Irvine, CA; see Figs. 32.31 and 32.32).[470,471] The sensors contain pads of fluorescent chemicals, which emit light in response to gas and hydrogen ion changes, with intensity of the light correlated to concentration. The microprocessor then uses predetermined algorithms to calculate bicarbonate levels and base deficit on the arterial side and S_{VO_2}. Calibration of the microsensor is achieved before each operation using tonometered gases. This process takes approximately 20 minutes but can be bypassed and a single-point calibration performed in the event of an emergency.

An alternate technology is the use of online systems for blood gas analysis (Gem Systems; Instrumentation Laboratories, Ann Arbor, MI).[472,473] These machines differ from in-line monitors in a number of ways. First, they provide discrete sampling of blood from either an arterial or a venous line. Therefore they can be used independently of the heart-lung machine and do not require blood flow through cells and sensors for operation. They also function by continuously

correcting for sensor drifts through automatic washings and calibrations. In addition to measuring P_{O_2}, P_{CO_2}, and pH, they measure ionized calcium, potassium, sodium, and hematocrit.

As with the use of any device, standards must be set to ensure that performance is accurate and reproducible, incorporating sensitivity and specificity. In the OR, these standards are usually set by blood gas analyzer machines calibrated and maintained by medical technologists or pathologists according to national regulations and guidelines. The accuracy of in-line monitors compared with standard blood gas analyzers recently has come under question.[473–475] Nevertheless, they provide important information on blood gas and acid-base trends, which are subject to rapid change during CPB.

If inadequate oxygenator gas exchange is suspected, several immediate actions should be performed in troubleshooting the problem. The first step is to check that the gas line is properly connected to the gas inlet port of the oxygenator and to ensure that there are no obstructions, kinks, or leaks in the line impeding the delivery of ventilating gas. An important preoperative check would be to ensure that the disposable 0.2-mm gas line filter is set in the proper direction and that gas passes freely through the filter. Second, the air-oxygen mixer (blender) and flowmeter should be examined to ensure that they are functioning properly. A breach in the gas delivery system may be exacerbated by the use of excessive vacuum on the anesthetic gas scavenging system.[476] The integrity of the gas delivery system may be tested by temporarily occluding the gas supply line near the oxygenator and observing the increase in the gas system pressure on a manometer or by observing a decline in the level of the gas flow meter's indicator ball. Use of a suction bulb to test the gas supply system is an alternative method.[477] Algorithms for solving poor gas exchange have been described.[478] The placement of an in-line oxygen monitor in the gas delivery line will reflect the F_{IO_2} of the ventilating gas. If a blender malfunction or gas supply leak is suspected, the problem may be mitigated by attaching a separate supply of 100% oxygen (ie, a regulated E cylinder of oxygen) directly to the oxygenator gas inlet port. This maneuver will exclude any breach in the gas delivery system, including the oxygen and air sources, the gas blender and flowmeter, and anesthetic vaporizer. If inadequate gas exchange continues, additional checks should include the following: the oxygen consumptive rate of the patient (reflecting metabolic activity), whether the oxygenator was correctly sized to the patient, and oxygenator failure (or any combination of the three). An oxygenator may fail because of deposition of clotted blood or platelets on the membrane surface that interfere with gas exchange. This disruption of the gas exchange surface is characterized by increased pressure excursion across the oxygenator. Measurement of the TMP (preoxygenator minus postoxygenator) may be used to confirm this type of malfunction. Separation from CPB and change out of the oxygenator are indicated should poor gas exchange and an increase TMP occur. Groom and associates[479] described a technique for rapid change-out of an oxygenator during CPB that may be conducted in less than 90 seconds without necessarily discontinuing CPB. Early recognition of an oxygenation problem is paramount because prolonged exposure to hypoxic conditions can cause patient injury. Practice drills aimed at detection and correction of an oxygenator failure should be periodically performed to improve detection and correction of a device failure.

Historically, S_{VO_2} or venous P_{O_2} was considered a good indicator of adequacy of tissue perfusion during CPB.[480–482] In the absence of anatomic or synthetic shunts, the relation between oxygen delivery and uptake is reflected in S_{VO_2}. A further indicator of the adequacy of perfusion is the development of acidosis caused by either a loss of blood buffers or an excess of carbon dioxide. Low S_{VO_2} values are treated by either increasing the delivery of oxygen to the tissues or decreasing oxygen demand. This is accomplished by decreasing the metabolic rate (through hypothermia or anesthesia), increasing pump flow, or increasing the hemoglobin level of the pump perfusate. Each patient must be assessed individually for the condition causing the decline in S_{VO_2}, with specific treatment administered that best corrects the deficit.[483]

Ranucci and colleagues set out to investigated the role of the lowest oxygen delivery, lowest hematocrit, and pump flow during CPB as possible risk factors for ARF and renal dysfunction. They found that the best predictor for ARF and peak postoperative SCr levels was the lowest oxygen delivery, with a critical threshold at less than 272 mL/minute/m^2.[484] A similar threshold for oxygen deliver was subsequently reported by de Somer and colleagues.[485] They also reported that nadir D_{O_2}/V_{CO_2} was also somewhat predictive of renal injury. This work is the premise for the Sorin CONNECT Perfusion EMR (Sorin Group), previously mentioned, with GDP monitoring that is capable of calculating and displaying these values in real time (see Fig. 32.12).

In addition to monitoring oxygenator function and maintaining blood gas homeostasis, the perfusionist is charged with controlling hemodynamic indices of adequate perfusion. What value of MAP provides optimal perfusion remains controversial. The majority of research on target MAP during CPB has centered on cerebral blood flow. However, distant organ and tissue function may be altered by setting standards based on single organ characteristics. Many factors influence cerebral blood flow, including autoregulation,[486] pump flow rate, and acid-base balance.[487,488] It generally is accepted that autoregulation is maintained during CPB when MAP is kept between 30 and 110 mm Hg[486,488] (see Chapter 31). This is true in patients who are neither hypertensive nor suffering from cerebrovascular disease. In both these conditions, standards have yet to be established for MAP control that would ensure adequate perfusion, although most would agree that maintenance of greater perfusion pressures is justified. In the presence of atherosclerosis, the changes in viscosity induced through hemodilution will increase flow to the microcirculation by reducing SVR. Pulsatile CPB will result in increased capillary patency when compared with nonpulsatile perfusion, even at the same MAP; this is discussed in the next section.

Pulsatile Versus Nonpulsatile Flow

When designing early extracorporeal systems, engineers and clinicians attempted to mimic the body's normal hemodynamic state. The earliest pumps, therefore, were designed to deliver a pulse waveform and were complicated devices that required specific engineering skills to operate. In the late 1950s and early 1960s, several events led to the decline of pulsatile flow as a preferred method in the conduct of perfusion. These included the complexity of pumping systems and the realization that patients tolerated periods of nonpulsatile flow without significant morbidity. The physiologic benefits of pulsatile flow are a direct function of the transmission of energy into the blood, from which it is transduced to tissue.[489] It is now realized that earlier comparisons between the two methods of CPB were fraught with methodologic insufficiencies that may have artificially negated the beneficial effects of pulsatile perfusion. The elegant studies of Taylor[490] and others[491–495] have resurrected interest in pulsatile perfusion and resulted in a heightened awareness of its potential benefits. Wright[496] summarized the relationship of the human heart and pulsatile flow in transmitting power to the microcirculatory bed to facilitate fluid movement into the tissues.

The most common operational methods used to generate a pulse wave include alternating the flow rate of the RP or CP or using an intraaortic balloon pump during CPB to generate a pulse wave form. Pulsatility is produced in a RP accelerating during the systolic phase and decelerating in diastole. The pulse wave is defined by setting the cyclic rate (pulses/minute), the cyclic width (the percentage of the time the pump operates at high speed for each cycle), and the percentage of the base flow rate (the percentage of the continuous flow rate). Pulsatile flow produced with CPs has characteristically poorer wave morphology, and there is some evidence that it is less effective.[497] Alternating occlusion systems, such as those used in VADs and artificial hearts, use intermittent occlusive-phase generators to produce a pulse wave. The physiologic benefits of pulsatile perfusion are related to the geometry of the pulse waveform. These include the rate of rise of flow

and/or pressure in the central aorta, as well as the total amplitude of the pulsation.[490,491]

Pulsatile perfusion has been classified by three general theories that attempt to establish quantitative methods of comparison.[490] The theory of energy-equivalent pressure (EEP) states that the benefits of a pulse wave are related to the energy content within the pulsation.[491] The pulsatile arterial wave dissipates energy, used to produce the pulse wave, to the tissues:

$$\text{EEP} = \int \text{P}f\text{d}\text{T} \Big/ \int f\text{d}\text{T}$$

where P = pressure (mm Hg), f = flow (mL/sec), dT = change in time. The increase in energy developed by a pulse waveform is made available to the tissue, which results in maintaining capillary patency, increasing tissue lymph flow, and stimulating cellular metabolism.[494,498] The second theory is that of *capillary critical closing pressure,* which states that peaks of pulsatile systolic pressure will ensure greater flow through the microcirculation by maintaining capillary caliber for greater periods, when compared with nonpulsatile flow. The critical closing pressure at precapillary arterioles, which obliterates tissue perfusion, occurs at higher levels with pulsatile perfusion. Finally, the theory of *neuroendocrine reflex mechanism* is based on the fact that baroreceptors respond to both static and pulsatile aspects of an arterial pressure wave. The baroreceptor mechanism of nonpulsatile perfusion causes a marked increase in discharge frequency of the carotid sinus baroreceptors, inducing reflex vasoconstriction in the systemic circulation.

The concepts of EEP and surplus hemodynamic energy (SHE) have been introduced in studies using pulsatile and nonpulsatile flow. Their main advantage lies in their focus on energy gradients rather than pressure gradients as the driving force of blood flow. These formulas can precisely quantify different levels of pulsatility and nonpulsatility, allowing direct and meaningful comparisons.[499,500]

$$\begin{aligned}\text{SHE (ergs/cm}^3) &= 1{,}332\left[\int_{t1}^{t2} fp\,dt \Big/ \int_{t1}^{t2} f\,dt\right] - 1{,}332\ \text{MP} \\ &= 1{,}332\text{EEP} - 1{,}332\text{MP} \\ &= 1{,}332(\text{EEP} - \text{MP})\end{aligned}$$

The benefits of pulsatile perfusion during CPB include increased blood flow in the microcirculation,[493] reduced fluid overloading and "third spacing,"[494] and decreased release of baroreceptor reflex hormones, which limit reflex vasoconstriction.[494] Pulsatile perfusion has been shown to increase renal, cerebral,[493] and pancreatic[492] flow. In a prospective, double-blind study, Murkin and colleagues[501] recently identified nonpulsatile perfusion as a significant risk factor for postoperative morbidity. In a review of pulsatile perfusion, Hornick and Taylor[502] have identified certain high-risk patients as being particularly susceptible to postoperative morbidity when nonpulsatile perfusion techniques are used. They identified patients as being at risk if they presented with any of the following conditions: occult coronary artery disease, significant preexisting atherosclerosis, chronic arterial hypertension, and chronic organ insufficiency. The authors advocated pulsatile perfusion as a treatment of choice.

More than 150 basic science and clinical investigations that directly compared pulsatile and nonpulsatile perfusion have been published. Although there is an extensive body of literature, there remains uncertainty about the effects of pulsatile perfusion on clinical outcomes.[503] Henze and others[504] compared patients undergoing CABG surgery and found no difference in neurologic outcome in patients treated with either pulsatile or nonpulsatile CPB. In a similar study, Azariades and associates[505] questioned the benefits of pulsatile flow on the stress-related release of cortisol and were unable to show any differences between patients treated with either pulsatile or nonpulsatile flow. Taggart and colleagues[506] studied pulsatile perfusion and its effects on limiting post-CPB endotoxemia in a prospective randomized study of 60 patients. There were no differences in endotoxin levels, complement fragments, or granulocyte elastase between nonpulsatile or pulsatile perfusion groups at any time. Ohri and others[507] evaluated pulsatile and nonpulsatile perfusion on gastric mucosal perfusion and found that pulsatility showed clinical benefit only during normothermic periods and was lost when moderate (28°C) hypothermia was used (see Chapter 31). The sample size and variation in the quality of pulse characteristics in individual studies has lead to inconclusive results.[508,509] Metaanalyses by Nam and colleagues[510] and Sievert and colleagues[511] both showed improvements in renal function. Sievert's further reported that the studies with intraaortic balloon pump (IABP) generated pulsatile flow had the best results and also noted significant reduction in lactate levels in the pulsatile groups.[511] Zangrillo and colleagues carried out a metaanalysis of preoperative use of IABP in 625 high-risk CABG patients and reported a significant reduction in 30-day mortality (risk ratio 0.38 p for effect 0.004).[512] More recently, Lim and colleagues undertook a metaanalysis to look at pulmonary function with pulsatile perfusion and found a significant improvement in pulmonary function and ICU length of stay.[513] Clearly pulsatile flow is an area ripe for future RCTs or observation studies from clinical registries. Growing evidence suggests that it improves end organ function, yet it is not commonly utilized clinically.

Methods of Extracorporeal Circulation

The techniques involved in the practice of ECC have evolved largely from the conduct of CPB during CABG surgery, valvular surgery, congenital cardiac surgery, or a combination of the three. Applications involving alternate means of ECC transcend the conduct of routine CPB and have included various specialties such as neurosurgery, vascular surgery, and general thoracic surgery. The limitations of incorporating ECC in the treatment of disorders once thought not to be amenable to this process now are being reevaluated because of advances in enhancing the biocompatibility of extracorporeal circuits and components.[514,515] This section focuses on the evaluation of new techniques, as well as the reexamination and elucidation of previously accepted practices.

Left-Heart Bypass

Total CPB is attempted in most situations in which the heart will be rendered quiescent to facilitate surgical manipulation and repair, usually involving the administration of cardioplegia. In certain situations, however, the need to arrest the heart is obviated when the surgical repair can be performed without interfering with normal circulatory flow patterns. An alternate situation also arises when the surgery is performed at some point distant from the heart, through incisions not suitable for normal cannulation sites for CPB. *Left-heart bypass* (LHB) and *right-heart bypass* (RHB) are terms used to denote the process whereby univentricular diversion of flow is performed by the creation of a parallel circuit to blood flow. Although this definition also serves as a description for a VAD, in the OR, each term has a specific distinctive meaning, and they are not used interchangeably. LHB is a technique often used in repair of descending thoracic aortic aneurysms (see Chapter 23). Without the use of LHB, cross-clamping of the descending aorta results in a tremendous increase in afterload and a decrease in CO, most likely the result of increased ventricular end-diastolic volumes and reduced ejection fractions.[516] The major purpose of LHB is to ensure adequate perfusion to the distal body, which should reduce the potential for paraplegia caused by hypotension and tissue hypoxia.[517,518] The ensuing discussion primarily focuses on LHB because of its predominant use, although RHB is performed during certain procedures in pediatric cardiac surgery, such as reoperation for right ventricle-to-pulmonary artery conduit replacement.

The term *LHB* is somewhat of a misnomer because it denotes the bypassing of *all* flow through an ECC around the left ventricle. This rarely occurs. Instead, the technique is a form of partial LHB that enables the perfusionist to vary the preload of the left ventricle, thereby controlling the volume of blood ejected into the aorta. This alteration in preload therefore directly affects the patient's hemodynamic status and is influenced by the rate at which volume is shifted from the left

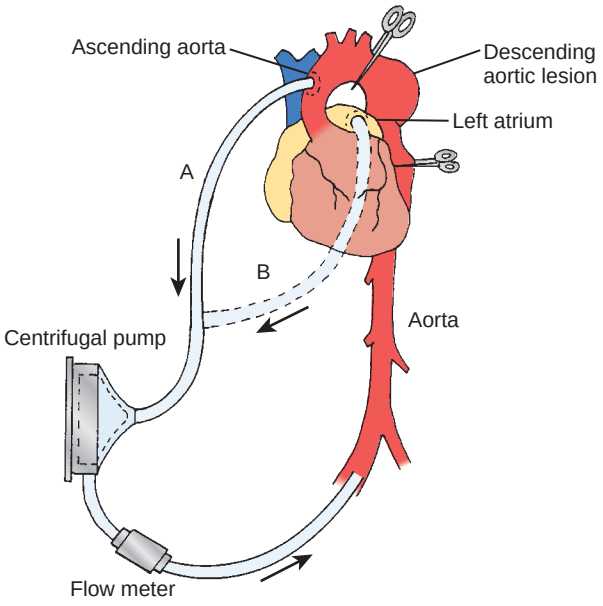


Fig. 32.41 Left-heart bypass with use of a centrifugal pump. *A* is the inflow from ascending aortic cannulation, and *B* is the inflow from left atrial cannulation.

heart. It has been reported that during LHB with seemingly adequate reduction of preload, ventricular dysfunction, as evidenced by TEE, can occur.[519] The most frequently used applications of LHB include repair of thoracic aneurysms or dissections involving the descending aorta, thoracoabdominal aneurysms,[520] and coarctation of the aorta. The bypass circuit used in LHB is an extremely different variation from that used during total CPB, and these differences must be understood by the anesthesiologist to facilitate patient management.

The most prominent difference in the conduct of partial LHB compared with total CPB is the absence of an oxygenator from the circuit. Therefore it is impossible to augment the ventilatory capacity of the patient during LHB. Fig. 32.41 shows the typical LHB circuitry with the use of a CP as the main drive unit.[517] The entire circuit usually consists of two 6- to 8-foot sections of 3/8-inch polyvinylchloride tubing, which have been attached to the inflow and outflow ports of the centrifugal head. Besides not having an oxygenator, the circuit contains neither a cardiotomy reservoir nor a venous reservoir, so that fluids cannot be added to the circuit. The cannulation sites vary, with the most frequent techniques involving drainage from the LA and return to the femoral artery. Purse-string sutures are placed in either the left atrial appendage or superior pulmonary veins for draining blood from the LA. Left atrial cannula size varies, but in most adult patients, the typical single cannula ranges from 32 Fr to 40 Fr. Alternate cannula locations for draining blood from the heart involve the ascending aorta or the left ventricular apex. Blood is returned to the patient via isolation of the femoral artery by cutdown technique, with retrograde flow into the abdominal aorta. The typical cannula sizes used for femoral artery cannulation range from 16 Fr to 22 Fr. Alternate cannulation sites for the return of blood include the descending thoracic aorta.

Management of the patient during LHB can be accomplished only by a combined effort between the anesthesiologist and perfusionist. The risk for perioperative bleeding is high because of the combined use of prosthetic graft materials and large anastomotic sites.[520] For this reason, minimal anticoagulation is used, with a low dose of systemic heparin to increase the activated coagulation time to approximately two times baseline. The use of heparin-bonded circuits in these patients may offer distinct benefits in reducing bleeding associated with systemic heparinization.[514] The regulation of volume is primarily controlled by the rate of blood removal from the LA, which is a function of pump flow. As the pump flow is increased, the rate of emptying of the LA concomitantly increases, reducing the flow into the ascending aorta, which reduced MAP. At the same time, the return of flow to the femoral artery is increased. Likewise, as the pump flow is decreased, the amount of blood ejected into the ascending aorta is increased, with a resultant increase in proximal aortic MAP. With the initiation of LHB, MAPs remain identical in the absence of significant restrictions in the descending aorta. When the upper body circulation is isolated from the lower body circulation by the placement of vascular clamps, the two circulations are separated and pulsatile flow is lost in the lower body. At the time of aortic clamping, the proximal aortic pressure increases precipitously as a result of the dramatic change in afterload. The next several minutes of LHB are usually the most difficult to control, with frequent shifts in pressure and flow most likely a function of baroreceptor response. Radial artery pulsatile pressure is maintained at around 120/80 mm Hg, whereas the femoral artery MAP is maintained between 50 and 70 mm Hg, with a flow rate of 50 mL/kg. Filling pressures, measured with a pulmonary artery catheter or left atrial catheter, usually decline by approximately 50%. Once these flow parameters have stabilized, any alteration in hemodynamics should be adjusted either by pharmacologic control or by fluid replacement. Drugs used most often to treat the initial hypertension are nitroprusside, nitroglycerin, and inhalation agents. Other commonly used drugs are phenylephrine, epinephrine, dobutamine, and dopamine.

Methods of volume replacement during repair of thoracic aortic aneurysms must be considered carefully before the start of the case because the potential for rapid blood loss is high. Rapid-infuser devices capable of large volume transfusions over short periods often are used because the LHB circuit has no capability for replacing volume. The success of LHB is directly dependent on the establishment of excellent communication among the surgeon, anesthesiologist, and perfusionist.

Cerebral Protection During Circulatory Arrest

As mentioned in the previous section, aneurysms of the descending thoracic and abdominal aorta represent a major challenge to the anesthesiologist, surgeon, and perfusionist in developing plans for patient management. Aneurysms involving the ascending and/or transverse aortic arch represent a distinctly different challenge for which the plan of ECC differs greatly. The current options for managing patients with these lesions include deep hypothermic circulatory arrest (DHCA),[521–523] retrograde cerebral perfusion (RCP),[524–526] and selective cerebral perfusion of one or more brachiocephalic vessels[527–529] (see Chapters 23, 26, and 31). The next three sections review some of the specific practices involved in managing a patient with these challenging lesions.

Deep Hypothermic Circulatory Arrest

Use of various methods of DHCA has long been standard practice in treating pediatric patients with congenital heart disease. This technique also has been efficacious in treating various other critical disease processes, including neurologic lesions and renal cell carcinoma.[530–532] More recent adaptations in ECC practices have questioned the need for DHCA in select patients[326,533] and have stressed the benefits of low-flow hypothermic perfusion in preserving neurologic function.[534]

The primary determinant in selecting an extracorporeal technique for treating various lesions is ensuring cerebral protection through the maintenance of either adequate perfusion or sustained protection. Although the morbidity associated with CPB has declined significantly over time, perturbations of the central nervous system remain a significant factor in assessing postoperative neuropsychologic dysfunction[535] (see Chapter 40). Many factors have been shown to affect cerebral blood flow during CPB, including MAP, viscosity of the perfusate, cannula placement, and/or the presence of carotid stenoses. However, in the absence of mechanical limitations, one of the most influential factors affecting cerebral blood flow is acid-base management,[536] specifically, the control of $PaCO_2$.[537,538] Concurrent use of hypothermia with CPB has been shown to be an effective treatment in reducing organ and tissue oxygen demands. However, the use of DHCA results

in metabolic deregulation and changes in membrane integrity, altering cellular maintenance.[539] Hemorrhagic complications induced by DHCA frequently are encountered, necessitating the use of prophylactic transfusion replacement therapy to correct bleeding diathesis.[540,541] Fox and colleagues[542] have shown that, when cerebral temperatures of monkeys were cooled to 20°C, the whole-brain blood flow was decreased concomitantly with the reduction in systemic flow, but the proportion of total flow to the brain was increased. Furthermore, brain oxygen extraction increased as perfusion flow declined, which was unlike other tissue beds in the body. It has been shown that even when nasopharyngeal temperatures are reduced to 15°C, severe cerebral hypoxia quickly develops once DHCA is achieved.[543]

The extracorporeal techniques of DHCA are centered around the regulation and control of circuit and patient temperatures. Core cooling of the patient is achieved through high-flow CPB with cooling temperatures never exceeding 10°C differences between the perfusate temperature (circuit) and the patient core (rectal, bladder) temperature. The perfusate temperature is maintained between 10°C and 15°C during cooling. Other temperatures that can be measured include esophageal, nasopharyngeal, tympanic, and skin temperature. Both tympanic and nasopharyngeal temperatures are remeasured to reflect brain temperatures. The depth of cooling remains controversial, with most clinicians choosing to monitor electroencephalographic activity. Once the electroencephalogram is isoelectric, usually between 15°C and 20°C nasopharyngeal temperature, the patient is cooled for another 5 to 10 minutes before initiating DHCA. Such a technique promotes further global cooling. Some authors advocate monitoring jugular venous bulb oxygen saturation and terminating perfusion only after the saturation is greater than 95%.[544] The period of safe circulatory arrest will vary from patient to patient and depends on a large number of variables, including the degree of preexisting neuropathy, the transmural cooling profile of the brain, and reperfusion-related phenomena. In general, the limit of safe circulatory arrest time in adult patients undergoing profound hypothermia is between 40 and 50 minutes.[544,545] Other authors have successfully monitored brainstem activity with somatosensory-evoked potentials for determining the optimal temperature for circulatory arrest.[546] Surface cooling of the cranium is performed by packing the head with ice at the onset of cooling and throughout the DHCA period.

Warming should be accomplished following the same principle of no greater than a 10°C temperature differential between the core and perfusate temperatures. Patients tend to warm at the same rate at which they were cooled. However, the warming rate should never exceed 1°C core temperature increase per 3 minutes of bypass time. Use of vasodilators to facilitate distal perfusion is warranted and treatment of metabolic acidosis should proceed vigorously. Termination of warming should occur when the nasopharyngeal temperature is between 35°C and 36°C. This mild hypothermia provides additional cerebral protection in the early postoperative period.

The use of barbiturates in providing added cerebral protection has not been clearly defined, and their benefits in cardiac surgery may be related to their early use at the onset of surgery.[547] Barbiturates may possibly provide protection by reducing intracranial blood volume, pressure, and edema, as well as acting as oxygen free radical scavengers.[548–550] The level at which barbiturates provided effective protection was seen at doses that abolished synaptic transmission and electrical activity,[548] which in one study was achieved with a mean thiopental dose of 39.5 mg/kg.[547] However, these patients had depressed myocardial contractility and required longer pulmonary recovery periods. It is not known whether barbiturates and hypothermia have an additive effect on cephaloplegia, but profound cerebral depressant effects are seen during CPB with thiopental doses of 8 to 24 mg/kg at 25°C to 30°C.[550]

The term *cerebroplegia* has appeared in the literature, and it reflects isolated pharmacologic manipulation of the perfusate delivered to the brain.[529,551] The authors in both studies advocated the use of either sanguineous[529] or asanguineous[551] oxygen-rich solutions to protect the brain via carotid perfusion during low-flow hypothermic CPB.

Retrograde Cerebral Perfusion

Despite the relative safety of DHCA, there is a finite time limit for nutrient decoupling before irreversible central nervous system damage occurs. In 1990, Ueda and colleagues[524] described a technique of RCP and circulatory arrest that provided perfusion of arterialized blood to the cerebral vasculature during the period of circulatory arrest. The use of RCP had been described previously as a treatment for catastrophic air embolism arising during CPB.[552] This technique provides an alternative to selective cerebral perfusion that requires cannulation of one or more of the brachiocephalic vessels and is considered technologically challenging. Although there are similarities in patient management between DHCA and RCP, the major difference has to do with the placement of a cannula into the superior vena cava (SVC) (Fig. 32.42). This can be accomplished with either bicaval cannulation or with an isolated SVC cannula and a dual-stage right atrial cannula.[553] The use of a retrograde cardioplegia cannula placed in the SVC may be desirable because it also contains an end-lumen pressure port for monitoring infusion pressure. During the period of circulatory arrest, blood flow is directed away from the systemic circulation and into the SVC retrograde into the cerebral venous system. The perfusion pressure of RCP as measured in the SVC or jugular vein should be maintained between 20 and 40 mm Hg. Flow rates for RCP range between 250 and 500 mL/min. The temperature of the cerebral perfusate usually ranges between 15°C and 18°C, and despite these cold temperatures, desaturated blood is seen returning from the arch vessels.[544]

Some of the benefits of RCP include the maintenance of cerebral temperature via the delivery of a hypothermic perfusate, a decreased risk for air and atheromatous debris from open brachiocephalic vessels, and a continuous delivery of nutrients to the cerebral tissue. Stroke rates also have been shown to be significantly reduced with the use of RCP.[525] Potential problems with RCP include increased cerebral venous resistance caused by cortical vein collapse, the presence of competent jugular valves, which restrict perfusate delivery, and questionable delivery of nutritive flow to the target tissue.[526]

Selective Cerebral Perfusion

Initial efforts to protect the brain during repair of lesions requiring circulatory arrest included the isolated cannulation of brachiocephalic vessels.[554,555] The primary mandate for ECC is the protection of the central nervous system, and selective cerebral perfusion remains attractive because it supplies a continuous source of nutritive perfusate to metabolically active brain tissue during circulatory arrest. Similar to RCP, by continuously perfusing the brain, the extracorporeal management of the patient can be modified with the lower levels of hypothermia and an extension of the period for surgical repair.[527,528]

The technique of selective cerebral perfusion involves the cannulation of one or more of the brachiocephalic vessels or axillary arteries with small (8 Fr to 14 Fr) cannulae that are connected to a separate circuit with a dedicated heat exchanger (Fig. 32.43). During this technique, the systemic ECC continues to perfuse the patient via femoral cannulation with cold (20°C to 28°C) perfusate at a rate of 60 to 70 mL/kg/min. Arterialized blood is drawn from the oxygenator through a separate pump, either roller or centrifugal, and passed through a cardioplegia heat exchanger (Fig. 32.44) that decreases the temperature to approximately 15°C. The perfusate then passes through a 40-μm filter before perfusing the brachiocephalic vessels. Flow rates to the brain are controlled between 5 and 10 mL/kg/minute, with a perfusion pressure at the circuit kept under 150 mm Hg. As with RCP, acid-base homeostasis is maintained according to alpha-stat principles. Oxygen extraction is assessed through measurement of the venous oxygen saturation returning to the SVC cannula. Because autoregulatory mechanisms in the brain have been shown to be maintained at low blood temperatures (20°C), cerebral blood flow should be adequate under these conditions.[556]

The problems associated with selective cerebral perfusion arise from the use of a secondary circuit and additional cannulation sites. The risk for embolization of atheromatous matter may be of concern because of the additional manipulation of the arch vessels, and the

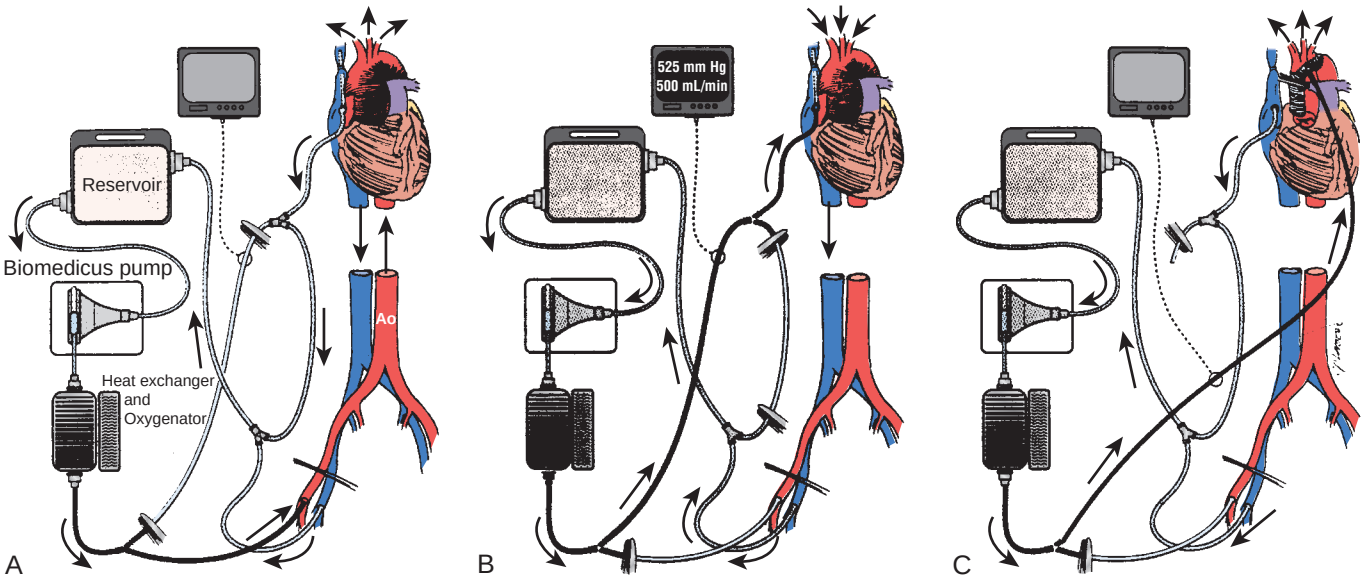


Fig. 32.42 Extracorporeal circuit design for retrograde cerebral perfusion. (A) Cooling period. Venous drainage occurs from superior vena cava and femoral vein cannulae with arterial return to the femoral artery. (B) Retrograde cerebral perfusion with circulatory arrest. Oxygenated blood flows from the arterial line into the superior vena cava, and pressure and flow are monitored. (C) Warming period. A side arm arterial cannula is placed into the transverse arch graft. *(From Safi HJ, Letsou GV, Iliopoulos DC, et al. Impact of retrograde cerebral perfusion on ascending aortic arch and arch aneurysm repair.* Ann Thorac Surg. *1997;63:1601.)*

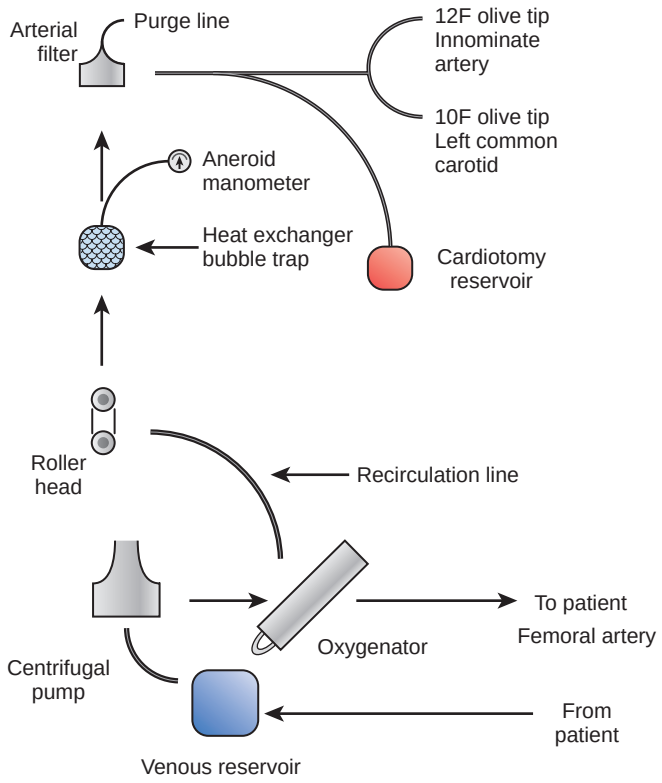


Fig. 32.43 Extracorporeal circuit design for selective cerebral perfusion. *(From Stammers AH, Butler RR, Kirsh MM. Extracorporeal circulation during treatment of aneurysms of the ascending aorta.* Proc Am Soc Extra-Corp Tech. *1990;28:72.)*

presence of additional cannulae also clutters the field.[544] When multiple cannulae are utilized connected to a single RP, the downstream flow cannot be independently determined without individual monitoring devices for each line. This is not of major concern because of the anatomic nature of the circle of Willis and distribution of cerebral blood flow. The improved safety resulting from technologic enhancements to pressure control modules and air detection systems of heart-lung machines makes these arguments moot. Monitoring of jugular bulb oxygen saturations or cerebral oxygenation with near-infrared spectroscopy provides feedback information that is used to adjust flow rates and delivery pressures so that adequate delivery of oxygen is matched with extraction rates.[528,557]

Communication and Teamwork

The American College of Cardiology (ACC) and the American Heart Association (AHA) in a scientific statement on safety in cardiac surgery reported that communication skills have been measured as the worst aspect of team behavior in the cardiac OR and that communication failures are the most common cause of errors and adverse events.[558] Teamwork failures occurred frequently during cardiac surgery (5.4 per case with familiar teams and 15.4 per case with unfamiliar teams).[559] Breakdowns in teamwork that lead to surgical flow or operative disruptions are exceedingly common, having been noted at a rate of 17.4 per hour in one cardiac surgery study[560] and at 11 per case in another.[561] The AHA Scientific Statement on Safety in Cardiac Surgery task force published a list of suggested improvements titled "Opportunities to Facilitate Translation of Current Knowledge Regarding Communication and Teamwork Into Clinical Practice" (Box 32.12).

Most human errors emanate from three specific failures: a failure of perception (things are not as they appear), a failure of assumption (the 10-mL vial in the middle drawer with a blue label is always heparin), and a failure in communication. It is always possible for an individual to fail; however, through teamwork and communication, a system can be designed that is highly reliable in which potential errors are mitigated through situational awareness and communication. Although one team member's perception may be distorted at times, another team

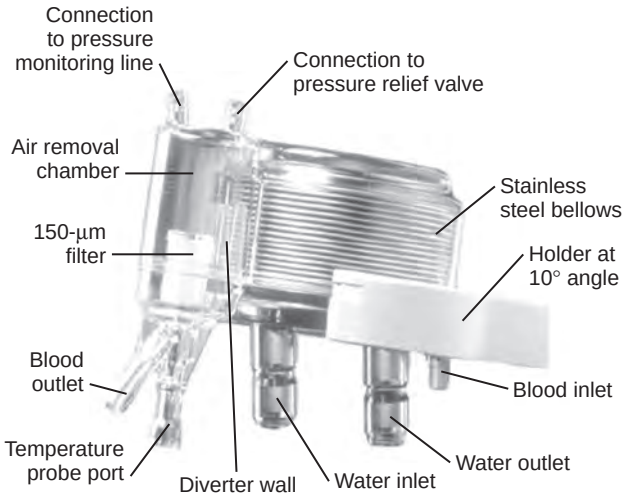
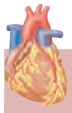


Fig. 32.44 Cardioplegia heat exchanger. *(Courtesy Medtronic Cardiovascular.)*



BOX 32.12 OPPORTUNITIES TO FACILITATE TRANSLATION OF CURRENT KNOWLEDGE REGARDING COMMUNICATION AND TEAMWORK INTO CLINICAL PRACTICE

1. Checklists and/or briefings should be implemented in every cardiac surgery case, and postoperative debriefings should be encouraged by leadership in cardiac operating rooms *(ORs; Class I; Level of Evidence B)*.
2. Team training to improve communication, leadership, and situational awareness should be implemented in cardiac ORs and should involve all members of the cardiac operative team *(Class I; Level of Evidence B)*.
3. Formal handoff protocols should be implemented during transfer of the care of cardiac surgical patients to new medical personnel *(Class I; Level of Evidence B)*.
4. It is reasonable to conduct event scenario training for significant and rare nonroutine events (ie, emergency oxygenator change out) on a regular basis that involves the complete cardiac surgery team *(Class IIa; Level of Evidence C)*.
5. It is reasonable to conduct future studies of teamwork and communication that (a) investigate optimal communication models (eg, briefings and structured communication protocols in the cardiac surgical OR); (b) investigate team-training models to determine the "best product" for use in the cardiac OR; (c) investigate impediments to implementation of formal training in teamwork and communication skills; (d) include long-term studies of the sustained impact of such training on provider outcomes (eg, attitudes regarding safety, compliance with best practices, and communication skills); (e) investigate efficacy of formal training in teamwork and communication skills in improving patient outcomes (eg, satisfaction, blood product use, infections, intensive care unit readmissions, mortality, and costs); and (f) include establishment of an anonymous national multidisciplinary event-reporting system to obtain data about events and near-misses *(Class IIa; Level of Evidence C)*.

From Wahr JA, Prager RL, Abernathy JH 3rd, et al. Patient safety in the cardiac operating room: human factors and teamwork: a scientific statement from the American Heart Association. *Circulation*. 2013;128:1139–1169.)

member may detect a problem. Clinicians are prone to assume that aspects of the working environment are reliable. In highly functional teams, the members have an expectation that there will be failure and are constantly observing and questioning. Highly functional teams utilize a shared mental model of expectations that trusts and encourages everyone in the OR to be comfortable speaking up if something of concern is observed. Communication failures are the leading cause of inadvertent patient harm. Analysis of 2455 recent sentinel events reported to the Joint Commission for Hospital Accreditation showed that the primary root cause in more than 70% was communication failure, and approximately 75% of these patients died of their injuries.[562,563] An estimated 234 million patients undergo surgical procedures and more than 1 million succumb to complications related to the surgery, many of which are related to how the surgical team interacts and communicates. Use of a simple checklist could have prevented half of these deaths each year.[564] The World Health Organization has designed a checklist that serves as a tool to enhance communication within a team. The checklist has been tested in eight cities around the world and resulted in a reduction of mortality from 1.5% to 0.8% ($P = 0.003$) and a reduction of inpatient complications from 11.0% to 7.0% ($P > 0.001$). Checklists also should be used to improve reliability of infrequent tasks or unexpected occurrences. For example, a checklist may be used to improve the reliability of completing all of the required interventions before the initiation of DHCA (head packed in ice, cooling blanket on, steroids given, acid-base balance corrected, and timer started). Checklists help clinicians perform simple tasks reliably and allow more cognitive engagement for the things that are complicated and complex.

It is important to see variation as an opportunity to improve and to diminish the likelihood of errors. The perfusion team at Boston Children's Hospital have developed a novel system to record unexpected events and bring about subsequent action to prevent a future occurrence.[565]

Communication and safety training transformed aviation into a highly reliable industry. Gladwell[566] described a pathologic type of communication that he referred to as "mitigated speech." Mitigated speech is a tendency to downplay or sugar-coat the meaning of what is being said. This occurs when an individual experiences a problem but there is a reluctance to speak up about it, when trying to be polite, when ashamed or embarrassed, or when being deferential to authority. The key to breaking this pattern of flawed communication is for leaders to understand that their number-one job is to get the best performance possible out of their team, acknowledge their own fallibility, and let those who work on the team know that they are expected to speak up about anything unusual or anything that is of concern.

More commonly, communication may be difficult because of an abrasive or difficult team member whose behavior exasperates staff. Recipients of this type of behavior can be at a loss for words to respond to this type of abuse. The danger is that communication may be avoided with difficult individuals because it is too painful and frightening to engage such an individual. Frankel[567] has described the "Five Cs," a pattern for responding to individuals who exhibit this type of abusive behavior. The scripted responses to this abuse are designed in a way that one learns to escalate until the pattern is broken. A respondent begins with 1: "I'm *Curious* about why you …" If this is not effective, then escalate to 2, "I'm *Concerned* that …" or 3, "I'm feeling *Challenged* by this problem we are having …" then 4, "We need to *Collaborate* with ____ to get another point of view …" If all else fails, then the fifth "C" is to activate the "*Chain of Command*" and involve leadership in resolving the issue.

Often leaders are not aware of how disruptive their behavior is to the team. They perceive themselves as good communicators and collaborators. Makary and colleagues[568] used a survey to examine the perceptions of collaboration among 3000 team members in the OR. The survey revealed drastic differences in how professional groups in the OR perceived the quality of collaboration of other professionals. For example, 84% of surgeons reported good collaboration with anesthesiologists; however, only 70% of anesthesiologists reported

BOX 32.13 AGENCY FOR HEALTHCARE RESEARCH AND QUALITY SURVEY ELEMENTS

- Communication openness
- Feedback and communication about error
- Frequency of events reported
- Handoffs and transitions
- Management support for patient safety
- Nonpunitive response to error
- Organizational learning–continuous improvement
- Overall perceptions of patient safety
- Staffing
- Supervisor/manager expectations and actions promoting safety
- Teamwork across units and within units

BOX 32.14 PROPOSED USES OF THE ORPHEUS SIMULATOR

- Training in perfusion crisis resource management
- Training in the use of other forms of cardiorespiratory support devices
- Proficiency checking of experienced perfusionists
- Continuing education of experienced perfusionists
- Recertification of perfusionists
- Demonstration of bypass techniques to surgeons, anesthesiologists, and intensivists
- Evaluation of new circuits and/or equipment

good collaboration with surgeons. Furthermore, 88% of surgeons thought there was good collaboration between surgeons and nurses, whereas only 48% of nurses considered surgeons good collaborators with nurses. Until recently, relationship issues have been unexplored. There is a growing interest in studying the culture in the OR. The Agency for Healthcare Research and Quality (AHRQ) has responded to requests from hospitals interested in comparing their safety culture survey results with those of other hospitals. AHRQ funded the development of a comparative database on the survey in 2006.[569] The database is composed of voluntarily submitted data from US hospitals that administered the survey. Comparative database reports were produced in 2007 and 2008 and will be produced yearly through at least 2012. Survey elements for the AHRQ survey are shown in Box 32.13.

Overall, survey respondents to the AHRQ survey reported that the level of teamwork is generally quite good. The areas surveyed that appeared to be opportunities for improvement include development of a nonpunitive response to error, handoffs and transitions, and the number of events reported. These surveys are valuable in that they identify areas where there is an opportunity to improve. The survey results can be used as a tool to help leaders to become knowledgeable about the culture within units and professional groups and lead to the development of training and exercises to improve the safety culture.

Perfusion Simulation

Catastrophic perfusion incidents require the delivery of a complex, coordinated response by the perfusionist within a very short timeframe.[570] Human factors research has shown that simulation of clinical events prepares the clinician for an unexpected event by attenuating a clinician's emotional arousal to a level that allows optimal performance.[571] Pioneering work in CPB simulation was reported by Riley and colleagues in 1977[572] and 1984,[573] who built their system on an IBM personal computer platform and predicted that these systems would mature as processing power, storage, and display technology improved. The aim of their work was to develop systems that would simulate important processes that occur during CPB and would reinforce thought processes that would be dangerous and impractical to conduct in the clinical setting. Later, Austin and colleagues[574] emulated the Air Force's flight simulation model by designing a simulation training model for cardiovascular perfusion education. Orpheus, the first commercially available system, is a computer-controlled hydraulic model of human circulation, intended for use in the training of personnel involved in the procedure of CPμ[10] (Fig. 32.45). The system can be used in a number of educational settings (Box 32.14). It may be easily configured to simulate a number of routine and nonroutine scenarios (Box 32.15). Similarly, the Califia simulator has a hydraulic interface that provides a high-fidelity responsive display to changing patient or CPB parameters. In addition to actual changes in flow rate, restriction of venous return, or other pump parameters, the test subject may make changes to oxygenator settings, request blood tests, or display other test results such as cerebral saturation or echocardiography displays (Figs. 32.46–32.48). In the educational setting, a simulator provides a standardized experience and evaluation process for students. The simulation setting allows the student to experience the cognitive challenge, stress, and physical demands in a setting far removed from an OR. Students or experienced perfusionists may be subjected to a particularly challenging clinical problem over and over again, and their response to the clinical problem can be accurately evaluated.[575] Ninomiya and colleagues have developed a simulator for adult and infant perfusion crisis management.[576] The system reports the relative percent of the time the adult's or infant's hemodynamic parameters are maintained within range. The authors believe that these systems will supplant recertification requirements based on completing an actual number of clinical cases with periodic required simulation examinations (see Chapter 17).

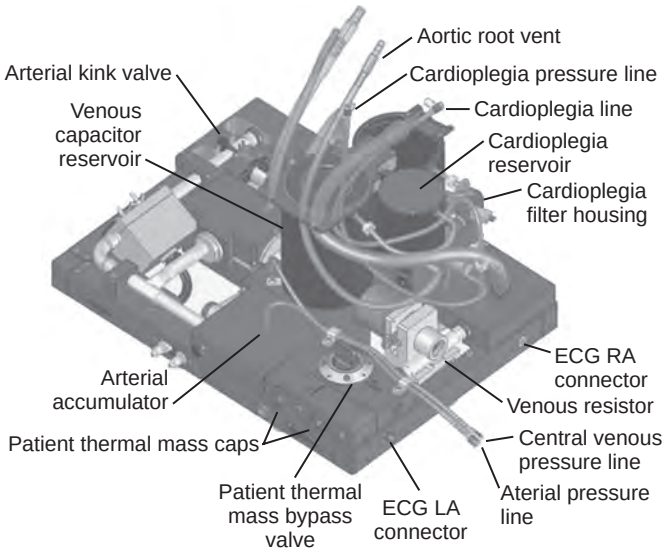


Fig. 32.45 Orpheus, the first commercially available system, is a computer-controlled hydraulic model of human circulation. *ECG,* Electrocardiograph; *LA,* left atrium; *RA,* right atrium. *(From Morris RW, Pybus DA. "Orpheus" cardiopulmonary bypass simulation system.* J Extra Corpor Technol. *2007;39:228–233.)*

Periodic performances of drills that simulate various CPB crises may be conducted in any OR setting using a mock setup and scripted scenarios. A survey of 314 perfusionists from centers in the Northeastern region of the United States in 2002 revealed that 97% of the perfusionists surveyed believed that such practice drills would be beneficial; however, only 17% reported that such drills are conducted at their centers.[577] A wide range of reasons was reported for not doing so: left up to the individuals to maintain proficiency (19 [39%]), not motivated (11 [22%]), confident of proficiency (9 [19%]), no time (8 [17%]), dubious value (1 [2%]), and cost prohibitive (1 [2%]).

BOX 32.15 ROUTINE AND NONROUTINE PERFUSION SIMULATION SCENARIOS

- Routine bypass
- Initiation of bypass
- Weaning from bypass
- Cooling and rewarming
- Use of centrifugal pumps
- Variations in patient resistance
- Variations in patient coagulability
- Patient emergencies
- Blood loss
- Left ventricular dysfunction
- Cardiac arrhythmias
- Failure of anticoagulation
- Air embolism
- Anaphylaxis
- Use of vasodilators
- Use of vasoconstrictors
- Oxygen consumption changes
- Protamine reaction
- Transfusion reaction
- Blood gas abnormalities
- Drug errors
- Equipment malfunctions
- Aortic cannula obstruction
- Aortic cannula displacement
- Venous line kinking/venous cannula obstruction
- Oxygen supply failure
- Pump power supply failure
- Heat exchanger failure
- Monitor failure
- Oxygenator failure
- Venous air entrainment
- Circuit leaks

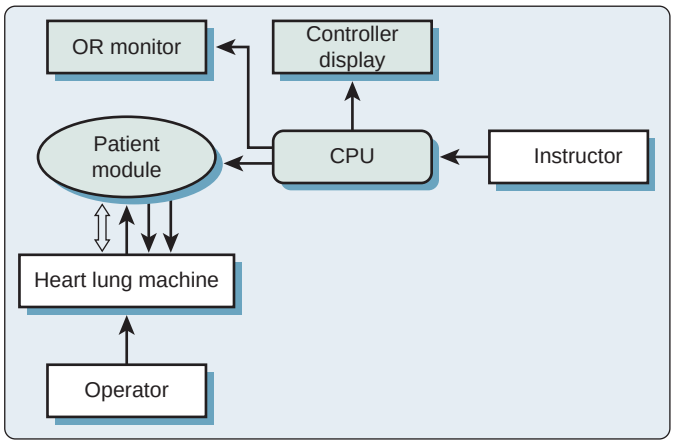


Fig. 32.46 Schema for the Califia Simulation System. *CPU*, Central processing unit; *OR*, operating room.

Figure 32.47 Califia Patient Simulator Hydraulic component. Arterial, venous, vent, and cardioplegia connections.

Fig. 32.48 Califia Simulated Patient Monitor. Display with action buttons to call for point of care test/results and with controls screens for gas blender and cooler/heater.

Summary

Substantial innovations and improvements have been made in CPB devices and techniques over the past six decades, and the use of CPB has increased from a few hundred procedures per year at a handful of centers around the world in 1955 to the current rate of more than a million procedures performed per year at a few thousand centers worldwide. Great strides have been made in conserving blood and reducing transfusions, attenuation of the systemic inflammatory response, and organ protection. Despite the many advances and widespread use of CPB, there remain substantial opportunities to improve devices, techniques, and safety. Certain techniques have demonstrated

sound evidence for efficacy—for example, miniaturized CPB systems, modified UF for adults, and pulsatile flow during CPB—but have not been adopted into clinical practice. Perfusion devices will continue to improve with the introduction of improved design and the introduction of improved gas exchange surfaces and biocompatible surface coatings. The use of computer technology, human factors, science, and simulation training will improve the operator-machine interface and the nontechnical skills of teams, further enhancing safety and improving patient outcomes.

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33

Extracorporeal Membrane Oxygenation

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KEY POINTS

1. Extracorporeal membrane oxygenation (ECMO) has had a profound resurgence as therapy for acute cardiopulmonary failure.
2. Advancements in equipment and improvements in techniques and management have led to better outcomes for patients undergoing ECMO.
3. Venoarterial (VA) ECMO should be considered for patients with acute cardiac or combined cardiac and respiratory failure.
4. Venovenous (VV) ECMO is indicated for patients with adequate cardiac function in the setting of severe acute respiratory failure refractory to standard management.
5. Cerebral hypoxia can complicate the management of patients on VA ECMO who have pulmonary failure and recovery of cardiac function.
6. Complete cardiac rest for patients on VA ECMO may require placement of ventricular drains or assist devices to prevent ventricular distention.
7. Bleeding and thrombosis remain the two most common complications associated with ECMO.
8. Careful titration of anticoagulation may require multiple laboratory modalities, including a heparin assay to guide anticoagulation management.
9. ECMO can produce changes in drug pharmacokinetics that may affect systemic concentrations of lipophilic or highly protein-bound medications.
10. ECMO is increasingly used for newer indications such as acute pulmonary hypertension and accidental hypothermia and to facilitate surgery in patients with compromised pulmonary or cardiac function.
11. Walking ECMO (ie, awake ECMO) can provide a bridge to transplantation for patients with end-stage lung disease.

The development of modern extracorporeal membrane oxygenation (ECMO), also called extracorporeal life support (ECLS), for cardiopulmonary support can be traced to the original heart-lung machine, which was designed by Gibbon and first successfully used for cardiac surgery in 1953.[1] The original cardiopulmonary bypass (CPB) machine was insufficient for prolonged extracorporeal support because it damaged cells and proteins circulating in blood due to direct exposure to gas during exchange. In the 1960s, the creation of silicon membranes to separate gas from blood during oxygen and carbon dioxide (CO_2) exchange facilitated the construction of membrane oxygenators that could be used clinically for prolonged periods with less harm to blood components.[2,3] Further advancements in technology and design of the oxygenator, pump, and circuit technology have facilitated the expansion of ECMO use (see Chapters 31 and 32).

There are two basic types of ECMO: venoarterial (VA) ECMO, which supports the heart and lungs, and venovenous (VV) ECMO, which supports the lungs only. ECMO can temporarily support cardiopulmonary function as the patient recovers or serve as a bridge to a permanent solution such as a ventricular support device or transplantation.[4] Although ECMO is challenging to manage and is associated with relatively high morbidity and mortality rates, increased experience and the durability of ECMO circuits have allowed care teams to support patients for several weeks. In this chapter, the history of ECMO, basics of the circuitry and cannulation, and care of the patient on ECMO are reviewed.

History, Evolution, and Current Status of ECMO

Interest in ECMO for respiratory support has dramatically increased in the past decade and been aided by advancements in extracorporeal technology, publication of key randomized trials, and the resurgence of viral infections causing respiratory failure (particularly the H1N1 influenza pandemic in 2009).[5] The first published report of its use for long-term support of adult patients was by Hill and associates in 1972; they used the Bramson Membrane Lung for support of patients in acute posttraumatic respiratory failure.[6] The first use of ECMO in infants was published in 1976 by Bartlett and colleagues.[7]

The early years of ECMO were marked by relatively basic circuit technology and significant complications from bleeding and anticoagulation. This was exemplified by the first randomized, prospective trial, which was published in 1979.[8] This landmark trial compared VA ECMO with conventional mechanical respiratory support of patients with acute, severe respiratory failure. It was terminated after randomization of only 90 patients because of unacceptably high mortality rates (>90%) for both groups.[8] Key problems in the trial included the choice of VA ECMO, the use of high-pressure mechanical ventilation in patients with acute respiratory distress syndrome (ARDS), and severe bleeding.[8]

After the negative study, Gattinoni and coworkers, in a series of papers in the 1980s, described the concept of extracorporeal removal of CO_2 in patients with severe respiratory failure in conjunction with low-frequency, positive-pressure ventilation that allowed the lungs to rest.[9,10] The next decade saw further growth in the United States, with Bartlett and colleagues at the University of Michigan publishing data on the use of extracorporeal support (along with standard mechanical ventilation) for patients with respiratory failure who had better outcomes.[11,12]

In the neonatal population, ECMO has become the standard of care for cardiopulmonary support, and it was recommended in 2013

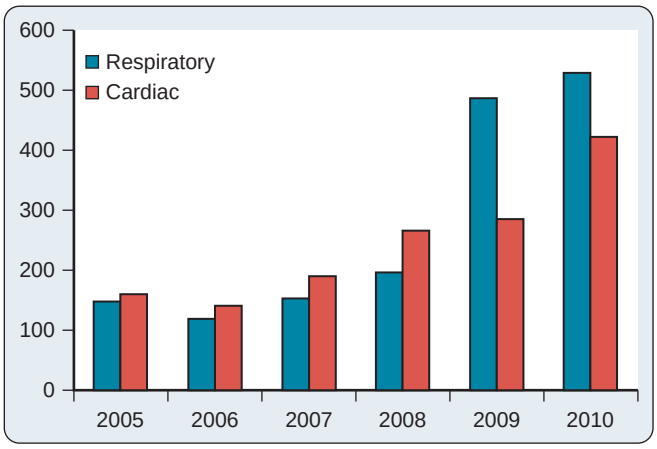


Fig. 33.1 Extracorporeal Life Support Organization (ELSO) registry data for venoarterial (VA) and venovenous (VV) extracorporeal membranous oxygenation (ECMO). VA ECMO is indicated for patients with acute cardiac or cardiopulmonary failure. VV ECMO is indicated for those with adequate cardiac function but acute respiratory failure refractory to standard management. *(Data from Extracorporeal Life Support Organization.* ECLS registry report: international summary. *July 2015. http:*www.elso.org.*)*

by the Pediatric Cardiac Intensive Care Society and the Extracorporeal Life Support Organization (ELSO) in a statement on mechanical circulatory support in children.[13] Extracorporeal circulatory support in the adult population has become common in the setting of refractory cardiogenic shock; VA ECMO is recommended by the American Heart Association to bridge patients to recovery or a ventricular assist device (VAD).[14] However, the widespread use of ECMO for adult respiratory support, particularly in the setting of the 2009 H1N1 pandemic, has been controversial in North America despite being recommended in Europe.[15]

The dramatic increase in the use of ECMO worldwide in the past 5 years (Fig. 33.1) can be attributed to two important events. The first was publication of the results of the Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial in 2009, which randomized patients with severe respiratory failure to conventional medical therapy in general hospitals or ECMO support in specialized medical centers (ie, 70 centers in the United Kingdom, 180 patients, and a 6-month monitoring period).[16] Key inclusion criteria included severe, potentially reversible respiratory failure with a Murray lung injury score of 3.0 or greater in conjunction with uncompensated hypercapnia (pH <7.2). Key exclusion criteria were prolonged high-pressure ventilation with a fraction of inspired oxygen (FIO_2) greater than 0.8 for longer than 7 days and any contraindication to ECMO. The investigators found significantly lower rates of death and disability for the ECMO group 6 months after randomization (37%, vs 53% in the mechanical ventilation group, $P = .03$), although the study was criticized for lack of standardization of lung-protective ventilation in the control group.[16]

The second event that promoted ECMO was the 2009 influenza A (H1N1) pandemic, which dramatically increased VV ECMO use worldwide as emergent salvage therapy for patients with severe viral pneumonia or ARDS unresponsive to mechanical ventilation. The first report attesting to the success of ECMO in this group came from Australia and New Zealand[17] and was quickly followed by data from Europe,[18,19] South America,[20] Canada,[21] Taiwan,[22] and Hong Kong.[23]

Gattinoni and coworkers reviewed the upsurge in ECMO use and found that more than 1000 papers on ECMO were reported on Medline between early 2009 and May 2011. Most ECMO use was related not to H1N1 but to other causes of respiratory failure and cardiac failure.[24]

The trend has continued, as demonstrated in a 2014 study that reported a significant (433%) increase in ECMO use in adults in the United States from 2006 to 2011.[25] Using data from the Nationwide Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ), and summary data sets from the ECMO registry maintained by ELSO, Sauer and colleagues calculated ECMO use rates, survival rates, and overall costs for patients 18 years or older.[25] In terms of ECMO use, there was no significant difference from 1999 to 2007, but the rate increased by 433% between 2006 and 2011, from 375 to 2004 patients.

Survival rates from 2006 to 2011 showed a trend toward improvement that was not statistically significant. Patients in 2011 were twice as likely to be categorized as critically ill as those in 2006. Analysis of the ELSO registry showed survival rates of 41%, with no significant change between 2006 and 2011. There were also no significant changes in costs incurred due to ECMO over the same period.[25]

Survival rates have dramatically improved since the original study by Zapol and colleagues[8] for both types of ECMO (Table 33.1), with respiratory ECMO survivors having a clear survival advantage over cardiac ECMO patients. Fig. 33.2 illustrates the growth in ECMO centers reported by the ELSO registry. In a 2009 metaanalysis, Cardarelli and associates[26] reported that survival rates for ECMO-treated adults after cardiac arrest increased from 30% in 1990 to 59% in 2007.

TABLE 33.1 ECMO Overall Outcomes

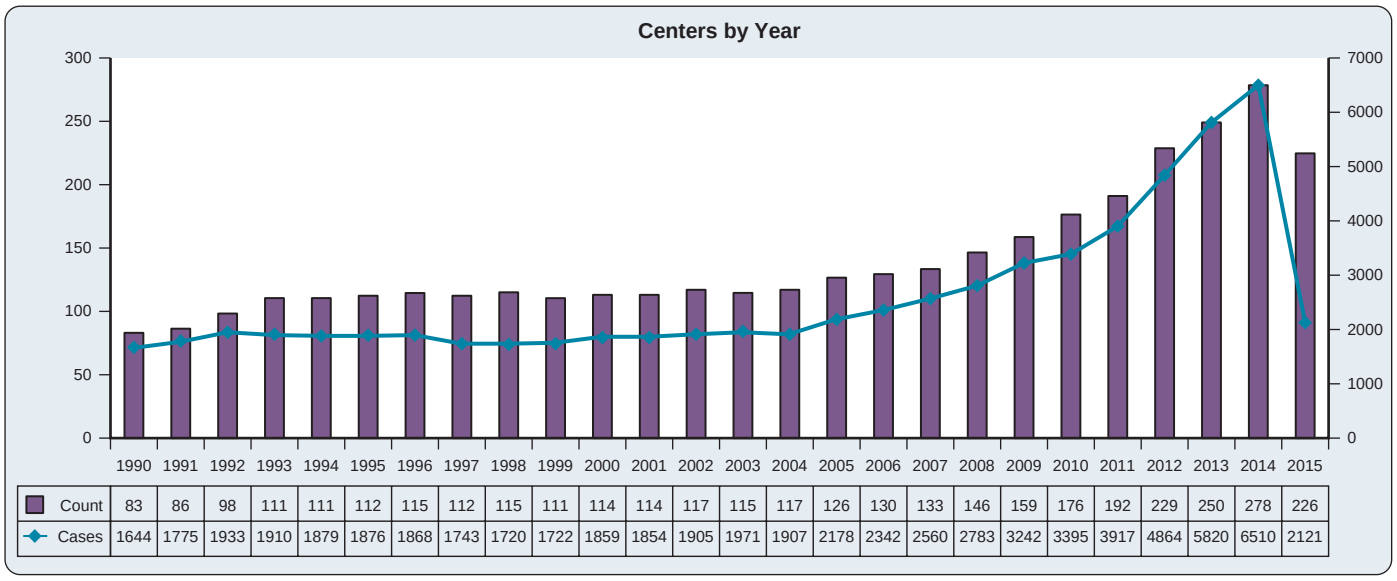
Type of Support Needed	*Total Patients* (N)	Survived ECLS		Survived to Discharge or Transfer	
		n	%	n	%
Neonatal					
Respiratory	28,271	23,791	84	20,978	74
Cardiac	6,046	3,750	62	2,497	41
ECPR	1,188	766	64	489	41
Pediatric					
Respiratory	6,929	4,579	66	3,979	57
Cardiac	7,668	5,084	66	3,878	51
ECPR	2,583	1,432	55	1,070	41
Adult					
Respiratory	7,922	5,209	66	4,576	58
Cardiac	6,522	3,661	56	2,708	42
ECPR	1,985	791	40	589	30
Total	69,114	49,063	71	40,764	59

ECLS, Extracorporeal life support; *ECPR*, extracorporeal cardiopulmonary resuscitation; *ECMO*, extracorporeal membrane oxygenation.
Modified from Extracorporeal Life Support Organization. ECLS registry report July 2015. http://www.elso.org.

ECMO Physiology and Gas Exchange

A basic ECMO circuit consists of inflow and outflow cannulas, tubing, a pump, and a membrane oxygenator with heat exchanger (Fig. 33.3). The oxygen and CO_2 levels in the blood pumped through the ECMO circuit are controlled by altering the oxygen content and the flow rate (ie, sweep) of gas through the membrane oxygenator.

The success of ECMO reflects the advancements made in oxygenator, pump, and circuit technology. The film and bubble oxygenators used in the early days of ECMO were associated with significant hemolysis, platelet destruction, systemic inflammation, and microemboli formation, but most current ECMO circuits employ hollow-fiber polymethylpentene (PMP) oxygenators (Fig. 33.4) that are designed to function as complete nonmicroporous membranes with a well-defined blood-gas interface.[27–29] They confer the significant advantages of lower resistance to blood flow and smaller priming volumes (<300 mL) in addition to lower platelet consumption, less plasma leakage, a relatively large gas exchange surface area (1.5–2 m^2), and better gas exchange at blood flow rates that can vary from 1 to 7 L/min. Modern membrane oxygenators are coated with biocompatible thrombus-resistant polymers that limit inflammation and thrombus formation.[30–34] When PMP oxygenators do fail, it is from deposition of a fibrinous network



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Count	83	86	98	111	111	112	115	112	115	111	114	114	117	115	117	126	130	133	146	159	176	192	229	250	278	226
Cases	1644	1775	1933	1910	1879	1876	1868	1743	1720	1722	1859	1854	1905	1971	1907	2178	2342	2560	2783	3242	3395	3917	4864	5820	6510	2121

Fig. 33.2 The growth in the number of extracorporeal membranous oxygenation centers. Refer to y-axis on left for *purple bars* and to y-axis on right for *blue line*. *(Data from Extracorporeal Life Support Organization.* ECLS registry report. *July 2015.* http://www.elso.org.*)*

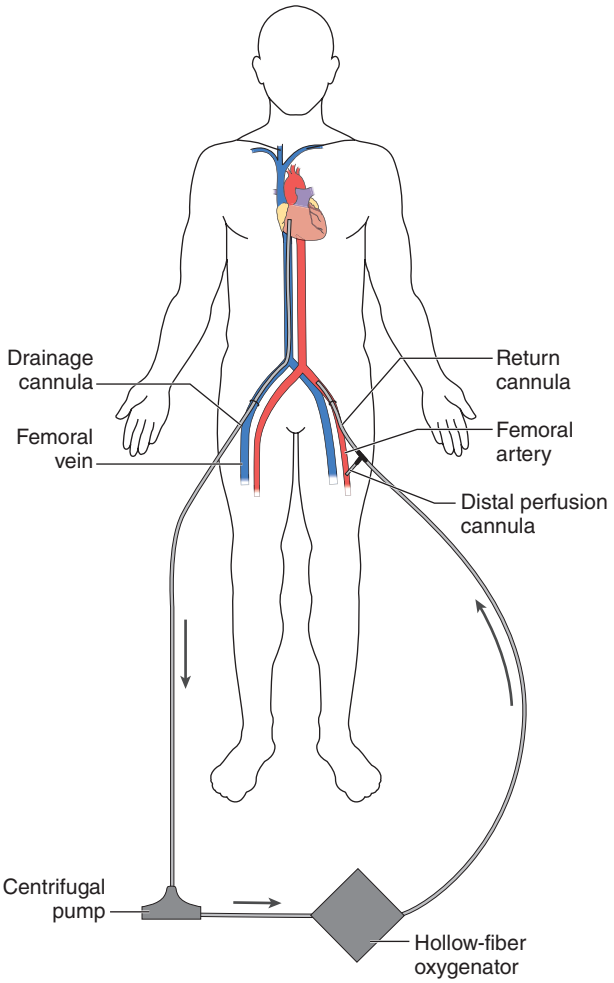


Fig. 33.3 Standard ECMO circuit. *(From Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults. Part 2: technical considerations.* J Cardiothorac Vasc Anesth. *2010;24:164–172.)*

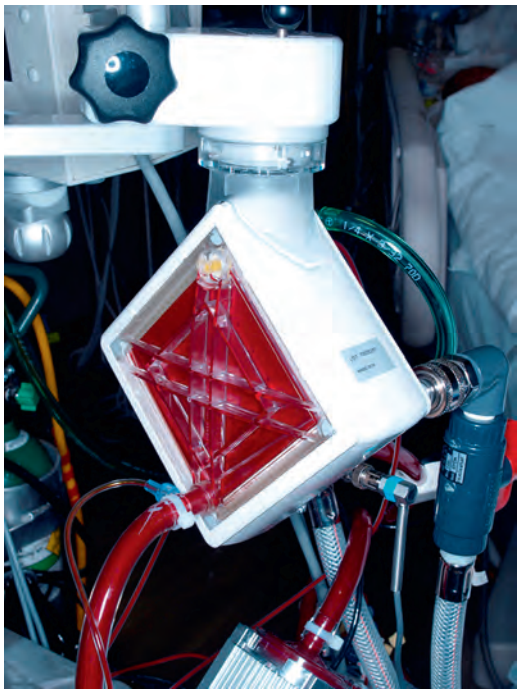


Fig. 33.4 Polymethylpentene membrane oxygenator.

of red cells and platelets on the membrane that eventually creates resistance to blood flow and gas diffusion.

The modern centrifugal pump is integral to ECMO, and it is usually preload and afterload dependent. The older generations of pumps were prone to excessive heat production, stagnation, and thrombosis.[5] In the mid-1990s, Mendler and colleauges[35] created a new generation of more efficient and safer pumps, referred to as Mendler-designed pumps, with significantly smaller priming volumes (<40 mL). The pumps do not need circuit bridges, venous reservoirs, or gravity drainage, and they can operate for longer periods than the older generation of pumps because of their unique design with a central opening in the rotor. The newer-generation pumps are impeller driven at 2000 to 5000 rpm, creating a negative upstream pressure and positive downstream pressure

Fig. 33.5 Rotaflow centrifugal pump. *(Courtesy Maquet Holding Company, Rastatt, Germany.)*

BOX 33.1 INDICATIONS FOR VENOARTERIAL ECMO

- Pulmonary embolism
- Myocardial infarction
- Myocarditis
- Postcardiotomy cardiac failure
- Heart transplantation
- Acute-on-chronic heart failure
- Cardiac arrest
- Acute respiratory distress syndrome with severe cardiac dysfunction
- Refractory ventricular arrhythmia
- Cardiac trauma
- Acute anaphylaxis
- Cardiac support for percutaneous cardiac procedures

(Fig. 33.5). Components are magnetically suspended to reduce friction, and small contact bearings are used. Hemolysis, a significant concern with ECMO, is less of an issue with the new generation of pumps (eg, CentriMag, Thoratec Corporation, Pleasanton, CA; Rotaflow, Maquet Cardiovascular, Wayne, NJ; Revolution, Sorin Cardiovascular, Milan, Italy) compared with the older-generation centrifugal pumps (eg, BioMedicus, Medtronic, Eden Prairie, MN) and roller pumps.[29,36,37]

Management of Venoarterial ECMO

ECMO for Hemodynamic Support

VA ECMO may be used to provide circulatory support or a combination of pulmonary and circulatory support.[38] The VA ECMO circuit consists of venous drainage to a centrifugal pump in series with a membrane oxygenator and return of oxygenated blood to the arterial circulation to maintain end-organ perfusion.

There are numerous acute and subacute indications for VA ECMO (Box 33.1), but most can be classified as severe cardiac insufficiency causing end-organ ischemia.[39] Practitioners determining the need for VA ECMO or VV ECMO in cases of pulmonary insufficiency must evaluate right and left ventricular function. Although no established standards exist for the minimal ventricular function that should trigger the use of VA ECMO, patients with severe ventricular dysfunction do not benefit from VV ECMO. VA ECMO may be used as a means of support during recovery of native cardiac function or in patients with little hope of cardiac recovery as a bridge to a mechanical VAD or heart transplantation.

Contraindications to VA ECMO include disseminated malignancy, advanced age, severe brain injury, and unwitnessed arrest. VA ECMO may be technically difficult to implement or manage in patients with significant aortic regurgitation, aortic dissection, or contraindications to anticoagulation.

Cannulation for Venoarterial ECMO

Cannulation for VA ECMO can be broadly divided into central and peripheral types. Central cannulation is used in patients failing to wean from CPB after cardiotomy. Access is obtained by direct cannulation of the right atrium (RA) and aorta (Fig. 33.6). The benefits of central cannulation include the ability to place large-diameter cannulas and direct insertion of a left ventricular drainage catheter (ie, vent), but cannula placement may preclude closure of the chest unless the cannula is placed through the chest wall. Central aortic cannulation eliminates the risk of limb ischemia associated with peripheral arterial cannulation.

Peripheral cannulation includes one or more venous drainage catheters and an outflow cannula inserted into the arterial system (Fig. 33.7). Any large peripheral artery may be used, but the usual method is placement of a cannula in the femoral artery with the percutaneous Seldinger technique. Leg ischemia may result from femoral artery cannulation, and a distal small cannula should be placed and connected to the outflow circuit. We typically insert a 6- or 8-Fr catheter before insertion of the proximal cannula because the proximal cannula reduces distal blood flow, making it difficult to isolate the vessel. In emergent cases, such as during cardiopulmonary resuscitation, it may be necessary to place the proximal arterial cannula before placement of the distal catheter. In this circumstance, we perform a surgical cutdown and confirm distal catheter position and flow with fluoroscopic guidance. Alternative methods for distal leg perfusion include placement of an 8-Fr cannula in the posterior tibial artery of the foot.[40] Many venous cannulation combinations can be used to gain full venous drainage. In almost all cases, at least one femoral venous catheter is advanced to the RA.

During VA ECMO, blood returns to the left ventricle (LV) through the sinus venosus, thebesian vessels, and bronchial circulation despite adequate venous cannula access. This blood must be ejected through the aortic valve or be adequately drained (vented). Without treatment, distention of the LV results in elevated left ventricular pressures, pulmonary edema, ventricular clot formation, pulmonary venous hypertension, and impeded ventricular recovery. Serial echocardiographic examinations are recommended to screen for left ventricular distention in all patients on VA ECMO. Patients with no left ventricular contractility or significant aortic insufficiency should have venting strategies implemented early.[41]

Methods to facilitate left ventricular ejection during percutaneous ECMO include use of inotropes, insertion of an Impella VAD (Abiomed, Danvers, MA),[42] and placement of an intraaortic balloon pump. Methods to vent blood from the LV include insertion of a TandemHeart percutaneous VAD (Cardiac Assist, Pittsburgh, PA) with an oxygenator,[43] balloon atrial septostomy,[44] percutaneous drainage through the pulmonary artery,[45] and surgical or percutaneous placement of venting cannulas in the left atrium and LV. No randomized, controlled trials have favored any venting strategy over another.[46] The most important consideration is the ability of the lungs to oxygenate blood. If the patient is unable to oxygenate, venting strategies that drain the blood to the ECMO circuit should be used to prevent proximal-distal syndrome.

Proximal-distal syndrome exists in patients on VA ECMO when poorly oxygenated blood is ejected from the heart. In patients with poor pulmonary oxygenation, the watershed within the aorta (ie, the point at which oxygenated blood from the ECMO circuit meets the poorly oxygenated blood ejected from the heart) may be located distal to the aortic valve, and poorly oxygenated blood may be delivered to the heart or arch vessels.[47] Strategies to treat proximal-distal syndrome include using maneuvers to improve oxygenation of blood shunting through the pulmonary circulation, increasing right heart venous drainage, placing a vent in the left heart, and placing an arterial outflow cannula in the ascending aorta or other aortic arch branch vessel.

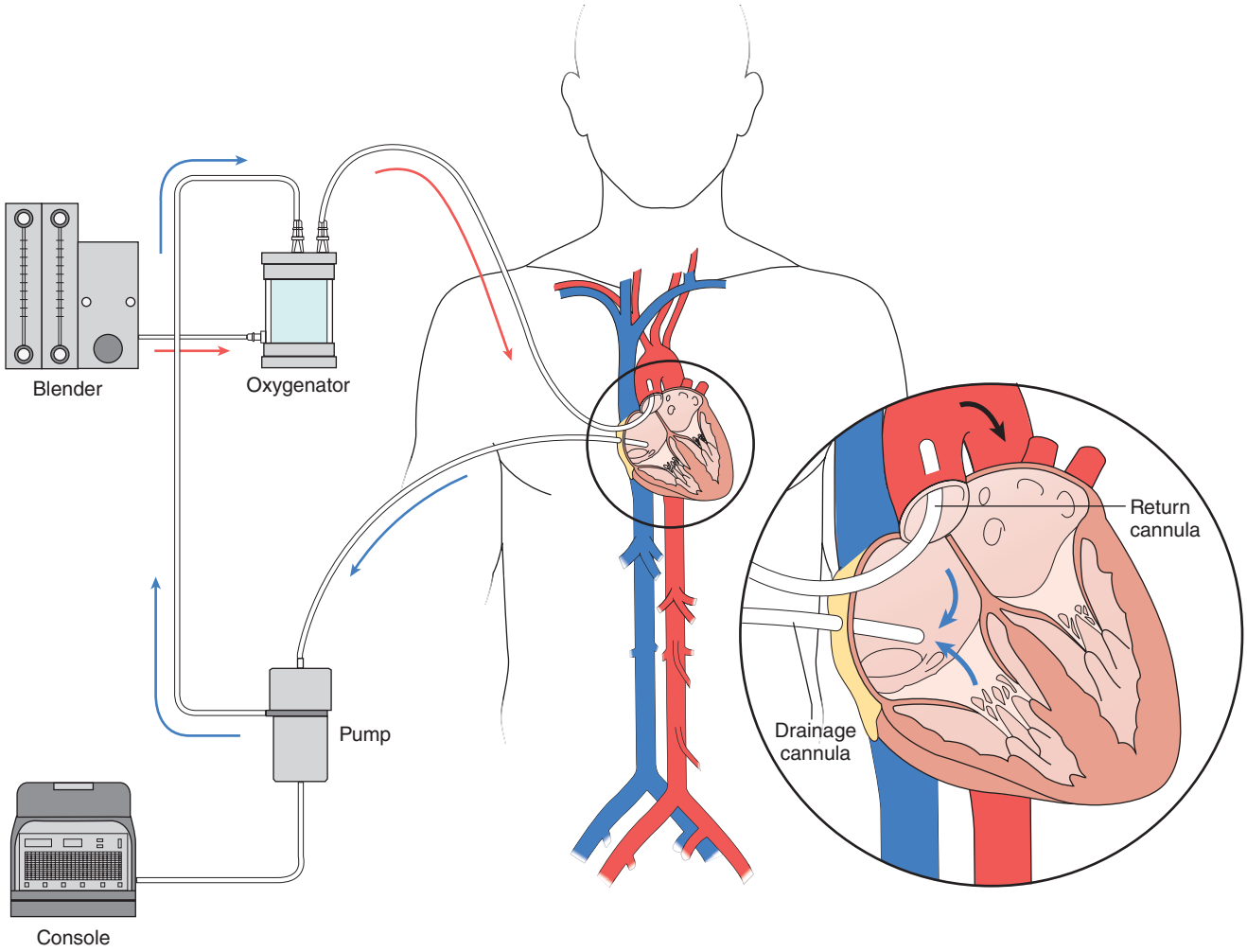


Fig. 33.6 Central venoarterial ECMO cannulation and circuit.

Initiation of Venoarterial ECMO

After cannulation, the ECMO circuit flows are increased to the target range, which should be based on clinical parameters, including arterial blood pressure, oxygen saturation of the venous return to the circuit, and measures of global ischemia such as serum lactate (Box 33.2). Initial settings should be standardized based on patient size (estimated at 50–60 mL/kg per minute).[48] Additional determinants of arterial blood pressure include arterial blood flow and arterial vascular tone.

The volume of arterial blood flow is supplied by the combination of native heart function and the ECMO circuit.[49] Patients with an adequate volume of blood flow who have persistent hypotension need vasopressors to maintain sufficient vascular resistance and preserve adequate blood pressure. In some cases, increases in pump speed may not increase flow, and drainage line "chatter" may indicate insufficient venous return volume or catheter malposition. If flows are still insufficient after cannula repositioning and augmentation of central venous volume, additional venous drainage cannulas should be placed. Sweep flows should initially be set to match arterial flow and then adjusted based on system arterial partial pressure of carbon dioxide ($PaCO_2$) and pH. Regardless of the indication for ECMO, the ventilator should be managed with lung-protective strategies.

BOX 33.2 INITIAL SETTINGS AND GOALS AFTER IMPLEMENTATION OF VENOARTERIAL ECMO

Circuit flow	≥2 L/min per 1 m^2
Sweep gas flow	Equal to blood flow
Fractional of inspired oxygen (sweep gas)	100%
Inlet pressure (centrifugal pump)	≥100 mm Hg
Oxygen saturation (outflow cannula)	100%
Oxygen saturation (inflow cannula)	>65%
Arterial oxygen saturation	>95%
Mixed venous oxygen saturation	>65%
Arterial carbon dioxide tension	35–45 mm Hg
pH	7.35–7.45
Mean arterial pressure	60–90 mm Hg
Hematocrit	30–40%
Activated partial thromboplastin time (aPTT)	1.5–2.0 times normal
Platelet count	>100,000/mm^3

Adapted from Sidebotham D, McGeorge A, McGuinness S, et al. Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults. Part 2: technical considerations. *J Cardiothorac Vasc Anesth*. 2010;24:164–172.

Weaning From Venoarterial ECMO

Daily clinical, hemodynamic, and echocardiographic evaluation of cardiac function should guide the strategy and timing of weaning

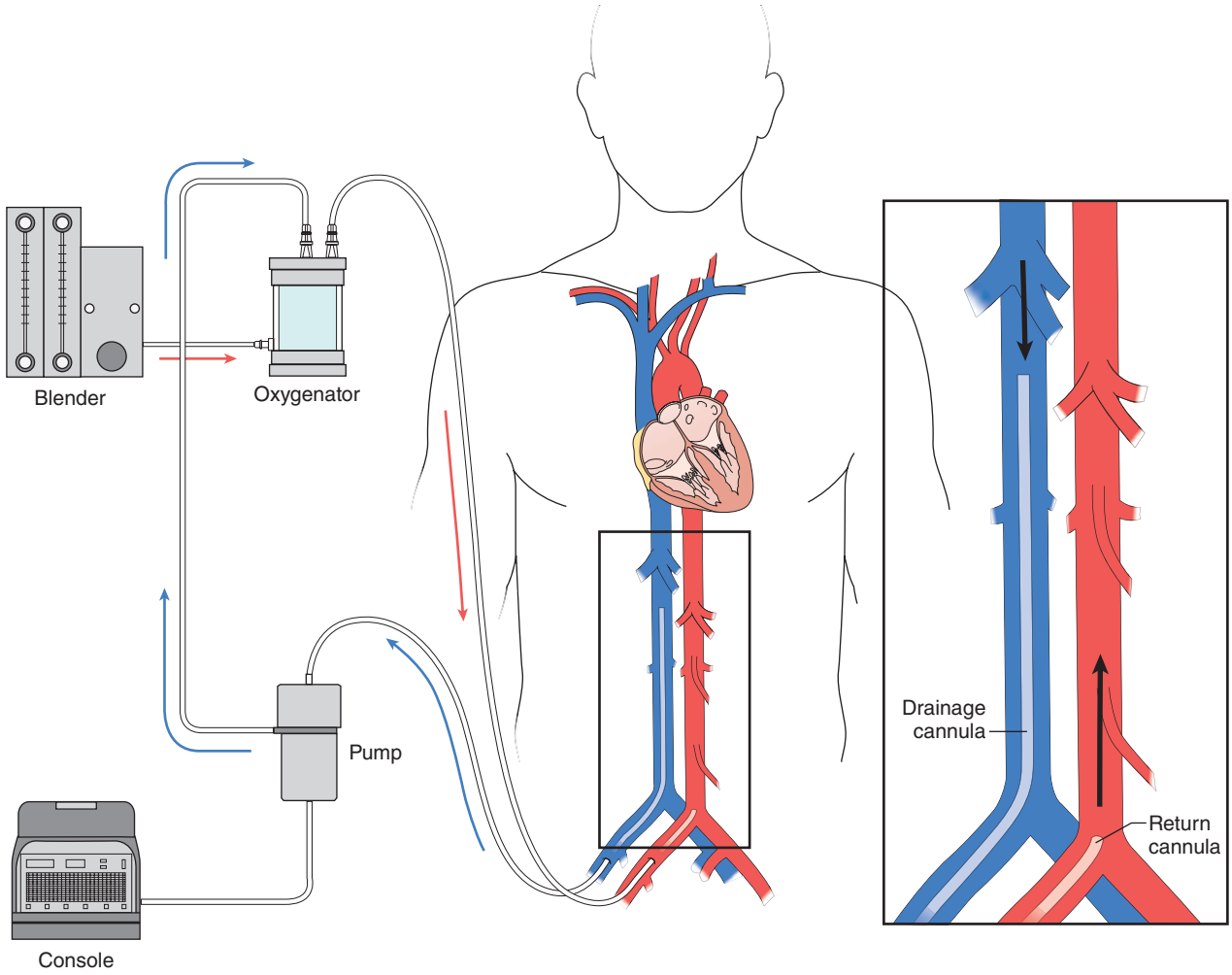


Fig. 33.7 Peripheral venoarterial ECMO standard cannulation and circuit.

from ECMO.[50] Weaning is not commenced until after cardiac rest for at least 24 to 48 hours to facilitate recovery. After successful cardiac rest and recovery, the arterial monitor should demonstrate pulsatility on low doses of an inotrope and a mean arterial pressure of at least 60 mm Hg.[51] Metabolic disturbances should be corrected, and lung function should be adequate to increase the chance of successful weaning. If cardiac function has recovered but lung function remains compromised, conversion to VV ECMO should be considered.

Pump flows are systematically decreased over a period of hours under echocardiographic and hemodynamic guidance. As circuit flows decrease in increments of 0.5 to 1 L/min, preload increases and afterload decreases, facilitating cardiac ejection. If hemodynamic parameters are met and organ and limb perfusion are satisfactory, the patient is evaluated on a 1-L/min flow for up to 1 hour before decannulation. During this low-flow period, extra heparin should be given to prevent pump thrombosis. Several parameters have been proposed and studied to predict successful ECMO weaning and decannulation,[51–53] but in our experience, serial echocardiographic assessment, a left ventricular ejection fraction of at least 20% to 25%, and a multidisciplinary approach are important to maximize successful liberation from VA EMCO support.[52,54]

Management of Venovenous ECMO

Indications for Venovenous ECMO

According to the ECLS registry (see Fig. 33.1), the most rapidly growing aspect of ECLS remains VV ECMO, spurred on by the CESAR trial results and the 2009–2010 H1N1 pandemic.[16,17] In the key data published, ECMO duration averaged 9 to 10 days, and it was initiated within the first 7 days of mechanical ventilation; mortality rates ranged from 21% to 37%.[16,17] VV ECMO is considered in patients with life-threatening but potentially reversible respiratory failure who otherwise do not have contraindications to ECLS.[55]

The Murray score played a key role in determining the need for ECMO support in the CESAR trial. The score is based on the assessed severity of respiratory failure. It uses four criteria (Table 33.2): PaO_2/FIO_2 ratio, positive end-expiratory pressure (PEEP), dynamic lung compliance, and the number of quadrants infiltrated on the chest radiograph.[29,56] In this trial, a Murray score greater than 3.0 was the

TABLE 33.2 Murray Lung Injury Score for Grading ARDS Severity

	ARDS Severity				
Parameter	*0*	*1*	*2*	*3*	*4*
Consolidation on chest radiograph (no. of quadrants)	0	1	2	3	4
PEEP (cm H_2O)	≤5	6–8	9–11	12–14	≥15
PaO_2/FIO_2	300	225–299	175–224	100–174	<100
Compliance (mL/cm H_2O)	≥80	60–79	40–59	20–39	≤19

ARDS, Acute respiratory distress syndrome; *FIO_2*, fraction of inspired oxygen; *PaO_2*, arterial partial pressure of oxygen; *PEEP*, positive end-expiratory pressure.
Modified from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988;138:720–723.

key criterion for patient enrollment in addition to uncompensated hypercapnia with a pH lower than 7.20.[57]

As described in the 2013 ELSO guidelines,[48] VV ECMO recommendations are based on the impending mortality risk. For patients with a 50% risk of death (ie, PaO_2/FIO_2 <150 on FIO_2 >90% and/or Murray score of 2–3), ECMO should be considered. When the anticipated risk of death approaches 80% (PaO_2/FIO_2 <100 on FIO_2 >90% and/or Murray score 3–4 despite optimal care for ≥6 hours), VV ECMO is indicated.

In addition to ARDS, the ELSO guidelines also recommend VV ECMO for severe air leak syndromes, for CO_2 retention in mechanically ventilated patients despite a high (>30 cm H_2O) plateau pressure (Pplat), and for miscellaneous patient conditions such as airway support in a patient listed for lung transplantation and a patient with acute respiratory failure unresponsive to optimal care.[58–60] The ongoing Extracorporeal Membrane Oxygenation for Severe Respiratory Distress Syndrome (EOLIA) trial uses a set of three criteria, and a patient must meet at least one:

1. PaO_2/FIO_2 ratio greater than 50 with an FIO_2 greater than 0.8 for more than 3 hours despite optimization of mechanical ventilation (MV) and despite possible recourse to the usual adjunctive therapies (eg, nitric oxide [NO], recruitment maneuvers, prone position, high-frequency oscillating [HFO] ventilation, almitrine infusion)
2. PaO_2/FIO_2 ratio greater than 80 with an FIO_2 greater than 0.8 for more than 6 hours despite optimization of MV and despite possible recourse to usual adjunctive therapies (eg, NO, recruitment maneuvers, prone position, HFO ventilation, almitrine infusion)
3. pH less than 7.25 for more than 6 hours (ie, respiratory rate increased to 35 breaths per minute) resulting from MV settings adjusted to keep Pplat less than 32 cm H_2O (ie, tidal volume reduction by steps of 1–4 mL/kg and then PEEP reduction to a minimum of 8 cm H_2O).

Table 33.3 summarizes the current ECLS options for respiratory failure.[46]

Contraindications for Venovenous ECMO

Aside from the inability to anticoagulate for ECMO, there are no absolute contraindications. Conditions that are recognized to have poor outcomes on ECMO according to the ELSO guidelines are considered to be relative contraindications and include high-pressure ventilation (end-expiratory plateau pressure >30 cm H_2O) for more than 7 days, high FIO_2 requirements (>0.8) for more than 7 days, nonrecoverable conditions such as major central nervous system (CNS) bleeding or trauma, malignancy, immunosuppression, and limited vascular access.[58]

Age and body mass index (BMI) as contraindications vary by center and country. Age greater than 65 years is considered a contraindication in some countries.[61] BMI does present practical limitations related to cannulation and maximal pump flows. Tulman and collaborators suggest that patients with BMIs greater than 35 may develop early hemolysis from flow-related issues resulting from elevated driveline pressures.[62]

TABLE 33.3 Available ECLS Strategies for Respiratory Failure

Strategy	*Principal Indications*
VV ECMO standard (femoral vein–femoral vein)	Default strategy for complete extracorporeal respiratory support
VV ECMO (dual-lumen cannula)	Complete or partial respiratory support predominantly Bridge to lung transplantation
VV ECMO high flow (SVC and IVC access)	Complete respiratory support for larger patients (eg, male >90 kg)
VV ECMO high flow with two oxygenators in parallel	Complete respiratory support for very large patients (eg, male >120 kg)
Femoral VV with pump (iLA Activve, Novalung, Hechingen, Germany)	Complete or partial respiratory support
Pulmonary artery–left atrium pumpless with oxygenator (iLA; Novalung)	Bridge to lung transplantation Salvage for refractory hypoxia during complete respiratory support on VV ECMO Salvage for severe pulmonary hypertension with normal left heart
Femoral arteriovenous pumpless (iLA, Novalung)	Partial respiratory support only if patient is hemodynamically very stable
VV ECCOR (Hemolung, Alung Technologies, Pittsburgh, PA)	Partial respiratory support

ECCOR, Extracorporeal carbon dioxide removal; *ECLS*, extracorporeal life support; *ECMO*, extracorporeal membrane oxygenation; *IVC*, inferior vena cava; *SVC*, superior vena cava; *VV*, venovenous.

Modified from Shekar K, Mullany DV, Thomson B, et al. Extracorporeal life support devices and strategies for management of acute cardiorespiratory failure in adult patients: a comprehensive review. *Crit Care.* 2014;18:219.

Venovenous ECMO Cannulation Strategies

VV ECMO cannula configuration should maximize flow and minimize recirculation. As Sidebotham and colleagues[63] emphasize, the former can be maximized by placement of a long, multiport (>50 cm), 23- to 29-Fr drainage cannula in the inferior vena cava (IVC) and the latter minimized by returning oxygenated blood directly to the RA and directed flow through the tricuspid valve (away from the IVC, as demonstrated in Fig. 33.8).

Standard ECMO cannula design uses wire-reinforced polyurethane (ie, resistant to kinking or collapse), and kits include guidewires (>2 m) to facilitate the Seldinger technique. Commonly used cannulas include the HLS (Maquet Cardiovascular) and Avalon Elite (Avalon Laboratories, Rancho Dominquez, CA). Cannulation is described elsewhere, but a few key principles are summarized here. There are three commonly used VV ECMO cannulation options (Fig. 33.9):

1. Femorofemoral option: Venous drainage is achieved by a femorally introduced cannula. The cannula tip is placed 5 to 10 cm below the IVC-RA junction. Return occurs through a long (>50 cm) cannula inserted into the contralateral femoral vein and advanced until its tip lies in the RA directed toward the tricuspid valve (see Fig. 33.9B).
2. Femoroatrial option: Venous drainage is achieved through a femorally inserted cannula placed 5 to 10 cm below the RA-IVC junction. Oxygenated blood is typically returned through a 20-cm long, 17- to 19-Fr cannula placed in the right internal jugular vein (RIJV) at the SVC-RA junction (see Fig. 33.9A). In a modification of this technique (ie, atriofemoral cannulation), the drainage cannula is placed in the RA through the RIJV with oxygenated blood returned though the femoral vein, and the cannula is advanced to mid-IVC. This technique produces more recirculation than femoroatrial ECMO and is not recommended.[63,64]
3. Single cannula option: Advances in cannula design led to the creation of dual-lumen, 27- and 31-Fr catheters (Avalon Elite, Bi-caval Dual Lumen Catheters, Avalon Laboratories) for exclusive RIJV placement. The cannula is advanced until the tip lies in the mid-IVC, just distal to the hepatic vein (Fig. 33.10; see Fig. 33.9C). Drainage occurs from the SVC and IVC. The return lumen opens 10 cm from the tip of the cannula and is designed to return blood back to the RA.[64] Imaging during insertion is commonly assisted by transesophageal echocardiography (TEE) and fluoroscopy. Positioning is critically important; if the distal tip or the return jets (directed toward the tricuspid valve) are not accurately placed, low flows and significant recirculation can occur. Advantages of this cannula include technical simplicity with one catheter, low rates of recirculation if appropriately positioned, easier use of prone positioning, easier aeromedical transport, and the ability to mobilize and ambulate patients with long durations of ECLS (ie, walking or awake ECMO) (discussed later). Initial experience is encouraging, but longer-term experience is needed.[65] Tulman and associates described disadvantages with this technique that include a limited range of catheter sizes, the need for expert TEE or fluoroscopic

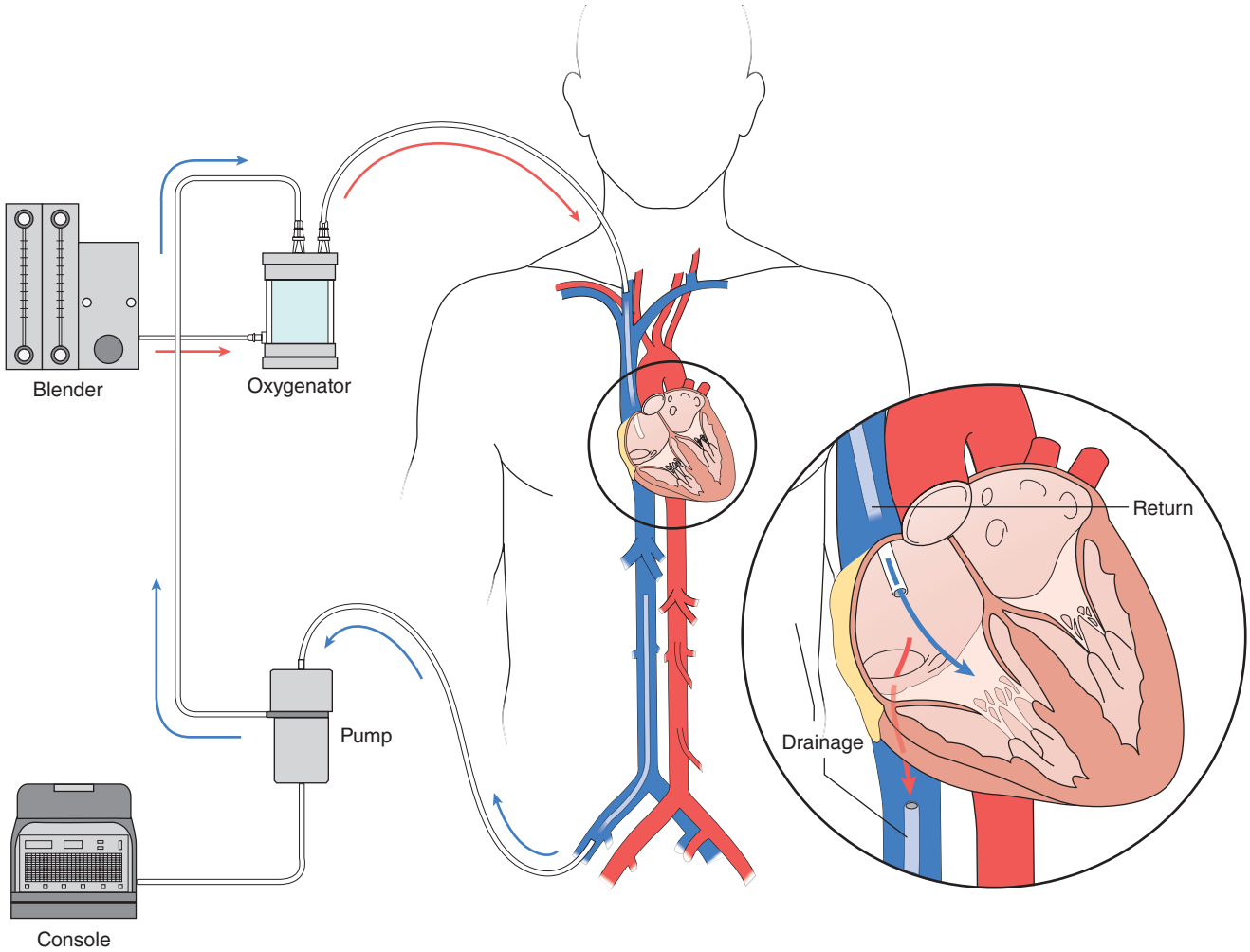


Fig. 33.8 Peripheral bicaval cannulation veno-venous ECMO standard cannulation and circuit.

guidance during insertion, relative instability of the catheter in the neck, and the potential for cerebral venous congestion with malposition.[62]

Care of Patients on Venovenous ECMO

The standard of care requires intravenous administration of 5000 U of heparin when the guidewires are in place during percutaneous insertion, and the dose should be titrated to an activated coagulation time (ACT) greater than 160 seconds. Most patients requiring ECMO are intubated, deeply sedated, and mechanically ventilated at this point, but they may require additional neuromuscular blockade and opiates. Sidebotham and coworkers[63] suggest that awake VV ECMO may be indicated in two situations: acute airway compromise needing emergent ECMO and acute cardiogenic shock needing VA ECMO because anesthesia induction may precipitate cardiac arrest. Compared with VA ECMO, VV ECMO has a lower risk of arterial injury and lower extremity ischemia.

Initial Venovenous ECMO Management

After cannulation has been performed along with heparinization, ECMO is commenced by unclamping the circuit and slowly increasing flows to the target range. For VV ECMO, key parameters used to determine pump flows are Sa_{O_2} and Sd_{O_2} (ie, oxygen saturation of blood in the VV ECMO drainage cannula).[66] The European Consensus Conference data suggest that for ideal oxygenation in VV ECMO, the pump blood flow should be 60% or greater of the calculated cardiac output (CO), with an arterial saturation goal of 88% or greater and a sweep gas rate that produces a Pa_{CO_2} between 30 and 40 mm Hg.[58] The 2013 ELSO guidelines for VV ECMO also recommended a sweep gas flow titrated to maintain Pa_{CO_2} at 40 mm Hg.[49] Unlike VA ECMO, VV ECMO does not provide added hemodynamic support. The need for pressors, inotropes, vasodilators, and volume replacement does not change.

Ventilator settings for VV ECMO can vary based on clinical pathophysiology. Current ELSO guidelines recommend rest settings, with F_{IO_2} as low as possible (<40%) and the avoidance of plateau pressures greater than 25 mm Hg.[48] Typical rest settings consist of pressure-controlled ventilation with low respiratory rates, very low tidal volumes, low F_{IO_2}, peak inspiratory pressure no higher than 25 cm H_2O, and PEEP of 10 to 15 cm H_2O.

A progressive, tapered sedation plan should be instituted for all VV ECMO patients with moderate to heavy sedation for the first 24 hours. The goal is minimal to no sedation to accompany a plan to extubate or perform tracheotomy within 3 to 5 days of VV ECMO commencement.[58] Most ECMO centers have protocols for management of temperature, blood volume, and nutrition; infection prevention; patient positioning; and management of bleeding. For VV ECMO patients with the primary goal of CO_2 removal (eg, status asthmaticus, chronic obstructive pulmonary disease [COPD] exacerbation), the goal should be a gradual reduction in blood CO_2 to avoid acid-base and neurologic complications. Recommendations from ELSO suggest an arterial P_{CO_2} reduction rate of 20 mm Hg/hour.

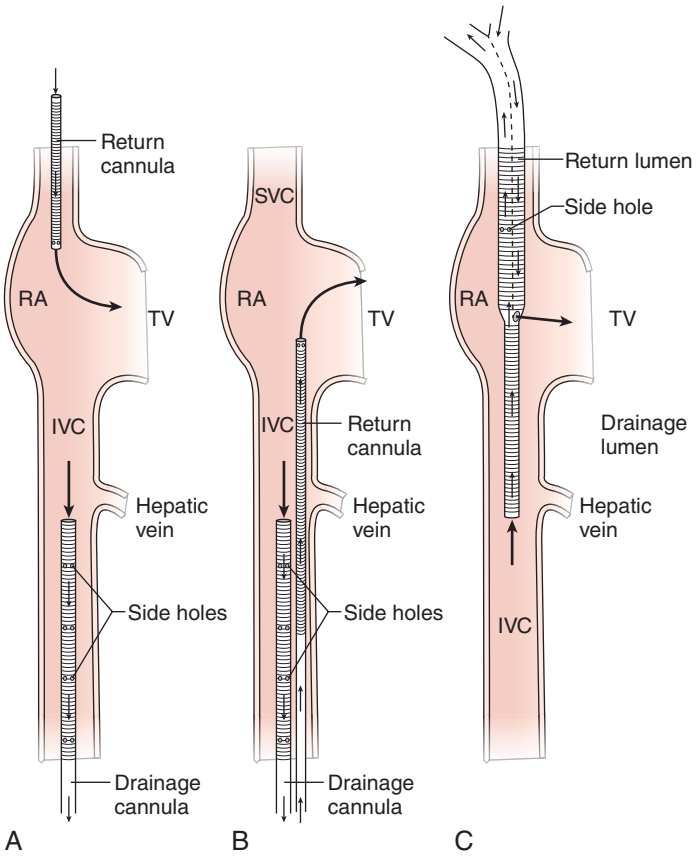


Fig. 33.9 Common venovenous ECMO cannulation options. (A) Bicaval cannulation. (B) Bilateral femoral cannulation. (C) Single dual-lumen catheter. *IVC*, Inferior vena cava; *RA*, right atrium; *SVC*, superior vena cava; *TV*, tricuspid valve.

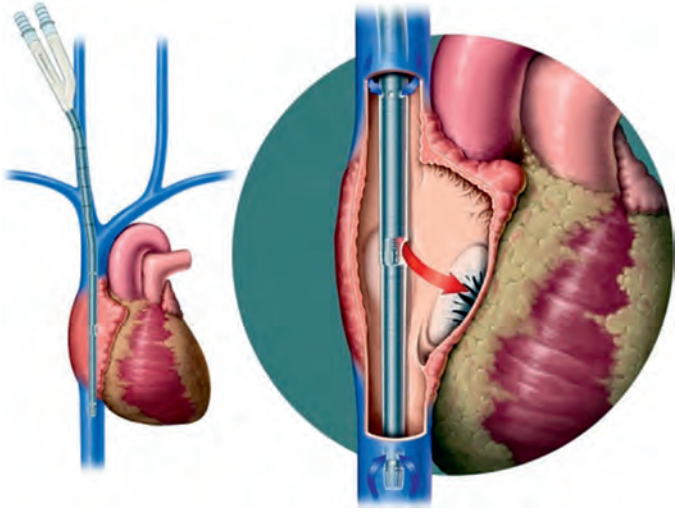


Fig. 33.10 Single-cannula, dual-lumen venovenous ECMO.

Analogous to CPB, ECMO creates significant alterations in drug pharmacokinetics that require dose adjustments, particularly in the ICU setting. With additional multisystem organ dysfunction, systemic inflammatory response, hemodilution from the circuit, and acute renal failure that is associated with critically ill patients, drug responses can be difficult to predict, and possibilities range from drug toxicity to lack of effect.[67] The increased volumes of distribution, decreased drug elimination, and sequestration of drugs in the ECMO circuit contribute to altered pharmacokinetics.

Most of the relevant data are found in the neonatal and pediatric literature.[68,69] Lipophilic agents (eg, fentanyl) and highly protein-bound drugs tend to be significantly sequestered in the ECMO circuit, whereas hydrophilic agents (eg, morphine) tend to be affected by hemodilution. Circuit priming with crystalloid-, colloid-, and blood-containing solutions contribute to the hemodilution and affect hydrophilic agents more than lipophilic agents. Other factors that are associated with critical illness (eg, pH alterations) affect drug protein binding, distribution, and elimination and alterations in the renin-angiotensin system.[70,71]

Data suggest that ECMO circuit design makes a difference in drug sequestration, with older circuits generating more drug losses.[72] Wildschut and colleagues, using neonatal and pediatric circuits, compared roller pumps with centrifugal pumps and two types of oxygenators (ie, silicone membrane and hollow fiber). They demonstrated significantly more drug losses with roller pumps equipped with membrane oxygenators compared with the newer centrifugal pumps with polypropylene hollow-fiber oxygenators.[73]

Weaning From Venovenous ECMO

Weaning from ECMO is a complex process. The question of when a VV ECMO patient should be weaned should be posed daily with each clinical assessment. For most patients, recovery can take 1 to 3 weeks. Possibilities for recovery or discontinuation due to futility should be explained to the family before ECMO institution. Patients should be carefully watched for signs of potential irreversibility, such as fluid overload refractory to aggressive diuresis and progressively worsening pulmonary hypertension (PH). Sidebotham and colaborators[63] suggested that right ventricular failure in conjunction with a mean pulmonary artery pressure that is more than two-thirds of systemic pressure usually indicates irreversibility.

The decision to discontinue VV ECMO for futility should be considered if there is no hope of organ recovery or replacement, particularly in the setting of irreversible and permanent brain, heart, lung, and other organ failure. VV ECMO patients with improving chest radiographs, improving lung compliance, reduced airway resistance, reduced extravascular lung fluid, and improving oxygen saturations (with lower circuit flows) in conjunction with reduced SvO_2 suggest a potential for weaning. According to ELSO guidelines, after the native lung is supporting 50% to 80% of gas exchange, ECMO weaning can be actively considered. In terms of improved gas exchange, most centers contemplate weaning from VV ECMO when $PaCO_2$ and PaO_2 are acceptable on moderate ventilator support (ie, FIO_2 of 50% or less, PEEP of 10 cm H_2O, peak inspired pressures of 25 to 30 cm H_2O, and ventilatory rate of 10 to 16 breaths per minute). In practice, circuit flows are dropped to 1 to 2 L/min, and the flow of sweep gas is stopped.

VV ECMO weaning durations are not established. Weaning trials can be 1 to 6 hours or longer. Key monitoring issues include hemodynamic stability (ie, standard parameters, including TEE to monitor cardiac function with or without inotropes and vasopressors), serial arterial blood gas measurements, and assessment of respiratory mechanics, particularly if the patient is on spontaneous assisted ventilation. If the patient meets all criteria, circuit flows are reduced to zero, the cannulas are clamped, and decannulation takes place.

Expanded Indications for Venovenous ECMO

The resurgence of VV ECMO can be largely attributed to its success in the management of H1N1-induced respiratory failure. The rapid advances in circuit and oxygenator technology ensure a far greater use of ECLS in the future. With smaller cannulas and more efficient, portable circuits, the opportunities to use VV ECMO for rapid CO_2 removal will continue to increase.

ECMO in Thoracic Surgery

Depending on the surgical indications, cannulation options, and patient pathophysiology, ECMO can be a versatile tool for providing complete cardiopulmonary support (ie, VA ECMO) or respiratory support alone (ie, VV ECMO). VV ECMO is preferred for adults with respiratory failure with little or no cardiac decompensation. Congenital diaphragmatic hernia is a typical, life-threatening condition that has a well-documented association with ECMO use. Data attesting to its successful use exists in the pediatric literature. Studies have shown that ECMO use in these patients, regardless of timing, improves survival compared with no ECLS.[74,75] In a 2009 outcome analysis of neonates with congenital diaphragmatic hernia treated with VV ECMO and VA ECMO, Guner and associates found both techniques comparable, but VV ECMO had the added benefit of carotid artery preservation in neonates.[76]

The use of ECMO in the trauma setting is increasing; particularly for cases of penetrating chest trauma with transfusion-associated acute lung injury and posttraumatic ARDS, for which VV ECMO has been lifesaving.[77] Mediastinal masses with the associated high risk of airway compression and collapse are well-established indications for elective or emergent VV ECMO, which can be instituted in awake and upright patients.[78] Pulmonary thromboendarterectomy, a high-risk procedure for the surgical management of recurrent pulmonary emboli, has benefitted from the use of VV ECMO and VA ECMO preoperatively and as a bridge[79] and postoperative ECLS (see Chapter 26).[80]

There is growing interest in the use of ECMO for airway surgery, particularly in situations with a high risk of airway collapse. Published case reports indicate successful use of VV ECMO with femoral cannulation for tracheal resections, bronchial repairs, tracheal papilloma resections, and tracheal injury from blunt trauma.[80–82]

VV ECMO is also used for the surgical management of severe lung infections, facilitating emergent surgery in high-risk patients. In 2010, Brenner and coworkers[83] published a successful case of thoracotomy and decortication on VV ECMO support (ie, femoral-jugular) in a critically ill young man with ventilator-associated pneumonia and a large empyema. Souilamas and colleagues reported the successful use of VV ECMO in a patient with severe bronchopulmonary aspergillosis resistant to medical treatment who had borderline pulmonary function and was not a candidate for traditional one-lung anesthesia. VV ECMO was implemented using an Avalon cannula, and uncomplicated lung resection was performed with weaning of VV ECMO support 12 hours postoperatively.[84] VV ECMO support has also been reported in the repair of large bronchopleural fistulas. Video-assisted thoracoscopic repair was performed in a postpneumonectomy patient who was not a candidate for one-lung ventilation.[85]

Because of the increasing use of ECMO, its utility for thoracic surgical procedures and associated outcomes are being reported. All procedures for ECMO patients are high risk, largely because of the possibility of coagulopathy and bleeding. Joshi and associates from the United Kingdom published the largest retrospective series, which reviewed 569 ECMO patients over a 16-year period.[86] They found that the most common primary thoracic operation was hemothorax evacuation, which was performed in 63% of patients. The most common thoracotomy indication for ECMO patients was bleeding after chest drain insertion (58%), followed by uncontrolled air leak (47%) and pleural effusion (21%). Although the overall rate of thoracotomy among ECMO patients was 3.2%, the in-hospital mortality rate was significant at 39%. The investigators concluded that experienced thoracic surgical expertise was needed in all ECMO centers.[86]

Venovenous ECMO in Accidental Hypothermia

ECMO is becoming an increasingly attractive option for rapid rewarming of patients with profound accidental hypothermia. VA ECMO is the gold standard for rapid treatment,[87] and it has improved survival rates.[88] Compared with conventional CPB, ECMO has certain key advantages. A relatively shorter setup time with the smaller portable circuits allows use outside the operating room and interhospital transport. Lower levels of systemic anticoagulation and percutaneous Seldinger-guided access contribute to its relatively greater use recently.

Although the primary technique used is VA ECMO with femoral-femoral cannulation, VV ECMO has been used in selective cases.[89] VV ECMO can also be used instead of VA ECMO for upper body hypoxemia that occurs in patients on prolonged VA ECMO. When myocardial function recovers faster than pulmonary function, the recovering heart ejects poorly oxygenated blood into the ascending aorta and proximal branches, whereas the more distal aorta is perfused by well-oxygenated blood from the VA ECMO circuit. This is best monitored by an arterial catheter and pulse oximeter in the right upper extremity to detect proximal arterial desaturation. A prompt switch to VV ECMO usually is indicated in this situation [90]

Venovenous ECMO in Pulmonary Hypertension

VA ECMO is typically used in hemodynamically unstable patients with severe PH and acute heart failure, and it has been used as a bridge to lung, heart, and heart-lung transplantation.[91–93] VV ECMO has been used successfully in the setting of acute right ventricular failure after pulmonary embolism and thromboendarterectomy[79,94] as a bridge and for postoperative support until recovery (see Chapter 26). In a 2011 study of patients with chronic thromboembolic PH that was surgically managed, Mayer and coworkers found an overall incidence of ECMO use of 3.1%, a 16.7% incidence of persistent PH after treatment, and a 9.6% incidence of reperfusion pulmonary edema.[95]

VV ECMO also has been used in acute PH crises to help unload the right ventricle. In situations with significant left-to-right intracardiac shunting, VV ECMO has been successfully used to manage acute right ventricular failure.[96] VV ECMO and atrial septostomy have been used to treat acute right ventricular failure and severe pulmonary venoocclusive disease.[97,98]

Using VV ECMO to treat acute lung failure (ie, acutely impaired gas exchange, with hypoxemia, hypercapnia, and respiratory acidosis) of any cause is becoming increasingly popular. Tsushima and colleagues suggested that the annual incidence of acute lung failure was approximately 190,000 cases per year in the United States alone.[99] The use of ECMO in these patients has dramatically increased because of advances in circuit technology (eg, portable ECMO system [Cardiohelp]) and improved interhospital transport, including the ability to safely transport critically ill patients by air.[100,101]

VV ECMO for acute lung failure has been widely used in Europe, as described by Schmid and associates for a large series of patients in Germany.[102] Over a 3-year period, 176 patients with acute lung failure refractory to conventional management were supported with VV ECMO. All patients underwent peripheral cannulation, predominantly femoral-jugular, and the Cardiohelp system was used for 20. For 59 patients, ECMO was placed at another hospital. The mean duration of VV ECMO support was 12.0 ± 9.0 days (range, 1–67 days), and 7% were extubated while on ECMO. The overall survival rate was 56%, with 33% of patients dying during mechanical support and 11% dying after weaning.

Trauma patients had the best outcomes. Sepsis and multiorgan failure were the leading causes of death. Outcomes were also better for patients who had VV ECMO placed in another facility, which was attributed to their relatively younger age and earlier ECMO support (mean, 4 vs 7 days). There was no correlation between BMI, sex, duration of mechanical ventilation before ECMO, and severity of lung injury as demonstrated by gas exchange indices (eg, hypoxia, hypercapnia) between survivors and nonsurvivors. Risk factors that did affect survival included renal failure, advanced age, and multiple organ failure. In their series, the worst outcomes were seen for patients with H1N1 pneumonia.[102]

Venovenous ECMO as a Bridge to Lung Transplantation

Lung transplantation is still the gold standard for selected end-stage lung failure patients (see Chapter 25). The past decade has witnessed a dramatic increase in the number of lung transplantations and a significant improvement in 1-year survival rates, increasing from 75% to more than 80%.[103] Although the lung allocation score, which replaced the accrued time method of lung donor distribution, has reduced the overall mortality rates of wait-listed patients for lung transplantation,[104] certain subsets of critically ill patients, such as those with resistant PH and idiopathic pulmonary fibrosis with secondary PH, have not obtained the same wait list survival benefit as others and remain at high risk for decompensation because they are not candidates for prolonged mechanical ventilation.[104,105]

Mortality rates for patients on mechanical ventilation awaiting lung transplantation remain high. Stern and coworkers reported a 90% mortality rate for patients with idiopathic pulmonary fibrosis on mechanical ventilation.[106] Prolonged mechanical ventilation can be detrimental for patients with severe emphysema needing lung transplantation; high airway pressures can lead to pneumothorax and predispose to significant air leaks. Ventilator-induced lung injury can worsen PH and predispose to ventilator-associated pneumonia, which can be fatal for subsets of patients with cystic fibrosis.[107] The use of VV ECMO in these patients remains a controversial topic due to the cost-benefit analysis.

Some recent case series have reported encouraging short- and medium-term survival rates for the bridge-to-lung transplantation group. Lang and associates[108] reviewed their single-institution data on the use of VV ECMO used as a bridge to lung transplantation for 38 patients between 1988 and 2011. In this group, 34 patients eventually underwent lung transplantation, and 4 patients died on ECMO awaiting transplantation. The 1-, 3-, and 5-year survival rates were not significantly worse than for other lung transplant recipients undergoing elective transplantation without ECMO bridging.[108]

In a retrospective review of lung transplantation candidates receiving awake ECMO support as a bridge to transplantation, Fuehner and collaborators[109] described slightly different outcomes from those found in other studies. Outcomes were compared for 26 ECMO patients and 34 controls who received conventional mechanical ventilation. The overall survival rates at 6 months after transplantation was 50% for the conventional-ventilation group and 80% for the VV ECMO group.[109]

The issue of the survival of mechanically ventilated patients who require lung transplantation also has been studied by Mason and colleagues.[110] Focusing on a group of 15,934 patients who underwent lung transplantation between 1987 and 2008, they identified 586 patients who were receiving mechanical ventilation at the time of lung transplantation and 51 who were on ECMO. The 1-year survival rate was 50% for ECMO patients, 62% for those on ventilator support, and 79% for those not requiring either. Bermudez and coworkers[111] from the University of Pittsburgh reported a 16% mortality rate for 17 VV ECMO patients who underwent transplantation.

As more centers begin to use earlier and awake ECMO strategies, more experience is needed with bridging critically ill patients because long-term data is lacking. The choice between VV ECMO and VA ECMO as a bridge is largely based on whether patients have associated hemodynamic instability or severe PH. Both factors are likely to mandate the use of VA ECMO. Multiorgan failure, sepsis, significant nutritional debility, uncontrolled bleeding, and uncontrolled infection are usually considered contraindications to VV ECMO as a bridge to transplantation.

Awake ECMO

The concept of using ECMO earlier and as a substitute for mechanical ventilation has developed significant momentum in the past decade. It has been spurred by improvements in circuit technology and development of less invasive, more user-friendly ECMO.[5,112] As Iotti and associates[112] suggest, the term *awake ECMO* indicates the use of ECMO without mechanical ventilation.

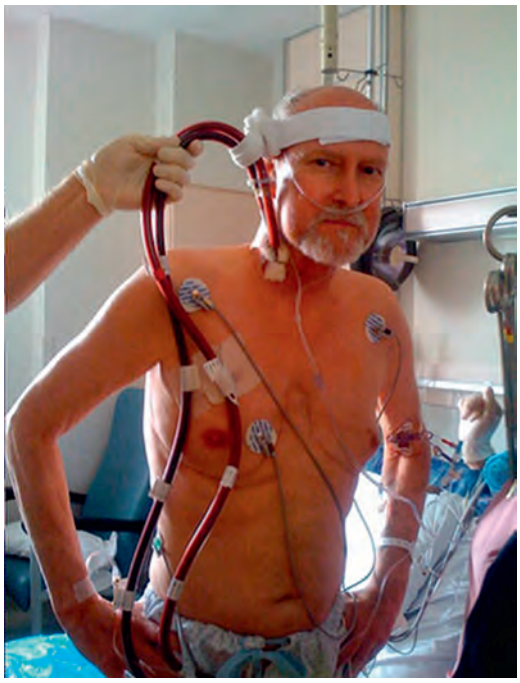


Fig. 33.11 Awake or walking ECMO.

For the lung transplantation population, awake ECMO has the advantage of avoiding the sequelae that accompany prolonged intubation and mechanical ventilation, such as muscle deconditioning and hospital acquired or ventilator associated infections.[113] It allows the patient to ambulate and exercise under supervision, which aids pretransplantation rehabilitation (Fig. 33.11).[114] As Iotti and associates suggest,[112] awake ECMO can be used early as a planned alternative to mechanical ventilation in patients such as those with cystic fibrosis or idiopathic pulmonary fibrosis, for whom the associated risks may be unacceptable, or used in patients with established or resolving respiratory failure as a means to weaning from mechanical ventilation. Most publications on awake ECMO describe lung transplantation patients[109,115,116] patients with life-threatening COPD exacerbations,[117] and as a bridge to recovery for patients with acute lung failure.[118]

VV ECMO is considered the ideal technique for nonintubated patients. It can remove CO_2 and significantly rescue the work of breathing and oxygen consumption.[119] Various cannulation options using local or general anesthesia have been described. Garcia and colleagues[120] described use of the jugular, bicaval, double-lumen, 23-Fr Avalon Elite cannula. They obtained an oxygen transfer rate of 100 mL/min at a flow of 2.5 L/min in a spontaneously breathing adult.[120]

The interventional lung assist (iLA) membrane ventilator is marketed by Novalung (Hechingen, Germany). This pumpless arteriovenous bypass approach has been used in awake patients primarily for CO_2 removal but also as a bridge to lung transplantation.[121] The low-gradient device is designed for femoral access and return and allows complete CO_2 removal in hemodynamically stable patients. Its use has been described in patients with severe asthma,[122] ARDS from H1N1 infection,[123] and a bridge to lung transplantation.[124]

For patients with severe PH, a modification of the cannulation approach (ie, pulmonary artery–left atrial approach) for ECMO has been used as a bridge to lung transplantation.[125,126] CO_2 removal of 200 to 250 mL/min has been described, but its oxygenation capacity is minimal, defining its use primarily as a means to treat severe hypercapnia, not hypoxemia.[127,128] Awake VA ECMO has also been suggested, particularly in the setting of severe PH and right ventricular failure.

BOX 33.3 VENOVENOUS ECMO COMPLICATIONS

Oxygenator failure	10.2%
Cannula site bleeding	13.9%
Gastrointestinal hemorrhage	6.0%
Hemolysis	5.6%
Disseminated intravascular coagulation	3.1%
CNS infarct	2.0%
CNS hemorrhage	3.8%
Pulmonary hemorrhage	6.5%
Renal failure requiring dialysis	10.4%

CNS, Central nervous system.
Data from the Extracorporeal Life Support Organization. *ECLS registry report: international summary*. http://www.elso.org.

TABLE 33.4 Factors Affecting Anticoagulation Levels Needed to Prevent Thrombosis

Factor	*Effect*
Circuit flow rate	Lower flow rates should trigger higher levels of anticoagulation.
Platelet count	Platelet counts less than 100 may increase the risk for bleeding.
Bleeding	Active hemorrhage may require anticoagulation discontinuation.
Hypothermia	Reduced platelet function may increase the risk of bleeding.
Antiplatelet agents	Reduced platelet function may increase the risk of bleeding.
Thrombophilic conditions (eg, cancer)	May increase the levels of anticoagulation required
Heparin-induced thrombocytopenia	Require novel anticoagulants and increased risk of pump thrombosis

Mojoli and associates[129] described a small series of 16 patients in whom VA ECMO was used for primary cardiogenic shock as a bridge to recovery or to transplantation. For these patients, 29% of 3514 hours on VA ECMO were awake hours, and 4 of 16 patients were never intubated. Larger studies are needed, but experienced centers have demonstrated that awake ECMO is feasible and may reduce mortality rates for selected patients.

Ventilatory support on awake ECMO can range from simple nasal cannula oxygen to noninvasive ventilation. High-volume awake ECMO centers support the use of helmet continuous positive airway pressure (CPAP) with active humidification, which has better flow characteristics compared with mask CPAP, and it is better tolerated by awake and ambulating patients.[130]

Complications of Venovenous ECMO

ECMO is used to treat critically ill neonates, infants, and adults worldwide, with a trend toward earlier use in high-risk patients. Despite the high-risk population, overall outcomes suggest that almost 50% of patients who have received ECMO survive to discharge from the hospital.[12] Improvements in pump circuitry allow longer periods of extracorporeal circulatory support.

Complications from ECMO can be devastating, and troubleshooting circuit issues can be challenging in an unstable patient.[131] ECMO complications can arise from the circuit or be patient related (Box 33.3). Complications are discussed further in the following sections.

Anticoagulation for ECMO

Contact of the blood with the nonendothelial surfaces of the ECMO circuit activates the coagulation cascade to form clots within the circuit. The clots can disrupt the function of the membrane oxygenator, inhibit pump function, and embolize to vital organs.

Maintenance of an ECMO circuit for a prolonged period may require anticoagulants to prevent thrombosis.[132] Heparin infusion is the most commonly used anticoagulant in patients without a contraindication. Clinicians can use heparin-bonded circuits to reduce the risk of thrombus formation and lower the level of anticoagulation needed in the immediate period after circuit implementation. In addition to reducing the risk of thrombus formation, heparin-bonded circuits reduce inflammation by decreasing complement and granulocyte activation.[12,133] Newer PMP membrane oxygenators have biocompatible coatings that can reduce inflammation and thrombus formation. Patients with heparin-induced thrombocytopenia should avoid contact with heparin-bonded circuits, and the circuit should be changed to a non–heparin-bonded circuit. Direct thrombin inhibitors may be used to systemically anticoagulate patients on ECMO, but they are second-line therapy due to the difficulty in controlling bleeding.[134]

The level of anticoagulation required to prevent thrombosis depends on many factors (Table 33.4). Bleeding remains one of the most common complications associated with ECMO, which must be factored into the anticoagulation level maintained. Bleeding complications for ECMO patients include cannula site bleeding, gastrointestinal hemorrhage, surgical site bleeding, cardiac tamponade, pulmonary hemorrhage, and CNS bleeds.[131] Antithrombogenic coating has become standard in ECMO circuits. It allows patients to be maintained on low levels of anticoagulation for prolonged periods.[135] ECMO circuits tend to cause thrombocytopenia because of a combination of dilution and platelet damage.

The ACT is a simple, rapidly performed test that has been the traditional monitor for anticoagulant levels in ECMO patients (see Chapter 19).[134] In patients on high-dose heparin, the ACT is used because the activated partial thromboplastin time (aPTT) is not useful. To measure the ACT, whole blood is mixed with an activator (ie, celite or kaolin) to provide a functional test for anticoagulation. The test result is reported as the duration in seconds, with longer times reflecting higher degrees of anticoagulation. Factors that affect the ACT include coagulation factor deficiencies, hypothermia, and platelet count and function. The ACT correlates poorly with pediatric and adult heparin levels, whereas aPTT levels correlate more closely with heparin levels and are considered more desirable.

Occasionally, bleeding or thrombosis occurs that does not correlate with the level of anticoagulation measured by the ACT or aPTT. For these patients, an anti-Xa level can be used to measure heparin activity.[136] An anti-Xa level of 03 to 0.7 U/mL is considered appropriate for patients on ECMO.[137] If the heparin dose required is exceedingly high, the antithrombin III level may be below 50%, and administering plasma or recombinant antithrombin III should be considered.[134]

Complications in ECMO

Circuit-Related Complications

Circuit thrombi and blood clots can form from blood and tubing interactions. Thrombi can occur anywhere in the circuit and have devastating consequences. Constant vigilance with an appropriate plan for anticoagulation, especially in longer ECMO runs, is warranted. In the case of flow abnormalities, pump head thrombosis must be ruled out, and it can be suggested by a sudden change in the sound from the pump, hemolysis, or thrombocytopenia.[138] Evidence suggests that the most common equipment-related complication for ECMO patients is clot formation.[139,140] Immediate system exchange is warranted in these situations.

A retrospective review by Lubnow and colleagues[140] studied technical complications during VV ECMO and illustrated the need for vigilance. Using the Regensburg ECMO Registry of patients on VV

ECMO ($N = 265$), 31% of VV ECMO patients required one or more system exchanges. Life-threatening acute mechanical failure of the VV ECMO circuit occurred in 10% of patients, and acute thrombosis of the oxygenator or blood pump occurred in 35%. More than 50% of cases showed preceding, significant alterations in gas exchange, laboratory values (ie, increased D-dimers, decreased fibrinogen, decreased platelet count, lactate dehydrogenase level elevation, and an increase in plasma free hemoglobin), or increased resistance to blood flow through the circuit. Pump exchanges were urgent in 45% of cases. They concluded that most ECMO circuit system changes were predictable and could be anticipated by regular inspection of the ECMO circuit; daily monitoring of gas exchange, coagulation indices, and hemolysis parameters; and assessment of pressure drops in the ECMO circuit.

Circuit fractures can occur, and their effects depend on size and location. If they are on the venous side of the circuit, air aspiration and gas embolism can occur. Immediate replacement of the affected portion of the circuit or the entire apparatus may be indicated.

Gas embolism can be a sudden, devastating complication. It is usually caused by creation of a significant negative pressure and air entrainment in the circuit.[141] Cavitation, in which gas is forced out of the liquid medium by a circuit obstruction, can also lead to gas embolism. Treatment must be immediate, with prompt circuit shutoff and clamping, simultaneous full ventilator support, and circuit de-airing.

Patient-Related Complications

Neurologic complications in ECMO patients remain a significant cause of morbidity and mortality. For these high-risk patients, many pre-ECLS factors (eg, low CO, hypoxia, acidosis, infection) and ECLS-related factors (eg, bleeding, multisystem failure) should be considered.

About 50% of ECMO use is for neonates and pediatric patients, a group that has the highest incidence of neurologic complications. For neonates treated with VV ECMO, ELSO data indicate a 9.0% incidence of clinical seizures and a 7.4% incidence of intracranial hemorrhage. For the pediatric VV ECMO group, data show a 5.2% incidence of clinical seizures and a 6.2% incidence of intracranial hemorrhage.[142]

Although adults comprise a smaller group of ECMO patients, the data show a lower incidence of neurologic complications with VV ECMO compared with VA ECMO. According to cumulative ELSO data, adult VV ECMO patients have a 1.0% incidence of clinical seizures and a 3.8% incidence of intracranial hemorrhage. Adults on VA ECMO have a 1.7% incidence of seizures and a 2.4% incidence of intracranial hemorrhage.[142] Rollins and coworkers[143] suggested that adults were predominantly supported with VV ECMO, which has been associated with lower rates of neurologic complications. Long-term functional neurologic outcome data for adults and children need more study.

Data on outcomes from the use of ECMO for cardiac support continues to grow. VA ECMO ELSO data show survival rates of 39% for neonates, 39% for adults, and 49% for pediatric patients, with lower survival rates after cardiopulmonary resuscitation (28% for adults, 41% for children, and 39% for neonates).[142] Among cardiac patients supported by VA ECMO, adults tend to have the lowest incidence of neurologic complications compared with neonates, with a 2% incidence of seizures, 3.7% incidence of infarction, and 2% incidence of intracranial hemorrhage.[142] Long-term neurodevelopmental data from the neonatal and pediatric literature[144,145] show a 50% incidence of moderate to severe cognitive delays and a 12% to 25% incidence of neuromotor delay in long-term survivors needing VA ECMO. In this group, chromosomal abnormalities, time to lactate normalization, and high inotrope scores predict poor cognitive outcomes.[144,145]

In a 2013 metaanalysis of complications and deaths related to ECMO[146] that included 1763 adults, Zangrillo and colleagues[146] found an in-hospital mortality rate of 54% and suggested that VV ECMO was safer than VA ECMO; possibly due to the lack of arterial involvement. The most common complications in ECMO patients were renal failure requiring ultrafiltration (52%), bacterial pneumonia (33%), bleeding (33%), oxygenator dysfunction requiring replacement (29%), sepsis (26%), hemolysis (18%), liver dysfunction (16%), leg ischemia (10%), venous thrombosis (10%), central nervous complications (8%), gastrointestinal bleeding (7%), aspiration pneumonia (5%), and disseminated intravascular coagulation (5%).

Bleeding is common in ECMO patients, particularly from cannulation sites due to systemic anticoagulation. Arterial cannulation presents a higher bleeding risk compared with venous ECMO. All ECMO patients are monitored with daily indices of coagulation status such as ACT, PT, aPTT, and platelet counts and with thromboelastography as indicated, especially before an invasive procedure. Other than cannulation site bleeding, mucosal bleeding can occur from the airway to stomach, colon or rectum, and bladder with minor, repeated trauma or instrumentation. Gastrointestinal bleeding can be a source of significant morbidity.

Anemia can be an issue because the circuit is usually primed with a crystalloid solution that causes dilution of blood cells. Thrombocytopenia is common, with up to a 40% reduction from baseline in the first few hours on ECMO.[147] Platelet transfusion thresholds can vary, but ELSO guidelines recommend 80,000 as the minimum platelet count for ECLS. Heparin-induced thrombocytopenia can occur on ECMO, and in its most severe form, it can be associated with white arterial thrombi and profoundly reduced platelet counts, mandating the use of alternative agents such as argatroban.[148] Hemolysis can trigger coagulopathy and is suggested by pink urine and an elevated level of plasma-free hemoglobin.[149] The level can be raised by thrombus in the circuit and red cell trauma resulting from excessive suction from the centrifugal pump.

Summary

The reemergence of ECMO as an option for patients with severe cardiopulmonary failure has increased its availability. Trials are investigating the utility of ECMO in treating various diagnoses, but much more research needs to be performed to clarify the indications, inclusion criteria, and management paradigms of this technology.[132] As ECMO use becomes more common, centers of excellence with high volumes will emerge as the safest locations to deploy this high-risk therapy.

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Blood and Fluid Management During Cardiac Surgery

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KEY POINTS

1. Practice guidelines are useful tools to guide patient management in the setting of wide practice variations or costly therapies.
2. Practice guidelines often are not effective in changing clinical practice for a variety of reasons.
3. Effective guidelines require effective implementation and the tools to follow the guidelines.
4. ABO and Rh blood groups are defined by the presence or absence of surface antigens on the red blood cell membrane.
5. The purpose of crossmatching is to reduce the mixing of patient and donor antigens and antibodies that elicit immune reactions.
6. Transfusion-related complications can be immune mediated (eg, graft-versus-host disease, transfusion-related acute lung injury) or nonimmune mediated (eg, infectious transmission, transfusion-associated circulatory overload).
7. Genetic variations affect circulating levels of coagulation factors and platelet numbers.
8. It is likely that genetic variation influences the risk for perioperative hemorrhage.
9. Reoperation for bleeding is associated with increased postoperative morbidity and mortality.
10. Implementation of a massive transfusion protocol and consideration of a higher fresh frozen plasma–to–red blood cell ratio may improve hemorrhage and patient outcomes.
11. Factor replacement with recombinant factor VIIa is effective for the treatment of refractory bleeding in the perioperative setting, but it may be associated with an increased risk of thrombotic complications.
12. Human fibrinogen concentrates are approved for use in patients with dysfibrinogenemias. Use in patients with low-normal levels of fibrinogen undergoing surgery is uncertain and may place the patient at risk for thrombotic complications.
13. Prothrombin complex concentrates are prepared from pooled plasma and contain four vitamin K–dependent clotting factors: II, VII, IX, and X.
14. Appropriate volume replacement to avoid tissue hypoperfusion is more important than the choice of colloid or crystalloid.
15. Despite decades of research, there are no blood substitutes approved for clinical use in the United States.
16. Anemia while on cardiopulmonary bypass has been associated with increased perioperative renal injury and patient morbidity. However, the results of observational studies are not entirely consistent, and a specific cutoff value for a safe hematocrit while on cardiopulmonary bypass has not been determined.

Appropriate perioperative blood and fluid management is critical to the care of patients undergoing cardiac surgical procedures. A conservative strategy to minimize the use of red blood cells (RBCs) and component therapy is strongly recommended. Transfusion guidelines have been developed to assist clinicians with transfusion decisions, as have clinical studies examining the use of component therapy and choice of fluid therapy for maintaining adequate intravascular volume. This chapter reviews transfusion guidelines as they apply to cardiothoracic surgical patients, examines genetic background of blood type groupings, explains immunologic and nonimmunologic-related complications associated with RBC transfusion, and explores risk factors and treatment strategies for perioperative bleeding.

Transfusion Guidelines

Rationale for Guidelines

Clinical guidelines are a ubiquitous part of medicine. They are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[1] The US National Guideline Clearinghouse (http://www.guideline.gov) includes more than 2480 recently generated guidelines. Guidelines are valuable methods for reducing practice variations and errors, and they ensure efficient use of health care resources.[2] Despite the availability of well-constructed guidelines, clinicians often are reluctant to implement them in daily practice. Several studies have shown that guidelines may do little to change practice behavior.[3]

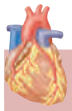
Formulation of Guidelines

Groups developing guidelines require support from a national or international society that can endorse and disseminate the guidelines. Committee members should be recognized experts in the field and be assisted by people with expertise in guideline preparation. American Heart Association guidelines are the model for well-crafted guidelines that were developed using well-conducted, peer-reviewed studies as their evidence base (Box 34.1).

Guidelines can be based on a spectrum of evidence from case reports, series without control groups, or randomized, controlled trials. The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Transfusion Guidelines were published in 2007[4] and are a good example of well-crafted guidelines, but they were based on limited available evidence. There were 57 recommendations in the guidelines. Only 13 were level A evidence (ie, best level of evidence), 27 were level B (ie, limited evidence), and 17 were level C (ie, very limited evidence). Only 7 were class I recommendations (ie, benefit strongly outweighs risk), 18 were class IIa (ie, benefit outweighs risk), 23 were class IIb (ie, benefit may outweigh risk), and 10 were class III (ie, risk outweighs benefit).[5] The relatively low level of evidence for the guidelines likely is reflected by the lack of wide implementation by clinicians.

Implementation of Guidelines

To be effective, guidelines should be widely disseminated using commercial marketing tools. Anesthesia and surgical societies have been comparatively slow in adopting guidelines. Although the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Transfusion guidelines were widely distributed throughout societies and to the perfusion community, many practitioners were not aware of the content of the guidelines. Several other studies have found a similar lack of awareness of other guidelines.[6,7]



BOX 34.1 REQUIREMENTS FOR SUCCESSFUL GUIDELINE DEVELOPMENT AND IMPLEMENTATION

Guideline Writing Group Formation
Support at a societal level
Perception of a need to define practice standards
Senior leadership for guideline preparation
Statistical support for examination of evidence

Guideline Preparation
Sufficient evidence base for guideline preparation
Sufficient expertise for guideline preparation
Dedicated time and effort for guideline generation
Dissemination to content and structure experts for commentary

Guideline Dissemination
Wide dissemination using an authoritative journal in the field
Wide dissemination using traditional and nontraditional mechanisms such as Web sites, conferences, and special interest groups

Guideline Conformity at the Local Institutional Level
Senior leadership within the institution
Incorporation of guidelines into the local context of clinical practice
Providing practitioners with the resources to conform to the guidelines
Providing practitioners with timely, accurate, and pertinent feedback on measured conformity with guidelines

Other factors may hinder effective implementation by practitioners, such as guidelines that are too complicated or lack rigorous scientific evidence as a basis. In other fields, such as general medicine practices, several studies have demonstrated low rates of change in response to guidelines.[8–10] In the surgical environment that relies on multispecialty teams, the entire team must understand the rationale for practice guideline implementation. However, it is equally important that guidelines remain flexible enough to permit a degree of patient-specific departures from specified prevention, diagnostic, and treatment protocols.[11]

Other key components for successful implementation of guidelines lie in senior institution leadership and endorsement[12] and practice-specific feedback about performance. Implementation of guidelines in cardiac surgery has been poor,[13,14] but focused implementation of guidelines at single institutions has been successful.[15,16] Quality improvement initiatives used in industry such as Total Quality Management and Six Sigma, which appear applicable to surgical processes, depend on collection of verifiable data on processes.[17,18] The notion that clinicians can improve cardiac surgical care and the performance of individual members of the team without proper timely feedback is not reasonable. Real-time feedback has been particularly effective.[19]

In summary, individuals involved in the management of cardiac surgical patients are obligated to provide the best possible clinical care, often by consulting guidelines. Societies have a key role in endorsement, dissemination, and use of guidelines to improve care.

Blood Groups and Transfusion

ABO Blood Groups

ABO and Rh blood groups are the most well known of more than 30 antigen-based classifications of human blood types. The ABO blood group system is based on identification of A and B antigens on RBCs, and it was originally described by Janský and Landsteiner.[20] Wide variation exists in the frequency of the ABO groups across different populations. For example, group B is the most common type among Asians but uncommon among whites.[21]

The ABO blood grouping is defined by presence or absence of surface antigens on the RBC membrane. The *ABO* gene is located on chromosome 9q34.2 and has three principal isoforms (ie, A, B, and O) that are determined by single nucleotide polymorphisms (SNPs) and single-base deletions in the *ABO* gene (Table 34.1). Four missense SNPs determine the structural and functional differences between the A and B transferases. The different transferases result from four amino acid substitutions at amino acid positions (codons) 176, 235, 266, and 268, and they usually occur together. Two SNPs (ie, L266M and G268A) change the substrate specificity of the ABO enzyme for galactose. The protein produced by the *ABO* gene is not the antigen. Instead, O, A, and B antigens are formed by the action of three glycosyltransferases (ie, isoforms) encoded by the *ABO* gene that modify a cell membrane glycoprotein (ie, H antigen).[22]

The O blood group results from a single base deletion (261delG) in exon 6 of the *ABO* gene that causes a frameshift mutation and translation of a truncated ABO protein, the O isoform. Because it has

TABLE 34.1 Genetic Profiles of the ABO Blood Groups

ABO gene exon	6	7	7	7	7
Nucleotide position	261	526	703	796	803
Common allele[a]	G	C	G	C	G
Rare allele[a]	del	G	A	A	C
Amino acid position	118	176	235	266	268
Blood group O	Deleted	Deleted	Deleted	Deleted	Deleted
Blood group A	Leucine	Arginine	Glycine	Leucine	Glycine
Blood group B	Leucine	Glycine	Serine	Methionine	Alanine

[a]Nitrogenous bases are given for the specified nucleotide positions.

no enzymatic activity, the H antigen is unmodified, and the A and B antigens are not created.[23]

In the A transferase, the amino acids are leucine (L) and glycine (G) at codons 266 and 268, respectively. The A isoform (ie, L266 and G268) encodes a glycosyltransferase (ie, A transferase) that bonds α-*N*-acetylgalactosamine to the H antigen, producing the A antigen of the ABO blood group system. Individuals who exclusively synthesize A isoforms have blood group A and have the genotype AA (ie, homozygotes with the same A allele on both chromosomes) or AO (ie, heterozygotes with an A allele only on one chromosome).[23]

In the B transferase, the amino acids are methionine (M) and alanine (A) at codons 266 and 268, respectively. The B isoform (ie, M266 and A268) encodes a glycosyltransferase (ie, B transferase) that joins α-D-galactose to the H antigen, creating the B antigen. Blood group B individuals have the genotype BB (ie, homozygotes) or BO (ie, heterozygotes). Individuals who express both A and B isoforms of the ABO gene (ie, A allele on one chromosome 9 and B allele on the other chromosome 9) are blood group AB.[23]

Other variations in the *ABO* gene can create functionally similar antigens. For example, the A(2) isoform, comprising only 20% of group A individuals, is caused by deletion of a protein-coding termination point, extending the enzyme by 21 extra amino acids and altering its specificity. These structural differences reflect the different catalytic activities of the enzymes encoded by the A(1) and A(2) alleles and result in different antigenic properties of A(1) and A(2) antigens.[24] Different molecular mechanisms may be responsible for seemingly identical ABO blood groups. For example, the B3 phenotype may be caused by a missense mutation (D291N), a splicing mutation (B303), or the combination of a missense mutation and a single nucleotide deletion (V277M and 1060delC).

ABO blood groups also can be measured by genotyping the variants in the *ABO* gene instead of measuring the presence or absence of the A and B antigens. The ABO antigens are also expressed on the surface of many other cells types, indicating the importance of ABO crossmatching of organ transplants. Several other rare variants of the ABO gene that change activity or specificity, or both, of the enzyme have been identified and generate several rare blood groups.[25]

Anti-A and anti-B antibodies (ie, isohemagglutinins) are IgM antibodies that appear in the first years of life. Early in the postnatal period, the immune system generates IgM antibodies against ABO antigens even when they are absent from the individual's RBCs. If present in the fetus, the IgM antibodies are too large to cross the placenta and are not a relevant cause of hemolytic disease of the newborn. The antibodies are thought to be produced in response to infantile exposure to influenza virus and gram-negative bacteria. Antibodies usually are not generated against the H antigen. An individual with blood group A therefore makes IgM antibodies against the B antigen. An individual with blood group B makes IgM antibodies against the A antigen. An individual with blood group AB does not make IgM antibodies against the A and B antigens. An individual with blood group O makes IgM antibodies against the A and B antigens.[23]

If an individual with blood group A receives group B RBCs, anti-B IgM isohemagglutinins in the recipient plasma bind to the B antigen on donor RBCs, generating a locus for complement-mediated lysis of transfused donor RBCs and generating a hemolytic transfusion reaction. Similar events occur in group O and B individuals receiving RBCs containing non–self-antigens. However, blood group AB individuals do not generate anti-A and anti-B antibodies, and they can receive RBCs from all groups and are universal RBC recipients.[23]

Rhesus Blood Groups

The rhesus (Rh) blood group system consists of about 50 blood group antigens, among which five antigens—D, C, c, E, and e—are the most important. The proteins that carry the Rh antigens form a transmembrane transporter complex that resembles NH_3 and CO_2 transporters of evolutionary origin.[26] The proteins are encoded by two adjacent genes on chromosome 1p36.13-p34.3: the *RHD* gene that encodes the RhD protein with the frequent D antigen and the *RHCE* gene that encodes the RhCE protein with the C, E, c, and e antigens.[27] The term *Rh factor* refers only to the D antigen that is normally present. Unlike the ABO system, the absence of the normally present D antigen is called the *d antigen,* but there is no protein corresponding to the d antigen. Lowercase *d* indicates the absence of the D antigen, often as a result of the deletion of the gene or other variants that prevent expression of the antigenic protein on RBCs.[27] To be Rh negative, the individual must have the gene absent on both chromosomes.

The frequency of Rh-negative individuals ranges from about 16% in white populations to less than 1% in Asian populations.[28] Rh incompatibility of an RhD-negative mother and RhD-positive fetus is the predominant cause of hemolytic disease of the newborn, which occurs when maternal IgG anti-RhD antibodies pass through the placenta into the fetal circulation and cause hemolysis of RhD antigen-positive fetal RBCs.[29]

Other Blood Groups

At least 30 other antigens are expressed on the RBC surface, defining the Kell-Cellano, MNS, Lewis, and other blood groups. These blood groups are capable of causing transfusion reactions, although most are less common and produce less severe transfusion reactions than ABO incompatibility. Several can produce hemolytic disease of the newborn.[29]

The Kell-Cellano antigens are variants of a transmembrane glycoprotein encoded by *ET3* on chromosome 7q33. In contrast to many other blood groups, the function of the enzyme is known, and it is responsible for producing endothelin 3, a potent bioactive peptide with many biologic roles. There are several variants of the gene, of which K_1 (Kell) and K_2 (Cellano) are the most common and result from an SNP generating a Thr193(K_2) from the more frequent Met193(K_1) isoform. Kell incompatibility is second to Rh incompatibility for generation of hemolytic disease of the newborn.[29]

The MNS antigens are variants of two genes, glycophorin A (containing the *M* and *N* alleles) and glycophorin B (containing the *S* and *s* alleles), adjacent to each other on chromosome 4q28-q31. The glycophorins are the most common sialoglycoproteins on the RBC membrane, but their function is not clear. Unlike most other blood group systems in which individual SNPs or deletions create the antigens, the MNS antigens are created by complex rearrangements of the protein structure that generate antigens.[30]

The Lewis blood group antigens are structurally similar to the ABO and the H blood group systems. The antigens are generated by variants in the fucosyl transferase gene *(FUT3)*, residing on chromosome 19p13.3; they act on the Lewis antigens in a similar fashion to the galactose transferase function of the *ABO* gene acting on the H antigen. The Lewis antigens are not synthesized in erythrocyte progenitor cells like the ABO antigens and are more likely created in the gut. The Le-a or Le-b antigens circulate in plasma bound to serum lipoproteins and are adsorbed to circulating erythrocytes, usually only after birth.[31]

Crossmatching

The use of citrate and refrigeration and a nascent understanding of blood incompatibility during World War I enabled the development of blood banking.[32] The first US hospital blood bank was created at Cook County Hospital in 1937.[32] About 16 million units of blood were transfused in the United States in 2008.[33]

Crossmatching of donor blood products to an individual recipient is a sequence of procedures performed to prevent transfusion reactions. American Association of Blood Banks' *Standards for Blood Banks and Transfusion Services* defines the procedures performed before blood is transfused to a recipient. The first laboratory component for the recipient blood specimen is a *type and screen*, which consists of two separate tests.[34] First, the recipient's ABO and RhD blood groups are determined (ie, typed) by using commercially produced anti-A and anti-B antibodies that react with the A or B antigens, if present, on the

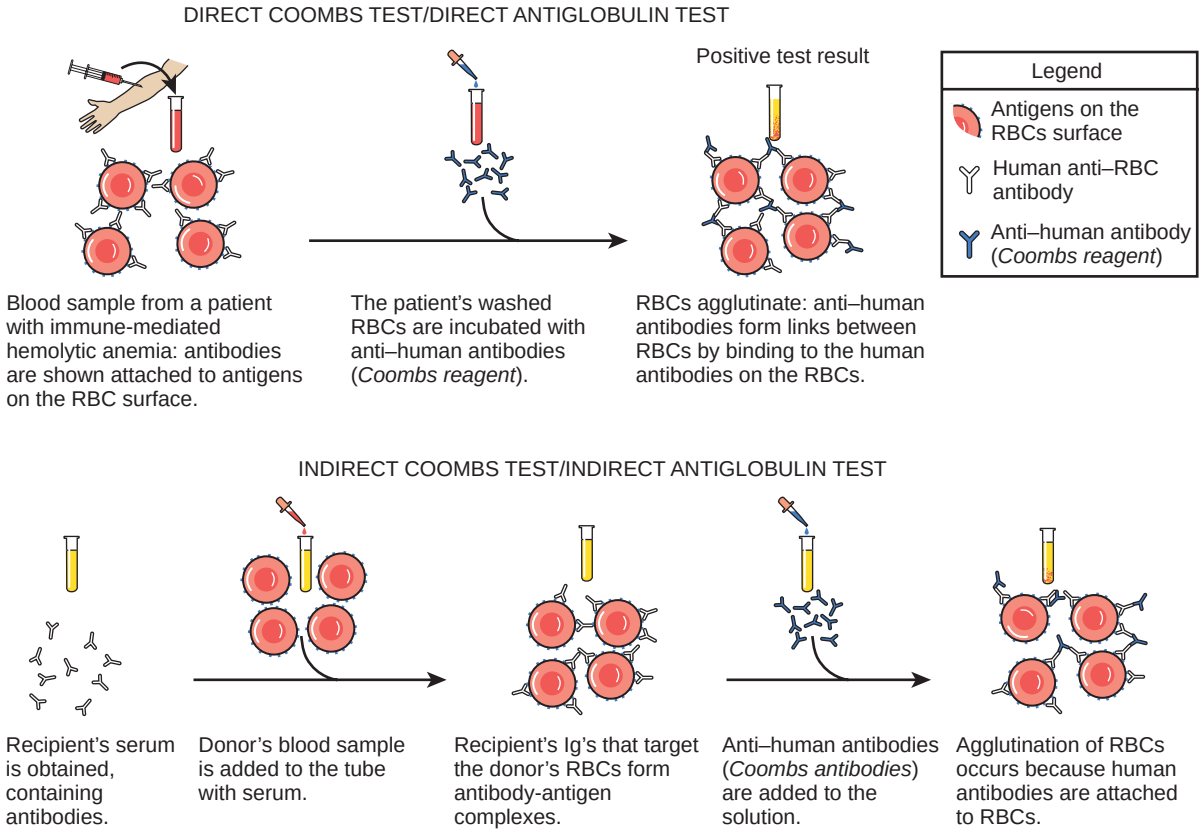


Fig. 34.1 Indirect and direct Coombs (antiglobulin) tests. The recipient's serum or plasma is separately mixed with three or more commercially available type O washed red blood cells *(RBCs)* that express about 20 of the most clinically significant RBC antigens to detect unexpected antibodies. The recipient's serum and reagent RBCs are incubated at 37°C for 30 minutes and examined. Spun cells are then washed and tested with antihuman immunoglobulin and reexamined for hemolysis or agglutination. When antibodies bind to RBC surface antigens, the cells agglutinate during incubation with an anti–human globulin (ie, Coombs reagent), and the indirect Coombs test result is positive. *(Modified from Wikipedia: Coombs test schematic. Updated March 2006.* http://en.wikipedia.org/wiki/File:Coombs_test_schematic.png.*)*

recipient's RBCs, causing the RBCs to agglutinate. The RhD antigen is tested in the same manner, with commercially available anti-D antibodies mixed with the recipient's RBCs.[34]

In the second step, antibody screening is done to identify whether the recipient has formed antibodies to nonself blood groups, such as Duffy, MNS, Kell, Kidd, and P system antigens, using an updated version of the classic Coombs test, also called the *indirect antiglobulin test* (Fig. 34.1). The recipient's serum or plasma is mixed separately with three or more commercially available type O washed RBCs that express about 20 of the most clinically significant RBC antigens to detect unexpected RBC antibodies.

If transfusion is required, the recipient sample that is already typed and screened is crossmatched with donor units. Provided recipient antibodies were not identified on the type and screen, it is possible to perform a crossmatch serologically using an immediate spin crossmatch or perform an electronic match. If clinically significant antibodies have been found on the type and screen, electronic crossmatching is not sufficient, and an antiglobulin crossmatch must be performed.[34] An electronic or computerized crossmatch is performed by identifying donor units on hand that have appropriate ABO and RhD blood groups for the recipient.[35] Electronic crossmatching can be used only if a patient has a negative antibody screen, which means that they do not have any active RBC atypical antibodies. It is assumed that the proper testing (ie, type and screen) of the recipient and donor blood is sufficient to identify clinically important incompatibility and to identify matching donor blood.[36]

When serologic crossmatching (ie, immediate-spin crossmatch) is performed, RBCs from an ABO- and RhD-compatible RBC unit are mixed with the recipient's plasma. The mixture is centrifuged and examined for hemolysis or agglutination. Agglutination is considered a positive reaction, indicating that the donor unit is incompatible for that specific patient. If both are absent, ABO compatibility is verified, and the RBC unit issued. This procedure is repeated for each donor RBC unit. If agglutination or hemolysis occurs, additional screening of the recipient's plasma is performed to identify the unexpected antibodies.[36] Performing a serologic crossmatch over electronic crossmatching before transfusing RBCs is preferred by some laboratories because it detects rare ABO errors and detects most recipient IgM antibodies to antigens on donor RBCs.[37] In an emergency, *uncrossmatched blood* can be transfused and the risk for a serious transfusion reaction minimized by administration of type O and RhD-negative RBCs.[38]

Because plasma contains the anti-ABO, RhD, and other antibodies of the donor, only ABO and RhD-compatible units are transfused. The recipient and donor unit must undergo a type and screen; however, crossmatching is not performed. Platelets have ABO antigens on their surface. However, ABO compatibility for platelet transfusion is desirable but not required because of the relatively small volume of plasma in a bag of platelets. If ABO-incompatible platelets are administered for operational reasons, the recipient may have a positive direct antiglobulin test result, but significant hemolysis is rare. A donor-recipient ABO mismatch may result in poor function of donor platelets after transfusion.[39–41]

Complications of Transfusion

Immediate Immune-Mediated Complications

Hemolytic transfusion reaction is the result of complement-mediated destruction of transfused RBCs, usually because of incompatibility of antigen on the transfused RBCs with antibody in the recipient's circulation. The most common cause of acute hemolytic reactions is transfusion of ABO-incompatible blood; rarely, undetected serologic incompatibility is a cause of acute hemolysis.[42]

Transfusion has been associated with greater pulmonary morbidity after cardiac surgery.[43] Transfusion-related acute lung injury (TRALI) occurs when increased permeability of the pulmonary endothelium causes pulmonary edema, usually within a few hours of transfusion. Hypotension and fever also may occur.[44,45] TRALI accounts for most transfusion-associated deaths in the United States.[45,46] The specific cause of TRALI is unknown, but in many cases, it is associated with antibodies in donor plasma directed toward the recipient's leukocyte or neutrophil antigens.[45,46] These antibodies are seen more frequently in multiparous women and individuals who have had a prior transfusion.[47]

Transfusion of blood components, especially products containing high volumes of plasma such as fresh frozen plasma (FFP), is associated with the greatest risk of TRALI.[47] Plasma from women is typically used for processed protein fractions rather than transfusion. No routinely available pretransfusion testing is available.

Immune-mediated platelet destruction is the result of recipient antibodies to the human leukocyte- or platelet-specific antigens on transfused platelets. Most cases of immune-mediated platelet destruction occur in individuals who have had several prior platelet transfusions. For some patients, platelet matching may be required.[41]

Anaphylactoid reactions rarely occur in transfusion of IgA-containing plasma in a blood product given to IgA-deficient patients who have anti-IgA antibodies. The reaction is characterized by hypotension, bronchospasm, and laryngeal edema.[48]

Febrile nonhemolytic reactions are relatively common and typically manifest by a temperature increase of 1°C or more during or shortly after transfusion. They may result from antibodies to white blood cells or from high levels of cytokines in transfused blood products.[49]

Delayed Immune-Mediated Complications

Delayed hemolytic reactions occur in patients who have had previous exposure to incompatible blood but who do not have circulating antibodies. Reexposure to the antigen provokes delayed production of antibody that reaches a significant circulating level while the transfused RBCs are still present in the circulation, usually 2 to 14 days after transfusion.[50]

Graft-versus-host disease (GVHD) is a rare condition that occurs when viable donor T lymphocytes in the transfused blood product successfully engraft in the recipient. Normally, donor T cells are recognized as foreign by the recipient's immune system. However, in immunocompromised patients and rarely when the donor is homozygous and the recipient is heterozygous for an HLA haplotype (as occurs in directed donations from first-degree relatives), the recipient's immune system is not able to destroy the donor T cells. This can result in GVHD. Irradiation of the donor unit prevents T-cell proliferation and GVHD.[51,52]

Nonimmune Complications

Transmission of infectious disease may occur with transfusion despite standard blood-banking operational procedures. Routine testing of donor blood is performed for Chagas disease, hepatitis B and C, human immunodeficiency viruses types 1 and 2, human T-lymphotropic virus, syphilis, West Nile virus, and in some situations, cytomegalovirus.[33] Bacterial contamination occurs rarely and manifests by fever and hemodynamic instability after transfusion of the blood product.[53] Circulatory overload, hypothermia, and metabolic and electrolyte derangements may occur with high-volume transfusions.[54]

Transfusion and Morbidity Outcomes

Morbidity and Mortality

Although transfusion of RBCs is necessary for some patients, its use has been associated with a dose-dependent greater prevalence of morbidity after cardiac surgery.[55] Greater rates of postoperative infectious complications, prolonged postoperative ventilatory support, renal injury, and reductions in short- and long-term survival are more common for patients transfused with RBCs.[43,55–57] Greater rates of bacteremia, septicemia, and deep and superficial sternal wound infections are higher for transfused patients. Some investigators hypothesize that this results from downregulation of the immune system.[56,58–60]

A metaanalysis by Rohde and colleagues examined the association between RBC transfusion strategies and health care–associated infection.[59] The investigators reported reduced risk of health care–associated infections for patients who had a restrictive RBC transfusion strategy compared with a liberal transfusion strategy. They posited that implementation of restrictive strategies might have the potential to lower the incidence of health care–associated infections. The relative risk for the association between transfusion strategy and serious infection was 0.82 (95% confidence interval [CI], 0.72 to 0.95).[59]

Transfusion has been related to increased development of postoperative atrial fibrillation due to the influence of RBC transfusion on inflammation. RBC transfusion results in a direct infusion of inflammatory mediators and augments the inflammatory response to cardiopulmonary bypass (CPB) and cardiac surgery.[61,62]

Work by Clifford and colleagues characterized the epidemiology of pulmonary complications related to perioperative transfusion (ie, transfusion-associated circulatory overload [TACO] and TRALI).[63,64] In a noncardiac surgical population, the researchers found an overall 4.3% incidence of TACO, with increasing age, total intraoperative fluid balance, and increasing amounts of transfused products also related to TACO development. They highlighted the importance of recognizing TACO because circulatory overload due to transfusion was the second most common complication related to transfusion.[64]

In a separate investigation of a non-cardiac surgery population, the investigators examined the epidemiology of TRALI and found that it was the leading cause of death related to transfusion. They reported no reductions in the occurrence of TRALI despite TRALI reduction efforts over time. The rate of TRALI was 1.3% in 2004 and 1.4% in 2011.[63]

Length of Storage Duration and Morbidity

Storage duration of the RBC product may contribute to adverse outcomes. A series of structural and functional changes occur with increasing RBC storage. Some changes are reversible, others are not, and together they may result in decreased microvascular tissue flow.[65–67] One investigation reported that transfusion of RBCs stored longer than 14 days was associated with a greater risk for death and complications after cardiac surgery.[68] A laboratory investigation by Sweeney and coworkers[69] found increased thrombin generation for RBC units of increasing storage duration, suggesting a cause for increased complications observed with transfusion of RBCs of increased storage duration.

Steiner and colleagues reported results from a randomized, controlled trial that assessed the effects of RBC storage on patients undergoing cardiac surgery.[70] The primary outcome was the multiple organ dysfunction score (MODS) through day 7; the change in MODS was similar for the fresh and old blood groups. The study was not powered for assessing postoperative mortality.

Genetic Causes of Hemorrhage

The coagulation system can be thought of as being highly optimized for rapid cessation of hemorrhage. There likely has been a strong evolutionary pressure toward rapid coagulation and wound healing. There must be an equally highly developed system that prevents overwhelming coagulation of the entire blood volume in response to a trivial intravascular insult. There was likely little or no pressure to avoid a

deep venous thrombosis in older age because most individuals did not live beyond 40 years until a few centuries ago. Similarly, there has been no evolutionary pressure to successfully undergo blood exposure to foreign surfaces such as the CPB circuit.

Because severe bleeding abnormalities are strongly selected against evolutionarily, they are rare. A sentinel example is the hemophilias, in which a rare variant causes production of a nonfunctional protein with severe consequences. In contrast, trivial abnormalities have not undergone marked evolutionary pressures and are likely to be more common. A good example is the wide but seemingly unimportant heritable variation seen in the circulating level of many coagulation proteins.[71–74]

In some individuals, the coagulation system is not optimized to achieve rapid coagulation. Most abnormalities are a quantitative deficiency of a normal protein or a qualitatively defective (ie, hypofunctional) protein in normal concentrations. The measurement of protein concentration and activity are importantly different. Protein concentrations usually are measured by the amount of binding of a manufactured antibody against a portion of the protein (ie, antigen). Antibody-based assays detect quantitative deficiencies of the protein but cannot detect qualitative defects unless the antibody is specifically directed against the structural abnormality of the protein. The function of a protein usually is measured by the enzyme or other functional activity of the protein, often by measuring the amount of enzyme product formed. Results of activity-based assays may be reduced because the amount of the protein is reduced or its activity is reduced, and the cause of reduced function likely must include the measurement of the amount of protein using a quantitative assay.

Genetic causes of impaired coagulation can be thought of as a qualitative defect arising from abnormal protein structure because of a coding genetic variant or a quantitative defect arising from abnormal and usually reduced production of a normal protein because of a noncoding (promoter) genetic variant. This rudimentary approach gives a basic understanding of the genetic mechanisms of coagulation disorders.

The overall effect of a genetic variant on the individual or surgical population is a product of the frequency of the genetic variant and its biologic effect.[75] Rare variants such as the hemophilias are problematic for single individuals, but the overall effect on daily practice is low. A more common variant may have greater effects. Similarly, for two variants of equal frequency, the one with a low biologic effect has less overall influence than the one with a higher biologic effect. No frequent variants with high biologic effect on coagulation have been identified.[74]

Variation in Coagulation Protein Levels

Several studies have demonstrated the strong heritability of levels of plasma proteins and platelet levels in normal populations.[73,76–79] This type of research is undertaken by examining the plasma level of coagulation proteins in multigenerational families and estimating the within-family variation compared with the whole-population variation.[80] In accordance with the strong evolutionary importance of coagulation function, there is similar strong inheritance within families, with up to 70% of the variation in plasma protein levels determined by genetic heritability. Similar heritability of platelet count and platelet volume has been observed.[81,82]

Genetic variation associated with the circulating level of a coagulation protein is usually in or around the gene for that coagulation protein. For example, the circulating level of plasminogen activator inhibitor 1 (PAI-1) principally is determined by a common promoter variant that alters the binding of the transcription factor inhibitor.[72,73] Similarly, the circulating level of thrombin-activated fibrinolysis inhibitor is determined by two variants,[83] and circulating prothrombin levels are determined by a single variant.[84] However, some coagulation protein levels are regulated by genetic variation that is not in or around the protein's gene. Platelet count and platelet volume are regulated by genes that would not be intuitive choices.[81,82]

Hemophilias

Hemophilias are well-known examples of a rare, severe genetic disorder of coagulation. Hemophilia A (ie, factor VIII deficiency) is the most common hemophilia, occurring in about 1 in 5000 male births.[85] Hemophilia B (ie, factor IX deficiency) occurs in about 1 in 34,000 male births. Both genes lie on the X chromosome, meaning that in males, only one copy of the chromosome is present, and a single variant may result in hemophilia, which is often called a *sex-linked* or *X-linked disease*. Female hemophiliacs must have two copies of the rare variant, an event that usually occurs only in consanguineous births in which the father has hemophilia. Although most hemophilias are maternally inherited, about 30% are spontaneous mutations not found in the mother.

An obvious question is why females do not have twice the factor VIII and IX levels as male individuals. In females, one of the X chromosomes is usually inactivated and does not generate messenger RNA for translation of proteins. However, it is possible for female carriers to have mild hemophilia because of lyonization (ie, inactivation) of the X chromosome that carries the normal gene, leaving the abnormal gene as the most active. Women may experience menorrhagia because of the bleeding tendency.

Hemophilia C is an autosomal genetic disorder (not an X-linked trait) involving a lack of functional clotting factor XI. Hemophilia C is not completely recessive because heterozygous individuals also have increased bleeding.[86]

The *F8* gene encodes factor VIII of the intrinsic pathway. Factor VIII is a cofactor for factor IXa, which converts factor X to the activated form Xa. There are almost 700 known coding variations of the *F8* gene, many of which have been seen in only one individual or family. More than 170 variations produce severe forms of hemophilia A, and more than 180 produce milder forms.[87,88] Some mutations change one amino acid; many have little effect on protein function because only one amino acid is changed, often to a similar type of amino acid.[89] Others cause a frameshift mutation that usually truncates the protein and markedly reduces its function. Another severe mutation is an inversion of a portion of the genome, and the sequence of a portion of the protein is back-to-front, with a marked reduction in function. Rarely, the entire gene is deleted so that quantitative and qualitative assays show the absence of factor VIII. The diagnosis of hemophilia A is based on reduced factor VIII activity, prolonged activated partial thromboplastin time except in mild disease, and a normal prothrombin time (PT) and platelet count.[89]

The *F9* gene encodes the vitamin K–dependent factor IX of the intrinsic pathway. Factor IX is activated by factor XI to factor IXa. Because hemophilia B is less common than hemophilia A, fewer mutations have been described, but the mechanisms of protein dysfunction caused by genetic variations are similar. The diagnosis of hemophilia B is made by reduced factor IX activity, prolonged activated partial thromboplastin time except in mild disease, and a normal PT and platelet count.[89]

Hemophilia is not a contraindication for cardiac surgery, but it is an absolute indication for involvement of a hematologist and blood banker. Most experience has been with small case series or single case reports, but all emphasize the need for prolonged factor therapy and subsequent excellent outcomes. For hemophilia A, the factor VIII activity level should be corrected to 100% of normal for cardiac surgery, although some hematologists use 50% to 70% of normal as a goal. One unit of factor VIII is the normal amount of factor VIII in 1 mL plasma. Because the volume of distribution of factor VIII is that of plasma, the amount of factor VIII in an individual is about 50 mL/kg. The factor VIII dose needed to correct the level is calculated as follows[90,91]:

$$\text{Units factor VIII} = (\text{weight in kg}) \cdot (50\ \text{mL plasma/kg}) \cdot (\text{desired \% factor VIII level} - \text{current \% of factor VIII level})/100\%$$

Approximately 30% of people with severe hemophilia A develop antibodies to transfused factor VIII. These antibodies (ie, inhibitors)

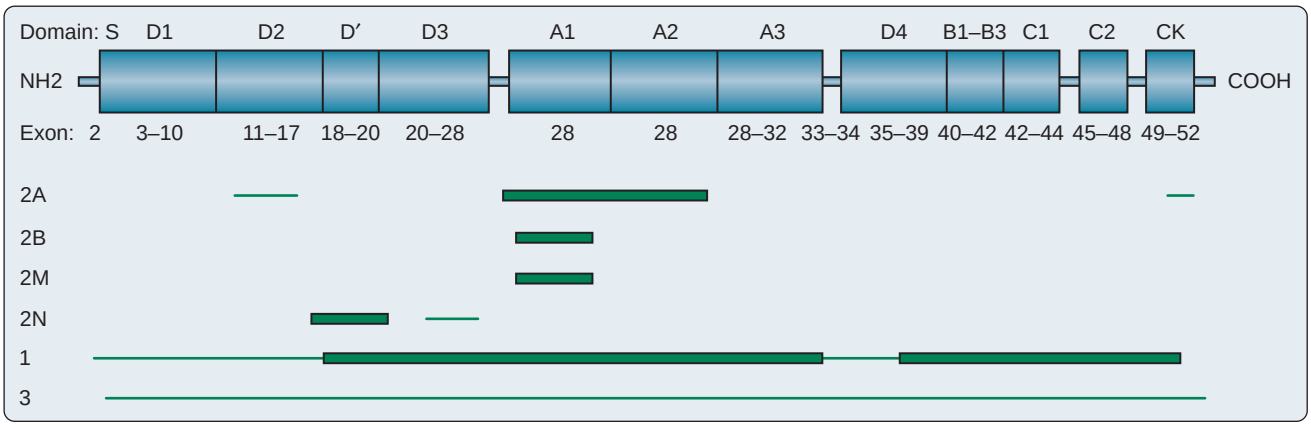


Fig. 34.2 Location of von Willebrand factor (vWF) mutations by von Willebrand disease (vWD) type. *Thick lines* indicate the approximate position of exons where mutations are most prevalent; *thin lines* indicate exons with mutations of lower frequency. Mutations that result in type 2 vWD affect vWF function and cluster in domains primarily disrupted by missense mutations. *(From* http://www.ncbi.nlm.nih.gov/books/NBK7014/; GeneReviews [Internet]. von Willebrand disease. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=von-willebrand*)*

bind to transfused factor VIII and reduce its activity, increasing the doses of factor VIII required.[92] The next dose should be administered 6 to 12 hours after the initial dose, together with repeated factor VIII activity monitoring with the goal of keeping the trough activity greater than 50%. During hemorrhage, cryoprecipitate and FFP can be given to restore levels of factor VIII, other coagulation factors, and blood volume. 1-Deamino-8-D-arginine vasopressin (DDAVP) at a dose of 0.3 μg/kg can be used in mild or moderate hemophilia A. It works by increasing circulating factor VIII and von Willebrand factor (vWF) levels. DDAVP works only when some normal factor VIII activity is present and usually with only modest success.[93]

For hemophilia B, the factor IX activity level should be corrected to 100% of normal for cardiac surgery, although some hematologists use 50% to 70% of normal as a goal. One unit of factor IX is the normal amount of factor IX in 1 mL plasma. Unlike factor VIII, the volume of distribution of factor IX in an individual is 100 mL/kg. The factor IX dose needed to correct the level is calculated as follows[94]:

$$\text{Units factor IX} = (\text{weight in kg}) \cdot (100\ \text{mL plasma/kg}) \cdot (\text{desired \% of factor IX level} - \text{current \% of factor IX level})/100\%$$

The next dose should be administered 12 to 24 hours after the initial dose, together with repeated factor IX activity monitoring with the goal of keeping the trough activity greater than 50%. During hemorrhage, FFP can be given to restore levels of factor IX, other coagulation factors, and blood volume. DDAVP is not effective.[93]

Von Willebrand Disease

Von Willebrand disease (vWD) is the most common inherited coagulation abnormality, occurring in about 1% of individuals.[95] vWD also can be an acquired disease. It arises from quantitative (ie, reduced amounts of usually normal protein) or qualitative (ie, normal amounts of a defective protein) deficits of vWF, which is a multimeric plasma glycoprotein produced by endothelium and platelets. The protein binds factor VIII (ie, platelet GPIb receptor), the activated form of the GPIIb/IIIa receptor, and collagen.[96]

Unlike the serine proteases of the intrinsic and extrinsic pathways of the coagulation system, vWF is not an enzyme and functions by binding to other proteins.[96] It has an important role in platelet adhesion to exposed subendothelial collagen by binding to exposed collagen and to the GPIb receptor of circulating platelets, especially in high-shear environments such as arterial bleeding. vWF decelerates platelets from rapid flow by uncoiling; it appears to be the critical initiator of platelet adhesion in high-flow environments. Platelet adhesion initiates rapid platelet activation, with switching of the most common platelet receptor, GPIIb/IIIa, from a quiescent protein that poorly binds to fibrinogen and fibrin to an activated protein that strongly binds fibrinogen and fibrin. vWF also can bind to activated GPIIb/IIIa receptors expressed on activated platelets.

There are four types of hereditary vWD caused by mutations in the *VWF* gene (Fig. 34.2).[97,98] Other factors, including having an O blood group, increase the clinical severity of vWD. Type 1 vWD (60–80% of cases) is a mild quantitative defect of normal vWF. Affected individuals have about 10% to 50% of normal vWF levels and often have low levels of factor VIII. The disease is inherited in an autosomal dominant fashion, and most individuals are heterozygous who possess one copy of the abnormal gene, with variants principally found between exons 18 and 28.[99] Rarely, homozygotes (ie, two copies of the abnormal gene) have extremely low levels of vWF. Most heterozygotes have normal or near-normal coagulation and are identified by having abnormal bleeding after tooth extraction or surgery or having menorrhagia.[100]

Type 2 vWD (20–30% of cases) is a qualitative defect with four subtypes: 2A, 2B, 2M, and 2N.[95] Type 2A vWD is caused by decreased activity but normal levels of vWF. The vWF multimers are structurally abnormal and usually small. In contrast to hemophilia, type 2A vWD is inherited in an autosomal dominant fashion and is caused by variants in exons 12 to 16, 28, and 52 of the gene. Type 2B vWF is a rare gain-of-function defect leading to spontaneous binding to platelets and subsequent rapid clearance of the platelets and large vWF multimers. Patients with this subtype should not receive desmopressin because it can induce platelet aggregation. Type 2M vWD is characterized by a platelet function defect caused by a decrease in high-molecular-weight multimers. Type 2N vWD is caused by the inability of vWF to bind factor VIII; it has an autosomal recessive inheritance pattern and is most often associated with variants in exons 18 to 20. Type 2N vWD produces a normal vWF antigen level and normal functional test results, but it has a low factor VIII levels. This probably has led to some 2N patients being misdiagnosed in the past as having hemophilia A, and it should be suspected if the patient has the clinical findings of hemophilia A but a pedigree suggesting autosomal rather than X-linked inheritance.[95]

Type 3 vWD is caused by a quantitative lack of vWF and premature proteolysis of factor VIII, similar to type 2A vWD, but in an autosomal recessive fashion. Type 3 is the most severe form of vWD because individuals are homozygous for the defective gene and protein. They

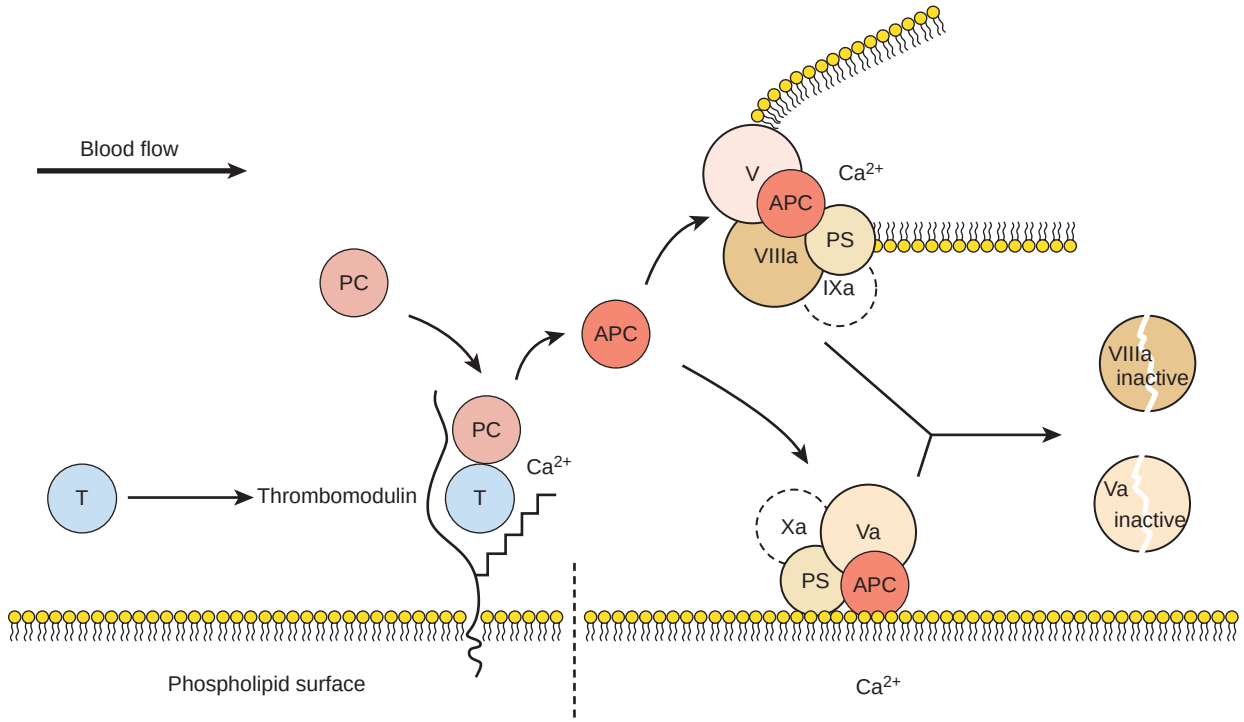


Fig. 34.3 Protein C anticoagulant pathway. Activated protein C functions as a circulating anticoagulant that degrades factors Va and VIIIa. This effectively downregulates the coagulation cascade and limits clot formation to sites of vascular injury. *APC,* Activated protein C, *PC,* protein C; *PS,* protein S; *T,* thrombin. *(From Wikipedia. Protein C anticoagulant.* http://en.wikipedia.org/wiki/File:Protein_C_anticoagulant.jpg.)

have no detectable vWF antigen and may have sufficiently low factor VIII that they have hemarthroses, similar to hemophilia.[100]

Acquired vWD can occur in patients with autoantibodies. In this case, the function of vWF is not inhibited, but the vWF-antibody complex is rapidly cleared from the circulation by antibody binding. A form of vWD occurs in patients with aortic valve stenosis, leading to gastrointestinal bleeding (ie, Heyde syndrome).[101] This form of acquired vWD may be more prevalent than currently thought. Acquired vWD also has been described in cases of Wilms tumor and hypothyroidism.

Laboratory diagnosis is based on a usually normal hemoglobin level, activated partial thromboplastin time, and partial PT but a reduced quantity of vWF measured by an antigenic assay, reduced vWF-ristocetin cofactor (vWF:RCo) assay, or reduced functional factor VIII assay result.[97] If abnormalities in these three tests are identified, specialized coagulation studies may be performed to determine the subtype of vWD. Bleeding can be treated with plasma-derived clotting factor concentrates containing vWF and factor VIII. Depending on the vWD type, mild bleeding episodes usually respond to DDAVP.[102]

Platelet-type vWD (ie, pseudo-vWD) is an autosomal dominant type of the disease caused by gain-of-function coding mutations of the vWF receptor (ie, GPIb) on platelets, not of the vWF gene.[98] GPIb is a dimeric protein that is part of the larger complex (ie, GPIb/V/IX), which forms the full vWF receptor on platelets. The loss of large vWF multimers is similar to that seen in type 2B vWD, but genetic testing of the vWF gene does not find mutations. The hyperresponsiveness of the platelet receptor results in increased interaction with vWF in response to minimal or no stimulation in vivo. This leads to a decline in plasma vWF levels and typically to a decreased or low normal platelet count.[96] Replacement therapy in the form of VIII/vWF preparations or drugs aimed at increasing the release of endogenous vWF exacerbate the condition and lead to further reduction of the platelet count. Platelet transfusions are therapeutic.

Factor V

Normal factor Va and its cofactor, factor Xa, are the first members of the *final common pathway* (ie, thrombin pathway) and combine to form the prothrombinase complex.[103,104] The prothrombinase complex catalyzes the conversion of prothrombin (ie, factor II) to thrombin (ie, factor IIa). To produce thrombin, the prothrombinase complex cleaves two peptide bonds in prothrombin. The action of factor Va is terminated by cleavage by activated protein C (aPC) (Fig. 34.3).

Factor V Leiden is a common SNP that results in a factor V variant that cannot be easily degraded by aPC.[105] The nucleotide variant (G1691A) results in conversion of an arginine to a glycine (Arg506Gln). This amino acid is normally the cleavage site for aPC, and the protein change markedly reduces the activity of aPC on factor Va.[104] When factor Va remains active, it facilitates overproduction of thrombin, leading to excess fibrin generation and excess clotting. It creates a gain of function by inhibiting the termination of factor Va. Clotting is almost always venous, resulting in deep vein thrombosis or pulmonary embolus.[104]

About 5% of whites in North America have factor V Leiden.[105] The SNP is less common in Hispanics and African Americans, and it is rare in Asians. About 30% of people who have a deep vein thrombosis or pulmonary embolism, especially younger patients, carry the SNP. Having the SNP and having other risk factors for deep vein thrombosis, including smoking, taking oral contraceptives, pregnancy, and recent surgery, markedly increase risk. Efforts to show that the prothrombotic factor V Leiden variant results in less bleeding have been mixed.[106,107]

Cold Agglutinins

Cold agglutinin disease is rare (about 2 cases per 100,000 people). Causes include a lymphoma-induced monoclonal gammopathy, renal cell carcinoma, and infection; but most commonly, no cause is found.[108] Cold agglutinins are usually IgM autoantibodies that react

at cold temperatures with RBC polysaccharide antigens. Low titers (1:16) of cold agglutinins often are found in the sera of healthy individuals, but high titers of cold agglutinins (>1:1000 at 4°C) can lead to hemagglutination and thrombosis at low temperatures, followed by complement activation and subsequent hemolysis on rewarming.[109,110] Screening for cold agglutinins before cardiac surgery is not warranted because of their rarity.[109]

In contrast to the warm agglutinins, patients with cold agglutinins do not respond to steroids or splenectomy but sometimes respond to the monoclonal antibody rituximab.[108] Rituximab destroys normal and malignant B lymphocytes and is used to treat B-cell lymphomas and rheumatoid arthritis. It specifically targets the CD20 antigen expressed on B cells. The exact function of CD20 is unclear, although it has been determined that CD20 has a nonredundant role in generating optimal B-cell immune responses.[108]

Variation in Platelet Count and Volume

There are wide variations in platelet counts and volumes in normal individuals undergoing surgery. Platelet function is often markedly depressed from purposeful administration of antiplatelet agents such as aspirin, clopidogrel, and other drugs.

Mean platelet volume is a measurement of the average size of platelets found in blood and is positively correlated with platelet count and function and with adverse thrombotic outcomes. Genetic variants associated with mean platelet volume and platelet count have been identified in or near *WDR66, ARGHEF3, TAOK1, TMCC2, TPM1, PIK3CG, EHD3, ATXN2, PTPN11, AK3*, and other genes.[82] Few of these associations are intuitive or supported by well-understood biologic mechanisms; nevertheless, they indicate the complexity and importance of genetic causes of normal coagulation function.

Bleeding After Cardiac Surgery

Do genetics affect bleeding after cardiac surgery? For many of the well-identified bleeding diatheses mentioned earlier, the answer is yes. However, clinicians rarely encounter these patients in their practice. More commonly, they see a patient who is bleeding for no apparent reason—without a surgical bleeding site, without a drug cause, and with normal or near-normal coagulation test results. The reason for this in an individual patient is almost never known, and the patient is treated symptomatically until the bleeding stops. It is possible, although unproved, that these patients have a genetically inherited bleeding diathesis. Few studies have examined this question, and their limited findings are unreplicated[107,111–113] (see Chapter 35).

Reoperation for Bleeding

Reexploration for bleeding is a serious complication, which significantly impacts the postoperative course by increasing morbidity and mortality rates. Approximately 2% to 4% of patients undergoing cardiac surgery require reoperation for bleeding with greater reported rates for more complex procedures. An investigation evaluating incidence, risk factors, and outcomes for 528,686 coronary artery bypass grafting (CABG) patients requiring reoperation for bleeding from the Society of Thoracic Surgeons National Cardiac Database (2004–2007) reported a 2.4% rate of reoperation. Risk factors for reoperation were older age, male sex, comorbidity such as peripheral vascular and cerebrovascular disease, chronic lung disease, renal insufficiency, heart failure, previous interventions, urgent or emergent surgery, preoperative intra–aortic balloon pump, percutaneous coronary intervention less than 6 hours before CABG, and thienopyridine use less than 24 hours before surgical intervention. Patients requiring reoperation had a greater risk for morbidity such as septicemia, stroke, and prolonged ventilatory support after surgery. The risk-adjusted mortality rate was significantly greater for patients requiring reoperation: 5.9% versus 1.97%. Risk was not increased for patients receiving aspirin therapy less than 24 hours before surgery.[114]

Additional studies have characterized risk factors for reoperation and its relation to patient outcome. Moulton and associates[115] identified a 4.2% reoperation rate and identified increasing age, renal insufficiency, reoperations, and prolonged CPB time as risk factors for this complication. Antiplatelet drugs (eg, preoperative aspirin) and preoperative use of heparin or thrombolytic agents were not significant predictors. The investigators reported that the incidence of death, renal failure and sepsis, and the need for prolonged ventilatory support were significantly greater for patients who underwent reoperation for bleeding.[115] Choong and collaborators[116] reported that the demographic and comorbidity risk factors previously described, cessation of aspirin within 4 days of surgery, preoperative use of clopidogrel, lack of antifibrinolytic agents during surgery, type of operation, and CPB duration were risk factors for postoperative bleeding necessitating reexploration.

In a contemporary cohort of patients, Karthik and colleagues[117] examined risk factors for reoperation and effect of time delay on morbidity after surgery. The rate of reoperation in their investigation was 3.1%. Factors associated with the need for reoperation included demographics such as increasing age, smaller body mass index, and nonelective surgery. They similarly reported that reoperation was associated with increased morbidity, hemodynamic instability, and transfusion of RBCs and component therapy. Among the 89 patients requiring reoperation, 31 had a greater than 12 hours time delay to reexploration; there were four deaths in delayed-reoperation group. The investigators concluded that mortality outcomes were worse if the time delay was greater than 12 hours after surgery and recommended an early reexploration policy for bleeding.[117]

Ranucci and coworkers[118] reported an increased risk for reoperation. They found that much of the morbidity risk was attributable to the amount of RBCs transfused. Delay for reoperation was related to risk only if the delay involved excess use of blood products.

Hall and associates[119] sought to differentiate coagulopathy from hemorrhage due to surgery in patients undergoing reoperation for bleeding. Both groups had increased morbidity and mortality rates compared with those not requiring reoperation. Excess risk was attributed to more hemodynamic instability, transfusions, and inotropic support, which were more common in patients undergoing reoperation. The investigators recommended normalization of coagulation profiles within 4 hours of intensive care unit admission, and if significant bleeding persisted with a normal coagulation profile, reexploration should be undertaken.[119]

Ratios in Resuscitation: Implications for Massive Transfusion in Cardiac Surgery

Patients requiring massive transfusion in the perioperative period may become coagulopathic due to loss, hemodilution, consumption of coagulation factors, and insufficient component replacement. Hypothermia is common in the perioperative period and can cause platelet dysfunction by its effect on platelet activation and adhesion.[120] Hypothermia also may contribute to reductions in clotting factor functional activity.[121–123] Development of acidosis may act synergistically with hypothermia to further worsen coagulopathy through its impact on pH-sensitive enzyme complexes involved in the clotting cascade.[124–126] Choice of volume administration (eg, starches) may further worsen coagulopathy in patients.[127]

Traditionally, a step-wise approach has been recommended for the massively bleeding patient, starting with fluid replacement (using crystalloids with or without colloids), followed in order by RBCs, plasma, cryoprecipitate, and platelet transfusions according to the amount of blood loss relative to the patient's blood volume (Fig. 34.4).[128]

A different approach that uses greater FFP-to-platelet-to-RBC ratios has been proposed. These proposals are based on publications that reported improved outcomes after traumatic injury for patients receiving a greater ratio of blood products to RBC early in the course of resuscitation.[129–132]

Borgman and colleagues[129] recommended implementation of massive transfusion protocols consisting of a 1:1 ratio of FFP to RBC,

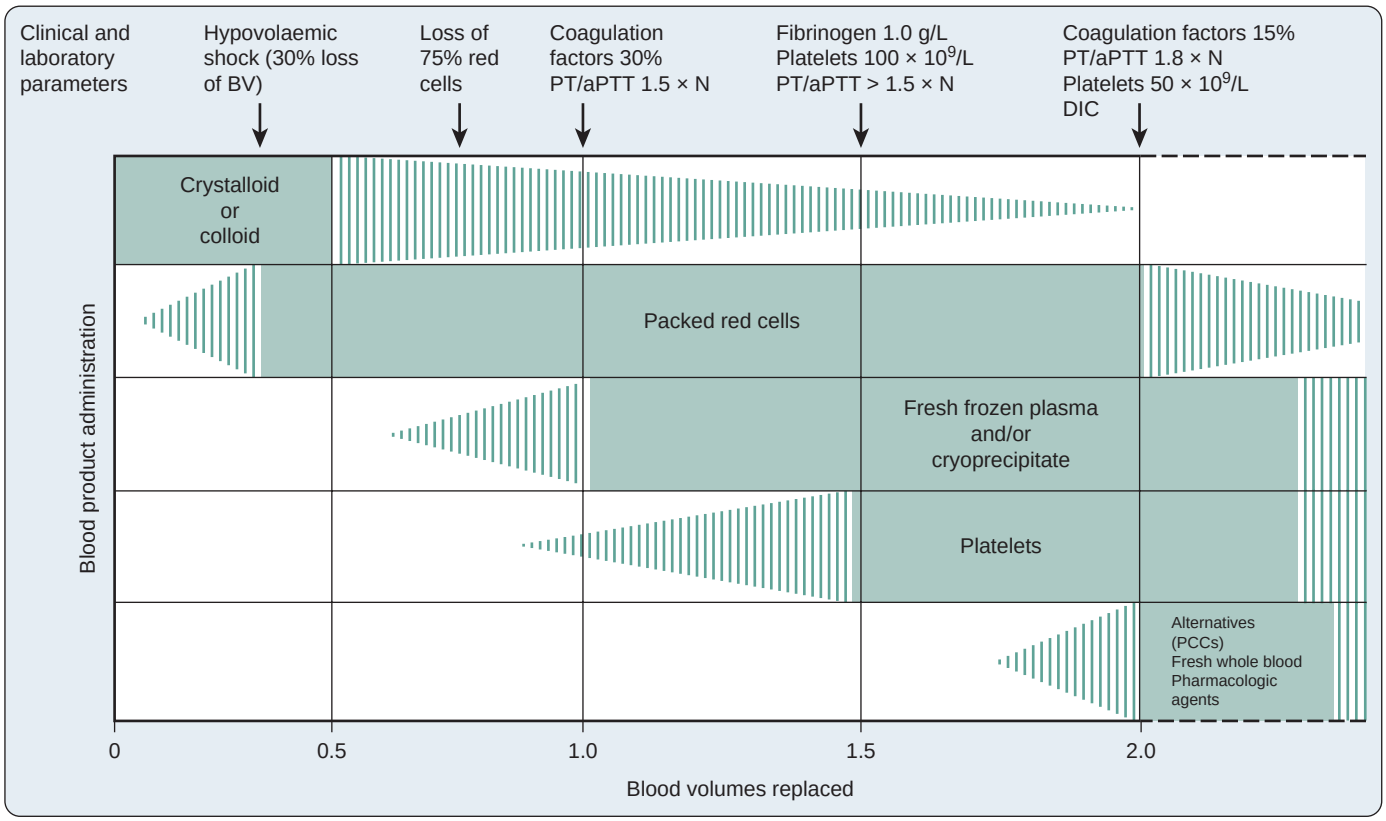


Fig. 34.4 Transfusion therapy for massive hemorrhage. *(Modified from Erber WN. Massive blood transfusion in the elective surgical setting. aPTT*, activated partial thromboplastin time; *BV*, blood volume; *DIC*, disseminated intravascular coagulation; *N*, normal; PCCs, prothrombin complex concentrates; *PT*, prothrombin time. *(From Erber WN. Massive blood transfusion in the elective surgical setting.* Transfus Apher Sci. *2002;27:83–92.)*

using evidence of improved survival and possibly less use of RBCs primarily from the trauma literature. Holcomb and coworkers[130] recommended a massive transfusion protocol that included a 1:1:1 ratio of FFP, platelets, and RBCs to improve patient outcomes. They analyzed four groups based on high and low plasma- and platelet-to-RBC ratios. The combination of high plasma-to-RBC and high platelet-to-RBC ratios was associated with decreased truncal hemorrhage and increased 6-hour, 24-hour, and 30-day survival rates.

In a subsequent prospective, observational study, Holcomb and associates found that the use of higher amounts of plasma and platelets relative to RBC transfusions during the first 6 hours after admission was associated with reduced mortality rates for trauma patients.[133] The risk of death was three to four times higher among patients with ratios less than 1:2 compared with those with ratios of 1:1 or higher.

Others have suggested a U-shaped curve depicting higher mortality rates at low and higher FFP-to-RBC ratios and better outcomes when the ratio was 1:2 or 1:3. A 1:1 ratio of FFP to RBC reduced coagulopathy but failed to improve survival, prompting the investigators to caution against adopting the 1:1 ratio without further testing.[134] An important limitation of observational studies in assessing transfusion ratios is that results may be influenced by survival bias; the most severely injured patients do not survive long enough to receive FFP or platelets, which are often not immediately available.[135]

In a computer simulation model of dilutional coagulopathy, Hirshberg and colleagues[136] reported that current massive transfusion protocols used for bleeding patients underestimate dilution of clotting factors to correct dilutional coagulopathy. The researchers provided a sensitivity analysis of a wide range of replacement protocols by programming their model to administer FFP and platelets after transfusion of a predefined number of RBC units. The model was calibrated to data from 44 patients. They determined that the optimal replacement ratios were 2:3 for plasma and 8:10 for platelets with RBC[136] (Figs. 34.5 and 34.6).

The most definitive study on the transfusion ratios was a randomized trial that compared mortality rates for patients who received plasma, platelets, and RBCs in a 1:1:1 ratio or a 1:1:2 ratio.[137] This multicenter study included 680 severely injured patients who were predicted to require massive transfusion on admission to the trauma unit. The two groups had similar 24-hour (13% vs 17%, respectively; $P = .12$) and 30-day mortality rates (22% vs 26%; $P = .26$), which were the primary outcomes. (The critical level for significance was 0.044, accounting for two interim analyses.) Among the predefined outcomes, the only significant benefit in the high-ratio group was in the subjective outcome of *achieving hemostasis* (86% vs 78%; $P = .006$), although this did not translate into a reduced 30-day mortality rate due to exsanguination or any other benefits. The high-ratio group consumed substantially more plasma (median, 7; interquartile range [IQR], 3–13 units vs median, 5; IQR, 2–10 units; $P < .001$) and platelets (median, 12; IQR, 6–18 units vs median, 6; IQR, 0–12 units; $P < .001$).

Using empiric transfusion ratios is not beneficial and increases transfusions in trauma, and by extension, their use in cardiac surgery cannot be recommended, particularly in the era of point-of-care coagulation testing that allow rapid identification of coagulation defects[138–140] (see Chapter 19). It is, however, likely that protocols for massive transfusion improve outcomes by improving access and availability of blood products irrespective of their content. Riskin and colleagues[141] emphasized the importance of expeditious product availability because a survival benefit did not appear related to any alteration in the volume or ratio of blood components used.

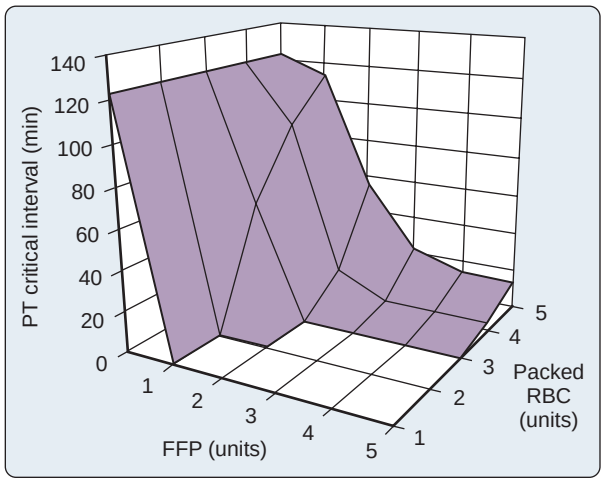


Fig. 34.5 Response surface of the effect of a matrix of fresh frozen plasma–to–red blood cell *(RBC)* replacement ratios on the prothrombin time *(PT)* critical interval. The optimal ratio (2:3) is the point at the edge of the surface where the highest value for red blood cells intersects with the lowest value for fresh frozen plasma *(FFP)* to maintain a critical interval of zero. *(From Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation.* J Trauma. *2003;54:454–463.)*

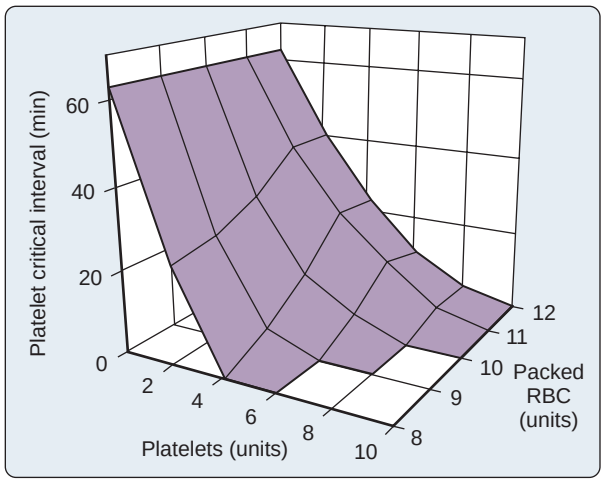


Fig. 34.6 Response surface of the effect of a matrix of platelets–to–red blood cell *(RBC)* replacement ratios on the platelet critical interval. The optimal ratio is 8:10. *(From Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation.* J Trauma. *2003;54:454–463)*

Replacement Therapy

Factor VIIa

Recombinant factor VIIa (rFVIIa, NovoSeven, Novo Nordisk, Bagsværd, Denmark) is approved for the treatment of bleeding in patients with hemophilia A or B with inhibitors against factors VIII and IX. Factor VII acts locally at the site of vessel injury by binding to tissue factor on subendothelial cells and facilitates transformation of factors IX and X to active forms, ultimately resulting in a thrombin burst and clot formation.[142,143] A laboratory investigation examined the effect of rFVIIa-mediated thrombin generation on platelet adhesion and aggregation at normal and reduced platelet counts. The results suggested that administration of rFVIIa in patients with or without thrombocytopenia enhanced platelet deposition and aggregation at the site of vascular injury, which may in part explain the efficacy of rFVIIa in thrombocytopenic patients.[144]

Off-label use of rFVIIa has been reported as a rescue therapy for patients with hemorrhage refractory to conventional therapy. However, the safety of rFVIIa in the cardiac surgical setting has not been clarified. Safety concerns are related to the risk for thrombosis, and reports of thrombotic events have tempered consideration for use in patients beyond rescue therapy, such as prophylactically in patients at high risk for bleeding to avoid blood transfusion.

Since the early 2000s, there have been numerous case reports and case series on the use of rFVIIa in cardiac surgery. Most suggest that rFVIIa is effective in reducing bleeding and decreasing RBC and component therapy requirements in the setting of refractory bleeding. Several, however, have reported increased complication rates associated with rFVIIa use.

In a comprehensive evaluation of off-label use of rFVIIa in Canada, Karkouti and coworkers[145] found that rFVIIa administration (median dose of approximately 60 μg/kg) was associated with significant reductions in transfusion without increases in deaths or major morbid events. They also found that the drug might be more effective given early in the course of bleeding after correction of identifiable coagulation defects.

The Australian and New Zealand Hemostasis Registry found that rFVIIa (median dose of approximately 90 μg/kg) was associated with fewer blood product transfusions.[146] They reported an 11.5% incidence of thromboembolic adverse events, but lacking a control group, they could not determine the relative contribution of rFVIIa versus patients' underlying risk status to the high complication rate. Reduced bleeding occurred in 86% of cases, but the rate was lower for patients whose pH was less than 7.1 before therapy. Patients in whom rFVIIa was effective had reduced mortality rates. Review of the US Food and Drug Administration Adverse Event Reporting System found a total of 431 adverse events related to the use of rFVIIa, among which 185 were thromboembolic events.[147]

In a phase II, randomized, placebo-controlled, dose-escalation trial that included 172 bleeding cardiac surgical patients, Gill and associates[148] reported that patients who received rFVIIa had fewer transfusions after randomization and fewer reoperations for bleeding. However, they also reported an increase in serious adverse events for patients randomized to rFVIIa compared with placebo. Although this increase was not significantly different, it was concerning. Soon after the publication of this study, the manufacturer of rFVIIa ceased further research of rFVIIa use in cardiac surgery.

Prevailing evidence suggests that rFVIIa is effective in refractory bleeding after cardiac surgery but that it does increase the risk of thromboembolic events. This has generated a dichotomy in approach. Although some think that its use should be limited to clinical studies,[149,150] others maintain that it is appropriate to consider its use in the setting of life-threatening, refractory bleeding.[151–153]

Fibrinogen Concentrates

Human fibrinogen concentrates have been used for substitution therapy in cases of hypofibrinogenemia, dysfibrinogenemia, and afibrinogenemia. Accumulating data suggest that fibrinogen, which is both the precursor of fibrin and a cofactor in platelet aggregation,[154,155] plays a critical role in hemostasis, especially in bleeding patients with an acquired fibrinogen deficiency.[156–159] Clinical use of fibrinogen concentrates is based on the supposition that plasma fibrinogen concentrations may become critically reduced somewhat early in a bleeding patient and that this may contribute to the coagulopathy associated with hemorrhage. A functional fibrinogen deficiency may develop with excessive hemodilution.

Normal plasma fibrinogen levels vary from 1.5 to 4.5 g/L,[154,160] and the minimum or critical fibrinogen level that is needed for proper clot formation in bleeding patients is unknown. The traditional critical level for fibrinogen replacement is 0.8 to 1.0 g/L, but several studies have found that clot formation and strength are impaired and that blood loss and transfusion rates are increased when fibrinogen levels are substantially higher than 1.0 g/L.[155,161–169] Later guidelines recommend that the critical level should be increased to between 1.5 and 2.0 g/L.[159]

Because of the importance of fibrinogen in clot formation, some have proposed that the fibrinogen target should be near the upper level of the normal range. Karlsson and collaborators[170] hypothesized that preoperative fibrinogen plasma concentrations within the reference range may be a limiting factor for hemostasis. In a pilot study, the investigators randomized CABG patients with preoperative plasma fibrinogen levels less than 3.8 g/L to an infusion of 2 g fibrinogen concentrate or placebo. End points were vessel occlusion assessed by multislice computed tomography, blood loss, transfusion, and hemoglobin levels 24 hours after surgery. One subclinical vein graft occlusion was reported in the fibrinogen group, with similar global measures of hemostasis assessed by thromboelastography. The fibrinogen group had lower postoperative blood loss and greater hemoglobin concentrations. The study authors appropriately addressed the concern of creating a prothrombotic state with increased incidence of graft occlusion. They were not able to clarify the mechanism behind the reduced bleeding. Fibrinogen plasma levels were increased in the fibrinogen group immediately after infusion, but there were no differences between the groups 2 hours after surgery, and measures of hemostasis also were similar.[170]

In another placebo-controlled pilot study, Rahe-Meyer and colleagues[171] reported a reduction in transfusions with administration of fibrinogen concentrate to a target of approximately 4.0 g/L (using point-of-care fibrinogen assays to estimate fibrinogen levels). A larger multicenter confirmatory study,[171a] however, did not find any benefits with this strategy.[171a] Of note, the median pretreatment fibrinogen level in this study was 1.9 g/L (SD 0.66 g/L), and many of the subjects did not have fibrinogen deficits. This study illustrates that fibrinogen supplementation is not an appropriate first-line therapy in bleeding patients who do not have fibrinogen deficits.

Where indicated, correction of fibrinogen deficits can be accomplished with administration of FFP, cryoprecipitate, and plasma-derived fibrinogen concentrates.[157,172,173] Benefits of fibrinogen concentrates over FFP and cryoprecipitate include viral inactivation, rapid reconstitution, accurate dosing, and a lower volume of administration for equivalent fibrinogen supplementation.

A theoretical model developed by Collins and coworkers suggests that to raise the fibrinogen concentration from 0.9 to 2.0 g/L requires 41 units of cryoprecipitate (ie, 4 g of fibrinogen concentrate) and that it cannot be achieved with FFP transfusion.[174] Data on the safety of fibrinogen concentrate is limited. Fassl and associates[175] used propensity score matching to compare the outcomes of 190 patients who received fibrinogen concentrates (median dose of 2 g) with 190 patients who did not receive fibrinogen concentrates during cardiac surgery. They found no significant between-group differences in 1-year mortality or thromboembolic cardiac event rates (hazard ratio = 0.57; 95% CI, 0.25 to 1.17; $P = .1$ in favor of the fibrinogen group).

Factor XIII

Factor XIII is the terminal enzyme in the coagulation cascade, and it is necessary for cross-linking of fibrin monomers to form a stable and strong fibrin clot.[176,177] Cardiac surgery with CPB leads to a reduction in plasma factor XIII levels, and an association between low factor XIII levels and increased bleeding has been found in some settings, including cardiac surgery.[178–182] Preliminary studies indicated that administration of factor XIII may improve clot strength and reduce blood loss in cardiac surgery, but a multicenter, randomized, phase II study that included 409 cardiac surgical patients at moderate risk for transfusion did not find factor XIII supplementation to be efficacious in reducing transfusions.[183]

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are virally inactivated, lyophilized products that are prepared from pooled plasma and primarily contain the vitamin K–dependent coagulation factors II, VII, IX, and X (Table 34.2).[184] Other components include coagulation inhibitors proteins C and S, heparin, and antithrombin. After reconstitution with small amounts of water, PCCs can be administered rapidly without the need for thawing or blood group matching.

Four-factor PCCs are approved for rapid reversal of oral vitamin K antagonists in patients requiring emergency surgery or invasive procedures. Recommended dosage is based on factor IX content, ranging from 25 to 50 IU of factor IX per 1 kg of body weight, depending on the patient's international normalized ratio (INR) (eg, 25 IU/kg for INR 2.0–3.9; 50 IU/kg for INR 4.0–5.9; 50 IU/kg for INR >5.9).[184] In a phase IIIb study that randomized 181 patients who needed rapid vitamin K antagonist reversal before urgent surgical or invasive procedures to a four-factor PCC or FFP, Goldstein and collaborators[185] found that the four-factor PCC was more efficacious and potentially safer than FFP. Rapid INR reversal was achieved in 55% of the PCC group compared with 10% of the FFP group (difference of 45%; 95% CI, 32–56%). Deductively defined adverse events were similar between the two groups, but the PCC group had fewer adverse events related to the study treatment (9% vs 17%; $P = .2$) and had fewer fluid overload or similar cardiac events (3% vs 13%; $P = .05$).[185]

Three-factor PCCs contain low levels of factor VII, and activated PCCs such as FEIBA, a factor VIII inhibitor bypassing agent, contain trace amounts of activated factor VII and X. These products are primarily indicated for the prevention and treatment of hemophilia-related bleeding.[186] There may be a role for PCCs in the management of surgical coagulopathy instead of FFP outside of vitamin K antagonist reversal; however, data on safety and efficacy are limited.[186,187]

Volume Replacement: Colloids and Crystalloids

Maintenance of intravascular volume is a common goal for perioperative management in cardiovascular surgery. Merits of specific choices for fluid therapy to replace ongoing fluid loss continue to be debated. Although there may be theoretical advantages of using colloid or crystalloid for volume replacement, clinical trial data do not definitively support one over the other in terms of mortality outcomes. Both have distinct advantages and disadvantages.[188] More important than the choice of volume replacement is appropriate volume replacement to avoid tissue hypoperfusion.

Volume of distribution for a particular fluid administered depends on fluid composition. Saline-based crystalloids usually result in expansion of the plasma volume by approximately 200 to 250 mL for each 1 L administered; glucose-based solutions expand the plasma volume by approximately 60 to 70 mL for each 1 L infused; and colloid solutions result in expansion of the plasma volume similar to the volume infused. Within the semisynthetic colloid solutions, there is variation in the degree of plasma volume expansion and a differential influence on hemostasis and inflammatory processes.[189,190]

Those favoring crystalloids for volume replacement have found problems with hemostasis, adverse reactions, and greater risk of volume overload with colloidal fluids. Those favoring colloids highlight larger volumes of crystalloid required to achieve volume resuscitation, tissue edema, and a potential for reduction in tissue oxygen delivery.[191] It is unclear whether the type of fluid therapy for hypovolemia affects development of pulmonary edema. Verheij and colleagues[192] reported that type of fluid given to patients with pulmonary vascular injury without fluid overloading did not influence pulmonary vascular permeability or pulmonary edema.

A key characteristic of colloid solutions is their persistence within the intravascular space, which is determined by rate of loss from the circulation.[190] Albumin is monodisperse substance (ie, uniformity of particle molecular weight), whereas semisynthetic colloids are polydisperse substances (ie, wide distribution of particle molecular weight). The molecular weight of a colloid has pharmacokinetic implications in terms of degree of oncotic effect, viscosity, intravascular persistence, and initial degree of volume expansion. In addition to molecular weight, other properties of colloids such as surface charge affect the degree of loss through capillary endothelium and the rate of glomerular filtration.[189,190,193]

TABLE 34.2 Constituents of Commercially Available Prothrombin Complex Concentrates[a]

Product (Manufacturer), International Availability	Factor Content[b]								Antithrombotic Content				
	II		*VII*		*IX*		*X*		*Protein C*				
	Label (U/mL)	*Ratio (%)*	*Label (U/mL)*	*Ratio (%)*	*Label (U/mL)*	*Ratio (%)*	*Label (U/mL)*	*Ratio (%)*	*C Label (U/mL)*	*S Label (U/mL)*	*Z Label (U/mL)*	*ATIII Label (U/mL)*	*Heparin Label (U/mL)*
Beriplex P/N (CSL Behring); major western European countries	20–48	133	10–25	69	20–31	100	22–60	161	15–45	13–26	Not in label	0.2–1.5	0.4–2.0
Octaplex (Octapharma); major western European countries	11–38	98	9–24	66	25	100	18–30	96	7–31	7–32	Not in label	Not in label	Not in label
Prothromplex Total/ S-TIM 4 Immuno (Baxter); Sweden, Germany, Austria	30	100	25	83	30	100	30	100	20	Not in label	Not in label	0.75–1.5	15
Prothromplex TIM 3 (Baxter); Italy, Austria	25	100	Not in label	—	25	100	25	100	Not in label	Not in label	Not in label	Not in label	3.75
Cofact/PPSB SD (Sanquin/CAF); Netherlands, Belgium, Austria, Germany	15	75	5	25	20	100	15	75	Not in label	Not in label	Not in label	Present, not quantified	Not in label
Kaskadil (LFB); France	40	160	25	100	25	100	40	160	Not in label	Not in label	Not in label	Not in label	Present, not quantified
Uman Complex D.I. (Kedrion); Italy	25	100	Not in label	0	25	100	20	80	Not in label	Not in label	Not in label	Present, not quantified	Present, not quantified
PPSB-human SD/Nano (Octapharma); Germany	25–55	130	7.5–20	45	24–37.5	100	25–55	130	20–50	5–25	Not in label	0.5–3	0.5–6
Profilnine (Grifols); United States	Present	150	Present	35	Present	100	Present	100	Not in label	Not in label	Not in label	Not in label	Not present
Bebulin (Baxter); United States	Present	—	Present (low)	—	Present	100	Present	—	Not in label	Not in label	Not in label	Not in label	0.15 U per U of factor IX
FEIBA (Baxter); USA	Present, not quantified (nonactivated)	Present, not quantified (activated)	500, 1000, or 2500 U per vial (nonactivated)	Present, not quantified (nonactivated)	—	Not in label	Not in label	Not in label	Not in label	Not present	—	—	—

[a]Information is based on product labeling. In Europe, ranges are usually given on the product label in accordance with the European Pharmacopoeia; single values usually are from older, national registrations.
[b]Factor content ratios are based on the content of factor IX.
ATIII, Antithrombin III.
From Levy JH, Tanaka KA, Dietrich W. Perioperative hemostatic management of patients treated with vitamin K antagonists. *Anesthesiology.* 2008;109:918–926.

Albumin is derived from pooled human plasma and has minimal side effects or contraindications. Results from the Saline versus Albumin Evaluation (SAFE) trial, which randomized 7000 critically ill medical and surgical patients to 4% albumin or normal saline, provided evidence on the safety of albumin in critically ill patients. The groups had similar mortality outcomes at the 28-day follow-up and similar secondary outcomes of length of stay, ventilatory requirements, and renal replacement therapy.[194–196]

Semisynthetic colloids are dissolved in a crystalloid carrier solvent consisting of isotonic or hypertonic saline or glucose or an isotonic balanced electrolyte solution. Clinical data provide supportive evidence in terms of patient outcomes for colloids with a balanced solvent solution mirroring the composition of plasma.[189,190] Semisynthetic colloids increase the risk of bleeding, largely because of hemodilution of clotting factors, reductions in factor VIII/vWF (also caused by hemodilution), and functional platelet abnormalities.[189,190,195,197,198] A retrospective chart review concluded that intraoperative use of hetastarch in cardiac surgery requiring CPB increased bleeding and transfusion requirements.[199]

A laboratory investigation examined the effect of fluid resuscitation with three colloids (ie, Hextend, Dextran 70, and 5% albumin) on coagulation and uncontrolled bleeding in rabbits subjected to a splenic injury. Although the prothrombin and partial thromboplastin times were prolonged in all rabbits, thromboelastography and thrombin generation assays identified more severe coagulopathy with Hextend and Dextran 70 than with albumin. Their results suggested resuscitation with albumin-maintained coagulation function, decreased blood loss, and improved survival time compared with synthetic colloids.[200]

Lang and coworkers[201] examined the impact of volume replacement with 6% hydroxyethyl starch or Ringer lactate solutions on tissue oxygen tension during and after major surgical procedures. Patients who received 6% hydroxyethyl starch had improved tissue oxygenation compared with a crystalloid-based volume replacement strategy. Improvements in tissue oxygen tension in the hydroxyethyl starch–treated group were thought to result from improved microperfusion and less endothelial swelling.

Jacob and associates[190] examined the impact of albumin, hydroxyethyl starch, and saline as resuscitation fluids on vascular integrity in an isolated guinea pig perfused heart model. The study authors hypothesized that fluid extravasation might lead to myocardial edema and consequent reduction in ventricular function. Albumin more effectively prevented fluid extravasation in the heart than crystalloid or artificial colloid, and this effect was partly independent of colloid osmotic pressure. Others have found that using albumin for the CPB prime better preserved platelet counts than a crystalloid prime and more favorably influenced colloid oncotic pressure, positive fluid balance, and postoperative weight gain.[202]

Blood Substitutes

Risks associated with RBC transfusion in terms of morbidity, mortality, survival, and availability of supply have spurred development of alternatives to blood transfusion for decades. Ideal characteristics of a blood substitute include long shelf life, no need to crossmatch, immediate availability, and lack of toxic side effects.[203] Hemoglobin-based oxygen carriers (HBOCs) are engineered human, animal, or recombinant hemoglobin products in a cell-free hemoglobin preparation. There are no approved products in the United States.[204,205] Perfluorocarbon-based oxygen carriers are aqueous emulsions of a perfluorocarbon derivative that dissolve relatively large amounts of oxygen and usually require patients to breathe oxygen-enriched air.[204]

Failure to bring a product to the clinical arena has been attributed to toxicity-related issues. First-generation HBOCs had issues with the way oxygen was carried and released from RBCs. Several adverse events have been reported in clinical trials of oxygen carriers, including death, stroke, hypertension, anemia, and abdominal pain.[206] Others have reported adverse effects that included rash, diarrhea, hemoglobinuria, elevated lipase levels, vasoconstrictive effects, and increased hemostatic effects because of the reversal of inhibition effect of nitric oxide on platelet aggregation. Free plasma hemoglobin generates reactive oxygen species and is a potent scavenger of nitric oxide[205] (Table 34.3).

In a review of oxygen carriers, Winslow[206] found the solutions caused vasoconstriction, which has been one of the limiting factors for clinical use. Vasoconstriction may be caused by scavenging nitric oxide by hemoglobin or an oversupply of oxygen from free hemoglobin through facilitated diffusion. An understanding of the proposed mechanisms of vasoconstriction (ie, oversupply theory) led to new product development involving modification of hemoglobin with a lower P_{50} (ie, oxygen tension at which hemoglobin is 50% saturated) and increased molecule size, reducing the release of oxygen in resistance vessels and resultant vasoconstriction.[207]

Yu and colleagues[208] described profound vasoconstrictor side effects that limited the clinical utility of HBOCs, and they attributed this side effect to nitric oxide scavenging. The investigators found that by inhaling nitric oxide, changes occur in body stores of nitric oxide metabolites without producing hypotension and may prevent hypertensive side effects of HBOC infusion. Others have reported the nitric oxide–scavenging properties of HBOCs as a likely mechanism of vasoconstriction associated with infusion and proposed modifications that could ameliorate this side effect.[209,210]

A basic science working group from the National Heart, Lung, and Blood Institute Division of Blood Diseases and Resources provided recommendations for a basic science focus in the area of blood substitutes. The working group highlighted impediments to further HBOC product development due to the significant side effects of excessive cardiovascular and cerebrovascular events and death.[211]

Lowest Hematocrit on Cardiopulmonary Bypass

Anemia while on CPB and transfusion of RBCs have been associated with adverse perioperative outcomes. Hemodilution due to fixed priming volume and pre-CPB fluid administration contribute to anemia and transfusion need.[212,213] Minimum hematocrit values less than or equal to 14% on CPB have been associated with postoperative deaths of CABG patients; and for high-risk patients, values less than 17% increase mortality risk.[214] The morbidity risk associated with hemodilutional anemia is thought to result from inadequate oxygen delivery leading to organ dysfunction.[215]

The lowest hematocrit while on CPB is a risk factor for postoperative low-output syndrome and renal failure. Ranucci and coworkers[216] reported a cutoff hematocrit value of 23% for renal failure and 24% for development of the low-output syndrome. RBC transfusion also was associated with renal failure and the low-output syndrome in their investigation. The risk for renal injury further increased when RBC transfusions were associated with a nadir hematocrit of less than 23% while on CPB.

Swaminathan and associates[217] reported more perioperative renal injury with hemodilution, targeting CPB hematocrit levels of 22% to 24%. The investigators highlighted the renal benefits of hemodilution related to reductions in blood viscosity and improved regional blood flow. However, a well-defined cutoff value for hemodilution has not been clarified. They were unable to find an "elbow" for a cutoff between the hematocrit and a change in creatinine values. The significant association between the lowest CPB hematocrit and a change in creatinine values was highly influenced by body weight in their investigation.[217] Others have reported that hemodilution while on CPB to hematocrit values less than 24% and associated renal injury were further exacerbated by longer CPB times and RBC transfusion.[215]

Karkouti and collaborators[218] suggested a U-shaped relationship between the nadir hematocrit while on CPB and renal failure requiring dialysis. Moderate hemodilution (ie, hematocrit values between 21% and 25%) were associated with the lowest risk for acute renal failure; risk increased as nadir hematocrit concentrations decreased to

TABLE 34.3 Adverse Events Reported in the Literature or Publicly Available[a]

	Apex		*Baxter*[24–26,37,69,71–78]		*Biopure*[b 76,79–86]		*Enzon*		*Hemosol*[87–89]		*Northfield Laboratories*[c 19,90–92]		*Sangart*[17,18]		*Somatogen*[30,93,94]	
Cohort Characteristics	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*	*Test*	*Ctl*
No. of subjects	Not reported		504	505	708	618	Not reported		209	192	623	457	85	45	64	26
1. Death	—	—	78	61	25	14	—	—	1	4	73	39	2	0	—	—
2. Hypertension	—	—	76	38	166	59	—	—	113	75	—	—	7	1	8	0
3. Pulmonary hypertension	—	—	1	0	3	0	—	—	—	—	—	—	—	—	—	—
4. Chest pain/chest tightness	—	—	—	—	21	16	—	—	—	—	—	—	—	—	12	0
5. Congestive heart failure	—	—	0	1	54	22	—	—	0	2	17	20	—	—	—	—
6. Cardiac arrest	—	17	6	—	—	1	1	14	9	—	—	—	—	—		
7. Myocardial infarction	—	—	6	1	14	4	—	—	14	7	29	2	2	0	—	—
8. Cardiac arrhythmias/ conduction abnormalities	—	—	23	17	153	100	—	—	1	1	—	—	15	5	1	1
9. Cerebrovascular accident, cerebrovascular ischemia, TIA	—	—	—	—	16	3	—	—	2	1	3	1	—	—	—	—
10. Pneumonia	—	—	—	—	35	22	—	—	—	—	27	21	—	—	—	—
11. Respiratory distress/failure	—	—	—	—	22	12	—	—	—	—	21	17	—	—	—	—
12. Acute renal failure	—	—	1	3	10	4	—	—	2	2	—	—	—	—	—	—
13. Hypoxia, cyanosis, decreased oxygen saturation	—	—	—	—	76	35	—	1	1	1	—	—	—	—	3	1
14. Hypovolemia	—	—	—	—	19	4	—	—	—	—	—	—	—	—	—	—
15. Gastrointestinal	—	—	51	31	345	195	—	—	23	1	—	—	57	20	36	6
16. Liver, LFTs abnormal	—	—	27	8	20	5	—	—	8	0	—	—	—	—	6	3
17. Pancreatitis	—	—	11	0	5	3	—	—	1	0	—	—	—	—	—	—
18. Coagulation defect, thrombocytopenia, thrombosis	—	—	—	—	45	17	—	—	1	0	13	4	—	—	—	—
19. Hemorrhage/bleeding/anemia	—	—	33	22	108	55	—	—	1	1	20	17	—	—	—	—
20. Sepsis, septic shock, MOF	—	—	2	2	15	6	—	—	0	1	26	20	—	—	—	—
21. Pancreatic enzyme inc	—	—	13	4	3	0	—	—	—	—	—	—	—	—	—	—
22. Lipase increase	—	—	29	9	48	12	—	—	19	2	—	—	8	4	7	1
23. Amylase increase	—	—	48	45	—	—	—	—	35	20	—	—	7	2	4	1

[a]Not all clinical trials conducted by commercial sponsors have been published, and the published results are not synonymous with line listings that would be found in a comprehensive final study report. For each paper, editorial decisions were made about what information should be included or excluded and data presentation (numbers vs percentages), making derivation of the number of subjects experiencing an event and aggregation of information to derive a comprehensive list of adverse events difficult and potentially incomplete. Not all studies were controlled. Not all enzyme elevations were captured as adverse events, and in some instances, the number of subjects experiencing enzyme elevations was not captured. Differences in reporting methods may have resulted in counting subjects more than once in each category of events (ie, rows).

[b]See also http://www.fda.gov/ohrms/dockets/ac/cber06.html#BloodProducts.

[c]See also http://northfieldlabs.com.

Ctl, Control; *LFTs*, liver function tests; *MOF*, multisystem organ failure; *TIA*, transient ischemic attack; —, no information available.

From Silverman TA, Weiskopf RB. Hemoglobin-based oxygen carriers: current status and future directions. *Transfusion. 2009;*49:2495–2515.

less than 21% or were greater than 25%. In congenital heart surgery, Jonas and colleagues[219] reported that lower hematocrit strategies (21% ± 2.9%) compared with higher hematocrit strategies (28% ± 3.2%) were associated with higher serum lactate levels 60 minutes after CPB, greater percentage of increase in total body water on postoperative day 1, and at 1 year of age, worse scores on the Psychomotor Development Index. The study authors concluded that a lower hematocrit strategy was associated with increased risk for developmental impairment.

Loor and colleagues examined the relationship between a lower nadir hematocrit and postoperative complications in more than 7000 cardiac surgical patients who did not receive RBC transfusions. A lower nadir hematocrit was associated with higher mortality rates and more postoperative morbidity.[220] It appeared that after the threshold of a hematocrit of less than 24% was reached, risk increased. A separate study by the same group of investigators examined the risks of a single exposure to anemia, a single RBC transfusion, and both exposures. They reported exposure to both anemia and RBC transfusion was associated with the highest risk of poor outcomes. The lowest risk was with neither exposure; the risk of a single exposure to anemia or transfusion depended on the organ system. For example, the kidneys were more sensitive to anemia exposure, as reflected by a decrease in the estimated glomerular filtration rate, and the lungs were more sensitive to an RBC transfusion exposure.[221]

DeFoe and coworkers[222] reported a risk-adjusted increased risk for mortality, need for an intraaortic balloon pump, and return to CPB after initial separation for a nadir hematocrit while on CPB. Smaller patients and those with lower preoperative hematocrit values were at greater risk for lower CPB values. They reported trends toward increasing risk for death among patients with hematocrit values less than 23%, and for those with hematocrit values less than 19%, the mortality rate was almost twice as high as for patients with hematocrit values of 25% or more.[222] Others have reported the association between hemodilution to hematocrit values of 24%, RBC transfusion, and increased risk of renal and splanchnic injury.[223]

Not all investigations have reported adverse consequences with lower nadir hematocrit values while on CPB; von Heymann and associates[224] examined oxygen delivery, oxygen consumption, and outcomes for low-risk CABG patients assigned CPB hematocrit values of 20% or 25%. They reported similar oxygen delivery, oxygen consumption, blood lactate levels, and clinical outcome measures for the two groups. They concluded that CPB hematocrit values of 20% were adequate to maintain calculated whole-body oxygen delivery above critical levels.

Similarly, Berger and collaborators randomized patients to profound hemodilution with CPB hematocrit values between 19% and 21% or standard values of 24% to 26%. They reported similar changes in intestinal permeability and cytokine release for the two groups and concluded that CPB hematocrit values between 19% and 21% did not adversely affect outcomes.[225]

Orlov and colleagues[226] described the clinical utility of using the oxygen extraction ratio as an adjunct to hemoglobin concentration for guiding RBC transfusion decisions in cardiac surgery. They suggested that a normal oxygen extraction ratio in patients with anemia and no evidence of organ dysfunction indicated adequate tissue oxygen delivery and that by incorporating this measure into the transfusion decisions, RBC transfusions could be reduced.

Variations in transfusion practice reflect the continuing controversy about when to transfuse RBCs.[227,228] Although a single trigger is not ideal, it is often what initiates transfusion discussions in the perioperative period. Several publications have described liberal versus restrictive transfusion strategies. Many have reported similar outcomes, with the study authors supporting a more restrictive approach.

An editorial highlighted the complexity of the issue of when to transfuse. It suggested that there may an adaptive response to anemia up to the point of organ damage and that the point may vary by patient, organ system, and level of anemia. Without a way to measure when a tissue bed is signaling stress related to tissue hypoxia, the definitive answer on when to transfuse remains uncertain.[229]

Conclusions

Proper blood and fluid management in the perioperative period are critical to the care of cardiac surgical patients and can significantly influence patient outcomes. A better understanding of the role of genetics in perioperative bleeding may enable a more proactive approach to patients before surgical intervention. Technologic advances in the measurement of tissue oxygenation will allow better, evidenced-based decisions about transfusion in the future.

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35

Transfusion Medicine and Coagulation Disorders

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KEY POINTS

1. It is easiest to think of coagulation as a wave of biologic activity occurring at the site of tissue injury consisting of initiation, acceleration, control, and lysis.
2. Hemostasis is part of a larger body system: inflammation. The protein reactions in coagulation have important roles in signaling inflammation.
3. Thrombin is the most important coagulation modulator, interacting with multiple coagulation factors, platelets, tissue plasminogen activator, prostacyclin, nitric oxide, and various white blood cells.
4. The serine proteases that compose the coagulation pathway are balanced by serine protease inhibitors, termed *serpins*. Antithrombin is the most important inhibitor of blood coagulation, but others include heparin cofactor II and alpha I antitrypsin.
5. Platelets are the most complex part of the coagulation process, and antiplatelet drugs are important therapeutic agents.
6. Heparin requires antithrombin to anticoagulate blood and is not an ideal anticoagulant for cardiopulmonary bypass. Newer anticoagulants are actively being sought to replace heparin.
7. Protamine can have many adverse effects. Ideally, a new anticoagulant will not require reversal with a toxic substance such as protamine.
8. Antifibrinolytic drugs are often given during cardiac surgery; these drugs include ε-aminocaproic acid and tranexamic acid.
9. Recombinant factor VIIa is an off-label "rescue agent" to stop bleeding during cardiac surgery, but it can also be prothrombotic, which is an off-label use of the drug.
10. Every effort should be made to avoid transfusion of banked blood products during routine cardiac surgery. In fact, bloodless surgery is a reality in many cases. Patient blood management, including techniques to reduce coagulation precursors, has been shown to be cost effective and to have better outcomes than routine surgery.
11. The evolving risks of transfusion have shifted from viral transmission to transfusion-related acute lung injury (TRALI) and immunosuppression. Those patients who receive allogeneic blood have a measurable increased rate of perioperative serious infection (approximately 16% increase per unit transfused).
12. Cardiac centers that have adopted multidisciplinary blood management strategies have improved patient outcomes and decreased costs. The careful application of these strategies in use of coagulation drugs and products is very beneficial.
13. Whole blood viscoelastic testing in conjunction with platelet count and fibrinogen concentration laboratory testing is of value in guiding coagulation therapy. All available testing modalities are most effective when teams have discussed and created accepted algorithms for care of the bleeding patient in their institution.
14. New purified human protein adjuncts are replacing FFP and cryoprecipitate with four-agent prothrombin complex concentrate (PCC) and human lyophilized fibrinogen.

Coagulation and bleeding assume particular importance when surgery is performed on the heart and great vessels using extracorporeal circulation. This chapter provides an understanding of the depth and breadth of hemostasis relating to cardiac procedures, beginning with coagulation pathophysiology. The pharmacology of heparin and protamine follows. This background is then applied to treatment of the bleeding patient. Coagulation monitoring is covered in Chapter 19, and fluid and blood management is further discussed in Chapter 34. This chapter will, however, point out how monitoring can help with appropriate coagulation management decisions under certain circumstances.

Overview of Hemostasis

Blood cannot coagulate to stop hemorrhage unless there is closure of large vessels. Any vascular structure larger than 50 μm cannot contract enough to allow platelets and proteins to perform their actions. Superb, meticulous surgical technique is the single most important variable in decreasing postoperative bleeding/blood transfusion requirements. Those centers with surgeons who are not only fast, but willing to spend a few extra minutes conserving blood by detailed hemostasis, will exhibit better outcomes.

Proper hemostasis requires the participation of innumerable biologic elements (Box 35.1). This section groups them into four topics

to facilitate understanding: coagulation factors, platelet function, the endothelium, and fibrinolysis. The reader must realize this is for simplicity of learning, and that in biology, the activation creates many reactions (perhaps >800) and control mechanisms, all interacting simultaneously. The interaction of the platelets, endothelial cells, and proteins to either activate or deactivate coagulation is a highly buffered and controlled process. It is perhaps easiest to think of coagulation as a wave of biologic activity occurring at the site of tissue injury (Fig. 35.1).[1] Although there are subcomponents to coagulation itself, the injury/control leading to hemostasis is a four-part event: initiation, acceleration, control, and lysis (recanalization/fibrinolysis). The initiation phase begins with tissue damage, which really is begun with endothelial cell destruction or dysfunction. This initiation phase leads to binding of platelets, as well as protein activations; both happen nearly simultaneously, and each has feedbacks into the other. Platelets adhere, creating an activation or acceleration phase that gathers many cells to the site of injury. From that adhesion a large number of events of cellular/protein messaging cascade. As the activation phase ramps up into an explosive set of reactions, counter-reactions are spun off, leading to control proteins damping the reactions. It is easiest, conceptually, to think of these control mechanisms as analogous to a nuclear reactor. The activation phase would continue to grow and overcome the whole organism unless control rods were inserted (eg, thrombomodulin, proteins C and S, and tissue plasminogen activator [t-PA]) to stop the spread of the reaction. The surrounding normal endothelium acts quite differently from the disturbed (ischemic) endothelium. Eventually, the control reactions overpower the acceleration reactions and lysis comes into play. The diagram in Fig. 35.1 shows lysis as a relatively quick process, but it can take from 24 hours to days to have its full effects. A key concept is that hemostasis is part of a larger body system: inflammation. Most, if not all, of the protein reactions of coagulation control have importance in signaling inflammation leading to other healing mechanisms. Entire books have been written merely to examine these fascinating interactions. It is no wonder that cardiopulmonary bypass (CPB) has such profound inflammatory effects when it is considered that each of the activated coagulation proteins and cell lines then feeds into upregulation of inflammation.

During cardiac surgery, the endothelium (locally and systemically) is disturbed.[2] The coronary arteries are made either partially or fully ischemic for periods with cardioplegia (perfused CPB being relatively rare today). Little known is that high concentrations of potassium are particularly insulting to endothelial cells. Ischemia/reperfusion injury is, therefore, the norm for every cardiac surgical case using CPB.[3] Systemic ischemia and reperfusion occur throughout every capillary bed because micro-air, thrombus, and fat emboli are by-products of CPB[4] (see Chapters 31–35 and 40). It is quite possible that transfusion of red blood cell (RBC) products, through blocking of the microcirculation, actually may contribute to ischemia/reperfusion injury. Transfusion has been shown to evoke endothelial cell hyper-reactivity mediated through erythrocyte cell membrane microparticles liberated during blood bank storage.[4] Furthermore, the dysfunctional erythrocytes given during transfusion may plug the microcirculation and probably contribute to endothelial cell dysfunction.

The coagulation proteins and platelets are both hemodiluted and consumed during CPB. Platelets are activated/inhibited by various means. Coagulation dysfunction in cardiac surgery has been studied for more than 60 years. The complexity of the myriad number of dysfunctions should impress the student of this area. Unfortunately, when a patient is bleeding in the operating room (OR) or intensive care unit (ICU), there is no universal way to quickly sort out the causative events. Furthermore, the interventions are limited; yet an educated and planned approach (algorithm-driven transfusion/coagulation intervention) does decrease unnecessary transfusion and influences subsequent bleeding.

BOX 35.1 COMPONENTS OF HEMOSTASIS

- Coagulation factor activation
- Platelet function
- Vascular endothelium
- Fibrinolysis and modulators of coagulation

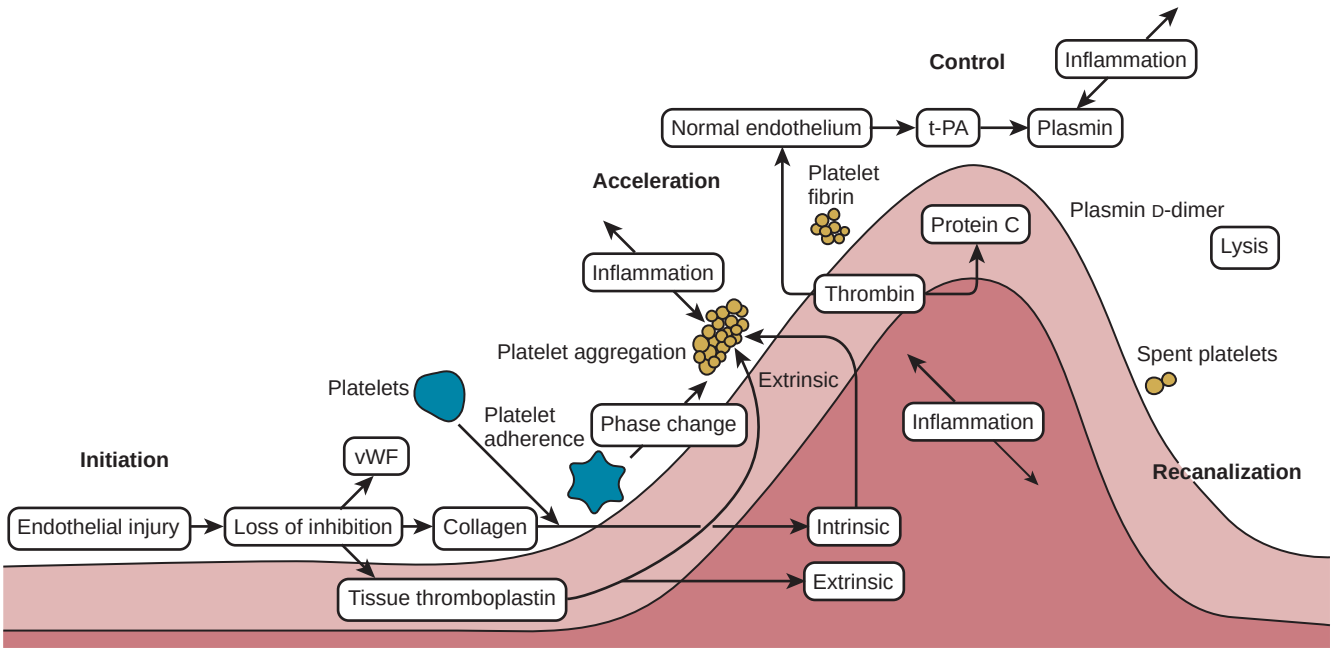


Fig. 35.1 Coagulation is a sine wave of activity at the site of tissue injury. It goes through four stages: initiation, acceleration, control, and lysis/recanalization. *t-PA,* Tissue plasminogen activator; *vWF,* von Willebrand factor. *(Redrawn from Spiess BD. Coagulation function and monitoring. In: Lichtor JL, ed.* Atlas of Clinical Anesthesia. *Philadelphia: Current Medicine; 1996.)*

Protein Coagulation Activations

Coagulation Pathways

The coagulation factors participate in a series of activating and feedback inhibition reactions, ending with the formation of an insoluble clot.[5] A *clot* is the sum total of platelet-to-platelet interactions, leading to the formation of a platelet plug (initial stoppage of bleeding). The cross-linking of platelets to each other by way of the final insoluble fibrin leads to a stable clot. Clot is not simply the activation of proteins leading to more protein deposition. Clinicians have been shaped in their thinking about coagulation by the historic way that coagulation proteins were discovered and the resulting coagulation tests (prothrombin time [PT] and activated thromboplastin time). It is that teaching of the coagulation cascade, with resultant monitoring technology, that has led to some transfusion behaviors. The way coagulation has been classically taught (separate protein cascades) is not the way coagulation proceeds biologically.

With few exceptions, the coagulation factors are glycoproteins (GPs) synthesized in the liver, which circulate as inactive molecules termed *zymogens.* Factor activation proceeds sequentially, each factor serving as substrate in an enzymatic reaction catalyzed by the previous factor in the sequence. Hence this reaction sequence classically has been termed a *cascade* or *waterfall.* Cleavage of a polypeptide fragment changes an inactive zymogen to an active enzyme often by creating a conformational change of the protein exposing an active site. The active form is termed a *serine protease* because the active site for its protein-splitting activity is a serine amino acid residue. Many reactions require the presence of calcium ion (Ca^{2+}) and a phospholipid surface (platelet phosphatidylserine). The phospholipids occur most often either on the surface of an activated platelet or endothelial cell and occasionally on the surface of white cells. So anchored, their proximity to one another permits reaction rates profoundly accelerated (up to 300,000-fold) from those measured when the enzymes remain in solution. The factors form four interrelated *arbitrary* groups (Fig. 35.2): the contact activation, intrinsic, extrinsic, and common pathways. They were so labeled historically by the human need for order. In biology, they are all highly interactive, occur simultaneously on the surface of cells, and have feedback loops with cross-reactions.

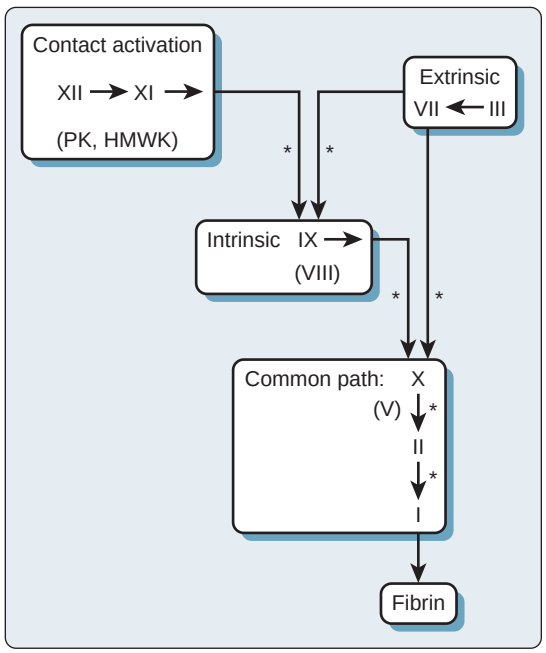


Fig. 35.2 Depiction of coagulation protein activation sequence. *Asterisks* denote participation of calcium ion. *HMWK,* High-molecular-weight kininogen; *PK,* prekallikrein.

When you look at the coagulation cascade with its multiple arrows, one cannot see which direction some reactions are flowing or which is the predominant reaction.

Contact Activation

Factor XII, high-molecular-weight kininogen (HMWK), prekallikrein (PK), and factor XI form the contact or surface activation group. The in vivo events that activate factor XII remain unconfirmed, because this seems to be built to recognize foreign surfaces. Clinicians do know that ex vivo contact with ionically charged surfaces will activate factor XII. Because factor XII autoactivates by undergoing a shape change in the presence of a negative charge, in vitro coagulation tests use glass, silica, kaolin, and other compounds with negative surface charge (see Chapter 19). The glycocalyx of endothelial cells has a repelling charge for coagulation proteins. One potential in vivo mechanism for factor XII activation is disruption of the endothelial cell layer, which exposes the underlying negatively charged collagen matrix. Activated platelets also provide negative charges on their membrane surfaces. HMWK anchors the other surface activation molecules, PK and factor XI, to damaged endothelium or activated platelets. Factor XIIa cleaves both factor XI, to form factor XIa, and PK, to form kallikrein. Fig. 35.3 depicts the events of surface activation.

This system interlinks to the complement cascade and fibrinolytic process as follows. Kallikrein converts HMWK to bradykinin, which activates the complement proteins. Kallikrein also may convert plasminogen to plasmin (see later). This latter function is quite weak, however, and of unknown significance in vivo.

It was rather tempting historically to attribute all coagulation abnormalities of cardiac surgery to activation of the contact system. This seemed an obvious explanation for the coagulopathy of CPB. The circuits are most often made of polyvinylchloride with a negatively charged surface. Today, it is known that the effects of contact activation in the entire scheme of CPB coagulation dysfunction are actually quite small. Of note, patients with completely absent factor XII do just fine and do not exhibit excess bleeding, nor are they particularly devoid of microvascular bleeding after CPB. Therefore the presence or absence of factor XII in the evolution of humankind seems to not be critical for survival. It also should reveal that the surface activation mechanism is not the driving force behind the bleeding/consumptive coagulopathy of CPB.

Intrinsic System

Intrinsic activation forms factor XIa from the products of surface activation. Factor XIa splits factor IX to form factor IXa, with Ca^{2+} required for this process. Then factor IXa activates factor X with help from Ca^{2+}, a phospholipid surface (platelet-phosphatidylserine), and a GP cofactor, factor VIIIa. Fig. 35.4 displays a stylized version of factor X activation. Please note that the phospholipids and GP cofactors are on the surface of platelets.

Extrinsic System

Activation of factor X can proceed independently of factor XII by substances classically thought to be extrinsic to the vasculature (hence the name). This is of historic interest because today it is known that the expression of tissue factor is actually a highly regulated event in endothelial cells. Any number of endothelial cell insults can lead to the production of tissue factor by the endothelial cell.[3–10] At rest, the endothelial cell is quite antithrombotic. However, with ischemia, reperfusion, sepsis, or cytokines (particularly interleukin [IL]-6), the endothelial cell will stimulate its production of intracellular nuclear factor-κB and send messages for the production of messenger RNA for tissue factor production.[6] This can happen quickly and the resting endothelial cell can turn out large amounts of tissue factor. It is widely held today that the activation of tissue factor is what drives many of the abnormalities of coagulation after cardiac surgery, rather than contact activation.[7,8] In some tissues, cells outside the vasculature contain large amounts of tissue factor. They are released when cells are damaged/ruptured. Thromboplastin, also known as tissue factor, released from

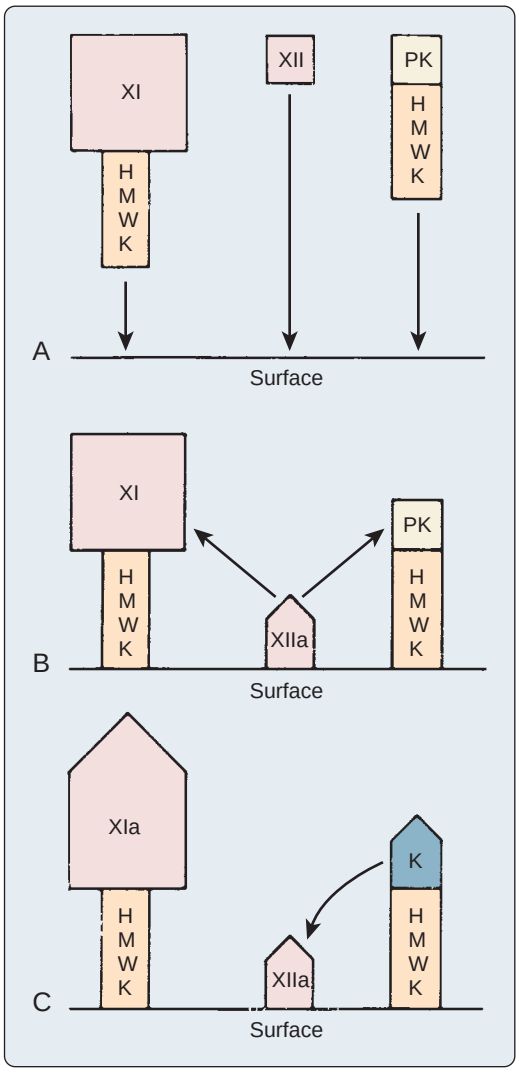


Fig. 35.3 (A–C) Activation of the contact factors XII, XI, and prekallikrein (PK). The cofactor, high-molecular-weight kininogen (HMWK), binds factor XI and PK to the endothelial surface. Kallikrein (K) amplifies factor XII activation. *(From Colman RW, Marder VJ, Salzman EW, Hirsh J. Overview of hemostasis. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds.* Hemostasis and Thrombosis. *3rd ed. Philadelphia: JB Lippincott; 1994:3.)*

tissues into the vasculature, acts as a cofactor for initial activation of factor X by factor VII. Factors VII and X then activate one another with the help of platelet phospholipid and Ca^{2+}, thus rapidly generating factor Xa. (Factor VIIa also activates factor IX, thus linking the extrinsic and intrinsic paths.)

Thromboplastin straddles the extravascular cell membrane, with its extracellular portion available to bind factor VIIa. Cytokines (particularly tumor necrosis factor-α and IL-6) and endotoxins can stimulate its expression on endothelium.[9,10] Thromboplastin anchors factor VIIa to the cell surface, thus facilitating activation of factor X. The amount of available factor Va also seems to be quite important for the adequate functioning of the normal coagulation cascades.

Common Pathway

Using membrane phospholipids (phosphatidylserine) as a catalyst site, Ca^{2+} as a ligand, and factor Va as cofactor, factor Xa splits prothrombin (factor II) to thrombin (factor IIa). The combination of factors Xa, Va, and Ca^{2+} is termed the *prothrombinase complex*—a critical step. Factor Xa anchors to the membrane surface (of platelets) via Ca^{2+}. Factor Va, assembling next to it, initiates a rearrangement of the complex,

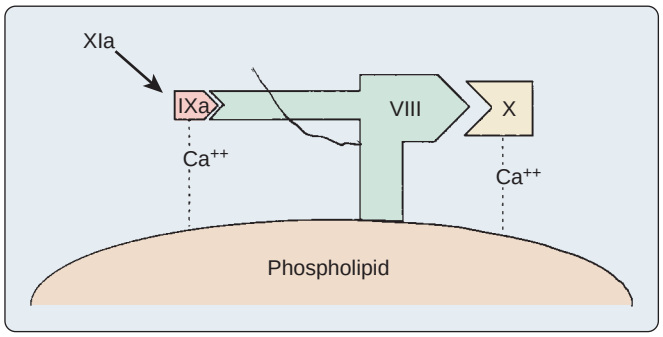


Fig. 35.4 Factor VIII facilitates the activation of factor X by factor IXa. Calcium tethers the molecules to the phospholipid surface. *(From Horrow JC: Desmopressin and antifibrinolytics.* Int Anesthesiol Clin. *1990;28:230.)*

vastly accelerating binding of the substrate, prothrombin. Most likely, the factor Xa formed from the previous reaction is channeled along the membrane to this next reaction step without detaching from the membrane.

Fig. 35.5 depicts the steps involved in formation of thrombin from its precursor, prothrombin. The by-product, fragment F1.2, serves as a plasma marker of prothrombin activation. An alternative scheme generates a different species, meizothrombin, involved more specifically in activation of coagulation inhibitors.[11]

Thrombin cleaves the fibrinogen molecule to form soluble fibrin monomer and polypeptide fragments termed *fibrinopeptides A* and *B*. Fibrin monomers associate to form a soluble fibrin matrix. Factor XIII, activated by thrombin, cross-links these fibrin strands to form an insoluble clot. Patients with lower levels of factor XIII have been found to have more bleeding after cardiac surgery.[11,12]

Vitamin K

Those factors that require calcium (II, VII, IX, X) depend on vitamin K to add between 9 and 12 γ-carboxyl groups to glutamic acid residues near their amino terminal. Calcium tethers the negatively charged carboxyl groups to the phospholipid surface (platelets), thus facilitating molecular interactions. Some inhibitory proteins also depend on vitamin K (proteins C and S) for their functional completion.

Modulators of the Coagulation Pathway

Thrombin, the most important coagulation modulator, exerts a pervasive influence throughout the coagulation factor pathways. It activates factors V, VIII, and XIII; cleaves fibrinogen to fibrin; stimulates platelet recruitment, creates chemotaxis of leukocytes and monocytes; releases t-PA, prostacyclin, and nitric oxide from endothelial cells; releases IL-1 from macrophages; and with thrombomodulin, activates protein C, a substance that then inactivates factors Va and VIIIa.[12] Note the negative feedback aspect of this last action (Fig. 35.6). Coagulation function truly centers on the effects of thrombin as far reaching accelerant. The platelets, tissue factor, and contact activation all are interactive and activated by a rent in the surface of the endothelium or through the loss of endothelial coagulation control. Platelets adhere to a site of injury and, in turn, are activated, leading to sequestration of other platelets. It is the interaction of all of those factors together that eventually creates a critical mass of reacting cells and proteins, which in turn, leads to clot formation. Once enough platelets are interacting together, with their attached surface concomitant serine protease reactions, then a thrombin burst is created. Only when enough thrombin activation has been encountered in a critical time point is a threshold exceeded, and the reactions become massive—much larger than the sum of the parts. It is thought that the concentration and ability of platelets to react fully affect the ability to have a critical thrombin burst. CPB may affect the ability to get that full thrombin burst because it reduces platelet number, decreases platelet-to-platelet interactions, and decreases the concentration of protein substrates.

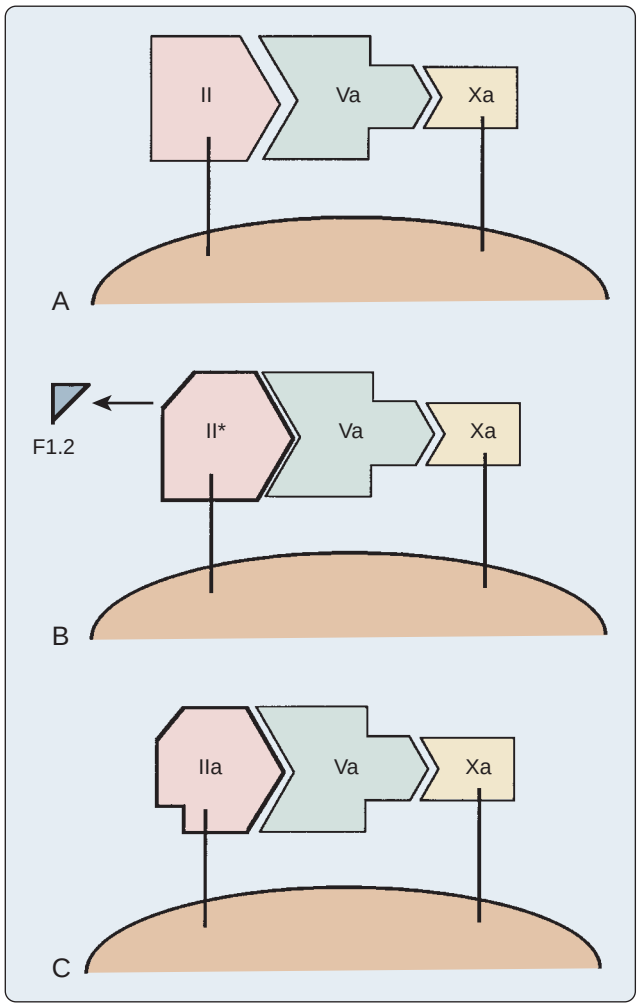


Fig. 35.5 Activation of prothrombin by factor Xa proceeds in a multistep fashion. (A) On the phospholipid surface, the prothrombinase complex consists of prothrombin (factor II), factor Xa, and factor Va. (B) The first activation step in which the prothrombin fragment F1.2 is split from prothrombin to form prethrombin (II*). (C) Molecular rearrangement of prethrombin yields thrombin.

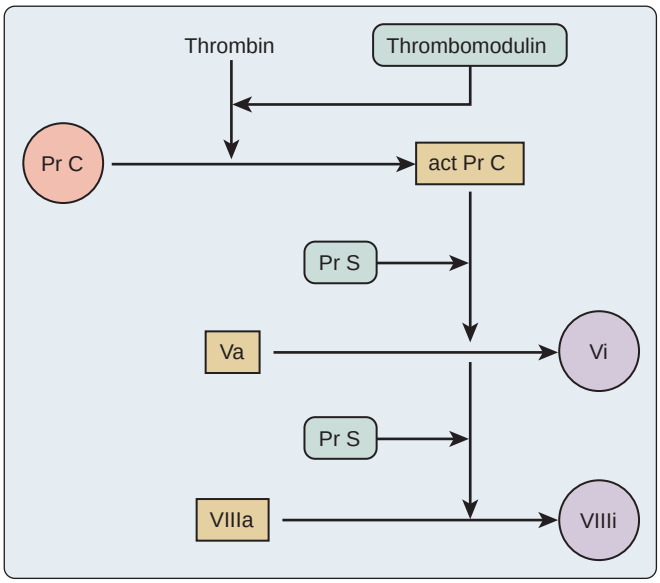


Fig. 35.6 Modulating effects of protein C on coagulation. Thrombomodulin from endothelial cells accelerates thrombin activation of protein C *(Pr C)*. In the presence of protein S *(Pr S)*, activated protein C [(act Pr C)a] inactivates factors V and VIII. Protein C and protein S are vitamin K dependent.

The many serine proteases that compose the coagulation pathways are balanced by serine protease inhibitors, termed *serpins*.[13] Thus a biologic yin and yang leads to an excellent buffering capacity. It is only when the platelet-driven thrombin burst so overwhelms the body's localized anticoagulation or inhibitors that clot proceeds forward. Serpins include α_1-antitrypsin, α_2-macroglobulin, heparin cofactor II, α_2-antiplasmin, antithrombin (AT; also termed *antithrombin III* [AT III]), and others.

AT III constitutes the most potent and widely distributed inhibitor of blood coagulation. It binds to the active site (serine) of thrombin, thus inhibiting action of thrombin. It also inhibits, to a much lesser extent, the activity of factors XIIa, XIa, IXa, and Xa; kallikrein; and the fibrinolytic molecule, plasmin. Thrombin bound to fibrin is protected from the action of AT, thus partially explaining the poor efficacy of heparin in treating established thrombosis. AT III is a relatively inactive zymogen. To be most effective, AT must bind to a unique pentasaccharide sequence contained on the wall of endothelial cells in the glycosaminoglycan surface known as heparan; the same active sequence is present in the drug heparin.

An important point is that activated AT III is active only against free thrombin (fibrin-bound thrombin cannot be seen by AT III).[14] Prothrombin circulates in the plasma but is not affected by heparin-AT III complexes; it is only thrombin, and thrombin does not circulate freely. Most thrombin in its active form is either bound to GP binding sites of platelets or in fibrin matrices. When blood is put into a test tube and clot begins to form (such as in an activated coagulation time [ACT]), 96% of thrombin production is yet to come. Most thrombin generation is on the surface of platelets and on clot-held fibrinogen. Platelets, through their GP binding sites and phospholipid folds, protect activated thrombin from attack by AT III. Therefore the biologic role of AT III is to create an anticoagulant surface on endothelial cells. It is not present biologically to sit and wait for a dose of heparin before CPB.

CPB dilutes AT III substantially, and the further consumption of AT III during CPB (thrombin generation) leads, in some patients, to profoundly low levels of this important inhibitor.[15] Research work adding AT III back to the CPB circuit has shown promise in that by doing so there is better preservation of serine protease proteins and platelets. The level of AT III on entry to the ICU, and probably over the first few days, has been shown to affect the risk of thrombotic events.[15-17] A large trial of added AT III to CPB is underway to assess whether supplementation will reduce thrombotic events without increasing bleeding. Congenital AT III deficiency can lead to in utero fetal destruction if the fetus is homozygous for the abnormal AT III. However, patients who are heterozygous for AT III abnormalities have about 40% to 60% of normal AT III activity. They have a particularly high risk for deep vein thrombosis. Low AT III levels have been described during extracorporeal membrane oxygenation, and the addition of AT III to the extracorporeal membrane oxygenation circuit has been effective in improving outcome and decreasing bleeding in some circumstances.[18] How useful it would be in which patients on CPB is not clear because only small trials have been performed, but these have been encouraging and a single larger trial is underway.[19,20] Both human AT III concentrate (harvested from multiple plasma donors and pasteurized) and a pharmaceutically engineered, goat milk–produced AT III (slightly different structure than human AT III) are commercially available.

Heparin cofactor II also inhibits thrombin, once it is activated. Although large doses of heparin activate heparin cofactor II, dermatans on endothelial cell surfaces activate it far more effectively, suggesting dermatans as alternative drugs to heparin.[21] Dermatan sulfates are not available for use today in the United States.

TABLE 35.1 The Coagulation Pathway Proteins, Minimal Amounts Needed for Surgery, and Replacement Sources

Factor	*Activated By*	*Acts On*	*Minimal Amount Needed*	*Replacement Source*	*Alternate Name and Comments*
XIII	IIa	Fibrin	<5%	FFP, CRYO	Fibrin-stabilizing factor; not a serine protease, but an enzyme
XII	Endothelium	XI	None	Not needed	Hageman factor; activation enhanced by XIIa
XI	XIIa	IX	15%–25%	FFP	Plasma thromboplastin antecedent
X	VIIa or IXa	II	10%–20%	FFP, 9C	Stuart-Prower factor; vitamin K dependent
IX	VIIa or XIa	X	25%–30%	FFP, 9C, PCC	Christmas factor; vitamin K dependent
VIII	IIa	X	>30%	CRYO, 8C, FFP	Antihemophilic factor; a cofactor; RES synthesis
VII	Xa	X	10%–20%	FFP, PCC	Serum prothrombin conversion accelerator; vitamin K dependent
V	IIa	II	<25%	FFP	Proaccelerin; a cofactor; RES and liver synthesis
IV	—	—	—	—	Calcium ion; binds II, VII, IX, X to phospholipid
III	—	X	—	—	Thromboplastin/tissue factor; a cofactor
II	Xa	I	20%–40%	FFP, PCC	Prothrombin; vitamin K dependent
I	IIa	—	1 g/L	CRYO, FFP	Fibrinogen; activated product is soluble fibrin
vWF	—	VIII	See VIII	CRYO, FFP	von Willebrand factor; endothelial cell synthesis

Unless otherwise specified, all coagulation proteins are synthesized in the liver. Note that there is no factor VI. For von Willebrand factor, cryoprecipitate or fresh frozen plasma (FFP) is administered to obtain a factor VIII coagulant activity >30%. *8C,* Factor VIII concentrate; *9C,* purified factor IX complex concentrate; *CRYO,* cryoprecipitate; *PCC,* prothrombin complex concentrate; *RES,* reticuloendothelial system.

Another serpin, *protein C,* degrades factors Va and VIIIa. Like other vitamin K–dependent factors, it requires Ca^{2+} to bind to phospholipid. Its cofactor, termed *protein S,* also exhibits vitamin K dependence. Genetic variants of protein C are less active and lead to increased risk for deep vein thrombosis and pulmonary embolism. When endothelial cells release thrombomodulin, thrombin then accelerates by 20,000-fold its activation of protein C[22] (see Fig. 35.6). Activated protein C also promotes fibrinolysis through a feedback loop to the endothelial cells to release t-PA.[23]

Regulation of the extrinsic limb of the coagulation pathway occurs via tissue factor pathway inhibitor (TFPI), a glycosylated protein that associates with lipoproteins in plasma.[24] TFPI is not a serpin. It impairs the catalytic properties of the factor VIIa–tissue factor complex on factor X activation. Both vascular endothelium and platelets appear to produce TFPI.[25,26] Heparin releases TFPI from endothelium, increasing TFPI plasma concentrations by as much as sixfold, which should be viewed as a biologic indicator of how poor heparin is as an anticoagulant. TFPI is not tested for in routine coagulation testing. It may be that some individuals with certain types of TFPI or who have very large amounts of circulating TFPI could be at risk for severe adverse bleeding after cardiac surgery.[27–32] This area is just beginning to be examined today both in terms of whether TFPI is responsible for abnormal bleeding and whether its genetic variants have abnormal bleeding or thrombosis.

von Willebrand factor (vWF), a massive molecule composed of disulfide-linked glycosylated peptides, associates with factor VIII in plasma, protecting it from proteolytic enzymes. It circulates in the plasma in its coiled inactive form.[33] Disruption of the endothelium either allows for binding of vWF from the plasma or allows for expression of vWF from tissue and from endothelial cells. Once bound, vWF uncoils to its full length and exposes a hitherto cryptic domain in the molecule. This A-1 domain has a very high affinity for platelet GPs. Initially, vWF attaches to the glycoprotein Iα (GPIα) platelet receptor, which slows the platelet forward movements against the shear forces of blood flow. Shear forces are activators of platelets. As the platelet's forward movement along the endothelial brush border is slowed (because of vWF attachment), shear forces actually increase; thus the binding of vWF to GP1 acts to provide a feedback loop for individual platelets, further activating them. The activation of vWF and its attachment to the platelet are not enough to bind the platelet to the endothelium, but it creates a membrane signal that allows for early shape change and expression of other GPs, GPIb, and GPIIb/IIIa. Then secondary GPIb binding connects to other vWF nearby, binding the platelet and beginning the activation sequence. It bridges normal platelets to damaged subendothelium by attaching to the GPIb platelet receptor. An ensuing platelet shape change then releases thromboxane, β-thromboglobulin, and serotonin, and exposes GPIIb/IIIa, which binds fibrinogen.

Deficiency States

Decreased amounts of coagulation proteins may be inherited or acquired. Deficiencies of each part of the coagulation pathway are considered in turn. Table 35.1 summarizes the coagulation factors, their activation sequences, and vehicles for factor replacement when deficient.

Contact Activation

Although decreased amounts of factor XII, PK, and HMWK can occur, these defects do not have clinical sequelae. The autosomal dominant deficiency of factor XI is very rare.[34] However, its incidence among Ashkenazi Jews is as high as 0.1% to 0.3%.[35] Most of these patients require factor replacement with fresh-frozen plasma (FFP) for surgery. Spontaneous bleeding does not occur, but increased bleeding after a surgical event or trauma is possible. Factor XI concentrations do not directly correlate with bleeding after trauma or surgery, suggesting that factor XI deficiency can be easily overcome by activation of platelets, factor IX, and other signaling mechanisms. An FFP dose of 10 mL/kg (700 mL or roughly 4 units of FFP) will yield target concentrations of only 20% activity, and it is often given for this rare deficiency. Note that the amount of FFP required to get to a 20% level might well dilute platelets and red cells and put complex cardiac patients into a fluid overload situation.

Intrinsic System

Hemophilia occurs worldwide, with a prevalence of 1 in 10,000. Hemophilia A, which constitutes about 80% to 85% of cases, originates from decreased activity of factor VIII. Because platelet function remains normal, minor cuts and abrasions do not bleed excessively. Joint and muscle hemorrhages ensue from minor trauma or, seemingly, spontaneously. Airway issues include epistaxis and obstruction from bleeding into the tongue. The bleeding time and prothrombin time (PT) remain normal, whereas the activated partial thromboplastin time (aPTT) is prolonged.[35] Desmopressin, a synthetic analog of vasopressin, will increase factor VIII activity by releasing vWF from endothelial cells, except in patients with severe hemophilia A who have too little functional factor VIII available for vWF.[36] Major surgery requires replenishment of factor VIII functional activity to greater than 80% of normal with FFP, cryoprecipitate (cryo), or factor VIII concentrate.[37] Factor VIII concentrate is the preferred method today. After surgery, factor VIII concentrations should be maintained greater than 30% for 2 weeks with repeat doses. Current plasma-derived concentrates are solvent detergent and heat-treated to remove lipid-coated viruses (human immunodeficiency virus [HIV], hepatitis B, human T-lymphotropic virus [HTLV]. However, this was not historically the case, and in Europe during the early parts of the HIV/acquired immune deficiency syndrome (AIDS) crisis, most individuals with hemophilia who contracted HIV/AIDS were exposed to it through

contaminated products. A recombinant product also is available but costs about three times that of the plasma-derived one.

Factor IX deficiency manifests as hemophilia B, constituting 15% to 20% of all hemophilia cases. Patients present with symptoms identical to those with hemophilia A. No study has demonstrated a salutary effect of desmopressin here. Prothrombin complex (factor IX) concentrates will replenish levels, but consumptive coagulopathy remains a possible complication, stemming from the presence of activated coagulation factors, principally factor VIIa, in the preparation.[38] Purified factor IX concentrate, a plasma-derived, solvent detergent and heat-treated product, currently constitutes the replacement vehicle of choice for patients with hemophilia B.[39] Recombinant pure factor IX concentrate will be available, but at considerable expense (factor VIIa is now available as well). Consultation with an experienced hematologist aids in the care of patients with hemophilia undergoing surgery.

Extrinsic System

Inheritance of factor VII deficiency follows an autosomal recessive pattern, with a prevalence of 1 in 500,000. Although factor VII deficiency may mimic hemophilia in presentation, most often, clinical bleeding is absent and surgery is well tolerated without replacement. The PT is elevated, whereas the PTT is normal. When necessary, replacement of factor VII levels to 10% to 20% of normal with FFP suffices.

Common Pathway

Deficiency of either factor V or factor X, both extremely rare autosomal recessive disorders, increases both the PT and PTT. The bleeding time is normal in factor X deficiency but prolonged in one-third of patients with factor V deficiency. The bleeding time prolongation arises from the role of factor V in platelet function.[40] Prothrombin complex concentrate (PCC) or FFP supplies prothrombin, factor V, and factor X. Numerous inherited abnormalities (polymorphisms) of prothrombin and fibrinogen occur, with varying characteristics. Cryoprecipitate, which contains 250 mg of fibrinogen and 100 units of factor VIII per 10-mL bag, as well as vWF and factor XIII, treats inherited or acquired disorders of fibrinogen. Many of the prothrombin and fibrinogen polymorphisms are associated with hypercoagulability and, perhaps, accelerated atherosclerosis rather than bleeding. Therefore they may be seen in CABG surgery that serves as a selection process for people with inherited hypercoagulability. There is no consensus yet on how to handle these cases in the OR.

Liver Disease

Hepatic compromise decreases the circulating amounts of factors II, VII, and X, but the level of factor IX is often normal. Decreases in factor V are variable. Factor VIII levels, in contrast, can reach as much as five times normal in acute hepatitis. Factors XIII, XII, and XI, HMWK, and PK suffer mild decreases. Administration of FFP restores these factors to normal levels. Liver disease also leads to decreases in the production of AT III and protein S. Therefore the buffering capacity of coagulation is thrown off. A small change in activation could, therefore, lead to a large and diffuse whole-body event such as consumptive coagulopathy.

Warfarin

Administration of this vitamin K antagonist affects plasma levels of factors II, VII, IX, and X, as well as proteins C and S.[41] Protein C has the shortest half-life, followed by factors VII (6 hours), IX (24 hours), X (2 days), and II (3 days).[42] Substantial PT prolongation and some aPTT prolongation accompany warfarin therapy. For immediate restoration of clotting function, FFP has been given in the past as the standard of care. Today, the recommendation is for the use of a PCC (20–25 μg/kg) or factor VIIa (20 μg/kg) as pharmaceuticals.[42-44] Studies have shown that these create immediate reversal and the normalization of coagulation function that lasts at least 24 hours. There is no reason why these agents cannot be given prior to CPB or even during full heparinization on CPB. The use of PCC will not reverse heparin's effect, nor will it make the patient intrinsically hypercoagulable. Thus if a patient comes to the OR with a prolonged INR and has been taking warfarin up until surgery, reversal can be immediate and blood loss during the dissection phase before CPB can be reduced. Physicians appear concerned about giving a PCC, but it will not in itself make the patient intrinsically hypercoagulable. The contents of the available 4 protein PCCs are shown in Table 34.3. These have been available in Europe for a number of years but are just now being adopted across the United States.

Parenteral vitamin K or cessation of warfarin suffices if the patient has several days before surgery. Clinicians should be extremely careful in administering these compounds if a patient is suspected of having heparin-induced thrombocytopenia (HIT). Treatment with commercially available factor VIIa or PCC restores PT to normal and appears to stop bleeding when warfarin therapy has not had time to be reversed. The use of factor VIIa or PCC for this intervention before surgery is effective and, perhaps, worthwhile because it avoids the use of FFP (very real risk for TRALI). The time scale of factor VIIa or PCC effectiveness may not be as long as if one normalized circulating levels through FFP administration, but that has not been studied. It makes sense, therefore, that if the PT is prolonged again approximately 8 to 12 hours after a dose of factor VIIa or PCC, redosage of the drugs could be given.

Inherited Thrombotic Disorders

A number of genetic abnormalities lead to thrombosis. The most prevalent (2%–5%) in European-derived populations is factor V Leiden, in which a point mutation at residue 1691 on factor V renders it resistant to inactivation by activated protein C. Venous thromboembolism risk increases sevenfold in heterozygotes and 80-fold in homozygotes, but episodes are less severe than in other thrombotic disorders. Pregnancy and oral contraceptives greatly exacerbate the thrombotic tendency.

Congenital AT III deficiency (1:1000 patients) causes venous thromboembolism and heparin resistance. This autosomal dominant disorder involves three types: absence of AT (type I), dysfunctional AT (type II), and AT with dysfunction limited to a reduced response to heparin (type III). Clinical presentation begins at age 15 or later, with venous thrombosis occurring with surgery, pregnancy, or bed rest. Replacement AT III is now available for use in the United States.

Protein C or S deficiencies, if homozygous, present at birth as neonatal purpura fulminans. Protein C deficiency heterozygotes demonstrate 40% to 60% protein C activity and present with venous thrombosis beginning in adolescence. The role of reduced concentrations of protein S in causing thrombosis has come into question. Together, deficiencies of AT, protein C, and protein S account for 10% to 15% of inherited thrombosis.[45]

Deficiency of heparin cofactor II is rare. Its role in thrombosis is uncertain. Other conditions that cause thrombosis are dysfibrinogenemia with lysis-resistant fibrinogen, plasminogen deficiency, t-PA deficiency, excess plasminogen activator inhibitor 1 activity (plasminogen activator inhibitor 1 inhibits t-PA), and homocysteinemia.

Homocysteinemia is the mild heterozygous state of cystathione β-synthetase deficiency, known as homocystinuria in its more serious homozygous form. Increased plasma concentrations of homocysteine induce endothelial cell tissue factor activity, stimulate factor V activation, and impair protein C activation, all of which contribute to thrombosis. Folic acid and vitamins B_6 and B_{12} reduce homocysteine plasma concentrations.[46] AT has been used to treat homocystinuria and its thrombosis situations as well. Elevated homocysteine levels prior to CABG surgery makes these patients particularly hypercoagulable.[47]

Platelet Function

Most clinicians think first of the coagulation proteins when considering hemostasis. Although no one element of the many that participate in hemostasis assumes dominance, platelets may be the most complex.[48,49] Without platelets, there is no coagulation and no hemostasis, so it could be argued that they are most important. Without the proteins, there is hemostasis, but it lasts only about 10 to 15 minutes because the platelet plug is inherently unstable and breaks apart under the shear stress of the vasculature. Platelets provide phospholipid for

coagulation factor reactions; contain their own micro-skeletal system and release coagulation factors; secrete active substances affecting themselves, other platelets, the endothelium, and other coagulation factors; and alter shape (through active actin-myosin contraction) to expose membrane GPs essential to hemostasis. Their cell signaling is highly regulated, is present in other cell lines (RBCs, leukocytes, and endothelial cells), and has been intensively studied. Platelets have perhaps as many as 30 to 50 different types of cell receptors, with many ways of these being activated and inhibited.

The initial response to vascular injury is formation of a platelet plug. Good hemostatic response depends on proper functioning of platelet adhesion, activation, and aggregation. This section first discusses these aspects and then follows with the effects of platelet disorders and platelet-inhibiting pharmaceuticals. Clinicians talk about platelet dysfunction, which is largely overarching and grossly too general a term. The complexity that is platelet function really needs careful study.

Platelet Adhesion

Capillary blood exhibits laminar flow, which maximizes the likelihood of interaction of platelets with the vessel wall. Red cells and white cells stream near the center of the vessels and marginate platelets. However, turbulence causes reactions in endothelium that lead to the secretion of vWF, adhesive molecules, and tissue factor. Shear stress is high as fast-moving platelets interact with the endothelium. When the vascular endothelium becomes denuded or injured, the platelet has the opportunity to contact vWF, which is bound to the exposed collagen of the subendothelium. A platelet membrane component, GPIb, attaches to vWF, thus anchoring the platelet to the vessel wall. Independently, platelet membrane GPIa and GPIIa and IX may attach directly to exposed collagen, furthering the adhesion stage.[49–51]

After activation (see later), additional adhesive mechanisms come into play. Release of selectin GPs from α-granules allows their membrane expression, thus promoting platelet-leukocyte adhesion. This interaction ultimately may allow expression of tissue factor on monocytes, thus amplifying coagulation.[51]

The integrin GPs form diverse types of membrane receptors from combinations of 20 α and 8 β subunits.[52,53] One such combination is GPIIb/IIIa, a platelet membrane component that initially participates in platelet adhesion. Platelet activation causes a conformational change in GPIIb/IIIa, which results in its aggregator activity.

Platelet adhesion begins rapidly—within 1 minute of endothelial injury—and completely covers exposed subendothelium within 20 minutes.[50] It begins with decreased platelet velocity when GPIb/IX and vWF mediate adhesion, followed by platelet activation, GPIIb/IIIa conformational change, then vWF binding and platelet arrest on the endothelium at these vWF ligand sites.[49,51]

Adhesion requires margination of platelets; high hematocrits concentrate RBCs in the central regions of a vessel, promoting marginal placement of platelets. Dilute hematocrit (eg, post-CPB) impairs this effect, thus adversely affecting platelet adhesion. Low hematocrit also may affect platelet prostaglandin levels because RBCs are required for preprocessing of arachidonic acid before platelets make thromboxane. Because of rheology, RBC transfusions have been thought by some to improve hemostasis. However, transfusion should not be used primarily to achieve this goal because RBC concentrates carry a high concentration of cytokines and platelet-activating factor, which may contribute to platelet dysfunction or consumptive coagulopathy. Some of the most recent data-based studies looking at only several units of blood transfusion have noted that when transfusion is used, the postoperative chest tube output is greater. That finding is, however, fundamentally different from the observation that if a patient is bleeding and has a particularly low hematocrit, the use of RBCs may well increase margination of platelets.

Platelet Activation and Aggregation

Platelet activation results after contact with collagen, when adenosine diphosphate (ADP), thrombin, or thromboxane A_2 binds to membrane receptors, or from certain platelet-to-platelet interactions. Platelets then release the contents of their dense (δ) granules and α granules. Dense granules contain serotonin, ADP, and Ca^{2+}; α granules contain platelet factor V (previously termed platelet factor 1), β-thromboglobulin, platelet factor 4 (PF4), P-selectin, and various integrin proteins (vWF, fibrinogen, vitronectin, and fibronectin). Simultaneously, platelets use their microskeletal system to change shape from a disk to a sphere, which changes platelet membrane GPIIb/IIIa exposure. Released ADP recruits additional platelets to the site of injury and stimulates platelet G protein, which in turn, activates membrane phospholipase. This results in the formation of arachidonate, which platelet cyclooxygenase converts to thromboxane A_2. Other platelet agonists besides ADP and collagen include serotonin, a weak agonist, and thrombin and thromboxane A_2, both potent agonists. Thrombin is by far the most potent platelet agonist, and it can overcome all other platelet antagonists, as well as inhibitors. In total, more than 70 agonists can produce platelet activation and aggregation.

Agonists induce a graded platelet shape change (the amount based on the relative amount of stimulation), increase platelet intracellular Ca^{2+} concentration, and stimulate platelet G protein. In addition, serotonin and thromboxane A_2 are potent vasoconstrictors (particularly in the pulmonary vasculature). The presence of sufficient agonist material results in platelet aggregation. Aggregation occurs when the integrin proteins (mostly fibrinogen) released from α granules form molecular bridges between the GPIIb/IIIa receptors of adjacent platelets (the final common platelet pathway).

Platelet Disorders

Dysfunctional vWF produces von Willebrand disease (vWD), an autosomal dominant disorder of variable expressivity.[36,54] With an incidence of 1.4 to 5 cases per 1000 population, vWD is the most common inherited coagulopathy. Patients present with mucocutaneous hemorrhages rather than hemarthroses. Common symptoms include epistaxis, ecchymoses, and excessive bleeding after trauma, with surgery, or during menses. Because vWF concentrations vary greatly with time, symptoms have variable expressivity. Desmopressin reverses the prolonged bleeding time in patients with mild vWD.[55] As with hemophilia A, severe cases of vWD do not benefit from desmopressin therapy. In one rare class of vWD (type IIB, 3%–5% of vWD), desmopressin aggregates platelets, inducing thrombocytopenia and worsening rather than helping hemostasis. Table 35.2 summarizes features of the more common types of vWD. When blood products are needed, cryoprecipitate constitutes the replacement vehicle of choice in vWD, although recent factor VIII concentrates retain vWF activity and have been used successfully during cardiac surgery.

The addition of agonist (ADP or collagen) to platelets allows measurement of platelet aggregation in vitro. In Glanzmann thrombasthenia, the GPIIb/IIIa receptor is absent, preventing aggregation. However, ristocetin, a cationic antibiotic similar to vancomycin, can agglutinate platelets directly via GPIb receptors and vWF. Absence of the GPIb receptor, Bernard–Soulier syndrome, prevents adhesion and agglutination with ristocetin, but aggregation to ADP is normal, because the GPIIb/IIIa receptor is intact. Patients with vWD also exhibit impaired platelet adhesion and normal aggregation. Decreased amounts of vWF antigen distinguish it from the Bernard–Soulier syndrome. In platelet storage pool deficiency, impairment of dense granule secretion yields no ADP on adhesion. In vitro addition of collagen will not aggregate platelets because of absence of ADP release, whereas added ADP will initiate some aggregation. Table 35.3 summarizes these diagnostic findings. Uremia impairs the secretory and aggregating functions of platelets, resulting in an increased bleeding time. However, the most common effect of renal dysfunction is hypercoagulability. It is only with severe uremia that the platelets are poisoned. It is, therefore, a common misconception in the OR that a patient with mild-to-moderate renal failure will be at increased risk for bleeding. The utilization of thromboelastography (TEG) can help in deciding whether the extent of renal failure is causing hypocoagulability. The cause and clinical significance remain poorly defined (see Chapter 19).

TABLE 35.2 Major Types of von Willebrand Disease

Classification	*Prevalence Rate*	*vWf:Ag*	*R:Co*	*Molecular Pathology*
I (Classic)	70%–80%	Decreased	Decreased	Normal multimers; decreased quantity
IIA	10%–12%	Decreased	Decreased	Intermediate and large multimers decreased
IIB	3%–5%	Decreased	Near normal	Abnormal, large multimers that bind platelets
III	1%–3%	None	None	No vWF present
Platelet-type	0%–1%	Decreased	Decreased	Normal vWF; platelet glycoprotein Ib receptors bind large multimers

R:Co, Ristocetin cofactor activity measurement; *vWF:Ag,* von Willebrand factor antigen measurement.
Data from Montgomery RR, Colier BS. von Willebrand disease. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostasis and Thrombosis,* 3rd ed. Philadelphia: JB Lippincott; 1994:134–168.

TABLE 35.3 Diagnosis of Some Inherited Platelet Disorders

Disorder	*Deficiency*	*Platelet Adhesion*	*Platelet Aggregation*	*Ristocetin Agglutination*	*vWF:Ag Level*
Glanzmann thrombasthenia	GPIIb/IIIa	Normal	Absent	Occurs	Normal
Bernard–Soulier syndrome	GPIb	Absent	Normal	Absent	Normal
Storage pool deficiency	Dense granule secretion	Normal	Impaired	Occurs	Normal
von Willebrand disease	vWF	Absent	Normal	Absent or decreased	Low

GP, Glycoprotein receptor; *vWF,* von Willebrand factor; *vWF:Ag,* von Willebrand factor antigen.

Prostaglandins and Aspirin

Endothelial cell cyclooxygenase synthesizes prostacyclin, which inhibits aggregation and dilates vessels. Platelet cyclooxygenase forms thromboxane A_2, a potent aggregating agent and vasoconstrictor. Aspirin irreversibly acetylates cyclooxygenase, rendering it inactive. Low doses of aspirin, 80 to 100 mg, easily overcome the finite amount of cyclooxygenase available in the nucleus-free platelets. However, endothelial cells can synthesize new cyclooxygenase. Thus with low doses of aspirin, prostacyclin synthesis continues, whereas thromboxane synthesis ceases, decreasing platelet activation and aggregation. High doses of aspirin inhibit the enzyme at both cyclooxygenase sites.[53]

Reversible platelet aggregation is blocked by aspirin, as the platelet cyclooxygenase is inhibited. However, the more powerful agonists that yield the calcium release response can still aggregate and activate platelets, because cyclooxygenase is not required for those pathways (Fig. 35.7).

In many centers, a majority of the patients presenting for CABG will have received aspirin within 7 days of surgery in hopes of preventing coronary thrombosis.[56–59] Platelets have a life span of approximately 9 days, so the idea of taking somebody off aspirin for 5 to 7 days seems reasonable in that the majority of platelets circulating will not have cyclooxygenase poisoned by aspirin. Aspirin is a drug for which an increased risk for bleeding often has been demonstrated.[60] Although most early research studies stated that aspirin leads to increased bleeding, since the mid-1990s, that early impression has not been confirmed. Today, it probably is more likely that, in some patients, a mild-to-moderate increased risk for bleeding is possible.

Unfortunately, most of the early studies of aspirin were not blinded, and it may be that the pervading belief that aspirin caused increased bleeding was actually self-fulfilling. Since the early 1990s, there have been a number of therapeutic changes, including use of lower doses and greater use of antifibrinolytics. These changes alone may have decreased the overall risk for bleeding from aspirin. Follow-up prospective studies have, thus, yielded varied results. In the largest cohort of 772 men, aspirin increased bleeding after CABG by 33%,[59] and a group of 101 aspirin-taking patients bled 25% to 56% more than a control group.[60] In another study, the need to explore the mediastinum for excessive bleeding nearly doubled (factor of 1.82) in patients taking aspirin.[61] However, many other studies have not shown increased bleeding with aspirin.[62–67] Although a single aspirin can irreversibly inhibit platelet cyclooxygenase for the life of the platelet, aspirin-related bleeding after surgery usually requires more extensive exposure to the drug. Early use of aspirin after CABG surgery has been shown to decrease thrombosis and infarction.[67]

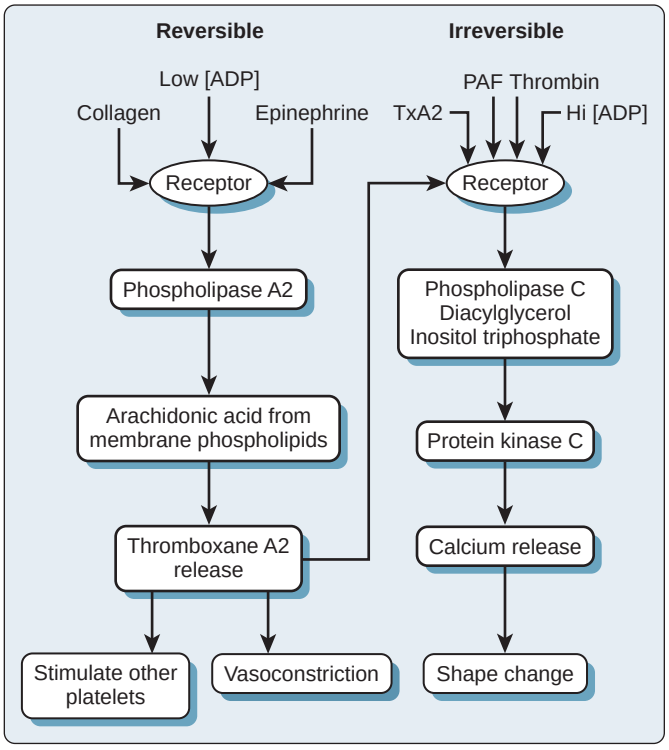


Fig. 35.7 Pathways for reversible *(left column)* and irreversible *(right column)* platelet aggregation. Note the different agents that activate distinct receptors. Aspirin inhibits reversible platelet aggregation via the phospholipase A_2 pathway by affecting the arachidonic acid enzyme cyclooxygenase, but it does not prevent more powerful agonists from aggregating platelets by directly stimulating phospholipase C pathway receptors. *(Adapted from Kroll MH, Schafer A: Biochemical mechanisms of platelet activation.* Blood. *1989;74:1181.)*

Drug-Induced Platelet Abnormalities

Many other agents inhibit platelet function. β-Lactam antibiotics coat the platelet membrane, whereas the cephalosporins are rather profound but short-term platelet inhibitors.[68] Many cardiac surgeons may not realize that their standard drug regimen for antibiotics may be far more of a bleeding risk than aspirin. Hundreds of drugs can inhibit platelet function. Calcium channel blockers, nitrates, and β-blockers are ones commonly used in cardiac surgery. Nitrates are effective

antiplatelet agents, and that may be part of why they are of such benefit in angina, not only for their vasorelaxing effect on large blood vessels. Nonsteroidal antiinflammatory drugs reversibly inhibit both endothelial cell and platelet cyclooxygenase. In addition, anecdotal reports of platelet inhibition, without clear confirmatory studies, exist for many pharmaceuticals, including dextran, and for innumerable foods (eg, onion, garlic, alcohol) and spices (eg, ginger, turmeric, cloves).[26]

Rofecoxib (Vioxx), a cyclooxygenase 2 (COX-2) inhibitor, was withdrawn from the US market because of its cardiovascular risk profile (a small increase in associated acute myocardial infarctions).[69] This COX-2 inhibitor has the highest selectivity for COX-2 versus COX-1 and thus leads to an imbalance between thromboxane A_2 and prostacyclin production. The other COX-2 inhibitors are currently also undergoing cardiovascular investigation.

In addition to the partial inhibitory effects of aspirin and the other drugs mentioned earlier, new therapies that inhibit platelet function in a more specific manner have been developed. These drugs include platelet adhesion inhibitor agents, platelet-ADP-receptor antagonists, and GPIIb/IIIa receptor inhibitors (Table 35.4).[70]

Adhesion Inhibitors

Dipyridamole (Persantine) and cilostazol (Pletal) alter platelet adhesion by various mechanisms, including cyclic adenosine monophosphate, phosphodiesterase III, and thromboxane A_2 inhibition. Dipyridamole has been used with warfarin in some patients with artificial valves and with aspirin in patients with peripheral vascular disease.

Adenosine Diphosphate Receptor Antagonists

Clopidogrel (Plavix), prasugrel (Effient), and ticlopidine (Ticlid) are thienopyridine derivatives that inhibit the ADP receptor pathway to platelet activation. They have a slow onset of action because they must be converted to active drugs, and their potent effects last the lifetime of the platelets affected (5–10 days). Clopidogrel and prasugrel are the preferred drugs. They are administered orally once daily to inhibit platelet function and are quite effective in decreasing myocardial infarctions after percutaneous coronary interventions (see Chapter 3). The combination of aspirin and clopidogrel has led to increased bleeding but is sometimes used in an effort to keep vessels and stents open. Recently, two new nonthienopyridine ADP P_2Y_{12} inhibitors have become available. Ticagrelor is a direct-acting oral drug, and cangrelor is a short-acting intravenous agent. The latter drug may be a very valuable bridging drug for use in the PCI laboratory and perioperative period.[71] The TEG and now the RoTEM (a modified TEG) with ADP or other additives can be used to determine the degree of inhibition caused by these drugs. Other new tests are coming onto the market to allow testing for relative platelet inhibition caused by thienopyridines. Some of these are modifications of platelet flow cytometry or automated platelet aggregometers. Verify Now (Accumetrics, San Diego, CA) and the PFA-100 (Siemens USA, Deerfield, IL) have been used in dosing clopidogrel for cardiology procedures. These platelet function tests are now finding their way into hospitals, and some facilities are starting to use them before or after surgery.[72–78] In at least one study, the use of the Verify Now P_2Y_{12} test has been shown to have predictive value for early graft thrombosis.[79] Modification of the TEG with platelet mapping have been used to define the amount of platelet inhibition by aspirin and P_2Y_{12} antagonists[80–84] (see Chapter 19).

Glycoprotein IIb/IIIa Receptor Inhibitors

GPIIb/IIIa receptor inhibitors are the most potent (>90% platelet inhibition) and important platelet inhibitors because they act at the final common pathway of platelet aggregation with fibrinogen, no matter which agonist began the process. All of the drugs mentioned earlier work at earlier phases of activation of platelet function. These drugs are all administered by intravenous infusion, and they do not work orally. The GPIIb/IIIa inhibitors often are used in patients taking aspirin because they do not block thromboxane A_2 production. The dose of heparin usually is reduced when used with these drugs (ie, percutaneous coronary intervention to avoid bleeding at the vascular puncture sites). Platelet activity can be monitored to determine the extent of blockade. Excessive bleeding requires allowing the short-acting drugs to wear off, while possibly administering platelets to patients receiving the long-acting drug abciximab (see Table 35.4). Most studies have found increased bleeding in patients receiving these drugs who required emergency CABG.

Vascular Endothelium

The cells that form the intima of vessels provide an excellent nonthrombogenic surface. Characteristics of this surface, which may account for its nonthrombogenicity, include negative charge; incorporation of heparan sulfate in the grid substance; the release of prostacyclin, nitric oxide, adenosine, and protease inhibitors by endothelial cells; binding and clearance of activated coagulation factors both directly, as occurs with thrombin, and indirectly, as evidenced by the action of

TABLE 35.4 Antiplatelet Therapy

Drug Type	*Composition*	*Mechanism*	*Indications*	*Route*	*Half-Life*	*Metabolism*
Aspirin	Acetylsalicylic acid	Irreversible COX inhibition	CAD, AMI, PVD, PCI, ACS	Oral	10 days	Liver, kidney
NSAIDs	Multiple	Reversible COX inhibition	Pain	Oral	2 days	Liver, kidney
Adhesion inhibitors (eg, dipyridamole)	Multiple	Block adhesion to vessels	VHD, PVD	Oral	12 hours	Liver
ADP receptor antagonists						
-Clopidogrel (Plavix), prasugrel (Effient)	Thienopyridines	Irreversible	AMI, CVA, PVD, ACS, PCI	Oral	5 days	Liver
-Ticagrelor (Brilinta)	Nonthienopyridine	Reversible	AMI, CVA, PVD, ACS, PCI	Oral	3–5 days	Liver
-Cangrelor (Kengreal)	Nonthienopyridine	Reversible	AMI, CVA, PVD, ACS, PCI	IV	3–5 min	Blood
PAR-1 inhibitors						
-Vorapaxar (Zontivity)	PAR-1 antagonist	Irreversible—inhibits thrombin-induced platelet activation	AMI, PVD	Oral	20 hr–4 wk	Liver
GPIIb/IIIa receptor inhibitors						
Abciximab (ReoPro)	Monoclonal antibody	Nonspecific—binds to other receptors	PCI, ACS	IV	12–18 hours	Plasma proteinase
Eptifibatide (Integrilin)	Peptide	Reversible—specific to GPIIb/IIIa	PCI, ACS	IV	2–4 hours	Kidney
Tirofiban (Aggrastat)	Nonpeptide-tyrosine derivative	Reversible—specific to GPIIb/IIIa	PCI, ACS, AMI, PVD	IV	2–4 hours	Kidney

ACS, Acute coronary syndrome; *AMI*, acute myocardial infarction; *CAD*, coronary artery disease; *COX*, cyclooxygenase; *CVA*, cerebrovascular disease; *IV*, intravenous; *NSAID*, nonsteroidal antiinflammatory drug; *PAR-1*, protease-activated receptor; *PCI*, percutaneous coronary intervention; *PVD*, peripheral vascular disease; *VHD*, valvular heart disease.

thrombomodulin to inactivate factors Va and VIIIa via protein C; and stimulation of fibrinolysis.

Nitric oxide vasodilates blood vessels and inhibits platelets. Its mechanism involves activation of guanylate cyclase with eventual uptake of calcium into intracellular storage sites. Prostacyclin (prostaglandin I_2) possesses powerful vasodilator and antiplatelet properties. Endothelium-derived prostacyclin opposes the vasoconstrictor effects of platelet-produced thromboxane A_2. Prostacyclin also inhibits platelet aggregation, disaggregates clumped platelets, and at high concentrations, inhibits platelet adhesion. Prostacyclin increases intracellular concentrations of cyclic adenosine monophosphate, which inhibits aggregation. Thromboxane acts in an opposite manner. The mechanism of prostacyclin action is stimulation of adenylyl cyclase, leading to reduced intracellular calcium concentrations. Some vascular beds (eg, lung) and atherosclerotic vessels secrete thromboxane, endothelins, and angiotensin, all vasoconstrictors, as well as prostacyclin. Activation of platelets releases endoperoxides and arachidonate. These substances, used by nearby damaged endothelial cells, provide substrate for prostacyclin production.[5]

The endothelial cell also participates in coagulation factor activation. Playing a role similar to that of platelet phospholipid, the endothelial surface facilitates activation of factor IX. Thrombospondin, a substance formed in endothelial cells and platelets, helps complete platelet aggregation and binds plasminogen. The latter effect decreases the amount of locally available plasmin, thus inhibiting fibrin breakdown.

Fibrinolysis

Fibrin breakdown, a normal hematologic activity, is localized to the vicinity of a clot. It remodels formed clot and removes thrombus when endothelium heals. Like clot formation, clot breakdown may occur by intrinsic and extrinsic pathways. As with clot formation, the extrinsic pathway plays the dominant role in clot breakdown. Each pathway activates plasminogen, a serine protease synthesized by the liver, which circulates in zymogen form. Cleavage of plasminogen by the proper serine protease forms plasmin. Plasmin splits fibrinogen or fibrin at specific sites. Plasmin is the principal enzyme of fibrinolysis, just as thrombin is principal to clot formation. Plasma normally contains no circulating plasmin because a scavenging protein, α_2-antiplasmin, quickly consumes any plasmin formed from localized fibrinolysis. Thus localized fibrinolysis, not systemic fibrinogenolysis, accompanies normal hemostasis.

Extrinsic Fibrinolysis

Endothelial cells synthesize and release t-PA. Both t-PA and a related substance, urokinase plasminogen activator, are serine proteases that split plasminogen to form plasmin. The activity of t-PA magnifies on binding to fibrin. In this manner, also, plasmin formation remains localized to sites of clot formation. Epinephrine, bradykinin, thrombin, and factor Xa cause endothelium to release t-PA, as do venous occlusion and CPB.[85] Fibrinolysis during and after CPB is discussed later.

Intrinsic Fibrinolysis

Factor XIIa, formed during the contact phase of coagulation, cleaves plasminogen to plasmin. The plasmin so formed then facilitates additional cleavage of plasminogen by factor XIIa, forming a positive feedback loop. Kallikrein also can activate plasminogen; the physiologic importance of this pathway for fibrin breakdown has not been established.

Exogenous Activators

Streptokinase (made by bacteria) and urokinase (found in human urine) both cleave plasminogen to plasmin but do so with low fibrin affinity. Thus systemic plasminemia and fibrinogenolysis, as well as fibrinolysis, ensue. Acetylated streptokinase plasminogen activator complex provides an active site, which is not available until deacetylation occurs in blood. Its systemic lytic activity lies intermediate to those of t-PA and streptokinase. Recombinant t-PA (Alteplase) is a second-generation agent that is made by recombinant DNA technology and is relatively fibrin specific.

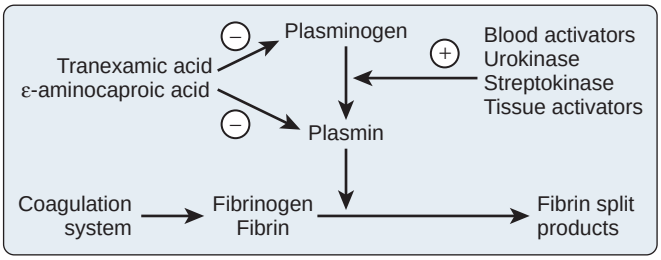


Fig. 35.8 The fibrinolytic pathway. Antifibrinolytic drugs inhibit fibrinolysis by binding to both plasminogen and plasmin. Intrinsic blood activators (factor XIIa), extrinsic tissue activators (tissue plasminogen activator, urokinase plasminogen activator), and exogenous activators (streptokinase, acetylated streptokinase plasminogen activator complex) split plasminogen to form plasmin. *(From Horrow JC, Hlavacek J, Strong MD, et al: Prophylactic tranexamic acid decreases bleeding after cardiac operations.* J Thorac Cardiovasc Surg. *1990;99:70.)*

Clinical Applications

Fig. 35.8 illustrates the fibrinolytic pathway, with activators and inhibitors. Streptokinase, acetylated streptokinase plasminogen activator complex, and t-PA find application in the lysis of thrombi associated with myocardial infarction. These intravenous agents "dissolve" clots that form on atheromatous plaque. Clinically significant bleeding may result from administration of any of these exogenous activators or streptokinase.[86]

Fibrinolysis also accompanies CPB. This undesirable breakdown of clot after surgery may contribute to postoperative hemorrhage and the need to administer allogeneic blood products. Regardless of how they are formed, the breakdown products of fibrin intercalate into sheets of normally forming fibrin monomers, thus preventing cross-linking. In this way, extensive fibrinolysis exerts an antihemostatic action. Factor XIII is an underappreciated coagulation protein. It circulates and, when activated, cross-links fibrin strands and protects fibrin from the lytic actions of plasmin. It has been known for some time that low levels of factor XIII are associated with increased hemorrhage after CPB. Factor XIII levels are reduced by hemodilution, but it also appears that there is active destruction in some patients with CPB. Several new studies have begun testing adding factor XIII to patients and assessing bleeding.[87–89] The problem, however, is that currently there is no good way to assess factor XIII levels. Clearly, factor XIII will be quite expensive, and using it for most patients may well be ill advised.

Heparin

In 1916, in the course of experiments to determine whether the phospholipid component of cephalin caused clotting, a second-year medical student, Jay McLean, instead discovered a substance derived from liver that prolonged coagulation.[90] His mentor, William Howell, named this substance *heparin* (after *hepatic* for "liver"). Heparin has been used almost exclusively as the anticoagulant for CPB for more than 50 years.

Pharmacology

Chemical Structure

In the 1920s, Howell's group isolated heparin and identified it as a carbohydrate containing glucuronic acid residues. In the 1930s, Jorpes demonstrated a hexosamine component to heparin (glucosamine, in particular) that is present in a ratio of 1:1 with glucuronic acid. Of greater importance, he discovered that heparin contains many sulfate groups—two per uronic acid residue—making it one of the strongest acids found in living things. In the 1950s, Jorpes' group identified the sulfate groups at the N-position on glucosamine, where solely acetyl groups previously were thought to reside. In the 1960s, they corrected

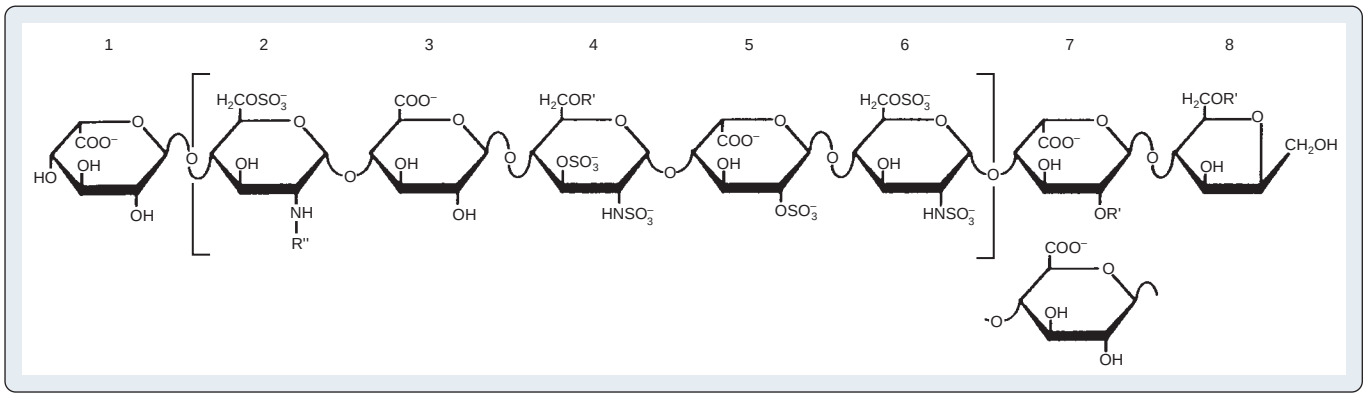


Fig. 35.9 An octasaccharide fragment of heparin, a substituted alternating copolymer of iduronic acid and glucosamine. The leftmost sugar is iduronic acid. Note the numerous sulfate groups and the acetyl substitution on the second sugar. Variations in sugar substitutions and in chain length produce molecular heterogeneity. Brackets indicate the pentasaccharide sequence that binds to antithrombin. *(From Rodén L. Highlights in the history of heparin. In: Lane DA, Lindahl U, eds.* Heparin. *Boca Raton, FL: CRC Press; 1989:1.)*

identification of the uronic acid as L-iduronic acid, an epimer of D-glucuronic acid, and refined its structural detail.[90]

The *N*-sulfated-D-glucosamine and L-iduronic acid residues of heparin alternate in copolymer fashion to form chains of varying length (Fig. 35.9). As a linear anionic polyelectrolyte, the negative charges being supplied by sulfate groups, heparin demonstrates a wide spectrum of activity with enzymes, hormones, biogenic amines, and plasma proteins. A pentasaccharide segment binds to AT.[91,92] Heparin is a heterogenous compound; the carbohydrates vary in both length and side-chain composition, yielding a range of molecular weights from 5000 to 30,000, with most chains between 12,000 and 19,000.[92] Today, the standard heparin is called *unfractionated heparin (UFH)*.

Heparin Versus Heparan

Heparan, a glycosaminoglycan found in the connective tissue and the coating of the endothelial surfaces of nearly all species, can be distinguished from heparin by the following characteristics: (1) a predominance of glucuronic acid over iduronic acid and (2) *N*-acetylation, rather than *N*-sulfation, of more than 20% of glucosamine residues. Bound to cellular proteins, heparan resides inside cells, on cell surfaces, and in the extracellular matrix.[90–95]

Source and Biologic Role

Heparin is found mostly in the lungs, intestines, and liver of mammals, with skin, lymph nodes, and thymus providing less plentiful sources.[94] Abundance of heparin in tissues rich in mast cells suggests these as the source of the compound. Its presence in tissues with environmental contact suggests a biologic role relating to immune function. Heparin may assist white blood cell movements in the interstitium after an immunologic response has been triggered. Mollusks have no coagulation system yet possess heparin, arguing against a biologic role in hemostasis. It is clear that heparin, per se, was never intended biologically to be circulating in large dosages throughout the vascular tree.

Most commercial preparations of heparin now use pig intestine, 40,000 pounds of which yield 5 kg heparin.[90] Prevention of postoperative thrombosis constituted the initial clinical use of heparin in 1935 by Best, Jaques, and colleagues in Toronto, and by Craford in Stockholm.[91]

Potency

Heparin potency is determined by comparing the test specimen against a known standard's ability to prolong coagulation.[96] Current United States Pharmacopeia (USP) and British Pharmacopoeia (BP) assays use a PT-like method on pooled sheep's plasma obtained from slaughterhouses. The plasma commonly is contaminated with tissue extracts or other hemostatically active substances. The European Pharmacopoeia's method, an aPTT on fresh sheep's plasma, is superior to that of the USP.[97] Modern research assays use human FFP, an aPTT-like method, and require linear log versus log plots of standard and test samples.[96]

UFH dose should not be specified by weight (milligrams) because of the diversity of anticoagulant activity expected from so heterogenous a compound. Unfortunately, because of the flawed USP assay, even units of activity often do not reflect clinical effects. As originally defined, 1 unit of heparin prolongs the clotting of cat's blood for only 24 hours at 0°C.[98] Milligram usage, introduced in 1937 as a Swedish standard, was superseded by the first international standard, in which 130 units of activity corresponded to 1 mg. The fourth international standard uses a porcine mucosal preparation.[96]

One USP unit of heparin activity is the quantity that prevents 1.0 mL of citrated sheep's plasma from clotting for 1 hour after addition of calcium.[99] Units cannot be cross-compared among heparins of different sources, such as mucosal versus lung, or low-molecular-weight heparin (LMWH) versus UFH, or even lot to lot, because the assay used may or may not reflect actual differences in biologic activity. None of these measures has anything to do with the effect of a unit on anticoagulation effect for human cardiac surgery.

Pharmacokinetics and Pharmacodynamics

The heterogeneity of UFH molecules produces variability in the relation of dose administered to plasma level of drug. In addition, the relation of plasma level to biologic effect varies with the test system. A three-compartment model describes heparin kinetics in healthy humans: rapid initial disappearance, saturable clearance observed in the lower dose range, and exponential first-order decay at greater doses[99–101] (Fig. 35.10). The rapid initial disappearance may arise from endothelial cell uptake.[101,102] The reticuloendothelial system, with its endoglycosidases and endosulfatases, and uptake into monocytes, may represent the saturable phase of heparin kinetics. Finally, renal clearance via active tubular secretion of heparin, much of it desulfated, explains heparin's exponential clearance.

Male sex and cigarette smoking are associated with more rapid heparin clearance.[103] The resistance of patients with deep vein thrombosis or pulmonary embolism to heparin therapy may be caused by the release from thrombi of PF4, a known heparin antagonist.[104,105] Chronic renal failure prolongs elimination of high, but not low, heparin doses.[103] Chronic liver disease does not change elimination.[106,107]

Loading doses for CPB (200–400 U/kg) are substantially greater than those used to treat venous thrombosis (70–150 U/kg). Plasma heparin levels, determined fluorometrically, vary widely (2–4 units/

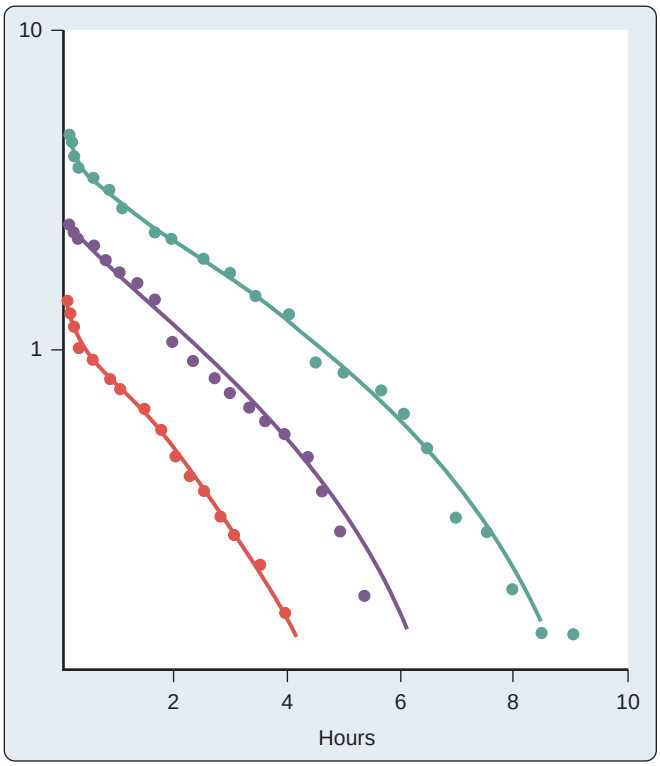


Fig. 35.10 Decay of heparin anticoagulant activity (U/mL on a logarithmic scale) after injections of 75, 150, and 250 U/kg to a single healthy volunteer. Note the rapid initial decline in all curves and nonlinearity at greater doses.

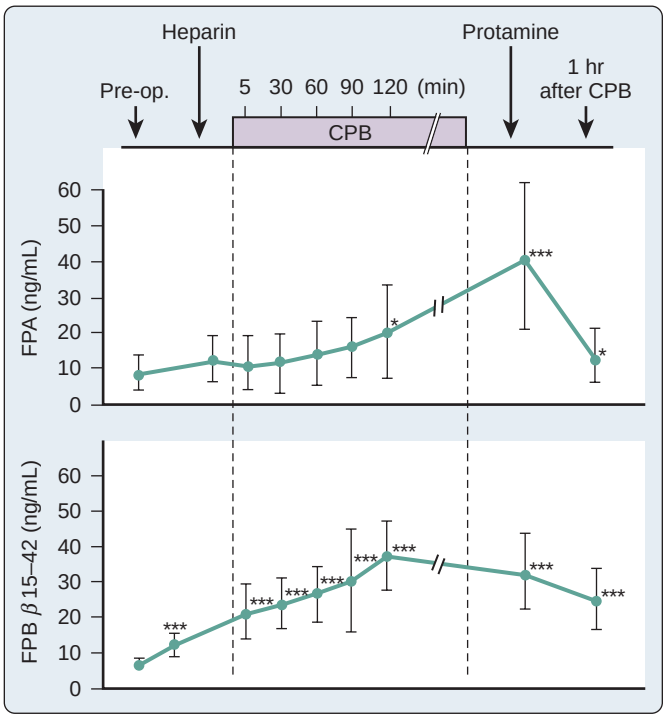


Fig. 35.11 Serial measurements of fibrinopeptides A *(top)* and B *(bottom)* during cardiopulmonary bypass (*CPB*) in 20 patients. *Asterisks* denote statistically significant changes compared with the preoperative measurement. Note continued presence of these markers of thrombin activity despite heparin administration. *FPA,* Fibrinopeptides A; *FPB,* fibrinopeptides B. *(From Tanaka K, Takao M, Yada I, et al. Alterations in coagulation and fibrinolysis associated with cardiopulmonary bypass during open heart surgery.* J Cardiothorac Anesth. *1989;3:181.)*

mL) after doses of heparin administered to patients about to undergo CPB.[107,108] The ACT response to these doses of heparin displays even greater dispersion. Gravlee and colleagues[109] identified thrombocytosis and advanced age as causing a decreased ACT response to administered heparin. This effect may arise from alterations in pharmacokinetics, pharmacodynamics, or both. Interpatient variability in heparin response (pharmacodynamics) does affect the clotting time[109,110]; however, the clinical response to heparin administered to various patients is more consistent than suggested by in vitro measurements.

Although not substantiated formally, most clinicians would agree that hypothermia prolongs the effect of heparin. Precise documentation remains impeded by inability to warm the patient's blood immediately to 37°C for standardized measurement of its ACT. Delayed metabolism or excretion, or both, most likely account for the prolongation of heparin presence during systemic hypothermia, whereas prolongation of the ACT more likely relates to decreased activity of coagulation enzymatic processes (see later).

Actions and Interactions

Heparin exerts its anticoagulant activity via AT III, one of the many circulating serine protein inhibitors (serpins), which counter the effects of circulating proteases.[111,112] The major inhibitor of thrombin and factors IXa and Xa is AT III; that of the contact activation factors XIIa and XIa is α_1-proteinase inhibitor; kallikrein inhibition arises mostly from C1 inhibitor. AT activity is greatly decreased at a site of vascular damage, underscoring its primary role as a scavenger for clotting enzymes that escape into the general circulation.

AT inhibits serine proteases even without heparin. The extent to which heparin accelerates AT inhibition depends on the substrate enzyme; UFH accelerates the formation of the thrombin-AT complex by 2000-fold but accelerates formation of the factor Xa-AT complex by only 1200-fold[112] (Table 35.5). In contrast, LMWH fragments

TABLE 35.5 Some Coagulation Factor Inhibitors and the Effects of Heparin

Factor	*Major Inhibitor*	*Acceleration of Antithrombin Activity by Heparin*
Kallikrein	C1 inhibitor	—
XIIa	α_1-Proteinase inhibitor	—
Xia	α_1-Proteinase inhibitor	40-fold
Xa	Antithrombin	1,200-fold
IXa	Antithrombin	10,000-fold
IIa	Antithrombin	2,000-fold

preferentially inhibit factor Xa. Enzyme inhibition proceeds by formation of a ternary complex consisting of heparin, AT, and the proteinase to be inhibited (eg, thrombin, factor Xa). For UFH, inhibition of thrombin occurs only on simultaneous binding to both AT and thrombin. This condition requires a heparin fragment of at least 18 residues.[111–113] A pentasaccharide sequence binds to AT (see Fig. 35.9). LMWHs, consisting of chains 8 to 16 units long, preferentially inhibit factor Xa. In this case, the heparin fragment activates AT, which then sequentially inactivates factor Xa; heparin and factor Xa do not directly interact.[114–116]

Several investigators have demonstrated continued formation of fibrinopeptides A[116,117] and B[118] (Fig. 35.11), as well as prothrombin fragment F1.2 and thrombin-AT complexes,[119] despite clearly acceptable anticoagulation for CPB by many criteria. These substances indicate thrombin activity. The clinical significance of this ongoing thrombin activity has had limited study. The ACT must be more prolonged to prevent fibrin formation during cardiac surgery compared with during extracorporeal circulation without surgery because surgery

itself incites coagulation. UFH in conjunction with AT appears to work in plasma only on free thrombin. When considering what is known today about thrombin burst and thrombin activity, heparin appears to be relatively inefficient because there is not much free thrombin. Thrombin is held on the surface of activated platelets at various GP binding sites including the GPIIb/IIIa site. Most thrombin is fibrin bound, and heparin-AT complexes do not bind at all to this thrombin unless the level of heparin is pushed far above what is used routinely for CPB. The idea behind using heparin for CPB is that by creating a large circulating concentration of activated AT, whenever a thrombin molecule is produced, an available AT molecule will be there to immediately bind to it before it can have any further activating effect. Clearly, that is unrealistic with the knowledge that thrombin exerts its main activity by binding to the surface of platelets.

Bovine Versus Porcine Preparations

Bovine lung heparin contains greater amounts of iduronic acid and sulfoamino groups than pork mucosal heparin. Because endothelial endoglycosidases degrade heparin at sulfoamino groups, elimination of beef lung heparin proceeds more quickly than that of pork mucosal heparin. Its AT III affinity and anticoagulant activity are less than those of porcine heparin. Either preparation can establish suitable anticoagulation for CPB. Beef lung heparin may be more amenable to protamine neutralization than the pork mucosal preparation because it exerts less anti–factor Xa activity.[120,121] HIT is less common with pork heparin (see later). This information may be of historic value only because bovine heparin is no longer available in the United States.

Heparin Resistance

In the course of continuous infusions of UFH to treat venous thrombosis, some patients experience development of tachyphylaxis, requiring increasing amounts of heparin to maintain the laboratory measurement of anticoagulation, the aPTT, at its designated therapeutic level. In some reports, up to 22% of patients do not adequately respond to heparin and are termed *heparin resistant.*[121–124] To most practitioners, that number seems high, but the definition of what constitutes heparin resistance is highly variable from institution to institution. Likewise, patients receiving UFH infusions exhibit a much-diminished ACT response to full anticoagulating doses of UFH for CPB (200–400 U/kg). With widespread use of heparin infusions to treat myocardial ischemia and infarction, heparin resistance or, more appropriately, "altered heparin responsiveness" has become more problematic during cardiac surgery (Box 35.2).[125,126]

Mechanism

Although several observations suggest that decreased levels of AT III mediate heparin resistance, these observations lack sufficient evidence to establish this relation.[126] In one study of 500 CABG patients, 21% demonstrated heparin resistance, and 65% of these responded to added AT III; this translates into 35% being nonresponders.[122] First, a patient with congenital AT III deficiency displayed heparin resistance[127]; this hardly proves that all heparin resistance stems from AT III deficiency. Second, of six patients with venous thrombosis, three receiving heparin infusions displayed a 25% shorter half-life for AT III compared with the three untreated patients.[128] Accelerated AT III consumption could have resulted from the thrombotic process rather than the heparin infusion. Third, plasma levels of AT III decreased by 17% to 33% during heparin administration by intravenous or subcutaneous routes[129–134] It is possible that this measurement resulted merely from formation of heparin-AT complexes. Perhaps accelerated elimination of AT III arises from some modification of the protein during or after its interaction with heparin.[133] Also, it has been postulated that excesses of platelet activity, releases of PF4, could neutralize heparin in these patients. That has yet to be studied, as has a great deal to do with hypercoagulable states in cardiac surgery.[135]

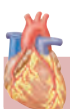
Hemodilution accompanying CPB decreases AT levels to about 66% or even half of normal levels.[107] There are, however, outlier patients who have profoundly low AT levels. It is possible to see AT III levels as low as 20% of normal, and these levels correspond to levels seen in septic shock and diffuse intravascular coagulation.[15] However, supplemental AT may not prolong the ACT, which means that the heparin available has been bound to sufficient or available AT. The only way that the ACT would be prolonged is if there is excess heparin beyond available AT. Reports of heparin resistance for CPB ascribe its occurrence variously to the use of autotransfusion,[135] previous heparin therapy,[136–139] infection,[140,141] and ventricular aneurysm with thrombus.[139–150] The differential diagnosis also includes hypereosinophilia, oral contraceptive therapy, consumptive coagulopathy, thrombocytosis, and congenital AT deficiency.[138] Heparin resistance also might occur in patients with subclinical thrombotic processes releasing PF4.

The individual anticoagulant response to heparin varies tremendously.[143] Some presumed cases of heparin resistance may represent nothing more than this normal variation. Regardless of cause, measurement of each individual's anticoagulant response to heparin therapy for CPB is warranted.[144] Heparin resistance helps focus the debate regarding whether anticoagulation monitoring should measure heparin concentrations or heparin effect; the goal of anticoagulation is not to achieve heparin presence in plasma but to inhibit the action of thrombin on fibrinogen, platelets, and endothelial cells (see Chapter 19). Therefore the effect of heparin usually is measured.

Treatment

Most commonly, additional heparin prolongs the ACT sufficiently for the conduct of CPB. Amounts up to 800 U/kg may be necessary to obtain an ACT of 400 to 480 seconds or longer. Although administration of FFP, which contains AT,[144] should correct AT depletion (Fig. 35.12) and suitably prolong the ACT,[145] such exposure to transfusion-borne infectious diseases should be avoided whenever possible. The use of FFP is outdated and the guidelines by The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (STS/SCA) call for the use of AT concentrate. The use of 2 units of FFP might increase the circulating AT levels by roughly 10% to 15%. Today, the risks of blood transfusion have shifted away from blood-borne viral transmission, with TRALI being noted as the greatest mortality-associated event with transfusion. FFP and platelet transfusions carry the greatest risk for TRALI.[146–148] Although TRALI has not been studied in relation to use of FFP for heparin resistance, it makes great sense to use one of the AT products. This modality is reserved for the rare refractory case. Rather than administer FFP, centers normally accepting only ACTs of 480 seconds or longer for CPB might consider accepting 400 seconds or less, or administering AT III concentrate.[145–149]

AT concentrate specifically addresses AT deficiency.[15–18,145] Two products are available for utilization. One is a recombinant DNA engineered product made from goat's milk and the other is a purified human plasma harvest derivative. There are currently no head-to-head studies to recommend one over the other at this time. The literature supports success in treating heparin resistance during cardiac surgery.[126,150] A multicenter study on the efficacy of using a recombinant human AT in heparin-resistant patients undergoing CPB was published.[151] The patients received 75 U/kg recombinant human AT, which was effective in restoring heparin responsiveness in most



BOX 35.2 PROBLEMS WITH HEPARIN AS AN ANTICOAGULANT FOR CARDIOPULMONARY BYPASS

- Heparin resistance
- Heparin-induced thrombocytopenia
- Heparin rebound
- Heparin's heterogeneity and variable potency
- AT III decrease

AT III, Antithrombin.

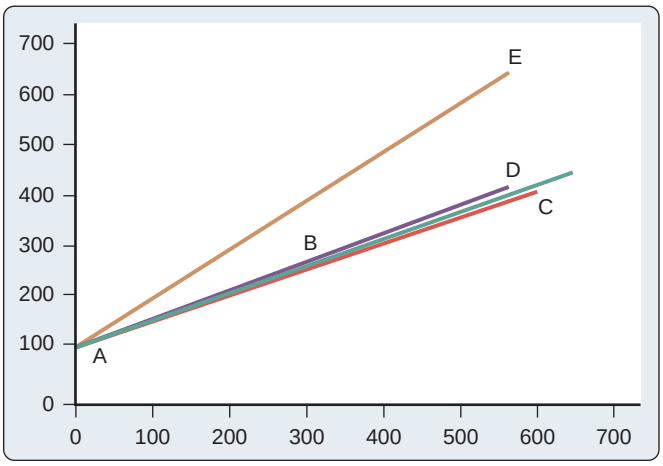


Fig. 35.12 Activated coagulation time response in seconds (vertical axis) to heparin administered in units per kilogram (horizontal axis) to a single patient. *(A)* Baseline measurement; *(B)* after 300 U/kg; *(C)* after an additional 300 U/kg; *(D)* soon after *C*; *(E)* after 2 units of fresh frozen plasma. *(From Sabbagh AH, Chung GKT, Shuttleworth P, et al. Fresh frozen plasma: a solution to heparin resistance during cardiopulmonary bypass.* Ann Thorac Surg. *1984;37:466.)*

patients. However, some patients still required FFP, and the patients bled more than did a control group after surgery.

Heparin Rebound

Several hours after protamine neutralization for cardiac surgery, some patients experience development of clinical bleeding associated with prolongation of coagulation times. This phenomenon is often attributed to reappearance of circulating heparin. Theories accounting for "heparin rebound" include late release of heparin sequestered in tissues, delayed return of heparin to the circulation from the extracellular space via lymphatics, clearance of an unrecognized endogenous heparin antagonist, and more rapid clearance of protamine in relation to heparin.[152,153] Studies demonstrating uptake of heparin into endothelial cells suggest that these cells may slowly release the drug into the circulation once plasma levels decline with protamine neutralization.[102] It is questionable how much heparin rebound contributes to actual bleeding. This phenomenon may be caused by TFPI release from the surface of endothelial cells or other causes of bleeding.

Incidence and Timing

Although initial reports placed the incidence of heparin rebound after cardiac surgery at about 50%, modifications in the timing and amount of protamine administration decreased the incidence.[153–155] Heparin rebound can occur as soon as 1 hour after protamine neutralization.[137] When present, prolonged coagulation times or more direct evidence of circulating heparin may persist for 6 hours or longer.[107,154–158]

Treatment and Prevention

Although still debated by a few, most clinicians accept heparin rebound as a real phenomenon. However, clinical bleeding does not always accompany heparin rebound. When it does, administration of supplemental protamine will neutralize the remaining heparin (Box 35.3). Can the initial protamine dose be adjusted to prevent heparin rebound? Available studies yield conflicting results. All six patients who received protamine based on the estimated amount of *remaining* heparin developed heparin rebound, compared with none of six who received protamine based on the total administered dose of heparin.[154,155] However, 42% of patients receiving large, fixed doses of both drugs experienced heparin rebound and increased bleeding compared with patients whose doses were titrated to clotting assays[155] (Fig. 35.13). Likewise, patients receiving smaller doses of protamine bled less than those receiving protamine doses based on the total amount of heparin administered.[158] In contrast, a fourth study recommended that the ratio of protamine given to heparin remaining be as much as 1.6 mg/100 units.[108]

BOX 35.3 CONSIDERATIONS IN DETERMINING THE PROPER DOSE OF PROTAMINE TO REVERSE HEPARIN

- The proper dose is broad and difficult to determine exactly.
- The dose should be determined by a measurement of coagulation.
- The dose should be administered over at least 10 minutes.
- Excess protamine is a mild antithrombin agent; it may well lead to bleeding itself.

It should be noted that in vitro work shows that as little as one-third the heparin dose is all the protamine that is actually required to reverse the heparin in a test tube. It is still difficult to know exactly what the best heparin reversal dose is by protamine. Some effort at titration with a heparin dose–response curve seems worthwhile.

Although larger initial doses of protamine may decrease the likelihood of heparin rebound, two potential complications of protamine over dosage must be considered: adverse cardiovascular sequelae of protamine administration and the anticoagulant effects of protamine itself. Although protamine is an in vitro anticoagulant, doses up to 6 mg/kg in volunteers, in the absence of heparin, do not prolong the clotting time.[159] However, doses four times in excess of a neutralizing dose doubled the ACT in dogs.[160] The dose after CPB that causes anticoagulation in patients remains unknown. Clinical studies comparing fixed-ratio protamine doses with protocols that gauge protamine dose to remaining heparin activity and protamine drug lot potency demonstrated decreased doses of protamine, decreased chest tube drainage after surgery, and fewer transfusions.[160–162]

Heparin Effects Other Than Anticoagulation

UFH was never biologically intended to circulate freely in plasma.[162–164] As such, it has a number of underappreciated and untoward effects. All too often the effects of CPB have been asserted as causing a coagulopathy; however, the effect of heparin contributing to this has not been widely studied. This is because there has not been an alternative anticoagulant to compare with heparin until now. In the future, there may be better anticoagulants to use during cardiac surgery (see later).

Heparin exerts its anticoagulant activity by activating a binding site on AT III, and without AT, heparin has no intrinsic anticoagulation effect. AT does have anticoagulant effects of its own, but its ability to bind to thrombin is increased 100- to 2000-fold by the presence of the pentasaccharide sequence of heparin. Less than one-third of all mucopolysaccharides present in a dose of heparin contain the active pentasaccharide sequence. The other molecules may have a number of adverse properties.

Heparin binds AT III during CPB, and through ongoing thrombin generation, the AT III levels are decreased over time, as well as via hemodilution. Thus the AT III levels may become quite low, in the range seen during disseminated intravascular coagulopathy, septic shock, and eclampsia.[15,164–167] AT III is not able to be constitutively increased by production. Therefore the level at the beginning of a CPB case is all that is available. The liver will manufacture more AT III, but it may take 1 to 3 days to return to normal after cessation of CPB. In at least one study in which AT III was repleated to normal, the levels of coagulation proteins were much improved after CPB in patients who received exogenous AT III.[15,144]

UFH chelates calcium.[168] When a large bolus dose of heparin is given, there is a slow and steady decline in blood pressure, probably because of decreased vascular resistance and decreased preload. Both

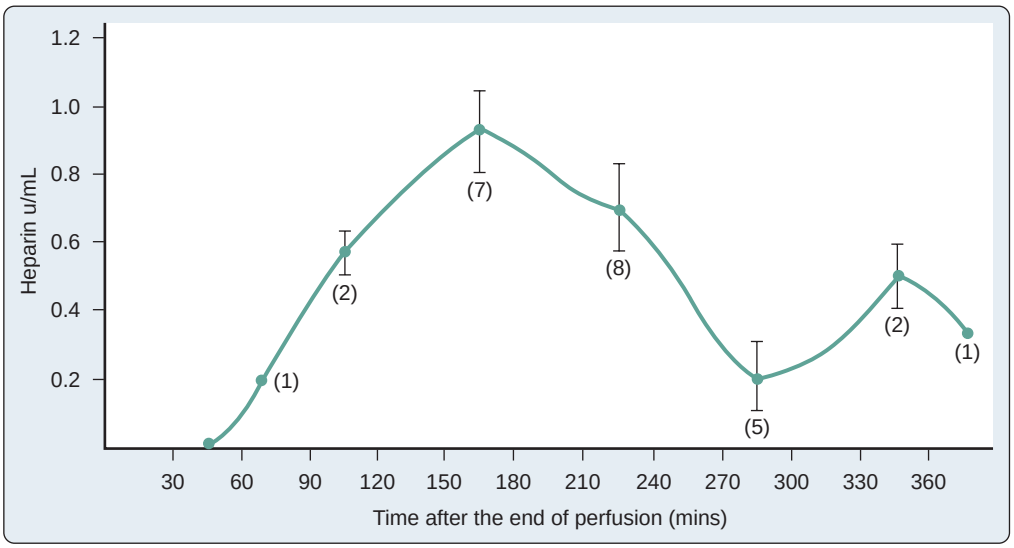


Fig. 35.13 Heparin rebound measured by protamine titration in 10 of 24 patients given heparin by a fixed-time protocol. Parentheses denote number of patients. *(From Kaul TK, Crow MJ, Rajah SM, et al. Heparin administration during extracorporeal circulation.* J Thorac Cardiovasc Surg. *1979;78:95.)*

arterial and venous vessels are dilated by the decrease in the calcium level. The heparin is given while patients are being prepared for CPB, and numerous mechanical events (ie, catheters being inserted into the right atrium and vena cava and arrhythmias) can be blamed for the hypotension, rather than the heparin itself.

Heparin, even in very small doses, partially and reversibly activates platelets and forces them to express many, if not all, of their GP binding sites.[169,170] This fact alone makes clinicians wonder whether there is not a better anticoagulant that might not do this. Heparan, the endothelial analog of heparin, does not break off freely into the circulation; if it does, it is immediately neutralized by platelets through expression of PF4 and adsorption. Thus it makes sense that platelets seeing loose heparin would suspect a site of tissue injury nearby and, therefore, an evolutionary advantage would be created by making these cells react and get ready to create a thrombus. Every coagulation activation is also an inflammatory signal. The fact that platelets take this reactive step means that they are now primed to become highly reactive or contribute to the inflammatory events or have their receptors targeted by other subsequent events. After CPB, platelets have many of their membrane GPs either destroyed or competitively occupied by a number of products of inflammation produced during CPB. The expression of binding sites in response to heparin, therefore, is important and probably has profound implications.

Heparin causes the competitive release of some heparan from endothelial cells and the release of TFPI.[27,28] Endothelial cells all over the body change from being anticoagulant producing to rapidly producing tissue factor. What role large doses of heparin have in this whole-body event is hard to define, but it is known that heparin also causes the release of single-chain urokinase from endothelial cells.[171] The amount of fibrinolysis caused by heparin infusion is not as great as the release of t-PA, which probably is mediated by cytokines as a result of the inflammatory reactions. When released from mast cells, heparin promotes leukocyte chemotaxis and movement through the interstitium.[162,163] However, it is unclear whether heparin upregulates or decreases white cell activations.[163]

Heparin is important for a number of angiogenesis and repair activities of tissue, and these effects may have something to do with its antineoplastic effect.[164] Heparin also affects lipid, sodium and potassium, and acid-base metabolism. These effects are not usually seen acutely but come into play when patients have been on heparin infusions for days in the ICU.

The immunologic effects of heparin are profound. The next section discusses HIT, but recent work shows that 30% to 50% of cardiac surgery patients have heparin antibodies present in their blood by the time of hospital discharge.[172,173] The clinical implications of these prevalent antibodies remain unknown and are the subject of investigation.

Heparin-Induced Thrombocytopenia

Heparin normally binds to platelet membranes at GPIb and other sites and aggregates normal platelets by releasing ADP.[172,173] A moderate, reversible HIT, now termed *type I,* has been known for half a century.[174] The fact that heparin actually triggers an acute decline in platelet count should be considered a biologic event, because heparin, even in trace amounts, triggers the expression of many different platelet GPs. This has been termed *activation of platelets,* but it is not total activation. Heparin's prolongation of the bleeding time probably is related to activation of the platelets, as well as heparin binding to the GPIb surface. It may be that a number of platelets adhere to endothelial cells simply because of their expression of these GP binding sites. Margination, particularly within the pulmonary vasculature, may be an event of HIT type I.

In contrast with these predictable effects of heparin, occasionally patients experience development of progressive and severe thrombocytopenia (<100,000/mm^3), sometimes accompanied by a debilitating or fatal thrombosis (HIT with thrombosis [HITT]). This syndrome is termed *type II heparin-induced thrombocytopenia (HIT II).* A platelet count in excess of 100,000/mm^3 does not mean that HIT II is not present. A decline in platelet count in excess of 30% to 50% over several days in a patient who is receiving or who has just finished receiving heparin is probably caused by HIT II.

Mechanism

These patients with HITT demonstrate a heparin-dependent antibody, usually IgG, although others are described, which aggregates platelets in the presence of heparin.[172,173] During heparin therapy, measured antibody titers remain low because of antibody binding to platelets. Titers rise after heparin therapy ceases; but paradoxically, antibody may be undetectable a few months later.[175] Two other features are unexpected: first, the antibody does not aggregate platelets in the presence of excess heparin; and second, not all re-exposed patients experience development of thrombocytopenia.[176–178]

The platelet surface contains complexes of heparin and PF4. Affected patients have an antibody to this complex. Antibody binding activates platelets via their FcγII receptors and activates endothelium[179–181] (Fig. 35.14). The activation of the platelet surface triggers a secondary

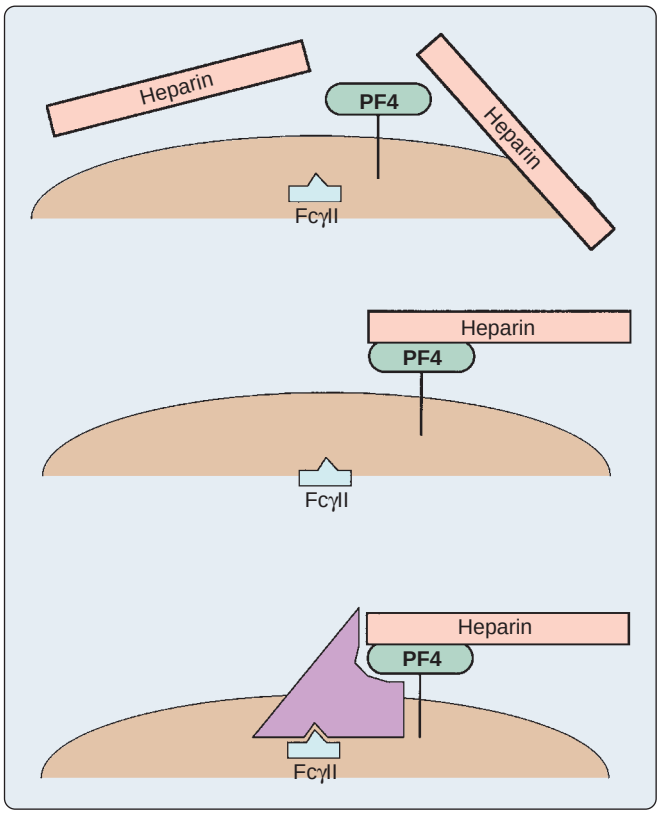


Fig. 35.14 Presumed mechanism of the interaction among heparin, platelets, and antibody in heparin-induced thrombocytopenia. *Top,* Platelet factor 4 (*PF4*) released from platelet granules is bound to the platelet surface. *Middle,* Heparin and PF4 complexes form. *Bottom,* The antibody binds to the PF4-heparin complex and activates platelet FcγII receptors.

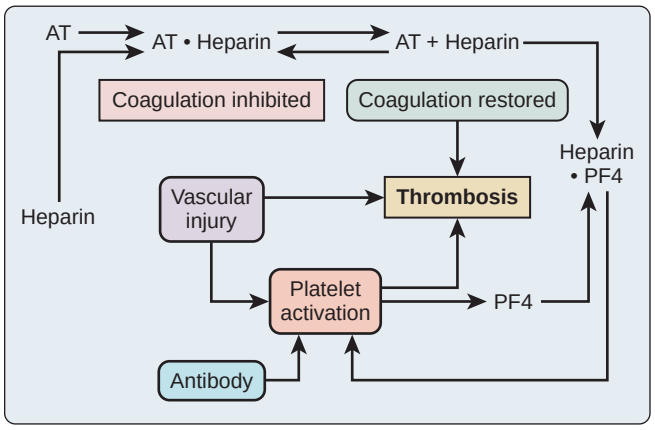


Fig. 35.15 Mechanism of thrombosis accompanying heparin-induced thrombocytopenia. Normally, heparin and antithrombin (*AT*) form a complex that inhibits coagulation. Platelet factor 4 (*PF4*), released from platelets on activation, binds heparin and drives the dissociation reaction of the AT-heparin complex to the right, restoring coagulation locally. Restored coagulation mechanisms and activated platelets form thrombus in the presence of vascular injury. *(Adapted from Parmet JL, Horrow JC: Hematologic diseases. In: Benumof J, ed.* Anesthesia and Uncommon Diseases. *3rd ed. Philadelphia: WB Saunders Company; 1997.)*

thrombin release. Platelets can attach to each other, creating what is known as a white-clot syndrome, but if secondary thrombin generation is created through antibody activation of the platelets, then a fibrin clot can be the result. In the absence of heparin, the heparin-PF4 antigen cannot form. However, there seems to be some sort of continuum between idiopathic thrombocytopenia and HIT.

In the absence of an endothelial defect, the only responses to the antibody-antigen interaction are platelet consumption and thrombocytopenia. Atheroma rupture, endovascular interventions such as balloon angioplasty, vascular surgery, and other procedures that disrupt endothelium can provide a nidus for platelet adhesion and subsequent activation. PF4, released with platelet activation, binds to heparin locally, thus not only removing the inhibition of coagulation but also generating additional antigenic material (Fig. 35.15). Clumps of aggregated platelets thrombose vessels, resulting in organ and limb infarction. Amputation, death, or both often occur with established HITT. The presence of heparin-PF4 antibodies recently has been associated with other adverse effects. It appears that if a patient undergoes cardiac surgery with positive antibodies, the risk for mortality or MI, or both, may at least double.

Incidence and Diagnosis

Estimates of the true incidence of HIT are confounded by different diagnostic thresholds for platelet count, varying efforts to detect other causes, and incomplete reports.[182,183] After 7 days of therapy with UFH, probably 1% of patients experience development of HIT; after 14 days of therapy, the prevalence rate is 3%.[181] Using a platelet count of 100,000/mm^3, multiple reports comprising more than 1200 patients revealed an overall incidence rate of HIT of 5.5% with bovine heparin and 1.0% with porcine heparin.[172] Other recent research has found the preoperative incidence rate of enzyme-linked immunosorbent assay (ELISA)–positive patients to be between 6.5% to 10%. This means that antibodies are present, and that may not mean that thrombocytopenia is occurring. Of great interest is that many more patients develop positive tests for ELISA antibodies by days 7 to 30 after cardiac surgery. Somewhere between 25% and 50% of patients develop these antibodies.[172] In a study of patients after cardiac surgery wherein all patients were screened for HIT antibodies, the group also looked for platelet counts well less than the patient's baseline[184]; 21 of 153 patients (14%) tested positive for antibodies by heparin-induced platelet activation (HIPA) testing. Those patients with a low platelet count and a high HIT antibody titer after surgery were at very high risk for mortality (59%). Therefore a decline in platelet count or persistence of a low platelet count after cardiac surgery should be considered HIT until proved otherwise and taken very seriously. Anticoagulation with alternative non-triggering anticoagulants is imperative.[184] Warfarin should be avoided until such time as the platelet count is recovered and vitamin K therapy can be instituted; this is because the use of warfarin compounds will decrease protein C, which has been known to trigger an HITT crisis.

In the bivalirudin trials, wherein patients thought to have HIT were given an alternative anticoagulant, the presence of antibodies after surgery was associated with adverse events. Particularly worrisome were the presence of a low platelet count or a blunted return toward a normal platelet count after surgery.[185–188]

Some particular lots of heparin may be more likely to cause HIT than others.[189] HIT can occur not only during therapeutic heparin administration but with low prophylactic doses, although the incidence is dose related. Even heparin flush solution or heparin-bonded intravascular catheters can incite HIT.[189–193] Cases of platelet-to-platelet adhesion creating a "white clot" in otherwise normal patients have been observed in the oxygenator and the reservoir of CPB machines. The fact that such events have been reported even when all other tests appeared normal signals the unpredictable nature of the heparin-PF4 antibody, as well as the biologic activity of UFH.

Although HIT usually begins 3 to 15 days (median, 10 days) after heparin infusions commence, it can occur within hours in a patient previously exposed to heparin. Platelet count steadily decreases to a nadir between 20,000 and 150,000/mm^3. Absolute thrombocytopenia is not necessary; only a significant decrease in platelet count matters,

as witnessed by patients with thrombocytosis who experience development of thrombosis with normal platelet counts after prolonged exposure to heparin. Occasionally, thrombocytopenia resolves spontaneously despite continuation of heparin infusion.[194]

Clinical diagnosis of HIT requires a new decrease in platelet count during heparin infusion. Laboratory confirmation is obtained from several available tests. In the serotonin release assay, patient plasma, donor platelets, and heparin are combined. The donor platelets contain radiolabeled serotonin, which is released when donor platelets are activated by the antigen-antibody complex. Measurement of serotonin release during platelet aggregation at both low and high heparin concentrations provides excellent sensitivity and specificity.[177]

A second assay measures more traditional markers of platelet degranulation in a mixture of heparin, patient plasma, and donor platelets.[195] The most specific test is an ELISA for antibodies to the heparin-PF4 complex.[172,173,195,196]

The type, source, and lot of heparin used affect the outcome of these tests. The heterogenous nature of heparin demands that a lot-specific drug be used in serotonin release assays, especially when used to determine suitability of future administration. For example, if LMWH administration is planned for a patient who experienced development of HIT II with UFH, testing of patient plasma with the lot of LMWH to be given should precede its administration.

Measurement of platelet-associated IgG is poorly specific for HIT because of numerous other causes of antiplatelet IgG. This test should not be used in the diagnosis of HIT.

Heparin-Induced Thrombocytopenia With Thrombosis

The incidence rate of HITT is 1.7% with bovine heparin and 0.3% with porcine heparin; thus thrombosis accompanies more than one in five cases of HIT.[172,173] It is clear that the longer patients are on heparin, the more likely it is that they will develop antibody; and with the knowledge that today close to 50% of cardiac patients develop antibodies, it is possible that a significant number of long-term or early mortalities might be because of undiagnosed HITT.[172] In several studies in the catheterization laboratory, it has been shown that if HITT antibodies are present before the performance of angioplasty, the mortality and combined morbidity are greatly increased, perhaps double or more.[197,198] One study has been conducted in almost 500 patients undergoing CABG surgery looking for the presence of antibodies and outcome. The incidence rate of antibody-positive patients was approximately 15%, and their length of stay in the hospital and mortality were more than doubled. Occasional rare situations in which the CPB circuit suddenly clots or when early graft thrombosis or whole-body clotting occurs may all be variants of HITT, but none of these cases can be readily studied because they are so rare.[198,199] If such an occurrence does happen, HITT should be in the differential diagnosis. The occurrence of thrombosis at first seems a paradox. However, HITT has as its hallmark a huge thrombin burst that can occur all over the body. With such massive thrombin generation, the triggering of thrombosis is natural. Thrombosis may then activate the fibrinolytic system to produce a picture of consumptive coagulopathy.[189]

Between 15% and 30% of patients who experience development of HITT will have severe neurologic complications, require amputation of a limb, or die. Lower limb ischemia constitutes the most frequent presentation. Venous clots occur probably as frequently as arterial ones but are not detected as often. Unfortunately, no test predicts the thrombosis component of HIT; thrombosis should be anticipated in the presence of vascular injury, such as puncture sites for catheterization.

The 4Ts system (thrombocytopenia, timing, thrombosis, and other [lack of other reasons]) has been used to increase the index of suspicion with regard to HIT.[200] The use of this scoring system is quite effective, but after cardiac surgery, the decline in platelet count is expected for at least 24 hours. If platelet count stays down after that time, then suspicion for HIT should be high. A study of critically ill patients (noncardiac) using the 4Ts showed an incidence rate of 4.1% for HIT. Low scoring appears to be reliable, whereas high and intermediate scoring showed patients with antibody-positive tests.

Treatment and Prevention

In the absence of surgery, bleeding from thrombocytopenia with HIT is rare. In contrast with other drug-induced thrombocytopenia, in which severe thrombocytopenia commonly occurs, more moderate platelet count nadirs characterize HIT. Platelet transfusions are not indicated and may incite or worsen thrombosis. Heparin infusions must be discontinued, and an alternative anticoagulant should be instituted. LMWHs can be tested in the laboratory using serotonin release before patient administration. Although thrombosis may be treated with fibrinolytic therapy, surgery often is indicated. No heparin should be given for vascular surgery. Monitoring catheters should be purged of heparin flush, and heparin-bonded catheters should not be placed. Antiplatelet agents, such as aspirin, ticlopidine, or dipyridamole, which block adhesion and activation and, thus, PF4 release, provide ancillary help (see Table 35.4).

The patient presenting for cardiac surgery who has sustained HIT in the past presents a therapeutic dilemma. Antibodies may have regressed; if so, a negative serotonin release assay using the heparin planned for surgery will predict that transient exposure during surgery will be harmless. However, no heparin should be given at catheterization or in flush solutions after surgery.[172,173]

Patients with HIT who require urgent surgery may receive heparin once platelet activation has been blocked with aspirin and dipyridamole[171–209] or, in the past, the prostacyclin analog iloprost.[205–208] Unfortunately, iloprost is no longer available. The problem with this strategy is obtaining sufficient blockade of platelet activity. The ultrashort-acting platelet blocking agent cangrelor would seem perfect to create "platelet anesthesia."

Another alternative, delaying surgery to wait for antibodies to regress, may fail because of the variable offset of antibody presence and the unpredictable nature of platelet response to heparin rechallenge. Plasmapheresis may successfully eliminate antibodies and allow benign heparin administration.[209] Finally, methods of instituting anticoagulation without heparin may be chosen (see later). Of these, the alternative thrombin antagonists pose the greatest risk for uncontrolled bleeding, whereas LMWHs and heparinoids afford the greatest chance of success.[209]

LMWH heparin, as an alternative to UFH, has been used for urgent surgery.[210–217] Although LMWHs also can induce thrombocytopenia, and by displaying different antigenic determinants, they may prove acceptable alternatives for patients who experience development of HIT from UFH. Box 35.4 summarizes the therapeutic options available for urgent cardiac surgery in patients with HIT. For additional information on HIT, see recent reviews.[172,173,218]

Alternative Modes of Anticoagulation

The hemostatic goal during CPB is complete inhibition of the coagulation system. Unfortunately, even large doses of heparin do not provide this, as evidenced by formation of fibrinopeptides during surgery.[117–119] Despite being far from the ideal anticoagulant, heparin still performs better than its alternatives. Heparans, dermatans, and other glycosaminoglycans with minimal antihemostatic properties may replace heparin in the future. Current substitutes for heparin include ancrod, a proteinase obtained from snake venom that destroys fibrinogen; heparin fragments, which provide less thrombin inhibition than the parent, unfractionated molecule; direct factor Xa inhibitors; and direct thrombin inhibitors (Box 35.5).

Ancrod

Ancrod abnormally cleaves fibrinogen, resulting in its rapid clearance by the reticuloendothelial system. Thrombin, thus, has no substrate on which to act. Proper patient preparation for CPB (plasma fibrinogen, 0.4–0.8 g/L) requires more than 12 hours. Fig. 35.16 demonstrates

BOX 35.4 THERAPEUTIC OPTIONS FOR ANTICOAGULATION FOR BYPASS IN PATIENTS WITH HEPARIN-INDUCED THROMBOCYTOPENIA

1. Ancrod
2. Low-molecular-weight heparin or heparinoid (test first!)
3. Alternative thrombin inhibitor (hirudin, bivalirudin, argatroban)
4. Use a single dose of heparin, promptly neutralize with protamine, *and*
   a. Delay surgery so antibodies can regress; *or*
   b. Use plasmapheresis to decrease antibody levels; *or*
   c. Inhibit platelets with iloprost, aspirin and Persantine, abciximab, or RGD blockers

In all cases:

1. No heparin in flush solutions
2. No heparin-bonded catheters
3. No heparin lock intravenous ports

No agent is currently indicated for anticoagulation in cardiopulmonary bypass. *RGD,* Receptor glycoprotein derived.

BOX 35.5 POTENTIAL REPLACEMENTS AS AN ANTICOAGULANT FOR CARDIOPULMONARY BYPASS

- Ancrod
- Low-molecular-weight heparins
- Factor Xa inhibitors
- Bivalirudin or other direct thrombin inhibitors (hirudin, argatroban)
- Platelet receptor inhibitors

BOX 35.6 PROPERTIES OF UNFRACTIONATED HEPARIN

1. Anti*thrombotic*[a]—prevents thrombus formation in vivo
2. Anti*coagulant*[a]—prolongs clotting time in vitro
3. Anti*hemostatic*—promotes bleeding
4. Anti*platelet*—activates platelets

[a]Properties of an ideal agent.

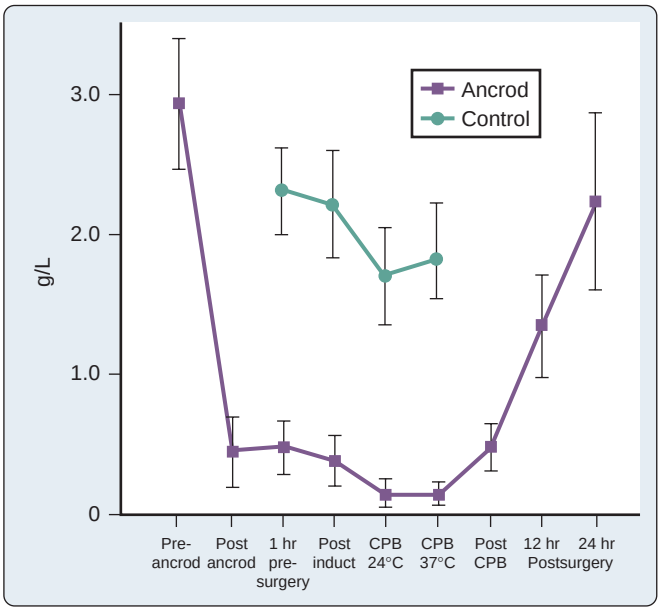


Fig. 35.16 Plasma fibrinogen concentrations (normal, 1.5 to 4.5 g/L) in 20 patients who received snake venom (Ancrod; *squares*) and 20 patients who received heparin (control; *circles*) for anticoagulation during cardiopulmonary bypass (CPB). Note the slow return of plasma fibrinogen, despite administration of 9.3 ± 16.3 SD units of cryoprecipitate and 5.6 ± 3.1 units of fresh frozen plasma to the Ancrod group. *(From Zulys VJ, Teasdale SJ, Michel ER, et al. Ancrod [Arvin] as an alternative to heparin anticoagulation for cardiopulmonary bypass.* Anesthesiology. *1989;71:870.)*

the extent of fibrinogen depletion (from normal value of 1.5–4.5 g/L) and repletion for cardiac surgery using ancrod.[219] Replenishment of fibrinogen via hepatic synthesis is slow; cryoprecipitate, fibrinogen, or FFP administration will speed restoration of coagulation. Patients anticoagulated in this fashion bleed more and require more cryoprecipitate and FFP compared with heparin-anticoagulated patients. One case was done with ancrod in which the coagulation activation was carefully studied.[220] Unbridled thrombin production led to massive platelet activation with a secondary precipitous decline in platelet count. No clot formed, but a gray slime of platelets adhered to the wall of the oxygenator and the reservoir. The platelet count declined to less than 1000/mm^3. However, transfusion with platelet concentrates and cryoprecipitate reestablished normal coagulation, and the patient had less than 500 mL of blood loss for the first 24 hours. No neurologic deficits occurred. However, ancrod is not commercially available in the United States.[219]

Low-Molecular-Weight Heparins

Thrombin inhibition requires chains longer than 18 saccharide units, and aPTT activity follows anti–factor IIa activity more closely than it does anti–factor Xa activity.[114] Thrombin must bind to a portion of the heparin chain for AT to inhibit it. In contrast, factor Xa inhibition by AT does not require interaction of factor Xa with the heparin molecule. Only about 1% to 2% of standard heparin consists of low-molecular-weight (molecular weight, 6000–7000) fragments.[103] Short polysaccharide chains of heparin can be synthesized, or extracted from standard heparin, but both processes cost much more than depolymerization of standard heparin utilizing nitric acid, peroxides, or the enzyme heparinase. Preparations of LMWH formed by these methods include fraxiparine, dalteparin, and enoxaparin.

Standard heparin can inhibit thrombus formation in vivo (antithrombotic activity) and prolong in vitro clotting tests (anticoagulant activity). It also leads to clinical bleeding (antihemostatic activity). Box 35.6 highlights these definitions. LMWHs may dissociate these activities, displaying greater antithrombotic activity and less antihemostatic activity.[103] Unfortunately, coagulation tests sensitive to thrombin inhibition and insensitive to inhibition of factor Xa, namely, the aPTT and ACT, do not adequately monitor the antithrombotic effects of LMWHs. For additional information regarding LMWHs, there are several good reviews.[212–223]

LMWHs have undergone clinical trials for antithrombosis after orthopedic procedures and for prevention of deep vein thrombosis.[223–226] The traditional LMWHs, such as enoxaparin, have not been used for CPB cases because of a limited ability of protamine to neutralize them.[227,228]

Heparinoids

Danaparoid (Orgaran), a mixture of LMWHs and dermatans, can provide anticoagulation for CPB, but lack of readily available

monitoring and sure neutralization limit its application to cases in which UFH clearly is contraindicated.[229] Dermatans alone might prove suitable, but much more investigative work must first occur.[7] Case reports of these agents have shown severe bleeding and, in some cases, death from hemorrhage after cardiac surgery. It appears at this point that dermatan sulfate will not be used for cardiac surgery, and danaparoid was removed from the US market.

Fondaparinux (Arixtra) is a synthetic pentasaccharide identical to that in heparin. It is a primary factor Xa inhibitor that requires AT III, which does not affect thrombin, platelets, or fibrinolytic activity. It is being used for prophylaxis of deep vein thrombosis after surgery, but it does not alter routine coagulation tests (requires a factor Xa assay).[230] Since 2008, there have been some reports of patients with HIT not responding successfully to therapy with fondaparinux.[231,232] Supratherapeutic dosages for fondaparinux were required to inhibit binding of antibodies to platelets. Danaparoid in very low concentrations increased PF4 antibodies; however, in therapeutic concentrations, it decreased production of antibodies. There is no direct antidote for either of these agents, but patients may respond to factor VIIa (see later).

Direct Thrombin Inhibitors

Hirudin, a single-chain polypeptide containing 65 amino acids with a molecular weight of 7000 and produced by the medicinal leech *Hirudo medicinalis,* binds directly to thrombin without need of a cofactor or enzyme, inhibiting all the proteolytic functions of thrombin. This inhibition includes actions on fibrinogen; factors V, VIII, and XIII; and platelets.

Modifications of hirudin include hirugen, a synthetic peptide containing residues 53 to 64 of the native hirudin, and Hirulog, formed by attaching the amino acid sequence d-phe-pro-arg-pro-(gly) to the amino-terminal end of hirugen. Hirugen inhibits the action of thrombin on fibrinogen, but not on factor V. Hirulog has full inhibitory properties but is slowly cleaved by thrombin itself to a hirugen-like molecule.

Hirudin depends on renal excretion; renal failure prolongs its elimination half-life of 0.6 to 2.0 hours. Although there are no known direct neutralizing agents for these drugs, administration of prothrombin complex may partially restore coagulation by enhancing thrombin generation. Clinical trials of hirudin compounds have yielded mixed results. It has been used for patients with HITT, but the longer half-life of approximately 90 minutes means that many of these patients bleed after cardiac surgery.[233] Hirudin is highly antigenic and will lead to immune complexes being created to itself in about 40% of patients. If it is used a second time, the overall incidence rate of anaphylaxis may be as high as 10% of all patients who have received it before. Currently, it is not recommended to use hirudin as a primary agent to perform CPB even if a patient has HIT antibodies.

New direct thrombin inhibitors are now available (Fig. 35.17). These include argatroban and bivalirudin. Argatroban, a derivative of L-arginine, is a relatively small molecule and functions as a univalent direct thrombin inhibitor.[234–249] It binds at the active cleavage site of thrombin and stops thrombin's action on serine proteases. It is completely hepatically cleared and has a reported half-life of 45 to 55 minutes with prolongation when liver function is depressed or liver blood flow is decreased. One case report examined argatroban's half-life after CPB. It was found to be prolonged to 514 minutes in a patient undergoing heart transplantation. This led to the use of massive transfusion (55 units of RBCs, 42 units of FFP, 40 units of cryoprecipitate, 40 units of platelets, as well as 3 doses of factor VIIa).

There is no reversal agent for argatroban, although factor VIIa has been given to increase thrombin generation. It has been approved by the US Food and Drug Administration (FDA) for anticoagulation in the face of HITT, but there has not been, to date, a large-scale, prospective, randomized trial for cardiac surgery or any type of comparison with heparin/protamine. Some case reports do exist of successful usage of argatroban in patients with HITT both on- and off-pump with

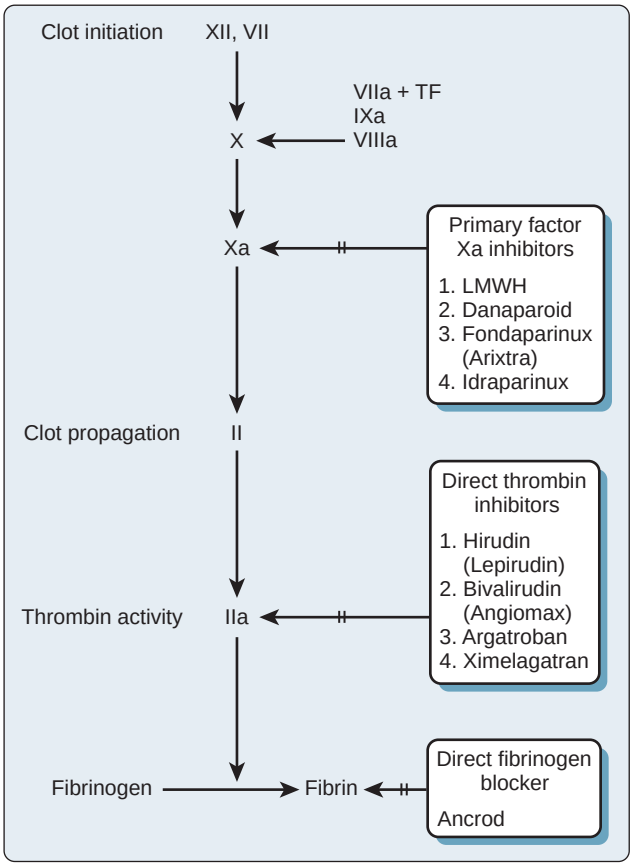


Fig. 35.17 Alternatives to heparin. New modes of anticoagulation are shown in the boxes on the right side of the figure where they inhibit either factor Xa, thrombin, or fibrinogen. *LMWH,* Low-molecular-weight heparin.

acceptable amounts of postoperative bleeding.[236–240] The dosing for off-pump cases has been reported to be about 2 to 3 μg/kg/min, with a goal of an ACT longer than 200 seconds.[239,240] For on-pump cases, the dose is at least doubled (5–10 μg/kg/min), with an effort to achieve an ACT of 300 to 400 seconds.[242] There is no safe and effective dose that has been clinically studied, so any use of this drug for cardiac surgery is off-label and based on experience, as well as case reports. Successful case completions have been noted without undue excess bleeding. However, as noted earlier in the transplant case, some very large bleeds have been encountered. Some cases of thrombosis also have occurred.[241–246] It has been more commonly used in the ICU for patients with hypercoagulable syndromes and HITT.[237,238] Argatroban is a viable direct thrombin inhibitor for use in the cardiac catheterization laboratory. It is far more likely that anesthesiologists will encounter the drug either in the ICU being used for patients with HIT or in patients who have come from the catheterization laboratory directly to the ORs.

Bivalirudin is a bivalent synthetic 20-amino acid peptide based on the structure of hirudin (previously called *Hirulog*).[250–259] Pharmacologists have taken the active amino acids at either end of the hirudin molecule and biosynthesized them. One active site competitively binds to the fibrinogen-binding site of thrombin; the other end of the molecule, the amino-terminal sequence, binds to the active serine cleavage site of thrombin. The two sequences of amino acids are connected together by a tetraglycine spacer. This fully manufactured molecule is highly specific for thrombin and has the unique property that it binds to both clot-bound and free thrombin. Heparin binds only to free plasma thrombin. Bivalirudin has a shorter half-life than argatroban and hirudin; the $t_{1/2}$ is approximately 20 to 25 minutes (with normal renal function and not on CPB). One of the most unique

features of bivalirudin is that its binding to thrombin is reversible and the molecule itself is cleaved by thrombin.

Like the other direct thrombin inhibitors, bivalirudin also has no reversal agent analogous to protamine, so when it is used, it must wear off. Bivalirudin undergoes destruction by the molecule to which it binds and deactivates, thrombin; it is destroyed by thrombin (proteolytic cleavage). The more thrombin activation that is present (ie, the less bivalirudin that is present), the shorter is the half-life. Only about 20% of the molecular activity is eliminated by renal clearance.[250] In mild-to-moderate renal failure, the effect on bivalirudin clearance is thought to be small, but bleeding in patients with renal failure has been noted.

Several clinical trials of bivalirudin for cardiology procedures or cardiac surgery have been completed and published.[251–259] Two pivotal trials aiming for FDA approval of bivalirudin for cardiac surgery with known/suspected HIT were conducted several years ago.[187,188] In trials comparing bivalirudin with either heparin/protamine alone or heparin plus the use of a GP IIb/IIIa inhibitor for percutaneous interventions, bivalirudin was found to have at least equal or better safety and less bleeding than either of the other therapies. When compared with heparin/protamine alone in percutaneous coronary intervention, bivalirudin was found to be superior, not just in bleeding, but also in terms of morbidity and mortality (as a combined end point).[258] In a trial of 100 off-pump routine CABG patients without suspected HIT, patients were randomized to receive either bivalirudin or heparin/protamine, and bleeding and outcome were equal between the groups.[251] These patients underwent recatheterization at 3 months, and it was found that the bivalirudin patients had overall better flow down their grafts than did the patients who had received heparin/protamine. That finding is consistent with the work noted in the HIT section earlier wherein the presence of antibodies bodes poorly for postoperative complications. It also suggests that heparin-protamine in the face of ischemia and reperfusion may lead to adverse thrombotic outcomes with or without heparin-PF4 antibodies. This trial, in conjunction with subsequent trials, raises questions with regard to heparin-protamine and suggests that for off-pump CABG, a more routine usage of bivalirudin might produce improved outcomes.

A phase I/II safety trial of bivalirudin in 30 on-pump CABG patients has also shown good safety, but no comparison was conducted to look at advantages against heparin/protamine. When used, the doses for CPB have been a 0.50- to 0.75-mg/kg bolus followed by an infusion at 1.75 to 2.5 mg/kg/hr titrated to the ACT (target, 2.5 times baseline). The CPB system also was primed with 50 mg, and no stasis can be allowed in the CPB circuit because of metabolism of bivalirudin during CPB. The infusion is stopped about 15 to 30 minutes before CPB is discontinued, and patients bleed for up to 4 to 6 hours. OPCAB cases have used similar doses to ACT targets of 350 to 450 seconds.[253,254] There certainly are some tricks to using bivalirudin for cardiac cases. The drug itself is broken down by thrombin, and thrombin is produced by CPB, as well as through tissue destruction. Any blood left alone without a continuous infusion of bivalirudin will, because of its generation of thrombin, overcome the anticoagulation of bivalirudin in time. Therefore it is expected that stagnant blood in the mediastinal or the chest cavities, or both, will clot. This is alarming to the first-time user of bivalirudin and completely different from what is seen in cases with heparin anticoagulation. Also, the use of mediastinal suction during bypass is not recommended because the mediastinum is a source of a great deal of thrombin activity. Suctioning that back into the CPB reservoir has led to clots being present in a hard-shell reservoir, wherein there is stasis or incomplete mixing of bivalirudin. Once the patient is separated from CPB, it is important to make a decision regarding whether the patient is likely to need to return to bypass. The bypass system, if left stagnant, will have ongoing production of thrombin. Over time, that thrombin will overcome the bivalirudin present in the plasma. Therefore within 10 minutes of separation from CPB, it is wise to decide to either drain the blood from the pump, process it through a cell-saver machine, or reestablish flow and have a slow infusion of bivalirudin into the pump. The reestablishment of flow can be easily accomplished by reattaching the ends of the venous and arterial cannulae. If it is necessary to reestablish CPB, the system should be maintained warm and either a bolus (25 to 50 mg) of bivalirudin should be put into the pump or the infusion that had been running to the patient should be switched to the pump.[252] Furthermore, some surgeons have suggested that in areas of stasis, such as in an internal mammary artery, it is important to flush the artery every 10 to 15 minutes to allow for new bivalirudin to be perfused, or clot could build up in the "dead end" if it is clamped. The other option is to not completely clamp off the internal mammary artery until just before it is to be anastomosed.

There has been some confusion regarding how best to monitor anticoagulation with bivalirudin for cardiac surgery. Originally, Koster and colleagues [233,255] utilized the ecarin clotting time (ECT) to follow circulating levels of bivalirudin. The ECT has a straight-line dose-response relation in the critical range between 300 and 550 seconds. The ACT has a less specific and more variable relation. With circulating bivalirudin concentrations of 10 to 15 μg/mL, the ECT will be 400 to 450 seconds. It is known that clot will not be able to be generated with a bivalirudin concentration greater than 3 to 5 μg/mL, so a level of 10 to 12 will be well greater than a therapeutic threshold to ensure that fibrin formation does not occur on bypass. The dose-responsiveness of bivalirudin is highly predictable. There is no secondary reaction necessary such as with AT III and UFH. Therefore, when bivalirudin is given, there is an absolute amount of AT available. Debates among researchers have gone forward as to whether ACT or ECT monitoring is even necessary at all. The consensus is that ACT will work (the ECT is no longer commercially available). The other reason for using an ACT is that during CPB, if a drug pump malfunctions or the infusion is somehow disconnected, it is important to know that earlier rather than later. If the ACT begins to elevate to more than 500 seconds, then the team really does not know whether to back off on the bivalirudin infusion, stop it altogether, or attribute the effect to some other ACT-prolonging situation such as hemodilution or hypothermia. It is known that hypothermia retards the production of thrombin, but no studies have been done of bivalirudin half-lives in the face of mild-to-moderate hypothermia.

The two trials of bivalirudin in the face of known or suspected HIT antibodies did show effectiveness and safety.[187,188] The CABG Hit On- and Off-Pump Safety and Efficacy (CHOOSE) study and the Evaluation of Patients During Coronary Artery Bypass Operation: Linking Utilization of Bivalirudin to Improved Outcomes and New Anticoagulant Strategies (EVOLUTION) trial were performed as parts of a program to get bivalirudin approved for patients undergoing cardiac surgery with known or suspected HIT. EVOLUTION (ON and OFF) trials randomized patients to receive either heparin-protamine or bivalirudin as the primary anticoagulant regimen for either on- or off-pump CABG surgery. In EVOLUTION-OFF, 157 patients were scheduled for OPCAB at 21 centers. The dosing of bivalirudin was 0.75 mg/kg as a bolus and 1.75 mg/kg/h while the grafts were being prepared and anastomosed. Heparin was dosed to reach an ACT target of 300 seconds and reversed with protamine. There were no differences in death, myocardial infarction, or need for repeat revascularization. However, there was a significant reduction in strokes seen with the use of bivalirudin. Bleeding was about the same with both groups. In the EVOLUTION-ON trial, 150 patients underwent a number of cardiac procedures at the 21 sites. There were, again, no major differences in procedural success (death, MI, need for redo) in the heparin versus bivalirudin groups. There was a statistically, but clinically insignificant, difference (78 mL) in blood loss at 2 hours and not at 24 hours with bivalirudin.

The CHOOSE trials undertook to use bivalirudin in patients with known or suspected HIT. In the CHOOSE-ON trial, 50 patients were enrolled. Immediate success of surgery was achieved in 94% of patients (treated with bivalirudin); at 30 days, success was 86%, and at 12 weeks that had decreased to 82%. Unfortunately, only historic controls could be examined to compare, and conjecture comes into play as to what might happen in such a high-risk group with known/suspected HIT.

Bleeding and transfusion were greater in patients who received bivalirudin. In a single German center with a large experience using bivalirudin, 40 patients had heparin antibodies.[253] These investigators noted that their procedural success rate was 99.4%; however, they did have an increased use of transfusion in those patients who received bivalirudin.

In the face of HITT syndrome, case reports continue to show effectiveness and utility of bivalirudin.[250,255,256] This is an off-label use of the drug because it has not been FDA approved. In animal studies, bivalirudin does not activate platelets, and those animals that have received the drug for CPB have a better platelet count at the end of surgery. Other inflammatory mediators such as cytokines also may be decreased with bivalirudin administration as compared with heparin/protamine administration. Heparin, even in small doses, activates platelets to express their binding sites, whereas bivalirudin seems to leave the platelets quiescent. It also has no cross-reactivity with any immunoglobulin that is present to heparin/PF4 and does not produce an immune response of its own, which can be seen with hirudin.

New Oral Anticoagulants

The introduction of new oral anticoagulants (NOAC) that specifically target thrombin (factor IIa or FIIa) or factor Xa has increased the complexity of coagulation management in patients presenting for cardiac and noncardiac surgery. These NOACs or target-specific oral anticoagulants (TSOACs) include one FIIa inhibitor, dabigatran (Pradaxa), and three factor Xa inhibitors—rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa)—that are increasingly encountered in clinical practice. These drugs are prescribed in place of warfarin or LMWH for the prevention and treatment of thromboembolism in various clinical settings.[260] Advantages for patients include shorter half-life, more favorable risk-benefit profile, and fixed daily dosing without the need for frequent laboratory tests because of more predictable pharmacokinetics (Table 35.6). Dabigatran has been found unsuitable for patients with artificial valves in place, because it caused more bleeding and thromboembolic episodes than warfarin.[261] Dabigatran has a half-life of 12 to 14 hours, whereas the factor Xa inhibitors half-lives range from 5–15 hours. Dabigatran is 80% excreted by the kidneys, whereas the factor Xa inhibitors are protein bound and metabolized by cytochrome P450s in the liver.

These medications do not require regular laboratory testing as occurs with warfarin. In fact, they have variable effects on the various coagulation tests. The preferred tests are the direct thrombin time or an ECT for dabigatran and the anti–factor Xa assays for the other drugs. In an emergency, an aPTT with calibrated reagents can be used for dabigatran and a dilute PT for the factor Xa agents.[262]

In the case of surgical bleeding, patients can be treated with the usual blood products. In addition, the PCCs can be used, with or without FVIIa, to further improve coagulation in life-threatening situations. The four factor PCCs (eg, Kcentra) have been approved by the FDA for warfarin reversal and have had some positive results with the factor Xa inhibitors (see Chapter 34). The best ways to treat bleeding with dabigatran are to either prevent its absorption from the stomach with charcoal or to remove it from the blood with hemodialysis. Extensive work is leading to reversal agents for these NOACs. Idarucizumab (Praxbind) is a fully humanized antibody fragment that has completely reversed dabigatran in clinical trials. It has been studied in more than 100 patients who are either bleeding or undergoing surgery in the RE-VERSE AD phase III trial.[263] The thrombin time and coagulation time have been normalized very rapidly and sustained for 24 hours, whereas the plasma levels of dabigatran have been lowered significantly. Reversal agents are also being developed for the factor Xa inhibitors (eg, andexanet alfa, PER 977), but these are at earlier stages of development.

TABLE 35.6 New Oral Anticoagulants

	Dabigatran	*Rivaroxaban*	*Apixaban*	*Edoxaban*
Action	IIa Inhibitor	II Inhibitor	Xa Inhibitor	Xa Inhibitor
Administration	bid	daily	bid	daily
Peak plasma level	2 h	2–4 h	1–4 h	1–2 h
Half-life	12–14 h	11–13 h	8–15 h	9–11 h
Renal exc.	80%	35%	25%	50%
Protein bind	35%	90%	87%	—

Nonthrombogenic Surface

Considered the holy grail of extracorporeal circulation, an artificial surface that does not incite thrombus formation remains undiscovered. The endothelial surface, which the artificial one should mimic, performs a host of biochemical functions related to antithrombosis. Two that appear crucial are (1) secretion of substances that inhibit both platelet activation and aggregation and (2) surface and matrix adsorption of heparin and heparan, which may locally potentiate AT.[264]

Heparin may be immobilized onto surfaces by ionic bonding onto cationic surfactants. Unfortunately, both heparin and surfactant leach off the coated surface on exposure to blood. Covalent binding or surface grafting of heparin provides a more stable preparation. A properly heparin-bonded surface should bind AT sufficiently to prevent fibrinogen-induced platelet adhesion. Heparin-coated CPB tubing reduces the need for systemic heparin but has not been sufficiently effective to replace systemic anticoagulation.[265–270] Other approaches include increasing surface hydrophilicity with polyethylene oxide and sequestration of the thrombogenic surface by endothelialization, albumin activation, or phospholipid mimicking. New materials might permit cardiac surgery with minimal doses of heparin or even without it (see Chapters 31–33).

Protamine

Pharmacology

Protamine neutralizes heparin-induced anticoagulation. This section considers the history, pharmacology, and clinical use of protamine during cardiovascular surgery, including toxic and idiosyncratic adverse effects. Alternatives to protamine complete the discussion.

History

Miescher, investigating cell nuclei in 1868, discovered and named protamine, a nitrogenous alkaline substance in sperm heads of salmon. Composed of nearly two-thirds arginine, protamines contain many positive charges (Fig. 35.18). Their biologic role is to associate with the negatively charged phosphate groups of nucleic acids[269] (Fig. 35.19).

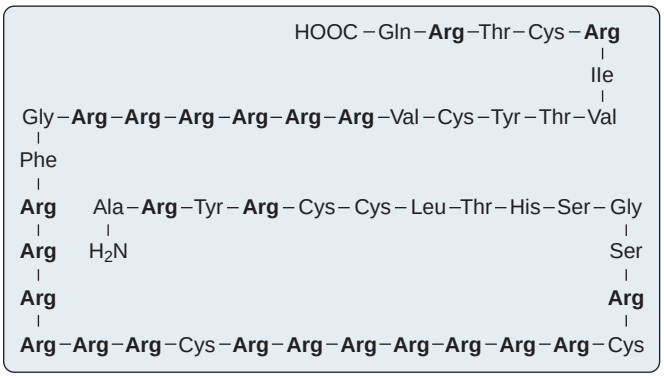


Fig. 35.18 The complete amino acid sequence of protamine from steer. Note the abundance of arginine residues (50% for this species). *(Modified from Coelingh JP, Monfoort CH, Rozijn TH, et al. The complete amino acid sequence of the basic nuclear protein of bull spermatozoa.* Biochim Biophys Acta. *1972;285:1.)*

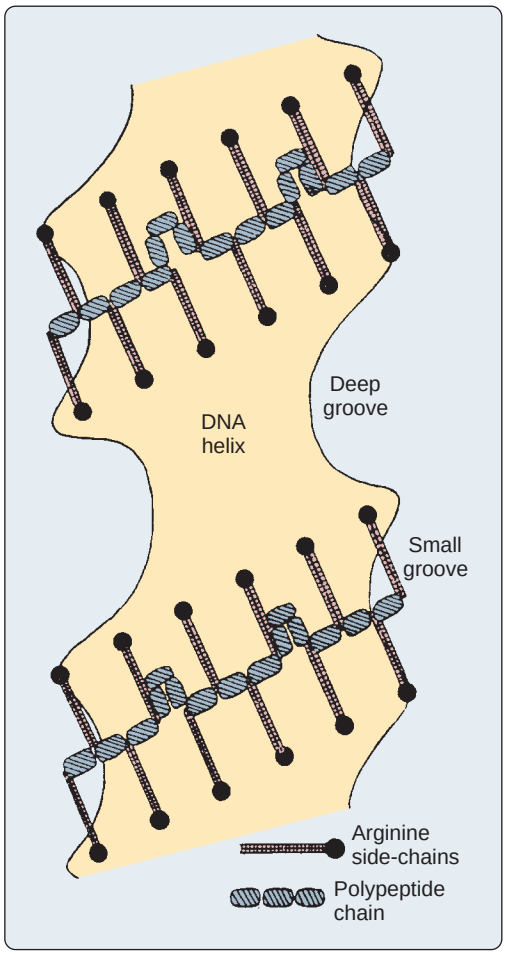


Fig. 35.19 The polypeptide chain of protamine with its arginine residues seen residing in the small groove of the DNA helix. *(From Wilkins MHF: Physical studies of the molecular structure of deoxyribonucleic acid and nucleoprotein.* Cold Spring Harbor Symp Quant Biol. *1956;21:83.)*

In 1936, Hagedorn and colleagues used protamine to delay the absorption of insulin administered subcutaneously. They (correctly) chose protamine, hoping that its alkaline pH would maintain insulin in an ionized, slowly absorbed state. When others attempted to mix protamine with heparin to make a long-acting subcutaneous preparation for thrombosis prophylaxis, they obtained a white precipitate instead of a useful mixture. Chargaff and Olson[271] recognized that this precipitate represented the salt of polycationic protamine and polyanionic heparin. They established protamine as the neutralizing drug for heparin's anticoagulant effect. Jaques[272,273] developed the in vitro protamine titration test for blood heparin levels and documented adverse circulatory effects from protamine.

Source and Preparation

Most vertebrate species synthesize a protamine residing in the heads of sperm. Human protamine closely resembles that of other species.[274] Salmon milt provides the pharmaceutical source of protamine. The crushed gonads of male salmon undergo a crude extraction and filtration process using salt and alcohol. The final product, a dried powder, commonly is reconstituted as a 10-mg/mL solution. Like insulin and some other protein products, it is stable without refrigeration for several weeks. Protamine is available as sulfate and chloride salts. Protamine chloride may have a more rapid onset compared with protamine sulfate.[275] Nevertheless, clinical study reveals no superiority of one preparation over the other.[276]

BOX 35.7 BASIS FOR VARIABILITY IN PROTAMINE DOSE

- Ratio of protamine to heparin
- Amount of heparin to neutralize
- Heparin rebound
- Protamine overdose

Uses and Actions

Two long-acting insulin preparations contain protamine. Protamine-zinc insulin contains 10 to 15 µg protamine per unit of insulin, whereas NPH (neutral protamine Hagedorn) insulin contains 3 to 6 µg/unit. The former compound, with more protamine, exhibits a 36-hour duration, compared with 24 hours for the NPH insulin. Both heparin and protamine alter cell division and influence angiogenesis and tumor size.[277,278] However, these effects have not yet developed into therapeutic modalities. In addition, both protamine and its substitute polycation, hexadimethrine, possess broad antimicrobial activity, suggesting application as a topical antibiotic.[279]

Neutralization of heparin-induced anticoagulation remains the primary use of protamine. Formation of complexes with the sulfate groups of heparin forms the basis for this "antidote" effect. Protamine neutralizes the AT effect of heparin far better than its anti–factor Xa effect.[120] This distinction may arise from the need for thrombin, but not factor Xa, to remain complexed to heparin for AT to exert its inhibitory effect. Because porcine mucosal heparin has more potent anti–factor Xa activity than bovine lung heparin,[280] today's available heparin may prove to be more difficult to neutralize with protamine. Protamine's poor efficacy in neutralizing anti–factor Xa activity limits the utility of LMWH compounds as anticoagulants for CPB.

Protamine exhibits antihemostatic properties by affecting platelets and by releasing t-PA from endothelial cells.[120] Thrombocytopenia follows protamine administration in dogs and in humans.[281–284] Heparin-protamine complexes inhibit thrombin-induced platelet aggregation.[285] In addition, protamine appears to bind to thrombin, inhibiting its ability to convert fibrinogen to fibrin.[286] Initial attempts to document an in vivo antihemostatic effect of protamine proved unsuccessful.[154] Rapid degradation of protamine by circulating proteases may account for this discrepancy.

Administration, Distribution, and Fate

Neutralization of heparin occurs by intravenous injection of protamine. Subcutaneous administration is limited to prolongation of insulin absorption. Presumably, these highly charged polycations distribute only to the extracellular space.

In the presence of circulating heparin, protamine forms large complexes with heparin.[287] Excess protamine creates larger complexes. The reticuloendothelial system may then dispose of these particles by endocytosis. Although this action has not been proved, macrophages in the lung may constitute the site for elimination of these complexes because intravenous administration of protamine permits formation of heparin-protamine complexes in the pulmonary circulation first. Protamine also may bind to circulating plasma proteins, the significance of which remains unclear.[288] Proteolytic degradation of the protamine complexed to heparin conceivably results in free heparin. Protamine degradation in vivo proceeds by the action of circulating proteases, among them carboxypeptidase N, an enzyme that also clears anaphylatoxins and kinin pathway products.[289] The time course of protamine disappearance from plasma in patients remains poorly investigated.

Dosage

The recommended dose of protamine to neutralize heparin varies widely. Box 35.7 lists factors accounting for this variability. The first

factor is the proper ratio of protamine to heparin. Reports of the optimal ratio of milligrams of protamine to units of heparin cite values as low as zero (ie, they do not neutralize heparin)[290] to as much as 4 mg/100 units.[168] This variability has been accounted for by differences in timing, temperature, and other environmental factors; choices for coagulation tests and outcome variables; and speculation and unproven assumptions. Second, the basis for calculating protamine dose, the total amount of heparin given or the amount remaining in the patient, must be determined. Protamine titration tests at the conclusion of CPB can determine the amount of heparin remaining in the patient. With automated versions of this test and simple assumptions regarding the volume of distribution of heparin, the amount needed to neutralize the heparin detected in the patient's vasculature can be calculated. However, this technique may invite heparin rebound, the third concern (see Chapter 19).

An alternative regimen splits a 1 mg/100 units calculated dose of protamine into two separate doses: an initial dose (75% of the total) after CPB, with the remainder after reinfusion of blood from the bypass circuit. This regimen prevented increased plasma heparin levels and prolongation of the aPTT, compared with a control group.[291] The ACT remained unchanged, perhaps a reflection of its insensitivity to small amounts of circulating heparin. Protamine chloride did not prove superior to protamine sulfate in preventing the occurrence of heparin rebound.[276]

A system using coagulation test tubes that contain lyophilized heparin and protamine matched by lot to that administered to the patient permits calculation of dosages to account for variations arising from patient and pharmaceutical factors. It results in increased doses of heparin and decreased doses of protamine compared with those calculated by weight alone. Nevertheless, decreased bleeding and less use of allogeneic blood products result.[161]

Finally, lest fear of heparin rebound prompt the clinician to administer protamine in excess, gross overdosage may likely anticoagulate patients. Dogs given excess protamine exhibited a dose-dependent prolongation of the ACT, with the ACT nearly doubling after a protamine dose four times that needed to neutralize heparin. At a tenfold dose, the aPTT prolonged and thrombocytopenia developed[160] (Fig. 35.20). Without prior heparin, the coagulation test abnormalities occurred at lower protamine doses. The cautious clinician realizes that the protease enzyme system that degrades protamine can be saturated. Prolongation

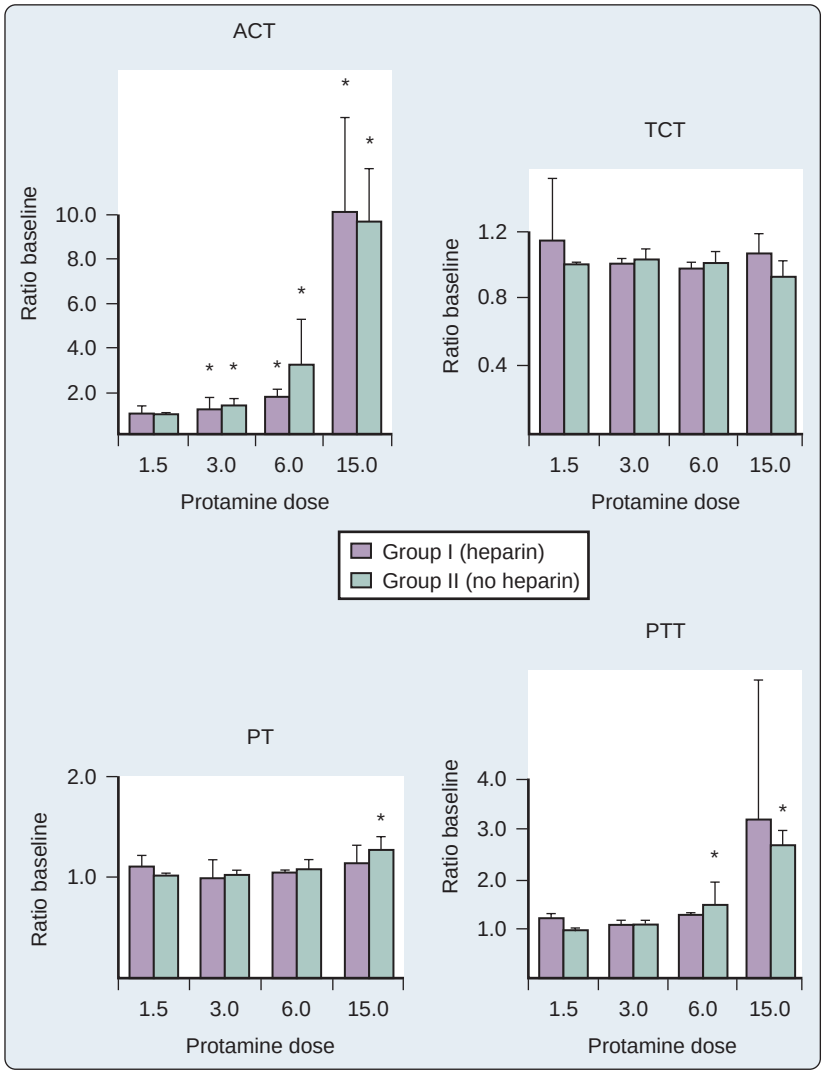


Fig. 35.20 Effect on the activated coagulation time (*ACT*), thrombin clotting time (*TCT*), prothrombin time (*PT*), and activated partial thromboplastin time (aPTT) of protamine dose (in mg/kg) given to dogs 10 minutes after 150 U/kg heparin *(dark bars)* or without prior heparin *(light bars)*. Error bars represent standard deviation (SD). *Asterisks* denote statistical significance compared with baseline values. *(From Kresowik TF, Wakefield TW, Fessler RD, Stanley JC. Anticoagulant effects of protamine sulfate in a canine model.* J Surg Res. *1988;45:8.)*

of coagulation times may conceivably result from protamine overdose, as well as from unneutralized heparin. Fortunately, the safe range of protamine dose regarding neutralization of anticoagulation is large; therefore the prudent clinician will not hesitate to administer a small additional dose of protamine should incomplete neutralization or heparin rebound be suspected, while limiting administration so as not to overwhelm the proteases that degrade protamine.

Adverse Reactions

The potential for a deleterious response to protamine administration raises serious questions and difficult choices in clinical care before, during, and after cardiac operations. This section presents the spectrum of adverse reactions, the presumed mechanism for each, and treatment options. These adverse events can be reduced with proper clinical technique. Thus a clinical perspective at the end of this section discusses preventive measures to guard against untoward responses. The causes of hypotension after protamine (rapid administration, anaphylactic reaction, and pulmonary vasoconstriction) are considered in turn.

Rapid Administration

Peripheral Cardiovascular Changes

Jaques determined initially that systemic hypotension from protamine administered to dogs required a rapid (15-second) injection. Subsequent studies confirmed that hypotension accompanies intravenous protamine.[273,292–299] However, repeat doses are benign when given slowly or rapidly within 4 to 6 hours of an initial reaction unless heparin is given before the second dose.[293,300] Pulmonary arterial pressures also increase.[293,301] Although increased pulmonary arterial pressure and pulmonary vascular resistance follow protamine predictably in dogs, pigs, and sheep, humans respond in a more idiosyncratic fashion. Decreased systemic vascular resistance accompanies the systemic hypotension,[281,296,297] whereas venous return and cardiac filling pressures decrease.[296,287] Rapid volume administration may avert systemic hypotension in both dogs and humans.[296,302]

Slow administration of a neutralizing dose over 5 minutes or longer rarely will engender cardiovascular changes[303] Systemic hypotension from rapid injection in humans has been ascribed to pharmacologic displacement of histamine from mast cells by the highly alkaline protamine, similar to the mechanism by which curare, morphine, and alkaline antibiotics (eg, vancomycin and clindamycin) cause hypotension. However, protamine alone, in concentrations similar to those expected in vivo, fails to release histamine from minced animal lung tissue,[304] or from dispersed human mast cells.[305] More recent investigations linked hypotension to the release of nitric oxide from endothelium.[306]

Effects on Cardiac Inotropy

Cardiac output (CO) predictably decreases after rapid administration to animals when preload is allowed to decrease.[281,292,294,295,299,301] Most human studies document no change in CO with rapid[307–309] or slow administration.[310–314] When volume infusion accompanies protamine, CO increases[302]; however, the effects of protamine on CO do not assess its impact on inotropy, which constitutes only one of many determinants of CO.

Initial reports indicated a myocardial depressant effect.[292,294,295,297] Studies using strips of myocardium bathed in concentrated protamine solutions produced similar results[315–318]; clinically relevant bath concentrations yielded conflicting results regarding depressed myocardial mechanics.[319–321] One study suggested that only concentrated noncomplex protamine would compromise patients clinically.[318] Another suggested that patients with established ventricular compromise might suffer further degradation of contractile performance on exposure to unbound protamine.[322] The mechanism may relate to altered membrane ion conductances that increase intracellular calcium.[322] Well-conducted studies in intact organisms revealed no effect of protamine on contractility in animals[298,313,323] or humans[293,323–329] (Fig. 35.21).

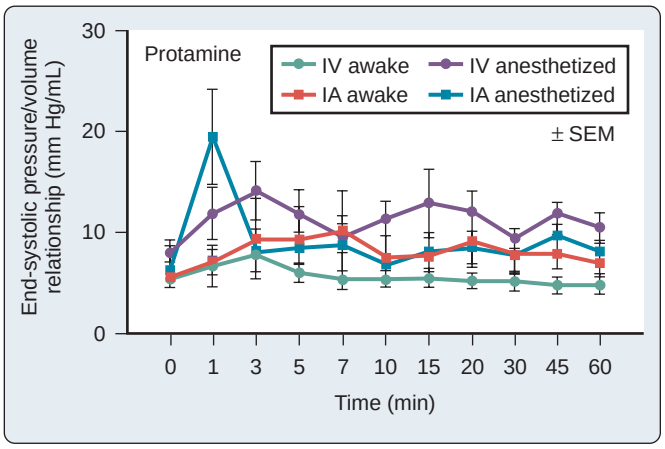


Fig. 35.21 Effect of protamine infusion to dogs on a measure of inotropic state, the end-systolic pressure-volume relation. Neither route of administration (intra-aortic [*IA*], intravenous [*IV*]) nor the presence of anesthesia modified the absence of an effect of protamine on inotropic state. *(From Taylor RL, Little WC, Freeman GL, et al. Comparison of the cardiovascular effects of intravenous and intraaortic protamine in the conscious and anesthetized dog.* Ann Thorac Surg. *1986;42:22.)*

Left-Sided Injection

Based on early reports claiming protection from adverse responses, injection of protamine directly into the left side of the circulation (left atrium or aortic root) became popular.[326,327] Some subsequent animal investigations confirmed a left-sided advantage[328,329]; others demonstrated no advantage[323,330] or more compromised hemodynamics[331–333] compared with a control right-sided group. Left-sided injection provides no protection from pulmonary hypertension.[331] In humans, the published evidence weighs against left-sided injection; three separate investigations in a total of 130 patients demonstrated more hypotension from left-sided than right-sided injection.[309,332,333] The clinician must consider that left-sided injection also increases the risk for systemic particulate and air embolization.

Platelet Reactions

The most underappreciated reaction to protamine is thrombocytopenia. The heparin-protamine complex activates the microcirculation. For a quick graphic example, the reader should merely mix heparin and protamine in a well or syringe. A milky precipitate is observed that grows into larger beads of precipitate. It is clear that when protamine is administered, it binds heparin wherever it comes into contact with it. It may find heparin attached to the surface of platelets and then coat the surface of the platelets with heparin-protamine complexes. It also is possible that heparin and protamine could form cross-links between platelets because the protamine is polycationic and can bind a number of heparin molecules. The end result is a decrease in platelet count within 10 to 15 minutes of administration of protamine. The usual is roughly a 10% decline in platelet count, but it can be larger, when normalization of coagulation is expected. It appears that the platelets are sequestered by the reticuloendothelial and pulmonary vasculature. It is unclear whether those patients with the largest drop in platelets develop the worst bleeding or whether they are at the greatest risk for pulmonary vasoconstriction and pulmonary hypertension secondary to thromboxane release. The sequestered platelets come back into the circulation over the next few hours, and by 1 to 4 hours, the platelet count returns toward normal.

Anaphylactoid Reaction

Allergy, Anaphylaxis, and Adverse Responses

Not all adverse responses to protamine are allergic reactions. Rapid protamine injection decreases blood pressure just as morphine induces nausea; neither side effect is allergic. Immediate hypersensitivity

allergic reactions involve release of vasoactive mediators resulting from antigen-antibody interaction. The broader term *anaphylactoid reactions* includes not only severe immediate hypersensitivity allergy, termed *anaphylaxis,* but also other life-threatening idiosyncratic responses of nonimmunologic origin[334–336] (Fig. 35.22). The initial classification of protamine reactions split the anaphylactoid category (type II) into three subsets: anaphylaxis (IIA), nonimmunologic anaphylactoid reaction (IIB), and delayed noncardiogenic pulmonary edema (IIC).[336] The last two are poorly defined phenomena. Complement-mediated nonimmunologic effects do occur but are not discussed here.[337] This section deals mainly with allergic responses and polycation lung injury.[336–338]

Diabetes Mellitus

Patients receiving protamine-containing insulin develop antibodies to protamine. Between 38% and 91% of these patients demonstrate an antiprotamine IgG[339–341]; far fewer patients develop an antiprotamine IgE. Do these antibodies cause adverse responses to protamine administration? Few patients with diabetes actually experience development of hemodynamic compromise from protamine.[341] The numerous case reports of patients with diabetes who had adverse responses to protamine reflected either a truly increased incidence of adverse response in this population or merely a reporting bias, because cases in nondiabetics are not published.[342–353] Retrospective attempts to determine the risk for protamine reaction in diabetes patients yield diverse results.[354,355] A case-control study found a 95-fold increase in risk relative to patients taking NPH insulin,[356] whereas prospective studies [341,357] demonstrated no increased risk. Table 35.7 displays these data. If risk is increased, it remains quite small (0.6%).[341]

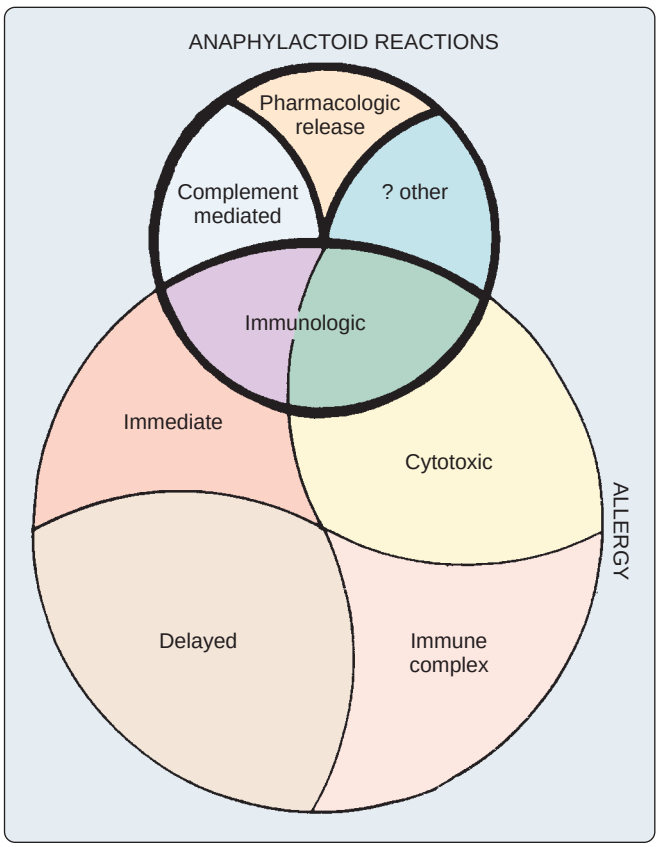


Fig. 35.22 Venn diagram depicting the spectrum of allergy and of anaphylactoid reactions. Anaphylaxis to protamine is an immunologic-type anaphylactoid reaction classified as an immediate allergic reaction. *(From Horrow JC: Protamine allergy.* J Cardiothorac Vasc Anesth. *1988;2:225.)*

Prior Exposure to Protamine

Previous protamine exposure may occur at catheterization,[344,358] at prior vascular surgery,[342,345] at dialysis,[359] or during blood component donation,[360] although modern techniques for the latter two procedures no longer use heparin and protamine. Multiple exposures at intervals of about 2 weeks maximize the chance of an allergic response.[361]

A single intravenous exposure to protamine will engender an IgG or IgE antibody response in 28% of patients.[362] Nevertheless, many thousands of patients each year receive protamine at both catheterization and then later at surgery without sequelae. They offer evidence of the safety of this sequence and the rarity of intravenous exposure to protamine generating clinically significant antibodies.

Fish Allergy

Salmon is a vertebrate or true fish (also known as "fin" fish), as opposed to shellfish, which are invertebrates. Patients allergic to fin fish can respond to protamine with anaphylaxis. Several case reports support this statement.[363,364] As with patients with diabetes, patients with fish allergy followed prospectively do not exhibit an adverse response to protamine challenge.[341] One of this chapter's authors (J.H.) has documented negative skin tests in several patients with fish allergy in whom subsequent protamine administration was benign, as well as a positive skin test in one patient who did not receive protamine (unpublished data). Because skin tests have high sensitivity and poor specificity, negative results suggest lack of allergy. No data link shellfish and protamine allergies.

Vasectomy

Within 1 year of vasectomy, 22% of men develop cytotoxic (IgG) antibody to human protamine, which may cross-react with salmon protamine because of similarity among protamines.[365] These autoantibodies exist in weak titers, however. Prospective studies demonstrate that patients with prior vasectomy receive protamine during cardiac surgery without adverse response.[365,366] Case reports of vasectomy-related protamine allergy[367] display insufficient evidence to demonstrate a causal relation[336,368]; thus vasectomy remains only a theoretic risk for protamine allergy.

Noncardiogenic Pulmonary Edema

Systemic hypotension accompanied by massive pulmonary capillary leak, accumulation of alveolar fluid, decreased pulmonary compliance, wheezing, and pulmonary edema can occur after CPB. Originally attributed to protamine, these rare responses occur sporadically at least 20 minutes after protamine administration.[348,369–372] Others have

TABLE 35.7 Studies on the Incidence of Protamine Reactions (Type Unspecified)

Authors	*Type*	*Size*	*Situation*	*Nondiabetics*	*Diabetics, No Insulin*	*Diabetics-NPH*
Stewart et al[354]	Retrospective	651	Catheterization	0.50%	0.0%	27.0% (4/15)
Gottschlich et al[355]	Retrospective	2996	Catheterization	0.07%	—	2.9% (2/68)
Levy et al[304]	Prospective	3245	Surgery	0.06%	—	0.6% (1/160)
Weiss et al[356]	Case control	27	Various	25 × (IgG)[a]	—	95 × (IgE)[b]

[a]Nondiabetics who sustained an adverse response to protamine were 25 times more likely to demonstrate an antiprotamine IgG than nondiabetics who did not suffer an adverse protamine response.

[b]Diabetics taking NPH insulin who sustained an adverse response to protamine were 95 times more likely to demonstrate an antiprotamine IgE than NPH-taking diabetics who did not suffer an adverse protamine response.

attributed the problem to administration of banked blood products[373,374] or other substances.[375] CPB itself activates complement via the alternate pathway, which can (but usually does not) result in leukocyte aggregation, free radical formation, and lung injury.[34,376]

Many polycations, including protamine, hexadimethrine, and polylysine, can directly induce delayed pulmonary vascular damage.[376] Verapamil may attenuate polycation injury via its inhibitory effects on calcium channels.[377] The delayed noncardiogenic pulmonary edema seen clinically might arise from protamine, from administration of leukocytes that accompany banked blood products,[374] or from CPB.[378,379] Perhaps the marked decrease in occurrence of this phenomenon since 2000 arises from less frequent use of FFP, more widespread administration of calcium channel blockers perioperatively, or both.

Pulmonary Vasoconstriction

Clinical Features

Several years after PACs achieved common usage and case reports sensitized clinicians to adverse responses to protamine, Lowenstein and colleagues[380] reported a series of patients in whom protamine caused systemic hypotension, decreased left atrial pressure, increased rather than decreased pulmonary arterial pressure, and right ventricular distention and failure. This syndrome resembles the predictable response seen in certain laboratory animals.[380–384] Unlike in anaphylaxis, plasma histamine levels do not change during this idiosyncratic, catastrophic pulmonary vasoconstriction,[382] thus justifying a separate classification for this unusual response.[383]

The duration of pulmonary hypertension may vary substantially from brief episodes[384] (Fig. 35.23) to those requiring reinstitution of CPB.[380,384,385] Rechallenge with protamine immediately after recovery from this type III reaction can be benign,[384] similar to the results in laboratory animals. However, because rechallenge could induce repeat pulmonary vasoconstriction, it is best avoided whenever possible.

Proposed Mechanism

Animal models of type III protamine responses demonstrate that heparin must precede the protamine,[386] that heparin–protamine complexes activate the complement pathway,[387] and that blockade of complement activation attenuates pulmonary damage.[388] Furthermore, leukocytes respond to complement activation by forming free radicals, which stimulate the arachidonate pathway.[377,389] Blockade of this pathway mitigates the pulmonary response,[390,391] whereas antihistamines do not.[331,382]

Unlike the immediate pulmonary damage induced by heparin-protamine complexes, polycations alone (eg, poly-l-lysine) induce pulmonary damage in a more delayed fashion. Polycation-induced injury probably involves pulmonary macrophages and arachidonate metabolites.[377,387,392–395] Heparin-protamine complex size varies with the molar ratios of heparin and protamine present[348]; an excess of protamine forms larger complexes.[287] Rapid protamine administration in humans may not predictably cause pulmonary hypertension because, unlike those of the pig and sheep, human lungs do not contain large numbers of macrophages.[348,377] Polycations can block nitric oxide synthetase, leading to speculation that this pathway also participates in the development of pulmonary vasoconstriction. Fig. 35.24 summarizes the speculative mechanisms of various adverse responses to protamine.

Treatment and Prevention

Theoretically, slow administration should limit type III reactions because large heparin-protamine complexes would less likely form. Slow dilute infusion (see later) has decreased this adverse response to protamine.

Some have suggested routine administration of antihistamines to prevent protamine-induced circulatory changes. For type III reactions, in which histamine has no mechanistic role, such a plan should fail. Indeed, antihistamines confer no advantage in general.[396] Hydrocortisone or aminophylline prophylaxis may lessen any circulatory changes with protamine administration, but for nonspecific reasons.[397,398]

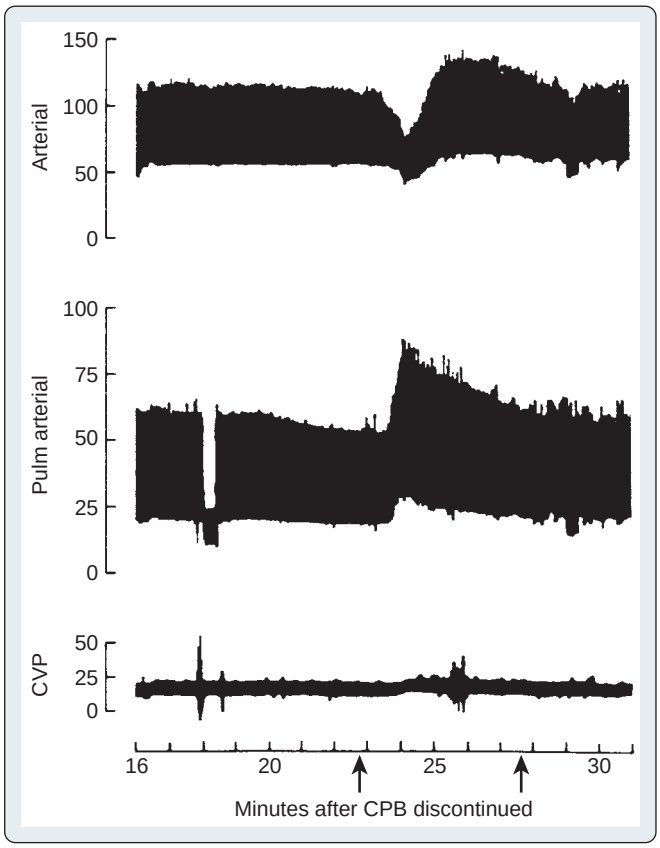


Fig. 35.23 Example of a type III protamine reaction of brief duration. Compressed waveforms of radial arterial, pulmonary arterial, and central venous pressures (*CVP;* all in mm Hg) demonstrate sudden systemic hypotension and pulmonary hypertension soon after administration of 10 mg protamine sulfate (arrow at 23 minutes after bypass). Note lack of adverse response to an additional 10 mg protamine sulfate 5 minutes later. *(From Horrow JC. Thrombocytopenia accompanying a reaction to protamine sulfate.* Can Anesth Soc J. *1985;32:49.)*

On detection of sudden pulmonary hypertension and systemic hypotension, protamine infusion should cease, as should administration of any cardiovascular depressant. Administration of a heparin bolus should be considered in an attempt to reduce heparin-protamine complex size.[385] Excess heparin would theoretically attract protamine away from large complexes to yield a larger number of smaller size particles. If hemodynamics have not deteriorated sufficiently to warrant immediate reinstitution of CPB, 70 U/kg of heparin should be tried first, then 300 U/kg if that fails. Inotropic support should be selected so as not to worsen the pulmonary hypertension; isoproterenol (0.1–0.2 μg/kg bolus followed by 0.1–0.3 μg/kg/min) or milrinone appear best suited for this purpose. Milder cases may revert without intervention,[384] merely by halting protamine administration,[399] a highly desirable outcome insofar as the treatments outlined earlier all extract a price, whether it be arrhythmias from inotropes or bleeding from heparin. Rechallenge with protamine should be avoided.

Guidelines for Clinical Use

The most important principle in avoiding adverse responses to protamine is to administer the drug slowly. Dilution aids this goal by limiting the impact of an undetected rapid administration. A neutralizing dose (3 mg/kg, or 21 mL on average of 10 mg/mL solution) can be added to 50 mL clear fluid; then the diluted drug can be administered into a central vein by a small-drop infusion (60 drops/mL) over 10 to 15 minutes. It is important to provide a carrier flow

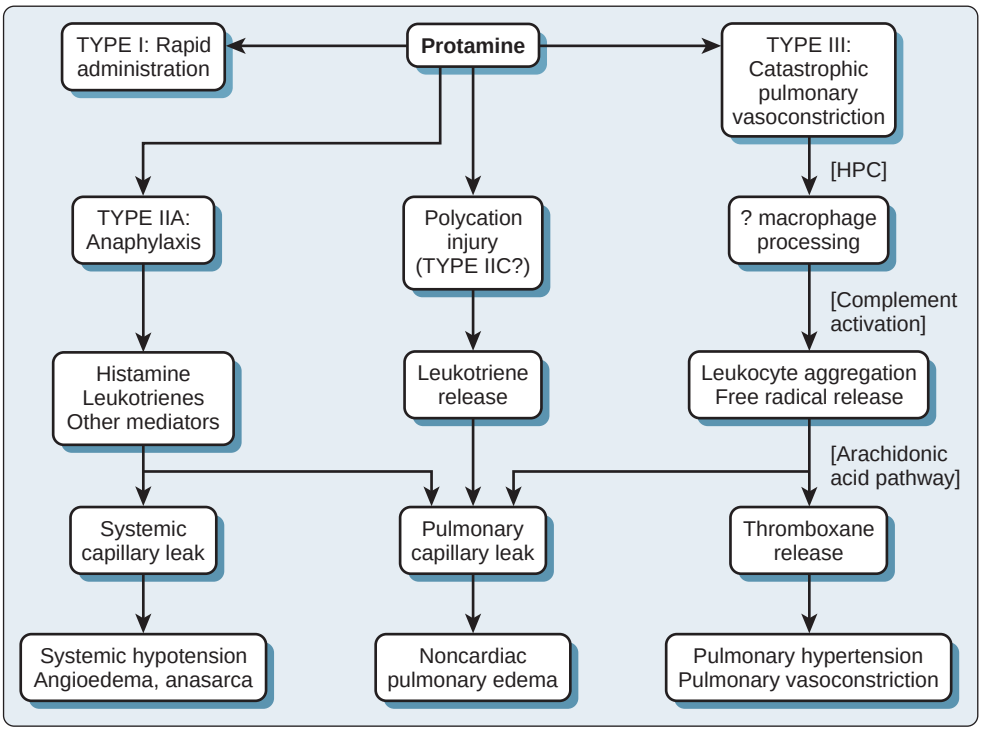


Fig. 35.24 Speculative mechanisms of some protamine reactions to heparin-protamine complex (*HPC*). *(From Horrow JC: Heparin reversal of protamine toxicity: have we come full circle?* J Cardiothorac Vasc Anesth. *1990;4:539.)*

when administering by peripheral vein so that the long tubing does not slowly fill with drug rather than the drug entering the patient. Additional doses of undiluted protamine are given from small syringes (5 mL) at a maximum rate of 20 mg/min to adults. Proper choice of materials (small syringes, small-drop administration sets, and use of diluent) helps protect against too-rapid drug delivery. Slow administration should decrease the likelihood of a type I and III adverse response. However, anaphylactic response (type IIA) may occur at any delivery rate. Preparation for groups at risk to receive protamine is discussed in the following sections.

Patients With Diabetes

No screening test predicts an adverse response to protamine; serum IgE levels are nonspecific; and skin tests do not correlate with antiprotamine antibody measurements.[400,401] Using too concentrated a protamine solution in performing skin tests may produce false-positive results.[402,403] Antiprotamine antibody determinations, available by radio allergosorbent test or ELISA, appear equally nonspecific and are expensive.[400,401] Although most patients with diabetes have antiprotamine immunoglobulin (38% to 91%), most receive protamine without adverse sequelae (>99.4%).

Vasectomy and Patients With Fish Allergy

Like patients with diabetes, vasectomy patients demonstrate antibodies but show a benign response to protamine. All skin tests on vasectomy patients by these authors have displayed negative results and benign responses to protamine after CPB, including one who demonstrated an anaphylactoid reaction at catheterization, probably arising from radiocontrast administration.

Patients with strong evidence by history or laboratory tests of allergy to fin fish are uncommon. After CPB, these patients receive 1 mg protamine diluted in 50 mL intravenous fluid over 10 minutes. If hemodynamics do not deteriorate, the neutralizing dose is administered as previously outlined. Otherwise, protamine is withheld. Skin testing may predict this allergy but would not change the approach, because false-positive skin tests are common, and too few reported cases of protamine–fin fish cross-allergy exist to warrant more aggressive drug administration to those demonstrating negative skin tests. Heparin has been successfully neutralized in a patient with a history of fin fish anaphylaxis and positive skin tests to protamine by using the enzyme heparinase I (Neutralase). This case is unpublished.

Prior Reaction to Protamine

For patients with prior reaction to protamine, skin testing, radio allergosorbent test, and ELISA are appropriate, because negative responses provide greater comfort in attempting a rechallenge. If the historic or laboratory evidence for protamine sensitivity is poor, then a challenge as described for patients with fish allergy may be attempted. Otherwise, an alternative to protamine should be chosen. Availability of a safe alternative would save the cost of these tests and any prolonged hospitalization that accompanies them.

Alternatives to Protamine

This section discusses techniques for neutralizing heparin other than with administration of protamine. Substitutes for protamine in long-acting insulin preparations are not considered.

Hexadimethrine

This synthetic polycation (Fig. 35.25) is 1.1 to 2.0 times more potent than protamine.[404,405] Hexadimethrine (Polybrene) engenders the same biologic responses as protamine when administered rapidly: systemic hypotension, decreased systemic vascular resistance, and rapid disappearance from plasma.[405,406] Pulmonary hypertension occurs after hexadimethrine neutralization of UFH.[407] Patients allergic to protamine have received hexadimethrine without adverse effects.[344]

After reports of renal toxicity, hexadimethrine was withdrawn from clinical use in the United States.[408,409] Animal studies confirmed glomerular injury from hexadimethrine. Urinary excretion of lactic dehydrogenase, aspartase aminotransferase, and other enzymes occurs.[410] Binding of the polycation to the carboxyl groups of proteoglycans in the glomerular basement membrane probably mediates this

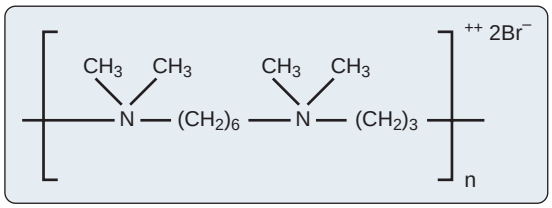


Fig. 35.25 Hexadimethrine, a synthetic polycationic polymer. *(From Horrow JC: Protamine. A necessary evil. In: Ellison N, Jobes DR, eds.* Effective Hemostasis in Cardiac Surgery. *Philadelphia: WB Saunders Company; 1988:15.)*

injury.[411] Although protamine also causes renal toxicity, larger doses are required.[412,413] Hexadimethrine appears unlikely to replace protamine for routine clinical use.[414]

Platelet Factor 4

Platelets contain the potent antiheparin compound PF4. An early attempt to neutralize heparin by platelet concentrate transfusion in two patients produced poor results, however. Despite 18 units of platelets and 400 mL of FFP, 1 patient bled 4 L, whereas 12 units of platelets and 1100 mL of FFP accompanied more than 2 L of blood loss in another.[341]

Rather than bind to heparin electrostatically, like protamine, PF4 utilizes lysine residues at its C termini to neutralize heparin. Both native and recombinant PF4 effectively neutralize heparin in rats without adverse effects at one-fifth the potency of protamine, that is, 5 mg/100 U heparin.[105] In heparinized human blood, recombinant PF4 was half as potent as protamine in restoring the ACT and whole-blood clotting time.[415] Doses of 2.5 and 5.0 mg/kg of recombinant PF4 neutralized the 5000 units of heparin given for cardiac catheterization.[416] Doses of 5 mg/kg of recombinant PF4 to a small number of patients successfully neutralized the 300 U/kg of heparin given for CPB.[417]

Does PF4 avoid the adverse effects of protamine? Kurrek and colleagues[418] demonstrated pulmonary hypertension in lambs when neutralizing heparin with PF4. The lamb, like the dog, responds predictably to protamine with increased pulmonary artery pressures, and thus serves as a model for predicting the idiosyncratic effects of protamine in humans. Those patients likely to respond to protamine with pulmonary hypertension might respond likewise to PF4.[418] Another less likely explanation is that PF4 constitutes a foreign protein to the lamb, thus engendering the adverse pulmonary hemodynamic response.[419] Further clinical work on PF4 as a protamine substitute appears to have slowed.

Interposed Filters

The enzyme, heparinase, bonded to an exit filter of an experimental bypass circuit and interposed at the conclusion of CPB, decreased blood heparin levels within two passes[420]; current filters achieve 90% heparin removal with a single pass.

A modification of this concept uses a hollow-fiber filter to which protamine has been immobilized. Although not a true alternative to protamine, the protamine filter traps heparin extracorporeally, limiting tissue interaction with heparin-protamine complexes.[421,422] This "protamine filter" attenuates both thrombocytopenia and leucopenia. The clinical efficacy and safety of this technique have not yet been clearly demonstrated. Heparin removal proceeds slowly, requiring 10 minutes to remove half of circulating heparin.

Methylene Blue

This positively charged chemical dye binds to heparin in an electrostatic fashion similar to that of protamine. Sloan and colleagues[423] administered 2 mg/kg to a patient who had sustained a severe reaction to protamine, successfully restoring the ACT and aPTT, and decreasing chest tube output. Follow-up work ex-vivo confirmed a potential benefit.[424] However, more rigorous laboratory testing[425] and a clinical trial of ascending doses of methylene blue to neutralize heparin administered for elective CPB demonstrated no efficacy whatsoever in restoring the ACT to normal.[426] Furthermore, doses greater than 6 mg/kg resulted in moderate-to-severe pulmonary hypertension, necessitating administration of inotropic support.[427] Methylene blue, an inhibitor of nitric oxide synthetase, predictably increases pulmonary and systemic vascular resistances at greater doses. Methylene blue should not be used to neutralize heparin.

Omit Neutralization

Heparin activity will decay spontaneously with time because of drug elimination. Castaneda omitted heparin neutralization in 92 patients[290]; despite lower doses of heparin and meticulous hemostasis, most of those patients bled excessively. Another patient in whom heparin was not neutralized bled 5 L over 13 hours and required more than 15 units of blood products.[427] Although this option avoids exposure to protamine, hemodynamic instability and consumptive coagulopathy may result from massive hemorrhage.

Heparinase

Systemic administration of the enzyme heparinase I, produced by *Flavobacterium,* resulted in a return of the ACT to normal in an ex vivo model,[428] animal models of CPB,[428] and healthy volunteers.[429] Initial investigation in patients undergoing elective CABG operations confirmed the utility of heparinase in neutralizing heparin-induced anticoagulation.[430]

Because the enzyme remains in the vasculature for some time after administration (the half-life is 12 minutes in healthy subjects), should an immediate need arise to reinstitute CPB, patients would require not only repeat doses of heparin, but an infusion of heparin to counter the lingering effects of the enzyme. All work on the development of heparinase has stopped after failure of initial clinical trials.

Designer Polycations

DeLucia, Wakefield, and associates[431,432] generated a series of artificial polycation molecules to neutralize heparin. Unfortunately, adverse effects appear to correlate with the ability to neutralize UFH. However, some of the polycations developed can neutralize LMWH species without adverse sequelae. Much more investigation must precede clinical trials. The future may be in using the new direct thrombin inhibitors and completely avoiding the need for protamine.

Bleeding Patient

After cardiac surgery, some patients bleed excessively (probably about 20%). Prompt diagnostic and therapeutic action will avoid impaired hemodynamics from hemorrhage, decreased oxygen-carrying capacity from anemia, and impaired hemostasis from depletion of endogenous hemostatic resources. Many factors govern whether a particular patient will experience excessive bleeding after cardiac surgery. This section details the causes, prevention, and management of the bleeding patient (see Chapters 19 and 31–34).

Although many different criteria can define excessive bleeding, chest tube drainage of more than 10 mL/kg in the first hour after operation or a total of more than 20 mL/kg over the first 3 hours after operation for patients weighing more than 10 kg is considered significant. Also, any sudden increase of 300 mL/hr or greater after minimal initial drainage in an adult usually indicates anatomic disruption warranting surgical intervention.

Patient Factors

The medical history can reveal information relevant to hemostasis. Any patient with a personal or family history of abnormal bleeding after surgery deserves specific coagulation testing for an inherited disorder. Routine PT, aPTT, and bleeding times probably offer little as screening tests.[433–435] The bleeding time has been investigated in a metaanalysis of more than 800 published articles, and it was concluded that it has no correlation with postoperative coagulopathic bleeding.[435] The other

routine tests have less than a 50% accuracy for predicting who will bleed and who will have normal chest tube outputs.

The TEG has been tested extensively both alone and in conjunction with a number of other tests including PT, platelet count, and fibrinogen. The TEG has been shown to have the best predictive accuracy for postoperative bleeding.[436–443] In work using an algorithm based on the TEG and other tests, blood product utilization was cut considerably.[442] Chest tube bleeding was not different, but the TEG did predict which patients might bleed abnormally. Work with TEG monitoring has shown that it can detect both hypocoagulable and hypercoagulable states. New additives to the testing make it sensitive to the ADP-receptor platelet antagonists, as well as the IIb/IIIa inhibitors (see Chapter 19).

Concurrent systemic disease affects hemostasis during surgery as well. Uremia from renal failure results in platelet dysfunction. Severe hepatic compromise impairs every aspect of hemostasis: PK and most coagulation factors circulate in decreased concentration; additional sialic acid residues on fibrinogen and other coagulation factors impair clotting function; splenomegaly induces thrombocytopenia; maldistribution of vWF multimers impairs platelet adhesiveness and aggregation; impaired clearance of endogenous plasminogen activators accentuates fibrinolysis; and decreased levels of coagulation inhibitors induce a consumptive coagulopathy.[444]

Medications significantly affect surgical bleeding. Many patients taking aspirin or other platelet-inhibiting drugs regularly cannot halt that therapy within 7 days of surgery. No antidote can correct the platelet defect. Fortunately, most patients taking aspirin within 7 days of surgery do not exhibit excessive bleeding. The new antiplatelet drugs can all lead to postoperative bleeding (see Table 35.4).

Patients taking warfarin require 2 to 5 days without therapy for correction of the international normalized ratio. Patients for urgent surgery may receive parenteral vitamin K, FFP, or PCC, which corrects the warfarin defect more quickly. Some patients may receive thrombolytic therapy for acute ischemic events just before surgery. Systemic fibrinogenolysis resulting from use of nonspecific thrombolytic agents such as streptokinase should respond to antifibrinolytic therapy with ε-aminocaproic acid (EACA) or tranexamic acid (TA).

Insult of Cardiopulmonary Bypass

More so than patient factors, CPB itself acts to impair hemostasis. Bypass activates fibrinolysis, impairs platelets, and affects coagulation factors. Hypothermia, used in most centers during CPB, adversely affects hemostasis as well.

Fibrinolysis

Numerous investigations support the notion that CPB activates the fibrinolytic pathway.[445,446] Despite clinically adequate doses and blood concentrations of heparin, coagulation pathway activity persists. Formation of prothrombin and fibrinopeptide fragments and thrombin-AT complexes document continued thrombin activity in this setting (see Fig. 35.11). The site of thrombin activity probably resides in the extracorporeal circuit, which contains a large surface of thrombogenic material. Thrombin activation results in fibrinolytic activity; activation of fibrinolysis may be localized to those external sites of fibrin formation. Plasminogen activator concentrations increase during CPB, whereas levels of its inhibitor plasminogen activator inhibitor 1 remain unchanged. This scenario is consistent with activation of fibrinolysis during CPB. Neither of the labels "primary" or "secondary" applies to the fibrinolysis peculiar to CPB.

Does fibrin formation during CPB constitute a consumptive coagulopathy? It is not a systemic event. Presuming that plasminogen activation occurs only where fibrin is formed (extracorporeally), a systemic fibrinogenolytic state should not ensue. Should α_2-antiplasmin become overwhelmed by plasmin formation, however, systemic manifestations may result. Previous generations of oxygenators may have engendered systemic fibrinogenolysis more easily because of their more thrombogenic designs. In these (now more uncommon) instances of fibrinolysis, the TEG may demonstrate clot lysis. Even when fibrinolysis remains limited to the sites of extravascular fibrin formation, the fibrin degradation products so formed might impair hemostasis. In many cases, the mild fibrinolytic state engendered during CPB resolves spontaneously with little clinical impact.

Platelet Dysfunction

Thrombocytopenia occurs during CPB as a result of hemodilution, heparin, hypothermia-induced splenic sequestration of platelets, and platelet destruction from the blood-gas and blood-tissue interfaces created by cardiotomy suction, filters, and bubble oxygenators.[447–450] Platelet count rarely declines to less than 50,000/mm^3, however.

Not only does the number of platelets decrease during CPB, but remaining platelets become impaired by partial activation. Fibrinogen and fibrin, which adhere to artificial surfaces of the extracorporeal circuit, form a nidus for platelet adhesion and aggregation. A reduced content of platelet α-granules constitutes the evidence for partial activation[447]; nearly one-third of circulating platelets undergo α-granule release during CPB.[448] Bypass also depletes platelet GP receptors Ib and IIb/IIIa.[448–450] These platelets cannot respond fully when subsequent hemostatic stimuli call for release of granule contents. Use of frequent cardiotomy suction and bubble oxygenators aggravates the extent of platelet activation.

Activation of the fibrinolytic system may contribute to platelet dysfunction. Local formation of plasmin affects platelet membrane receptors.[450] Antifibrinolytic medications preserve platelet function and prevent some platelet abnormalities that occur during CPB[451] (Fig. 35.26).

Clotting Factors

Denaturation of plasma proteins, including the coagulation factors, occurs at blood-air interfaces. Liberal use of cardiotomy suction and prolonged use of bubble oxygenators potentially impair coagulation by decreasing coagulation factor availability. Hemodilution also decreases factor concentrations. However, rarely do coagulation factor levels decline to less than the thresholds for adequate formation of fibrin in adult surgery. In infants, however, the smallest achievable pump priming volumes can dilute factors to less than 30% of normal levels.

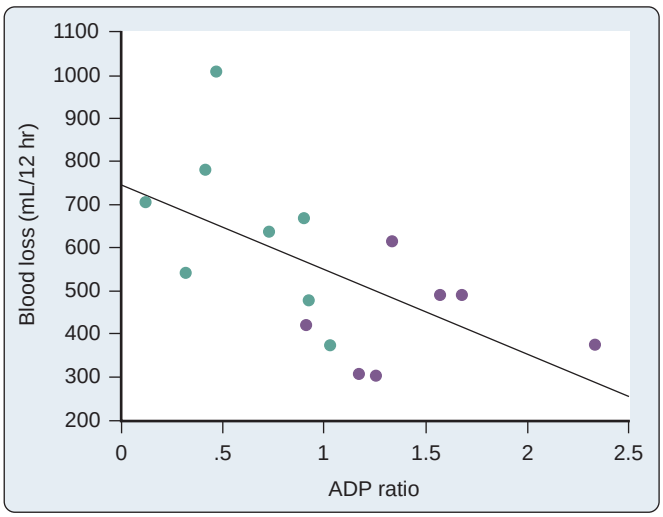


Fig. 35.26 Antifibrinolytics may aid hemostasis by platelet preservation. Here, blood loss appears as a function of platelet adenosine diphosphate (*ADP*), expressed as a ratio (after bypass/before bypass). *Purple circles* represent patients who received prophylactic tranexamic acid. Placebo-treated patients appear as *green circles*. Note that the antifibrinolytic afforded less bleeding after operation and greater platelet ADP. *(From Soslau G, Horrow JC, Brodsky I. The effect of tranexamic acid on platelet ADP during extracorporeal circulation.* Am J Hematol. *1991;38:113.)*

Hypothermia

Hypothermia potentially affects hemostasis in many ways. First, the splanchnic circulation responds to hypothermia with sequestration of platelets.[452,453] After warming, the accompanying thrombocytopenia reverses over 1 hour. Second, transient platelet dysfunction occurs, evidenced by a platelet shape change, increased adhesiveness, inhibition of ADP-induced aggregation, and decreased synthesis of both thromboxane and prostacyclin.[454,455] Third, a specific heparin-like inhibitor of factor Xa becomes more active[456]; protamine cannot neutralize this factor, which might be heparan. Fourth, hypothermia slows the enzymatic cleavage on which activation of coagulation factors depends. Many biologic phenomena display a 7% attenuation of activity for each decrease of 1°C in temperature.[457] Although coagulation factor structure remains unaltered, formation of fibrin may be sluggish when the patient is cold. Fifth, hypothermia accentuates fibrinolysis[455]; the fibrin degradation products so formed then impair subsequent fibrin polymerization. Cold-induced injury of vascular endothelium can release thromboplastin, which then incites fibrin formation and activates fibrinolysis. Table 35.8 summarizes these effects.

Prevention of Bleeding

The possible transmission of serious viral illness and impairment of immune function during transfusion of blood products may generate great concern among clinicians and patients. Many techniques attempt to limit viral exposure, including donation of autologous blood or directed blood, blood scavenging during and after surgery, and efforts to limit perioperative hemorrhage (Table 35.9). Advances in blood banking have decreased infectious disease transmission.[458] Blood sterilization techniques may render such concerns moot.[459]

Preoperative Factors

What can be done before surgery to minimize the extent of bleeding during and after surgery? Existing disorders of hemostasis must be identified and treated. The bleeding diathesis of uremia responds to hemodialysis, RBC transfusion, and administration of desmopressin.[460,461] Because impaired hemostasis from hepatic failure may respond to intravenous desmopressin, preoperative verification of an appropriate response will permit proper administration of this drug after protamine neutralization of heparin after CPB.[462] Likewise, patients with hematologic disorders potentially amenable to desmopressin therapy, such as hemophilia and vWD, should receive desmopressin before surgery to determine the extent of response, if any.[463] When specific factor replacement is indicated, withholding it until after neutralization of heparin will provide less extensive exposure to allogeneic blood products.

Administration of platelet-inhibiting drugs should cease before surgery. Two to three days should elapse for nonsteroidal antiinflammatory medications, which cause reversible inhibition of cyclooxygenase. Seven to ten days are required for regeneration of platelets after administration of aspirin, which irreversibly acetylates cyclooxygenase and some other platelet inhibitors (see Table 35.4).

TABLE 35.8 Antihemostatic Effects of Hypothermia

Hemostatic Component	*Effect of Hypothermia*
Factors	Increased anti–factor Xa activity; heparan?
	Slows enzymes of the coagulation cascade
Platelets	Splanchnic sequestration
	Partial activation
Fibrinolysis	Enhanced
Endothelium	Tissue factor release

TABLE 35.9 Ways to Prevent Excessive Bleeding in Decreasing Order of Importance

Intervention[b]	*Purpose*
Ligatures	Repair all vascular trespass
Neutralize	Heparin fully neutralized
Blood pressure	Avoid hypertension after aortotomy
Suction	Limit cardiotomy suction
Drugs	Cease platelet-inhibiting drugs in advance
Preoperative	Diagnose and treat first
Oxygenator	Membrane oxygenators for long cases
ε-Aminocaproic acid (EACA)	Antifibrinolytic prophylaxis
Temperature	Rewarm sufficiently
Go	Act with deliberate speed (tardiness begets bleeding)
Intravenous	Limit fluids, hemoconcentrate, and diurese
Extracorporeal circuit	Minimize volume

[a]These maneuvers do not all apply to the treatment of excessive bleeding after operation.
[b]The entries in this column form a mnemonic device: the initial letters of each entry, when rearranged, form the words STOP BLEEDING.

Physical Factors

Hypothermia still forms an essential component of organ protection during CPB in many centers. Sufficient rewarming with adequate distribution of heat from central to intermediate and peripheral zones should help prevent hypothermia-induced impairment of hemostasis.

Incomplete surgical hemostasis may occur from a slipped ligature, unclipped vessel branch, loose anastomosis, unattended open vessel at the wound edge, or sternal wire placed through the internal mammary artery. Because few fresh aortic suture lines fail to leak at high systemic pressures (systolic pressure > 180 mm Hg or mean arterial pressure > 120 mm Hg), control of hypertension after CPB promotes hemostasis (see Chapter 38).

Limiting the intensity and frequency of use of the cardiotomy suction fosters platelet preservation during CPB and improves hemostasis after surgery.[464] Selection of a membrane rather than a bubble-type oxygenator for cases involving prolonged CPB limits platelet destruction and fibrinolysis, thus aiding hemostasis.[465]

A small priming volume of the extracorporeal circuit restricts the extent of hemodilution. Hemodilution engenders bleeding not only by providing decreased concentrations of clotting factors and platelets, but also by decreasing the margination of platelets, making them less available for adhesion and aggregation. Other measures that help include regulating cardioplegia volumes, restricting intravenous fluids, administering mannitol or loop diuretics, and providing hemoconcentration with filtration devices during CPB (see Chapter 32).

Removal of platelet-rich plasma at the induction of anesthesia for return to the patient after CPB by plasmapheresis supplies autologous, functional thrombocytes when they are most needed.[466,467] Previously, some centers collected autologous whole blood from patients at the beginning of surgery, reinfusing it after CPB, with controversial benefit.[468–470]

Speed of surgery receives less attention now than in the past, when the therapeutic index of available anesthetics was less favorable. However, patients undergoing short surgery enjoy several advantages. Shorter CPB duration preserves platelet function and limits the coagulant stimulus for subsequent fibrinolysis; more rapid closure after CPB limits tissue exposure to the hypothermic OR environment.

Pharmacologic Factors

Heparin and Protamine

Too little heparin invites active fibrin formation during CPB with consumption of clotting factors and platelets, and excessive activation of the fibrinolytic system; too much heparin risks postoperative heparin rebound. With too little protamine, the remaining unneutralized heparin impairs hemostasis by its anticoagulant action. Doses of protamine excessive enough to overwhelm the endogenous proteases may exert an anticoagulant effect, as well as invite polycation-induced lung injury and pulmonary vasoconstriction. The optimal approach uses coagulation testing to estimate the appropriate heparin

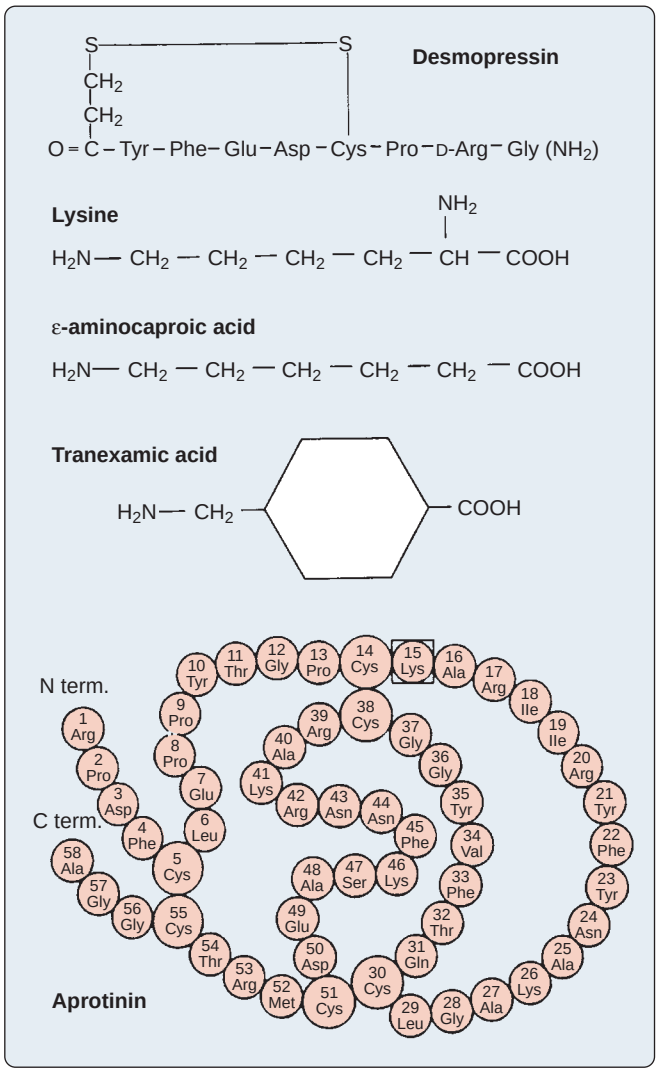


Fig. 35.27 Molecular configurations of drugs used to decrease surgical bleeding. For comparison, the amino acid lysine is also depicted. *(Modified from Horrow JC: Desmopressin and antifibrinolytics. Int Anesthesiol Clin 28:230, 1990; and Fritz H, Wunderer G. Biochemistry and applications of aprotinin, the kallikrein inhibitor from bovine organs.* Drug Res.*1983;33:479.)*

and protamine doses, and confirm both adequate anticoagulation and its neutralization.

Desmopressin

Desmopressin, an analog of vasopressin (Fig. 35.27), provides more potent and longer-lasting antidiuretic activity than vasopressin, with little vasoconstriction (Box 35.8). Like the parent compound and like epinephrine and insulin, desmopressin releases coagulation system mediators from vascular endothelium. Factor VIII coagulant activity increases 2- to 20-fold and is maximal about 30 to 90 minutes after injection.[471–473] Factor XII levels also increase. In response to desmopressin, endothelium releases the larger multimers of vWF, as well as t-PA and prostacyclin. The latter two compounds potentially thwart clot formation and stability. Nevertheless, the overall effect of desmopressin is procoagulant, perhaps because of the impact of factor VIII and vWF.

The optimal dose of desmopressin is 0.3 μg/kg. Intravenous, subcutaneous, and intranasal routes are all acceptable. After plasma redistribution with an 8-minute half-life, metabolism in liver and kidney and urinary excretion yield a plasma half-life of 2.5 to 4 hours.[461] Levels of

BOX 35.8 USEFUL DRUGS TO REDUCE BLEEDING DURING CARDIAC SURGERY

- Tranexamic acid or epsilon aminocaproic acid
- Recombinant factor VIIa
- Desmopressin

factor VIII persist in plasma long after desmopressin excretion because of the release of vWF. Depletion of vWF stores in endothelial cells accounts for the drug's tachyphylaxis. Rapid intravenous administration decreases systemic blood pressure and systemic vascular resistance, possibly by prostacyclin release or stimulation of extrarenal vasopressin V_2 receptors.[474–478] The antidiuretic action of the drug poses no problem in the absence of excessive free water administration.[479]

Specific applications of desmopressin's hemostatic benefit include uremia, cirrhosis, aspirin therapy, and surgery of various types. Correction of prolonged bleeding times in patients with uremia follows desmopressin administration, making desmopressin the treatment of choice for bleeding emergencies in uremia.[461] Administration of desmopressin to patients with cirrhosis also shortens prolonged bleeding times.[462] Desmopressin corrected the aspirin-induced prolongation in bleeding time in 2 patients and 10 healthy volunteers.[480] It is also effective in some rare platelet disorders.[471] Evidence of a hemostatic effect during surgery is varied. Early success in adolescents undergoing Harrington rod placement was not confirmed with subsequent studies.[481]

Initial reports of a hemostatic effect during cardiac surgery were largely unsubstantiated by subsequent investigations.[482–488] vWF activity increased in both control and desmopressin-treated patient groups, thus explaining the absence of a salutary effect of desmopressin on blood loss[486,487] (Fig. 35.28). Desmopressin-induced release of t-PA does not overcome its hemostatic action during cardiac surgery because antifibrinolytic therapy fails to uncover an additional hemostatic effect of desmopressin.[488]

Which subgroups of patients undergoing cardiac surgery might benefit from desmopressin? Certainly, those with uremia or cirrhosis benefit. Those who display decreased maximum amplitude on TEG for whatever reason constitute a third group.[488–491] The heparinase-augmented TEG permits timely identification of patients in this subgroup.

Desmopressin afforded no hemostatic benefit to patients taking aspirin before cardiac surgery,[488,489] and the bulk of evidence currently points away from desmopressin as a prophylactic hemostatic agent for patients undergoing elective cardiac surgery.[490,491]

Synthetic Antifibrinolytics

Synthetic antifibrinolytics, simple molecules (see Fig. 35.27), and analogs of the amino acid lysine, bind to plasminogen and plasmin, thus inhibiting binding of plasminogen at the lysine residues of fibrinogen. Antifibrinolytics may be administered intravenously or orally and undergo renal concentration and excretion with a plasma half-life of about 80 minutes. Effective fibrinolysis inhibition requires an intravenous loading dose of 10 mg/kg for TA followed by 1 mg/kg/hr or 50 mg/kg of EACA followed by infusion of 25 mg/kg/hr.[492,493] Infusion rates require downward adjustment when serum creatinine concentration is increased. Plasma concentrations of TA achieve greater values with decreasing glomerular function. The author's practice is to administer only a loading dose of TA to patients with serum creatinine concentrations in excess of 2.0 mg/dL. Antifibrinolytics are not given to patients with significant upper urinary tract bleeding or consumptive coagulopathy because they prevent the clot lysis needed for continued patency of the ureters or circulatory system, respectively. However, they can also halt ongoing consumption.[494]

Pharmacokinetic studies demonstrated a need to readminister a bolus of EACA on institution of CPB.[493,495] This may not apply to

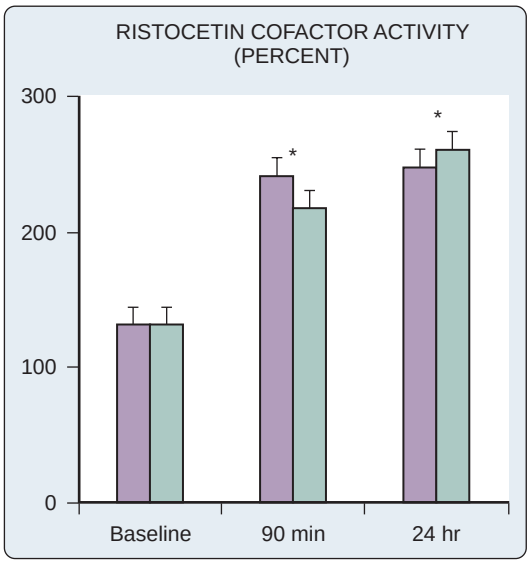


Fig. 35.28 At 90 minutes and 24 hours after receiving desmopressin *(green bars)*, ristocetin cofactor (von Willebrand factor) activity was not different from a placebo-treated group *(purple bars)*. However, in each group, ristocetin cofactor activity increased *(asterisks)* from baseline values, possibly from surgical stress. Blood loss did not differ in the two groups. Error bars denote standard error of the mean. *(Modified from Hackmann T, Gascoyne RD, Naiman SC, et al: A trial of desmopressin [1-desamino, 8-D-arginine vasopressin] to reduce blood loss in uncomplicated cardiac surgery.* N Engl J Med. *1989;321:1437.)*

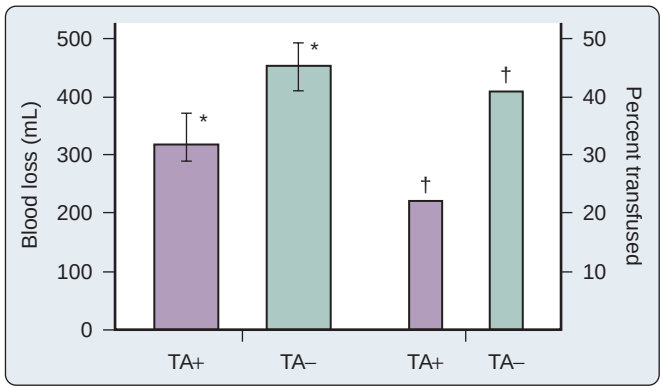


Fig. 35.29 Effect of prophylactic tranexamic acid on blood loss (left vertical axis) and on the percentage of patients receiving homologous red blood cell transfusion within 5 days of surgery (right vertical axis). Purple bars denote patients who received tranexamic acid; green bars denote those not receiving tranexamic acid. $*P < .0001$; $^{\dagger}P = .011$. *(From Horrow JC, Van Riper DF, Strong MD, et al: The hemostatic effects of tranexamic acid and desmopressin during cardiac surgery.* Circulation. *1991;84:2063.)*

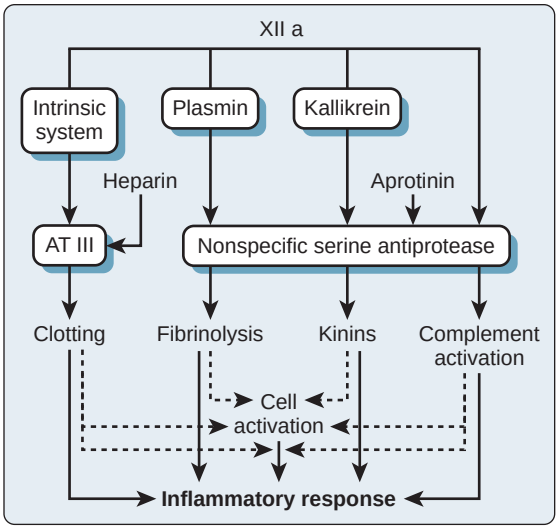


Fig. 35.30 Actions of aprotinin on the contact coagulation system, fibrinolytic pathway, and complement activation. *ATIII,* Antithrombin III. *(From Kassell B, Laskowski M Sr. The basic trypsin inhibitor of bovine pancreas. V. The disulfide linkages.* Biochem Biophys Res Commun. *1965;20(4):463–468; Anderer FA, Hörnle S. The disulfide linkages in kallikrein inactivator of bovine lung.* J Biol Chem. *1966;241(7):1568–1572.)*

TA,[496] perhaps because of a larger volume of distribution of this drug, although definitive data are still lacking.

Antifibrinolytics aid clotting in patients with hemophilia and patients with vWD by blocking lysis of whatever clot can form.[497,498] Spontaneous bleeding after chemotherapy is decreased with oral TA.[499] Prostate surgery, well known for excessive bleeding from release of t-PA, responds beneficially to antifibrinolytic therapy.[500] Fibrinolysis contributes to bleeding during the anhepatic phase of liver transplantation; antifibrinolytic therapy proves useful in this setting.

Ongoing thrombin activity with varied activation of fibrinolysis plagues cardiac surgery. Fig. 35.11 demonstrates thrombin activity as reflected in continuing formation of fibrinopeptides despite adequate heparin anticoagulation. For decades, antifibrinolytics have been proposed as potential hemostatic agents during cardiac surgery. Initial investigations of the efficacy of synthetic antifibrinolytics as hemostatic agents during or after cardiac surgery lacked blinding, randomization, and control groups.[501–509] Most subsequent studies administered EACA after CPB. One study demonstrated a salutary effect in cyanotic children, but not in acyanotic children.[504]

Several investigations, using prophylactic antifibrinolytics, documented savings in blood loss, as well as in blood transfused in a general population of cardiac surgery patients[489,507–509] (Fig. 35.29). By commencing administration of TA before CPB, chest tube drainage in the first 12 hours after surgery decreased by 30%, and the likelihood of receiving banked blood within 5 days of operation decreased from 41% to 22%.[489] Prophylactic antifibrinolytics may spare platelet function by inhibiting the deleterious effects of plasmin,[510] but administration of very large doses of antifibrinolytics appears to offer no greater savings.[511] Cardiac surgery patients undergoing repeat operation may benefit particularly from prophylactic antifibrinolytic administration.[512,513]

Some recent reports noted that TA is associated with increased risks for seizure. This has been known for some time in the neurosurgical literature; it is considered unwise to place TA directly on the surface of the brain. The mechanism for this potential neurologic toxicity is unknown.[514–517]

Aprotinin

Bovine lung provides the source of the 58-residue polypeptide serine protease inhibitor aprotinin.[518,519] Aprotinin inhibits a host of proteases, including trypsin, plasmin, kallikrein, and factor XIIa activation of complement[519] (Fig. 35.30). The adult intravenous dose for surgical hemostasis is 2 million kallikrein inhibitor units (KIU) for both patient and CPB circuit, followed by 600,000 KIU/hr.[520,521] The elimination half-life of aprotinin, 7 hours, is considerably longer than that of the synthetic antifibrinolytics; after 6 days, aprotinin continues to be excreted in the urine. Volume-loaded rats respond to aprotinin with decreases in glomerular filtration rate, renal plasma flow, and sodium and potassium excretion.

After the serendipitous discovery of unusually dry surgical fields while investigating high-dose aprotinin for respiratory distress syndrome, Royston and colleagues[522] documented more than a fourfold reduction in blood loss during repeat cardiac surgery. Subsequent studies using high-dose aprotinin confirmed conservation of blood products and a reduction in bleeding, ranging from 29% to 50%.[523–525]

Although studies clearly demonstrated decreased fibrinolysis in aprotinin-treated patient groups, preservation of platelet GPIb or blockade of a plasmin-mediated platelet defect may better explain the hemostatic mechanism of aprotinin.

High-dose aprotinin alone prolonged the celite ACT, leading some investigators to limit use of heparin during CPB.[525] Reports of clot formation during CPB, however, mandated continued use of heparin despite administration of aprotinin. Most investigators simply avoided the celite ACT and used kaolin ACT. The kaolin ACT adsorbs about 98% of aprotinin and any intrinsic AT effect that aprotinin had was mitigated. It was recommended to use the kaolin ACT and keep the length of ACT time the same as if aprotinin was not being used.[526–530] An animal protein, aprotinin caused anaphylaxis, although uncommon (<1 in 1000)[531] Aprotinin cost significantly more than equivalent doses of synthetic antifibrinolytic drugs.[532] The group at Duke University analyzed overall cost-effectiveness of aprotinin therapy and found it highly cost-effective.[533,534] Aprotinin was voluntarily withdrawn from the market in 2008 after two reviews of adverse outcomes by the FDA. Published reports of an association between high-dose aprotinin utilization and renal dysfunction/failure occurred in 2005 and 2006. These publications arose from the Multicentered Study of Perioperative Ischemia EPI-II database.[535] The study was complex, involving more than 4300 cases, and used sophisticated statistical analysis. Unfortunately, the patients who received aprotinin had been selected to get that drug, as opposed to two other antifibrinolytics, by physician choice. This channeling of therapy meant that those patients who were more ill would get aprotinin. To separate out cause and effect from such data becomes impossible; yet, with elegant propensity analysis methods, weighting of certain covariates can be accounted for. The study, although landmark, was widely criticized for all the potential covariates not examined, such as sites (European countries had different practice patterns) and the use of FFP and platelet transfusions. At the same time, a separate report from the University of Toronto examined cases within their own institution.[536] Their study used aprotinin in only the sickest patients. From their large series, they carefully propensity-matched more than 400 patients to ones of similar age and risk in the overall group of 10,000. There was a propensity for those patients to have more renal dysfunction once the statistics controlled for the other confounders. A third study performed using the Medicare billing database also found that patients who received aprotinin had worse overall outcomes.[537] The use of billing databases has always been fraught with problems in that they are incomplete. Billing data are only summary information and give little of the medical history necessary when trying to balance risk in terms of covariates. Finally, Fergusson and colleague's[538] study in Canada (BART study) confirmed a greater 30-day mortality rate with use of aprotinin compared with either EACA or TA and led to the immediate withdrawal of the drug by the manufacturer.[539] Many questions remain about aprotinin and whether it should be available for high-risk cardiac surgical patients. Some clinicians believe that its withdrawal has led to more bleeding and use of blood products and drugs to improve coagulation, all of which have their own complications.

The aprotinin story continues as the BART trial was reanalyzed when it became apparent that 137 patients were excluded from the original analysis.[540] Health Canada reanalyzed the data with all of these patients included, and the signal for early mortality related to aprotinin disappeared. In some high-risk groups aprotinin seemed to confer an advantage. The European Commission reviewed the data again and lifted its ban on aprotinin noting that the analysis may well have been flawed.[541]

The revised STS/SCA guidelines do not reflect the changing nature of the controversy; rather they present BART as a final conclusive study before the reanalysis by Health Canada.[542] Others continue to question the data analysis in the BART study. At present, aprotinin has been allowed back on the market in Europe and Canada, but it is not marketed in the United States. Work is underway to find other kallikrein-inhibiting agents, but at the time this chapter went to publication, there were no studies in late stages of development.

Management of the Bleeding Patient

The initial approach to perioperative bleeding violates the medical paradigm of treatment based on diagnosis. The clinician must simultaneously initiate diagnostic tests, begin treating a presumed cause, and replace lost hemostatic resources (see Chapter 34). The all-encompassing ("shotgun") approach to bleeding after operation should be shunned. Avoiding it will simplify patient management and yield superior results.

Risks of Coagulation Products

The standard blood bank products available to the cardiovascular team include FFP, cryoprecipitate, and platelet concentrates (either pooled or apheresis single-donor platelets). It should be stated emphatically that there are no data to support the "clinical impression" of use of these agents as a prophylactic method to reduce bleeding.[542] For example, if a patient is known to be using a P_2Y_{12} inhibitor, the use of prophylactic platelet transfusions will not decrease the bleeding. These products should be used only if coagulation data from a laboratory point towards appropriate use or if a patient is bleeding severely enough that the team feels it necessary to attempt empiric therapy.

Platelet transfusions and FFP carry a higher risk of TRALI than do RBCs from the blood bank.[543–551] It is known that the causes of TRALI are manyfold and not limited to recipients receiving HLA antibodies towards their pulmonary endothelium. Indeed, it has been shown that cytokines, red cell microparticles, and CD-40L (a platelet proinflammatory protein) all contribute to leaking pulmonary capillaries.[543] In studies from the Mayo Clinic, platelet concentrates were the most highly associated with TRALI followed by FFP.[549] Recent work in cardiac surgery has demonstrated that the overall risk of TRALI is soberingly high.[544,550] In 688 patients prospectively studied with rigorous predefinition of TRALI, 16 definite cases were discovered (2.4% incidence).[551] Others have reported that between 1% and 8% of all patients for cardiac surgery get TRALI from transfusion. Those with TRALI have a 13- to 15.5-fold increase in major organ morbidity and mortality; mortality has been 20% to 55%.[544,546,550] FFP contains most of the serine proteases found in plasma. There is a small diminution of some of the labile factors, and if the units given have had cryoprecipitate withdrawn from them, they are known as fibrinogen poor plasma. The literature on FFP shows that it does little to reduce bleeding.[552,553] Even in known liver failure, when used prophylactically, FFP cannot be shown to reduce the risk of bleeding. It is only after 10 to 15 mL/kg of FFP that changes in clotting factors will be seen; for most patients, 4 to 6 units of FFP are required before serine protease levels rise. However, by giving this much FFP, RBC and platelets are diluted. The use of 2 units of FFP in a bleeding patient after CPB does nothing other than increase the risk of lung dysfunction. Yet in cardiac surgery, approximately 25% to 50% of patients receive FFP with the idea that it does "something," which is completely unsupported by evidence-based research.

Today, the use of 4-component PCC is the recommended therapeutic intervention to reverse the effects of warfarin or low clotting factor levels. The use of platelet concentrates makes a great deal of sense when a patient is bleeding and there is a proven or suspected platelet function or number deficit.[542] Prophylactic platelet transfusions have never been shown to be of utility. Platelets are harvested by ultra-centrifugation and stored in the blood bank at room temperature on a rocker that keeps them from aggregating. Platelet concentrates can be kept for only 5 days; therefore they are the blood product in shortest supply. Because they are kept at room temperature, they have the potential for growth of bacterial contamination. The risk of bacterial contamination is somewhere between 1/5000–20,000 units. The most common bacteria isolated from platelet bags are *Yersinia* and *Staphylococcus* strains. Today, the blood bank uses surrogate testing (pH) to improve the chances of detecting a septic unit before dispensing it clinically.

Platelet concentrates are most often white cell depleted. The lack of white cells is both good and bad. The bad aspect is that reduction of white cells may well increase the risk of bacterial growth. If white

cells are present in the platelet bags, the concentration of inflammatory cytokines can be 1000 times normal. High levels of cytokines have been implicated as one of the potential precursors of the "two hit" model for TRALI. Even with white cell reduction, the platelet concentrates are profoundly proinflammatory. The levels of CD-40L are very high and rise every day the platelets are kept in the blood bank. CD-40L is a proinflammatory cellular messenger protein that platelets release upon being stressed, and CD-40L has been implicated in causing TRALI.[543,554–556]

Live circulating normal platelets move through the blood stream in a quiescent resting state. They have multiple different transmembrane proteins that signal the surrounding cellular milieu. Bank platelets rapidly become partially or totally activated and release their alpha and dense granules, further activating other platelets. The contents of the granules have a number of highly vasoactive compounds within them, including serotonin, epinephrine, and adenosine. Depending on the age of the unit to be infused, 20% to 60% of the platelets are dysfunctional or undergoing apoptosis; once infused, they circulate for a rather short time. The result of this partial/total activation is that infusions of platelet concentrates, when they are not required, are very prothrombotic. Therefore if a patient is not bleeding and platelets are given, they increase the risk of myocardial infarction, strokes, and other thrombotic events.

A number of investigations have led to controversy about the use of platelet transfusions in cardiac surgery. In a study of approximately 1800 patients undergoing CABG surgery and participating in an early trial of aprotinin, the question of platelet transfusions was investigated.[557] This pharmaceutical phase III study was chosen because it had defined criteria for transfusion of blood products and very careful monitoring/follow-up on predefined complications. With multivariate analysis (accounting for more than 100 potential confounders), use of platelet transfusions had significant relationships to perioperative infections, pneumonia/respiratory failure/TRALI, use of vasopressors (more vasoplegia), stroke, and death. The odds ratios for stroke and death were between 2.5- and 3-fold higher than patients not receiving platelet transfusions. This paper led others to examine additional databases to answer the same question regarding platelet transfusions. Karkouti and colleagues found univariate relationships between platelet transfusions and many of the same adverse outcomes.[558] However, when RBC use was added into this multivariate model, platelet transfusion no longer stood out as a predictor of bad outcome. The Cleveland Clinic team examined their database in two separate papers.[559,560] In one, they examined the effects of transfusion on the risk of development of vasoplegia[560]; in the other, they examined morbidity and mortality as directly related to platelet transfusions.[559] Their findings were that RBCs, FFP, and platelet transfusions all correlated with the development of vasoplegia. However, when they looked at the same data using propensity matching techniques and tried to answer the platelet transfusion question alone, they found that platelet transfusions by themselves did not increase morbidity or mortality.

The biology of platelet concentrates suggest they are highly inflammatory, and their use should thus be reserved for patients who are bleeding and have a demonstrable platelet defect (number or function). No pharmaceutical or manmade product is available for use now or in the near future to replace a platelet transfusion.

Cryoprecipitate is a product that contains a very high concentration of fibrinogen and factor VIII. The product is manufactured from harvested plasma and represents the total available soluble fibrinogen in 1 unit of banked blood/plasma. That precipitate is packaged in approximately 15 mL of plasma. Unlike FFP, cryoprecipitate has a very low volume for the concentration of protein it delivers. Most often when used in cardiac surgery, a dose of cryo is from 10 donors representing the fibrinogen of 10 units of whole blood (roughly one circulating volume). Therefore if a patient is bleeding because of a low fibrinogen concentration or a dysfibrinogenemia, a single infusion of 10 units of cryo should restore the levels above 200 mg/dL. Cryo represents the exposure of 10 donors and still may carry viruses not tested for such as Epstein Barr virus and TTV virus, both of which can cause hepatic failure in immunocompromised hosts. The risk of TRALI from cryo may be lower than that from FFP, because it carries a lower volume of fluid and should have a lower HLA antibody load.

New work from Europe supports the concept of maintaining fibrinogen levels near normal by using a lyophilized human fibrinogen concentrate.[561–563] The fibrinogen concentrate is supplied as a powder, can be mixed with sterile water and injected with very small fluid volumes (900–1300 mg/50 mL). Many US centers have not been concerned about bleeding and fibrinogen being causative until the levels fell below 100mg/dL. However, patients with the fibrinogen maintained at 200 mg/dL or above have demonstrated better TEGs (MA) and RoTEM (MCF) tracings with decreased bleeding.[561] It was thought that low preoperative fibrinogen could be a marker for bleeding after cardiac surgery, but that has not been borne out. Furthermore, trials of giving fibrinogen concentrate pre-bypass have not been shown to be as effective as testing post-bypass with maintenance of fibrinogen concentrations at 200 to 250 mg/dL. The natural course postsurgery is that fibrinogen rises dramatically by day 3 to 5 as an acute phase reactant. If a patient exhibits microvascular bleeding and the fibrinogen is below 200 mg/dL, it makes sense to administer fibrinogen.

Determine the Cause

Anatomic sources of bleeding frequently present once systemic blood pressure achieves sufficient magnitude. Some clinicians prefer to identify these sources before chest closure with a provocative test, that is, allowing brief periods of hypertension. Generous chest tube drainage early after surgery suggests an anatomic source. Retained mediastinal clot may engender a consumptive coagulopathy. A widened mediastinum on chest radiograph suggests the need for surgical drainage.

Nonsurgical causes of bleeding (platelets, coagulation factors, and fibrinolysis) usually manifest as a generalized ooze. Inspection of vascular access puncture sites aids in this diagnosis. Bleeding from other areas not manipulated during surgery (stomach, bladder) also may occur.

Coagulation tests aid diagnosis. Because the PT and aPTT usually are prolonged by several seconds after CPB, only values more than 1.5 times control suggest factor deficiency. Increase of the ACT should first suggest unneutralized heparin, then factor deficiency. The PT is often obtained, and after cardiac surgery it is out of normal range 85% of the time.[564] It has been thought that the protamine-heparin complex binds to the lipid cofactors in the PT test and artificially prolongs PT.

A decreased platelet count, usually denoting hemodilution or consumption, requires correction with exogenous platelets in any bleeding patient. However, bleeding patients with insufficient functional platelets may demonstrate normal platelet counts early after operation. For this reason, clinicians have sought rapid diagnostic tests of platelet function and attempted correlation with bleeding after CPB (see Chapter 19).

Low plasma fibrinogen occurs from excessive hemodilution or factor consumption and is usually corrected with cryoprecipitate or FFP. The thrombin time is useful here; clinical laboratories can perform this test with rapid turnaround. A prolonged thrombin time denotes unneutralized heparin, insufficient fibrinogen, or high concentrations of fibrin degradation products. Finally, direct measurement of fibrin degradation products denotes fibrinolytic activity. In the absence of a cause for a consumptive coagulopathy, antifibrinolytic therapy may be useful.

Table 35.10 lists a treatment plan for excessive bleeding after cardiac surgery. Interventions appear not in order of likelihood, but rather by priority of consideration. Thus, surgical causes should be ruled out before seizing on the diagnosis of a consumptive coagulopathy. The priority will also vary among institutions, depending on the availability and cost of resources.[565] This table provides a simple algorithm for treating postoperative bleeding. More complete schemes present a daunting level of complexity that deters implementation (Fig. 35.31).

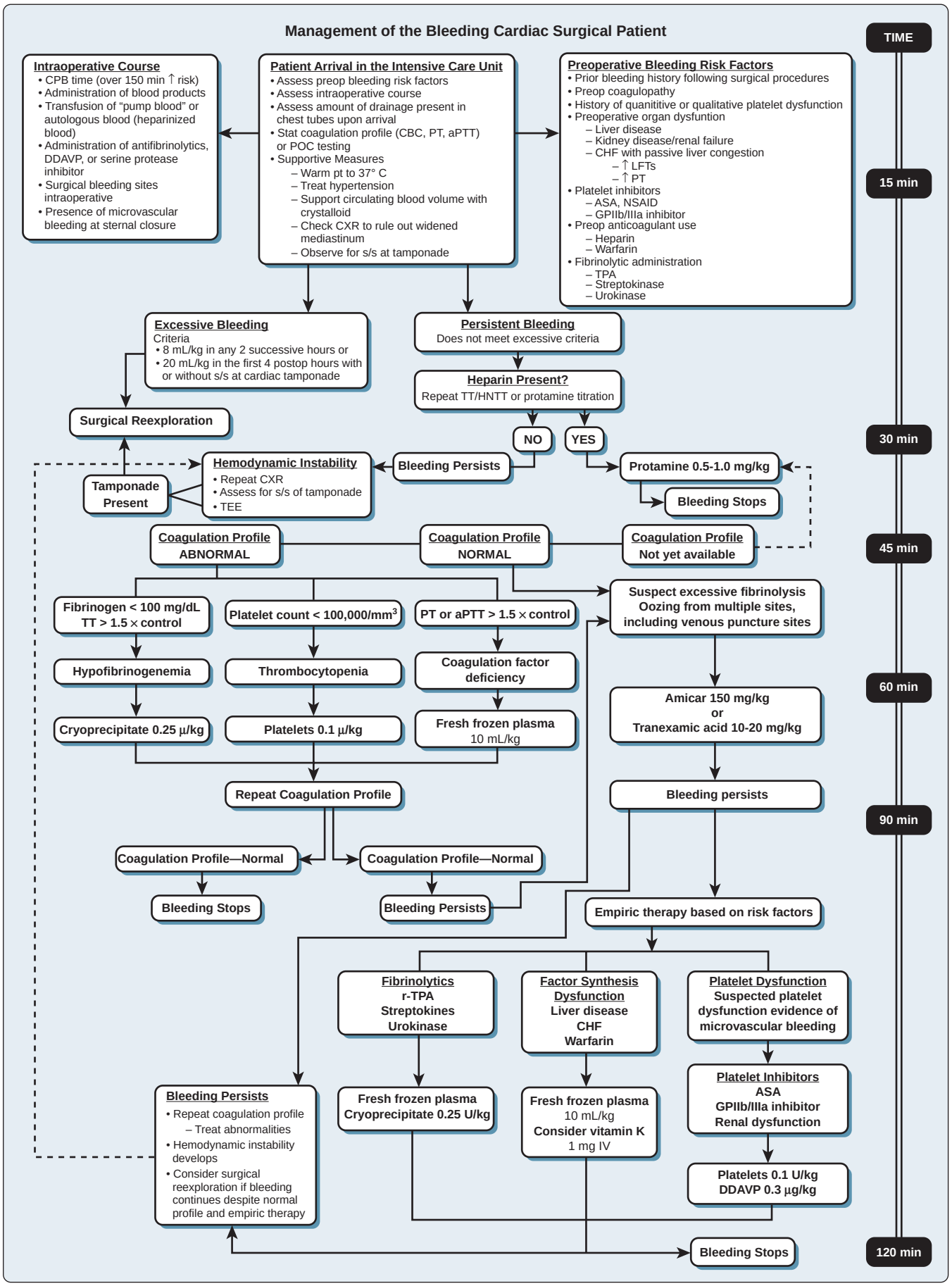


Fig. 35.31 Example of a scheme for treating excessive bleeding. *aPTT*, Activated partial thromboplastin time; *ASA*, acetylsalicylic acid; *CBC*, complete blood cell count; *CHF*, congestive heart failure; *CPB*, cardiopulmonary bypass; *CXR*, chest radiograph; *GP*, glycoprotein; *NSAID*, nonsteroidal antiinflammatory drug; *POC*, point of care; *PT*, prothrombin time; *r-TPA*, recombinant tissue plasminogen activator; *TEE*, transesophageal echocardiography; *t-PA*, tissue plasminogen activator. *(From Milas B, Johes D, Gorman R. Management of bleeding and coagulopathy after heart surgery.* Semin Thorac Cardiovasc Surg. *2000;12:326.)*

TABLE 35.10 Treatment Plan for Excessive Bleeding After Cardiac Surgery

Action	*Amount*	*Indication*
Rule out surgical cause	—	No oozing at puncture sites; chest radiograph
More protamine	0.5–1 mg/kg	ACT > 150 seconds or aPTT > 1.5 times control
Warm the patient	—	"Core" temperature < 35° C
Apply PEEP[a]	5–10 cm H_2O	—
Desmopressin	0.3 µg/kg IV	Prolonged bleeding time
Aminocaproic acid	50 mg/kg, then 25 mg/kg/hr	Increased D-dimer or teardrop-shaped TEG tracing
Tranexamic acid	10 mg/kg, then 1 mg/kg/hr	Increased D-dimer or teardrop-shaped TEG tracing
Platelet transfusion	1 U/10 kg	Platelet count < 100,000/mm^3
Fresh frozen plasma	15 mL/kg	PT or aPTT > 1.5 times control
Cryoprecipitate	1 U/4 kg	Fibrinogen < 1 g/L or 100 mg/dL
Fibrinogen	2 g	Fibrinogen < 100 mg/dL

ACT, Activated coagulation time; *aPTT*, activated partial thromboplastin time; *TEG*, thromboelastograph.
[a]Positive end-expiratory pressure (PEEP) is contraindicated in hypovolemia.

Adjunctive Therapy

Warming

Bleeding patients with core or intermediate zone temperatures less than 35°C will benefit from warming efforts, both passive (warm ambient temperature, adequate body coverings, low-ventilator fresh gas flows, airway heat and humidity exchangers) and active (heated humidifiers, warmed intravenous fluids, forced-air convective warming blankets). All too often, in the effort to maintain intravascular volume, ICU personnel administer liters of room-temperature (≤20°C) or refrigerated (0°C–4°C) fluids, which render patients hypothermic.

Positive End-Expiratory Pressure

One popular method to limit bleeding after cardiac surgery is application of positive end-expiratory pressure (5 to 10 cm H_2O).[566] A tamponade effect in the mediastinum may explain this salutary effect. Unfortunately, controlled studies have not confirmed this benefit.[567,568] In addition, excessive pressure impedes venous return, worsening hemodynamics in the patient with hypovolemia.

Blood Pressure

Maintenance of systemic blood pressure in the low-normal range promotes tissue perfusion while limiting leakage around suture lines. Adequate depth of anesthesia during surgery and sufficient postoperative analgesia and sedation should be verified before initiating vasodilator therapy (see Chapter 38).

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36 Discontinuing Cardiopulmonary Bypass

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KEY POINTS

1. The key to successful weaning from cardiopulmonary bypass (CPB) is proper preparation.
2. After rewarming the patient, correcting any abnormal blood gases, and inflating the lungs, make sure to turn on the ventilator.
3. To prepare the heart for discontinuing CPB, optimize the cardiac rate, rhythm, preload, myocardial contractility, and afterload.
4. The worse the heart's condition, the more gradually CPB should be weaned. If hemodynamic values are not adequate, immediately return to CPB. Assess the problem, and choose an appropriate pharmacologic, surgical, or mechanical intervention before trying to terminate CPB again.
5. Perioperative ventricular dysfunction usually is caused by myocardial stunning and is a temporary state of contractile dysfunction that should respond to positive inotropic drugs.
6. In addition to left ventricular dysfunction, right ventricular failure is a possible source of morbidity and mortality after cardiac surgical procedures.
7. The presence of diastolic dysfunction during the postbypass period may contribute to impaired chamber relaxation and poor compliance, resulting in reduced ventricular filling during separation.
8. Epinephrine is frequently chosen as an inotropic drug when terminating CPB because of its mixed α- and β-adrenergic stimulation.
9. Milrinone is an excellent inodilator drug that can be used alone or combined with other drugs such as epinephrine for discontinuing CPB in patients with poor ventricular function and diastolic dysfunction.
10. In patients with high preload and/or elevated systemic vascular resistance, vasodilators such as nitroglycerin, nicardipine, clevidipine, or nitroprusside may improve ventricular function.
11. Variable gene expression and genetic polymorphism in patients presenting for cardiac surgical procedures may provide the foundation for individualized tailoring of pharmacology based on molecular genotyping in the future.
12. Intraaortic balloon pump counterpulsation increases coronary blood flow during diastole and unloads the left ventricle during systole. These effects can help in weaning patients with poor left ventricular function and severe myocardial ischemia.

Cardiopulmonary bypass (CPB) has been used since the 1950s to facilitate surgical procedures of the heart and great vessels, and is a critical part of most cardiac operations. Managing patients undergoing CPB remains one of the defining characteristics of cardiac surgery and cardiac anesthesiology (see Chapters 31–35). Discontinuing CPB is a necessary part of every operation involving extracorporeal circulation. Through this process, the support of the circulation by the bypass pump and oxygenator is transferred back to the patient's heart and lungs. This chapter reviews important considerations for discontinuing CPB and presents an approach to managing this critical component of a cardiac operation, which may be routine and easy or extremely complex and difficult. The key to success in discontinuing CPB is proper preparation. The period during and immediately after weaning from CPB usually is busy for the anesthesiologist, and having to do tasks that could have been accomplished earlier in the operation is not helpful. The preparations for removing a patient from CPB may be organized into several parts: general preparations, preparing the lungs, preparing the heart, and final preparations.

General Preparations

Temperature

Because at least moderate hypothermia is used during CPB in most cardiac surgical cases, it is important that the patient is sufficiently rewarmed before attempts are made to wean the patient from CPB (Table 36.1).[1–3] Initiation of rewarming is a good time to consider whether additional drugs must be given to keep the patient anesthetized and to prevent shivering. Monitoring the temperature of a highly perfused tissue such as the nasopharynx is useful to help prevent overheating of the brain during rewarming. Cerebral hyperthermia may lead to neurologic injury and postoperative cognitive dysfunction. The central nervous system receives a greater proportion of warm blood, thus resulting in a more rapid increase in temperature compared with other sites such as the bladder, rectum, or axilla. This situation may lead to inadequate rewarming and temperature dropoff after CPB as the heat continues to distribute throughout the body.[4]

TABLE 36.1 General Preparations for Discontinuing Cardiopulmonary Bypass

Temperature	*Laboratory Results*
Adequately rewarm before weaning from CPB	Correct metabolic acidosis
Avoid overheating the brain	Optimize hematocrit
Start measures to keep patient warm after CPB	Normalize potassium
Use fluid warmer, forced air warmer	Consider giving magnesium or checking magnesium level
Warm operating room	Check calcium level and correct deficiencies

CPB, Cardiopulmonary bypass.

BOX 36.1 PREPARING THE LUNGS FOR DISCONTINUING CARDIOPULMONARY BYPASS

- Suction trachea and endotracheal tube.
- Inflate lungs gently by hand.
- Ventilate with 100% oxygen.
- Treat bronchospasm with bronchodilators.
- Check for pneumothorax and pleural fluid.
- Consider the need for positive end-expiratory pressure, intensive care unit ventilator, and nitric oxide.

Different institutions have various protocols for rewarming, but the important point is to warm gradually, avoiding hyperthermia of the central nervous system while providing enough heat to the patient to prevent significant dropoff after CPB (see Chapters 31 and 32). After CPB, the tendency is for the patient to lose heat, and measures to keep the patient warm (eg, fluid warmers, a circuit heater-humidifier, and forced-air warmers) should be set up and turned on before weaning from CPB is begun. The temperature of the operating room may need to be increased as well; this is probably an effective measure to keep a patient warm after CPB, but it may make the scrubbed and gowned personnel uncomfortable.

Laboratory Results

Arterial blood gases should be measured before the patient is weaned from CPB, and any abnormalities should be corrected. Severe metabolic acidosis depresses the myocardium and necessitates correction before separation from bypass.[5] The optimal hematocrit for weaning from CPB is controversial and probably varies from patient to patient.[6,7] It makes sense that sicker patients with lower cardiovascular reserve may benefit from a higher hematocrit (optimal is considered to be 30%), but the risks and adverse consequences of transfusion must be considered as well. The hematocrit should be measured and optimized before the patient is weaned from CPB (see Chapters 34 and 35). The serum potassium (K^+) level should be measured before weaning from CPB and may be high because of cardioplegia or low, especially in patients receiving loop diuretics. Hyperkalemia may make establishing an effective cardiac rhythm difficult and can be treated with sodium bicarbonate, ($NaHCO_3$), calcium chloride ($CaCl_2$), or insulin, but the levels usually decrease quickly after cardioplegia has been stopped. Low serum K^+ levels should be corrected before CPB is discontinued, especially if arrhythmias are present. Administration of magnesium (Mg^{2+}) to patients on CPB decreases postoperative arrhythmias and may improve cardiac function, and many centers routinely give all CPB-treated patients magnesium sulfate.[8,9] Theoretic disadvantages include aggravation of vasodilation and inhibition of platelet function.[10] If Mg^{2+} is not given routinely, the level should be checked before weaning from CPB, and deficiencies should be corrected. The ionized Ca (Ca^{2+}) level should be measured, and significant deficiencies should be corrected before discontinuing CPB. Many centers give all patients a bolus of $CaCl_2$ just before coming off CPB because it transiently increases contractility and systemic vascular resistance (SVR).[11] However, investigators have argued that this practice is to be avoided because Ca^{2+} may interfere with catecholamine action and aggravate reperfusion injury.[12]

Preparing the Lungs

As the patient is weaned from CPB and the heart starts to support the circulation, the lungs again become the site of gas exchange, by delivering oxygen and eliminating carbon dioxide. Before weaning from CPB, the patient's lung function must be restored (Box 36.1). The trachea should be suctioned and, if necessary, lavaged with saline solution to clear secretions. If the abdomen appears to be distended, the stomach should be suctioned so that gastric distention does not impair ventilation after CPB. The lungs are reinflated by hand gently and gradually, with sighs using up to 30 cm H_2O pressure, and then mechanically ventilated with 100% oxygen. Care should be taken not to allow the lungs to injure an in situ internal mammary artery graft as they are reinflated. The compliance of the lungs can be judged by their feel with hand ventilation; stiff lungs suggest more difficulty with oxygenation or ventilation after CPB. If visible, both lungs should be inspected for residual atelectasis, and they should be rising and falling with each breath. Ventilation alarms and monitors should be activated. If prolonged expiration or wheezing is detected, bronchodilators should be given. The surgeon should inspect both pleural spaces for pneumothorax, which should be treated by opening the pleural space. Examining the lung fields by transesophageal echocardiography (TEE) may assist in the detection of pleural effusions. This imaging technique is primarily performed by examining the lung fields just to the right and left of the heart in the midesophageal four-chamber view at 0 degrees. Any fluid present in the pleural spaces should be removed before attempting to wean the patient from CPB.

The apneic period during CPB has been suggested to contribute to ventilator-associated pneumonia and postoperative pulmonary dysfunction through a variety of mechanisms.[13,14] Continuing mechanical ventilation during CPB has been proposed as another option to attenuate the post-CPB impairment of lung function.[13,15] Results of several small trials that used continued ventilation during CPB were mixed, with some trials showing benefit and others showing no outcome difference.[1] At present, the evidence for intraoperative lung protection strategies such as continued ventilation is lacking and awaits larger randomized trials. In its most severe form, pulmonary dysfunction after CPB may require positive end-expiratory pressure, an intensive care unit–type ventilator, or nitric oxide (see Chapters 37, 39, and 41). If needed, this equipment should be obtained before attempting to wean the patient from CPB.

Preparing the Heart

Management of Intracardiac Air

During the bypass period, the heart is empty, cooled, and usually electrically silent to minimize consumption of adenosine triphosphate (ATP). Air is often introduced into the heart during the operation and can eventually cause deleterious effects during separation from CPB and in the postoperative period. TEE can be helpful in identifying and locating air in the heart and assisting in de-airing before CPB is discontinued. On TEE, air is often seen as echo-dense or bright foci floating to the highest point within the chamber.[1,16]

The time to begin looking with TEE for intracardiac air on CPB is usually after all the chambers and the aorta are closed and the aortic cross-clamp is removed. It is essential to identify macroscopic accumulations of air within the left side of the heart to minimize systemic emboli. With the patient in the supine position, air often is visualized in the left atrium along the interatrial septum, left atrial (LA) appendage, and near the entry points of the pulmonary veins. In the left ventricle and aortic root, air often accumulates along the apical portion

of the interventricular septum and right coronary sinus of Valsalva.[1] To scan for intracardiac air systematically, it may be useful to start in the midesophageal four-chamber view at 0 degrees and fully examine all aspects of the left atrium and ventricle, with special attention to the interatrial and interventricular septum. From this image plane, it may be useful to change the multiplane angle to approximately 120 to 145 degrees, to provide an additional image sector to examine the apical septum for air-fluid levels. As the heart ejects, close inspection of the left ventricular (LV) outflow tract (LVOT) and aortic root at this image plane may facilitate visualization of air emboli, mandating aggressive aspiration of the aortic root vent.

Although a correlation with the amount of intracardiac air seen with TEE and neurologic outcome has not been shown, one of the major concerns with systemic air emboli after CPB is the potential for cerebral injury (see Chapter 40). It is reasonable to proceed with the assumption that the less air pumped into the systemic circulation during and after CPB, the better. Another adverse consequence is the passage of air into the coronary circulation that leads to myocardial ischemia. In the supine patient, the right coronary artery takes off from the highest point of the aortic root, and intracoronary air is most commonly manifested by dramatic inferior ST-segment elevation and acute right-sided heart dysfunction. Saphenous vein grafts typically are anastomosed to the anterior aspect of the ascending aorta and are susceptible to air emboli as well. If this occurs while the patient is still on CPB or before decannulation, it is a simple matter to go back on CPB and wait a few minutes until the air clears from the coronary circulation, the ST segments normalize, and ventricular function improves before trying to wean the patient from CPB again. If, however, coronary air embolization occurs after decannulation, the hemodynamic status can quickly deteriorate to cardiac arrest. Smaller air emboli can be moved through the coronary vessels by acutely increasing the blood pressure with a vasopressor while dilating the coronary arteries with nitroglycerin (NTG). Perhaps the worst-case scenario is when a macroscopic air bubble in the left side of the heart is shaken loose while moving the patient from the operating table at the end of the case; acute right-sided heart failure (HF) and circulatory collapse may occur either then or while the patient is being transported to the intensive care unit.

Numerous maneuvers may be used to de-air the chambers.[1,17] They may include shaking the vented heart on partial CPB to jar loose any pockets of air, elevating and aspirating LV air directly from the apex, applying positive pressure to the lungs to squeeze air out of the pulmonary veins, and tipping the table from side to side to help the passage of bubbles through the heart to the ascending aorta where they are released through a vent. Additional air may appear in the left side of the heart during weaning from CPB as increasing flow through the pulmonary veins flushes air out from the lungs into the left atrium. Passage of air from the left atrium to the left ventricle may be facilitated with the head and right-side-down position, as well as from the left ventricle to the ascending aorta with the head and right-side up. It may be impossible to evacuate every last trace of air from the left side of the heart before discontinuing CPB, especially tiny bubbles trapped in the trabeculae of the left ventricle; it therefore becomes a matter of judgment and experience to know when enough is enough. The persistence of a macroscopic air-fluid level in the left side of the heart visible with TEE, however, suggests that more de-airing probably is needed before closing the vent in the ascending aorta and weaning from CPB. After adequate de-airing, preparing the heart to resume its function of pumping blood involves optimizing the determinants of cardiac output (CO). The five hemodynamic parameters that can be controlled are rate, rhythm, preload, contractility, and afterload (Table 36.2).

TABLE 36.2 Preparing the Heart for Discontinuing Cardiopulmonary Bypass

Hemodynamic Parameters	*Preparation*
Heart rate	Rate should be between 75 and 95 beats/min in most cases Treat slow rates with electrical pacing Treat underlying causes of fast heart rates Heart rate may decrease as the heart fills Control fast supraventricular rates with drugs, and then pace as needed Always have pacing immediately available during heart operations
Rhythm	Normal sinus rhythm is ideal Defibrillate if necessary when temperature >30°C Consider antiarrhythmic drugs if ventricular fibrillation persists more than a few minutes Try synchronized cardioversion for atrial fibrillation or flutter Look at the heart to diagnose atrial rhythm Try atrial pacing if atrioventricular conduction exists Try atrioventricular pacing for heart block
Preload	End-diastolic volume is the best measure of preload and can be seen with TEE Filling pressures provide a less direct measure of preload Consider baseline filling pressures Assess RV volume with direct inspection Assess LV volume with TEE Cardiac distention may cause MR and TR
Contractility	Carefully examine heart for air and employ de-airing maneuvers Assess and quantify RV function with direct inspection and TEE Assess and quantify LV function with TEE Inspect for new regional wall motion abnormalities Inspect for new or worsening valvular abnormalities Quantify cardiac output by TEE or PAC Assess need for inotropic agent
Afterload	Systemic vascular resistance is a major component of afterload Keep MAP between 60 and 80 mm Hg at full CPB flow Consider a vasoconstrictor if the MAP is low and a vasodilator if the MAP is high

CPB, Cardiopulmonary bypass; *LV,* left ventricular; *MAP,* mean arterial pressure; *MR,* mitral regurgitation; *PAC,* pulmonary artery catheter; *RV,* right ventricular; *TEE,* transesophageal echocardiography; *TR,* tricuspid regurgitation.

Heart Rate

Establishing an effective heart rate (HR) is a critical prerequisite and major determinant of CO. In most situations for adult patients, the HR should be between 75 and 95 beats/minute for weaning from CPB. It may be prudent to establish electrical pacing early in the weaning process to ensure a means to control the HR precisely. Lower rates theoretically may be desirable for hearts with residual ischemia or incomplete revascularization. Higher HRs may be needed for hearts with limited stroke volume (SV) such as after ventricular aneurysmectomy. Slow HRs are best treated with electrical pacing, but β-agonist or vagolytic drugs also may be used to increase the HR. Tachycardia before weaning from CPB is more worrisome and difficult to manage, and treatable causes such as inadequate anesthesia, hypercarbia, and ischemia should be identified and corrected. The HR often decreases as the heart is filled in the weaning process, and electrical pacing always should be immediately available during cardiac operations to treat sudden bradycardias. Supraventricular tachycardias should be electrically cardioverted if possible, but drugs such as β-antagonists or Ca^{2+} channel antagonists may be needed to control the ventricular rate if these arrhythmias persist, most typically in patients with chronic atrial fibrillation. If drug therapy decreases the HR too much, pacing may be used.

Rhythm

The patient must have an organized, effective, and stable cardiac rhythm before attempts are made to wean the patient from CPB. This rhythm can occur spontaneously after removal of the aortic cross-clamp, but the heart may resume electrical activity with ventricular fibrillation. If the blood temperature is greater than 30°C, the heart may be defibrillated with internal paddles applied directly to the heart by using 10 to 20 J. Defibrillation at lower temperatures may be unsuccessful

because extreme hypothermia can cause ventricular fibrillation.[18,19] If ventricular fibrillation persists or recurs repeatedly, antiarrhythmic drugs such as lidocaine, amiodarone, or Mg^{2+} may be administered to help achieve a stable rhythm. It is not unusual for the rhythm to remain unstable for several minutes immediately after cross-clamp removal, but persistent or recurrent ventricular fibrillation should prompt concern about impaired coronary blood flow. Because it provides an atrial contribution to ventricular filling and a normal, synchronized contraction of the ventricles, normal sinus rhythm is the ideal cardiac rhythm for weaning from CPB.[20] Atrial flutter or fibrillation, even if present before CPB, often can be converted to normal sinus rhythm with synchronized cardioversion, especially if antiarrhythmic drugs are administered. It often is helpful to look directly at the heart when any question exists about the cardiac rhythm. Atrial contraction, flutter, and fibrillation are easily seen on CPB when the heart is visible. Ventricular arrhythmias should be treated by correcting underlying causes such as K^+ or Mg^{2+} deficits and, if necessary, by administering antiarrhythmic drugs such as amiodarone.[9] If asystole or complete heart block occurs after cross-clamp removal, electrical pacing with temporary epicardial pacing wires may be needed to achieve an effective rhythm before weaning from CPB. If atrioventricular conduction is present, atrial pacing should be attempted because, as with normal sinus rhythm, it provides atrial augmentation to filling and synchronized ventricular contraction. Atrioventricular sequential pacing is used in patients with heart block, which may be temporarily present for 30 to 60 minutes as the myocardium recovers after cardioplegia and cross-clamp removal. Ventricular pacing remains the only option if no organized atrial rhythm is present, but this sacrifices the atrial "kick" to ventricular filling and the more efficient synchronized ventricular contraction of the normal conduction system[21,22] (see Table 36.2).

Preload

Once control of the rate and rhythm is established, priming the heart with volume or preload is the next step. Preload is the amount of stretch on the myocardial muscle fibers just before contraction. In the intact heart, the best measure of preload is end-diastolic volume. Less direct clinical measures of preload include LA pressure (LAP), pulmonary artery occlusion pressure, and pulmonary artery diastolic pressure, but the relationship between end-diastolic pressure and volume during cardiac surgical procedures may be poor[23,24] (see Chapters 6, 13, and 38). TEE is a useful tool for weaning from CPB because it provides direct visualization of the end-diastolic volume and contractility of the left ventricle[25,26] (see Chapters 14–16). TEE may also provide a means to calculate serial CO measurements during volume loading of the heart. In addition, diastolic filling indices (transmitral and pulmonary venous inflow) may assist in assessing fluid responsiveness and elevations in LA and LV filling pressures.[27,28] The process of weaning a patient from CPB involves increasing the preload (ie, filling the heart from its empty state on CPB) until an appropriate end-diastolic volume is achieved. When preparing to discontinue CPB, some thought should be given to the appropriate range of preload for the individual patient. The filling pressures before CPB may indicate what they need to be after CPB; a heart with high filling pressures before CPB may require high filling pressures after CPB to achieve an adequate preload.

Contractility

The contractile state of both the right and left sides of the heart should be considered individually before attempting to wean from CPB. The decision to institute inotropic support after CPB is complex, and intraoperative use of inotropes may be associated with higher mortality rates.[29] Some of the factors associated with the low CO syndrome (LCOS) or the need for inotropic support after CPB include preexisting right ventricular (RV) or LV dysfunction,[30–36] diastolic dysfunction,[37,38] elevated LV end-diastolic pressure (LVEDP),[30,32] advanced age,[30,32,34] prolonged CPB time,[37] and long aortic cross-clamp time[30,35,37] (Table 36.3). Assessment of the right ventricle may be easily attainable because the right-sided chambers are directly visible to the anesthesiologist. Direct visualization of the left ventricle is difficult, and TEE may be the only modality by which to visualize left-sided heart function directly. Both right-sided and left-sided heart function and the corresponding atrioventricular valves should be systematically examined by TEE. The use of TEE during gradual weaning from the pump may provide essential information on chamber filling and the contractile state.

TABLE 36.3 Summary of Factors Associated With the Use of Inotropic Drug Support or Low Cardiac Output Syndrome

Variable	*Odds Ratio*	*Reference*
Age (>60 y)	4.3	Butterworth et al., 1998[31]
Aortic cross-clamp time >90 min	2.32	Muller et al., 2002[36]
Bypass time (min)	3.40	Bernard et al., 2001[37]
CABG + MVR	3.607	McKinlay et al., 2004[35]
Cardiac index <2.5 L/m^2 per min	3.10	Ahmed et al., 2009[30]
CHF (NYHA class >II)	1.85	Muller et al., 2002[36]
CKD (stage 3–5; GFR <60 mL/1.73 m^2 per min	3.26	Ahmed et al., 2009[30]
COPD	1.85	Muller et al., 2002[36]
Diastolic dysfunction	4.31	Bernard et al., 2001[37]
Ejection fraction (%) <40	2.76	Ahmed et al., 2009[30]
Emergency operation	9.15	Ding et al., 2015[34]
Female sex	2.0	Alganrni et al., 2011[33]
LVEDP >20 mm Hg	3.58	Ahmed et al., 2009[30]
Myocardial infarction	2.01	Muller et al., 2002[36]
Moderate-to-severe mitral regurgitation	2.277	McKinlay et al., 2004[35]
Regional wall motion abnormality	4.21	McKinlay et al., 2004[35]
Repeat operation	2.38	McKinlay et al., 2004[35]

CABG, Coronary artery bypass graft; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *COPD,* chronic obstructive pulmonary disease; *GFR,* glomerular filtration rate; *LVEDF,* left ventricular end-diastolic pressure; *MVR,* mitral valve repair or replacement; *NYHA,* New York Heart Association.

A brief evaluation of cardiac function including both RV and LV contractility is achieved by a series of scan planes at the midesophageal level and advancing the probe into the transgastric position. The goal is to ascertain quickly the suitability of the heart to wean from CPB successfully. This goal may be achieved by scanning for RV and LV wall motion in the midesophageal (four-chamber view at 0 degrees, two-chamber view at 90 degrees, aortic long-axis view at 120 to 150 degrees, RV inflow-outflow at 45 to 60 degrees) and transgastric views (LV and RV short-axis view at 0 degree). If evidence of poor contractility is visualized on TEE, initiation or titration of inotropic agents can begin at this time. As the pump flow is gradually reduced, the ability of the heart to fill and eject is continuously assessed, and drug therapy is titrated as needed. Once the heart has demonstrated the ability to maintain adequate hemodynamic status, separation from CPB is commenced. At this point, serial volume transfusions from the venous reservoir can be carefully titrated as needed, and the heart's response to volume can be monitored by TEE.[25] After each volume bolus, assessments of biventricular function and the end-diastolic and end-systolic areas of the right and ventricles are critical to prevent overdistention and unwanted wall tension. Reinstitution of CPB is warranted if the heart begins to distend or displays inadequate function.

Because the use of intraoperative and postoperative inotropic support may be associated with increased mortality rates, the decision to initiate pharmacologic therapy should be made with caution.[29] A prudent approach, using a slow and gradual weaning process from the pump and assessing cardiac filling and biventricular contractility in a stepwise manner, may help reduce unnecessary use of inotropic agents. As the heart is allowed to fill gradually, if significant chamber distention or depression of contractility is evident on TEE or by direct visual inspection, the safest approach is to prevent cardiac distention by resuming CPB. At this point, the heart may benefit from a resting

period of 10 to 20 minutes on CPB, and then the decision to start inotropes may be warranted before the patient is weaned from CPB.

Extreme depression of contractile function of the myocardium despite adequate pharmacologic therapy may require mechanical support with an intraaortic balloon pump (IABP), ventricular assist device, or extracorporeal membrane oxygenator (see later and Chapters 28, 33, and 38).

Afterload

Afterload is the tension developed within the ventricular muscle during contraction. An important component of afterload in patients is the SVR (see Chapters 6, 13, and 38).[39] During CPB at full flow (usually ≈2.2 L/m^2 per min), mean arterial pressure (MAP) is directly related to SVR and indicates whether the SVR is appropriate, too high, or too low. Low SVR after CPB can cause inadequate systemic arterial perfusion pressure, and high SVR can significantly impair cardiac performance, especially in patients with poor ventricular function. SVR during CPB can be approximated by using the following equation:

$$\text{SVR (dynes} \cdot \text{s} \cdot \text{cm}^{-5}) = \text{MAP} \times 80 / \text{pump flow}$$

If the SVR is less than normal, infusion of a vasopressor may be needed to increase the SVR before attempting to wean the patient from CPB. If the MAP is high during CPB, vasodilator therapy may be needed.

Final Considerations and Preparations

The state of coagulation and the potential requirement for blood transfusion or component therapy must be considered before separation from CPB. Review of data from prebypass studies such as hemoglobin, platelet count, thromboelastography, and coagulation panels may help in recognizing preexisting coagulopathy and predict transfusion requirements in the presence of post-CPB bleeding after protamine administration. Risk factors that may be associated with higher rates of transfusion include emergency or urgent surgical procedures, reoperation, cardiogenic shock, older age, female sex, low body weight, and preoperative anemia.[40] Preoperative use of antiplatelet agents, warfarin, and novel anticoagulants may also portend higher transfusion rates and warrant special attention. Assessing coagulation status and the need for transfusion is an important consideration before attempting to wean a patient from CPB.

The final preparations before discontinuing CPB include leveling the operating table, resetting the pressure transducers to zero, ensuring the proper function and location of all monitoring devices, confirming that the patient is receiving only intended drug infusions, ensuring the immediate availability of resuscitation drugs and appropriate fluid volume, and verifying that the lungs are being ventilated with 100% oxygen (Table 36.4).

The surgeon must confirm that he or she has completed the necessary preparations in the surgical field before CPB is discontinued. Macroscopic collections of air in the heart should be evacuated as described in detail earlier before starting to wean the patient from CPB. This is also an appropriate time to reassess the five major determinants of CO by using all available monitors and TEE. Major sites of bleeding should be controlled, cardiac vent suction should be off, all clamps on the heart and great vessels should be removed, coronary artery bypass grafts (CABGs) should be checked for kinks and bleeding, and tourniquets around the caval cannulas should be loosened or removed before starting to wean a patient from CPB.

TABLE 36.4 Final Preparations for Discontinuing Cardiopulmonary Bypass

Anesthesiologist's Preparations	*Surgeon's Preparations*
Level operating table	Remove macroscopic collections of air from the heart
Reset transducers to zero	Control major sites of bleeding
Activate monitors	Ensure CABG is lying nicely without kinks
Check drug infusions	Turn off or remove cardiac vents
Have resuscitation drugs and fluid volume at hand	Take clamps off the heart and great vessels
Reestablish TEE or PAC monitoring	Loosen tourniquets around caval cannulas

CABG, Coronary artery bypass graft; *PAC,* pulmonary artery catheter; *TEE,* transesophageal echocardiography.

Routine Weaning From Cardiopulmonary Bypass

The perfusionist, the surgeon, and the anesthesiologist should communicate closely and clearly while weaning a patient from CPB, and the surgeon or the anesthesiologist should be in charge of the process. The anesthesiologist should be positioned at the head of the table, able to see the CPB pump and perfusionist, the heart, the surgeon, and the anesthesia monitor display readily. The TEE display also should be easily in view. Weaning a patient from CPB is accomplished by diverting blood back into the patient's heart by occluding the venous drainage to the CPB pump. The arterial pump flow is decreased simultaneously as the pump reservoir volume empties into the patient, and the heart's contribution to systemic flow increases. This can be accomplished most abruptly by simply clamping the venous return cannula and transfusing blood from the pump until the heart fills and the preload appears to be adequate. Some patients tolerate this method of discontinuing CPB, but many do not, and a more gradual transfer from the pump to the heart usually is desirable. The worse the function of the heart is, the slower the transition from full CPB to off CPB needs to be.

Before beginning to wean the patient from CPB, the perfusionist should communicate to the physicians involved the following three important parameters: (1) the current flow rate of the pump, (2) the volume in the pump reservoir, and (3) the oxygen saturation of venous blood returning to the pump from the patient. The flow along with MAP can be used to gauge the SVR of the patient before weaning from CPB. The current flow rate of the pump indicates the stage of weaning as it is decreased. Weaning is just beginning at full flow, is well under way when down to 2 or 3 L/minute in adults, and is almost finished at less than 2 L/minute. The reservoir volume indicates how much blood is available for transfer to the patient to fill the heart and lungs as CPB is discontinued. If the volume is low (<400 to 500 mL in adults), more fluid may need to be added to the reservoir before weaning from CPB. The oxygen saturation of the venous return ($S\bar{v}O_2$) gives an indication of the adequacy of peripheral perfusion during CPB. If the $S\bar{v}O_2$ is greater than 60%, oxygen delivery during CPB is adequate; if it is less than 50%, oxygen delivery is inadequate, and measures to improve delivery (eg, increase pump flow or hematocrit) or decrease consumption (eg, give more anesthetic agents or neuromuscular blocking drugs) must be taken before CPB is discontinued. An $S\bar{v}O_2$ between 50% and 60% is marginal and must be followed closely. As the patient is weaned from CPB, an increasing $S\bar{v}O_2$ suggests that the net flow to the body is increasing and that the heart and lungs will support the circulation; a declining $S\bar{v}O_2$ indicates that tissue perfusion is decreasing and that further intervention to improve cardiac performance will be needed before CPB is discontinued.

The actual process of weaning from CPB begins with partially occluding the venous return cannula with a clamp (Fig. 36.1). This may be done in the field by the surgeon or at the pump by the perfusionist. This maneuver causes blood to flow into the right ventricle. As the right ventricle fills and begins to pump blood through the lungs, the left heart begins to fill. When this occurs, the left ventricle begins to eject, and the arterial waveform becomes pulsatile. Next, the perfusionist gradually decreases the pump flow rate. As more of the venous return goes through the heart and less to the pump reservoir, it becomes necessary to decrease the pump flow gradually to avoid emptying the pump reservoir.

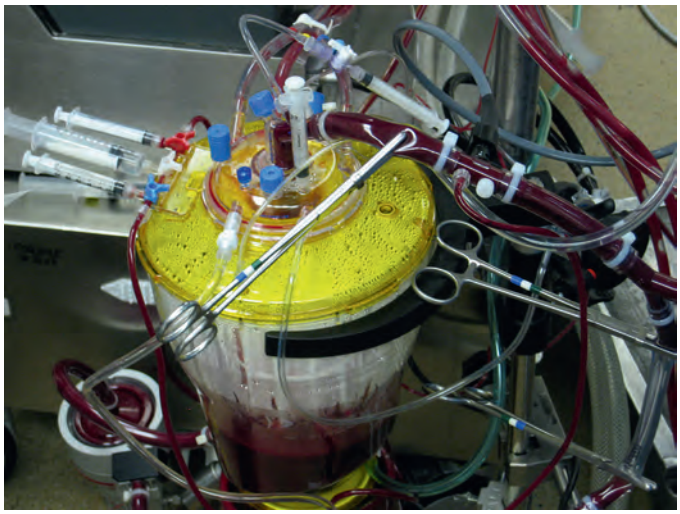


Fig. 36.1 The process of weaning from cardiopulmonary bypass is started by partially occluding the venous return cannula with a clamp.

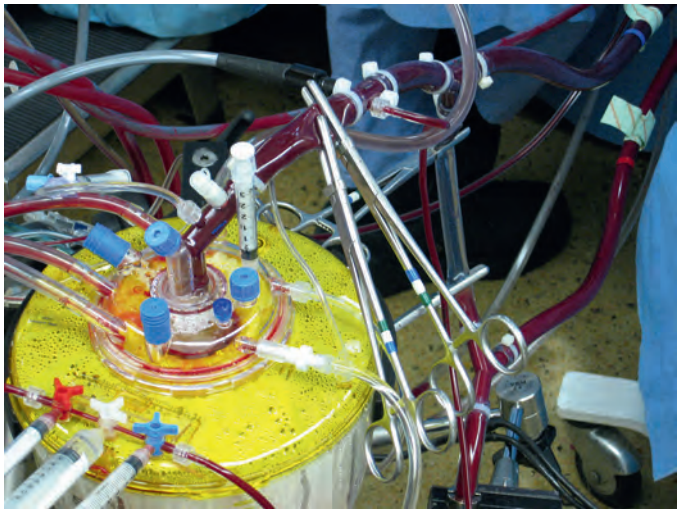


Fig. 36.2 When the venous return cannula is completely clamped, the patient is "off bypass."

One approach to weaning from CPB is to bring the filling pressure being monitored (eg, central venous pressure, pulmonary artery pressure, LAP) to a specific, predetermined level somewhat lower than may be necessary and then assess the hemodynamic status. Volume (preload) of the heart also may be judged by direct observation of its size or with TEE. Further filling is done in small increments (50–100 mL) while closely monitoring the preload until the hemodynamic status appears satisfactory as judged by the arterial pressure, the appearance of the heart, the trend of the $S\bar{v}O_2$, and CO measurements by TEE or pulmonary artery catheter. It typically is easy to see the right-sided heart volume and function directly in the surgical field and the left side of the heart with TEE; combining the two observations is a useful approach for weaning from CPB. Overfilling and distention of the heart should be avoided because they may stretch the myofibrils beyond the most efficient length and dilate the annuli of the mitral and tricuspid valves, thus rendering them incompetent, which can be detected with TEE. If the patient has two venous cannulas, the smaller of the two may be removed when the pump flow is half of the full flow rate to improve movement of blood from the great veins into the right atrium. When the pump flow has been decreased to 1 L/minute or less in an adult and the hemodynamics findings are satisfactory, the venous cannula may be completely clamped and the pump flow turned off. At this point, the patient is "off bypass" (Fig. 36.2).

This is a critical juncture in the operation. The anesthesiologist should pause a moment to make a brief scan of the patient and monitors to confirm that the lungs are being ventilated with oxygen, the hemodynamic status is acceptable and stable, the electrocardiogram shows no new signs of ischemia, the heart does not appear to be distending, and the drug infusions are functioning as desired. Further fine-tuning of the preload is accomplished by transfusing 50- to 100-mL boluses from the pump reservoir through the arterial cannula and observing the effect on hemodynamics. If acute failure of the circulation occurs, as evidenced by an unstable rhythm, falling arterial and rising filling pressures, or visible distention of the heart, the patient is put back on CPB by unclamping the venous return cannula and turning on the arterial pump flow. Once CPB has resumed, an assessment of the cause of failure to wean is made, and appropriate interventions are undertaken before attempting to wean the patient from CPB again. When the hemodynamic status appears to be stable and adequate, the surgeon may remove the venous cannula from the heart.

The next step in discontinuing CPB is to transfuse as much of the blood remaining in the pump reservoir as possible into the patient before removal of the arterial cannula. This technique is usually easier and quicker than transfusing through the intravenous infusions after decannulation. The blood in the venous cannula and tubing (usually ≈500 mL) may be drained into the reservoir for transfusion. The patient's venous capacitance can be increased by raising the head of the bed (ie, reverse Trendelenburg position) and/or giving NTG; more cautions is required with these maneuvers in patients with impaired cardiac function. Filling the vascular space with the patient's head up and while infusing NTG increases the ability to cope with volume loss after decannulation by allowing rapid augmentation of the central vascular volume by leveling the bed and decreasing the NTG infusion rate.

After discontinuing CPB, the anticoagulation by heparin is reversed with protamine. Depending on institutional preference, protamine may be administered before or after removal of the arterial cannula. Giving protamine before removal allows for continued transfusion from the pump and easier return to CPB if the patient has a severe protamine reaction (see Chapter 35). Giving protamine after removal of the arterial cannula may decrease the risk for thrombus formation and systemic embolization. After the infusion of protamine is started, pump suction return to the reservoir should be stopped to keep protamine out of the pump circuit in case subsequent return to CPB becomes necessary. Titrated dosing of protamine may be more effective in reducing postoperative bleeding compared with a standard protamine administration protocol.[41] Titrated dosing involves adjusting the protamine concentration to reflect measured circulating heparin levels. Protamine should be given slowly through a peripheral intravenous catheter over 5 to 15 minutes while the clinician watches for systemic hypotension and pulmonary hypertension, which may indicate that an untoward (allergic) reaction to protamine is occurring.[42–44] Technically flawed CABGs may thrombose after protamine administration, thus causing acute ischemia mimicking a protamine reaction.

When transfusion of the pump reservoir blood is completed, a thorough assessment of the patient's condition should be made before the arterial cannula is removed because after this is done, returning to CPB becomes much more difficult. The cardiac rhythm should be stable. Cardiac function and hemodynamic status, as assessed by arterial and venous filling pressures, CO, and TEE, should be satisfactory and stable. A more detailed and comprehensive TEE examination can be performed as time permits. RV free wall motion to assess RV function qualitatively can be obtained in the midesophageal four-chamber view (0 degrees) and midesophageal RV inflow-outflow view (45–60 degrees). In the midesophageal four-four-chamber view, RV function can also be quantified by measuring tricuspid annular systolic plane excursion (TAPSE) and comparing it with prebypass assessments.

Findings of interatrial septal bowing into the left atrium may indicate volume or pressure overload of the right atrium. Interventricular septal motion after CPB should be interpreted with caution because abnormal septal movement may be caused by several factors including epicardial pacing, stunned myocardium, volume or pressure overload,

and ischemia. The midesophageal four-chamber view at 0 degrees and the RV inflow-outflow view at 45 to 60 degrees may be used to assess for new or worsening tricuspid regurgitation, thereby indicating the possibility of RV dysfunction. Advancing the probe to the transgastric level allows for further evaluation of RV function in the short-axis view. After examining the right-sided chambers, all segments of the left side of the heart should be reviewed. This examination can be performed by using all sector planes in the midesophageal views (four-chamber view at 0 degrees, two-chamber at 90 degrees, and aortic long-axis view at 120–150 degrees) and transgastric views.

Special attention should be given to new regional wall motion abnormalities, systolic thickening, and excursion of all segments of the left ventricle, evidence of LVOT obstruction from systolic anterior motion of the mitral valve, new valvular abnormalities, and overall end-diastolic and systolic chamber dimensions. New regional wall motion abnormalities may signify a technically flawed CABG or intracoronary air. LVOT obstruction from systolic anterior motion may indicate the presence of inadequate chamber filling from hypovolemia and tachycardia or a hyperdynamic state of contractility. New valvular abnormalities may represent iatrogenic damage to the valvular apparatus, myocardial ischemia, volume overload, or ventricular dysfunction. It is also important to scan the aorta to rule out a new aortic dissection after aortic decannulation. As time permits, TEE can also be used to calculate SV and CO by Doppler interrogation of the LVOT and aortic outflow tract. Diastolic filling profiles of the left ventricle and left atrium may be obtained using transmitral and pulmonary venous inflow, respectively. Serial measurements of LA and LV inflow may allow for estimating filling pressures and chamber compliance.

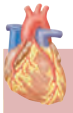
Adequate oxygenation and ventilation should be confirmed by arterial blood gas or pulse oximetry and capnography. Bleeding from the heart should be at a manageable level before removal of the arterial cannula. The perfusionist should not have to transfuse significant amounts of blood through the arterial cannula before removing it because keeping up with the blood loss through intravenous infusions alone may be difficult. Bleeding sites behind the heart may have to be repaired on CPB if the patient cannot tolerate lifting of the heart to expose the problem area. At the time of arterial decannulation, the systolic pressure should be lowered to between 85 and 100 mm Hg to minimize the risk for dissection or tearing of the aorta.[45] The head of the bed may be raised, or small boluses of a short-acting vasodilator may be given to lower the systemic blood pressure as necessary. Tight control of the arterial blood pressure may be needed for a few minutes until the cannulation site is secure. The routine process of discontinuing bypass is completed when removal of all cannulas is successful and full reversal of the anticoagulation is achieved.

Pharmacologic Management of Ventricular Dysfunction

Perioperative ventricular dysfunction usually is a transient state of contractile impairment that may require temporary support with positive inotropic agents. In a subset of patients, contractility may be significantly depressed such that combination therapy with positive inotropes and vasodilator agents is needed to improve CO and tissue perfusion effectively. The use of mechanical assist devices is reserved for conditions of overt or evolving cardiogenic shock.

Severe ventricular dysfunction, specifically the LCOS, occurring after CPB and cardiac operations differs from chronic congestive HF (CHF) (Box 36.2). Patients emerging from CPB have hemodilution, moderate hypocalcemia, hypomagnesemia, and altered K^+ levels. Depending on temperature and depth of anesthesia, these patients may demonstrate low, normal, or high SVR. Increasing age, female sex, decreased LV ejection fraction (LVEF), diastolic dysfunction, prolonged aortic cross-clamp time, and increased duration of CPB are associated with a greater likelihood that inotropic support will be needed after CABG procedures (see Table 36.3).[30,32,37,46]

Contractile dysfunction during or after cardiac operations can result from preexisting impairment in contractility or may be a new-onset condition. Abnormal contraction, especially in the setting of coronary artery disease (CAD), usually is caused by myocardial injury resulting in ischemia or infarction. The magnitude of contractile dysfunction corresponds to the extent and duration of injury. Brief periods of myocardial oxygen deprivation (<10 minutes) produce regional contractile dysfunction, which can be rapidly reversed by reperfusion. Extension of the ischemia to 15 to 20 minutes also is associated with restoration of cardiac function with reperfusion; however, this process is very slow and can take hours to days. This condition of postischemic reversible myocardial dysfunction in the presence of normal flow is referred to as *myocardial stunning*.[47–50] Irreversible cell injury occurs with longer periods of ischemia and produces myocardial infarction characterized by release of intracellular enzymes, disruption of cell membranes, influx of Ca^{2+}, persistent contractile dysfunction, and eventual cellular swelling and necrosis.[51]



BOX 36.2 RISK FACTORS FOR THE LOW CARDIAC OUTPUT SYNDROME AFTER CARDIOPULMONARY BYPASS

- Preoperative ventricular dysfunction
- Myocardial ischemia
- Poor myocardial preservation
- Reperfusion injury
- Inadequate cardiac surgical repair or revascularization

In addition to the previously described factors, RV dysfunction and RV failure are potential sources of morbidity and death after cardiac operations.[52–54] Numerous factors may predispose patients to the development of perioperative RV dysfunction, including CAD, RV hypertrophy, previous cardiac operation, and operative considerations such as inadequate revascularization or hypothermic protection. Technical and operative difficulties are associated with various cardiac surgical procedures (eg, right ventriculotomy), RV trauma, rhythm and conduction abnormalities, injury to the right ventricle during cessation of CPB, or protamine reaction.

The following discussion provides an overview of the pharmacologic approach to management of perioperative ventricular dysfunction in the setting of cardiac surgery. Management goals are described in Table 36.5. These are extensions of the routine preparations made for discontinuing CPB shown in Table 36.2.

Sympathomimetic Amines

Sympathomimetic drugs (ie, catecholamines) are pharmacologic agents capable of providing inotropic and vasoactive effects (Box 36.3). Catecholamines exert positive inotropic action by stimulation of the β_1- and β_2-receptors.[55–57] The predominant hemodynamic effect of a specific catecholamine depends on the degree to which the various α, β, and dopaminergic receptors are stimulated (Tables 36.6 and 36.7).

The physiologic effect of an adrenergic agonist is determined by the sum of its actions on α, β, and dopaminergic receptors. The effectiveness of any adrenergic agent is influenced by the availability and responsiveness of adrenergic receptors. Chronically increased levels of plasma catecholamines (eg, chronic CHF and long CPB time) cause downregulation of the number and sensitivity of β-receptors.[58] Acute depression of β-adrenergic receptor signaling has been reported following CPB.[59] Maintenance of normal acid-base status, normothermia, and electrolytes also improve the responsiveness to adrenergic-receptor stimulation.

The selection of a drug to treat ventricular dysfunction is influenced by pathophysiologic abnormalities, as well as by the physician's experience and preference. If LV performance is decreased primarily as a result of diminished contractility, the drug chosen should increase contractility. Although β-agonists improve contractility and tissue perfusion, their effects may increase myocardial oxygen consumption

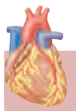
TABLE 36.5 Goals and Management of Cardiac Dysfunction

Variable	*Physiologic Management*
Heart rate and rhythm	Maintain normal sinus rhythm, avoid tachycardia; for tachycardia or bradycardia, consider pacing or chronotropic agents (atropine, isoproterenol, epinephrine), correct acid-base, electrolytes, and review current medications
Contractility	Assess hemodynamics, perform TEE to assess cardiac function, inspect for RWMA, rule out ischemia or infarction, inspect for dynamic outflow obstruction, consider inotropes; consider combination therapy with inotropes and/or vasodilators, and evaluate need for assist devices (IABP/LVAD/RVAD)
Preload	Assess end-diastolic volumes and chamber dimensions on TEE, rule out ischemia, significant valvular lesions, tamponade, and intracardiac shunts; reduce increased preload with diuretics or venodilators (nitroglycerin); monitor CVP, PCWP, and SV; consider using inotropes, IABP, or both
Afterload	Avoid increased afterload (increased wall tension), use vasodilators; avoid hypotension; maintain coronary perfusion pressure; consider IABP, inotropes devoid of α_1-adrenergic effects (dobutamine or milrinone), or both IABP and inotropes
Oxygen delivery	Increase Fio_2 and CO; check ABGs and chest radiograph; confirm adequate ventilation and oxygenation; correct acid-base disturbances

ABG, Arterial blood gas; *CO,* cardiac output; *CVP,* central venous pressure; *Fio_2,* fraction of inspired oxygen concentration; *IABP,* intraaortic balloon pump; *LVAD,* left ventricular assist device; *PCWP,* pulmonary capillary wedge pressure; *RVAD,* right ventricular assist device; *RWMA,* regional wall motion abnormality; *SV,* stroke volume; *TEE,* transesophageal echocardiography.

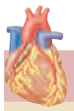
TABLE 36.6 Sympathomimetic Agents

	Dosage		Site of Action		
Drug	*Intravenous Bolus*	*Infusion*	*α*	*β*	*Mechanism of Action*
Dobutamine	—	2–20 μg/kg per min	+	++++	Direct
Dopamine	—	1–10 μg/kg per min	++	+++	Direct and indirect
Epinephrine	2–16 μg	2–10 μg/min Or 0.01–0.4 μg/kg per min	+++	+++	Direct
Ephedrine	5–25 mg	—	+	++	Direct and indirect
Isoproterenol	1–4 μg	0.5–10 μg/min Or 0.01–0.10 μg/kg per min		++++	Direct
Norepinephrine	—	2–16 μg/min Or 0.01–0.3 μg/kg per min	++++	+++	Direct



BOX 36.3 PHARMACOLOGIC APPROACHES TO VENTRICULAR DYSFUNCTION

- Inotropic drugs
- Phosphodiesterase inhibitors
- Calcium sensitizer
- Vasodilators
- Vasopressors
- Metabolic supplements



BOX 36.4 INOTROPIC DRUGS

- Epinephrine
- Norepinephrine
- Dopamine
- Dobutamine
- Isoproterenol

($M\dot{v}o_2$) and reduce coronary perfusion pressure (CPP). However, if the factor most responsible for decreased cardiac function is hypotension with concomitantly reduced CPP, infusion of α-adrenergic agonists can increase blood pressure and improve diastolic coronary perfusion.

Catecholamines also are effective for treating primary RV contractile dysfunction, and all the β_1-adrenergic agonists augment RV contractility. Studies have documented the efficacy of epinephrine, norepinephrine, dobutamine, isoproterenol, dopamine, levosimendan, and phosphodiesterase fraction III (PDE III) inhibitors in managing RV contractile dysfunction. When decreased RV contractility is combined with increased afterload, agents that exert vasodilator and positive inotropic effects may be used, including epinephrine, isoproterenol, dobutamine, levosimendan, PDE III inhibitors, and inhaled nitric oxide or prostaglandins.[60–66]

Epinephrine

Epinephrine is an endogenous catecholamine that stimulates both α- and β-adrenergic receptors in a dose-dependent fashion.[56,57] The β-selective pharmacology of epinephrine is characterized by a higher binding affinity for the β-receptor at lower doses and a stronger preference for the α-receptor at higher doses. This provides the clinical basis for the biphasic response observed for epinephrine, in which at lower doses the hemodynamic effects are predominated by increased inotropy and chronotropy of the heart (β-effect), and at higher doses a vasopressor effect (α-effect) is primarily observed.[56,57]

Epinephrine is often used to facilitate the separation from CPB (Box 36.4). In the earliest studies, epinephrine infusion at 0.03 μg/kg per minute following CPB resulted in an increase in cardiac index (CI), MAP, and HR by 30%, 27%, and 11%, respectively, compared with baseline.[67]

In another study, epinephrine infusion at dosages of 0.01, 0.02, and 0.04 μg /kg per minute was shown to increase SV by 2%, 12%, and 22%, respectively, corresponding to an increased CI of 0.1, 0.7, and 1.2 L/m^2 per minute.[68] In the lower dose range (0.01–0.04 μg/kg per min), the effect on the HR was less pronounced, with a maximum increase of 10 beats/minute in this study. Lobato and colleagues[69] similarly demonstrated, during CABG procedures, an increase in CO with a negligible increase in HR following CPB in response to an infusion of epinephrine at a dose of 0.03 μg/kg per minute. In a study comprising patients receiving preoperative β-blockers, epinephrine at a higher dose of 0.1 μg/kg per minute produced significant increases in CI and HR of 24.1% and 14.1%, respectively, compared with placebo.[70]

TABLE 36.7 Hemodynamic Effects of Inotropes

Drug	*CO*	*dP/dt*	*HR*	*SVR*	*PVR*	*PCWP*	*$M\dot{v}o_2$*
Dobutamine							
2–20 μg/kg per min[a]	↑↑↑	↑	↑↑	↓	↓	↓ or ↔	↑
Dopamine							
0–3 μg/kg per min	↑	↑	↑	↓	↓	↑	↑
3–10 μg/kg per min	↑↑	↑	↑	↓	↓	↑	↑
>10 μg/kg per min	↑↑	↑	↑↑	↑	(↑)	↑ or	↑↑
Isoproterenol							
0.5–10 μg/min	↑↑	↑↑	↑↑	↓↓	↓	↓	↑↑
Epinephrine							
0.01–0.4 μg/kg per min	↑↑	↑	↑	↑ (↓)	(↑)	↑ or ↔	↑↑
Norepinephrine							
0.01–0.3 μg/kg per min	↑	↑	↔ (↑↓)	↑↑	↔	↔	↑
Phosphodiesterase Inhibitors[b]	↑↑	↑	↑	↓↓	↓↓	↓↓	↓
Levosimendan[c]	↑↑↑	↑↑	↑	↓↓	↓↓	↓↓	↓ or ↔

[a]The indicated dosages represent the most common dosage ranges. For the individual patient, a deviation from these recommended doses may be indicated.
[b]Phosphodiesterase inhibitors are usually given as a loading dose followed by a continuous infusion: amrinone: 0.5 to 1.5 mg/kg loading dose, 5 to 10 μg/kg per minute continuous infusion; milrinone: 50 μg/kg loading dose, 0.375 to 0.75 μg/kg per minute continuous infusion.
[c]Levosimendan is usually administered as a loading dose followed by an infusion for 24 hours: 8 to 24 μg/kg loading dose, 0.1 to 0.2 μg/kg per minute (Toller W, Heringlake M, Guarracino F, et al. Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion. *Int J Cardiol.* 2015;184:323–336.)
CO, Cardiac output; *dP/dt,* myocardial contractility; *HR,* heart rate; *$M\dot{v}o_2$*, myocardial oxygen consumption; *PCWP,* pulmonary capillary wedge pressure; *PVR,* pulmonary vascular resistance; *SVR,* systemic vascular resistance; ↑, mild increase; ↑↑, moderate increase; ↑↑↑, major increase; ↔, no change; ↓, mild decrease; ↓↓, moderate decrease.
Modified from Lehmann A, Boldt J. New pharmacologic approaches for the perioperative treatment of ischemic cardiogenic shock. *J Cardiothorac Vasc Anesth.* 2005;19:97–108.

The results of these studies suggest that elevations in HR may be an effect observed at higher doses. Moreover, epinephrine is also used frequently after cardiac operations to support the function of the "stunned" reperfused heart following CPB. During emergence from CPB, Butterworth and associates[71] showed that epinephrine (0.03 μg/kg per min) increased CI and SV by 14% without increasing HR. In summary, epinephrine (0.01–0.04 μg/kg per min) at certain doses effectively increases CO with minimal increases in HR following CPB (see Table 36.7).[67–69,71] (see Chapters 11 and 38).

Dobutamine

Dobutamine is a synthetic catecholamine that displays a strong affinity for the β-receptor and results in dose-dependent increases in CO and HR, as well as reductions in diastolic filling pressures.[61] Administration of dobutamine in cardiac surgical patients produced a marked increase in CI and HR in several studies.[61,67,71,72] In patients with the LCOS, dobutamine resulted in an increase in HR in excess of 25% and a significant concomitant decrease in SVR.[61,72] The effects of epinephrine (0.03 μg/kg per min) were compared with those of dobutamine (5 μg/kg per min) in 52 patients recovering from CABG procedures.[71] Both drugs significantly and similarly increased SV index (SVI), but epinephrine increased the HR by only 2 beats/minute, whereas dobutamine increased the HR by 16 beats/minute. In an observational study of 100 cardiac surgical patients, HR increased by an average of 1.45 beats/minute per μg/kg per minute of dobutamine.[73] In the randomized multicenter trial comparing dobutamine and milrinone in patients with low CI (<2.0 L/m^2 per min), CI increased by 55% versus 36% after 1 hour in the dobutamine-treated group compared with the milrinone-treated group.[61] The hemodynamic effects of dobutamine were also characterized by a 35% increase in HR (vs 10% with milrinone) and a 31% increase in MAP (vs 7% with milrinone). Dobutamine was also associated with significantly higher incidences of hypertension and new atrial fibrillation (18% vs 5%; $P < .04$).[61]

In addition to increasing contractility, dobutamine may have favorable metabolic effects on ischemic myocardium. Intravenous and intracoronary injections of dobutamine increased coronary blood flow in animal studies.[74] In paced cardiac surgical patients, dopamine increased oxygen demand without increasing oxygen supply, whereas dobutamine increased myocardial oxygen uptake and coronary blood flow. However, because increases in HR are a major determinant of $M\dot{v}o_2$, these favorable effects of dobutamine could be lost if dobutamine induces tachycardia. During dobutamine stress echocardiography, segmental wall motion abnormalities suggestive of myocardial ischemia can result from tachycardia and increases in $M\dot{v}o_2$ (see Chapters 1 and 2).[75]

Dopamine

Dopamine is an endogenous catecholamine and an immediate precursor of norepinephrine and epinephrine. Its actions are mediated by stimulation of adrenergic receptors and specific postjunctional dopaminergic receptors (D_1 receptors) in the renal, mesenteric, and coronary arterial beds.[56,57,76] Dopamine is unique in comparison with other endogenous catecholamines because of its effects on the kidneys. It has been shown to increase renal artery blood flow by 20% to 40% by causing direct vasodilation of the afferent arteries and indirect vasoconstriction of the efferent arteries.[77] This action results in increases in glomerular filtration rate and in oxygen delivery to the juxtamedullary nephrons. In low doses (0.5–3.0 μg/kg per minute), dopamine predominantly stimulates the dopaminergic receptors; at doses ranging from 3 to 10 μg/kg per minute, it activates most adrenergic receptors in a nonselective fashion; and at higher doses (>10 μg/kg per min), dopamine behaves as a vasoconstrictor. The dose-dependent effects of dopamine are not very specific and can be influenced by multiple factors such as receptor regulation, concomitant drug use, and interindividual and intraindividual variability.[56,57,67]

In patients undergoing cardiac surgical procedures, dopamine in the dose range of 2.5 and 5.0 μg/kg per minute was observed to produce significant increases in CI and HR.[72,78] Doses greater than 5 μg/kg per minute may result in significant increases in MAP and pulmonary vascular resistance (PVR) without increasing CO.[78] In patients with the LCOS following cardiac operations, dopamine produced a 57.9% increase in CI compared with baseline and a simultaneous increase in HR by 25.5% in one study.[79] Tarr and colleagues[72] compared the efficacies of dopamine, dobutamine, and enoximone for weaning from CPB in a randomized trial of 75 patients. Nine of the 25 patients randomly assigned to dopamine displayed a poor and inadequate hemodynamic response. The remaining 16 patients recorded an increase in CI of 25.7% and elevations in HR of 44.3%, with minimal increase in SVI after receiving dopamine. The CI in the dopamine-treated group was significantly lower than in patients treated with dobutamine.[72] In the early study by Steen and associates,[67] dopamine caused more frequent and less predictable degrees of tachycardia than dobutamine or epinephrine at doses that produced comparable improvement in contractile function. These studies suggest that the hemodynamic

effects of dopamine at lower doses are predominately characterized by marked elevations in HR and moderate increases in CI. At higher doses, increases in MAP and PVR predominate without an increase in CO. The propensity of dopamine to increase HR and induce tachyarrhythmias may limit its utility in the cardiac surgical patient emerging from CPB.

Norepinephrine

Norepinephrine is an endogenous catecholamine exhibiting potent α-adrenergic activity with a mild-to-modest effect on the β-adrenergic receptor.[56,57] The higher affinity for norepinephrine for the α-adrenergic receptor provides the basis for its powerful vasoconstrictor effect and less potent inotropic and chronotropic properties. The overall hemodynamic effects of norepinephrine are characterized by an increase in systolic, diastolic, and pulse pressure, with minimal net impact on CO and HR. In this regard, norepinephrine is used primarily to manage low SVR secondary to vasodilation after CPB. In this setting, norepinephrine has been used to increase MAP in patients receiving inotropic support. Norepinephrine has been used in combination with milrinone, dobutamine, or levosimendan to counteract systemic vasodilation and hypotension in patients following CPB.[80,81] Norepinephrine has also been reported in the management of sepsis. Meadows and associates[82] treated 10 patients with severe sepsis and hypotension unresponsive to volume expansion, dopamine, and dobutamine. Norepinephrine infusion (0.03–0.89 μg/kg per min) alone improved arterial blood pressure, LV stroke work index, urine output, and, in most cases, CI. Desjars and colleagues[83] studied the renal effects of prolonged norepinephrine infusion in hypotensive patients with sepsis. Norepinephrine (0.5–1.0 μg/kg per min) in combination with low-dose dopamine improved urine flow and renal function compared with dopamine alone.[83] Norepinephrine may be effective in restoring MAP in patients with a low SVR after CPB (ie, vasoplegia syndrome).[84] When cardiac dysfunction is primarily a result of decreased CPP, vasoconstrictors may be used to optimize performance.

Isoproterenol

Isoproterenol is a potent, nonselective β-adrenergic agonist, devoid of α-adrenergic agonist activity. Isoproterenol dilates skeletal, renal, and mesenteric vascular beds and decreases diastolic blood pressure.[56] The potent chronotropic action of isoproterenol, combined with its propensity to decrease CPP, limits its usefulness in patients with CAD. Applications include treatment of bradycardia (especially after orthotopic heart transplantation), pulmonary hypertension, and HF after surgical treatment of congenital cardiac disease.[85] Isoproterenol remains the inotrope of choice for stimulation of cardiac pacemaker cells in the management of acute bradyarrhythmias or atrioventricular heart block. Its use for this purpose during cardiac surgery is limited because artificial pacing is usually easily accomplished in this setting. This drug reduces refractoriness to conduction and increases automaticity in myocardial tissues. The tachycardia seen with isoproterenol is a result of direct effects of the drug on the sinoatrial and atrioventricular nodes and reflex effects caused by peripheral vasodilation. Isoproterenol is routinely used in the setting of cardiac transplantation for increasing automaticity and inotropy, as well as for its vasodilatory effect on the pulmonary arteries.

Phosphodiesterase Inhibitors

The PDE III inhibitors milrinone and amrinone (inamrinone), are bipyridine derivatives that increase cyclic adenosine monophosphate (cAMP), Ca^{2+} flux, and Ca^{2+} sensitivity of contractile proteins.[56,57] PDE III inhibitors increase the level of cAMP by inhibiting its breakdown within the cell; this action leads to increased myocardial contractility. These drugs have a unique site of action in that they do not bind and activate the adrenergic receptor. Their positive effects on inotropy are mediated primarily through an inhibition of the PDE enzyme and not through β-receptor stimulation. As a result, the effectiveness of the PDE III inhibitors is not altered by previous β-blockade, nor is it reduced in patients who may experience β-receptor downregulation.[58] In addition to their positive inotropic effects, these agents produce systemic and pulmonary vasodilation and improve diastolic relaxation (lusitropy). For these reasons, the term *inodilator* has been used to describe this class of drugs (Box 36.5).

BOX 36.5 INODILATOR DRUGS AND OTHER AGENTS

- Inamrinone
- Milrinone
- Dobutamine
- Epinephrine plus nitroprusside ("epipride")
- Levosimendan
- Nesiritide

Milrinone has been shown to increase CO without increasing overall $M\dot{v}o_2$. Monrad and colleagues[86] administered milrinone to patients with CHF; CI increased by 45%, but overall $M\dot{v}o_2$ did not change.[86] Several studies also suggested that milrinone may improve myocardial diastolic relaxation and compliance (ie, positive "lusitropic" effect) while augmenting coronary perfusion.[30,69,87,88] The proposed mechanism for this effect on diastolic performance is that by decreasing LV wall tension, ventricular filling is enhanced, and myocardial blood flow and oxygen delivery are optimized (see Table 36.7). The ability of short-term administration of milrinone to augment ventricular performance in patients undergoing cardiac surgical procedures was shown in the results from the European Milrinone Multicentre Trial Group.[89] In this prospective study, intravenous milrinone was studied in patients after CPB. All patients received a bolus infusion of milrinone at 50 μg/kg over 10 minutes, followed by a maintenance infusion of 0.375, 0.5, or 0.75 μg/kg per minute for 12 hours. Significant increases in SV and CI were observed. In addition, significant decreases in pulmonary capillary wedge pressure, central venous pressure, pulmonary artery pressure, MAP, and SVR were seen. Eighteen patients (14%) had arrhythmias, most of which occurred in the group receiving 0.75 μg/kg per minute. Two arrhythmic events were deemed serious; both were bouts of rapid atrial fibrillation occurring with the larger dose.

In another study, Bailey and associates[90] also showed that after CPB, a loading dose of milrinone at 50 μg/kg, followed by a continuous infusion of 0.5 μg/kg per minute, resulted in a significant increase in CO. Moreover, in a dose-escalation study, Butterworth and colleagues[91] investigated the pharmacokinetics and pharmacodynamics of milrinone in adult patients undergoing cardiac operations; milrinone (bolus doses of 25, 50, or 75 μg/kg) was given if the CI was less than 3.0 L/m^2 per minute after separation from CPB. All three bolus doses of milrinone significantly increased CI. The 50 and 75 μg/kg doses produced significantly greater increases in CI than did the 25 μg/kg dose. The 75 μg/kg dose produced increases in CI comparable to those observed with the 50 μg/kg dose, but the higher dose was associated with more hypotension, despite administration of intravenous fluid, blood, and a phenylephrine infusion. The initial redistribution half-lives were 4.6, 4.3, and 6.9 minutes, and the terminal elimination half-lives were 63, 82, and 99 minutes for the 25, 50, and 75 μg/kg doses, respectively. The results of these investigations suggest that for optimizing hemodynamic performance (while minimizing potential for arrhythmias), the middle dose range (ie, loading dose of 50 μg/kg) of milrinone may be most efficacious, with a continuous infusion of 0.5 μg/kg per minute, leading to a plasma concentration of more than 100 ng/mL. In patients with poor LV function, the loading dose should be given during CPB to avoid a decrease in MAP and to minimize the need for other inotropes on discontinuing CPB.[91–93]

Amrinone represents the first-generation PDE III inhibitor used to wean from CPB. Compared with dobutamine, amrinone was found to be more effective for separation from CPB, with observed increases

in SV and CO and decreases in SVR and PVR.[94,95] Gage and colleagues[96] reported that when amrinone was used in combination with dobutamine, CO was significantly increased compared with therapy with dobutamine alone. Thrombocytopenia has been a potential clinical concern with the administration of PDE III inhibitors. Currently, amrinone has been implicated in causing dose-dependent thrombocytopenia, thus limiting its utility in cardiac surgical procedures.[97,98] By contrast, the potential negative effects of PDE III inhibitors on platelets were not demonstrated with milrinone. George and associates[99] were unable to demonstrate any significant reduction in platelet count after 48 hours of milrinone infusion in cardiac surgical patients. Similarly, Kikura and colleagues[100] found that milrinone administration did not cause significant changes in platelet number or function in patients undergoing cardiac operations with CPB compared with controls.

In summary, the PDE III class of inodilators has a unique mechanism of action independent of the β-receptor. These agents combine increases in contractility with reductions in SVR and PVR. In addition, the properties that govern relaxation and compliance of the heart are enhanced with PDE III inhibitors and allow these drugs to improve diastolic filling. These unique properties render PDE III inhibitors particularly useful in patients with β-receptor downregulation, right-sided heart dysfunction, pulmonary hypertension, diastolic dysfunction, and the LCOS.[57]

Calcium Sensitizers

Levosimendan is a positive inotropic drug belonging to the unique class of Ca^{2+} sensitizers.[56,57] Levosimendan binds three distinct sites of action, and this property characterizes its unique tripartite mechanism of action and pharmacologic effects.[101] In the myocardium, levosimendan selectively binds troponin C through a Ca^{2+}-dependent binding site stabilizing the cross-bridging mechanism and resulting in positive inotropy. Levosimendan also specifically binds to the ATP-dependent K^+ channel (K^+/ATP) in cardiac mitochondria, governing its protective effects against ischemia and reperfusion injury. By regulating Ca^{2+} influx in the mitochondria, opening of the K^+/ATP channel attenuates infarct size as a result of ischemia-reperfusion injury.[102] The third site of action is at the level of the smooth muscle in the vasculature. At this site, levosimendan binds and opens K^+/ATP channels and thus leads to decreases in SVR and cardiac preload and afterload. The vasodilatory effect on the vasculature has been shown to increase coronary and renal blood flow. Levosimendan is unique in that it confers positive inotropy without an increase in cardiac bioenergetics.[103] The salutary effects on the myocardium are achieved through an observed decrease in overall cardiac workload, cardioprotective effects, lusitropy, and a net increase in myocardial oxygen supply.[101,103,104]

The pharmacokinetics and pharmacodynamics of levosimendan are unique in that an active metabolite is formed with potency and efficacy similar to those of the parent compound.[105,106] Following a loading dose, steady-state levels are reached at approximately 4 hours after drug infusion. However, an active metabolite known as OR-1986 peaks at 48 hours and remains active for more than 300 hours (12–14 days after the end of infusion). The active metabolite, OR-1986, is primarily responsible for the sustained increase in SVI, decrease in cardiac workload, and improved coronary and renal blood flow in patients with the LCOS following cardiac surgical procedures. The formation of an intermediate- or long-acting metabolite may allow for earlier pharmacologic weaning without fear of losing the beneficial inotropic and hemodynamic effects as a result of drug discontinuation. Moreover, because the mechanism of action is independent of the β-receptor, concomitant administration of β-blocker therapy and levosimendan is not antagonistic.[107] This property allows for earlier reinstitution of β-blocker therapy for prevention or management of postoperative tachyarrhythmias.[108]

The effective perioperative use of levosimendan has been described in cardiac surgical patients with low LVEF.[109–112] In summary, levosimendan improved myocardial performance with an observed increase in SVI and coronary blood flow, as well as a decrease in SVR while minimizing oxygen consumption.[112] Levin and associates[113] demonstrated the superiority of levosimendan versus dobutamine in a randomized trial comprising 137 patients with the LCOS after CABG procedures. The postoperative 30-day mortality rate was lower in the levosimendan group compared with dobutamine (8.7% vs 25%; $P < .05$), as was the need for vasopressors, second or third inotropes, and IABP use.

In another study comparing the combined effects of levosimendan and dobutamine versus milrinone and dobutamine, patients receiving levosimendan and dobutamine demonstrated a sustained increase in SVI several hours after discontinuation of dual drug therapy compared with a dobutamine-milrinone combination.[114] Patients in the dobutamine-levosimendan arm of the trial also required less vasopressor support compared with the dobutamine-milrinone group. In a meta-analysis of clinical trials, Harrison and colleagues[115] evaluated the effects of levosimendan in cardiac surgical patients with and without preoperative systolic dysfunction. These investigators showed that death and other adverse outcomes, such as postoperative renal failure requiring dialysis, postoperative atrial fibrillation, and myocardial injury, were reduced with levosimendan treatment. These benefits were greatest for the patients with diminished LVEF. In the randomized, double-blind study by Eriksson and colleagues, levosimendan facilitated weaning from CPB and reduced the need for additional inotropic or mechanical circulatory support in patients with impaired LVEF (≤50%) who were undergoing CABG.[116] Sixty patients received either levosimendan as a 12 μg/kg bolus followed by 0.2 μg/kg per minute infusion, or placebo, immediately after the induction of anesthesia. Levosimendan significantly facilitated primary weaning from CPB as compared with placebo ($P = .002$). In four patients in the placebo group, the second weaning attempt failed, and these patients had to be supported by IABP, as compared with none in the levosimendan group (P = NS).

Currently, levosimendan is recommended by the European Society of Cardiology for treatment of acute worsening of HF and for acute HF after myocardial infarction.[112,117] It also has been found to enhance contractile function of stunned myocardium in patients with acute coronary syndromes.[118] It is available clinically in Europe and is now undergoing phase III trials in the United States.[112] The use of levosimendan has been reported in cardiac surgical patients with high perioperative risk, compromised LV function, difficulties in weaning from CPB, and severe RV failure after mitral valve replacement.[112,119–124] The drug has been used preoperatively, during emergence from CPB, and in the postoperative period for up to 28 days. The potential for levosimendan to produce increased contractility, decreased resistance, minimal metabolic cost, and minimal arrhythmias makes it a potentially useful addition to the treatments for patients with the LCOS or RV failure.

Vasodilators

The indications for using vasodilators such as NTG, sodium nitroprusside (SNP), nicardipine, and clevidipine in cardiac surgery include management of perioperative systemic or pulmonary hypertension, myocardial ischemia, and ventricular dysfunction complicated by excessive pressure or volume overload (Box 36.6).[125–128] In most conditions, NTG, SNP, or clevidipine may be used because of their shared features such as rapid onset, ultrashort half-lives, and easy titratability. Nevertheless, important pharmacologic differences exist among these vasodilators. In the setting of CAD or ischemia, NTG is preferred because it selectively vasodilates coronary arteries without producing coronary "steal." Similarly, in the management of ventricular volume overload or RV pressure overload, NTG may offer some advantage over SNP. NTG has a predominant influence on the venous bed such that preload can be reduced without significantly compromising systemic arterial pressure. The benefits of NTG are improvement in SV, reduction in wall tension and $M\dot{V}o_2$, increased perfusion to the subendocardium as a result of a lower LVEDP, and maintenance of CPP. SNP is a more potent arterial vasodilator and may potentiate myocardial

BOX 36.6 VASODILATOR MECHANISMS HELPFUL IN DISCONTINUING CARDIOPULMONARY BYPASS

- Decreased right and left ventricular wall stress (afterload)
- Decreased venous return (preload)
- Improved lusitropy
- Improved coronary blood flow

ischemia because of a coronary steal phenomenon or a reduction in CPP. Its greater potency, however, makes SNP a more rational choice for management of perioperative hypertensive disorders and for afterload reduction during or after operations for regurgitant valvular lesions.[125]

Although NTG and SNP have been used for the management of hypertension during cardiac surgical procedures, they both have notable limitations. NTG use as a primary antihypertensive agent is limited by its weak effect on arterial vasodilation. SNP is a potent arterial dilator, but its use is associated with reflex tachycardia, tachyphylaxis, inhibition of hypoxic pulmonary vasoconstriction, increase in intracranial pressure, and reduced renal blood flow.[128] The potential for cyanide toxicity is also an important consideration when administering SNP. This drug also may be difficult to titrate and often causes hypotension related to overshoot. In light of these limitations, the Ca^{2+} channel blocker class of antihypertensive agents such as clevidipine and nicardipine may prove to be valuable alternatives.

Clevidipine is an ultrafast-acting, dihydropyridine L-type Ca^{2+} channel blocker with a direct action on arteriolar resistance vessels and limited effects on venous capacitance vessels.[128–130] The fast onset and offset of approximately 1 minute make clevidipine especially suited for intraoperative management of acute hypertension.[131] Nicardipine is also a dihydropyridine Ca^{2+} channel blocker with a selective arterial vasodilator mode of action.[125,132,133] Nicardipine has a beneficial hemodynamic profile in that the drug reduces systemic and coronary artery resistance while increasing coronary blood flow. However, its use may be limited to the postoperative setting because of its longer half-life and slower offset of action compared with clevidipine.[134,135] In the ECLIPSE (Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events) trial, clevidipine was compared with NTG, SNP, and nicardipine in the perioperative treatment of hypertension during cardiac surgical procedures.[128] In an analysis of the individual treatment cohorts, clevidipine was significantly more effective at achieving blood pressure targets within the prespecified range compared with NTG or SNP in the perioperative period. In the postoperative period, the efficacy of clevidipine was similar to that of nicardipine in achieving blood pressure control after cardiac operations. With respect to safety profile, no differences in the incidences of myocardial infarction, stroke, or renal dysfunction were observed among the treatment groups. Mortality rates were similar between the clevidipine-treated versus NTG-treated groups and the clevidipine versus nicardipine-treated groups, whereas mortality rates appeared to be higher in the SNP-treated group compared with the clevidipine-treated group ($P = .04$ in a univariate analysis). The incidence of atrial fibrillation and sinus tachycardia were similar between clevidipine and all comparators.[128]

Despite the benefits of vasodilator therapy in the management of CHF, these drugs can be difficult to use in treatment of perioperative ventricular dysfunction. This is most evident in cases of the LCOS when impaired pump function is complicated by inadequate perfusion pressure. In these situations, multidrug therapy with vasoactive and cardioactive agents is warranted (ie, NTG or SNP in combination with epinephrine or milrinone and norepinephrine). Combination therapy enables greater selectivity of effect. The unwanted side effects of one drug can be avoided while supplementing the desired effects with another agent.[136,137] To maximize the desired effects of any particular combination of agents, frequent assessment of cardiac performance with a pulmonary artery catheter and TEE is needed. This approach allows the Starling curve and the pressure-volume loops to be visualized as they are shifted up and to the left with therapy (see Chapters 6, 13, and 38).

Vasoplegic Syndrome and Cardiopulmonary Bypass

The concept of the vasoplegic syndrome, characterized by hypotension associated with profound vasodilation unresponsive to conventional catecholamines or vasopressors, was introduced in association with CPB in the late 1990s.[138] It has been linked with preoperative use of vasodilators and shown to be a risk factor for increased morbidity and death after cardiac surgical procedures.[139] Two pharmacologic agents have been reported to be used to treat vasoplegic syndrome after CPB: vasopressin and methylene blue (MB).

Vasopressin

Arginine vasopressin (antidiuretic hormone) is a peptide hormone normally produced in the posterior pituitary that plays a crucial role in water homeostasis by controlling water resorption in the renal collecting ducts.[140] Administered as an intravenous infusion, vasopressin was initially used as a potent vasoconstrictor for vasodilatory shock associated with sepsis[141] and ventricular assist device implantation.[142] Because its vasopressor effect is mediated through a different mechanism (VP1 receptors) from that of the catecholamines, vasopressin can be infused at a constant rate as a strategy to decrease high doses of catecholamines such as norepinephrine and has been used in this way to treat vasodilation occurring after CPB.[143] The vasoconstricting effects of vasopressin may spare the pulmonary vasculature, thus making it an attractive choice to treat hypotension associated with RV dysfunction, but this effect has not been clearly demonstrated in intact humans.[144,145] Reported infusion doses vary widely from 0.01 to 0.6 IU/minute.[146] Use of vasopressin has been associated with necrotic lesions of the skin, and this agent should be used with caution and in the lowest possible effective dose.[147]

Methylene Blue

MB, a substance commonly used intravenously during surgical procedures for its ability to dye certain tissues, inhibits guanylate cyclase and hence the production of cyclic guanosine monophosphate, which is known to increase vascular smooth muscle relaxation.[148] MB has been used as a rescue treatment for profound vasodilatory shock in several settings, including cardiac surgery.[149–151] At a dose of 3 mg/kg given during CPB, MB was shown to increase SVR and MAP without adverse effects in a randomized trial of patients taking angiotensin-converting enzyme inhibitors, as well as decrease pressor requirements and serum lactate levels after CPB.[152] In another randomized trial, MB, 2 mg/kg, was given 1 hour preoperatively to patients at risk for CPB-associated vasoplegic syndrome. None of the treatment group developed vasoplegic syndrome, whereas 26% of the control group did.[153] MB causes transient discoloration of the urine and the skin and interferes with pulse oximetry measurements of arterial oxygen saturation. In a retrospective analysis of 57 patients with vasoplegia during cardiac surgical procedures and CPB, use of MB as treatment for vasoplegia was independently associated with poor outcomes.[154] The use of MB has also been implicated in causing serotonin syndrome through its inhibition of monoamine oxidase-A enzyme.[155] In another case report, MB was causally linked to the development of methemoglobinemia during CPB.[156] These reports highlight the need for more studies on the safety and possible poor outcomes associated with MB. Although more studies are warranted, it may be prudent to reserve MB for rescue therapy, as opposed to using it as a preventive agent.[154]

Additional Pharmacologic Therapy

Following the steps outlined in Tables 36.2 and 36.5, most patients can be weaned from CPB. However, a small percentage will be difficult to remove safely from CPB because of their chronic end-stage CHF or an acute insult during cardiac operation that produced cardiogenic shock. These patients probably will require mechanical circulatory support

(eg, IABP, ventricular assist device), as discussed later and in Chapter 28. However, while instituting these further steps, some clinicians may try additional pharmacologic therapy.

Controversial Older Treatments

Some studies suggest that a reduction in plasma thyroid hormone concentration may cause decreased myocardial function after CPB.[157,158] Multiple investigators have documented declines in the circulating triiodothyronine (T_3) concentration during and after CPB, and the most dramatic decreases in T_3 are seen at the end of CPB and during the first few hours after CPB.[157] Thyroid hormone in the form of an intravenous T_3 infusion (2 µg/h to a total dose of 0.5 µg/kg) has been used during cardiac surgical procedures and has resulted in increases in the MAP and HR, as well as reductions in LAP and central venous pressure, in patients who initially could not be weaned from CPB. Moreover, the administration of glucose-insulin-K^+ (GIK) or just glucose and insulin has been found to be useful for metabolic support of the heart after CPB. Insulin therapy may improve glucose use and energy metabolism during cardiac operations, thereby improving myocardial function.[159–163]

Emerging Intravenous Drugs for Heart Failure and Cardiogenic Shock

Natriuretic Peptide

The activation of several neuroendocrine pathways as a result of CPB may contribute to the pathophysiology of postbypass ventricular dysfunction, especially in patients with preoperative LCOS. Release of plasma epinephrine, norepinephrine, and arginine vasopressin has been observed in patients undergoing cardiac surgical procedures with CPB.[164] The overall effects of neuroendocrine activation are the promotion of Na^+ and volume retention and a concomitant increase in SVR, which may contribute to cardiac and renal dysfunction and increased mortality rates.[165,166] The identification of the humoral mediators of neuroendocrine activation has facilitated the development of therapeutic targets aimed at blocking specific neuroendocrine pathways.

The cardiac natriuretic peptides and brain natriuretic peptide (BNP) and their precursors may represent important targets for the modulation or attenuation of the neuroendocrine activation cascade observed in patients with postbypass cardiac dysfunction.[167,168] The recombinant human BNP, nesiritide, possesses both vasodilatory and diuretic effects. This 30–amino acid peptide may also play a role in inhibiting the activation of the renin-angiotensin axis and the release of plasma catecholamines.[169] In patients with HF, intravenous nesiritide acts as a vasodilator and reduces preload and SVR, and CI subsequently increases.[170–172] The drug has no positive inotropic effects. Compared with NTG and dobutamine, nesiritide had a greater effect on decreasing preload than NTG, and it did not cause as many arrhythmias as dobutamine.[173,174] In the Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery (NAPA) trial, patients with LVEF of less than 40% randomized to receive nesiritide during CABG benefited with improved postoperative renal function and enhanced intermediate survival after 180 days.[175] Chen and colleagues[176] studied the renal effects of low-dose nesiritide in patients with preexisting renal dysfunction undergoing cardiac surgical procedures. These investigators demonstrated that 24 hours of a low-dose infusion of nesiritide at 0.005 µg/kg per minute resulted in the preservation of renal function in the nesiritide-treated group at 48 and 72 hours in patients with preexisting renal insufficiency. The results of these two trials suggest that nesiritide may play a future role in preserving renal function in patients undergoing cardiac operations.

Human atrial natriuretic peptide (ANP) is a 28–amino acid peptide produced primarily by the atria in response to an increased intravascular volume.[177] A low-dose infusion of carperitide (Table 36.8), a recombinant form of ANP, in patients with poor LV function during CABG proved effective in improving renal function marked by lower serum creatinine levels and increased glomerular filtration rate in the treatment group.[178,179] In another randomized controlled study of 303 patients with chronic kidney disease who were undergoing CABG, carperitide infusion conferred a cardioprotective effect, as suggested by reduced rates of cardiac events and cardiac-related deaths in the treatment group compared with placebo.[180] Neurohormonal levels of angiotensin II and aldosterone were also reduced 1 week postoperatively in the treatment group. Sezai and associates[179] later investigated the efficacy of carperitide in patients undergoing CABG in a randomized controlled trial of 367 high-risk patients (European System for Cardiac Operative Risk Evaluation [EuroSCORE] >6). This investigation demonstrated that the rates of major adverse cardiac and cerebrovascular events were significantly lower in the carperitide-treated group compared with placebo ($P < .0001$). The rate of dialysis was also significantly lower in the carperitide-treated group ($P = .0147$) compared with the control group. These investigators concluded that in the early postoperative period, carperitide infusion may confer protection against postoperative major adverse cardiac and cerebrovascular events and hemodialysis in high-risk patients undergoing CABG.

In summary, the administration of low-dose carperitide during CABG improved renal and cardiac outcomes, possibly through a combination of vasodilatory and natriuretic effects and modulation of the neurohormonal response during cardiac surgical procedures with CPB. This drug may provide another option in the management of cardiac and renal dysfunction in patients undergoing cardiac operations with CPB.

TABLE 36.8 Emerging Intravenous Drugs for Heart Failure and Cardiogenic Shock

*Drug**	*Molecular Target and Mechanism of Action*	*Phase of Development*
Istaroxime	Inhibition of Na^+/K^+-ATPase and increased SERCA2a ATPase activity	Phase II
Carperitide	Recombinant atrial natriuretic peptide	Phase II
Levosimendan[a]	Calcium sensitizer-troponin C/K^+-ATP channel	Phase II
Nesiritide	Brain natriuretic peptide	Approved
Omecantiv mecarbil	Cardiac myosin ATPase activator	Phase II

[a]Levosimendan is currently approved in Europe and is undergoing phase III trials in the United States.

ATP, Adenosine triphosphate; *ATPase,* adenosine triphosphatase; *K^+,* potassium; *Na^+,* sodium; *SERCA2a,* sarcoplasmic reticulum calcium adenosine triphosphatase isoform 2a pump.

Modified from George M, Rajaram M, Shanmugam E, et al. Novel drug targets in clinical development for heart failure. *Eur J Clin Pharmacol.* 2014;70:765–774.

Istaroxime

Istaroxime is a first in class intravenous steroid derivative that activates the sarcoplasmic reticulum Ca^{2+} ATPase isoform 2a pump (SERCA2a; see Table 36.8). It also possesses a key inhibitory effect on the membrane Na^+/K^+-ATPase.[169,181] Regulating intracellular Ca^{2+} fluxes is a key mechanism in controlling the relaxation and contractile forces of the myocardium. Diminished activity of SERCA2a contributes to poor contractility and relaxation. Istaroxime has shown great promise in the treatment of HF in clinical trials.[182–184] It exerts its action during both the relaxation and contraction phases of the cardiac cycle.[169,183] This action is accomplished by inhibition of the membrane Na^+/K^+ ATPase, thus leading to an overall increase in cytosolic Ca^{2+} available for contraction.[185,186] During diastole, istaroxime enhances Ca^{2+} sequestration into the sarcoplasmic reticulum by increasing SERCA2a pump activity, which ultimately leads to more effective myocardial relaxation. In the phase II randomized, placebo-controlled, double-blind Hemodynamic Effects of Istaroxime in Patients with Worsening Heart Failure and Reduced LV Systolic Function (HORIZON-HF) trial, istaroxime reduced LVEDP and pulmonary capillary wedge pressures while increasing CI and systolic blood pressures in patients with a history of HF and an LVEF of up to 35%.[184] Escalating doses of 0.5, 1, and 1.5 µg/kg per minute were used to study the efficacy of istaroxime in 3 separate cohorts comprising 40 patients in each respective arm.

The investigators noted an increase in systolic blood pressure without a significant change in diastolic blood pressure. A transient increase in CI with the highest dose and a decrease in HR and diastolic and systolic volumes were observed without a change in ejection fraction. Improvement in diastolic filling parameters was also observed on echocardiography in the istaroxime-treated group.[183,184] Istaroxime has not been investigated in patients undergoing cardiac surgical procedures. Nevertheless, the unique properties of this agent make for a promising candidate for the treatment of the LCOS with separation from CPB.

Omecamtiv Mecarbil

Omecamtiv mecarbil is a first in class intravenous myosin activator (see Table 36.8).[169,187] The tight binding of myosin to actin leads to the contraction mechanism. Increasing the tight binding of myosin to actin proportionally enhances the force and the time of contraction. Omecamtiv mecarbil increases the rate of myosin binding onto actin and leads to both improved contractility and increased systolic ejection time.[169,188] This inotrope is unique in that it improves contractile forces at the level of the sarcomere, downstream from the activation of Ca^{2+}-dependent pathways that may be energetically deleterious.[187] In the phase II double-blind, placebo-controlled Acute Treatment with Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure (ATOMIC-AHF) study, patients receiving omecamtiv mecarbil exhibited a dose-dependent increase in blood pressure and systolic ejection time and a concomitant decrease in HR.[189] Although the primary end point of improvement in dyspnea was not observed, omecamtiv mecarbil may potentially prove to be a valuable drug because of its lack of chronotropic effects. This new drug is currently in phase II clinical trials and awaits further studies to examine its potential role in cardiac surgery.

Pharmacogenetics and Genotyping: the Rational Basis for Individualized Therapy

Variability in gene expression may play a pivotal role in how an individual patient responds to drug therapy.[190,191] Polymorphisms have been implicated in the differential effects of β-blockers, antiplatelet agents, anticoagulant agents, and antiarrhythmic agents in certain patients.[192–194] Similarly, individual differences in the degree of adrenergic receptor downregulation may mediate variable sensitivity to β-agonists.[192,195] Moreover, genotypic polymorphisms of the mediators of the β-adrenergic signaling pathway may be linked to poor outcome resulting from an increased incidence of major adverse cardiac events after cardiac surgical procedures.[192,196] For instance, specific haplotypes of the downstream effector protein, $G_{\alpha s}$, which is coupled to the adrenergic receptor, may be associated with altered cardiac contractility and hemodynamics.[59,197,198] In addition, inflammatory gene polymorphisms have been associated with increased risk of postoperative myocardial infarction.[199] These examples highlight the importance of molecular genotyping in the clinical management and risk stratification of cardiac surgical patients. The study of pharmacogenetics may lay the foundation for personalizing clinical management based on individual genotyping.[196,200] In the future, it may be conceivable to obtain a molecular "fingerprint" of a patient before a cardiac operation and modify prebypass and postbypass management based on the genotype data (see Chapter 8).

Intraaortic Balloon Pump Counterpulsation

The IABP is a device that is designed to augment myocardial perfusion by increasing coronary blood flow during diastole and unloading the left ventricle during systole (see Chapter 28). This is accomplished by mass displacement of a volume of blood (usually 30–50 mL) by alternately inflating and deflating a balloon positioned in the proximal segment of the descending aorta. The gas used for this purpose is carbon dioxide (because of its great solubility in blood) or helium (because of its inertial properties and rapid diffusion coefficients). Inflation and deflation are synchronized to the cardiac cycle by the electronics of the balloon console by producing counterpulsations. The results of effective use of the IABP are often quite dramatic. Improvements in CO, LVEF, coronary blood flow, and MAP frequently are seen, as well as decreases in aortic and ventricular systolic pressures, LVEDP, pulmonary capillary wedge pressure, LAP, HR, frequency of premature ventricular contractions, and suppression of atrial arrhythmias.

TABLE 36.9 Intraaortic Balloon Pump Counterpulsation Indications and Contraindications

Indications	*Contraindications*
1. Cardiogenic shock a. Myocardial infarction b. Myocarditis c. Cardiomyopathy 2. Failure to separate from CPB 3. Stabilization of preoperative patient a. Ventricular septal defect b. Mitral regurgitation 4. Stabilization of noncardiac surgical patient 5. Procedural support during coronary angiography 6. Bridge to transplantation	1. Aortic valvular insufficiency 2. Aortic disease a. Aortic dissection b. Aortic aneurysm 3. Severe peripheral vascular disease 4. Severe noncardiac systemic disease 5. Massive trauma 6. Patients with "do not resuscitate" instructions 7. Mitral SAM with dynamic outflow tract obstruction

CPB, Cardiopulmonary bypass; *SAM,* systolic anterior motion.

Indications and Contraindications

Since the introduction of the IABP, the indications for its use have grown (Table 36.9). The most common use of the IABP is for treatment of cardiogenic shock. This may occur after CPB or after cardiac operations in patients with preoperative shock, patients with acute postinfarction ventricular septal defects or mitral regurgitation, those who require preoperative stabilization, or patients who decompensate hemodynamically during cardiac catheterization. Patients with myocardial ischemia refractory to coronary vasodilation and afterload reduction are stabilized with an IABP before cardiac catheterization, and some patients with severe CAD prophylactically have an IABP inserted before undergoing CABG or off-pump CABG procedures.[201–205]

Contraindications to IABP use are relatively few (see Table 36.9). The presence of severe aortic regurgitation or aortic dissection is an absolute contraindication for the IABP, although successful reports of its use in patients with aortic insufficiency or acute trauma to the descending thoracic aorta have appeared. Other relative contraindications are listed; use of the IABP in these instances is at the discretion of the physician. Because the hemodynamic changes caused by an IABP theoretically would tend to worsen dynamic outflow tract obstruction caused by systolic anterior motion of the mitral valve, the device should be used with caution, if at all, in these patients.

Insertion Techniques

In the initial development of the IABP, insertion was by surgical access to the femoral vessels. In the late 1970s, refinements in IABP design allowed the development of percutaneous insertion techniques. Now the technique most commonly used, percutaneous IABP insertion, is performed rapidly with commercially available kits.

The femoral artery with the greater pulse is sought by careful palpation. The length of the balloon to be inserted is estimated by laying the balloon tip on the patient's chest at the Louis angle and appropriately marking the distal point corresponding to the femoral artery. Care must be taken when removing the balloon from its package to follow the manufacturer's procedures exactly, to avoid perforating the balloon before insertion. Available balloons come wrapped and need only be appropriately deflated before removal from the package. The femoral artery is entered with the supplied needle, a J-tipped guidewire is inserted to the level of the aortic arch, and the needle is removed.

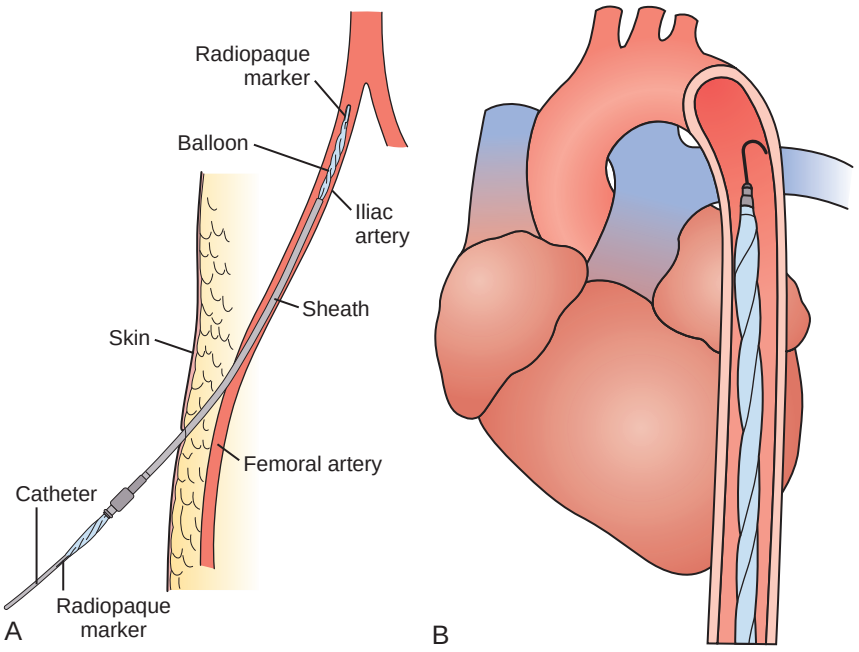


Fig. 36.3 Intraaortic balloon pump insertion. (A) Cannulation and insertion of the balloon through the femoral artery. Notice the tightly wrapped balloon as it traverses the sheath. A guidewire is not visible in this drawing. (B) Correct positioning of balloon in proximal descending aorta. The J-tipped guidewire is seen exiting from the balloon's central lumen. *(A, Courtesy Datascope Corporation, Fairfield, NJ; B, Courtesy Kontron, Inc., Augsburg, Germany.)*

The arterial puncture site is enlarged with the successive placement of an 8-Fr dilator and then a 10.5- or 12-Fr dilator and sheath combination (Fig. 36.3). In the adult-sized (30- to 50-mL) balloons, only the dilator needs to be removed, leaving the sheath and guidewire in the artery. The balloon is threaded over the guidewire into the central aorta and into the previously estimated correct position in the proximal segment of the descending aorta. The sheath is gently pulled back to connect with the leakproof cuff on the balloon hub, ideally so that the entire sheath is out of the arterial lumen to minimize risk for ischemic complications to the distal extremity. Alternatively, the sheath may be stripped off the balloon shaft much like a peel-away pacemaker lead introducer, thereby entirely removing the sheath from the insertion site. At least one manufacturer offers a "sheathless" balloon for insertion.

If fluoroscopy is available during the procedure, correct placement is verified before fixing the balloon securely to the skin. Position also may be checked by radiography or TEE after insertion. If an indwelling left radial arterial catheter is functioning at the time of insertion, a reasonable estimate of position may be made by watching balloon-mediated alteration of the arterial pulse waveform (Fig. 36.4). After appropriate positioning and timing of the balloon, 1:1 counterpulsation may be initiated. The entire external balloon assembly should be covered in sterile dressings.

Removal of a percutaneously inserted IABP may be by the open (surgical removal) or closed technique. If a closed technique is chosen, the artery should be allowed to bleed for several seconds while pressure is maintained on the distal artery after balloon removal to flush any accumulated clot from the central lumen. This maneuver helps prevent distal embolization of clot. Pressure is then applied for 20 to 30 minutes on the puncture site for hemostasis. If surgical removal is chosen, embolectomy catheters may be passed in antegrade and retrograde fashion before suture closure of the artery.

Alternate routes of IABP insertion exist. The balloon may be placed surgically through the femoral artery. This is now performed without the use of an end-to-side vascular conduit, although this placement still requires a second surgical procedure for removal. In patients with extreme peripheral vascular disease or in pediatric patients whose peripheral vasculature is too small, the ascending aorta or aortic arch may be entered for balloon insertion. These approaches necessitate median sternotomy for insertion and usually require reexploration for removal. Other routes of access include the abdominal aorta and the subclavian, axillary, and iliac arteries. The iliac approach may be especially useful for pediatric cases.

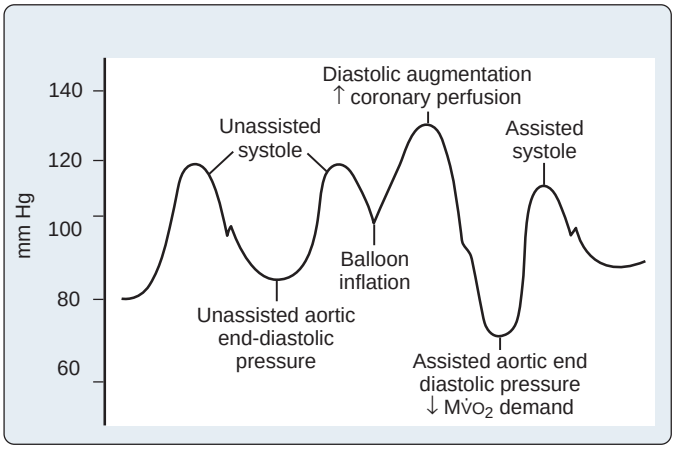


Fig. 36.4 Arterial waveforms seen during intraaortic balloon pump assist. The first two waveforms are unassisted, and the last is assisted. Notice the decreased end-systolic and end-diastolic pressures and augmented diastolic pressures caused by balloon pump augmentation and the (correct) point at which balloon inflation occurs. These are waveforms generated by a correctly positioned and timed balloon. $M\dot{V}O_2$, Myocardial oxygen consumption. *(Courtesy Datascope Corporation, Fairfield, NJ.)*

Timing and Weaning

IABP systems are commercially available from several different manufacturers. The basic console design includes electrocardiographic and

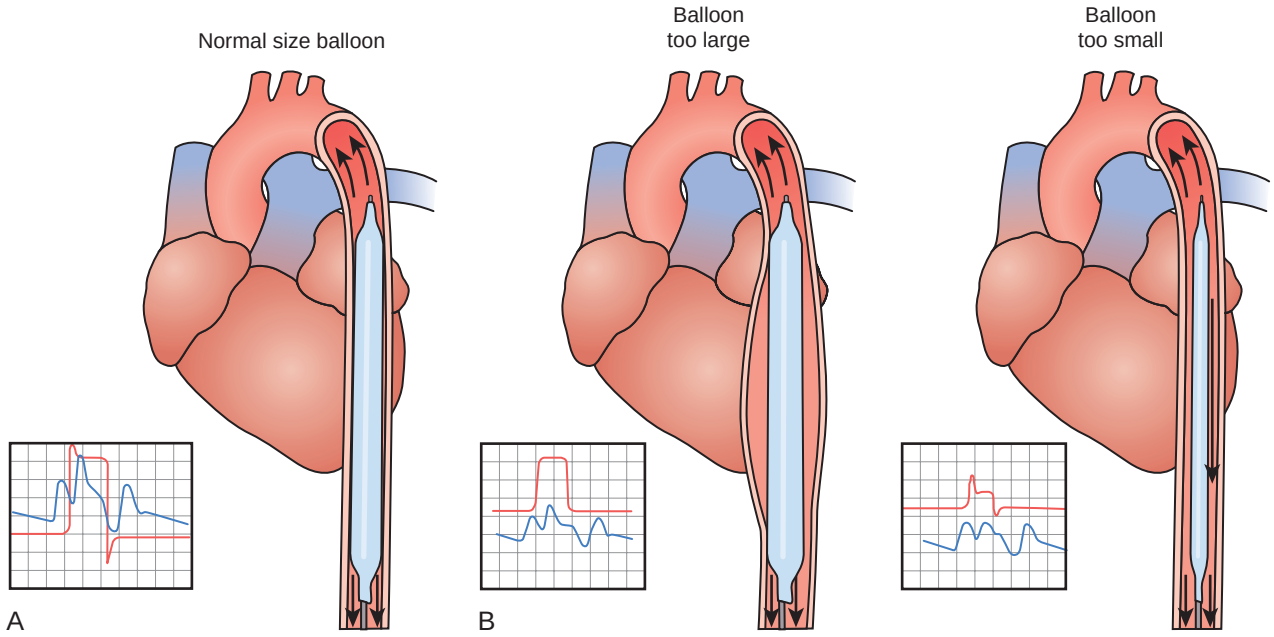


Fig. 36.5 Variations in waveform caused by incorrect balloon size. (A) The balloon is correctly positioned and appropriately sized for the aorta. Notice the arterial waveform diagram in the *lower left corner.* (B) Examples of too large *(left)* or too small *(right)* balloon sizes with their correspondingly altered arterial waveforms. A similar effect can result from overinflation and underinflation of the balloon. Compare the waveforms in B with the ideal waveform in A.

arterial blood pressure waveform monitoring and printing, balloon volume monitoring, triggering selection switches, adjustments for inflation and deflation timing, battery backup power sources, and gas reservoir. Some of these systems have become quite sophisticated, with advanced computer microprocessor circuits allowing triggering based on pacemaker signals or detection of and compensation for aberrant rhythms such as atrial fibrillation. Portable models exist for transportation of patients by ground, helicopter, or air ambulances.

For optimal effect of the IABP, inflation and deflation must be correctly timed to the cardiac cycle. Although certain variables, including positioning of the balloon within the aorta, balloon volume (Fig. 36.5), and the patient's cardiac rhythm, can affect the performance of the IABP, basic principles regarding the function of the balloon must be followed. Balloon inflation should be timed to coincide with aortic valve closure, or aortic insufficiency and LV strain will result. Similarly, late inflation results in a diminished perfusion pressure to the coronary arteries. Early deflation causes inappropriate loss of afterload reduction, and late deflation increases LV work by causing increased afterload, if only transiently. These errors and correct timing diagrams are shown in Figs. 36.4 and 36.6.

As the patient's cardiac performance improves, the IABP support must be removed in stages rather than abruptly. Judicious application and dosing of vasodilator and inotropic medications can assist this procedure. The balloon augmentation may be reduced in steps from 1:1 counterpulsation to 1:2 and then to 1:4, with appropriate intervals at each stage to assess hemodynamic and neurologic stability, CO, and $S\bar{v}O_2$ changes. After appropriate observation at 1:4 or 1:8 counterpulsation, balloon assistance can be safely discontinued, and the device can be removed by one of the methods discussed. If percutaneous removal is chosen, an appropriate interval for reversal of anticoagulation (if used) before removal of the balloon should be allowed.

Complications

Several complications have been associated with IABP use (Table 36.10). The most frequently seen complications are vascular injuries, balloon malfunction, and infection.[201–205] Treatment of these respective problems is straightforward. Flaps, dissections, perforations, embolic events, and pseudoaneurysms should be managed directly by surgical intervention and repair. Steal syndromes or ischemia, if not severe, may be managed with expectantly, but if severe extremity compromise is observed, the balloon should be moved to another site. An alternative means of treatment is a femoral-to-femoral crossover graft placed surgically to help alleviate the affected extremity.

Problems associated with the balloon are managed directly by removal or replacement or, if necessary, repositioning. Gas embolization, although rare, has been successfully treated with hyperbaric oxygen.

Infections usually require removal or replacement of the balloon in an alternate site. Appropriate antibiotic coverage should be instituted and adjusted as culture results become available. Prosthetic materials

TABLE 36.10 Intraaortic Balloon Pump Counterpulsation Complications

Vascular	*Miscellaneous*	*Balloon*
Arterial injury (perforation, dissection)	Hemolysis	Perforation (preinsertion)
Aortic perforation	Thrombocytopenia	Tear (during insertion)
Aortic dissection	Infection	Incorrect positioning
Femoral artery thrombosis	Claudication (postremoval)	Gas embolization
Peripheral embolization	Hemorrhage	Inadvertent removal
Femoral vein cannulation	Paraplegia	—
Pseudoaneurysm of femoral vessels	Entrapment	—
Lower extremity ischemia	Spinal cord necrosis	—
Compartment syndrome	Left internal mammary artery occlusion	—
Visceral ischemia	Aggravation of dynamic outflow tract obstruction	—

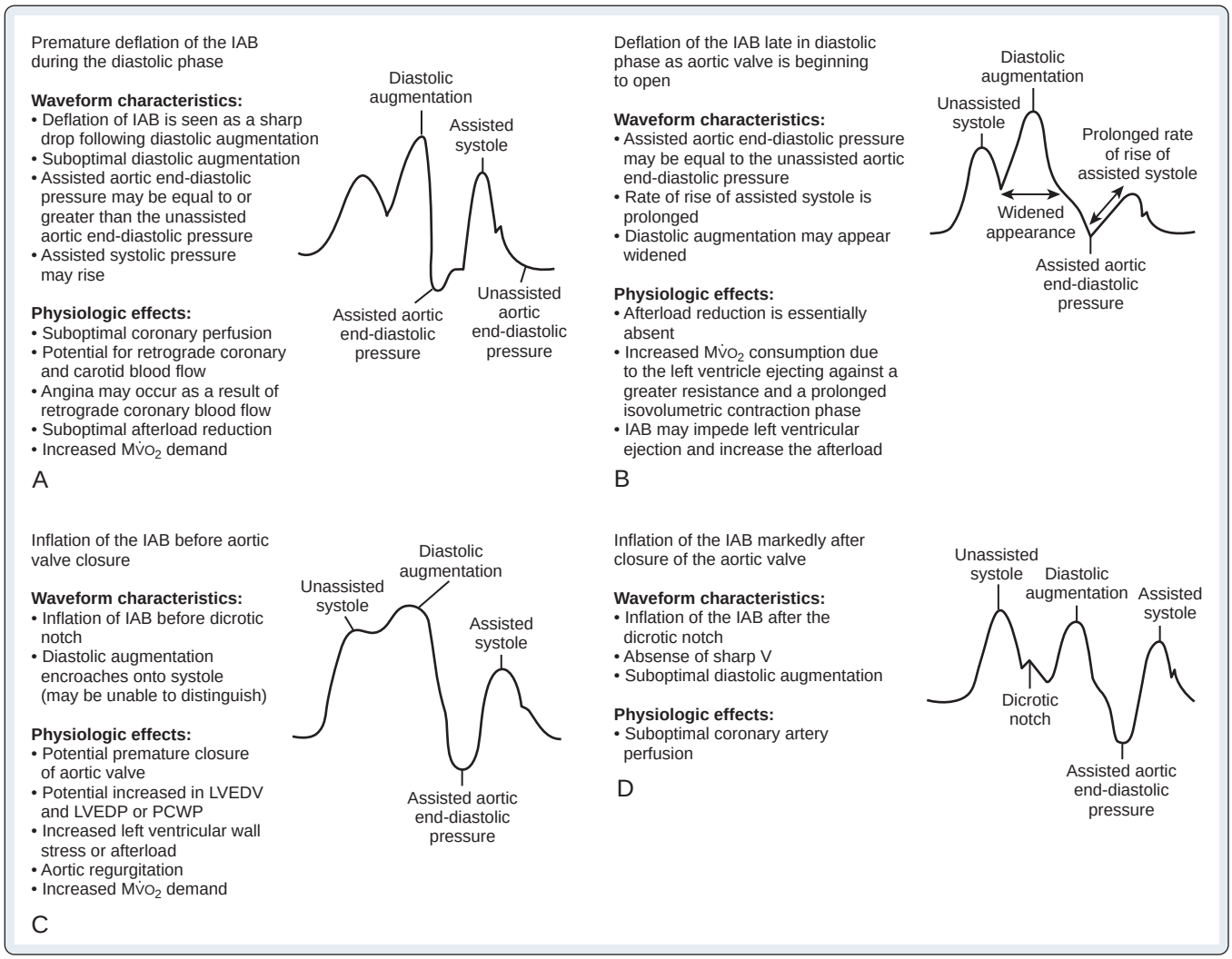


Fig. 36.6 Alterations in arterial waveform tracings caused by errors in timing of intraaortic balloon *(IAB)* pump. (A) The balloon was deflated too early. (B) The balloon was deflated too late. (C) The balloon was inflated too early. (D) The balloon was inflated too late. *LVEDP,* Left ventricular end-diastolic pressure; *LVEDV,* left ventricular end-diastolic volume; *MV̇O2,* myocardial oxygen consumption. *PCWP,* pulmonary capillary wedge pressure. *(Courtesy Datascope Corporation, Fairfield, NJ.)*

should be removed if present, and débridement of the insertion site should be performed as necessary. Septicemia can occur and have detrimental effects if not aggressively treated.

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37

Fast-Track Postoperative Cardiac Recovery and Outcomes

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KEY POINTS

1. Cardiac anesthesia has fundamentally shifted from a high-dose narcotic technique to a more balanced approach using moderate-dose narcotics, shorter-acting muscle relaxants, and volatile anesthetic agents.
2. This new paradigm has also led to renewed interest in perioperative pain management involving multimodal techniques that facilitate rapid tracheal extubation such as regional blocks, intrathecal morphine, and supplementary nonsteroidal antiinflammatory drugs.
3. This approach has prompted a change from the classical model of recovering patients in the traditional intensive care unit manner, with weaning protocols and intensive observation, to management more in keeping with the recovery room practice of early extubation and rapid discharge, which has shifted the care of cardiac patients to more specialized post–cardiac surgical recovery units.
4. Fast-track cardiac anesthesia appears to be safe in comparison with conventional high-dose narcotic anesthesia, but if complications occur that would prevent early tracheal extubation, the management strategy should be modified accordingly.
5. The goal of a post–cardiac surgical recovery model is a postoperative unit that allows variable levels of monitoring and care based on patients' needs.
6. The initial management in the postoperative care of fast-track cardiac surgical patients consists of ensuring an efficient transfer of care from operating room staff to cardiac recovery area staff, while at the same time maintaining stable patients' vital signs.
7. It is important to know the risk factors associated with cardiac surgical procedures and to review treatment options for patients with specific reference to outcomes, all within the context of cost and resource use, especially as medicine increasingly involves economic realities.

Cardiac anesthesia itself has fundamentally shifted from a high-dose narcotic technique to a more balanced approach using moderate-dose narcotics, shorter-acting muscle relaxants, and volatile anesthetic agents. This change primarily has been driven by a realization that high-dose narcotics delay extubation and recovery after surgical procedures. This new paradigm also has led to renewed interest in perioperative pain management involving multimodal techniques that facilitate rapid tracheal extubation such as regional blocks, intrathecal morphine, and supplementary nonsteroidal antiinflammatory drugs (NSAIDs). In addition to changes in anesthetic practice, the type of patients presenting for cardiac operations is changing. Patients are now older and have more associated comorbidities (stroke, myocardial infarction [MI], renal failure). Treatment options for coronary artery disease (CAD) have expanded, ranging from medical therapy only to percutaneous coronary interventions (PCIs) and surgical procedures. Surgical options, however, also have expanded and include conventional coronary artery bypass graft surgery (CABG), off-pump coronary artery bypass surgery (OPCAB), minimally invasive direct coronary artery bypass, and robotically assisted coronary artery bypass techniques. Change also has taken place in the recovery of patients undergoing cardiac procedures. Although cardiac surgical procedures often were associated with a high mortality rate and long intensive care unit (ICU) stays, the use of moderate doses of narcotics has allowed for rapid ventilator weaning and discharge from the ICU within 24 hours. This change has prompted a shift from the classical model of recovering patients in the traditional ICU manner, with weaning protocols and intensive observation, to management more in keeping with the recovery room practice of early extubation and rapid discharge. This, in turn, has shifted the care of cardiac patients to more specialized post–cardiac surgical recovery units.

Finally, hard clinical outcomes have driven change in the ongoing management of cardiac patients and are increasingly the focus of research. Intraoperative management now exists within the continuum of preoperative assessment and postoperative care. The outcome for a patient within the hospital setting is only one small aspect of success. Long-term mortality, morbidity, and quality of life indicators are becoming the gold standard in determining benefit or harm for interventions.

This chapter reviews fast-track cardiac anesthesia (FTCA) and its impact on cardiac recovery. The initial perioperative care of routine cardiac surgical cases, including postoperative pain management techniques such as regional blockade and intrathecal morphine, are discussed, followed by specific management issues of commonly occurring problems in the cardiac ICU. Finally, important cardiac outcomes are reviewed, focusing on the different treatment options available to patients with CAD and discussing available evidence for the implementation of these options.

Fast-Track Cardiac Surgical Care

Anesthetic Techniques

Few trials have compared inhalation agents for FTCA. A single trial comparing sevoflurane and isoflurane in patients undergoing valve operations was unable to demonstrate reductions in tracheal extubation times.[1] Several studies examined the effectiveness of propofol versus an inhalation agent; these studies demonstrated reductions in myocardial enzyme release (creatine kinase-MB, troponin I) and preservation of myocardial function in patients receiving inhalation agents.[2–5] Although this end point is a surrogate for myocardial damage

and does not show improved outcome per se, creatine kinase-MB release after CABG may be associated with a poor outcome[6] (Box 37.1).

The choice of muscle relaxant in FTCA is important to reduce the incidence of muscle weakness in the cardiac recovery area (CRA) that may delay tracheal extubation.[7] Several randomized trials compared rocuronium (0.5–1 mg/kg) with pancuronium (0.1 mg/kg) and found significant differences in residual paralysis in the ICU.[8–11] Two studies found statistically significant delays in the time to extubation in the pancuronium-treated group.[9,10] None of the trials used reversal agents, so the use of pancuronium appears acceptable as long as a reversal agent is administered to patients with residual neuromuscular weakness.

Several trials examined the use of different short-acting narcotic agents during FTCA. In these trials, fentanyl, remifentanil, and sufentanil all were found to be efficacious for early tracheal extubation.[12–14] The anesthetic drugs and their suggested dosages are listed in Box 37.2.

BOX 37.1 BENEFITS OF FAST-TRACK CARDIAC ANESTHESIA

- Decreased duration of intubation
- Decreased length of intensive care unit stay
- Decreased cost

BOX 37.2 SUGGESTED DOSAGES FOR FAST-TRACK CARDIAC ANESTHESIA

Induction
Narcotic
Fentanyl 5–10 µg/kg
Sufentanil 1–3 µg/kg
Remifentanil infusions of 0.5–1.0 µg/kg per min

Muscle Relaxant
Rocuronium 0.5–1 mg/kg
Vecuronium 1–1.5 mg/kg

Hypnotic
Midazolam 0.05–0.1 mg/kg
Propofol 0.5–1.5 mg/kg

Maintenance
Narcotic
Fentanyl 1–5 µg/kg
Sufentanil 1–1.5 µg/kg
Remifentanil infusions of 0.5–1.0 µg/kg per min

Hypnotic
Inhalational 0.5–1 MAC
Propofol 50–100 µg/kg per min

Transfer to Cardiac Recovery Area
Narcotic
Morphine 0.1–0.2 mg/kg

Hypnotic
Propofol 25–75 µg/kg per min

MAC, Minimum alveolar concentration.
From Mollhoff T, Herregods L, Moerman A, et al. Comparative efficacy and safety of remifentanil and fentanyl in 'fast track' coronary artery bypass graft surgery: a randomized, double-blind study. *Br J Anaesth*. 2001;87:718; Engoren M, Luther G, Fenn-Buderer N. A comparison of fentanyl, sufentanil, and remifentanil for fast-track cardiac anesthesia. *Anesth Analg*. 2001;93:859; and Cheng DC, Newman MF, Duke P, et al. The efficacy and resource utilization of remifentanil and fentanyl in fast-track coronary artery bypass graft surgery: a prospective randomized, double-blinded controlled, multi-center trial. *Anesth Analg*. 2001;92:1094.

Evidence Supporting Fast-Track Cardiac Recovery

Several randomized trials and one metaanalysis of randomized trials addressed the question of safety of FTCA.[15–21] None of the trials was able to demonstrate differences in outcomes between the fast-track anesthesia group and the conventional anesthesia group (Fig. 37.1). The metaanalysis of randomized trials demonstrated a reduction in the duration of intubation by 8 hours (Fig. 37.2) and in the ICU length of stay (LOS) by 5 hours in favor of the fast-track group. However, the hospital LOS was not statistically different.

One concern with FTCA is the potential for an increase in the incidence of adverse events, notably awareness. Awareness in patients

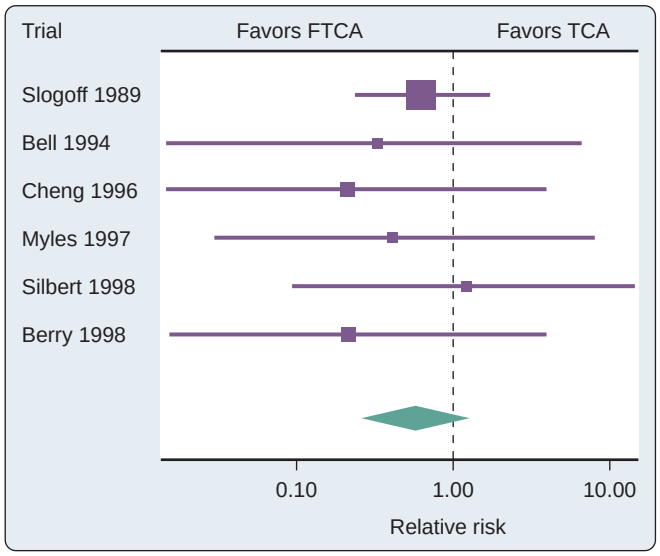


Fig. 37.1 Forrest plot of mortality indicating no difference when fast-track cardiac anesthesia *(FTCA)* was compared with conventional high-dose narcotic anesthesia. *TCA*, Traditional cardiac anesthesia. *(Data from Myles PS, Daly DJ, Djaiani G, et al. A systematic review of the safety and effectiveness of fast-track cardiac anesthesia.* Anesthesiology. *2003;99[4]:982–987.)*

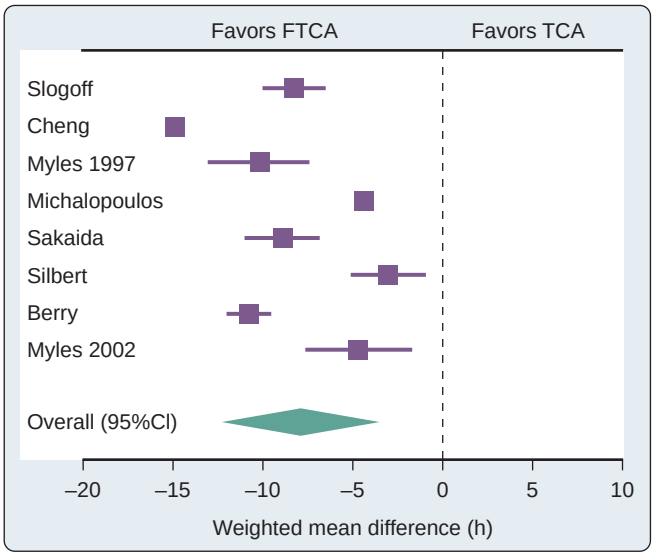


Fig. 37.2 Forrest plot showing the weighted mean difference in extubation times. The overall effect was an 8.1-hour reduction in extubation times. *CI*, Confidence interval; *FTCA*, fast-track cardiac anesthesia; *TCA*, traditional cardiac anesthesia. *(Data from Myles PS, Daly DJ, Djaiani G, et al. A systematic review of the safety and effectiveness of fast-track cardiac anesthesia.* Anesthesiology. *2003;99[4]:982–987.)*

undergoing FTCA was systematically investigated in 2 prospective observational studies with a total of 1131 patients undergoing FTCA. The reported incidence rate of explicit intraoperative awareness was 0.3% (2 of 608) in the first trial and 0.19% (1 of 514) in the second trial.[22,23] This finding is comparable to the reported incidence during conventional cardiac surgical procedures,[24] and it suggests that FTCA does not increase the incidence of awareness compared with conventional cardiac operations.

FTCA appears safe in comparison with conventional high-dose narcotic anesthesia. It reduces the duration of ventilation and ICU LOS considerably without increasing the incidence of awareness or other adverse events.[19–21] FTCA appears effective at reducing costs and resource use.[25,26] As such, it is becoming the standard of care in many cardiac centers. The usual practice at many institutions is to treat all patients as candidates for FTCA with the goal of allowing early tracheal extubation for every patient. However, if complications occur that would prevent early tracheal extubation, the management strategy is modified accordingly. Investigators have demonstrated that the risk factors for delayed tracheal extubation (>10 hours) are increased age, female sex, postoperative use of intraaortic balloon pump (IABP), inotropes, bleeding, and atrial arrhythmia. The risk factors for prolonged ICU LOS (>48 hours) are those of delayed tracheal extubation in addition to preoperative MI and postoperative renal insufficiency.[27] Care should be taken to avoid excessive bleeding (antifibrinolytic agents) and to treat arrhythmias either prophylactically or when they occur (β-blockers, amiodarone).

Post–Cardiac Surgical Recovery Models

The failure of many randomized trials of FTCA to show reductions in resource use likely stems from the traditional ICU models used by these centers during the study period. Even when trials were combined in a metaanalysis, the ICU LOS was reduced by only 5 hours even though patients were extubated a mean of 8 hours earlier.[21] Typically, patients who are extubated within the first 24 hours of ICU admission are transferred to the ward on postoperative day 1 in the morning or early afternoon. This approach allows the following daytime cardiac surgical patients to have available ICU beds, but it prevents patient transfers during nighttime hours. Two models have been proposed to deal with this issue: the parallel model and the integrated model (Fig. 37.3). In the parallel model, patients are admitted directly to a CRA, where they are monitored with 1:1 nursing care until tracheal extubation. The level of care is then reduced to reflect reduced nursing requirements, with ratios of 1:2 or 1:3. Any patients requiring overnight ventilation are transferred to the ICU for continuation of care. The primary drawback of the parallel model is the physical separation of the CRA and ICU, which leads to two separate units and thus does not eliminate the requirement to transfer patients. The integrated model overcomes these limitations because all patients are admitted to the same physical area, but postoperative management such as nurse-to-patient ratio is variable based on patients' requirements.[28–30] Because nursing care accounts for 45% to 50% of ICU costs, reducing the nursing requirements when possible creates the greatest saving. Other cost savings from reductions in arterial blood gas (ABG) measurements, use of sedative drugs, and ventilator maintenance are small. The goal is a postoperative unit that allows variable levels of monitoring and care based on patients' needs.[30] Furthermore, FTCA has been demonstrated to be a safe and cost-effective practice that decreases resource use after patients' discharge from index hospitalizations up to 1-year follow-up.[31]

Initial Management of Patients in Fast-Track Cardiac Anesthesia: The First 24 Hours

On arrival in the CRA, initial management of cardiac patients consists of ensuring an efficient transfer of care from operating room (OR) staff to CRA staff while at the same time maintaining stable patient vital signs. The anesthesiologist should relay important clinical parameters to the CRA team. To accomplish this, many centers have devised handoff sheets to aid in the transfer of care. Initial laboratory studies should be sent (Box 37.3). An electrocardiogram should be ordered, but a chest radiograph is required only in certain circumstances (Box 37.4). The patient's temperature should be recorded, and if low, active rewarming measures should be initiated with the goal of rewarming the patient to 36.5°C. Shivering may be treated with low doses of meperidine (12.5–25 mg, intravenously). Hyperthermia, however, is common later within the first 24 hours after cardiac operations and may be associated with an increase in neurocognitive dysfunction, possibly a result of hyperthermia exacerbating cardiopulmonary bypass (CPB)–induced neurologic injury[25,27] (Box 37.5) (see Chapters 31 and 40).

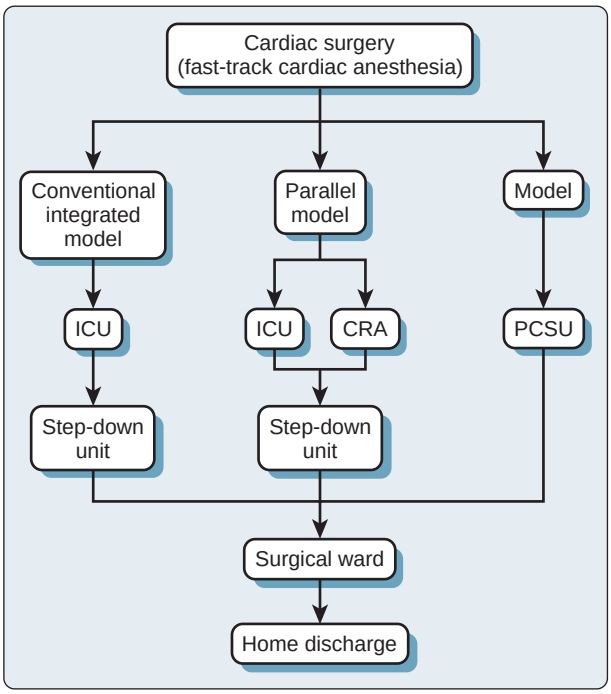


Fig. 37.3 Post–cardiac surgical recovery models. *CRA*, Cardiac recovery area; *ICU*, intensive care unit; *PCSU*, post–cardiac surgical unit.

BOX 37.3 SUGGESTED INITIAL LABORATORY WORK IN ROUTINE CASES, WITH ADDITIONAL LABORATORY WORK TO BE ORDERED AS INDICATED

Routine
Complete blood count
Electrolytes
Blood urea nitrogen/creatinine
aPTT/INR
Arterial blood gases

As Indicated
Fibrinogen
Liver function tests (AST/ALT)
Calcium
Magnesium
Cardiac enzymes (CK-MB, CK, troponin I)

ALT, Alanine aminotransferase; *aPTT*, activated partial thromboplastin time; *AST*, aspartate aminotransferase; *CK*, creatine kinase; *CK-MB*, creatine kinase myocardium band; *INR*, international normalized ratio.

BOX 37.4 SUGGESTED INDICATIONS FOR ORDERING A CHEST RADIOGRAPH

Respiratory
PaO_2/FIO_2 ratio >200
Peak pressure >30 cm H_2O
Asymmetric air entry

Circulatory
Uncertainty of pulmonary artery catheter position (poor trace, inability to wedge catheter)
Hypotension resistant to treatment
Excessive bleeding

Gastrointestinal
Nasogastric or orogastric tube feeding

PaO_2/FIO_2 ratio, Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.

BOX 37.5 INITIAL MANAGEMENT OF THE FAST-TRACK CARDIAC ANESTHESIA PATIENT

- Normothermia
- Hemoglobin >7 g/dL
- $PaCO_2$ 35–45 mm Hg
- SaO_2 >95%
- Mean blood pressure >50–70 mm Hg
- Potassium: 3.5–5.0 mEq/L
- Blood glucose <10.0 mmol/L (<200 mg/dL)

$PaCO_2$, Partial pressure of arterial carbon dioxide; *SaO_2*, arterial oxygen saturation.

Ventilation Management: Admission to Tracheal Extubation

Ventilatory requirements should be managed with the goal of early tracheal extubation in patients (Box 37.6). ABGs are initially drawn within one-half hour after admission and then repeated as needed. Patients should be awake and cooperative, hemodynamically stable, and have no active bleeding with coagulopathy. Respiratory strength should be assessed by hand grip or head lift to ensure complete reversal of neuromuscular blockade. The patient's temperature should be more than 36°C, preferably normothermic. When these conditions are met and ABG results are within the reference range, tracheal extubation may take place. ABGs should be drawn approximately 30 minutes after tracheal extubation to ensure adequate ventilation with maintenance of partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$). Inability to extubate patients as a result of respiratory failure, hemodynamic instability, or large amounts of mediastinal drainage necessitates more complex weaning strategies (see Chapter 39). Some patients may arrive after extubation in the OR. Careful attention should be paid to these patients because they may subsequently develop respiratory failure. The patient's respiratory rate should be monitored every 5 minutes during the first several hours. ABGs should be drawn on admission and 30 minutes later to ensure that the patient is not retaining carbon dioxide. If the patient's respirations become compromised, ventilatory support should be provided. Simple measures such as reminders to breathe may be effective in the narcotized or anesthetized patient. Low doses of naloxone (0.04 mg, intravenously) also may be beneficial. Trials of continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or noninvasive ventilation (NIV) may provide enough support to allow adequate ventilation. Reintubation should be avoided because it may delay recovery; however, it may become necessary if the earlier mentioned measures fail, with resulting in hypoxemia, hypercarbia, and a declining level of consciousness.

BOX 37.6 VENTILATION MANAGEMENT GOALS DURING THE INITIAL TRIAL OF WEANING FROM EXTUBATION

Initial Ventilation Parameters
A/C at 10–12 beats/min
Tidal volume 8–10 mL/kg
PEEP 5 cm H_2O

Maintenance of Arterial Blood Gases
pH 7.35–7.45
$PaCO_2$ 35–45 mm Hg
PaO_2 >90 mm Hg
Saturations >95%

Extubation Criteria
Arterial blood gases as above
Awake and alert
Hemodynamically stable
No active bleeding (<400 mL/2 h)
Temperature >36°C
Return of muscle strength (>5 s, head lift/strong hand grip)

A/C, Assist-controlled ventilation; *$PaCO_2$*, partial pressure of arterial carbon dioxide; *PaO_2*, partial pressure of arterial oxygen; *PEEP*, positive end-expiratory pressure.

Optimizing Hemoglobin Concentrations

Anemia is common during and after cardiac surgical procedures, a result of both dilution and blood loss. Although a hemoglobin transfusion threshold of 10 g/dL was once common, a large randomized trial indicated that a lower threshold of 7 g/dL was safe.[32] Many subsequent observational studies and small randomized trials suggested that blood transfusions were harmful and should be avoided. The concerns with most of the existing literature are the age of these studies, their observational design, and the small size of the few existing randomized trials.[33–35] A large randomized trial suggested that a higher target threshold may be of benefit in some patients.[36] In the post-CPB period, patients with incomplete revascularization or with poor target vessels may require a higher transfusion threshold.[32] The ideal hemoglobin level in patients following cardiac operations is unclear. However a minimum hemoglobin level of 7 g/dL. should be maintained. In patients who are acidotic and require high-dose vasopressor or inotropic support, a higher threshold of 8 or 9 g/dL should be targeted. As a result, blood transfusions should be individualized for each patient, but they certainly should be used to maintain a minimal hemoglobin level of 7 g/dL (see Chapters 30 and 35).

Management of Bleeding

Chest tube drainage should be checked every 15 minutes after ICU admission to assess a patient's coagulation status. Although blood loss is commonly divided into two types, surgical or medical, determining the cause of bleeding is often difficult. When bleeding exceeds 400 mL/hour during the first hour, 200 mL/hour for each of the first 2 hours, or 100 mL/hour over the first 4 hours, returning the patient to the OR for chest reexploration should be considered. The clinical situation must be individualized for each patient, however, and in patients with known coagulopathy, more liberal blood loss before chest reexploration may be acceptable. Bleeding after cardiac surgical procedures has numerous medical causes. Platelet dysfunction is common in this setting. The CPB circuit itself leads to contact activation and degranulation of platelets, thus resulting in platelet dysfunction. Residual heparinization is common following cardiac operations and frequently

occurs when either heparinized pump blood is transfused after CPB or insufficient protamine is administered. Fibrinolysis is also common after CPB, predominantly caused by a host of activated inflammatory and coagulation pathways. Coagulation factors may decrease from activation at air-blood interfaces or from dilution with the CPB pump-priming solution. Hypothermia also may aggravate the coagulation cascade and lead to further bleeding.

Conventional coagulation tests are helpful to identify the coagulation abnormality contributing to the bleeding. Common laboratory testing includes activated partial thromboplastin time, international normalized ratio (INR), platelet count, fibrinogen level, and D-dimers. Unfortunately, most conventional measures take 20 to 60 minutes before results are available. This situation has led to the development of new methods to help guide treatment. These bedside point-of-care tests are providing more rapid, clinically relevant results compared with laboratory testing. Point-of-care testing such as thromboelastography has been demonstrated to reduce transfusion requirements without increasing blood loss and is commonly used, especially following difficult cardiac operations[37,38] (see Chapters 19, 29, and 31–35).

Initial medical treatment of excessive blood loss consists of 50 to 100 mg of intravenous protamine to ensure complete heparin reversal. This treatment may need to be repeated if heparinized CPB pump blood has been administered after protamine reversal. Although the reinfusion of chest tube blood was common to avoid exposure to donor packed red blood cells, it is no longer used because this blood is known to contain activated coagulation and inflammatory mediators that may predispose to an increased risk for infection.[39] Tranexamic acid infusions may be used to reduce postoperative blood loss. The dose of tranexamic acid is up to 1 g/hour over a period of 5 hours. DDAVP may also be used and has been shown to be efficacious in patients with uremia or other disorders causing platelet dysfunction.[40] These three agents (protamine, an antifibrinolytic such as tranexamic acid, and DDAVP) represent a pharmaceutic approach to hemostasis and are usually readily available and can be given quickly. This therapy may be followed by the use of blood products as needed to treat ongoing blood loss.[41]

Fresh-frozen plasma usually is given in the setting of an increased INR (>1.5). In patients who have large chest tube drainage (>500 mL/h), fresh-frozen plasma may also be given as part of whole blood reconstitution in a manner similar to trauma resuscitation. This treatment prevents the inevitable coagulopathy caused by rapid blood loss and transfusion. Although approved only for the reversal of warfarin in the setting of an elevated INR, prothrombin complex concentrates are currently being investigated for treatment of bleeding associated with elevated INRs in postoperative cardiac surgical patients.[42]

Platelet levels of less than 100,000/mm^3 may warrant platelet transfusion. However, platelet transfusions carry the greatest risk for transfusion-related complications of any blood component, typically sepsis from bacterial contamination.[43] Platelets should be used only when platelet counts are low, platelet function assays indicate platelet dysfunction, or the patient has a suspected platelet dysfunction, secondary to the use of acetylsalicylic acid, glycoprotein IIb/IIIa inhibitors, or adenosine diphosphate receptor antagonists.

Fibrinogen concentrates are available, and a few studies have looked at the use of this product to prevent or treat bleeding. Few randomized trials exist, and currently the efficacy of these agents to reduce bleeding remains unclear. However, the current trials demonstrate few adverse events with fibrinogen concentrates.[44–46] A correlation between fibrinogen level and bleeding following cardiac surgical procedures was weak, but the potential of fibrinogen concentrates remains promising[47,48] (see Chapters 34 and 35).

Certain physical measures should be instituted, including warming of the hypothermic patient. The effects of positive end-expiratory pressure (PEEP) on postoperative bleeding are equivocal and likely have little benefit in the presence of surgical bleeding or in patients with coagulopathy.[49,50] The use of aprotinin after cardiac operations is likely of little benefit because several randomized trials were unable to demonstrate efficacy[51,52] (Box 37.7).

BOX 37.7 MANAGEMENT OF THE BLEEDING PATIENT

- Review activated coagulation time, prothrombin time, international normalized ratio, and platelet count.
- Administer protamine if bleeding is caused by excess heparin (reinfusion of pump blood).
- Treat the medical cause with platelets, fresh frozen plasma, and cryoprecipitate if bleeding is secondary to decreased fibrinogen.
- Factor VIIa should be considered if bleeding continues despite a normal coagulation profile.
- Treat the surgical cause with reexploration.

Factor VIIa may be used as rescue therapy in patients with uncontrolled bleeding, usually in the presence of normal coagulation test results and no surgical evidence of bleeding.[53] Factor VIIa is usually administered in the OR; however, it may be given in the ICU if bleeding persists despite corrected laboratory results (fibrinogen, INR, partial thromboplastin time). Doses initially were in the range of 75 to 100 μg/kg, but concern over thrombotic complications has led to dosage reductions ranging down to as low as 17 μg/kg.[53–55] Typically, 50 μg/kg total is given in one to two doses with 20 to 30 minutes in between dosing. If the chest tube drainage is reduced, the second dose may be omitted. Concern over a relatively high rate of complications (arterial thromboembolic) and the lack of efficacy (death and reductions in rates of transfusion) resulted in a reduction in the frequency of factor VIIa use postoperatively, and this use of factor VIIa remains an off-label indication.[56]

Electrolyte Management

Hypokalemia is common after cardiac surgical procedures, especially if diuretic agents were given intraoperatively. Hypokalemia contributes to increased automaticity and may lead to ventricular arrhythmias, ventricular tachycardia, or ventricular fibrillation. Treatment consists of potassium infusions (20 mEq potassium in 50 mL of D_5W infused over 1 hour) until the potassium level exceeds 3.5 mEq/mL. In patients with frequent premature ventricular contractions caused by increased automaticity, a serum potassium level of 5.0 mEq/mL may be desirable. Hypomagnesemia contributes to ventricular preexcitation and may contribute to atrial fibrillation (AF). This disorder is common in malnourished and chronically ill patients, a frequent occurrence in the cardiac surgical setting. Management consists of intermittent boluses of magnesium: 1 to 2 g over 15 minutes. Hypocalcemia also is frequent during cardiac operations and may reduce cardiac contractility. Intermittent boluses of calcium chloride or calcium gluconate (1 g) may be required (Box 37.8).

Glucose Management

Diabetes is a common comorbidity (up to 30%) and is a known risk factor for adverse outcomes in patients presenting for cardiac operations.[57–59] Hyperglycemia itself is common during CPB. The risk factors for hyperglycemia include diabetes, administration of steroids before CPB, volume of glucose-containing solutions administered, and use of epinephrine infusions.[60] Poor perioperative glucose control is associated with increases in mortality and morbidity, including an increased risk for infection and prolonged duration of ventilation.[61–65] In a large prospective, randomized, controlled trial of tight glucose control (blood glucose levels of 4.1–6.5 mmol/L) during the postoperative ICU stay, the investigators showed reductions in mortality rates were shown compared with more liberal glucose control (blood glucose levels of 12 mmol/L).[65] This trial enrolled both diabetic and nondiabetic hyperglycemic patients who underwent cardiothoracic

BOX 37.8 COMMON ELECTROLYTE ABNORMALITIES AND POSSIBLE TREATMENT OPTIONS

Hypokalemia (Potassium <3.5 mmol/L)
SSx: muscle weakness, ST-segment depression, "u" wave, T-wave flat, ventricular preexcitation
Rx: IV KCl at 10–20 mEq/h by central catheter

Hyperkalemia (Potassium >5.2 mmol/L)
SSx: muscle weakness, peaked T wave, loss of P wave, prolonged PR/QRS
Rx: $CaCl_2$ 1 g, insulin/glucose, HCO_3^-, diuretics, hyperventilation, dialysis

Hypocalcemia (Ionized Calcium <1.1 mmol/L)
SSx: hypotension, heart failure, prolonged QT interval
Rx: $CaCl_2$ or calcium gluconate

Hypercalcemia (Ionized Calcium >1.3 mmol/L)
SSx: altered mental state, coma, ileus
Rx: dialysis, diuretics, mithramycin, calcitonin

Hypermagnesemia (Magnesium >0.7 mmol/L)
SSx: weakness, absent reflexes
Rx: stop magnesium infusion, diuresis

Hypomagnesemia (Magnesium <0.5 mmol/L)
SSx: arrhythmia, prolonged PR and QT intervals
Rx: magnesium infusion 1 to 2 g

$CaCl_2$, Calcium chloride; *HCO_3^-,* bicarbonate; *IV KCl,* intravenous potassium chloride; *Rx,* treatment; *SSx,* signs and symptoms.

operations, and it demonstrated that tight management of glucose was beneficial in the CRA. However, another multicenter trial, as well as a metaanalysis of tight glucose control in the ICU, suggested an increase in harm, likely related to an increase in episodic hypoglycemia.[66] Therefore, it may be prudent to accept a more liberal blood glucose level (<10.0 mmol/L or <200 mg/dL) to reduce hypoglycemic episodes.

Pain Control

Pain control after cardiac surgical procedures has become a concern as narcotic doses have been reduced to facilitate fast-track protocols. Intravenous morphine or hydromorphone is still the mainstay of treatment in patients after cardiac operations. The most common approach is patient-demanded, nurse-delivered intravenous morphine, and this treatment remains popular because of the 1:1 to 1:2 nursing typically provided during cardiac recovery. However, with a change to more flexible nurse coverage and therefore higher nurse-to-patient ratios, patient-controlled analgesia (PCA) morphine use has become increasingly popular. Several studies examined PCA morphine use in patients after cardiac surgical procedures.[67–70] A metaanalysis looking at PCA morphine for postoperative pain showed small incremental benefits. However, young patients, those who took opioids preoperatively, or patients transferred to a regular ward on the day of the operation may benefit from PCA for pain management[71] (Box 37.9) (see Chapter 42).

Regional Analgesia Techniques

Intrathecal Morphine

Intrathecal morphine was investigated in randomized trials as an adjuvant for pain control in cardiac surgical patients, with doses ranging from 500 µg to 4 mg.[72–75] A metaanalysis of 17 randomized, controlled trials compared intrathecal morphine with standard treatment. No difference was noted in mortality rates, MI, or time to extubation. The investigators reported modest reductions in morphine use and pain scores, whereas the incidence of pruritus was increased.

BOX 37.9 PAIN MANAGEMENT OPTIONS AFTER CARDIAC SURGICAL PROCEDURES

Patient-Controlled Analgesia
Possible benefit in a step-down unit
Reduced 24-hour morphine consumption in 2 of 7 randomized trials

Intrathecal Morphine
Doses studied: 500 µg to 4 mg
Possible benefit in reducing intravenous morphine use
Possible benefit in reducing VAS pain scores
Potential for respiratory depression
Ideal dosing not ascertained; range, 250–400 µg

Thoracic Epidural Regimens
Common dosages from literature:
Ropivacaine 1% with 5 µg/mL fentanyl at 3–5 mL/h
Bupivacaine 0.5% with 25 µg/mL morphine at 3–10 mL/h
Bupivacaine 0.5–0.75% at 2–5 mL/h
Reduced pain scores
Shorter duration of intubation
Risk for epidural hematoma difficult to quantify

Nonsteroidal Antiinflammatory Drugs
Common dosages from literature:
Indomethacin 50–100 mg PR bid
Diclofenac 50–75 mg PO/PR q8h
Ketorolac 10–30 mg IM/IV q8h
Reduces narcotic utilization
Many different drugs studied; difficult to determine superiority of a given agent
Possible increase in serious adverse events (trial using cyclooxygenase-2–specific inhibitors)

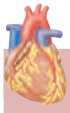
bid, Twice daily; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *PR,* rectally; *VAS,* visual analog scale.

Thoracic Epidural Analgesia

Thoracic epidural analgesia has gained some popularity as a method of providing intraoperative and postoperative pain control in cardiac surgery (see Box 37.9). The best evidence for benefit comes from a metaanalysis of 15 randomized, controlled trials.[73] Thoracic epidural analgesia did not significantly affect the incidence of death or MI. It did significantly reduce arrhythmias, pulmonary complications, and time to tracheal extubation. All the randomized trials were performed in patients undergoing CABG. No reported complications resulted from epidural insertion, specifically epidural hematoma; however, all trials were inadequately powered to detect this complication. Attempts have been made to calculate the risk for epidural hematoma by using available published series, with estimates of maximum risk ranging from 1 in 1000 to 1 in 3500, depending on the confidence limits chosen (99% vs 95%).[76] A large retrospective review reported no epidural hematomas in 727 patients undergoing cardiac surgical procedures with CPB and receiving thoracic epidural analgesia on the day of the operation (on entrance into the OR).[77] At least 1 hour elapsed between insertion of the epidural catheter and heparin administration. Nine failed catheter insertions and 4 failed analgesia blocks with 11 bloody taps occurred in this study.[77] Unfortunately, cardiac surgical patients are increasingly likely to be taking antiplatelet medications, such as clopidogrel or prasugrel, which increase the risk for epidural hematoma.[78] The risk for epidural hematoma and the potential delay of surgical procedures following a bloody tap have limited the widespread adoption of thoracic epidural analgesia in cardiac surgery, especially in the United States (see Chapter 42).

Nonsteroidal Antiinflammatory Drugs

The use of NSAIDs has gained popularity in a multimodal approach, by allowing reductions in both pain levels and narcotic side effects



BOX 37.10 MEDICATIONS FOR CARDIAC RISK REDUCTION AFTER CORONARY ARTERY BYPASS GRAFTING

- Aspirin: all patients after bypass grafting
- Clopidogrel: patients who have contraindication to aspirin (may have superior efficacy compared with aspirin)
- β-Blockers: especially with perioperative myocardial infarction
- Lipid-lowering agents: especially statin drugs

(see Box 37.9). The conventional NSAIDs, which nonselectively block the cyclooxygenase-2 (COX-2) isoenzyme, reduce inflammation, fever, and pain, and they also block the COX-1 isoenzyme, thus resulting in the side effects of gastrointestinal toxicity and platelet dysfunction.[79] Numerous randomized trials examined the benefit of NSAID use for postoperative pain control.[80–83] In addition, a metaanalysis looking at the benefit of NSAIDs in the setting of cardiac and thoracic surgery demonstrated reductions in narcotic consumption in patients given NSAIDs.[84] Most patients were younger than 70 years of age and had no coexisting renal dysfunction. The NSAIDs used in this metaanalysis were nonselective COX inhibitors. Several trials suggested increased adverse events, especially in patients with CAD, who receive the COX-2–selective NSAIDs both in the perioperative cardiac setting and while ambulatory. For this reason, COX-2–selective NSAIDs are no longer used in most cardiac centers.[85] Therefore, although NSAIDs have theoretic side effects, the benefit in reduced narcotic consumption and improved visual analog scale pain scores is well demonstrated; many centers continue to use nonselective NSAIDs as analgesia adjuvants in cardiac surgery.[86] However, NSAIDs should be avoided in patients with renal insufficiency, a history of gastritis, or peptic ulcer disease. Adjuvant ranitidine treatment may be considered to prevent gastric irritation.

Medications for Risk Reduction After Coronary Artery Bypass Graft Procedures

CABG surgical procedures reduce the risk of death and angina recurrence, but several medical management issues may help maintain the long-term benefit after CABG operations. Specifically, the use of aspirin, β-blockers, and lipid-lowering agents has been demonstrated to prolong survival or reduce graft restenosis, or both (Box 37.10) (see Chapters 1 and 20).

Aspirin

Many studies demonstrated the efficacy of aspirin (acetylsalicylic acid) use on graft patency and reductions in MI and mortality rates after CABG surgical procedures.[87–91] A large observational study showed a reduction in mortality rate of nearly 3% and a reduction in MI rate of 48% with the early postoperative use of aspirin (within 48 hours).[91] Acetylsalicylic acid dosages have ranged from 100 mg once daily to 325 mg three times daily orally or by suppository up to 48 hours after ICU admission. Typically, an 81-mg oral dose is used (150 mg rectally), with dosing ideally occurring within the first 6 to 8 hours after admission. No additional benefit results from the use of aspirin preoperatively.[92] The beneficial effect on saphenous vein graft patency appears to be lost after 1 year, with prolonged use of aspirin having no further benefit.[93] However, because aspirin, in doses of 75 to 325 mg/day, reduces mortality and morbidity in patients at risk for cardiovascular disease, its continued long-term use is warranted.[94] Clopidogrel, prasugrel, or ticagrelor may be suitable alternatives in patients who are allergic to aspirin. Clopidogrel, through reductions in all-cause mortality, stroke, and MI, may be superior to aspirin in patients who return with recurrent ischemic events after cardiac operations.[95]

β-Blockers

The use of β-blockers in patients after CABG surgical procedures was not shown to improve mortality rates.[96,97] These drugs also failed to reduce rates of perioperative myocardial ischemia in some studies, However, patients who received β-blockers after perioperative MI had reductions in mortality rates at 1 year.[98] Patients with a previous history of MI should continue β-blocker therapy. In addition, withdrawal of β-blockers is associated with increased rates of AF, so patients should be restarted on their β-blocker therapy as soon as it is safe to do so (see Chapter 11).

Statins

Statins should be continued in the postoperative period because clear evidence supports reductions in saphenous vein graft occlusion, AF, and postoperative mortality rates in patients receiving statins postoperatively. Statin use was shown to reduce the progression of atherosclerotic plaque formation within saphenous vein grafts. This resulted in reductions in the need for subsequent revascularization in several trials.[99,100] Statin use that is started in the preoperative period is associated with substantial reductions in the incidence of postoperative AF. An individual metaanalysis of randomized trials involving more than 1000 patients suggested a relative reduction in AF rates of 50% (from an absolute rate of 36% to an absolute rate of 19%).[101]

Anticoagulation for Valve Operations

Anticoagulation should be started in the early postoperative period for patients who have undergone valve replacement with either a mechanical prothesis or bioprosthesis, and it also should be considered when AF complicates the postoperative course.[102] The recommended approach to anticoagulation differs according to the society making the recommendation. The target INR in all cases is based on the valve type (tissue or mechanical), the valve position (mitral or aortic), and the presence of risk factors (AF, previous thromboembolic event, LV dysfunction, or any hypercoagulable state). The use of antiplatelet agents differs between the North American and European guidelines (Table 37.1)[103] The main difference is the routine use in North America of platelet agents (along with warfarin) for all mechanical valves and bioprosthetic valves, as suggested by the American Heart Association and the American College of Cardiology, whereas the European approach is more conservative, suggesting the use of antiplatelet agents in selected patients with mechanical valves and for only the first 3 months following a tissue valve replacement. Newer-generation heart valves are not as thrombogenic as older mechanical valves, and this feature is reflected in the recommendations. In addition, some newer valves may be even less thrombogenic and may require lower INR targets (1.5–2.0 in the aortic position) with the addition of aspirin.[104]

The decision whether to bridge anticoagulation with unfractionated heparin or low-molecular-weight heparin is based on the type of valve, the patient's risk of bleeding, and the patient's health status. Although the North American and European societies favor bridging with heparin, this strategy has no clear benefits over vitamin K antagonists alone. The use of bridging anticoagulants is more frequently seen with mitral valves or in patients with a history of thromboembolic disease. In patients in unstable condition, in whom repeat operations, insertion of chest tubes, or other bedside procedures such as tracheostomy may be performed, the use of heparin (usually low-molecular-weight heparin) is preferred because this agent can be easily discontinued before the procedure and quickly resumed.

Management of Postoperative Complications

Complications are frequent after cardiac surgical procedures. Although many are short-lived, some complications (eg, stroke) are long-term catastrophic events that seriously affect a patient's functional status (see Chapters 40 and 41). The incidence and predisposing risk factors

TABLE 37.1 Suggested Antithrombotic Therapy for Heart Valve Prophylaxis

		Mechanical Prosthesis				
		Target INR		Bioprosthesis		
Source	*Site*	*No Risk Factors*[a]	*Risk Factors*[a]	*Aspirin*	*3 Months Postoperatively*	*>3 Months Postoperatively*
ESC/EACTS	Aortic	2.5	3.0 or 3.5[b]	Selected[c]	Aspirin or VKA	/
	Mitral	3.0 or 3.5[b]	3.0 or 3.5[b]	Selected[c]	VKA	/
AHA/ACC	Aortic	2.5	3	Systematic	Aspirin or VKA	Aspirin
	Mitral	3	3	Systematic	VKA + aspirin	Aspirin
ACCP	Aortic	2.5	2.5	If low bleeding risk	Aspirin	Aspirin
	Mitral	3	3	If low bleeding risk	VKA + aspirin	Aspirin

[a]Risk factors include atrial fibrillation, previous thromboembolic event, left ventricular dysfunction, hypercoagulable state.
[b]According to whether prosthesis has low or intermediate thrombogenicity.
[c]Patients with concomitant atherosclerotic disease or with thromboembolism despite adequate INR.
ACCP, American College of Chest Physicians; *AHA/ACC,* American Heart Association/American College of Cardiology; *ESC/EACTS,* European Society of Cardiology/European Association of Cardiothoracic Surgeons; *INR,* international normalized ratio; *VKA,* vitamin K antagonist.
Modified from Iung B, Rodes-Cabau J. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. *Eur Heart J.* 2014;35:2942–9.

TABLE 37.2 Common Complications After Heart Operations

Complication	*Incidence Rate*	*Risk Factors*
Stroke	2–4%	Age Previous stroke/TIA PVD Diabetes Unstable angina
Delirium	8–15%	Age Previous stroke Duration of operation Duration of aortic cross-clamp
Atrial fibrillation	≤35%	Age Male sex Previous atrial fibrillation Mitral valve operation Previous CHF Atrial fibrillation Blood transfusion
Renal failure	1%	Low postoperative CO Repeat cardiac operation Valve operation Age Diabetes

CHF, Congestive heart failure; *CO,* cardiac output; *PVD,* peripheral vascular disease; *TIA,* transient ischemic attack.

BOX 37.11 TREATMENT FOR COMPLICATIONS AFTER CARDIAC SURGICAL PROCEDURES

Stroke
- Supportive treatment
- Avoidance of potential aggravating factors (eg, hyperglycemia, hyperthermia, severe anemia)

Delirium
- Usually self-limited
- Close observation required
- Sedatives (midazolam, lorazepam) possibly required

Atrial Fibrillation
- Rate control: calcium channel blockers, β-blockers, digoxin
- Rhythm control: amiodarone, sotalol, procainamide
- Thromboembolic prophylaxis: for atrial fibrillation >48 h

Left Ventricular Dysfunction
- Volume
- Inotropes: epinephrine, milrinone, norepinephrine
- Mechanical support: intraaortic balloon pump

Renal Failure
- Removal of the causative agent (nonsteroidal antiinflammatory drugs, antibiotics)
- Hemodynamic support if necessary
- Supportive care

are well studied for many of these complications (Table 37.2). Many complications have specific management issues that may improve postoperative recovery (Box 37.11).

Stroke

Stroke after cardiac surgical procedures occurs in 2% to 4% of patients and carries a very high 1-year mortality rate of 15% to 30%.[58,105–107] Known risk factors for stroke include age, diabetes, previous history of stroke or transient ischemic attack, peripheral vascular disease, and unstable angina.[58,106] The most common causes are emboli sheared off the aorta during aortic manipulation (proximal anastomosis of the vein grafts, clamping and unclamping of the aorta). However, hemorrhagic and watershed infarcts also occur secondary to the use of large doses of heparin and the frequent occurrence of hypotension during the operation, respectively. AF in the postoperative period also appears to be an important cause of stroke in cardiac surgical patients.[108] Resource use is increased in patients who have a stroke, with prolonged ICU and hospital LOS.[106] Numerous methods of preventing neurologic injury during the intraoperative period have been proposed, including epiaortic scanning, alpha-stat pH management during CABG with CPB, and OPCAB surgery with no-touch surgical techniques.[109–113] Prevention of postoperative neurologic injury may be possible with the aggressive treatment of AF (antiarrhythmic agents, anticoagulants, early cardioversion) to prevent thromboembolism (see the later section on AF). Patients who have an intraoperative stroke should be managed with the goal of preventing further brain injury. Hyperglycemia and hypoglycemia should be avoided because they are associated with poor outcome in brain injured patients.[114–116] Hyperthermia also is known to exacerbate brain injury and should be prevented.[117] Hemoglobin concentrations should be maintained at more than 7 g/dL. Whether maintaining hemoglobin levels greater than 10 g/dL is beneficial is uncertain, but raising the transfusion threshold may be prudent in patients with a perioperative stroke.

Delirium

Delirium is defined generally as an acute transient neurologic condition with impairment of cognitive function, attention abnormalities, and altered psychomotor activity. It often includes a disorder with the sleep/wake cycle. It may manifest as a spectrum from hypoactive delirium, in which the patient presents as listless, uncooperative, and difficult to arouse, to hyperactive delirium, in which the patient is aggressive and agitated. Delirium is fairly common after cardiac operations, with a prevalence rate of 8% to 15%.[118,119] Risk factors associated with delirium include age, previous history of stroke,

duration of the operation, duration of aortic cross-clamp, AF, and blood transfusion.[118–121] Delirium is self-limited and does not adversely affect a patient's outcome or hospital LOS.[120,121]

Prevention and treatment of delirium should focus on reducing or eliminating known predisposing factors. Exposure to benzodiazepines and opioids predisposes patients to delirium. Benzodiazepines should therefore be avoided, and opioids should be limited by adding acetaminophen or other analgesics when appropriate. Sleep/wake cycles are important to prevent delirium. If possible, exposure to sunlight and limits on disturbances at night may improve delirium. Other potentially beneficial interventions include simple measures such as the following: continually reviewing and reinforcing person, time, and place with the patient; removing physical restraints when possible; and encouraging activity and ambulation. Pharmacotherapy for delirium includes the α_2-agonists (dexmedetomidine, clonidine) and the antipsychotic agents (haloperidol, quetiapine, olanzapine, risperidone). The antipsychotic agents are frequently used for delirium, and the prototypical agent is haloperidol. The main concern with the antipsychotic agents is QTc prolongation, which may be additive when other medications such as amiodarone or ciprofloxacin are given. Thus, frequent electrocardiograms are required, especially during initiation of therapy or when a medication known to prolong the QT interval is added. In addition, haloperidol may cause extrapyramidal effects secondary to the blockade of dopamine receptors. All medications must be carefully titrated because delirium by definition has waxing and waning symptoms. Frequently different medications are tried until the patient responds to a particular drug.

Atrial Fibrillation

AF after cardiac surgical procedures is common and occurs in up to 35% of patients.[122] Although the cause of AF is not completely understood, this arrhythmia is associated with increases in death, stroke, and prolonged hospital LOS.[106,108,123] Known risk factors include age, male sex, previous AF, mitral valve operation, and a history of congestive heart failure.[106,124] Prevention and treatment of AF can be achieved effectively with amiodarone, sotalol, magnesium, or β-blockers.[125] Biatrial pacing also may be effective in prophylaxis.[125,126] Management of AF consists of rate control with conversion to sinus rhythm or anticoagulation. Two studies conducted to determine which strategy was superior (Atrial Fibrillation Follow-Up Investigation of Rhythm Management [AFFIRM] and Rate Control Versus Electrical Cardioversion [RACE]) were unable to find a difference between treatment strategies.[127–129]

Rate control may be achieved with a β-blocker or a calcium channel blocker. Digoxin also may be effective, but it is difficult to reach therapeutic levels quickly. An observational review of the AFFIRM trial suggested that β-blockers are superior to either calcium channel blockers or digoxin for rate control in AF.[130] Conversion to sinus rhythm in the patient in stable condition may be achieved with amiodarone, sotalol, or procainamide. Amiodarone is more commonly used in acute management of postoperative AF (150–300 mg, intravenously) than other antiarrhythmic agents, particularly in patients with compromised ventricular function, because it causes little cardiac depression. Finally, persistent AF over 48 to 72 hours requires thromboembolic prophylaxis. Warfarin is recommended for patients at high risk of thromboembolic complications. Patients at high risk are those with a CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, previous stroke or transient ischemic attack, history of vascular disease, age, sex category) score greater than 2. One point is given for each of the following: congestive heart failure, hypertension, diabetes mellitus, age 65 to 74 years, vascular disease, and female sex. Two points are given for patients with previous stroke, transient ischemic attack, or thromboembolism, or age greater than 75 years.[131] Recommendations for anticoagulation should be individualized for each patient based on the risks for thromboembolic complications versus bleeding risk. In general, patients with heart valves should be anticoagulated based on the type of valve after the operation, whereas patients with nonvalvular AF should be anticoagulated based on the CHA_2DS_2-VASC score (Table 37.3).[132] Use of the newer oral anticoagulants is effective to prevent thromboembolism, but lack of effective reversal agents limits the use of these drugs in the ICU setting.

TABLE 37.3 Suggested Atrial Fibrillation Thromboembolic Prophylaxis

	CHA_2DS_2-VASc Score		
Type of AF	*0*	*1*	*≥2*
Valvular	VKA, INR target based on valve	VKA, INR target based on valve	VKA, INR target based on valve
Nonvalvular	None	None, VKA, or NOAC	VKA or NOAC

AF, Atrial fibrillation; *CHA_2DS_2-VASc,* congestive heart failure, hypertension, age, diabetes mellitus, previous stroke or transient ischemic attack, history of vascular disease, age, sex category. *INR,* international normalized ratio; *NOAC,* new oral anticoagulant; *VKA,* vitamin K antagonist.

Data from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014;64:e1–76.

Left Ventricular Dysfunction

Patients with poor left ventricular (LV) function commonly require inotropes or mechanical support after cardiac surgical procedures (see Chapters 11, 28, 36, and 38). Preoperative factors that predict inotrope use in patients undergoing cardiac operations include age, underlying LV dysfunction, and female sex.[133,134] The significance of inotrope use on postoperative outcome is uncertain because some centers routinely use these drugs after CPB.[133] Although pulmonary artery catheters are useful for monitoring trends in cardiac function, transesophageal echocardiography (TEE) provides more detailed information for diagnosing the cause of acute hypotensive episodes and cardiac function. TEE is used commonly in the ICU to assess patients after cardiac operations and has demonstrated efficacy in the diagnosis of cardiac tamponade, cardiac ischemia, and valve dysfunction, thus resulting in improvements in the postoperative course for these patients.[135–138] TEE also provides information on the filling volumes after CPB (see Chapters 13–16).[139–141]

Patients who have an unstable intraoperative course should have filling pressures correlated to TEE findings and the results then passed to the ICU to allow for optimal initial management in the recovery unit. If the patient's condition remains unstable in the ICU, TEE is used and cardiac function is reassessed. When hypovolemia is thought to be the underlying cause of hypotension or low cardiac output, crystalloid may be used to optimize filling. The use of colloids in the critical care setting is controversial given several large trials of starches that showed either little efficacy in volume resuscitation end points and or an increase in adverse events.[142] Therefore intravascular hypovolemia is best treated with the use of intermittent boluses of crystalloid with continuous reassessment of central venous pressure, pulmonary artery pressures, systemic pressures, or LV end-diastolic area.[139] In patients who are actively bleeding or anemic, packed red blood cells may be given to treat the anemia, and fresh-frozen plasma may be used to treat coagulopathy.

If ventricular dysfunction is the main cause of hypotension or a low–cardiac output state, then inotropes and vasopressors should be added (see Chapter 38). Unfortunately, few articles have been published examining the superiority of one inotrope over another. Epinephrine or norepinephrine (0.02–0.04 μg/kg per /min) or dopamine (3–5 μg/kg per min) is commonly used to support patients during removal from CPB and is usually continued into the ICU. If systolic pressure remains low, the epinephrine infusion is usually increased to allow for greater α-receptor action (vasoconstriction). The major disadvantage of epinephrine is the frequent occurrence of lactic acidosis triggered by the agent as a metabolic response, unrelated to hypoperfusion. This response may create confusion about the patient's status if serial arterial lactate determinations are used as a surrogate for adequate perfusion. For patients with low cardiac output

or poor myocardial function noted on TEE, milrinone commonly is used (with or without a full loading dose). Milrinone has the advantage of bypassing β-adrenergic receptors, which are downregulated after cardiac operations.[143] Phosphodiesterase inhibitors appear to improve myocardial performance, especially with the concomitant use of epinephrine.[144] If blood pressure remains low despite this combination therapy, a vasopressin infusion may be started with doses ranging from 1 to 10 U/hour. When volume and medical strategies are insufficient, especially in the presence of ischemic heart disease, mechanical support is added (see Chapters 28 and 36).

IABPs are used in approximately 3% of cardiac surgical patients. The IABP can be placed preoperatively in patients with unstable angina unresponsive to medical treatment, intraoperatively in high-risk patients (redo sternotomy with poor LV function), in patients who fail to wean from CPB, or in patients on maximal inotropic support after CPB. For patients who do not successfully wean from CPB, one retrospective study found 85% success in weaning with the institution of an IABP; however, the overall mortality rate was 35%.[145] Several studies looked at the timing of IABP insertion and found reductions in mortality rates in patients who received the IABP before initiation of CPB.[146–149] Complications from the use of IABP are numerous and include wound site infections, leg ischemia, and renal dysfunction. Several retrospective reviews examined the outcomes after IABP insertion; again, mortality rates were high in patients who received an IABP in the OR or ICU (35%).[150,151]

Right Ventricular Dysfunction

Right ventricular (RV) dysfunction may manifest in patients before cardiac surgical procedures, immediately afterward, or many days after the operation. It is seen commonly in heart transplant recipients, usually secondary to LV failure. It is also seen in patients with pulmonary hypertension, or it may be caused by an RV MI (see Chapters 25 and 26).

RV dysfunction manifests with features of peripheral edema, hypotension, confusion, and abdominal pain or cramping. Liver function test results may be elevated, including INR, aspartate aminotransferase, and alanine aminotransferase. Thus the differential diagnosis frequently includes renal failure, sepsis, bowel ischemia, and liver failure.[152,153]

In patients with invasive monitoring, assessment of RV function may be made indirectly through measurement of central venous pressure, cardiac output, and pulmonary artery pressures. Unless the patient has direct myocardial dysfunction, pulmonary artery pressures are almost always increased. Echocardiography also is useful in assessing patients with suspected RV failure. RV volume overload manifests with an enlarged right ventricle and an associated small and underfilled left ventricle (because of both poor RV output and ventricular interdependence). Tricuspid regurgitation is also frequently present. If the right ventricle also is pressure overloaded, the interventricular septum shifts to the left, and the LV is said to have a D shape. Tricuspid annular-plane systolic excursion (TAPSE) may be helpful in measuring the degree of RV failure.[152–156]

Management of RV failure consists of reducing RV afterload, increasing systemic pressures to prevent RV ischemia, and ensuring adequate RV filling. Volume therapy, although often useful in LV failure and in cases of RV failure associated with normal pulmonary vascular resistance, frequently is detrimental in high-pressure RV failure; caution must be exercised to prevent overloading patients. Inotropes, often in combination with afterload reduction, increase both blood pressure and cardiac output. Norepinephrine, phenylephrine, and vasopressin may all help to increase systemic pressures and thus reduce RV ischemia. Afterload reduction with agents specific to the pulmonary vascular tree also may be beneficial. Nitric oxide and inhaled prostaglandin may be selective for pulmonary vasodilation. Milrinone (0.125–0.5 μg/kg per h) or sildenafil (up to 25 mg orally three times a day) also may be of benefit to reduce pulmonary vascular resistance and improve cardiac output (see Chapters 26, 28, 36, and 38).

In the ICU setting, supportive measures should be instituted, including providing adequate oxygenation, preventing acidosis and atelectasis, and ensuring minimal amounts of ventilatory support to prevent alveolar collapse.

Renal Insufficiency

Renal failure in the postoperative period is rare, occurring in approximately 1% of patients after cardiac surgical procedures (see Chapter 41). Not surprisingly, when it does occur, renal failure prolongs ICU LOS and hospital LOS and increases mortality rates.[59,157] Unfortunately, no clear definition exists for renal impairment or renal failure after CPB. Although the need for dialysis is a straightforward and easily measured outcome, it ignores patients who have reductions in creatinine clearance but do not require dialysis.[59,157] Change in calculated creatinine clearance, which predicts the need for dialysis, prolonged hospital LOS, and death, may be a more suitable outcome measure of renal failure.[158] Several risk factors for postoperative renal failure are recognized, including postoperative low cardiac output, repeat cardiac operation, valve procedures, age older than 65 years, and diabetes.[59,157,159] Management of these patients consists of supportive treatment, determination of the primary cause, and then specific treatment as needed. Supportive treatment consists of ensuring adequate cardiac output, perfusion pressure, and intravascular volume. The cause of renal failure is broadly defined as prerenal, renal, or postrenal. Prerenal causes commonly are related to poor cardiac output or low systemic pressure, and they may be associated with the use of angiotensin-converting enzyme inhibitors and NSAIDs. Renal causes include acute tubular necrosis from an ischemic insult or interstitial nephritis resulting from a host of medications including NSAIDs and antibiotics. Although uncommon in the presence of bladder catheterization, the potential for postrenal obstruction is possible.

Management of renal failure usually requires correction of the underlying problem, which may include improving renal blood flow (volume, inotropes) or discontinuing the offending agent (NSAIDs, antibiotic). To date, no specific treatment exists to prevent acute tubular necrosis. Although dopamine and diuretics were once both thought to be renoprotective, they have not demonstrated efficacy to prevent renal failure.[160] Fenoldopam, a D_1-receptor agonist, may improve renal function in cardiac surgical patients.[161] Investigators suggested that diuretics may be potentially harmful in patients experiencing renal failure.[162] If patients do require dialysis, continuous dialysis may be better than intermittent dialysis.[163] *N*-acetylcysteine has demonstrated efficacy in preventing further renal failure from radiocontrast agents in patients with chronic renal insufficiency.[164] This, however, does not appear to translate to cardiac surgical patients, because several metaanalyses of randomized trials showed little benefit from *N*-acetylcysteine.[164–166]

Postoperative Outcomes

Treatment Options for Coronary Artery Disease

Until the advent of CABG procedures, medical management was the only treatment option for patients with CAD. Today, treatment can be broadly categorized as medical or invasive, with invasive management divided geographically into interventions performed in the cardiac catheterization laboratory or in the OR. Catheterization procedures (percutaneous coronary intervention [PCI]) commonly performed include balloon angioplasty, cardiac stenting, and placement of drug-eluting stents, which release drugs capable of preventing restenosis (see Chapters 3 and 20). Surgical procedures include conventional CABG (with use of CPB) and OPCAB (without use of CPB). OPCAB procedures may be performed through a full sternotomy, a thoracotomy (minimally invasive direct coronary artery bypass), or by using robotically assisted thoracotomy surgery. With the ever-increasing number of available options, it becomes crucial to establish which option is superior with regard to angina recurrence, graft patency, and long-term survival with the least morbidity (MI, stroke, AF) at the lowest

TABLE 37.4 Treatment Options and Outcomes for Coronary Artery Disease

Comparison	*Outcome*	*Revascularization*
Medical vs surgical management	Absolute risk reduction in mortality 5.6% at 5 y 5.9% at 7 y 4.1% at 10 y Benefit of operation greatest in LM, three-vessel disease	37% of medically treated patients converted to surgical treatment
Angioplasty vs surgical management	Absolute risk reduction in mortality 1.9% at 5 y Rates of in-hospital MI and stroke significantly lower in angioplasty group Benefit of operation greatest in diabetes, multivessel revascularization	50% rate of revascularization at 5 y in angioplasty group
Stent vs surgical management	Mortality mixed results, relative reduction ranged from a 50% reduction in favor of CABG to a 75% reduction in favor of stenting MI rates at 1-y equivalent	15–25% rate of revascularization in stent group
OPCAB vs conventional surgical management	No difference in mortality No difference in in-hospital stroke No difference in in-hospital MI	Most OPCAB-treated patients received fewer grafts than CCAB group (0.2 fewer grafts per patient)

CABG, Coronary artery bypass grafting; *CCAB,* conventional coronary artery bypass; *LM,* left main coronary artery disease; *MI,* myocardial infarction; *OPCAB,* off-pump coronary artery bypass.

costs (hospital LOS, ICU LOS, blood transfusions) for each individual patient.

Medical Treatment Versus Surgical Management

Several large randomized trials examined the efficacy of medical versus surgical management in patients with symptomatic CAD (Table 37.4). Most trials were conducted between 1974 and 1984. A metaanalysis published in 1994 incorporated seven trials addressing medical versus surgical management with a 10-year follow-up.[167] Although surgical treatment and medical management have advanced since then (ie, only 9% of patients received internal mammary artery grafts), the findings clearly support the benefits of surgical treatment in high-risk patients. This study reviewed 2600 patients and observed an absolute risk reduction in mortality rates for patients undergoing CABG of 5.6% at 5 years, 5.9% at 7 years, and 4.1% at 10 years. This improvement was most marked in patients with left main CAD, proximal left anterior descending CAD, or triple-vessel CAD. The results tended to underestimate the benefits of surgical treatment because 37.4% of medically treated patients eventually underwent surgical procedures.

CABG procedures reduce mortality significantly compared with medical management alone. This benefit is significantly improved beyond 10 years. In addition, many patients who were initially treated medically eventually require surgical revascularization.

Balloon Angioplasty Versus Conventional Coronary Artery Bypass Graft Procedures

Numerous randomized trials compared percutaneous transluminal coronary angioplasty (PTCA) with CABG (see Chapters 3 and 20). One of the largest trials was the Bypass Angioplasty Revascularization Investigation (BARI), which enrolled 1829 patients who were randomized to undergo either PTCA or CABG.[168] The investigators found no significant differences in survival at both 1 and 5 years, with 5-year survival rates of 89.3% in the CABG group and 86.3% in PTCA group. The rates of in-hospital MI and stroke were greater in the CABG-treated patients compared with the PTCA group (4.6% and 2.1% for Q-wave MI, respectively; $P < 0.01$; 0.8% and 0.2% for stroke, respectively). For patients with diabetes, the 5-year survival rate was 80.6% in the CABG group compared with 65.5% in the PTCA group ($P = 0.003$). The need for repeated revascularization after initial intervention was greater in the PTCA group; at 5 years, only 8% of the patients assigned to CABG had undergone additional revascularization procedures, compared with 54% of those assigned to PTCA (31% of PTCA patients eventually underwent CABG). Several smaller randomized trials found similar results.[169,170]

A metaanalysis of randomized trials was published comparing PTCA with CABG for the management of symptomatic CAD. Thirteen trials involving 7964 patients were included.[171] The investigators reported a 1.9% absolute survival advantage favoring CABG over PTCA at 5 years ($P < 0.02$). No significant difference was noted at 1, 3, or 8 years. In subgroup analysis of patients with multivessel disease, CABG provided a significant survival advantage at both 5 and 8 years. Patients randomized to PTCA had more repeat revascularizations at all time points. This metaanalysis included some coronary stent trials, in which angina recurrence was reduced by 50% at 1 and 3 years, and the stent cohort had a significant decrease in nonfatal MI at 3 years compared with CABG.

These trials focused primarily on patients with multivessel disease. In patients with single-vessel left anterior descending CAD, few randomized trials have been conducted. One trial enrolled 134 patients randomized to PTCA or CABG. After 5 years, 6 patients (9%) had died in the PTCA group versus 2 (3%) in the CABG group (not significant). MI was more frequent after PTCA (15% vs 4%; $P = 0.0001$), but no differences were observed in the rates of Q-wave MI (6% in the PTCA group vs 3% in the CABG group; not significant). Repeat revascularization was required in significantly more patients assigned to the PTCA group (38% vs 9%; $P = 0.0001$).[172]

When compared with coronary angioplasty, CABG procedures reduce mortality rates at 5 years. CABG also reduces the need for additional revascularization procedures. This benefit is greatest in patients with multivessel disease or diabetes.

Stenting Versus Conventional Coronary Artery Bypass Graft Procedures

The SYNTAX trial, first published in 2009, randomized patients with left main CAD or three-vessel CAD to undergo either operation or PCI with a Taxus (Boston Scientific, Natick, Mass) drug-eluting stent. Overall, the study found similar outcomes at 5 years between patients who underwent stenting or surgical treatment, with slightly higher rates of stroke (1.5% vs 4.3%; hazard ratio: 0.33; 95% confidence interval [CI]: 0.12–0.92) in surgical patients. In patients with more complex lesions (as defined by a SYNTAX score >33), however, surgical treatment was clearly superior. The major adverse cardiac and cerebral events (MACCE) rate at 5 years in the cohort with a SYNTAX score greater than 33 was 29.7% for CABG versus 46.5% for PCI-treated patients (hazard ratio: 1.78; 95% CI: 1.21–2.63). This trial changed previously held beliefs in two ways. First, PCI was found to be suitable for patients with left main CAD, which was previously believed to be best managed surgically. Second, patients with three-vessel CAD and complex lesions did much better with surgical treatment than with PCI, for which previous data had been equivocal. For patients with less complex lesions (SYNTAX score <33) the MACCE outcome of death was higher for CABG, whereas revascularization was higher in PCI-treated patients, specifically the need for CABG.[173]

Off-Pump Coronary Artery Bypass Versus Coronary Artery Bypass Graft Procedures

The use of OPCAB techniques has increased in popularity. However, the net effect has been to see the technique become standard of care in some countries, such as India, while waning in popularity in others, such as in North America and Europe, where it has remained at approximately 20% to 30% of cases of CABG.[174] A comprehensive metaanalysis of randomized trials published in 2004 suggested that OPCAB reduces the rate of blood transfusion, AF, infections, and resource use (hospital LOS, ICU LOS, and ventilation time).[175] Unfortunately, the main hope of improvements in neurologic outcome, stroke, and cognitive

dysfunction has proved elusive. In addition, concern was raised over the quality of the anastomosis, especially in trials involving institutions that were low-volume or teaching OPCAB centers.[176,177] Concern has also been raised over the reduction in the number of grafts completed in the OPCAB arm of many randomized trials, a factor that may lead to a reduction in long-term survival.[178,179]

Taken together, the potential benefits of OPCAB procedures may rest with the experience of the center performing the procedure. As with many cardiac surgical procedures, this raises the issue of dedicated care teams to look after patients who require cardiac surgical interventions. Certain surgical approaches (no-touch aortic technique) or medical conditions (calcified ascending aorta) may make an OPCAB approach desirable. However, changing the surgical approach by itself may not reduce mortality or major morbidity rates in most patients.

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38

Postoperative Cardiovascular Management

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KEY POINTS

1. Maintaining oxygen transport and oxygen delivery appropriately to meet the tissue metabolic needs is the goal of postoperative circulatory control.
2. Cardiac function worsens after cardiac surgical procedures. Therapeutic approaches to reverse this dysfunction are important and often can be discontinued in the first few postoperative days.
3. Myocardial ischemia often occurs postoperatively, and it is associated with adverse cardiac outcomes. Multiple strategies have been studied to reduce this complication.
4. Postoperative biventricular dysfunction is common. It requires interventions to optimize the heart rate and rhythm, provide acceptable preload, and adjust afterload and contractility. In most patients, pharmacologic interventions can be rapidly weaned or stopped within the first 24 hours postoperatively.
5. Supraventricular tachyarrhythmias are common in the first postoperative days, with atrial fibrillation predominating. Preoperative and immediate postoperative pharmacotherapy can reduce the incidence and slow the ventricular response.
6. Postoperative hypertension has been a common complication of cardiac surgical procedures; newer vasodilator drugs are more arterial selective and allow greater circulatory stability than older, nonselective drugs.
7. Catecholamines, phosphodiesterase inhibitors, and the calcium sensitizer levosimendan have been studied for treating biventricular dysfunction.
8. Phosphodiesterase inhibitors and levosimendan are clinically effective inodilators that have important roles in patients with low cardiac output and biventricular dysfunction.
9. Long cardiopulmonary bypass times may cause a refractory vasodilated state ("vasoplegia") requiring combinations of pressors such as norepinephrine and vasopressin.
10. Positive-pressure ventilation has multiple effects on the cardiovascular system, with complex interactions that should be considered in patients after cardiac surgical procedures.
11. Critical care management of patients undergoing transcatheter aortic valve replacement who have experienced intraoperative complications includes understanding and managing the postoperative consequences of iatrogenic vascular injuries, stroke, significant paravalvular leaks, and/or cardiac conduction abnormalities.
12. Hemodynamic management after cardiothoracic operations may benefit from the use of transesophageal echocardiography to determine myocardial function and assess cardiovascular structures. Echocardiography is particularly helpful in the diagnosis of causes of obstructive shock, including pericardial effusions leading to tamponade physiology.
13. Echocardiography during the daily management of both venovenous and venoarterial extracorporeal membrane oxygenation (ECMO) may improve diagnosis of hemodynamic instability, troubleshoot common problems encountered during ECMO management, and aid in weaning the patient from mechanical support.

Postoperative cardiovascular dysfunction is becoming more common as older and increasingly critically ill patients undergo cardiac surgical procedures. Biventricular dysfunction and circulatory changes occur after cardiopulmonary bypass (CPB), but they can also occur in patients undergoing off-pump procedures. Pharmacologic therapy with suitable monitoring and mechanical support may be needed for patients in the postoperative period until ventricular or circulatory dysfunction improves. This chapter reviews management considerations of patients with postoperative circulatory failure.

Oxygen Transport

Maintaining oxygen transport (ie, oxygen delivery [Do_2]) satisfactory to meet the tissue metabolic needs is the goal of postoperative circulatory control. Oxygen transport is the product of cardiac output (CO) times arterial content of oxygen (Cao_2) (ie, hemoglobin concentration × 1.34 mL of oxygen per 1 g of hemoglobin × oxygen saturation [Sao_2]), and it can be affected in many ways by the cardiovascular and respiratory systems, as shown in Fig. 38.1. Low CO, anemia from

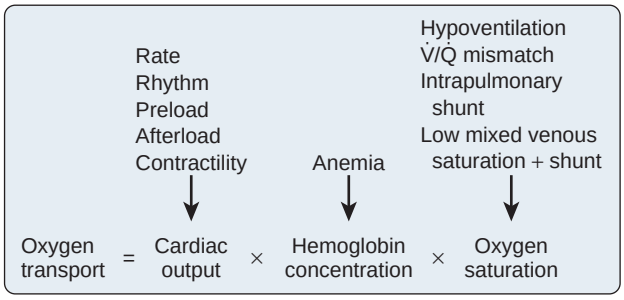


Fig. 38.1 Important factors that contribute to abnormal oxygen transport. $\dot{V}/\dot{Q}$, Ventilation/perfusion.

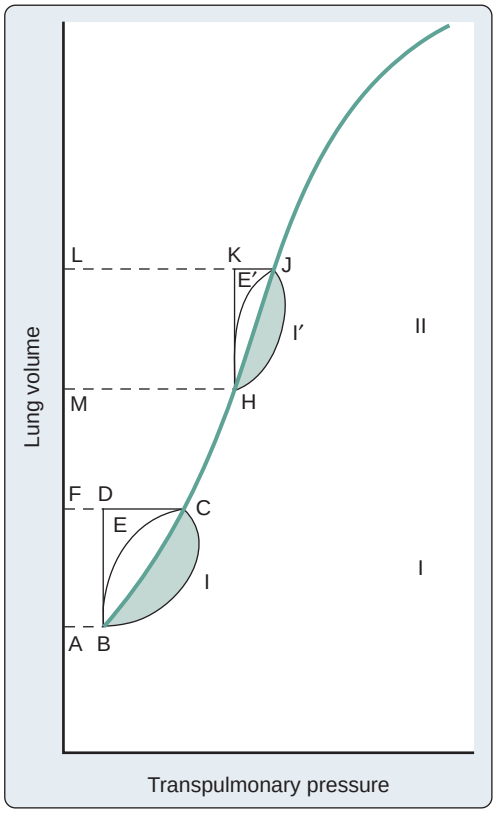


Fig. 38.2 Pressure-volume diagram of elastic and resistive (nonelastic) work done on noncompliant lungs. Breathing at ambient airway pressure and low lung volume (by T tube) *(I)* versus breathing with continuous positive airway pressure (CPAP) at increased lung volume *(II)*. *Solid line, BCHJ* is the elastic pressure-volume curve for the lung, determined by measuring transpulmonary pressures at the instant of zero flow. *Hatched areas* represent nonelastic work (*BIC* and *HI′J*), whereas elastic work is represented by *BCD* and *HJK*. With CPAP, both types of work are reduced. Without CPAP, the area *ABD*F is additional elastic work partly done by the patient and partly by elastic recoil of the chest wall, whereas with CPAP, the additional work represented by *MHKL* is mostly done by the CPAP system. *(From Katz JA, Marks JD. Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure.* Anesthesiology. *1985;63:598.)*

blood loss, and pulmonary disease can decrease D_{O_2}. Before altering the determinants of CO, including the inotropic state of the ventricles, an acceptable hemoglobin concentration and adequate Sa_{O_2} should be provided, thus enabling increases in CO to supply the maximum available D_{O_2}. As hemoglobin concentration increases, so does blood viscosity and therefore the work of the heart to eject the blood. In normal hearts (eg, athletes), increasing hemoglobin levels to supranormal increases performance, a finding suggesting that in this setting the increased viscosity is less important than the elevated oxygen-carrying capacity.[1] This issue has not been examined in patients with cardiac disease. Model analysis of data from animal investigations suggested that maintenance of the hematocrit between 30% and 33% provides the best balance between oxygen-carrying capacity and viscosity.[2] This analysis also suggested that in ischemic states a hematocrit in this range may be desirable. Patients needing continued inotropic or mechanical support of ventricular function beyond the first few postoperative hours, especially patients in need of intravascular volume expansion, should probably be transfused to a hematocrit in this range, bearing in mind that blood transfusion has been associated with decreased organ function and increased mortality rates in critically ill patients. Randomized trials suggested that a transfusion threshold of 7 g, rather than 9 g, was associated with at least equivalent outcomes in critically ill patients who did not have acute myocardial infarction (MI) or unstable angina.[3–5] These studies did not identify cohorts of patients who had undergone cardiac surgical procedures. Wu and colleagues[5] found that transfusion for a hematocrit of 30% or lower in older patients with acute MI was associated with a better outcome. This study supports the concept that this is the desirable hematocrit especially in older cardiac surgical patients or in patients experiencing a complicated course.

Hypoxemia from any cause reduces D_{O_2}, and acceptable arterial oxygenation (partial arterial pressure of oxygen [Pa_{O_2}]) may be achieved with the use of an elevated inspired oxygen fraction (F_{IO_2}) or positive end-expiratory pressure (PEEP) in the ventilated patient. Use of PEEP or continuous positive airway pressure (CPAP) in the spontaneously breathing patient may improve Pa_{O_2} by reducing intrapulmonary shunt; however, venous return may be reduced, causing a decrease in CO, with DO_2 decreased despite an increased Pa_{O_2}.[6] It is important to measure CO as PEEP is applied. Intravascular volume expansion may be used to offset this damaging effect of PEEP[7] (see Chapter 39).

In patients with marginal arterial oxygenation, pulmonary function must be closely monitored to allow prompt therapy to be undertaken for abnormalities. Measurements of airway resistance and respiratory system compliance should be made. When resistance is increased, treatment of bronchospasm may improve the Pa_{O_2} and CO because decreases in intrathoracic pressure improve venous return. Treatment of lung overinflation may decrease pulmonary vascular resistance (PVR) and benefit right ventricular (RV) function.[8] If compliance is decreased, application of PEEP or CPAP may help promote reexpansion of atelectatic areas and move the tidal volume to a more compliant section of the pressure-volume relationship of the respiratory system[9] (Fig. 38.2). This approach reduces the work expended by the patient during spontaneous efforts and may reduce PVR.[10]

Unexplained hypoxemia may be caused by right-to-left intracardiac shunting, most commonly by a patent foramen ovale. This situation is most likely to occur when right-sided pressures are abnormally increased; an example is the use of high levels of PEEP.[11] If this condition is suspected, echocardiography should be performed, and therapy to reduce right-sided pressures should be initiated.

Patients with pulmonary disease may experience dramatic worsening of oxygenation when vasodilator therapy is started because of release of hypoxic vasoconstriction in areas of diseased lung.[12] Although CO may be increased, the worsening in Ca_{O_2} results in a decrease in D_{O_2}. Reduced doses of direct-acting vasodilators or trials of different agents may be indicated.

When D_{O_2} cannot be increased to an acceptable level as judged by decreased organ function or development of lactic acidemia, measures to decrease oxygen consumption ($\dot{V}_{O_2}$) may be taken while awaiting improvement in cardiac or pulmonary function. For example, sedation and paralysis may buy time to allow reversible postoperative myocardial dysfunction to improve.

Temperature

Patients are often admitted to the intensive care unit (ICU) after cardiac operations with core temperatures lower than 35°C, especially after off-pump cardiac surgical procedures. The typical pattern of temperature change during and after cardiac operations and the hemodynamic outcomes are illustrated in Fig. 38.3. Decreases in temperature after CPB occur in part because of redistribution of heat within the body and in part because of heat loss. Previous reports found that administration of nitroprusside and the use of high flows (>2.2 L/m^2 per min) during rewarming on CPB could improve the uniformity of rewarming and reduce this afterdrop from 4°C to approximately 2°C.[13] Monitoring of body sites other than the blood and brain (eg, urinary bladder, tympanic membrane temperatures) can help provide more complete rewarming, but the body temperature usually falls after CPB, especially when difficulties are encountered and the chest remains open for an extended period; in such cases, some degree of hypothermia is an almost unavoidable result.[14,15] Intraoperative use of forced-air warming blankets or cutaneous gel pads[16] can help reduce the temperature loss during and after surgical procedures.

The normal thermoregulatory and metabolic responses to hypothermia remain intact after cardiac operations and result in peripheral vasoconstriction that contributes to the hypertension commonly seen early in the ICU.[17] As temperature decreases, CO is decreased because of bradycardia, whereas oxygen consumed per beat is actually increased.[18] Coagulation, platelet, and immune functions are also impaired by hypothermia to potentiate postoperative bleeding and infection.[19–21] Another adverse consequence of postoperative hypothermia is a large increase in ($\dot{V}O_2$ and carbon dioxide production during rewarming.[22] When patients cannot increase CO (ie, DO_2), the effects of this large increase in ($\dot{V}O_2$ include mixed venous desaturation and metabolic acidosis. Unless end-tidal carbon dioxide is monitored or arterial blood gases are analyzed often to show the increased carbon dioxide production and to guide increases in ventilation, hypercarbia will occur, causing catecholamine release, tachycardia, and pulmonary hypertension.[23] The effects of rewarming are most intense when patients shiver.[24] Shivering may be effectively treated with meperidine, which lowers the threshold for shivering. Muscle relaxation may provide more stable hemodynamic conditions than meperidine, but accompanying sedation must be administered to avoid having an awake and paralyzed patient.[25,26]

As the temperature rises, usually to approximately 36°C, vasoconstriction and hypertension are replaced by vasodilation, tachycardia, and hypotension, even without hypercarbia. Often, over minutes, a patient who needs vasodilators for hypertension then requires vasopressors or large volumes of fluid for hypotension. Volume loading during the rewarming period can help to reduce the rapid swings in blood pressure (BP) that may occur. It is important to recognize when these changes result from changes in body temperature, to avoid attributing them to other processes that may call for different therapy.

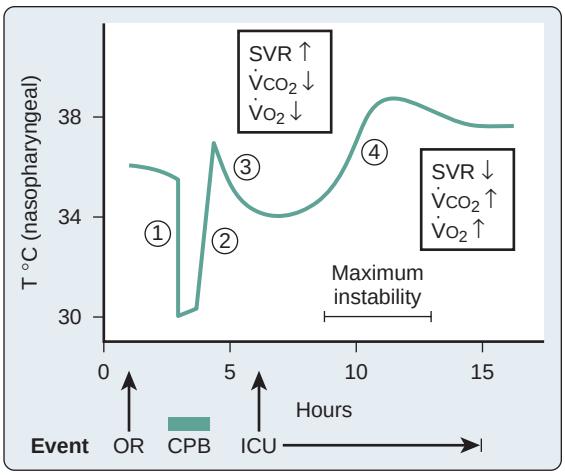


Fig. 38.3 Nasopharyngeal temperature during and after cardiac surgical procedures. *(1)* Core (ie, blood) cooling on cardiopulmonary bypass *(CPB). (2)* Core warming on CPB. *(3)* Afterdrop in temperature *(T)* after separation from CPB. *(4)* Rewarming after admission to the intensive care unit *(ICU).* Systemic vascular resistance *(SVR)* is increased, and carbon dioxide production *($\dot{V}CO_2$)* and oxygen consumption *($\dot{V}O_2$)* are decreased on admission to the ICU because of residual hypothermia. During rapid rewarming, SVR decreases and $\dot{V}CO_2$ and $\dot{V}O_2$ increase; these changes can cause marked cardiac and ventilatory instability. *OR,* Operating room. *(From Sladen RN. Management of the adult cardiac patient in the intensive care unit. In: Ream AK, Fogdall RP, eds.* Acute Cardiovascular Management: Anesthesia and Intensive Care. *Philadelphia: Lippincott; 1982:495.)*

Assessment of the Circulation

Physical Examination

Surgical dressings, chest tubes attached to suction, fluid in the mediastinum and pleural spaces, peripheral edema, and temperature gradients can distort or mask information obtained by the classic techniques of inspection, palpation, and auscultation in the postoperative period. However, the physician should not be deterred from applying these basic techniques in view of their potential benefit. Physical examination may be of great value in diagnosing gross or acute disease, such as pneumothorax, hemothorax, or acute valvular insufficiency, but it is of limited value in diagnosing and managing ventricular failure. For example, in the critical care setting, experienced clinicians (eg, internists) using only physical findings often misjudge cardiac filling pressures by a large margin.[27] Low CO in particular is not consistently recognized by clinical signs, and systemic BP does not correlate with CO after cardiac surgical procedures. Oliguria and metabolic acidosis, classic indicators of a low CO, are not always reliable because of the polyuria induced by hypothermia, oxygen debts induced during CPB that cause acidosis, and medications or fluids given during or immediately after bypass.[28]

Although clinicians are taught that the adequacy of CO can be assessed by the quality of the pulses, capillary refill, and peripheral temperature, no relationship exists between these indicators of peripheral perfusion and CO or calculated systemic vascular resistance (SVR) in the postoperative period.[29] By the first postoperative day, a crude correlation exists between peripheral temperature and cardiac index ($r = -0.60$). Many patients arrive in the ICU in a hypothermic state, and residual anesthetic agents can decrease the threshold for peripheral vasoconstriction in response to this condition.[30] A patient's extremities may therefore remain warm despite a hypothermic core or a decreasing CO. Even after temperature stabilization on the first postoperative day, the relationship between peripheral perfusion and CO is too crude to be used for hemodynamic management.

Invasive Monitoring

Concepts regarding invasive monitoring with a pulmonary artery catheter (PAC) have been modified as a result of several studies in a variety of settings that failed to show a benefit from PAC use. In addition, a poor relationship exists between filling pressures and end-diastolic volume, stroke volume (SV), or volume responsiveness. A review of patients admitted to medical ICUs in the United States demonstrated a reduction of more than 40% in PAC use from 1993–2004.[31] The same trend was evident in surgical patients, including those undergoing cardiac operations. PAC use also has decreased in cardiac surgical patients in many other countries. Greater availability of high-quality bedside echocardiography, often performed by intensivists, has made this modality a technique of choice in the postoperative period and has replaced or decreased PAC use in some centers. Measures of volume responsiveness in mechanically ventilated patients such as pulse pressure or SV variability (from arterial waveform analysis devices) are

widely recognized as more sensitive and specific indicators of the need for intravascular volume expansion than filling pressures.[32]

Despite the lack of a proven benefit with PAC use, many patients continue to have this monitor placed for cardiac surgical procedures. Cardiac anesthesiologists believe that the lack of evidence about the PAC may reflect the lack of a modern, well-designed randomized trial. That no such trials have been conducted in cardiac surgical patients probably attests to the reluctance of cardiac surgeons and anesthesiologists to manage their patients without what they consider to be important information. Postoperatively, many cardiac surgical centers do not have in-house physicians, and surgeons believe that the "objective" PAC data obtained over the telephone is valuable. As less invasive tools such as echocardiography or arterial waveform analysis devices become better known and more readily available, it seems likely that PAC use will diminish further in cardiac surgical patients.

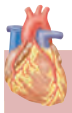
Specialized PACs permit continuous mixed venous oxygen saturation ($S\bar{v}O_2$) monitoring, continuous CO measurement, and calculation of RV volumes and ejection fraction (EF), or they have either imbedded electrodes or channels to pass atrial or ventricular pacing wires. The ability to pace through a PAC is particularly valuable in patients undergoing "minimally invasive" procedures in which the surgeon does not have adequate access to the heart to place epicardial leads. The $S\bar{v}O_2$ catheter helps evaluate the adequacy of DO_2 and allows continuous assessment of the response to therapy, which may affect DO_2 or $\dot{V}O_2$ (eg, PEEP therapy). The trend in the $S\bar{v}O_2$ may function as an early warning signal of worsening in the oxygen supply-demand relationship as DO_2 falls or $\dot{V}O_2$ increases. In the postoperative period, the $S\bar{v}O_2$ does not correlate with CO, because CO is only one of the factors in the oxygen supply-demand relationship.[33]

Echocardiography

Echocardiography is the technique of choice for acute assessment of cardiac function. Just as transesophageal echocardiography (TEE) has become essential for intraoperative management in various conditions, several studies document its utility in the postoperative period in the presence and absence of the PAC.[34–38] It provides information that may lead to urgent surgery or prevent unnecessary surgery, gives important information about cardiac preload, and can detect acute structural and functional abnormalities. Although transthoracic echocardiography (TTE) can be performed more rapidly in this setting, satisfactory images can be obtained only in about 50% of patients in the ICU[39] (see Chapters 14–16). A small lumen single plane disposable echocardiography device, Imacor, has been developed for use up to 72 hours for ICU management (see later).

Postoperative Myocardial Dysfunction

Studies using hemodynamic, nuclear scanning, and metabolic techniques have documented worsening in cardiac function after coronary artery bypass grafting (CABG) procedures.[40–53] Although improvements in myocardial protection, surgical techniques, and operative care have been reported, similar incidences of early biventricular dysfunction (90%) were reported between 1979 and 1990. All these studies showed significant declines in left ventricular (LV) or biventricular (when measured) function in the first postoperative hours, with a gradual return to preoperative values by 8 to 24 hours. In one study, this decline was evident only in one-half of the patients,[44] but in the other studies, more than 90% of patients showed at least a transient decrease in function. Decreased ventricular performance at normal or elevated filling pressures occurs, suggesting decreased contractility. Similarly, "flattening" of the ventricular function curves is usually obvious; this finding suggests that preload expansion greater than 10 mm Hg for central venous pressure (CVP) or 12 mm Hg for pulmonary capillary wedge pressure (PCWP) is of little benefit. In the classic study by Mangano,[45] patients with an LVEF of less than 0.45 or ventricular dyssynergy showed more marked and prolonged dysfunction than did those patients with normal ventricles.



BOX 38.1 RISK FACTORS FOR LOW CARDIAC OUTPUT SYNDROME AFTER CARDIOPULMONARY BYPASS

- Preoperative left ventricular dysfunction
- Valvular heart disease requiring repair or replacement
- Long aortic cross-clamp time and total cardiopulmonary bypass time
- Inadequate cardiac surgical repair
- Myocardial ischemia and reperfusion
- Residual effects of cardioplegia solution
- Poor myocardial preservation
- Reperfusion injury and inflammatory changes

Satisfactory myocardial protection is important to prevent postoperative dysfunction. In off-pump surgical procedures, the idea is to preserve coronary perfusion, but during mechanical manipulation, changes in CO and BP occur. For CABG with CPB, most surgeons use some combination of hypothermia and crystalloid or blood cardioplegia to arrest the heart and reduce its metabolism. Although little consensus exists that any one technique is preferable in all circumstances, cold intermittent crystalloid cardioplegia with systemic hypothermia is the most widely used technique clinically. Salerno and associates[54] recommended continuous, warm, retrograde blood cardioplegia without systemic hypothermia, and Mullen and colleagues[50] suggested that blood cardioplegia had at least a short-term benefit with less myocardial damage and better function; however, other studies of blood cardioplegia have had mixed results[47–52] (see Chapters 31 and 32).

Other proposed factors that contribute to postoperative ventricular dysfunction include myocardial ischemia,[55] residual hypothermia,[46,47] preoperative medications such as β-adrenergic antagonists,[53] and ischemia-reperfusion injury (Box 38.1). Inflammatory cell activation from cytokine generation, upregulation of neutrophil adhesion molecules with neutrophil activation, oxygen free radical formation, and lipoperoxidation after ischemia-reperfusion injury may be important pathways accounting for the dysfunction. Multiple studies showed the importance of limiting myocardial ischemia-reperfusion injury.[56,57] Briesblatt and associates[40] observed the timing of ventricular dysfunction and showed that recovery after CPB for CABG was similar to what had been suggested in animal models of reperfusion injury.[58–60] This nadir at 4 hours corresponds to the peak in cytokine levels. Cytokines can release nitric oxide (NO) from endothelium that produces myocardial depression. Studies evaluating complement inhibition with pexelizumab in improving outcomes described a novel strategy that unfortunately was never approved despite promising results[61] (see Chapter 9).

Postoperative Myocardial Ischemia

Although intraoperative myocardial ischemia has often been a focus, studies showed that ischemia frequently occurs postoperatively and is associated with adverse cardiac outcomes. Leung and colleagues[55] found the electrocardiographic (ECG) and segmental wall motion abnormality (SWMA) evidence of ischemia early postoperatively in up to 40% of patients undergoing CABG procedures. Postbypass SWMAs were significantly associated with adverse outcomes (eg, MI, death) (Fig. 38.4). Surprisingly, these abnormalities most often appeared in the regions of the heart that had been revascularized. Hemodynamic changes rarely preceded ischemia; however, postoperative heart rates (HRs) were, as reported in other studies, significantly higher than intraoperative or preoperative values. Jain and associates[62] found major ECG changes in the 8 hours after cross-clamp release in 58% of CABG-treated patients, and these changes were independent predictors of perioperative MI. Whether such changes occur because of operation and reperfusion or as a result of events after CPB is not known. These

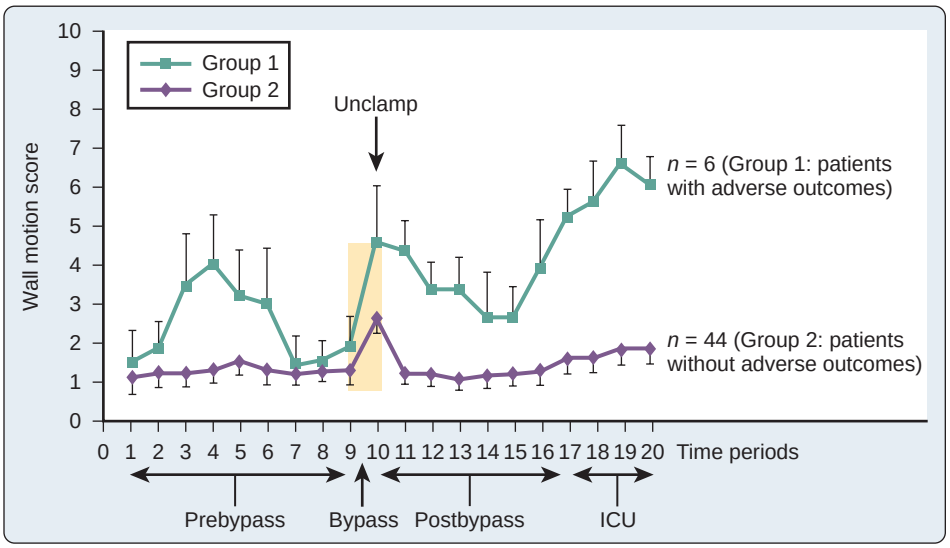


Fig. 38.4 Sequential changes in wall motion score, as measured by transesophageal echocardiography, in patients undergoing elective coronary artery bypass grafting. Score is defined as follows: 0, normal; 1, mild hypokinesis; 2, severe hypokinesis with myocardial thickening; 3, akinesis; and 4, dyskinesis. Adverse outcomes were myocardial infarction, death, or congestive heart failure. The time periods were as follows: 1, after tracheal intubation; 2, before incision; 3, after incision; 4, before sternotomy; 5, after sternotomy; 6 and 7, internal mammary dissection; 8, after pericardiotomy; 9, immediately before bypass; 10, unclamping of aortic side clamp; 11 to14, off bypass; 15, after chest closure; 16, skin closure; 17 to 20, intensive care unit *(ICU)* for the first 4 hours. The *shaded area* indicates the bypass period. *(From Leung JM, O'Kelly B, Browner WS, et al. Prognostic importance of postbypass regional wall motion abnormalities in patients undergoing coronary artery bypass graft surgery.* Anesthesiology. *1989;71:16.)*

findings do suggest that monitoring for ischemia must continue after revascularization. It may be that early recognition and treatment of ischemia or prophylactic medication can help prevent or reduce myocardial ischemia and dysfunction after CABG procedures (see Chapters 7, 11–15, and 20).

Early recovery, or fast-tracking, of the cardiac surgical patient has led to some concern that ischemia will occur as patients awaken early after the operation in pain, especially because Mangano and colleagues[63] showed that sedation with a sufentanil infusion could reduce ischemia in this period. A randomized study by Cheng and associates[64] reduced this concern because awakening and extubation within 6 hours of CABG were not associated with more creatine kinase MB isoenzyme (CK-MB) release or ECG changes than overnight ventilation. Wahr and colleagues[65] showed that even with the use of propofol sedation, hemodynamic episodes (significant changes in HR and BP) are common in the 12 hours after surgical procedures, and ST-segment changes occur in 12% to 13% of patients.

Therapeutic Interventions

Therapeutic interventions for postoperative biventricular dysfunction include the standard concerns of managing low-CO states by controlling the HR and rhythm, providing an acceptable preload, and adjusting afterload and contractility. In most patients, pharmacologic interventions can be rapidly weaned or stopped within the first 24 hours postoperatively.

Postoperative Arrhythmias

Patients with preoperative or newly acquired noncompliant ventricles need a correctly timed atrial contraction to provide satisfactory ventricular filling, especially when they are in sinus rhythm preoperatively. Although atrial contraction provides approximately 20% of ventricular filling, this may be more important in postoperative patients, when ventricular dysfunction and reduced compliance may be present. For example, in medical patients with acute MI, atrial systole contributed 35% of the SV.[66] The SV is often relatively fixed in patients with ventricular dysfunction, and the HR is an important determinant of CO. Rate and rhythm disorders must be corrected when possible, using epicardial pacing wires. Approaches to postoperative rate and rhythm disturbances are shown in Table 38.1. The use of a PAC with atrial or ventricular pacing electrodes or lumina for pacing wires can facilitate

TABLE 38.1 Postoperative Rate and Rhythm Disturbances

Disturbance	*Usual Causes*	*Treatments*
Sinus bradycardia	Preoperative or intraoperative β-blockade	Atrial pacing, β-agonist, anticholinergic
Heart block (first, second, and third degree)	Ischemia Surgical trauma	Atrioventricular sequential pacing Catecholamines
Sinus tachycardia	Agitation or pain Hypovolemia Catecholamines	Sedation or analgesia Volume administration Change or discontinuance of drug
Atrial tachyarrhythmias	Catecholamines Chamber distention Electrolyte disorder (hypokalemia, hypomagnesemia)	Change or discontinuance of drug Treatment of underlying cause (eg, vasodilator, diuresis, potassium or magnesium administration) May require synchronized cardioversion or pharmacotherapy
Ventricular tachycardia or fibrillation	Ischemia Catecholamines	Cardioversion Treat ischemia, may require pharmacotherapy Change or discontinuance of drug

temporary pacing if epicardial wires are not functioning. Failing that, temporary transvenous pacing wires can be placed if needed, and they are often required with the increasing use of minimally invasive cardiac surgical techniques (see Chapters 5 and 21).

Later in the postoperative period (days 1 through 3), supraventricular tachyarrhythmias become a major problem, with atrial fibrillation (AF) predominating. The overall incidence is between 30% and 40%, but with increasing age and valvular surgical procedures, the incidence may be in excess of 60%.[67] Many reasons are recognized for this development, including inadequate intraoperative atrial protection, electrolyte abnormalities, change in atrial size with fluid shifts, epicardial inflammation, stress, irritation, and genetic factors.[68] Randomized trials of off-pump CABG found a similar incidence of postoperative AF compared with on-pump CABG.[69,70]

Advanced age, a history of AF, and valvular heart operations are the most consistently identified risk factors for AF.[68] Because AF is difficult to treat and potentially increases the duration and cost of hospitalization, great interest has been expressed in effective therapy and prophylaxis.[67] Many studies showed that β-blockade significantly reduces the incidence of postoperative AF and that withdrawal of β-blockers in patients receiving them preoperatively is an important risk factor. Guidelines published by the American Heart Association, the American College of Cardiology, and the North American Society of Pacing and Electrophysiology recommended administration of β-blockers to prevent postoperative AF if the patient has no contraindications to this therapy.[71] Sotalol, which has some class III actions, is also effective[72] (see Chapters 4, 5, and 11).

Multiple studies examined the use of amiodarone for prophylaxis or treatment. Intravenous amiodarone is most often used in clinical practice because "acute" loading with oral therapy is often not feasible. Two pivotal studies of amiodarone deserve mention.

In the PAPABEAR (Prophylactic Oral Amiodarone for the Prevention of Arrhythmias That Begin Early After Revascularization, Valve Replacement, or Repair) study, oral amiodarone (10 mg/kg daily) or placebo was given from 6 days before the operation through 6 days postoperatively (13 days).[73] Atrial tachyarrhythmias occurred in fewer amiodarone-treated patients (48 of 299; 16.1%) than in placebo-treated patients (89 of 302; 29.5%) overall; in patients younger than 65 years of age (19 [11.2%] vs 36 [21.1%]; in patients >65 years old (28 [21.7%] vs 54 [41.2%]); in patients who had CABG only (22 [11.3%] vs 46 [23.6%]); in patients who had valve replacement or repair (25 [23.8%] vs 44 [44.1%]); in patients who received preoperative β-blocker therapy (27 [15.3%] vs 42 [25.0%]); and in patients who did not receive preoperative β-blocker therapy (20 [16.3%] vs 48 [35.8%]), respectively. Postoperative sustained ventricular tachyarrhythmias also occurred less frequently in amiodarone-treated patients (1 of 299; 0.3%) than in placebo-treated patients (8 of 302; 2.6%) ($P = .04$).

In another study, Guarnieri and associates[74] evaluated 300 patients randomized in a double-blind fashion to intravenous amiodarone (1 g/day for 2 days) or to placebo immediately after cardiac surgical procedures. The primary end points of the trial were incidence of AF and length of hospital stay. AF occurred in 67 (47%) of 142 patients receiving placebo versus 56 (35%) of 158 patients receiving amiodarone ($P = .01$). Length of hospital stay for the placebo-treated group was 8.2 ± 6.2 days, and it was 7.6 ± 5.9 days for the amiodarone-treated group.

After AF or other supraventricular arrhythmias develop, treatment is often urgently needed for symptomatic relief or hemodynamic benefit. The longer a patient remains in AF, the more difficult it may be to convert the rhythm, and the greater is the risk for thrombus formation and embolization.[68,72] Treatable underlying conditions such as electrolyte disturbances or pain should be corrected while specific pharmacologic therapy is being instituted. Paroxysmal supraventricular tachycardia (uncommon in this setting) can be abolished or converted to sinus rhythm by intravenous adenosine, and atrial flutter can sometimes be converted by overdrive atrial pacing with temporary wires placed at the time of operation. Electrical cardioversion may be needed if hypotension is caused by the rapid HR; however, atrial arrhythmias tend to recur in this setting.[67] Rate control for AF or atrial flutter can be achieved with various atrioventricular nodal blocking drugs, and conversion is facilitated by many of these drugs as well. Table 38.2 summarizes the various treatment modalities for supraventricular arrhythmias. If conversion to sinus rhythm does not

TABLE 38.2 Treatment Modalities for Supraventricular Arrhythmias

Treatment	*Specifics*[a]	*Indications*
Overdrive pacing by atrial wires[b]	Requires rapid pacer (≤800/min); start above arrhythmia rate and slowly decrease	PAT, atrial flutter
Adenosine	Bolus dose of 6–12 mg; may cause 10 s of complete heart block	AV nodal tachycardia, bypass-tract arrhythmia, atrial arrhythmia diagnosis
Amiodarone	150 mg IV over 10 min, followed by infusion	Rate control or conversion to NSR in atrial fibrillation or flutter
β-Blockade	Esmolol, up to 0.5 mg/kg load over 1 min, followed by infusion if tolerated	Rate control or conversion to NSR in atrial fibrillation or flutter
	Metoprolol, 0.5–5 mg, repeat effective dose q4–6h	Rate control or conversion to NSR in atrial fibrillation or /flutter
	Propranolol, 0.25–1 mg; repeat effective dose q4h[c]	
	Labetalol, 2.5–10 mg; repeat effective dose q4h[c]	Conversion of atrial fibrillation or flutter to NSR
	Sotalol, 40–80 mg PO q12h	Conversion of PAT to NSR
Ibutilide	1 mg over 10 min; may repeat after 10 min	Rate control or conversion to NSR in atrial fibrillation or flutter
Verapamil	2.5–5 mg IV, repeated PRN[c]	
Diltiazem	0.2 mg/kg over 2 min, followed by 10–15 mg/h[d]	Rate control or conversion to NSR in atrial fibrillation or flutter
Procainamide	50 mg/min up to 1 g, followed by 1–4 mg/min	Rate control or conversion to NSR in atrial fibrillation or flutter, prevention of recurrence of arrhythmias, treatment of wide-complex tachycardias[e]
Digoxin[f]	Load of 1 mg in divided doses over 4–24 h[g]; may give additional 0.125-mg doses 2 h apart (3–4 doses)	Rate control or conversion to NSR in atrial fibrillation or flutter
Synchronized cardioversion	50–300 J (external); most effective with anterior-posterior patches	Acute tachyarrhythmia with hemodynamic compromise (usually atrial fibrillation or flutter)

[a]See specific drug monographs for full descriptions of indications, contraindications, and dosages. Doses are for intravenous administration; use the lowest dose, and administer slowly in patients with hemodynamic compromise.
[b]Verify that the pacer is not capturing the ventricle.
[c]Infusion may provide better control. This drug is less useful than diltiazem because of myocardial depression.
[d]Limited experience; may cause less hypotension than verapamil.
[e]When diagnosis is unclear (ventricular versus supraventricular) and no acute hemodynamic compromise is present (ie, cardioversion not indicated).
[f]Less useful than other drugs because of its slow onset and modest effect.
[g]Rate of administration depends on the urgency of rate control.
AV, Atrioventricular; *IV,* intravenously; *NSR,* normal sinus rhythm; *PAT,* paroxysmal atrial tachycardia; *PO,* orally; *PRN,* as needed.

occur, electrical cardioversion in the presence of antiarrhythmic drug therapy should be attempted, or anticoagulation should be started.

In summary, AF is a frequent complication of cardiac surgical procedures, but the incidence can be significantly reduced with suitable prophylactic therapy. β-Adrenergic blockers should be administered to patients without contraindication to this treatment, and prophylactic amiodarone can be considered for patients at high risk for postoperative AF. Patients who are poor candidates for β-blockade may not tolerate sotalol, whereas amiodarone does not have this limitation. Further studies need to be performed to assess the role of prophylactic therapy in off-pump cardiac operations more definitively. After AF occurs, the incidence of recurrence is high, so continuing treatment with specific pharmacologic therapy is usually necessary.

Preload

The Frank-Starling law states that myocardial work increases as the resting length of the myocardial fiber increases.[75] In vivo, this implies that SV will increase with increasing end-diastolic volume, although at a certain limit SV reaches a plateau (and possibly decreases), with further increases in end-diastolic volume resulting from excessive muscle stretch. In the normal myocardium, the Frank-Starling mechanism is the most important mechanism for increasing CO, and hypovolemia is a common cause of decreased CO and hypotension in the postoperative period. Assessment of preload is probably the single most important clinical skill for managing hemodynamic instability. Preload rapidly changes in the postoperative period because of bleeding, spontaneous diuresis, vasodilation during warming, the effects of positive-pressure ventilation and PEEP on venous return, capillary leak, and other causes.

Direct assessment of preload is clinically feasible using echocardiography. Several studies have demonstrated a fair-to-good correlation between echocardiographic and radionuclide measures of end-diastolic volume and a good correlation between end-diastolic area measured by TEE and SV.[76–79] Although the use of echocardiography to assess preload must always be tempered by the realization that the clinician is viewing a two-dimensional image of a three-dimensional object, this is the most direct technique clinically available. Greater awareness of the value of TEE in the ICU and increased availability of echocardiography in general have made this modality a first choice for the assessment of preload in the setting of acute unexplained or refractory hypotension. Without echocardiography, pressure measurements are used as surrogates for volume measurements. For example, in the absence of mitral valve disease, left atrial pressure (LAP) is almost equal to LV end-diastolic pressure (LVEDP), and pulmonary artery occlusion pressure (PAOP) is almost equivalent to these two pressures. In patients without LAP catheters, the PAOP or the pulmonary artery diastolic pressure is used (see Chapters 6 and 13).

The use of PAOP as a measure of preload may be misleading in various settings, including after cardiac operations, when changes in pressure may not accurately reflect changes in ventricular end-diastolic volume. Previous studies by Ellis and colleagues[80] and Calvin and associates[81] suggested that fluid therapy in postoperative patients could cause a large increase in LV end-diastolic volume (LVEDV), with minimal or no change in PAOP. Mangano and colleagues[45,82] reported that fluid loading after CPB can uncover LV dysfunction, and these investigators also showed that little benefit is derived from exceeding a PAOP of approximately 12 mm Hg. Whether an elevated PAOP is secondary to an open pericardium, which allows overdistention of the left ventricle, the use of PEEP causing RV distention, or other factors is unclear. Briesblatt and associates[83] evaluated changes in ventricular pressure-volume relationships after CABG procedures while keeping a low-to-normal PAOP (10–15 mm Hg). The increase seen in LVEDV was not significant enough to explain the degree of ventricular dysfunction these investigators noted. Bouchard and colleagues[84] compared ventricular performance assessments from the PAC (ie, LV stroke work index [LVSWI]) with fractional area change and regional wall motion score index from TEE in 60 patients during and after cardiac surgical procedures. These investigators found no correlation between LVSWI and fractional area change and postulated that changes in ventricular compliance, loading conditions, and ventricular function alter the pressure-volume relationship of the left ventricle in a manner that leads to discordant interpretations between the two techniques.

When ventricular compliance is normal and the ventricle is not distended, small changes in end-diastolic volume are usually accompanied by small changes in end-diastolic pressure. In patients with noncompliant ventricles from preexisting congestive heart failure (HF), chronic hypertrophy resulting from hypertension or valvular disease, postoperative MI, or ventricular dysfunction, small increases in ventricular volume may produce rapid increases in end-diastolic pressure that require therapeutic intervention.[83–89] Increased intraventricular pressure elevates myocardial oxygen demand ($M\dot{V}O_2$) and decreases subendocardial coronary artery blood flow.[90] Myocardial ischemia may be the result. Elevations in LVEDP are transmitted to the pulmonary circulation, thus causing congestion and possibly hydrostatic pulmonary edema. Although PAOP or LAP may not always show true preload, good reasons exist to monitor them. The periods when patients are at particular risk for elevations in end-diastolic pressure include awakening, endotracheal suctioning, and rapid-volume resuscitation. If myocardial ischemia or acute HF occurs, sudden increases in the end-diastolic pressure may result.

Many drugs may be used to reduce cardiac preload. Direct-acting vasodilators, especially nitroglycerin, increase venous capacitance and thus decrease end-diastolic volume and pressure.[87–91] Intravenous furosemide, besides its diuretic effect, increases venous capacitance.[92] Diuretics are important to help remove the fluid that is mobilized in the days after surgical procedures. In patients who may not tolerate the acute volume loss that is induced by the loop diuretics, a furosemide infusion allows more gradual diuresis. Such infusions have been shown to be effective in patients with renal dysfunction.[93,94] In a patient who appears refractory to diuresis, it is important to evaluate the circulatory state. Such refractoriness may suggest that a renal insult has occurred, but it may also suggest renal underperfusion. In the latter case, the preload must be kept at the upper range of normal, and CO should be augmented.

A therapeutic agent previously used for acute decompensated left-sided HF was recombinant B-type natriuretic peptide (nesiritide). The mechanism of action occurs at specific cell-surface receptors, stimulation of which increases levels of intracellular cyclic guanosine monophosphate (cGMP). The physiologic effects are mainly vasodilation, natriuresis, and renin inhibition, which result is balanced vasodilation, reducing preload and afterload while simultaneously increasing SV and CO and promoting diuresis.[95] Nesiritide use in high-risk cardiac surgical patients with poor LV function improved renal function and decreased 6 month mortality in the NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) study.[96] A related drug, human atrial natriuretic peptide, was shown in a small, randomized trial to reduce the need for dialysis and to improve dialysis-free survival after complicated cardiac operations.[97] Further investigations of these drugs are needed in cardiac surgical patients.

Angiotensin-converting enzyme inhibitors can also cause venodilation and reduce preload. Alternatively, opioids or benzodiazepines, or both, used to reduce endogenous catecholamine release, should be considered in the patient who requires mechanical ventilation. Morphine causes histamine release, which directly induces venodilation. In the patient with oliguria and renal failure who has fluid overload, peritoneal dialysis, hemodialysis, or continuous hemofiltration may be needed.[98,99]

Contractility

Contractility is a well-defined concept in vitro, where it can be measured by the velocity of shortening of isolated muscle strips. However, quantifying the contractility of the intact heart has been complicated by the difficulty of finding a variable to measure contractility that is also independent of preload and afterload. The pioneering work of

Sagawa[100] and Suga and colleagues[101] showed that contractility can be measured by the end-systolic elastance of the ventricle, defined as follows:

$$E_{ES} = P_{ES}/(V_{ES} - V_0)$$

in which P_{ES} is the end-systolic pressure, V_{ES} is the end-systolic volume, and V_0 is a dead-space term.

E_{ES} is strictly determined by evaluating ventricular pressure-volume loops for different preloads or afterloads and by defining end-systole as the point in time at which the time-varying elastance is maximal.[102] The slope of the line connecting the points at end-systole is E_{ES}. This parameter varies with changes in inotropic state, but it is *nearly* independent of preload and afterload. Routine measurement of end-systolic elastance is not clinically feasible. However, consideration of the foregoing definition underscores the utility of TEE for the qualitative evaluation of contractility in the clinical setting. A decrease in contractility is manifested as some combination of a decrease in pressure or an increase in V_{ES} (ie, a decrease in SV). End-systolic volume can be estimated using TEE. A large V_{ES} (implying a low EF) with a low or normal BP suggests a low value for E_{ES} and poor contractility. If BP is high, a large value of V_{ES} may be seen even if contractility is normal. By interpreting end-diastolic volume, end-systolic volume, and EF in the context of BP, an assessment of contractility is possible with TEE (see Chapters 6 and 14–16).

An alternative measure of contractility is the preload-recruitable stroke work, which is the slope of the line relating stroke work to preload.[103] In the ICU, it is often estimated by the extent of the increase in CO that accompanies an increase in preload and is not dependent on the availability of TEE. If preload is increased by a change in the patient's position, BP can be a surrogate for CO because it is unlikely that SVR will change in the short time needed for the position change. A change in BP therefore is proportional to the change in CO.

Therapy for decreased contractility should be directed toward correcting any reversible causes, such as myocardial depressants, metabolic abnormalities, or myocardial ischemia. If the cause of depressed myocardial contractility is irreversible, positive inotropic agents may be necessary to keep CO satisfactory to support organ function (see Chapters 6, 11, and 36).

Afterload

Afterload is a concept that is well defined in vitro, where it refers to the added tension imposed on isolated muscle strips with contraction, but it is more difficult to define in vivo. In analogy with in vitro studies, afterload can be equated with ventricular wall stress, expressed as the product of cavity radius times transmural pressure divided by wall thickness, as described by the law of Laplace. However, many investigators find this definition unsatisfactory because it implies that the heart generates its own afterload and because afterload would be viewed as changing during the cardiac cycle.[104] If afterload is viewed as the external forces opposing ejection, possibly the best definition is the aortic input impedance, the complex ratio of pressure to flow, expressed in terms of magnitude, and the phase angle between flow and pressure for any given frequency. However, it has been difficult to analyze the impact of impedance on overall cardiac performance quantitatively (see Chapter 6). Therefore, Sunagawa and associates[105] proposed a simplified theory of ventricular-vascular coupling within the framework of the end-systolic pressure-volume relationship. Using the definition of end-systolic elastance produces the following:

$$E_{ES} = P_{ES}/(V_{ES} - V_0)$$

Equating SV with $V_E - V_{ES}$ (ignoring the difference between end-ejection and end-systole), it is a matter of algebra to show that

$$P_{ES} = E_{ES}(V_{ED} - V_0) - E_{ES} \cdot SV$$

This means that an increase in SV implies a decrease in P_{ES}. The interpretation of this statement from the cardiac perspective is that the work that can be done is finite and that a greater SV can be achieved only by lowering the end-systolic pressure, if contractility (E_{ES}) is fixed. At the same time, it is known that from the perspective of the vasculature, if SV increases, BP increases when vascular tone does not change.

The application of an electrical law describing constant voltages and flows to the circulation, in which pulsatile flow is generated by a pump, resulted in estimates of afterload that are questionable.[104] Although SVR is a component of impedance, it cannot be equated with it. The correct downstream pressure is probably not the CVP.[106] Instead, a critical opening pressure should be used in calculating SVR, and this pressure is not measurable in routine clinical care.[106] Clinical use of such calculated resistances is made complex by the relation of CO to body size; the normal resistance of a small patient is much higher than that of a large patient. A resistance index (ie, using cardiac index instead of CO) partly overcomes this problem, but it is not widely used.

Calculated SVR continues to be used in guiding therapy or drawing conclusions about the state of the circulation. This should be done only cautiously, if at all. SVR is not a complete indicator of afterload. Even if SVR were an accurate measure of impedance, the response to vasoactive agents depends on the coupling of ventricular-vascular function, not on impedance alone. Hemodynamic therapy should be guided based on the primary variables, BP and CO. If preload is appropriate, conditions of both low BP and low CO are treated with an inotropic drug. If BP is acceptable (and preload appropriate) but CO is low, a vasodilator alone or in combination with an inotropic drug is used. If the patient is hypertensive (with low CO), vasodilators are indicated; if the patient is vasodilated (low BP and high CO), vasoconstrictors are employed (Table 38.3).

TABLE 38.3 Hemodynamic Therapy Guidelines

Blood Pressure	*Cardiac Output*	*Treatment*
Low	Low	Inotrope
Normal	Low	Vasodilator with or without inotrope
High	Low	Vasodilator
Low	High	Vasopressor

Postoperative Hypertension

Hypertension has been a common complication of cardiac surgical procedures, and it was reported to occur in 30% to 80% of patients from studies in the 1970s when CABG was common in patients with normal ventricular function.[107–109] The current population of older, sicker patients appears to have fewer problems with hypertension than with low-output syndromes or vasodilation. Although hypertension most commonly occurs in patients with normal preoperative ventricular function, following aortic valve replacement or with a previous history of increased BP, any patient may develop hypertension. Multiple reasons contribute to postoperative hypertension, including preoperative hypertension, preexisting atherosclerotic vascular disease, awakening from general anesthesia, increases in endogenous catecholamines, activation of the plasma renin-angiotensin system, neural reflexes (eg, heart, coronary arteries, great vessels), and hypothermia.[110] Arterial vasoconstriction with various degrees of intravascular hypovolemia is the hallmark of perioperative hypertension.

The hazards of untreated postoperative hypertension include depressed LV performance, increased $M\dot{V}O_2$, cerebrovascular accidents, suture line disruption, MI, rhythm disturbances, and increased bleeding.[108,111,112] Historically, therapy for hypertension in cardiac surgery was sodium nitroprusside because of its rapid onset and short duration of action.[113] With multiple vasodilators available in the current era, sodium nitroprusside is no longer the drug of choice for many reasons. Nitroprusside is a potent venodilator, increasing venous capacitance (decreasing preload), and it can produce precipitous decreases in BP. Nitroprusside also can cause coronary arteriolar dilation with the potential for a steal phenomenon, resulting in

TABLE 38.4 Novel Vasodilators

Drug	*Mechanism of Action*	*Half-Life*
Nicardipine	Calcium channel blocker	Intermediate
Clevidipine	Calcium channel blocker	Ultrashort
Fenoldopam	Dopamine$_1$-agonist	Ultrashort
Nesiritide	Brain natriuretic agonist	Short
Levosimendan	K^+_{ATP} channel modulator	Intermediate

K^+_{ATP}, Adenosine triphosphate–sensitive potassium channel.

myocardial ischemia.[114] In patients with renal failure, the elimination of nitroprusside is reduced, potentially leading to toxic effects of its metabolites cyanide or thiocyanate. This effect also can occur if large doses are given to patients with normal renal function.

Many pharmaceutical alternatives to nitroprusside are available for treating hypertension after cardiac surgical procedures, including nitroglycerin,[115] β-adrenergic blockers,[116] and the mixed α- and β-adrenergic blocker labetalol.[117] Direct-acting vasodilators, dihydropyridine calcium channel blockers (eg, , nicardipine,[118] isradipine,[119] clevidipine[120–123]), angiotensin-converting enzyme inhibitors,[113] and fenoldopam (a dopamine$_1$ [D_1] receptor agonist)[124,125] also have been used. Novel therapeutic approaches are listed in Table 38.4.

Dihydropyridine calcium channel blockers are particularly effective in cardiac surgical patients because these drugs they relax arterial resistance vessels without negative inotropic actions or effects on atrioventricular nodal conduction and provide important therapeutic options. Dihydropyridines are arterial-specific vasodilators of peripheral resistance arteries that cause generalized vasodilation, including the renal, cerebral, intestinal, and coronary vascular beds. In doses that effectively reduce BP, the dihydropyridines have little or no direct negative effect on cardiac contractility or conduction. Although the dihydropyridines are more vasoselective than verapamil and diltiazem, differences exist among dihydropyridines in this respect. Nifedipine is the least vasoselective of the dihydropyridines, isradipine and clevidipine are the most selective, and nicardipine and nimodipine are intermediately selective.[126,127] Nicardipine is an important therapeutic agent to consider because of its lack of effects on vascular capacitance vessels and preload in patients after cardiac operations. The pharmacokinetic profile of nicardipine suggests that effective administration requires variable-rate infusions when trying to treat hypertension because of the half-life of 40 minutes. If even faster control of BP is essential, a dosing strategy consisting of a loading bolus or a rapid infusion dose with a constant-rate infusion may be more efficient. The effect of nicardipine may persist even though the infusion is stopped. Clevidipine, an ultrashort-acting dihydropyridine approved in 2008 in the United States for clinical use, has a half-life of only minutes; this drug represents an important alternative to nitroprusside and has been extensively studied in cardiac surgical patients.[122]

Fenoldopam is a short-acting dopamine agonist that causes arterial-specific vasodilation by stimulation of D_1-receptors. Unlike nitroprusside, D_1-receptor stimulation also increases renal blood flow to produce diuresis and natriuresis. Fenoldopam and nitroprusside were similarly effective in reducing BP in patients who developed hypertension after CABG procedures.[124] Fenoldopam often must be given at higher doses in patients with severe hypertension that may be associated with increases in HR, and this drug is decreasingly used in postoperative settings.

Postoperative Vasodilation

Vasodilation and a need for vasoconstrictor support are relatively frequent complications of cardiac surgical procedures, with and without CPB. The reported incidence is 4% to 44%, but this wide range largely results from the lack of a common definition.[128–130] Vasodilation alone should be associated with a hyperdynamic circulatory state manifesting as systemic hypotension in association with an increased CO (and a low calculated SVR). More commonly after cardiac operations, a combination of vasodilation and myocardial dysfunction occurs, requiring vasoconstrictor and inotropic therapy. Gomez and Biglioli and their colleagues[131–133] coined the term *vasoplegia syndrome* for the condition that requires high doses of vasoconstrictors, and they reported its occurrence after off-pump and on-pump surgical procedures.

Multiple humoral and inflammatory cascades are activated by surgical treatment and CPB, aortic cross-clamping, and reperfusion, with generation of complement anaphylatoxins, kinins, and cytokines, many of which cause vasodilation by direct and indirect vascular mechanisms.[134–136] Another potential cause of systemic vasodilation is splanchnic circulatory insufficiency resulting in endotoxemia, and this, too, has been noted after off-pump procedures.[137,138] The cellular mechanisms and pathogenesis of vasodilatory shock were summarized by Landry and Oliver.[135] Although the most common clinical context of vasodilatory shock is sepsis, the similarity in the cytokine response and the clinical syndrome seen in sepsis with the vasodilated state seen after cardiac surgical procedures is striking. The stimuli of cytokines and increased tissue lactate lead to increased NO synthase and the generation of vasodilating GMP. NO and metabolic acidosis activate potassium channels, which hyperpolarize the cell membrane, thus making it refractory to both calcium entry and norepinephrine and angiotensin II action. At this time, plasma vasopressin levels are low because of central depletion. Reports of marked vasodilatory shock after CPB responsive to vasopressin appeared when this pathophysiologic finding was being actively investigated.[139] The ability of vasopressin to block the potassium channels and interfere with NO signaling makes it an important therapy for this syndrome. Provided the patient has an acceptable CO, vasopressin is a valuable agent for treating vasodilation after cardiac operations, and this agent significantly reduces the dose requirement for norepinephrine. Systemic vasodilation also can result from hyperthermia caused by excessive warming during CPB and during warming in the ICU.

When patients develop acute systemic vasodilation after administration of drugs or blood products, an anaphylactic reaction should be considered. Acute anaphylaxis caused by immunoglobulin E–mediated responses can manifest with systemic vasodilation and increased CO.[140] Alternatively, complement-mediated transfusion reactions to any blood product can manifest with hypotension produced by systemic vasodilation or by thromboxane-mediated acute pulmonary vasoconstriction and RV dysfunction. Antibodies in the donor blood called leukoagglutinins, when directed against recipient white cell antigens, can actively produce white cell aggregation and thromboxane generation. These reactions can produce *transfusion-related acute lung injury,* which can manifest with hypotension, RV failure, and noncardiogenic pulmonary edema.[140] Monitoring of RV function may therefore help to identify these transfusion reactions.

While underlying causes are being sought and treated, the therapeutic approach to systemic vasodilation includes intravascular volume expansion, α-adrenergic agents, and vasopressin. Administration of vasoconstrictors for more than a brief period must be guided by measures of cardiac performance because restoration of BP may camouflage a low-output state. No established guidelines exist for beginning vasoconstrictor therapy; autoregulation in vital organs is lost at arterial mean pressures lower than 60 mm Hg, and it is reasonable to try to achieve this pressure in normotensive patients (possibly higher in hypertensive patients). A study in patients with septic shock was unable to show a benefit from mean arterial pressures (MAPs) greater than 65 mm Hg.[141]

Clinicians are often concerned about the potential for constricting supply vessels or the microcirculation to vital beds (eg, brain, kidney); although not fully evaluated in the postoperative setting, vasoconstrictor administration in septic states does not appear to have such harmful effects.[142] Use of relatively low doses of vasopressin to restore responsiveness to catecholamines makes physiologic sense, but no clear evidence suggests that the use of vasopressin in addition to or instead of norepinephrine is associated with a better outcome.

However, dopamine has been demonstrated to increase mortality rates in cardiogenic shock.[143]

Coronary Artery Spasm

Coronary artery or internal mammary artery vasospasm can occur postoperatively. Mechanical manipulation and underlying atherosclerosis of the native coronary circulation and the internal mammary artery have the potential to produce transient endothelial dysfunction. The endothelium is responsible for releasing endothelium-derived relaxing factor (EDRF), which is NO, a potent endogenous vasodilator substance that preserves normal endogenous vasodilation (see Chapters 7 and 9). Thromboxane can be liberated by heparin-protamine interactions, CPB, platelet activation, or anaphylactic reactions to produce coronary vasoconstriction.[144,145] Calcium administration, increased α-adrenergic tone from vasoconstrictor administration (especially in bolus doses), platelet thromboxane liberation, and calcium channel blocker withdrawal represent added reasons that may put the cardiac surgical patient at risk for spasm of native coronary vessels and arterial grafts. Engelman and associates[145] reported that four patients developed coronary artery spasm after discontinuation of their calcium channel blockers 8 to 18 hours preoperatively. In three of these patients, spasm was identified by the ECG pattern and was documented as the cause of ischemia in the distribution of a nondiseased right coronary artery; in the fourth patient, spasm developed in a bypassed native vessel. In two of the patients, the problem was recognized retrospectively; MIs developed, and one patient died. In the other two patients, spasm was recognized, and intravenous nitroglycerin was given (1–3 μg/kg per min) in combination with nifedipine, 10 mg sublingually every 5 to 6 hours, to reverse the ischemic process. The therapy of choice remains empiric. Nitroglycerin is a first-line drug, but nitrate tolerance can occur. Phosphodiesterase (PDE) inhibitors represent newer approaches to this problem and have been reported to be effective in vascular models of spasm.[146] Intravenous dihydropyridine calcium channel blockers are also important therapeutic considerations.[147]

The radial artery is still used by some surgeons as a bypass conduit for revascularization.[148–150] This conduit was abandoned by some groups because of its propensity to spasm. However, techniques developed in the use of the internal mammary artery have been applied to the radial artery, as well as prophylactic use of calcium channel blocker infusions.[148,150] Which components of this approach are responsible for the reported success are not known, but use of a calcium channel blocking drug is recommended by many surgeons. The arterial selectivity of the dihydropyridine drugs (eg, nicardipine) should be an advantage in this setting.

Decreased Contractility

Drugs that increase contractility all augment calcium mobilization from intracellular sites to and from the contractile proteins or sensitize these proteins to calcium. Although calcium chloride has been used to increase inotropy, evidence suggests that after CPB, its principal action is peripheral vasoconstriction.[151] The same group of investigators showed that exogenously administered calcium chloride attenuates the response to catecholamines in this setting.[152] The administration of calcium salts improves myocardial performance in patients with severe hypocalcemia or hyperkalemia, and it may be indicated during rapid transfusion of citrated blood.[153]

Catecholamines, through β_1-receptor stimulation in the myocardium, increase intracellular cyclic adenosine monophosphate (cAMP). This second messenger increases intracellular calcium and thus improves myocardial contraction.[154] Inhibition of the breakdown of cAMP by PDE inhibitors increases intracellular cAMP independent of the β-receptor.[155] Intracellular calcium availability can be increased by inhibiting sodium/potassium–adenosine triphosphatase (ATPase) with digitalis glycosides, to promote transmembranous sodium-calcium exchange. However, the use of digoxin to increase myocardial contractility for postoperative ventricular dysfunction is limited by its slow onset, low potency, and narrow therapeutic safety margin. The "calcium sensitizers" constitute a newer class of inotropic agents. One drug in this class, levosimendan, is already available in certain countries and is currently being evaluated in a US clinical trial (https://clinicaltrials.gov/ct2/show/NCT02025621?term=levosimendan&rank=12) (Box 38.2).

BOX 38.2 PHARMACOLOGIC APPROACHES FOR PERIOPERATIVE VENTRICULAR DYSFUNCTION

Inotropic Agents
Catecholamines
Phosphodiesterase inhibitors
Levosimendan

Vasodilator Therapy
Pulmonary vasodilators
Phosphodiesterase inhibitors (milrinone, sildenafil)
Inhaled nitric oxide
Prostaglandins (PGI_2, PGE_1, iloprost, and derivatives)

BOX 38.3 DISADVANTAGES OF CATECHOLAMINES

- Increased myocardial oxygen consumption
- Tachycardia
- Arrhythmias
- Excessive peripheral vasoconstriction
- Coronary vasoconstriction
- β-Receptor downregulation and decreased drug efficacy

TABLE 38.5 Catecholamines Used Postoperatively

Drug	*Infusion Dose (μg/kg per min)*
Dopamine[a,b]	2–10
Dobutamine[b]	2–10
Epinephrine[c]	0.03–0.20
Norepinephrine[c]	0.03–0.20
Isoproterenol[c]	0.02–0.10

[a]Less than 2 μg/kg per minute predominantly "dopaminergic" (renal and mesenteric artery dilatation).
[b]If 10 μg/kg per minute is ineffective, change to epinephrine or norepinephrine.
[c]Dose to effect; may require higher dose than indicated.

Catecholamines

The catecholamines used postoperatively include dopamine, dobutamine, epinephrine, norepinephrine, and isoproterenol (Box 38.3). These drugs have various effects on α- and β-receptors and therefore various effects on HR, rhythm, and myocardial metabolism (see Chapters 11 and 36). Dosing recommendations for the catecholamines are provided in Table 38.5.

Isoproterenol

Isoproterenol is a potent β_1-agonist in the heart and β_2-agonist in the periphery. Its positive inotropic effect is accompanied by an increase in HR and a propensity for arrhythmias. In patients with coronary artery disease, tachycardia and associated peripheral vasodilation increase $M\dot{V}O_2$ and decrease coronary perfusion pressure. In patients with bradycardias in whom pacing is not an immediate or practical option or in those in whom increased HR is desirable (eg, cardiac transplant

recipients, patients with regurgitant valvular lesions), isoproterenol has long been used for this purpose, but increasingly dobutamine is used.

Epinephrine

Epinephrine is a potent adrenergic agonist with the desirable feature that, in low doses (<3 μg/min), β_1 and β_2 effects predominate. As the dose is increased, α effects (eg, vasoconstriction) and tachycardia occur. However, in the acutely failing heart postoperatively, only drugs such as epinephrine or norepinephrine provide positive inotropy and perfusion pressure. These features and its low cost make epinephrine a common first-line drug in the postoperative setting. Despite what is often stated in textbooks, epinephrine causes less tachycardia than dopamine[156] or dobutamine[157] at equivalent inotropic doses.[158] Epinephrine is a first-line therapy for anaphylaxis and, when titrated, does not produce ventricular arrhythmias. Because of the metabolic actions of α_2 stimulation, epinephrine infusion can cause hyperglycemia and increased serum lactate levels.[159]

Norepinephrine

Norepinephrine, which has potent β_1- and α-receptor effects, preserves coronary perfusion pressure while not increasing HR, actions that are favorable to the ischemic, reperfused heart. When norepinephrine is used alone without a vasodilator or PDE inhibitor, the potent α_1 effects may have variable effects on CO. Ventricular filling pressures usually increase when this drug is given because of constriction of the capacitance vessels. Administration of a vasodilator, including the PDE inhibitors, with norepinephrine may partially oppose the vasoconstriction. Clinicians may express concern for the renal blood flow when norepinephrine is given for hypotension; however, norepinephrine has long been used as a first-line agent for hypotension and shock in ICU settings and following cardiac operations. Despite perceived concerns, when norepinephrine is infused to increase MAP to greater than 70 mm Hg in sepsis, increases in urine flow and in creatinine clearance rate occurred after 24 hours.[160] Further, the use of norepinephrine in circulatory shock did not increase mortality rates.[161] End-organ ischemia would appear to be unlikely if CO can be preserved at normal levels when norepinephrine is given. PDE inhibitors in combination with norepinephrine attenuate the arterial vasoconstrictive effects.[146]

Dopamine

A precursor of norepinephrine, dopamine probably achieves its therapeutic effects by releasing myocardial norepinephrine or preventing its reuptake, especially in high doses.[162] This indirect action may result in reduced effectiveness when dopamine is given to patients with chronic HF or shock states because the myocardium becomes depleted of norepinephrine stores.[163] In contrast to dobutamine, the α-agonist properties of dopamine cause increases in pulmonary artery pressure (PAP), PVR, and LV filling pressure.[164–166] At low doses (<2 μg/kg per min), dopamine stimulates renal dopaminergic receptors to increase renal perfusion more than can be explained by an increase in CO.[167] Despite this action, a multicenter study demonstrated that use of low-dose dopamine in critically ill patients confers no protection from renal dysfunction.[168] One review suggested that low-dose dopamine use in the ICU had no justification and that it was "bad medicine."[169] At doses higher than 10 μg/kg per minute, tachycardia and vasoconstriction become the predominant actions of this drug. Tachycardia is a consistent side effect, and in patients with cardiogenic shock, dopamine has been shown to increase mortality rates.[143,161]

Dobutamine

In contrast to dopamine, dobutamine shows mainly β_1-agonist properties, with decreases in diastolic BP and sometimes systemic BP observed.[170,171] Dobutamine is functionally similar to isoproterenol, with less tendency to induce tachycardia in the postoperative setting, although it is often infused at doses up to 40 μg/kg per minute to increase HR as part of a dobutamine stress echocardiographic evaluation.[172] However, Romson and colleagues[173] demonstrated that after CPB, the principal effect of dobutamine is a dose-related increase in HR. A very modest effect on SV was observed in patients with poor ventricular function. Salomon and associates[174] showed that dobutamine increased $M\dot{V}O_2$, a change matched by an increase in coronary blood flow, whereas dopamine increased $M\dot{V}O_2$ but failed to increase coronary blood flow. However, the favorable actions of dobutamine may be limited if tachycardia develops, and, as with dopamine, the inotropic potency of dobutamine is modest in comparison with that of epinephrine or norepinephrine.[174]

Phosphodiesterase Inhibitors

The PDE inhibitors are nonglycosidic, nonsympathomimetic drugs that have positive inotropic effects independent of the β_1-adrenergic receptor and unique vasodilatory actions independent of endothelial function or nitrovasodilators.[154,155] Patients with HF have downregulation of the β_1-receptor, with a decrease in receptor density and altered responses to catecholamine administration.[154,175] Milrinone, amrinone, and enoximone bypass the β_1-receptor and increase intracellular cAMP by selective inhibition of PDE fraction III (ie, fraction IV), a cAMP-specific PDE enzyme.[155,176] In vascular smooth muscle, these agents cause vasodilation in the arterial and capacitance beds.[177] PDE inhibitors increase CO, decrease PAOP, and decrease SVR and PVR in patients with biventricular dysfunction, and they are important therapeutic agents in postoperative cardiac surgical patients. Sildenafil and other PDE 5 inhibitors are also increasingly used for pulmonary hypertension.[178] The PDE 5 inhibitor sildenafil (marketed as, eg, Revatio) was approved for the treatment of pulmonary arterial hypertension by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2005, and other similar agents are also currently approved[178] (see Chapters 11 and 26).

Effects on Vascular Responses

Any drug that increases cyclic nucleotides (eg, cAMP, cGMP) in vascular smooth muscle produces vasodilation.[176–178] The concentration of cGMP can be increased by the release of nitric oxide produced by nitroglycerin, nitroprusside, and inhaled NO, and cAMP can be increased by prostaglandin E_1 or I_2 (PGE_1 or PGI_2), or by inhibiting its breakdown by PDE inhibition. Increasing cAMP in vascular smooth muscle promotes calcium uptake by the sarcoplasmic reticulum, thus decreasing calcium available for contraction. The net effect of increasing calcium uptake is smooth muscle relaxation. This effect can also occur through stimulation by drugs that inhibit the breakdown of cGMP (eg, nonspecific PDE inhibitor). Sildenafil and its congeners are type V PDE inhibitors that were originally developed for nitrate tolerance but are marketed for erectile dysfunction and pulmonary hypertension.[178]

PDE III inhibitors have a clinical effect as inodilators; they produce dilation of arterial and venous beds and decrease the MAP and central filling pressures. Increases in CO are induced by multiple mechanisms, including afterload reduction and positive inotropy, but not by increasing HR.[179–189] The net effect is a decrease in myocardial wall tension, representing an important contrast to most sympathomimetic agents.[181] Catecholamine administration often needs the simultaneous administration of vasodilators to reduce ventricular wall tension. Milrinone and other PDE inhibitors also have unique mechanisms of vasodilation that may be favorable for coronary artery and internal mammary artery flow[146] (Box 38.4).

Sildenafil inhibits PDE V, an enzyme that metabolizes cGMP, thereby increasing cGMP-mediated relaxation.[178] The current treatment modalities for pulmonary hypertension include conventional supportive therapies and more specific pharmacologic therapies that are targeted at abnormalities of endothelial function. NO and PDE V inhibitors induce pulmonary vasodilation by increasing intracellular cGMP concentrations. Sildenafil is a selective inhibitor of PDE V. Investigations in animal models and clinical reports including some studies in pediatric patients suggest that sildenafil may be a promising agent for treating pulmonary hypertension. The effect of sildenafil on pulmonary vasculature appears to be independent of the underlying cause, thereby providing a role in idiopathic pulmonary arterial

TABLE 38.6 Acute Heart Failure: Therapeutic Goals and Treatment Summary

Goals	*Treatment*
Reduce impedance to ventricular ejection	Vasodilator
Reduce wall stress	Vasodilator
Reduce filling pressures	Diuretics, venodilators
Increase contractility	Inotropic agents, phosphodiesterase inhibitors

BOX 38.4 ADVANTAGES OF PREEMPTIVE PHOSPHODIESTERASE INHIBITOR ADMINISTRATION

- Increased myocardial contractility (left and right ventricles)
- Pulmonary vasodilation
- Resolution and prevention of ischemia
- Minimal drug side effects during cardiopulmonary bypass
- Dilation of internal mammary artery
- Avoidance of mechanical intervention
- Prevention of "failed weaning"

hypertension (PAH), which is associated with congenital heart disease, pulmonary hypertension secondary to lung disease, or persistent pulmonary hypertension of the newborn. It may also be beneficial in postoperative pulmonary hypertension and in patients who are difficult to wean from inhaled NO. Sildenafil is easily administered and effective, and it has minimal systemic adverse effects although drug interactions can occur[182] (see Chapter 26).

Combination Therapy: Catecholamines and Phosphodiesterase Inhibitors

Catecholamine therapy depends on the myocardial cell's capacity to respond to β_1-agonist activity. In patients with preoperative HF, the number of effective β_1-receptors decreases because of downregulation, which refers to reduced density or uncoupling, such that fewer receptors are available for binding with the β_1-agonist.[154,175] When postoperative ventricular dysfunction is treated, a pharmacologic ceiling effect may occur with increasing doses of a single β_1-agonist or even when other catecholamines are added.[176] Combining PDE inhibitors with a catecholamine may significantly increase cAMP levels in patients with β_1-receptor downregulation, such as patients after cardiac surgical procedures.[190] The two forms of therapy may attenuate each other's adverse effects. Catecholamine stimulation of vascular α_1-receptors induces vasoconstriction, which is attenuated by PDE inhibitors.[146] Catecholamines with potent α_1-agonist effects may be needed to prevent hypotension when PDE inhibitors are given postoperatively; or, alternatively, when an α-adrenergic agent is required to obtain acceptable perfusion pressure, PDE inhibitors may be administered to augment CO. The additive improvement in hemodynamic effects of catecholamines in combination with amrinone, milrinone, or enoximone has also been described.[187,191–195] Combined therapy may theoretically avoid dose-related adverse effects of high doses of each individual agent and is useful in RV failure[196] (Table 38.6) (see Chapters 11 and 26).

Dosage and Administration

Suggested dosage regimens are provided in Table 38.7. Available drugs are reviewed in the following sections.

Amrinone

Amrinone, the first bipyridine evaluated for HF and cardiac surgical procedures, has a half-life of approximately 3.5 hours.[197–201] In patients with HF, an intravenous loading dose of 1.5 mg/kg and an infusion of 10 µg/kg per minute resulted in a plasma concentration of 1.7 µg/mL and produced a 30% increase in cardiac index.[197] Recommended dosing includes a bolus dose of 0.75 mg/kg given intravenously over 2 to 3 minutes, followed by a maintenance infusion of 5 to 10 µg/kg per minute. This dose regimen produces subtherapeutic concentrations after 5 to 10 minutes, and it failed to show any hemodynamic effect after it was given 10 minutes before termination of CPB.[201,202] A loading dose of 1.5 to 2.0 mg/kg of this drug during CPB produces therapeutic concentrations for 30 to 60 minutes, after which an infusion is required to keep therapeutic blood levels. With prolonged administration, amrinone produces thrombocytopenia. Amrinone has been replaced with milrinone for clinical use.

TABLE 38.7 Dosing for Phosphodiesterase Inhibitors (Cyclic Adenosine Monophosphate Specific) Used Postoperatively

Drug	*Loading Dose*[a]	*Infusion Rate*
Amrinone	1.5–2.0 mg/kg	5–20 µg/kg per min
Milrinone	50 µg/kg	0.375–0.75 µg/kg per min
Enoximone	0.5–1.0 mg/kg	5–10 µg/kg per min

[a]Loading doses should be administered over 5 to 10 minutes to avoid excessive vasodilation.

Milrinone

Milrinone, an analogue of amrinone, is a bipyridine derivative with inotropic activity that is almost 20 times more potent than that of amrinone and a shorter half-life.[183] Milrinone is an effective inodilator for patients with decompensated HF and low CO after cardiac surgical procedures. Suggested administration of milrinone is a loading dose of 50 µg/kg over 10 minutes, followed by an infusion of 0.5 µg/kg per minute (0.375–0.75 µg/kg per min). By using slower loading doses, high peak concentrations can be prevented, and the vasodilation that is observed with rapid loading can be attenuated.[183] A milrinone loading dose of 50 µg/kg in combination with an infusion of 0.5 µg/kg per minute consistently maintained plasma concentrations more than 100 ng/mL. Clearance was 3.8 ± 1.7 mL/kg per minute, volume of distribution was 465 ± 159 mL/kg, and terminal elimination half-time was 107 ± 77 minutes (values expressed as mean ± standard deviation [SD]).[183] Pharmacokinetic parameters were independent of dose. The relationship between plasma concentration and pharmacodynamic effects produced approximately a 30% improvement in cardiac index with plasma levels of 100 ng/mL, and a curvilinear relationship was noted between plasma levels and improvement in cardiac index. Bailey and colleagues[183] observed that a dose of 50 µg/kg with an infusion rate of 0.5 µg/kg per minute can keep plasma concentrations near the threshold of its therapeutic effects. Compared with amrinone, milrinone has a shorter context-sensitive half-time after administration is stopped without adverse effects on platelet function.[189]

Kikura and associates[194] reported the effects of milrinone on hemodynamics and LV function in cardiac surgical patients who were already treated with catecholamines. After emergence from CPB, patients were randomly assigned to a control group ($n = 10$) or to one of the milrinone dosing groups: intravenous milrinone at 50 µg/kg ($n = 8$), 50 µg/kg and 0.5 µg/kg per minute ($n = 10$), or 75 µg/kg and 0.75 µg/kg per minute ($n = 9$). Hemodynamics and TEE finding were recorded while constant filling pressures were maintained by volume reinfusion. In all three milrinone groups, cardiac index and velocity of circumferential fiber shortening significantly increased from the baseline, and both values were significantly higher at 5 and 10 minutes than those in the control group. The plasma concentration of milrinone with one-half of the maximal increase in velocity of circumferential fiber shortening was 139 ng/mL on the dose-response curve. Milrinone improves hemodynamics and LV function when constant loading conditions are maintained.[194]

TABLE 38.8 Hemodynamic Effect of Milrinone After Cardiac Surgical Procedures[a]

	% Change (Mean ± SEM)			
Parameter	*15 Min*	*60 Min*	*12 H*	*Post*
CI (L/m² per min)				
Low	+40[b] (4.2)	+42[b] (4.9)	+58[b] (8.8)	+44[b] (6.3)
Middle	+30[b] (4.5)	+34[b] (4.5)	+49[b] (5.1)	+27[b] (3.8)
High	+36[b] (4.9)	+44[b] (4.7)	+66[b] (6.5)	+47[b] (6.6)
PCWP (mm Hg)				
Low	−30[b] (4.7)	−20[b] (4.7)	−15[c] (7.2)	+22[d] (6.3)
Middle	−34[b] (4.5)	−25[b] (4.1)	−20[b] (4.3)	−3 (6.7)
High	−35[b] (4.0)	−22[b] (4.3)	−15[c] (6.0)	−6[d] (6.3)

[a]Loading dose of 50 µg/kg per minute over 10 minutes, then 0.375 (low, n = 34); 0.5 (middle, n = 34); and 0.75 (high, n = 31) µg/kg per minute.
[b]$P < .001$ versus control.
[c]$P < .05$ versus control.
[d]$P < .01$ versus control.
CI, Cardiac index; *PCWP,* pulmonary capillary wedge pressure; *SEM,* standard error of the mean.
From Feneck RO. Effects of variable dose milrinone in patients with low cardiac output after cardiac surgery. *Am Heart J.* 1919;121(suppl 2):1995.

Feneck[203] studied 99 adult patients with a low CO after elective cardiac surgical procedures. Milrinone was administered as a loading dose of 50 µg/kg over a 10-minute period, followed by a continuous infusion of 0.375, 0.5, or 0.75 µg/kg per minute (low-, middle-, and high-dose groups, respectively) for a minimum of 12 hours. These investigators observed that milrinone therapy was associated with a rapid and well-sustained increase in CO and a decrease in PAOP in all groups. These investigators also found that the increase in cardiac index was associated with elevations in SV and HR (Table 38.8).

Enoximone

Enoximone, an imidazolone derivative, is eliminated mostly by sulfoxidation, is solubilized in propylene glycol and cannot be diluted when administered intravenously. The recommended loading dose is 0.5 to 1.0 mg/kg, followed by an infusion of 5 to 10 µg/kg per minute. Gonzalez and associates[187] reported using enoximone for managing a cardiac index of less than 2.2 L/m² per minute despite a PCWP of 15 mm Hg, catecholamine administration (eg, dobutamine, dopamine), or intraaortic balloon pump counterpulsation after cardiac surgical procedures. Enoximone was administered as a 1 mg/kg loading dose over 10 minutes after a minimum of 4 hours of unsuccessful conventional therapy. An extra dose (0.5 mg/kg) was given if the increase in CO was less than 20%. A continuous infusion of the drug was administered at 3 to 10 µg/kg per minute and was continued for at least 8 hours. In all patients, significant increases in cardiac index and a significant decrease in PCWP occurred. Naeije and colleagues[204] also reported variable effects on BP, HR, and CO of enoximone in a dose of 0.5 mg/kg after cardiac surgical procedures.

Levosimendan

Levosimendan is a calcium-sensitizing drug that exerts positive inotropic effects by sensitization of myofilaments to calcium and vasodilation through opening of ATP-dependent potassium channels on vascular smooth muscle. These effects occur without increasing intracellular cAMP or calcium and without an increase in $M\dot{V}O_2$ at therapeutic doses. As would be expected with an inodilator, the hemodynamic effects include a decrease in PAOP in association with an increase in CO. β-Blockade does not block the hemodynamic effects of this drug. Levosimendan itself has a short elimination half-life, but it has active metabolites with elimination half-lives up to 80 hours. A study in patients with decompensated HF found that hemodynamic improvements at 48 hours were similar whether patients received the drug for 24 hours or 48 hours. Increasing plasma levels of the active metabolite were found for 24 hours after the drug infusion was stopped.[205] Levosimendan is approved in many European countries and is currently undergoing a cardiac surgical trial for use in the United States.

A randomized study enrolling 203 patients with low-output HF found that levosimendan improved hemodynamics more effectively than did dobutamine and was associated with a lower 6-month mortality rate.[206] However, the mortality rate finding may be caused more by adverse effects related to dobutamine than by a positive effect of levosimendan. Another study in 504 patients with LV dysfunction after acute MI demonstrated better 6-month survival with levosimendan, this time compared with placebo.[207] In a small study after cardiac operations, patients were given levosimendan; of 11 patients with severely impaired CO and hemodynamic compromise, 8 patients (73%) showed evidence of hemodynamic improvement within 3 hours after the start of levosimendan infusion. Specifically, cardiac index and SV were significantly increased, whereas MAP, indexed SVR, mean PAP, right atrial pressure (RAP), and PAOP were significantly lowered.[208] Clinical studies continue to evaluate the potential role for this positive inotropic agent in patients with HF.

Right-Sided Heart Failure

HF after cardiac surgical procedures usually results from LV impairment. Although an isolated right-sided MI can occur perioperatively, most perioperative inferior MIs show variable involvement of the right ventricle.[209] The myocardial preservation techniques that are best for the left ventricle may not offer ideal RV protection because the right ventricle is thin walled and more exposed to body and atmospheric temperature. Cardioplegic solution given through the coronary sinus (retrograde) may not reach parts of the right ventricle because of positioning of the cardioplegia cannula in relation to the venous outflow from this chamber and because the thebesian veins do not drain into the coronary sinus.[210] Impairment of RV function postoperatively is more severe and persistent when preoperative right coronary artery stenosis is present.[211] Although depression of the EF is compensated by preload augmentation, RVEF cannot be preserved if coronary perfusion pressure is reduced or impedance to ejection is increased.

Certain aspects of the physiology of the right ventricle make it different from the left ventricle. Normally, the RV free wall receives its blood flow during systole and diastole; however, systemic hypotension or increased RV systolic and diastolic pressures may cause supply-dependent depression of contractility when $M\dot{V}O_2$ is increased while coronary perfusion pressure is decreased.[212] The normal thin-walled right ventricle is at least twice as sensitive to increases in afterload as is the left ventricle[213] (Fig. 38.5). Relatively modest increases in outflow impedance from multiple causes in the postoperative period can exhaust preload reserve and cause a decrease in RVEF with ventricular dilation. RV pressure overload may be complicated by volume overload caused by functional tricuspid regurgitation.[214] Decreases in RV SV reduce LV filling, and dilation of the right ventricle can cause a leftward shift of the interventricular septum that interferes with diastolic filling of the left ventricle (ie, ventricular interaction) (Fig. 38.6). A distended right ventricle limited by the pericardial cavity further decreases LV filling. RV failure has the potential to affect LV performance by decreasing pulmonary venous blood flow, decreasing diastolic distending pressure, and reducing LV diastolic compliance. The resulting decrease in LV output further impairs RV pump function. The mechanical outcomes of RV failure in postoperative cardiac surgical patients are depicted in Fig. 38.7. It can therefore be appreciated how, once established, RV failure is self-propagating, and aggressive treatment interventions may be needed to interrupt the vicious cycle.

Although not consistently proved, PVR has been shown to be reversibly increased immediately after CPB and for several hours into

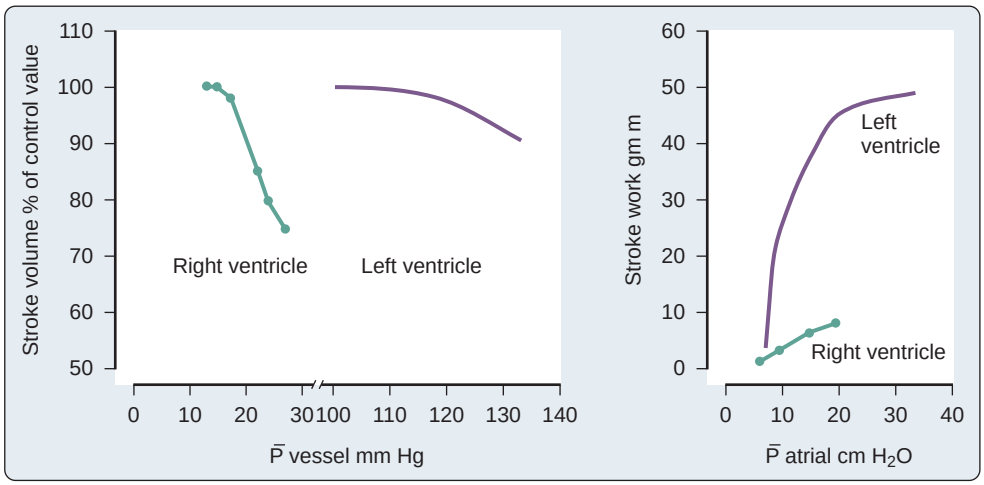


Fig. 38.5 Various effects of afterload and preload seen in ventricular function curves from the right and left ventricles. The right ventricular output is more afterload dependent and less preload dependent than the left ventricular output. $\bar{P}$, Pressure. *(From McFadden ER, Braunwald E. Cor pulmonale and pulmonary thromboembolism. In: Braunwald E, ed.* Textbook of Cardiovascular Medicine. *Philadelphia: Saunders; 1980:1643–1680.)*

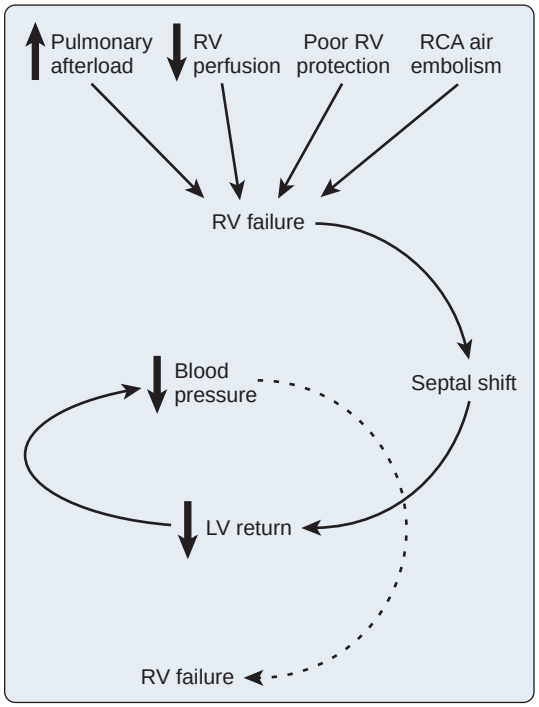


Fig. 38.6 Sequence inducing right ventricular failure and causing a downward spiral of events. *LV,* Left ventricular; *RCA,* right coronary artery; *RV,* right ventricular.

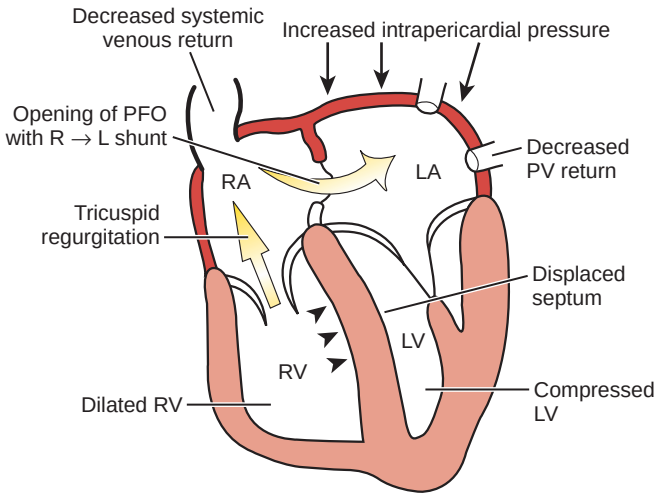


Fig. 38.7 Mechanical changes produced by acute right ventricular failure. *LA,* Left atrium; *LV,* left ventricle; *PFO,* patent foramen ovale; *PV,* pulmonary venous; *R → L,* right-to-left; *RA,* right atrium; *RV,* right ventricle.

the postoperative period.[215,216] The possible mechanisms include extravascular compression by increased lung water,[216] endocrine-mediated or autonomic nervous system–mediated increases in pulmonary vascular tone,[217] vasoactive substances released from activated platelets and leukocytes,[218] and leukocytes or platelet aggregates obstructing pulmonary vascular beds.[219] Hypoxic pulmonary vasoconstriction may result in increased PVR; more commonly, hypercarbia causes an important increase in PAP.[220,221] The pulmonary vascular bed has been shown to be more sensitive to the vasoconstrictor influences of respiratory acidosis after CPB as compared with the preoperative situation.[222] Moderate respiratory acidosis was shown to cause depression of the RVEF and increased RV end-diastolic volume, and these changes were immediately reversed when normocarbia was reinstituted.[223]

Diagnosis

In the postoperative cardiac surgical patient, a low cardiac index with RAP increased disproportionately compared with changes in left-sided filling pressures is highly suggestive of RV failure. The PAOP may also increase because of ventricular interaction, but the relationship of RAP with PAOP stays close to or higher than 1.0. The absence of a step-up in pressure in going from the right atrium to the pulmonary artery (mean), provided PVR is low, suggests that RV failure is severe and the right side of the heart is acting only as a conduit. This hemodynamic presentation is typical of cardiogenic shock associated with RV infarction. The venous waveforms are accentuated with a prominent Y descent similar to findings in constrictive pericarditis, thus suggesting reduced RV compliance.[224] Large V waves may also be discernible and may relate to tricuspid regurgitation.

The use of a volumetric PAC to calculate right-sided volumes and EF could potentially guide management in the setting of RV failure because increased end-diastolic volume in association with a decreased RVEF indicates decompensation. This catheter-computer system has been validated in comparison with radionuclear and ventriculographic

BOX 38.5 TREATMENT APPROACHES IN POSTOPERATIVE RIGHT-SIDED HEART FAILURE

Preload Augmentation
Volume, vasopressors, or leg elevation (CVP/PCWP <1)
Decrease juxtacardiac pressures (pericardium and/or chest open)
Establishment of atrial kick and treatment of atrial arrhythmias (sinus rhythm, atrial pacing)

Afterload Reduction (Pulmonary Vasodilation)
Nitroglycerin, isosorbide dinitrate nesiritide
cAMP-specific phosphodiesterase inhibitors, α_2-adrenergic agonists
Inhaled nitric oxide
Nebulized PGI_2
Intravenous PGE_1 (and left atrial norepinephrine)

Inotropic Support
cAMP-specific phosphodiesterase inhibitors, isoproterenol, dobutamine
Norepinephrine
Levosimendan

Ventilatory Management
Lower intrathoracic pressures (tidal volume <7 mL/kg, low PEEP)
Attenuation of hypoxic vasoconstriction (high FIO_2)
Avoidance of respiratory acidosis ($PaCO_2$ 30–35 mm Hg, metabolic control with meperidine or relaxants)

Mechanical Support
Intraaortic counterpulsation
Pulmonary artery counterpulsation
Right ventricular assist devices

cAMP, Cyclic adenosine monophosphate; *CVP/PCWP,* central venous pressure/pulmonary capillary wedge pressure; *FIO_2,* fraction of inspired oxygen; *$PaCO_2$,* partial pressure of arterial carbon dioxide; *PEEP,* positive end-expiratory pressure; *PGI_2,* prostaglandin I_2; *PGE_1,* prostaglandin E_1;.

measures, but it may not be accurate in the presence of tricuspid regurgitation.[34,225,226] Unfortunately, tricuspid regurgitation is a common finding in patients with RV dilatation.

Echocardiography allows qualitative interpretation of RV size, contractility, and configuration of the interventricular septum, and it can enable the clinician to provide a definitive diagnosis of RV dysfunction or RV failure. Because of the crescent shape of the right ventricle, volume determination is not easy, but the qualitative examination and assessment for tricuspid regurgitation are very valuable. TEE is also useful to determine whether the increased RAP opens a patent foramen ovale, thus producing a right-to-left shunt. This is important because traditional methods to treat hypoxemia such as PEEP and larger tidal volumes in this setting will only increase the afterload of the right ventricle and potentially increase the shunt and hypoxemia.

Treatment

Treatment approaches in postoperative RV failure may differ from those used in LV failure, and they are affected by the presence of pulmonary hypertension (Box 38.5). In all cases, preload should be increased to the upper range of normal; however, the Frank-Starling relationship is flat in RV failure, and to avoid ventricular dilation, the CO response to an increasing CVP should be determined. Volume loading should be stopped when the CVP exceeds 10 mm Hg and the CO does not increase despite increases in this pressure.[227,228] If a volumetric PAC is in use, an increase in the end-diastolic volume with unchanged or declining RVEF suggests no advantage to further volume loading. The CVP should not be permitted to exceed the PAOP because if these pressures equalize, any increase obtained in pulmonary blood flow will be offset by decreased diastolic filling of the left ventricle by ventricular interdependence.[229] The atrial contribution to RV filling is important when the ventricle is dilated and noncompliant. Maintenance of sinus rhythm and use of atrial pacing are important components of treating postoperative RV failure (see Chapters 6, 11, 16, 22, and 26).

Although vasodilators may lead to cardiovascular collapse in patients with RV infarction (as a result of decreases in RV filling and coronary perfusion), postoperative RV failure is often associated with increased PVR and pulmonary hypertension. In this context, attempts to decrease RV outflow impedance may be worthwhile. Intravenous vasodilators invariably reduce systemic BP and mandate the simultaneous administration of a vasoconstrictor. One way to reduce the pulmonary effects of the needed vasoconstrictor is to administer the vasoconstrictor through a LA catheter and treat RV dysfunction with intravenous prostaglandins and LA norepinephrine.[230] The PDE inhibitors are commonly used for their effect on the pulmonary vasculature and RV function. Interest in and availability of aerosolized pulmonary vasodilators have increased. This route of administration reduces or even abolishes undesirable systemic vasodilation. Delivery of the drug directly to the alveoli improves pulmonary blood flow to these alveoli and potentially improves oxygenation by better matching blood flow to ventilation. Three drugs have been used: NO, PGI_2 (ie, epoprostenol or prostacyclin), and milrinone.[231,232]

NO is an important signaling molecule throughout the body. In the lung, it rapidly diffuses across the alveolar-capillary membrane and activates soluble guanylate cyclase, thereby leading to smooth muscle relaxation by several mechanisms.[231] Inhaled NO is given through a specialized delivery system in a concentration of 5 to 80 parts/million. It is commercially available in the United States, but it is costly. NO has been used successfully to treat RV dysfunction associated with pulmonary hypertension after heart operations,[232] mitral valve replacement,[233] cardiac transplantation,[234] and placement of LV assist devices (LVADs).[235] Although it is widely used to treat the same problems in lung transplantation, a randomized trial of prophylactic inhaled NO in this population failed to show a benefit.[236] This finding should not prevent the use of NO should RV dysfunction occur in the lung transplant recipient. Potential adverse effects of inhaled NO include toxicity from forming nitrogen dioxide (NO_2) and methemoglobin, rebound pulmonary hypertension from abrupt disconnection or withdrawal, and pulmonary vascular congestion from increased pulmonary blood flow in patients with poor LV function. If NO is administered at the recommended dosage, toxicity should not be observed; patients should have the drug gradually withdrawn, and those with poor ventricular function should be closely monitored for increases in left-sided filling pressures.

A less expensive alternative to inhaled NO is aerosolized epoprostenol (ie, prostacyclin or PGI_2). This compound binds to cell-surface prostaglandin receptors, activating adenylate cyclase, which activates protein kinase A to cause a decrease in cytosolic free calcium. It also stimulates endothelial release of NO. It is a profound vasodilator and inhibitor of platelet aggregation. Similar to inhaled NO, delivery of epoprostenol to ventilated alveoli can improve oxygenation by augmenting blood flow to these alveoli. Aerosolized PGI_2 has been successfully used to treat pulmonary hypertension after cardiac surgical procedures[232,237] and pulmonary embolism[238] and to treat hypoxemia in patients with lung injury.[239,240] Use of this agent requires collaboration with pharmacy and respiratory therapy, as well as suitable care and monitoring of the nebulizer device. Adverse effects include the possibility of vagus-mediated bradycardia at low doses and risks similar to those of inhaled NO for abrupt withdrawal or left-sided HF.

Haraldsson and associates[241] studied the use of inhaled (ie, aerosolized) milrinone in patients with mild pulmonary hypertension after CPB. These investigators found that when delivered by this route, milrinone was an effective pulmonary vasodilator without causing systemic hypotension, and the pulmonary vasodilation was additive to that caused by inhaled PGI_2.

Even a moderate increase in arterial carbon dioxide tension ($PaCO_2$) should be avoided in patients with RV failure. Although induced

hypocarbia is of proven benefit in controlling low PVR in neonates, the evidence in adults does not warrant this as a standard therapy because mechanical ventilation–induced changes in intrathoracic pressure have important therapeutic implications[242,243] (see Chapter 39). An intraaortic balloon pump may be of great benefit, even in patients with a right ventricle that is mainly responsible for circulatory decompensation. This beneficial effect is mediated by increased coronary perfusion. Right-sided heart assist devices have a place as temporizing measures in severe intractable right-sided HF. Pulmonary artery counterpulsation is experimental, and its clinical role is uncertain.[244] In cases of severe RV failure it may be necessary to leave the sternum open or to reopen the chest if it has been closed. This approach decreases the tamponade-like compression of the left ventricle by the distended right ventricle, right atrium, and edematous mediastinal tissues.

Effects of Mechanical Ventilation in Heart Failure

HF at the time of a surgical procedure has been identified as a significant predictor of postoperative respiratory complications.[245] Maintenance of gas exchange in these situations usually mandates prolonged ventilatory support. Besides improving Pa_{O_2}, mechanical ventilation can influence D_{O_2} through its effects on CO. Suppression of spontaneous respiratory efforts may substantially decrease the work of breathing and improve the oxygen supply-demand relationship (see Chapter 39). Traditionally, the influence of mechanical ventilation on hemodynamics has been viewed as negative. The unavoidable rise in intrathoracic pressure caused by positive-pressure ventilation or PEEP is associated with decreased CO.[246] However, in the presence of HF or myocardial ischemia, raised intrathoracic pressure has the potential to affect the determinants of global cardiac performance favorably. Understanding these heart-lung interactions is essential for the integrated management of the ventilated patient with HF after cardiac operations. The effects of ventilation on RV and LV failure must receive independent consideration.

Systemic venous return is proportional to the pressure gradient between the systemic veins and the right atrium. Changes in intrathoracic pressure imposed by positive-pressure ventilation or PEEP are transmitted to the compliant right atrium and cause an increase in RAP. This change decreases the driving pressure for venous return, with a reduction in RV preload as the clinically most important mechanism of the decrease in RV SV caused by ventilatory support.[247] The effects of mechanical ventilation on RV preload may be accentuated by hypovolemia or by an increase in venous capacitance caused by vasodilator administration.[248] The effects of raised intrathoracic pressure can be overcome by fluid administration, leg elevation, or even vasopressors to raise the systemic venous pressure. Preload augmentation must be done cautiously if the patient has RV failure.

Two other factors related to raised intrathoracic pressure potentially impede the diastolic filling of the left ventricle. If positive-pressure ventilation or PEEP causes an increase in PVR, RV systolic emptying may be impaired, and the right ventricle will dilate. This change may cause leftward displacement of the interventricular septum and decrease LV compliance.[229] Independent of ventricular interaction, increased lung volume also raises juxtacardiac pressures, thus decreasing the transmural distending pressure.[249]

The end-diastolic volume and the systolic BP are directly proportional to systolic wall stress or ventricular afterload. Because the ventricles and the outflow vessels are surrounded by intrathoracic pressure, increases in this pressure by positive-pressure ventilation decrease the transmural pressure load (aortic or PAP relative to intrathoracic pressure) of each ventricle.[250] On the right side of the heart, the hemodynamic effects of ventilatory support usually result from changes in PVR. To the extent that PEEP increases lung volume above functional residual capacity, PVR may decrease from reduced compression of extraalveolar vessels.[251] Beyond that, large tidal volumes and high levels of PEEP increase PVR.[252] The increase in PVR may be obvious even with normal tidal volumes in airflow-limited diseases. The effects of increased PVR in RV failure are decreased CO and further dilation.

Raised intrathoracic pressure may significantly improve LV performance as a result of the reduced transmural pressure needed to give an acceptable systemic BP.[253] This pressure can be viewed as afterload reduction, a favorable effect separate from the resistance to venous return that may also help such patients. Clinically significant improvements in cardiac function have been documented in patients ventilated for cardiogenic respiratory failure produced by myocardial ischemia and after CABG operations.[254,255] High LV filling pressures may help identify a subgroup benefiting from reduced afterload with increased intrathoracic pressure.[256]

Raised intrathoracic pressure and PEEP have also been suggested to affect the inotropic state of the ventricles. Dilation of the right ventricle in response to an increase in afterload raises the RV distending pressure, which can reduce the pressure gradient for subendocardial coronary blood flow. Decreased RV contractility related to decreased coronary blood flow was described with high levels of PEEP in an animal model with critical right coronary artery obstruction,[212] as well as in patients with significant right coronary artery disease.[256] LV contractility does not seem to be affected by this mechanism.[257] Raised intrathoracic pressure and lung distention may also modulate contractility by stimulating vagal afferents[258] and releasing prostaglandins.[259] The impairment of contractility by these mechanisms appears to be minimal.

The circulatory responses to changes in ventilation should always be assessed in patients with cardiac disease; the goal of improving or maintaining D_{O_2} must be kept in mind. This usually requires measurement of arterial oxygenation and CO. In RV and biventricular failure the increase in the airway pressure caused by ventilatory support should be kept at a minimum compatible with acceptable gas exchange. This means avoidance of high levels of PEEP and trials of decreased inspiratory times, flow rates, and tidal volumes. Breathing modes that emphasize spontaneous efforts such as intermittent mandatory ventilation, pressure support, or CPAP should be considered. Alternatively, if isolated LV failure is the reason for ventilatory therapy, improvements in cardiac performance may be achieved by positive-pressure ventilation with PEEP. In particular, patients with increased LV filling pressures, mitral regurgitation, and reversible ischemic dysfunction may improve from afterload reduction related to increased airway and intrathoracic pressures. Newer modes of ventilatory support that decrease mean airway pressure, such as cardiac cycle–specific, high-frequency jet ventilation[260] and airway pressure release ventilation,[261] and their roles in supporting heart function, are discussed in Chapter 39.

Effects of Ventilatory Weaning on Heart Failure

Traditional criteria for weaning of ventilatory support assess the adequacy of gas exchange and peak respiratory muscle strength.[262] In the patient with HF, the response of global hemodynamics to spontaneous respirations must also be considered. The changes of the loading conditions of the heart brought about by resuming spontaneous ventilation can induce a vicious cycle resulting in hypoxemia and pulmonary edema.

Pulmonary congestion, often present in patients with LV dysfunction, decreases pulmonary compliance. Thus large decreases in inspiratory intrathoracic pressure are needed to cause satisfactory lung inflation. These negative swings of intrathoracic pressure increase venous return.[263] Increased diaphragmatic movements may raise intraabdominal pressure and further increase the pressure gradient for venous return.[264] Decreased intrathoracic pressure also raises the ventricular transmural pressures and the impedance to ventricular emptying. The increased afterload causes further increases in preload, and these changes jeopardize the myocardial oxygen balance. Accordingly, worsening of myocardial ischemia as shown by ST-segment deviations was demonstrated when ventilatory support was removed in patients ventilated after MI.[265] Spontaneous ventilation episodes also precipitated ischemic dysfunction and caused LV dilation and altered thallium-201 uptake in ventilator-dependent patients after lung injury caused by infection or surgical complications.[266]

In the patient with severe ventricular dysfunction, one of the main methods of improving cardiac performance to allow separation from CPB and to maintain function in the postoperative period is to augment preload with fluid therapy. The unavoidable consequences are a positive fluid balance and a weight gain of several kilograms, even after uncomplicated surgical procedures. Diuretic therapy to reduce this hypervolemia and vasodilator therapy to reduce ventricular wall stress should be considered before these patients are exposed to the afterload stress of ventilatory weaning.[263,277]

Cardiac Tamponade

Cardiac tamponade is an important cause of the low-CO state after cardiac operations and occurs when the heart is compressed by an external agent, most commonly blood accumulated in the mediastinum. Hemodynamic compromise, to some degree attributable to the constraining effect of blood accumulating within the chest, is often observed in the 3% to 6% of patients needing multiple blood transfusions for hemorrhage after cardiac surgical procedures.[268] Postoperative cardiac tamponade usually manifests acutely during the first 24 hours postoperatively, but delayed tamponade may develop 10 to 14 days after the operation, and it has been associated with postpericardiotomy syndrome or postoperative anticoagulation.[269–271]

The mechanism of hemodynamic deterioration during cardiac tamponade is discussed in Chapter 24 and mainly is the result of impaired filling of one or more of the cardiac chambers. As the external pressure on the heart increases, the distending or transmural pressure (external intracavitary pressure) is decreased. The intracavitary pressure increases in compensation lead to impaired venous return and elevation of the venous pressure. If the external pressure is high enough to exceed the ventricular pressure during diastole, diastolic ventricular collapse occurs. These changes have been documented in the right and the left sides of the heart after cardiac surgical procedures.[272] As the end-diastolic volume and end-systolic volume decrease, a concomitant reduction in SV occurs. In the most severe form of cardiac tamponade, ventricular filling occurs only during atrial systole. Adrenergic and endocrine mechanisms are activated in an effort to maintain venous return and perfusion pressure.[273,274] Intense sympathoadrenergic activation increases venous return by constricting venous capacitance vessels. Tachycardia helps to maintain CO in the presence of reduced SV. Adrenergic mechanisms may explain decreased urinary output and sodium excretion, but these phenomena may also be caused by reduced CO or a reduction in atrial natriuretic factor from decreased distending pressure of the atria.[237]

The diagnosis of cardiac tamponade depends on a high degree of suspicion. Tamponade after cardiac surgical procedures is a clinical entity distinct from the tamponade typically seen in medical patients in whom the pericardium is intact and the heart is surrounded by a compressing fluid. In the setting of cardiac surgery, the pericardial space is often left open and in communication with one or both of the pleural spaces, and the compressing blood is at least in part in a clotted, nonfluid state and able to cause localized compression of the heart. Serious consideration should be given to the possibility of tamponade after cardiac surgical procedures in any patient with an inadequate or worsening hemodynamic status, as evidenced by hypotension, tachycardia, increased filling pressures, or low CO, especially when chest tube drainage has been excessive. A more subtle presentation of postoperative tamponade is characterized by gradually increasing needs for inotropic and pressor support. Many of the classic signs of cardiac tamponade may not be present in these patients, partly because the patients are usually sedated and ventilated, but also because the pericardium is usually left open, resulting in a more gradual increase in the restraining effects of blood accumulation. Patients may have localized accumulations that affect one chamber more than another.[275] The classic findings of elevated CVP or equalization of CVP, pulmonary artery diastolic pressure, and PAOP may not occur.[276,277] It may therefore be difficult in the presence of declining CO and elevated filling pressures to distinguish tamponade from biventricular failure. A useful clue may be the pronounced respiratory variation in BP with mechanical ventilation in association with high filling pressures and low CO because the additional external pressure applied to the heart by positive-pressure ventilation may further impair the already compromised ventricular filling in the presence of tamponade.

Echocardiography may provide strong evidence for the diagnosis of cardiac tamponade.[277–280] Echolucent crescents between the RV wall and the pericardium or the posterior LV wall and the pericardium are visible with TTE or TEE. Echogenicity of grossly bloody pericardial effusions, especially when clots have been formed, may sometimes make delineation of the borders of the pericardium and the ventricular wall difficult, thus compromising the sensitivity of this technique. A classic echocardiographic sign of tamponade is diastolic collapse of the right atrium or right ventricle, with the duration of collapse bearing a relationship with the severity of the hemodynamic alteration, but such findings are often absent in patients after cardiac surgical procedures.[277,281,282] Often, TTE is difficult because of mechanical ventilation, and TEE is required for satisfactory imagining (see Chapters 15 and 16).

The definitive treatment of cardiac tamponade is surgical exploration with evacuation of hematoma. The chest may have to be opened in the ICU if tamponade proceeds to hemodynamic collapse. For delayed tamponade, pericardiocentesis may be acceptable. Medical palliation in anticipation of reexploration consists of reinforcing the physiologic responses that are already occurring while preparing for definitive treatment. Venous return can be increased by volume administration and leg elevation. The lowest tidal volume and PEEP compatible with adequate gas exchange should be used.[283] Epinephrine in high doses gives the needed chronotropic and inotropic boost to the ventricle and increases systemic venous pressures. Sedatives and opioids should be given cautiously because they may interfere with adrenergic discharge and precipitate abrupt hemodynamic collapse. Occasionally, patients develop significant cardiac tamponade without accumulation of blood in the chest. Edema of the heart, lungs, and other tissues in the chest after CPB may not allow chest closure at the first operation, and staged chest closure may be required after the edema has subsided.[284] Similarly, some patients with an inadequate hemodynamic status after cardiac surgical procedures despite maximum support in the ICU improve with opening of the chest because this tamponade effect is relieved. Reclosure of the chest in the operating room is often possible after a few days of continued cardiovascular support and diuresis.

Transplanted Heart

Postoperative circulatory control in the heart transplant recipient differs in three major respects from that of the patient who has not received a heart transplant: (1) the transplanted heart is noncompliant, with a relatively fixed SV; (2) acute rejection must be considered when cardiac performance is poor or suddenly deteriorates; and (3) these patients are at risk for acute RV failure if pulmonary hypertension develops.[285]

The fixed SV combined with denervation of the donor heart means that maintenance of CO often depends on therapy to maintain an elevated HR (110–120 beats/min). The drug most commonly used is isoproterenol because it is a potent inotropic agent and because it causes a dose-related increase in HR. Its vasodilating β_2-adrenergic effect on the pulmonary vasculature may be of benefit if PVR is greater than normal. Alternatively, atrial pacing may be used to maintain HR if contractility appears normal. Pacing is often used to allow the withdrawal of isoproterenol in the first postoperative days. Parasympatholytic drugs, such as atropine, do not have any effect on the transplanted heart (see Chapter 25).

Major concerns in monitoring and therapy for the transplant recipient are the potential for infection and rejection. Immunosuppressive therapy regimens include cyclosporine and usually steroids or azathioprine, or both. These drugs also suppress the patient's response to infection, and steroid therapy may induce elevations in the white blood

cell count, thus further confusing the issue. Protocols for postoperative care stress strict aseptic technique and frequent careful clinical evaluations for infection.

The adequacy of immunosuppression is monitored by percutaneous myocardial biopsy, usually performed at weekly intervals in the first month. Less invasive techniques, such as echocardiographic evaluation of diastolic function and sophisticated ECG analysis, are being evaluated.[286] Although acute rejection is diagnosed histologically, if it is suspected clinically (ie, acute deterioration in cardiac function), it must be treated with intense immunosuppressive therapy. The agents and doses used vary from institution to institution, but they usually include high-dose steroids and monoclonal antibody to T_3 lymphocytes (OKT3).[287] Pharmacologic management and sometimes mechanical support of biventricular function are required because severe impairment of contractility, ventricular dilation, and even cardiovascular collapse may occur.

Preoperative evaluation helps screen patients with fixed pulmonary hypertension because the normal donor right ventricle may acutely fail if it is presented with an elevated PAP in the recipient.[285] However, patients may have progression of disease between the time of evaluation and operation, or the right ventricle may be inadequately protected during harvest or transport. When separation from CPB is attempted, acute RV dilation and failure occur, and such patients may emerge from the operating room receiving multiple drug therapy, including the inhaled agents NO and prostacyclin, as described earlier, to focus on treating RV dysfunction and/or pulmonary hypertension.[288–292] Gradual withdrawal of these drugs occurs in the first postoperative days, with close monitoring of PAPs and oxygenation.

Concern for fluid balance is heightened in the perioperative period because transplant recipients are often fluid overloaded as a result of chronic biventricular failure and because of the potential for edema in the donor heart and even potentially the lungs. It is not unusual for vigorous diuretic therapy to be initiated within 24 hours of operation, with the goals of negative fluid balance and a PAOP less than 12 mm Hg. Inotropic agents rather than preload augmentation are used to keep CO at an acceptable level during this time. Electrolyte abnormalities induced by this therapy and the use of cyclosporine (which causes potassium and magnesium wasting) are common in this period. In patients with refractory respiratory failure and fluid overload, in whom oxygenation is a critical problem, early intervention with venovenous (VV) extracorporeal membrane oxygenation (ECMO) support is increasingly being considered as a therapeutic option.[293–296] In patients with persistent respiratory failure and/or cardiogenic shock, venoarterial (VA) ECMO also continues to evolve as an important and increasingly used therapeutic option.[297–300]

Advances in Cardiovascular Surgery and Postoperative Management

Advances in cardiothoracic surgery include minimally invasive transcatheter aortic valve replacement (TAVR), the incorporation of echocardiography in the cardiothoracic ICU, and improved biotechnology and durability related to cardiopulmonary support by ECMO. The following section explores these advances and highlights the major postoperative considerations for patients in the cardiothoracic ICU.

Postoperative Management of Complications After Transcatheter Aortic Valve Replacement

TAVR is increasingly used in clinical practice and is also described elsewhere (see Chapters 3, 21, and 27). Although the benefits and indications for TAVR are well established,[301,302] four major clinical challenges have emerged: vascular complications, stroke, paravalvular leak (PVL), and cardiac conduction abnormalities. The mechanisms of these intraoperative complications have immediate postoperative consequences and require appropriate management in the ICU.

Vascular Complications

Major vascular complications are independent predictors of major bleeding, transfusion, end-organ failure, and death.[303] Atherosclerotic disease of the femoral arteries and operator experience are other notable predictors of clinical outcomes. Strategies to minimize vascular injury involve designing smaller and sleeker delivery systems. The Valve Academic Research Consortium (VARC) provided standardized definitions for major and minor vascular injuries to guide clinician practice, communication among services, and comparability across clinical trials.[304,305] Major vascular complications were defined as thoracic aortic dissection, distal extremity or noncerebral vascular embolization requiring surgical intervention, and amputation. In addition, irreversible end-organ injury and iatrogenic access-related vascular injuries resulting in death, unplanned intervention, blood transfusion of 4 units or more, or permanent end-organ injury all meet criteria for major vascular complications related to TAVR.[304,305] Access-related vascular injuries included dissection, stenosis, perforation, pseudoaneurysm formation, arteriovenous fistula, hematoma, compartment syndrome, and irreversible nerve injury.[304,305]

Minor vascular complications were defined by the VARC as distal embolization not requiring surgical intervention or leading to irreversible end-organ damage. Furthermore, the VARC categorized minor vascular injuries as failure of percutaneous access-site closure requiring intervention but not leading to death, blood transfusion of 4 units or more, or permanent end-organ injury.[304,305]

An analysis of vascular complications from the transfemoral TAVR cohorts (n = 419) from the Placement of Aortic Transcatheter Valve (PARTNER) trials demonstrated that the incidence of major and minor vascular complications were 15.3% and 11.9%, respectively, within 30 days of TAVR.[306] Furthermore, the most common major vascular complications were dissection, access-site hematoma, and arteriotomy of the posterior femoral arterial wall. These findings are not surprising considering that the first-generation TAVR delivery systems required introducer sheaths as large as 24 Fr.[306] Moreover, major vascular complications significantly increased the risks of major bleeding (and therefore blood transfusions), renal failure requiring continuous renal replacement therapy, and death at 30 days and again at 1 year.[306] Female sex was the only identified independent predictor of vascular complications (hazard ratio, 2.31; 95% confidence interval [CI], 1.08–4.98; $P = .012$), and baseline renal disease (hazard ratio, 2.26; 95% CI, 1.20–4.43; $P = .002$) independently predicted 1-year mortality rates. Furthermore, the impact of major vascular iatrogenic injuries after TAVR on mortality rates was relatively higher in higher-risk patients.

Even though female sex was identified as the single independent predictor of vascular complications, one study showed that women had better short-term and long-term survival rates after TAVR.[307] One Canadian TAVR observational study found that although women had significantly more VARC-defined major vascular complications ($P = .003$), they had significantly lower 30-day (odds ratio [OR], 0.39; 95% CI, 0.19–0.80; $P = .01$) and 2-year mortality rates (hazard ratio, 0.60; 95% CI, 0.41–0.88; $P = .008$).[307]

Major vascular complications after TAVR remain an important barrier to further outcome improvement and cause much of the morbidity encountered postoperatively in the ICU. Contemporary data from the Mayo Clinic in Rochester, Minnesota showed that the TAVR learning curve reached a plateau after 30 cases of TAVR. For these reasons and the importance of having an experienced TAVR heart team, guidelines have set minimum operator and institutional requirements for these procedures.[308] In addition to operator experience, advances in hardware design with smaller-French introducer sheaths have been ushered into practice to decrease the risk of vascular complications further.[308–311] The delivery systems in second-generation devices are small than 20-Fr caliber,[312] and this change should significantly reduce the frequency of vascular complications.

Postoperative cardiovascular management of the patient who has undergone TAVR complicated by intraoperative vascular injury includes assessment of the degree of vascular injury as dictated by VARC guidelines and subsequent postoperative management in the

ICU. This care includes continuous monitoring of peripheral arterial pulses (focus on access site), adequate perfusion, development and treatment of end-organ dysfunction, and hemodynamic and hemostatic resuscitation.

Stroke

Asymptomatic cerebral embolism is common during TAVR. A detailed series of neuroimaging studies showed that clinically silent cerebral embolism occurs in up to 70% of these patients.[313–315] Major stroke, however, independently predicts prolonged recovery and increased mortality rates. Identified stroke predictors include history of previous stroke, functional disability, transapical approach, and AF. Embolic protection devices are under development to mitigate the risk of embolic stroke after TAVR (personal communication with Howard C. Herrmann, MD, PARTNER trial investigator, University of Pennsylvania, Philadelphia, February 2014).

The clinical stroke rate at 1 year after TAVR was 4.1% in a multicenter French registry ($n = 3195$; 34 centers).[316] The VARC definition of stroke after TAVR includes rapid onset of a neurologic deficit (global or focal), duration longer than 24 hours, absence of another cause of symptoms similar to a cerebrovascular accident, and confirmation of the diagnosis by a neurologist and neuroimaging.[304,305] The stroke was classified as major if the degree of disability was 2 or higher on the modified Rankin scale (ie, any disability that prevents a patient from carrying out his or her normal activities).[304,305] A weighted metaanalysis of TAVR studies (cumulative $n = 3519$; 16 studies from 2001 to 2011) reported a major stroke rate of 3.2% (95% CI, 2.1–4.8), as defined by the VARC criteria.[304,305,317]

Data have shown that the risk of stroke after TAVR is highest within the first week after TAVR while the patient may still be recovering in the hospital or sent home.[318,319] Stroke after TAVR significantly increases mortality rates.[318,319] The long-term effects of asymptomatic cerebral embolism associated with TAVR are unknown. The predictors of stroke early after TAVR include previous stroke, severe arterial atheroma, and a smaller aortic valve area.[318,319] Patients should be admitted to the ICU after undergoing TAVR and postoperatively monitored for immediate evidence of neurocognitive decline or focal neurologic deficit heralding a major stroke. Neurology consultation and activation of a stroke workup protocol native to the home institution should occur, and neuroimaging should be ordered to direct further clinical management. In the event of a stroke in the ICU, multidisciplinary decision making among physicians and patient care teams should be implemented regarding the initiation of permissive hypertension and procedural intervention.

Paravalvular Leak

PVL is common and significantly decreases survival. This undersizing is balanced against oversizing and aortic root trauma or rupture, which typically warrants emergency CPB and immediate repair. The formal grading of PVL severity in TAVR is based on its percentage of the circumferential extent of the aortic valve annulus. Further management strategies for PVL include a repositionable valve prosthesis and transcatheter plugging.

The immediate postoperative importance of PVL after TAVR relates to the presence of aortic regurgitation in an otherwise noncompliant left ventricle with diastolic dysfunction, as commonly seen with severe aortic stenosis. Grading of PVL is important because moderate to severe PVLs may result in symptoms of acute HF and pulmonary edema. The 1-year incidence of PVL of any severity after TAVR in France was 64.5%, with significant PVL independently predicting mortality rates (hazard ratio, 2.49; 95% CI, 1.91–3.25).[316] Two-year data from the PARTNER trial indicated that moderate or severe PVL is more common in TAVR compared with surgical aortic valve replacement (AVR) at 1 year and 2 years (7.0% vs 1.9% at 1 year and 6.9% vs 0.9% at 2 years; $P < .001$ for each comparison).[320] Mild or greater degrees of PVL in this series were associated significantly with mortality rates (hazard ratio, 2.11; 95% CI, 1.43–3.10; $P < .001$).[320] This mortality effect was proportional to the severity of PVL after TAVR. Data from an Italian TAVR registry (n = 663, 14 centers) indicated that although PVL was trace to mild in most cases, moderate or greater PVL (hazard ratio, 3.79; 95% CI, 1.57–9.10; $P = .003$) significantly increased late mortality rates.[321] The German multicenter TAVR registry ($n = 690$) showed that moderate or greater PVL independently predicted in-hospital mortality rates (OR, 2.43; 95% CI, 1.22–4.85; $P = .01$).[322] A single-center TAVR series (n = 145) reported that moderate or greater PVL significantly increased the risks of death (OR, 4.26; 95% CI, 1.59–11.45; $P = .004$) and poor clinical response to TAVR (OR, 10.1; 95% CI, 3.20–31.94; $P < .001$).[323]

The precise grading of PVL by echocardiography remains controversial.[304,305,324,325] The VARC defined the severity of PVL as a percentage of the circumferential extent of the aortic valve annulus as visualized on the midesophageal short-axis view of the aortic valve. The grading system, however, is imprecise, especially when the regurgitant jets may be multiple and eccentric. The diameters of all PVLs can be added together and then expressed as a percentage of the total aortic annular circumference.[326] Mild PVL is defined as having a less than 10% circumferential extent. Moderate PVL is defined as having a 10% to 20% circumferential extent.[304,305,326] In TAVR, it is vital to image the aortic valve in multiple esophageal and gastric views to obtain a comprehensive assessment of the PVL after valve deployment.[304,305,324–326] The cardiothoracic ICU physician should be informed if a post-TAVR patient has moderate or higher degree of PVL because this finding may have consequences for clinical management.

Cardiac Conduction Abnormalities

Cardiac conduction disturbances after TAVR are common and important.[327] Perioperative cardiac conduction disturbances after TAVR have been defined by VARC standardized clinical end-point definitions.[304,305] New-onset AF was defined by the VARC as an arrhythmia within the hospital stay that has the ECG characteristics of AF and lasts longer than 30 seconds.[304,305] The VARC guideline also recommended that the therapeutic approaches to AF are documented, including spontaneous conversion to sinus rhythm, electrical or medical cardioversion, and commencement of oral anticoagulation, as well as the clinical application of rate or rhythm control medications.[304,305] The VARC guidelines also highlighted the risk of atrioventricular (AV) block associated with TAVR.[304,305] The types of heart block may occur anywhere along the cardiac conduction pathway, including first-degree AV block, second-degree AV block (Mobitz I or Mobitz II), third degree AV block, bundle branch block, and AV block requiring pacemaker insertion. High-grade AV block was defined as persistent if it was present every time the underlying native heart rhythm was evaluated.[304,305]

Although AF and heart block are described complications after surgical AVR, these arrhythmias after TAVR currently are being investigated as TAVR enters the mainstream of clinical practice.[328–330] The management of postoperative AF after cardiothoracic procedures is described earlier in this chapter. The management of new-onset AF after TAVR is similar to that after open cardiothoracic surgical procedures, with the exception that pacer wires are not routinely present to facilitate overdrive pacing as they would be in more invasive cardiac operations. On occasion, a transvenous pacer may be present for reasons discussed later in this chapter. For clarity, perioperative pathophysiology and management of AV block after TAVR comprise the focus of this section.

Impact of Transcatheter Aortic Valve Replacement on the Cardiac Conduction System

The native aortic valve lies in close proximity to the AV conduction system, a location that puts the ventricular septal conductive system at risk during aortic valve procedures. A thorough understanding of the surgical anatomy allows the ICU physician to recognize the conductive consequences of aortic valve procedures (Fig. 38.8A). The basal attachments of the three aortic leaflets form an annulus that separates the aortic root from the LV outflow tract (LVOT). The noncoronary cusp lies adjacent to the membranous portion of the interventricular septum (Fig. 38.9A). The superior continuation of the membranous

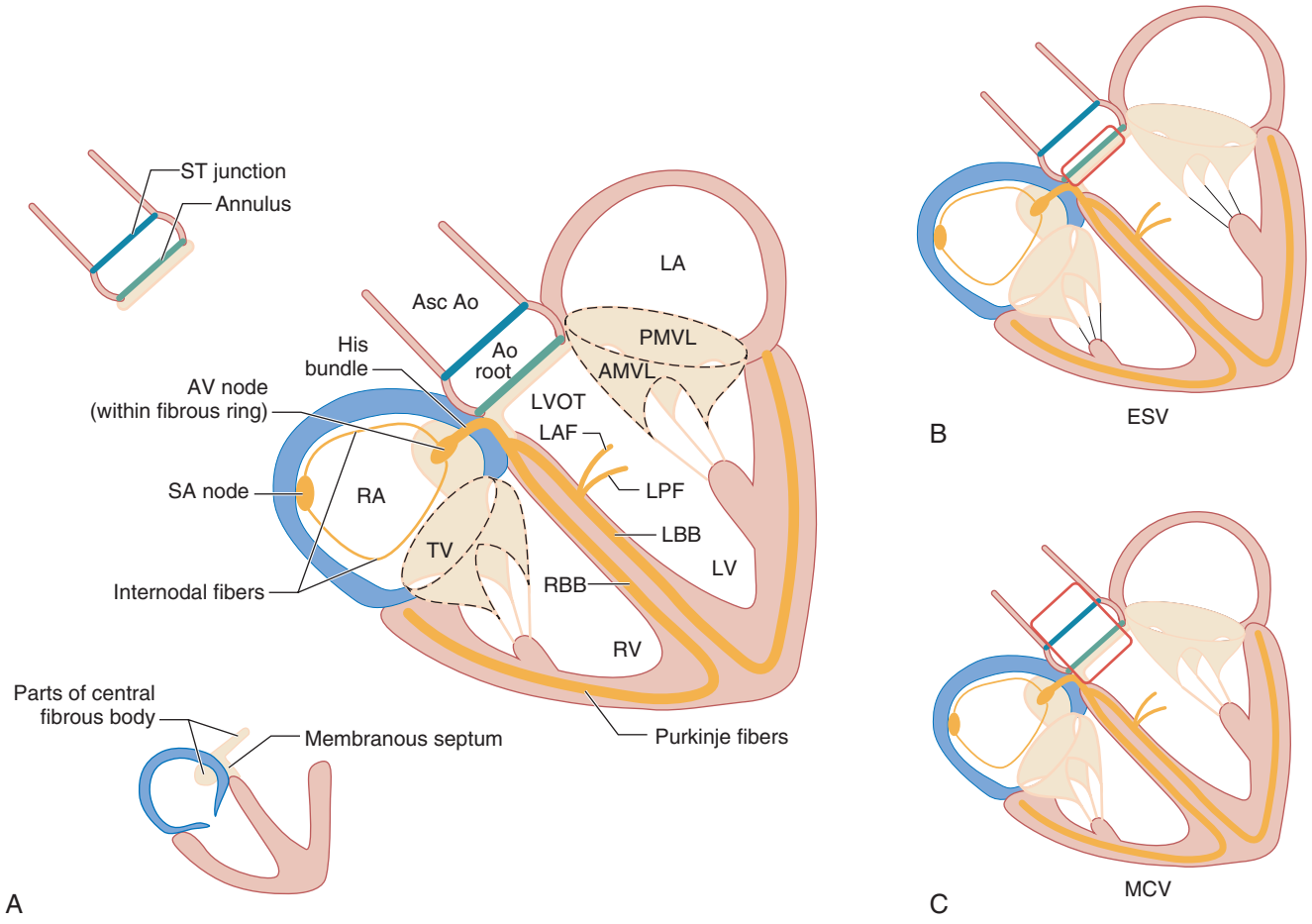


Fig. 38.8 The cardiac conduction system and its relationship with the transcatheter aortic valve replacement bioprostheses. (A) The atrioventricular *(AV)* node within the medial floor of the right atrium *(RA)* gives rise to the bundle of His, which traverses under the membranous septum within the distal left ventricular outflow tract *(LVOT)*. The right bundle branch *(RBB)* travels along the septal aspect of the RV. The left bundle branch *(LBB)* travels superficially along the septal aspect of the left ventricle *(LV)* to branch into the left anterior fascicle *(LAF)* and the left posterior fascicle *(LPF)*. Purkinje fibers mark the distal extent of the conduction system. (B) The typical implantation location for the Edwards SAPIEN Valve (*ESV;* Edwards Lifesciences, Irvine, Calif) bioprosthesis depicted by the *red box* at the level of the aortic annulus. Note the proximity to the cardiac conduction system. (C) The typical implantation location for the Medtronic CoreValve (*MCV;* Medtronic, Minneapolis, Minn) bioprosthesis depicted by the *red box* within the ascending aorta, aortic root, and distal LVOT. Note the proximity to the cardiac conduction system and the larger extent occupied by the MCV device. AMVL, Anterior mitral valve leaflet; *Ao,* aorta; *Asc Ao,* ascending aorta; *LA,* left atrium; PMVL, posterior mitral valve leaflet; *RV,* right ventricle; *ST,* sinotubular; *TV,* tricuspid valve. *(From Ghadimi K, Patel PA, Gutsche JT, et al. Perioperative conduction disturbances after transcatheter aortic valve replacement.* J Cardiothorac Vasc Anesth. *2013;27:1414–1420.)*

septum is an interleaflet triangle that separates the noncoronary from the right coronary cusp (see Fig, 38.9A). Both structures, the membranous septum and the interleaflet triangle, are in fibrous continuity and overlie the bundle of His as it extends leftward from the AV node (see Fig. 38.8A). The left bundle branch traverses below the membranous septum and penetrates superficially to traverse along the LV side of the interventricular septum.

The Edwards SAPIEN valve (ESV, Edwards Lifesciences, Irvine, Calif) bioprosthesis is a balloon-expandable trileaflet valve and is deployed through balloon expansion at the level of the annulus (see Figs. 38.8B and 38.9B).[331,332] The Medtronic CoreValve (MCV, Medtronic, Minneapolis, Minn) bioprosthesis is a self-expandable trileaflet valve with an elongated nitinol frame,[331,332] and the final position of the MCV valve covers three levels among the LVOT, aortic valve annulus, and ascending aorta (see Fig. 38.8C). The upper portion is situated within the ascending aorta and supports the position of the valve device in the same direction as blood flow. The middle third contains the leaflets with frame support above the native annulus. The lower third (ventricular) anchors the valve bioprosthesis within the LVOT (see Fig. 38.9B). The circumferential forces of the bioprosthetic valve in TAVR on the adjacent, underlying cardiac conduction system are believed to be a cause of cardiac conduction disturbances after TAVR (see Fig. 38.9B).[333–335]

Conduction disturbances may evolve during the postoperative period while the patient is being cared for in the ICU. In one trial ($n = 67$; MCV and ESV), complete heart block was observed in 22% (29% MCV vs 12% ESV; $P = .09$).[336] Early in the postoperative period, dynamic changes were noted in the patterns of AV block; new left bundle branch block (LBBB) at times resolved completely, and complete heart block developed into bundle branch block or first-degree AV block. Multivariate analysis identified baseline right bundle branch block (RBBB) as an independent predictor of permanent pacemaker

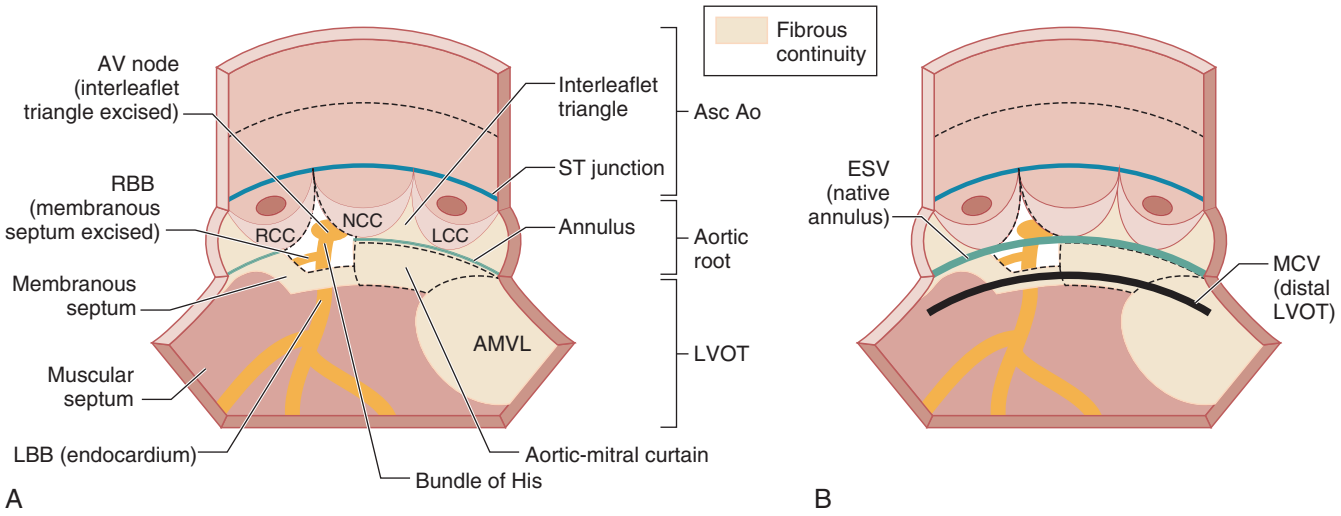


Fig. 38.9 The anatomic relationships of the cardiac conduction system, the aortic valve complex, and the transcatheter aortic valve replacement bioprostheses. (A) The left ventricular outflow tract *(LVOT),* aortic root, and ascending aorta *(Asc Ao)* are depicted to illustrate the proximity of the aortic valve complex to the conduction system. The aortic valve consists of three cusps (*RCC,* right coronary cusp; *LCC,* left coronary cusp; *NCC,* noncoronary cusp). The sinotubular *(ST)* junction represents the superior border of cusp attachment. The interleaflet triangle (between the RCC and the NCC) and relevant membranous septum have been removed to illustrate the underlying conduction tissue. (B) The LVOT, aortic root, and Asc Ao are depicted to illustrate the proximity of the aortic valve complex to the conduction system. The areas marked *MCV* (Medtronic CoreValve, Medtronic, Minneapolis, Minn) and *ESV* (Edwards SAPIEN Valve, Edwards Lifesciences, Irvine, Calif) indicate where the highest radial force is imposed for each bioprosthetic valve device. The maximal compressive effects of the ESV are exerted at the aortic valve annulus, whereas most of the compression from the MCV occurs in the distal LVOT, overlying the conduction system. *AMVL,* Anterior mitral valve leaflet; *LBB,* left bundle branch; *RBB,* right bundle branch. *(From Ghadimi K, Patel PA, Gutsche JT, et al. Perioperative conduction disturbances after transcatheter aortic valve replacement.* J Cardiothorac Vasc Anesth. *2013;27:1414–1420.)*

implantation (PPM) in the postoperative period following TAVR (relative risk [RR] 7.3; 95% CI 2.4–22.2).[336]

In a metaanalysis, the risk of heart block progressing to PPM was fivefold higher with the MCV than with the ESV (25.2% vs 5.0%).[337] The increased risk for complete AV block and PPM in TAVR, compared with surgical AVR, persists even when adjustments are made for age and baseline ECG characteristics.[337] One clinical trial identified baseline RBBB during multivariate analysis as a significant risk factor for pacemaker implantation after TAVR (OR, 8.61; 95% CI 3.14–23.67; $P < .0001$).[338]

It is readily apparent in the literature that the MCV has a significantly higher risk of AV block and pacemaker implantation compared with the ESV.[336–339] This difference is understandable from the anatomy of the AV conduction system and the MCV valve design, as outlined in Figs. 38.8 and 38.9.[340,341] Therefore the intensivist should be alerted if an MCV valve device has been implanted in patient with preoperative RBBB. Baan and colleagues[340] observed that the depth of MCV bioprosthesis implantation within the LVOT was a predictor of persistent new LBBB in 22 of 34 patients (65%). Bioprosthesis depth was assessed with contrast angiography after implantation and was defined as the distance between the ventricular end of the nitinol frame and the level of the native aortic valve annulus. The MCV bioprosthesis depth was 10.2 ± 2.3 mm in patients in whom LBBB had developed ($P = 0.02$).[340] This finding suggests that higher placement may lead to a decreased incidence of clinically significant conduction disturbances. In this same series, predictors of PPM included narrow LVOT diameter ($P = .01$) and mitral annular calcification ($P = .008$).

Risk factors for PPM postoperatively after TAVR have been investigated.[328,329] The following preoperative predictors were identified in a clinical trial with the MCV ($n = 34$; single-center study): (1) LBBB with left-axis deviation, (2) interventricular septal dimension greater than 17 mm, and (3) noncoronary cusp thickness greater than 8 mm.[342] In this trial, the risk of pacemaker implantation in the postoperative period after TAVR with the MCV bioprosthesis could be predicted with 75% sensitivity and 100% specificity if a patient had at least one of the foregoing predictors.[342] Preoperative RBBB has been associated with persistent AV block requiring PPM after TAVR with the MCV device.[343,344] In a larger trial ($n = 181$; all TAVR with MCV at a single Italian university medical center, 2007–2011), LBBB was the most common AV conduction abnormality, with an incidence of 50.3% at the time of discharge.[343] The incidence of PPM in this trial was 32.1%, and RBBB was the single independent predictor of PPM during multivariate analysis (hazard ratio, 16.5; 95% CI 3.3–82.3; $P < .001$).[343] A smaller trial ($n = 80$; 72% MCV and 28% ESV) also documented baseline RBBB ($P = .02$) and the MCV ($P = .01$) as independent predictors of PPM.[344] In a clinical trial ($n = 65$; all TAVR with MCV 2008–2009 at a Spanish university medical center), the only independent predictor of PPM was depth of valve implantation below the aortic valve annulus (OR, 1.9; 95% CI 1.19–3.05; $P < .007$).[345] A distance of 11.1 mm below the level of the annulus in the LVOT predicted the requirement for PPM with a sensitivity of 81% and a specificity of 84.6%.[345]

In a follow-up study ($n = 195$), the same group of investigators evaluated a new delivery system for MCV, which significantly decreased the MCV depth in the LVOT (6.4 ± 3 mm vs 9.6 ± 3.2 mm; $P < .001$) and the risk of PPM (14.3% vs 35.1%; $P = .003$).[346] Multivariate analysis in this larger sample identified the following predictors of PPM after TAVR with MCV: MCV depth in the LVOT (hazard ratio, 1.2; 95% CI 1.08–1.34; $P < .001$), baseline RBBB (hazard ratio, 3.5; 95% CI 1.68–7.29; $P = .001$), and application of the traditional delivery system (hazard ratio, 27; 95% CI 2.81–257; $P = .004$).[346] In a TAVR analysis ($n = 109$; all TAVR with the MCV at a single high-volume German university medical center), the risk factors for PPM also were investigated.[47] Significant predictors of PPM after TAVR in this series included age older than 75 years (OR, 4.6; $P = .02$), baseline HR less than 65 beats/minute

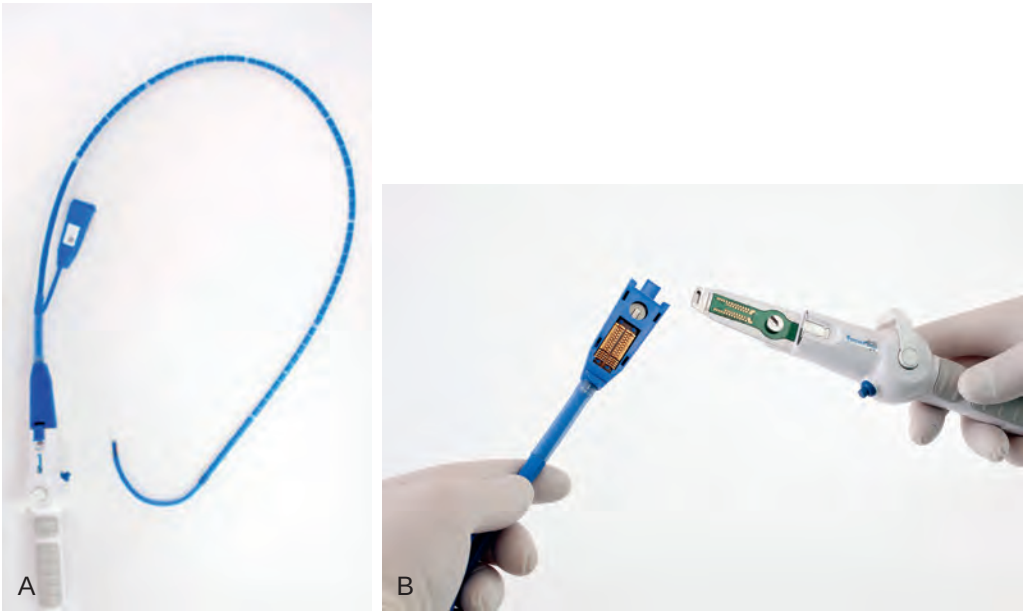


Fig. 38.10 (A) The miniaturized transesophageal echocardiography probe (ClariTEE, Imacor, Garden City, NY), which is 5.5-mm-diameter flexible probe *(blue)* capable of indwelling within the esophagus and providing echocardiographic images for up to 72 hours. The blue probe may be attached to the handle *(white and gray)* for maneuvering and image acquisition. (B) The probe may be detached and reattached from the ultrasound handle, with care taken to align the depicted prongs in the correct position. *(Courtesy Imacor, Garden City, NY.)*

(OR, 2.9; P = .04), MCV oversizing greater than 4 mm (OR, 2.8; P = .03), MCV bioprosthesis larger than 26 mm (OR, 2.2), AF (OR, 5.2; P = .001), and ventricular rate less than 65 beats/minute on postoperative day 1 (OR, 6.0).[347]

Anecdotally, preoperative implantation of a temporary ventricular screw-in lead ("temporary-permanent" pacemaker)[348] or a PAC with pacing capabilities[349] was described in patients meeting institutionally established criteria, to protect against life-threatening conduction abnormalities in the perioperative and postoperative periods. Future studies are under way to evaluate the safety and efficacy of these prophylactic strategies.

In summary, prompt recognition and proper management of AV blockade remain essential in the management of patients undergoing TAVR because hemodynamically significant heart block after TAVR may be common is selected patients and require PPM. It remains to be elucidated how the next generation of TAVR prostheses will affect the incidence, risk factors, and clinical outcomes of associated conduction disturbances. Certainly, in the postoperative ICU setting in the patient who does not have a preoperative pacemaker, new heart block and resulting hemodynamic instability may require swift intervention with transvenous pacing. This temporary measure may be implemented as a bridge to PPM.

Echocardiography in the Cardiothoracic Intensive Care Unit

Guidelines outlining basic TEE examinations have facilitated the adaptation of echocardiography in the ICU by intensivists without previous training in this modality.[350,351] The American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists developed a revised set of basic TEE views,[350,351] and they distinguished this document from the 1999 comprehensive guideline written by Shanewise and colleagues.[352,353] This document outlines 11 TEE views that together comprise the full basic TEE perioperative examination: the midesophageal 4-chamber view, the midesophageal 2-chamber view, the midesophageal long-axis view, the midesophageal ascending aortic long- axis view, the midesophageal ascending aortic short-axis view, the midesophageal aortic valve short-axis view, the midesophageal RV inflow-outflow view, the midesophageal bicaval view, the transgastric midpapillary short-axis view, and the descending aortic long-axis and short-axis views.[350,351] A publication sponsored by the Society of Critical Care Anesthesiologists put forward similar cardiac competencies for procedural TTE training of critical care trainees in the United States with a larger ICU-focused training paradigm.[354] These echocardiographic views may be particularly useful in the ICU when determining the causes of hemodynamic instability after cardiothoracic operations. In the immediate postoperative period, TTE may yield poor visualization as a result of postoperative change and positioning of support devices. For this reason, TEE is advocated during this early point-of-care setting for definitive and accurate diagnoses of hemodynamic aberrancies.

Miniaturized Transesophageal Echocardiography Probe

The use of a miniaturized, monoplane TEE probe (ClariTEE; ImaCor, Uniondale, NY) has been reported to provide benefit in the assessment of hemodynamically unstable patients in the cardiothoracic ICU (Fig. 38.10A).[355,356] This probe is capable of performing monoplane views of midesophageal four-chamber, midesophageal ascending aortic short-axis, and transgastric short-axis views (Fig. 38.11). The probe is 5.5 mm in diameter and is approved by the FDA to remain indwelling for up to 72 hours; it may connect to the portable ultrasound console (see Fig. 38.10A).[357] The probe may be disconnected when required from this portable ultrasound machine to facilitate evaluation of other patients with indwelling probes. The ultrasound machine (computer and monitor screen) is small and can be transported into patients' rooms. The ClariTEE probe uses a relatively high frequency (7 MHz) combined with specialized signal processing software to enhance penetration and contrast resolution. The inability to rotate the ultrasound scan sector, however, makes it difficult to obtain a complete diagnostic ultrasound scan of the cardiovascular structures. Furthermore, care must be taken to fasten the probe onto the ultrasound receiver to avoid damaging the prongs within this blue mini-probe (see Fig. 38.10B). In a retrospective study (n = 21; single academic medical center cardiothoracic ICU in the United States), the miniaturized TEE was used to

identify postoperative hemodynamic instability. In this observational study, discordance between hemodynamic monitoring and episodic TEE was qualitatively observed in 14 patients (66%), a finding suggesting that standard monitoring may be inferior to TEE in defining the clinical situation.[356]

Studies are limited, and caution should be used with any single monitoring device. We find these miniaturized probes satisfactory for hemodynamic management and assessment of gross RV and LV function. At this time, however, standard TEE probes and ultrasound machines are superior in imaging clarity, use of color-flow Doppler or Doppler profiles, and diagnosing causes requiring further procedural or surgical intervention in the setting of hemodynamic instability in the ICU.

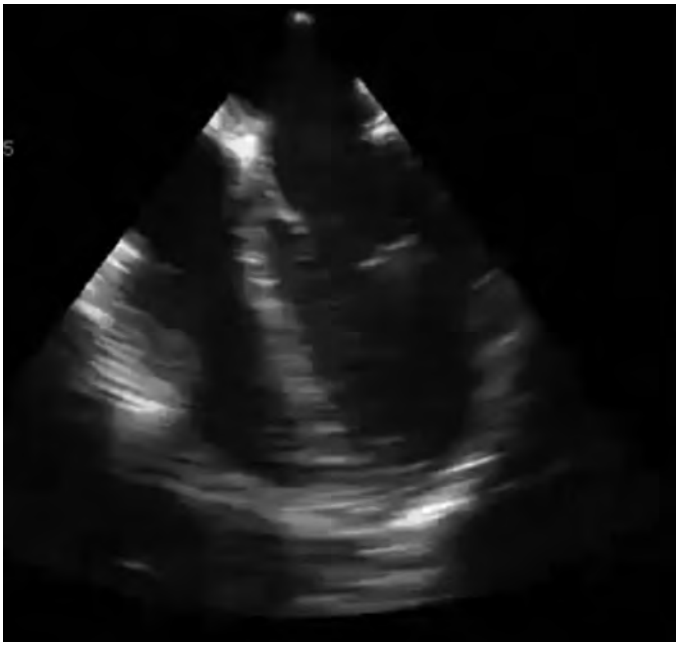


Fig. 38.11 Midesophageal four-chamber view provided by the ClariTEE (Imacor, Inc., Garden City, NY) transesophageal echocardiography probe. The image provides qualitative information (gross function) for hemodynamic management, as well as quantitative data in terms of calculating ejection fraction, but it lacks sufficient Doppler capability. *(Courtesy K. Ghadimi, MD.)*

Echocardiography During Postoperative Intensive Care Unit Management of Left Ventricular Assist Devices

Echocardiography is particularly useful for the postoperative management of patients after LVAD implantation. Assessment of RV function is central to the hemodynamic management of these patients in the immediate postoperative period, and echocardiography may help visualize interventricular septal position, RV systolic function, degree of the tricuspid valve regurgitation, and LV chamber size. TTE typically provides poor visualization of the cardiac chambers postoperatively as a result of inflammation, thoracostomy and mediastinal tubes, and echogenic dropout from the LVAD hardware. For this reason, we advocate TEE during the assessment of hemodynamics in this group of patients.

Right Ventricular Dysfunction After Left Ventricular Assist Device Placement

Classically, the patient may present to the ICU with central venous access, a PAC, and invasive arterial PB monitoring. This hemodynamic data alert the ICU physician to aberrancies that may suggest RV dysfunction, venous hypertension, and inadequate LVAD filling and ejection. The use of echocardiography together with these hemodynamic variables allows the immediate titration of pharmacologic support and LVAD speed to optimize CO, right-sided filling pressures, mixed venous oxygenation, RV systolic function, and LV filling.

Akin to the TEE examination on separation from CPB in the operating room, the TEE examination in the ICU similarly focuses on the position of the interventricular septum. Equal filling and emptying of both the right ventricle and the left ventricle result in a midline position of the septum. When LVAD flows are relatively higher than the ability of the right ventricle to deliver CO to the left ventricle, the interventricular septum tends to bow toward the left ventricle, thus resulting in an LV "suckdown" effect, RV failure, and increased tricuspid regurgitation (Fig. 38.12A).[358] Tricuspid regurgitations occurs as a result of tricuspid valve annular distortion (Fig. 38.12B). This effect may be somewhat offset by increasing SVR, increasing LV chamber size, and tempering the leftward interventricular septal shift. On occasion, titration of pharmacologic and mechanical support (LVAD settings) is ineffective, and a return to the operating room may be warranted for RV assist device (RVAD) placement.

In the event that cardiac filling pressures are low, RV systolic function seems adequate, but markers of systemic perfusion suggest reduced pressure and flow, TEE may be indicated to optimize LVAD speeds while maintaining a midline interventricular septum and determining the degree of mitral regurgitation and LV cavity size. The greatest yield of information through the use of TEE in the ICU comes from the direct visualization of the myocardium and the interplay

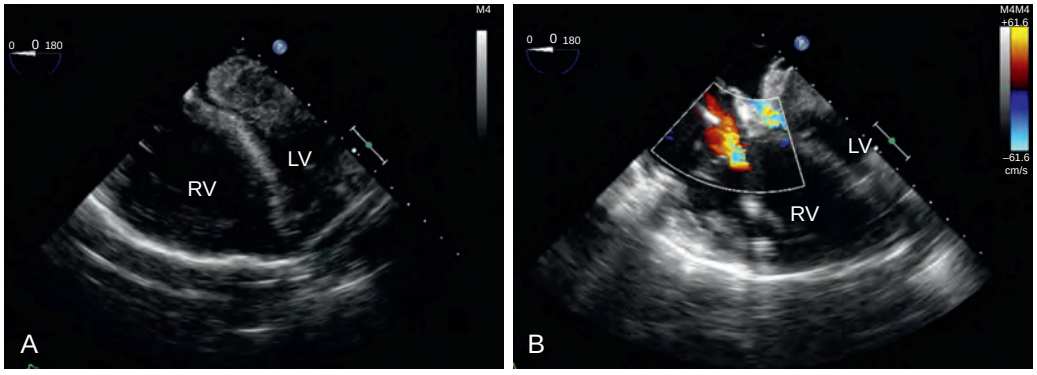


Fig. 38.12 Left ventricular assist device (LVAD) "suckdown" effect seen by transesophageal echocardiography (TEE) in the cardiothoracic intensive care unit. (A) Midesophageal four-chamber view using TEE to illustrate LVAD suckdown as a result of right ventricular failure and relatively increased and mismatched LVAD flows. (B) Midesophageal four-chamber view with color-flow Doppler illustrating severe tricuspid regurgitation during this suckdown event. *LV,* Left ventricle; *RV,* right ventricle. *(Courtesy K. Ghadimi, MD.)*

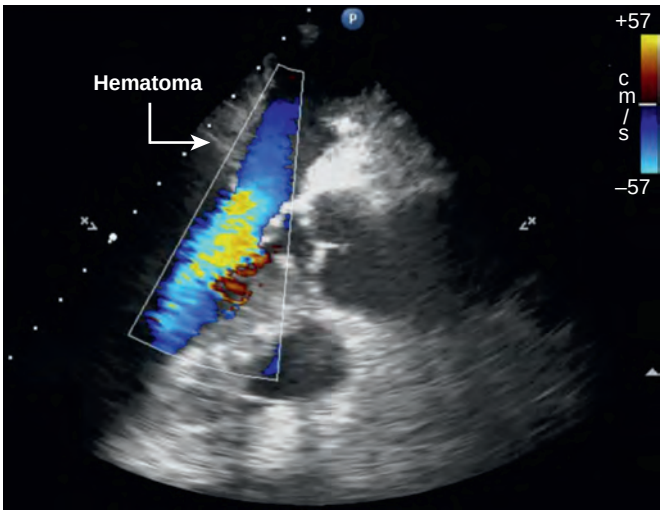


Fig. 38.13 Midesophageal long axis view illustrates left atrial compression by hematoma resulting in reduced left ventricular assist device (LVAD) inflow in a patient receiving high-dose vasoactive agents and observed LVAD suction events. *(Courtesy K. Ghadimi, MD.)*

among the cardiac chambers, as well as the simultaneous assessment of hemodynamic variables (eg, MAP, CVP, PAP, $S\bar{v}O_2$, cardiac index).[359]

Echocardiography to Rule Out Obstructive Shock After Left Ventricular Assist Device Placement

Increasing right-sided filling pressures, reduced cardiac index, and low mixed venous oxygenation saturation may alert the intensivist to problems with intrinsic RV function, but causes of obstructive shock should be excluded. Invasive hemodynamic monitoring cannot always discern among different causes of poor RV function. However, TEE enables the clinician definitively to diagnose new pericardial effusions, large right-sided pleural effusions, or bleeding resulting in mass compression of the atria and/or ventricles. In the setting of cardiac tamponade physiology, immediate return to the operating room is warranted to relieve mass compression of the involved cardiac chambers (Fig. 38.13).

Echocardiography in Patients Requiring Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is mechanical support of the lungs and/or heart for a period of days to weeks by a modified pulmonary or CPB machine; this support is discussed in detail in Chapter 32.[360–362] VV ECMO is primarily used for treating severe but potentially reversible respiratory failure, and VA ECMO is primarily used for treating severe cardiac or cardiorespiratory failure.

Venovenous Extracorporeal Membrane Oxygenation

With VV ECMO, deoxygenated blood is drained from the inflow cannula placed in a large central vein, typically the inferior vena cava (IVC), and oxygenated blood is returned through a cannula whose tip lies in or close to the right atrium. Ideally, all or most of the blood from the outflow cannula passes through the tricuspid valve into the pulmonary circulation. Under the condition that the oxygenated blood does not pass through the tricuspid valve but instead is "recirculated" into the inflow cannula, this blood does not contribute to systemic oxygenation and may result in hypoxemia if the recirculating volume is substantial. Although recirculation may be suspected by nonechocardiographic modalities, echocardiography can verify the diagnosis of clinically important recirculation by directly visualizing flow from the outflow cannula entering the inflow conduit. The relative positions of the inflow and outflow cannulas may be separated under direct echocardiographic guidance with color-flow Doppler imaging to eliminate clinically important recirculation (some degree of recirculation remains and in usually unavoidable). After the direct visual guidance

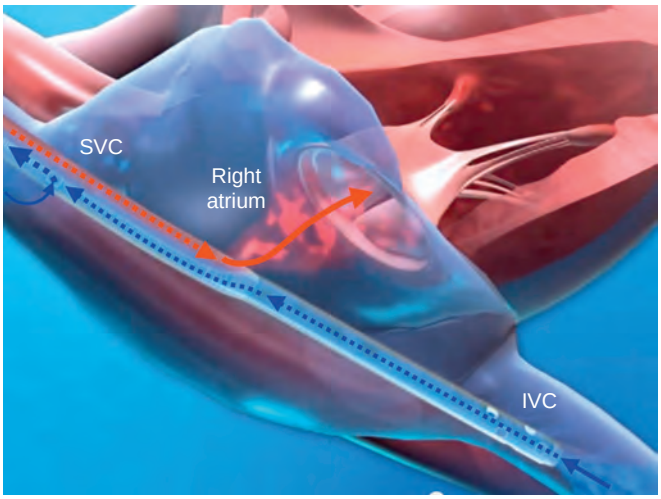


Fig. 38.14 The Avalon Elite Bicaval Dual-Lumen (Avalon Elite Bicaval Dual-Lumen Catheter and Vascular Access Kit, Maquet Cardiopulmonary, Rastatt, Germany) in the correct position. The cannula is inserted through the right internal jugular vein and is positioned through continuous imaging with the distal (inflow) tip in the inferior vena cava *(IVC)* and the proximal (inflow) tip within the superior vena cava (*SVC*) (systemic venous return shown by *blue arrows*). The outflow orifice is positioned medially toward the tricuspid valve and delivers extracorporeal membrane oxygenated blood to the right atrium *(red arrows). (Modified from Maquet, Cardiopulmonary, Rastatt, Germany.)*

of separating the inflow and outflow cannulas, standard assessment for recirculation (eg, preoxygenator PaO_2 < postoxygenator PaO_2) can verify the correction of systemic hypoxemia.

One single-cannula technique uses a double-lumen single cannula (Avalon Elite Bicaval Dual-Lumen Catheter and Vascular Access Kit, Maquet Cardiopulmonary, Rastatt, Germany), and it is designed for placement in the right internal jugular vein.[363] The tip of the (larger) inflow lumen is situated within the IVC, thus taking care to avoid insertion into a hepatic vein (Fig. 38.14). The inflow lumen has an end hole and a side fenestrations at the tip, as well as side holes proximal to the exit site of the inflow lumen that allow drainage from the both the SVC and the IVC (Fig. 38.15, and see Fig. 38.14). The outflow lumen of the single cannula opens 10 cm above the inflow cannula tip and is designed to return blood to the right atrium (see Fig. 38.14).[363] Once inserted, the outflow cannula lumen should be positioned inward and toward the tricuspid valve to direct flow through the valve, although this is more a theoretic than a practical consideration. On occasion, both the openings of the outflow and inflow cannula may be within the IVC because of advancement from the percutaneous insertion site. Certainly, outflow cannula tip position should be a consideration if significant recirculation or low flows are encountered on initiation of VV ECMO flow. TEE may be used to illustrate flow within the inflow and outflow cannula lumina and to illustrate position of each limb within the IVC (Fig. 38.16A) and the right atrium (Fig. 38.16B), respectively. The SVC inflow orifice may be challenging to view by TEE, but it can be assumed to be in correct position if the other two openings are positioned correctly.

Venoarterial Extracorporeal Membrane Oxygenation

During VA ECMO, systemic venous blood drains into the circuit through a cannula placed in the right atrium through either the IVC (femoral approach) or SVC (internal jugular vein approach). This may be visualized by TEE to establish flow through the cannula and correct positioning (Fig. 38.17). If TEE is contraindicated, TTE may provide utility in selected patients who allow adequate echocardiographic visualization through the chest wall (Fig. 38.18). Akin to VV ECMO, blood passes through the inflow cannula of the VA ECMO circuit into the pump and the oxygenator/heat exchanger before returning to the

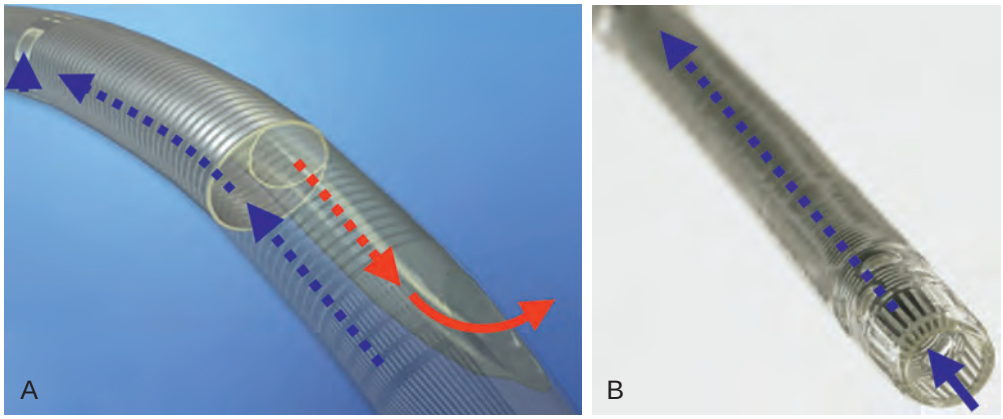


Fig. 38.15 Focused depiction of the Avalon Elite cannula. (A) A flexible membrane separates the oxygenated blood *(red arrows)* from the venous drainage *(blue arrows)*. The superior vena cava *(SVC)* inflow port is visible at *the top left (blue arrowhead)*. (B) The distal inflow tip has a single, fenestrated opening within the inferior vena cava *(IVC)*. *(Modified from Javidfar J, Brodie D, Wang D, et al. Use of bicaval dual-lumen catheter for adult venovenous extracorporeal membrane oxygenation.* Ann Thorac Surg. *2011;91:1763–1768.)*

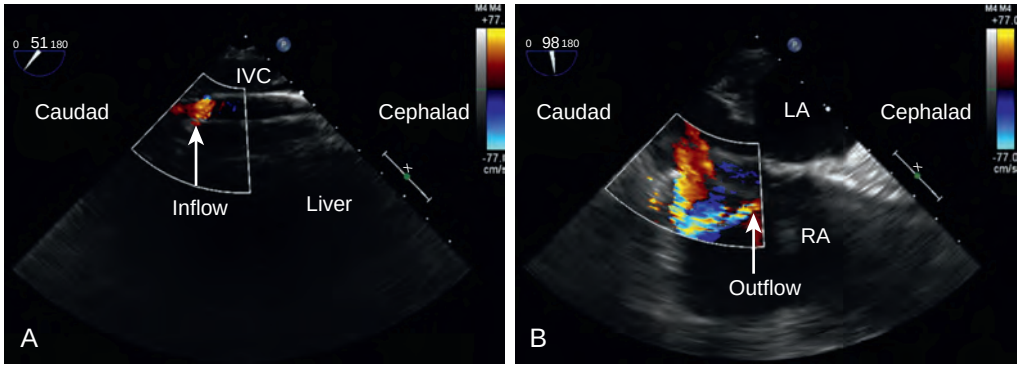


Fig. 38.16 Transesophageal echocardiographic visualization of the Avalon Elite cannula (Maquet Cardiopulmonary, Rastatt, Germany) during venovenous extracorporeal membrane oxygenation. Caudad and cephalad directions are marked on the images for orientation. (A) The inflow lumen of Avalon Elite Bicaval Dual-Lumen Catheter and Vascular Access Kit (is visible within the inferior vena cava *(IVC)* with color-flow Doppler illustrating blood flowing within the inferior intrahepatic IVC toward the inflow tip of the cannula. (B) The outflow cannula of Avalon Elite cannula is visible within the right atrium *(RA)*. Color-flow Doppler imaging illustrates blood flow from the outflow cannula directed medially toward the tricuspid valve (not seen). The color-flow Doppler box encompasses a smaller portion of the cannula outflow and shows a small amount of blood flowing away from the tricuspid valve; this finding is common but is presumably of no clinical significance (in the setting of normal flows and adequate extracorporeal gas exchange). *LA,* Left atrium. *(Courtesy K. Ghadimi, MD.)*

patient through a cannula placed within or grafted to a large artery (femoral, axillary, or aorta, commonly). Systemic arterial blood flow is the sum of the VA ECMO circuit flow and any ejection from the left ventricle. Systemic BP is determined by flow and vascular tone. Because oxygen and carbon dioxide tensions are controlled during extracorporeal support, the patient's systemic arterial oxygen saturation (Sa_{O_2}) is determined entirely by the oxygen saturation of the blood in the ECMO return cannula, which is normally 100%, in the absence of LV ejection. However, if LV ejection is present, Sa_{O_2} depends on the relative flow and oxygen saturation of blood from both the ECMO circuit and blood ejected by the left ventricle.

Using Echocardiography to Troubleshoot Common Complications of Venoarterial Extracorporeal Membrane Oxygenation

- **North-south syndrome:** This syndrome occurs in the specific circumstance of severely impaired lung function in conjunction with femoral placement of the VA ECMO outflow cannula. In this situation, the potential exists for upper body hypoxemia (coronary arteries, cerebral blood vessels, and upper limbs) because proximal branches of the aorta receive predominantly deoxygenated blood ejected from the left heart. This phenomenon of north-south syndrome may be seen on echocardiography as stagnant, "swirling" flow in the descending thoracic aorta as a result of the interface created by blood ejected from the left ventricle and blood returning to the patient from the outflow limb (Fig. 38.19). Even in the presence of significant LV ejection, this situation does not arise if pulmonary function is good or the outflow cannula is transitioned to central placement (proximal aorta or axillary artery). For this reason, institutional practice may dictate transition from peripheral (through the femoral artery) to central (through the aortic or axillary artery) cannulation as soon as the patient is clinically stable enough to handle this transition. Alternatively, after recovery of LV function is confirmed by echocardiography, but lung function continues to suffer, transition to VV ECMO may be initiated.

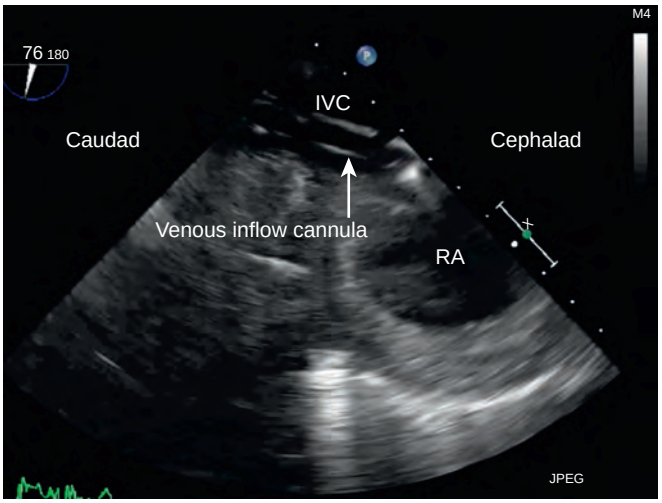


Fig. 38.17 Transesophageal echocardiographic image of the veno-arterial extracorporeal membrane oxygenation inflow cannula within the junction of the inferior vena cava *(IVC)* and the right atrium *(RA)*. Caudad and cephalad directions are marked on the image for orientation. The cannula (which has been inserted percutaneous from the right common femoral vein) tip sits within the RA, and the cannula contains side fenestrations to increase inflow volume. The cannula has been advanced into the superior vena cava (not pictured) under echocardiographic guidance to improve upper body venous drainage. *(Courtesy K. Ghadimi, MD.)*

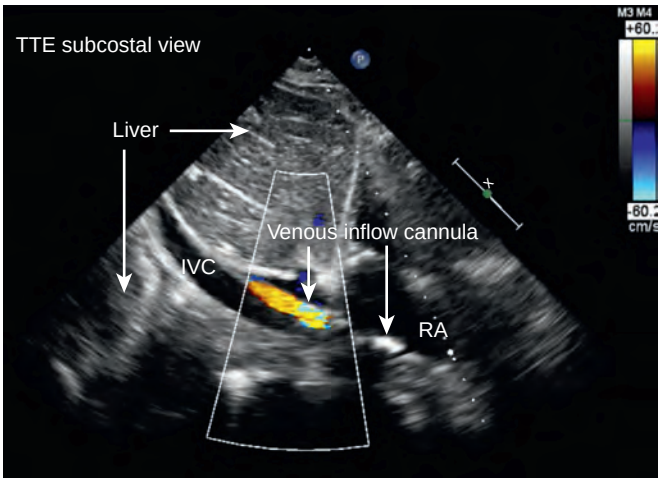


Fig. 38.18 Transthoracic echocardiographic *(TTE)* image of venoarterial (VA) extracorporeal membrane oxygenation (ECMO) inflow cannula within the inferior vena cava *(IVC)* and right atrium *(RA)*. In the subcostal TTE view, the "venous" inflow cannula for a patient undergoing peripheral VA ECMO is visible within the IVC and RA. Fenestrations within the cannula are marked by *white arrows*. In a patient with relative or absolute contraindication(s) to transesophageal echocardiography, TTE is warranted and may provide clear and diagnostic imaging for ECMO cannula placement. *(Courtesy K. Ghadimi, MD.)*

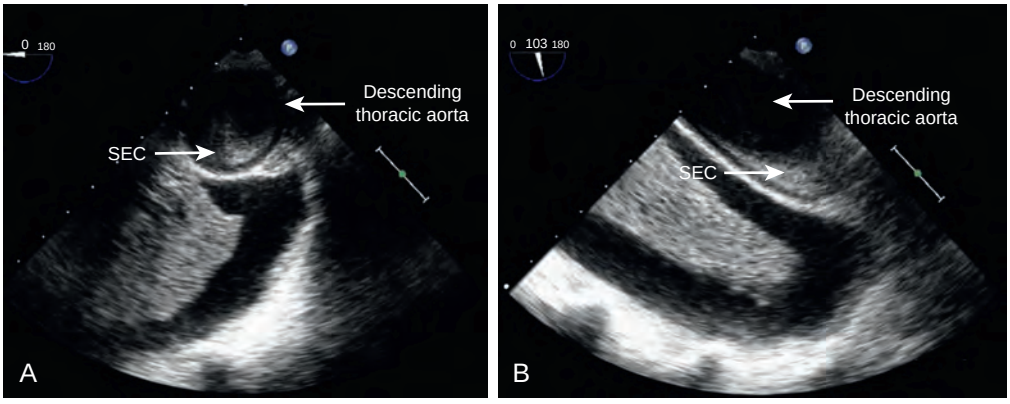


Fig. 38.19 Transesophageal echocardiographic image illustration north-south syndrome in a patient with upper body hypoxemia. Descending aorta (A) short-axis view and (B) long-axis view illustrate increased spontaneous echogenic contrast *(SEC)* within the descending thoracic aorta signifying stagnant flow. *(Courtesy K. Ghadimi, MD.)*

- **Hemodynamic instability:** Hypotension during "full-flow" VA ECMO and complete circulatory support in the absence of native cardiac function suggests vasodilation or LV distention. LV distention may become particular problematic in patients with aortic and mitral regurgitation. Clinically, the patient may present with pulmonary edema frothing from the endotracheal tube shortly after institution of VA ECMO and/or ventricular arrhythmia requiring defibrillation. The diagnosis may be confirmed by identifying a severely dilated left ventricle with TEE. Increasing pump flows reduce pulmonary blood flow and ameliorate the issue. Failing this, the left side of the heart must be vented. Surgically, the LV vent may be inserted through the right upper pulmonary vein and the cannula advanced across the mitral valve and into the left ventricle. Echocardiographic confirmation of LV vent placement is important to ensure that the left ventricle is decompressed and that the risk of developing LV thrombus has been significantly reduced (Fig. 38.20).

Weaning and Discontinuing Venoarterial Extracorporeal Membrane Oxygenation

An early sign of recovery of myocardial function is the presence of pulsatility on the arterial waveform. Patients are usually weaned from VA ECMO onto moderate doses of inotropic support (eg, epinephrine 0.04–0.1 μg/kg per min). The planned inotropic regimen should be started several hours before weaning. Circuit flows are slowly reduced to 1 to 2 L/minute, cardiac function is assessed with TEE during hemodynamic monitoring. If the patient is hemodynamically stable and TEE imaging demonstrates preserved cardiac function on pharmacologic support, then decannulation and discontinuation of VA ECMO are planned. Patients with an LVEF lower than 30% after 2 days of VA ECMO are significantly less likely to be successfully weaned than those with an EF greater than 30% (8% vs 54%; $P < .001$).[364] The previously described miniaturized TEE probe was used for weaning from VA ECMO in a single-center observational study using a standardized VA ECMO weaning protocol ($n = 21$).[365] The investigators indicated that

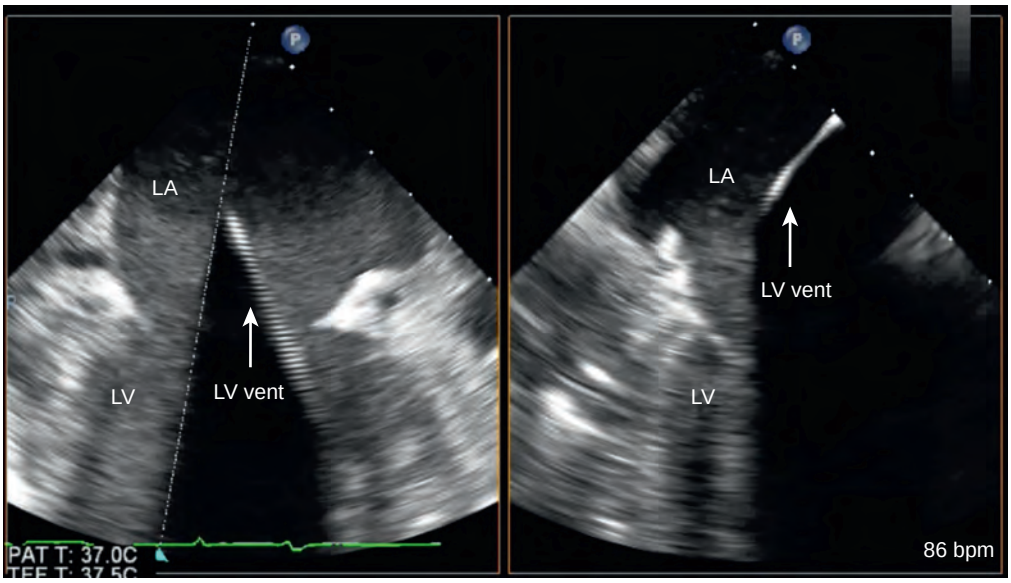


Fig. 38.20 Transesophageal echocardiographic (TEE) image of left ventricular vent *(LV vent)* placement in preparation for deployment of central venoarterial extracorporeal membrane oxygenation. The cross-plane feature of TEE illustrates the LV vent inserted from right upper pulmonary vein (not pictured) and advanced across the mitral valve to provide LV decompression. *LA,* Left atrium; *LV,* left ventricle. *(Courtesy K. Ghadimi, MD.)*

the positive predictive value for ventricular recovery by this mini-TEE probe was 100% using their standardized ECMO weaning protocol (95% CI, 73%–100%).[365]

In conclusion, understanding the process of initiation, management, weaning, and discontinuation from both VV and VA ECMO represents an important skill set for today's cardiothoracic intensivist. In particular, the utility of TEE in the care of these patients with complex conditions provides the intensive care physician with a tool that confirms the diagnosis of common complications or even routine management during VV and VA ECMO.

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39

Postoperative Respiratory Care

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KEY POINTS

1. Pulmonary complications following cardiopulmonary bypass are relatively common, with up to 12% of patients experiencing some degree of acute lung injury and approximately 1% requiring tracheostomy for long-term ventilation.
2. Risk factors for respiratory insufficiency include advanced age, presence of diabetes or renal failure, smoking, chronic obstructive lung disease, peripheral vascular disease, previous cardiac operations, and emergency or unstable status.
3. Patients with preexisting chronic obstructive lung disease have higher rates of pulmonary complications, atrial fibrillation, and death.
4. Operating room events that increase risk include reoperation, blood transfusion, prolonged cardiopulmonary bypass time, and low–cardiac output states, particularly if a mechanical support device is required.
5. Transesophageal color Doppler echocardiography is an important tool for real-time bedside monitoring in the postoperative period and has additional applications in assessing ability to wean from long-term ventilatory support.
6. Hospital-acquired infections are important causes of postoperative morbidity. Strategies to reduce the incidence of ventilator-associated pneumonia include early removal of gastric and tracheal tubes, formal infection control programs, hand washing, semirecumbent positioning of the patient, use of disposable heat and moisture exchangers, and scheduled drainage of condensate from ventilator circuits.
7. Patients at risk for acute lung injury and those developing acute respiratory distress syndrome should be switched to a lung-protective ventilation strategy, which involves maintaining peak inspiratory pulmonary pressure less than 35 cm H_2O and restricting tidal volumes to 6 mL/kg of ideal body weight.
8. Permissive hypercapnia may be necessary to implement a lung-protective ventilation strategy. It should be used judiciously in patients with pulmonary hypertension because acidosis can exacerbate pulmonary vasoconstriction and further impair right ventricular function and cardiac output.
9. Impediments to weaning from mechanical ventilation and extubation include delirium, unstable hemodynamic status, respiratory muscle dysfunction, renal failure with fluid overload, and sepsis.
10. Short-term weaning success can be achieved with any variety of ventilation modes. The patient receiving long-term ventilatory support requires an individualized approach that may encompass pressure-support ventilation, synchronized intermittent mandatory ventilation weaning, or T-piece trials. Noninvasive ventilation may assist in the transition from full support to liberation from mechanical ventilation.
11. Although several parameters exist to assess respiratory strength and endurance, the single best parameter is the frequency-to–tidal volume ratio.
12. Long-term administration of neuromuscular blocking agents is associated with persistent muscle weakness. Possible causes included accumulation of drug metabolites, critical illness polyneuropathy, or neurogenic atrophy.
13. A few patients are not able to be weaned from ventilation support. Characteristics of these patients include a persistent low-output state with multisystem organ failure. Echocardiography can be helpful in establishing ventricular filling, contractility, and cardiac output at baseline and during weaning trials. Long-term weaning may be best accomplished in a specialized unit rather than an acute cardiovascular recovery area.

Patients undergoing cardiac surgical procedures experience physiologic stresses from anesthesia, sternotomy or thoracotomy, surgical manipulation, and cardiopulmonary bypass (CPB). Each of these interventions can create transient deleterious effects on pulmonary function even in patients with normal lungs; the effects may be exaggerated in the presence of preexisting pulmonary disease. Important pulmonary changes after cardiac operations include diminished functional residual capacity following general anesthesia and muscle relaxants,[1] transient reduction in vital capacity following median sternotomy and intrathoracic manipulation, atelectasis, and increased intravascular lung water.[2] Acute functional residual capacity reduction creates arterial hypoxemia secondary to a mismatch between ventilation and perfusion and diminishes lung compliance with increased work of breathing. This additional work of breathing, which increases oxygen consumption by up to 20% in spontaneously breathing patients,[3] also increases myocardial work at a time when myocardial reserves may be limited. Changes in spirometric measurements and respiratory muscle strength can last up to 8 weeks postoperatively.[4]

Thus many cardiac surgical patients can be expected to have respiratory complications. Acute lung injury (ALI), sometimes progressing to acute respiratory distress syndrome (ARDS), can occur in up to 12% of postoperative cardiac patients.[5] Approximately 6% of cardiovascular surgical patients require more than 72 hours on the ventilator, and approximately 1% of patients undergo tracheostomy to facilitate recovery and weaning from prolonged support with mechanical ventilation.[6]

Risk Factors for Respiratory Insufficiency

The lung is especially vulnerable because disturbances may affect it directly (atelectasis, effusions, pneumonia) or indirectly (from fluid overload in heart failure; as the result of mediator release from CPB, shock states, or infection; or from changes in respiratory pump function, as with phrenic nerve injury). Postoperative status is determined in part by the patient's preoperative pulmonary reserve, as well as by the level of stress imposed by the procedure. Thus a patient with reduced vital capacity as a result of restrictive lung disease who is undergoing a minimally invasive surgical procedure may have fewer postoperative pulmonary issues than a relatively healthy patient who is undergoing simultaneous coronary artery bypass grafting (CABG) and valve replacement with its longer accompanying operative, anesthetic, and CPB times. Respiratory muscle weakness contributes to postoperative pulmonary dysfunction, and prophylactic inspiratory muscle training has been shown to improve respiratory muscle function, pulmonary function test results, and gas exchange, as well as reducing the incidence of delayed extubation.[7]

Assessing Risk Based on Preoperative Status

Robust models are available to stratify mortality outcome by preoperative risk factors in patients undergoing cardiac surgical procedures.[8–12] The independent (predictive) variables and their weighting vary from model to model. They also vary between models predicting mortality rates and those predicting morbidity or length of stay outcomes,[9] but the commonalities are greater than the differences. The Society of Thoracic Surgeons National Adult Cardiac Surgery Database is widely used in the United States, and it offers, in addition to a mortality prediction, a model customized to predict prolonged ventilation.[10,11] The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is commonly used in Europe.[12] Factors common to outcome risk adjustment models include age, sex, body surface area, presence of diabetes or renal failure, chronic lung disease, peripheral vascular disease, cerebrovascular disease, previous cardiac operation, and emergency or unstable status.[9–11] Chronic obstructive pulmonary disease (COPD) may be an expected major risk for postoperative respiratory morbidity and death, and it appears as a factor in some models. However, hospital mortality rates in patients with mild to moderate COPD are not especially high; the few patients with severe COPD, especially those older than 75 years of age and receiving steroids, are at highest risk.[13] Patients with preexisting COPD have higher rates of pulmonary complications (12%), atrial fibrillation (27%), and death (7%).[13] Obesity, defined by increased body mass index, does not appear to increase the risk of postoperative respiratory failure or death.[14,15] Conversely, even modest elevations of serum creatinine (>1.5 mg/dL) are independently associated with higher morbidity and mortality rates.[9,16]

At least four studies have used multivariate regression techniques to elucidate factors specifically associated with postoperative respiratory failure (Table 39.1). The studies differ in their end points for outcome, and in their choice of preoperative versus operative versus postoperative variables. Spivack and colleagues[17] examined 513 consecutive patients undergoing CAGB and identified reduced left ventricular ejection fraction, preexisting congestive heart failure, angina, current smoking, and diabetes mellitus as predictors of mechanical ventilation support beyond 48 hours. In this study, pulmonary diagnosis, lung mechanics, and blood gas parameters were not independently useful in predicting outcome. Branca and colleagues[18] found that the mortality rate predicted by The Society for Thoracic Surgeons model[10] was the single best predictor of mechanical ventilation support for longer than 72 hours but also identified mitral valvular disease, age, vasopressor and inotrope use, renal failure, operative urgency, type of operation, preoperative ventilation, previous cardiac operation, female sex, myocardial infarction within 30 days, and previous stroke as contributors. Rady and colleagues[19] examined both preoperative and intraoperative factors and noted that transfusion of more than 10 units blood products or total CPB time in excess of 120 minutes was an important operative event in addition to the usual preoperative predictors of extubation failure. Canver and Chandra[20] looked only at operative and postoperative predictors versus the end point of mechanical ventilation for more than 72 hours; these investigators found that prolonged CPB time, sepsis and endocarditis, gastrointestinal bleeding, renal failure, deep sternal wound infection, new stroke, and bleeding requiring reoperation were important predictors of prolonged ventilatory support. None of these models, general or specific to respiratory complications, is sufficiently sensitive or specific to prohibit consideration of surgical treatment for an individual patient, but these models do provide the clinician with an early warning for patients at high risk.

Operating Room Events

Identification of the patient who is difficult to intubate is important for planning extubation for a time when sufficient personnel and equipment are available to implement a potentially difficult reintubation. Opioids and neuromuscular blocking agents with long half-lives may be expected to influence extubation time, but it is the skill of the anesthesiologist in knowing how to use these drugs well and not the specific duration of drug action that influences extubation time. Patients undergoing reoperation are at risk[19–21] partly because of longer CPB times with reoperation, increased use of blood transfusion, and the additional likelihood of bleeding in this population. Length of time on CPB is repeatedly identified as a risk factor,[19–21] and a correlation between CPB time and inflammatory cytokine release has been demonstrated.[22] However, levels of C-reactive protein, an inflammatory marker, do not correlate with outcomes such as time spent on mechanical ventilation.[23] Genetic polymorphisms are associated with respiratory complications,[24] a finding suggesting that risk prediction may require more sophisticated understanding of individual patients' variables. Observations of dose-dependent reductions in adverse events after CABG in patients receiving statins are also intriguing.[25,26] In randomized, double-blind trials, both simvastatin and atorvastatin were shown to have beneficial effects on the systemic inflammatory response after CPB.[27,28]

Cardiovascular collapse occasionally occurs at the time of chest closure secondary to severe distention or edema of the lungs. Physiologically this condition acts much like cardiac tamponade, and the solution is to leave the chest open for 24 to 48 hours. An open chest delays early extubation, and it also has a potential to produce long-term ventilator dependency should infection or sternal osteomyelitis develop.

The prognostic and therapeutic implications of an intraaortic balloon pump (IABP) depend on the reasons for which the device was inserted. Not surprisingly, mortality and ventilation dependency rates are lowest in patients not requiring any mechanical support. In patients whose IABP was placed preoperatively for unstable angina, definitive surgical treatment should correct the problem, and removal of the IABP and extubation need not be delayed. In all other situations, intubation and ventilatory support may be required beyond the time of removal of the IABP because of residual cardiac dysfunction, fluid overload, or associated organ injury. Patients whose IABP was placed for preoperative cardiogenic shock, as an assist to separating from bypass, or for low-output states in the postoperative period have a high mortality risk and frequently need prolonged ventilatory support.

Positive end-expiratory pressure (PEEP) during CPB has been advocated as one method to prevent atelectasis. This approach is impractical in patients with obstructive lung disease because air trapping

TABLE 39.1 Factors Predicting Postoperative Respiratory Outcome

	Spivack et al, 1996[17]	*Branca et al, 2001*[18]	*Rady et al, 1999*[19]	*Canver and Chandra, 2003*[20]
End point	Mechanical ventilation >48 h	Mechanical ventilation >72 h	Extubation failure (reintubation after initial extubation)	Mechanical ventilation >72 h
Risk factors	Reduced LVEF Preexisting CHF Angina Current smoking Diabetes	STS-predicted mortality estimate Mitral valve disease Advanced age Pressors or inotropes Renal failure Operative urgency Type of operation Preoperative ventilation Previous CABG Female sex MI within 30 days Previous stroke	Age ≥65 y Inpatient status Vascular disease COPD or asthma Pulmonary hypertension Reduced LVEF Cardiac shock Hct ≤34% BUN ≥24 mg/dL Serum albumin ≤4.0 mg/dL DO_2 ≤320 mL/L^2 per min >1 previous CABG Thoracic aortic operation ≥10 units of blood products Total CPB time ≥120 min	CPB time Sepsis and endocarditis GI bleeding Renal failure Deep sternal wound infection New CVA Bleeding requiring reoperation

BUN, blood urea nitrogen, *CABG,* coronary artery bypass grafting; *CHF,* congestive heart failure; *COPD,* chronic obstructive pulmonary disease, *CPB,* cardiopulmonary bypass; *CVA,* cerebrovascular accident; DO_2, systemic oxygen delivery; *GI,* gastrointestinal; *Hct,* hematocrit; *LVEF,* left ventricular ejection fraction; *MI,* myocardial infarction; *STS,* The Society of Thoracic Surgeons.

interferes with surgical exposure. Recruitment maneuvers following CPB have a variable impact on intubation time; most studies show them to be ineffective in reducing the need for long-term ventilatory support. Alveolar recruitment maneuvers can be performed without deleterious effects, even in morbidly obese patients, as long as intravascular volume is adequate.[29] No compelling data indicate that fluid management choices or the use of steroids before CPB will have substantial effects on intubation time or respiratory failure.

Transcatheter aortic valve replacement (TAVR) has emerged as an option for treating severe aortic valve stenosis.[30] Percutaneous and transcatheter mitral valve replacement procedures have also been described.[31] Initial candidates for these procedures were older patients with comorbidities who were considered to be at high or extreme surgical risk for traditional open valve replacement, but the procedure is rapidly becoming a disruptive technology able to replace traditional open operations as delivery systems become smaller and multidisciplinary teams gain confidence. Randomized trials are under way to assess whether moderate-risk patients will also benefit from this procedure. TAVR is also frequently used as an alternative to reoperative tissue aortic valve replacement. The so-called "valve-in-valve" procedure inserts a new transcatheter valve within a previously placed degenerating tissue valve. TAVR procedures can be performed from multiple access points, including transfemoral, transapical (through a small left thoracotomy), and transaortic (through a small right anterior thoracotomy). In the United States, many centers conduct this procedure using general anesthesia in an operating room or hybrid suite, but increasingly in Canada and Europe, transfemoral TAVR is accomplished in catheterization laboratories, with anesthesia management akin to sedation for angioplasty. A systematic review of seven observational studies totaling 1542 patients suggested that either local or general anesthesia may be used, with similar short-term outcomes.[32]

The acute hemodynamic changes following TAVR are usually well tolerated, but decompensation (shock) may occur, particularly if a dynamic intraventricular pressure gradient develops after the relief of valvular obstruction. In this situation, inotropic (β-adrenergic) support may exacerbate the decompensation; volume expansion and selective α_1 vasopressor support are preferred. The incidence of rescue conversion to sternotomy after TAVR is not well studied (perhaps 1% to 3%[33]), but it carries substantial morbidity, especially in patients deemed too ill for conventional open valve replacement. Major stroke, vascular complications, and hemodynamic changes including new-onset atrial fibrillation can be expected events in the intensive care unit (ICU)[34]; because these events are also seen in patients undergoing CPB and off-bypass procedures, they are discussed later.

Randomized studies are lacking for optimal management of TAVR-treated patients requiring intubation, but extrapolating from the fast-track experience with CABG, even high-risk patients can be managed with early extubation and mobilization.[35] TAVR is a truly collaborative endeavor, requiring close collaboration and cross-training for the heart team, anesthesiology, vascular surgery, cardiac imaging, critical care, and nursing[35] (see Chapters 21 and 27).

Postoperative Events

Historically, patients undergoing CPB were kept intubated and sedated at least overnight to permit stabilization and metabolism of the large doses of opioids then used. This practice began to change in the 1990s with the advent of fast-track recovery, which spread from selected patients to general use.[36,37] The expected ICU course, if the patient is not extubated "on the table,"[38] is a short period of ventilation support while the patient is warmed, allowed to awaken, and observed for bleeding or hemodynamic instability. In low-risk patients, short-stay (8-hour) protocols can deliver clinical results at lower cost comparable to a standard overnight ICU stay.[39] Preoperative risks, issues with difficult intubation, and operating room events should be communicated from the operating room team to the ICU team at the time of ICU admission. Box 39.1 outlines criteria to be met before routine extubation. Laryngeal edema can often be identified by the absence of an air leak when the endotracheal tube cuff is deflated. Intravenous methylprednisolone can reduce the incidence of postextubation stridor.[40] Prophylactic nasal CPAP at 10 cm H_2O for a minimum of 6 hours has been shown to reduce hypoxemia, pneumonia, and reintubation rates after elective cardiac operations.[41]

Before extubation, a quick neurologic examination should be performed to rule out new cerebrovascular events, the presence of excess sedation, or residual neuromuscular blocking agents. Knowing that the work of breathing can consume up to 20% of cardiac output should preclude immediate extubation in the hemodynamically unstable patient. Although patients may be successfully extubated while on the IABP, the need to lie flat after balloon and sheath removal may interfere with their ability to resolve atelectasis and clear secretions. This limitation often dictates continued temporary ventilator support until the patient is able to sit up.

Health care–acquired infections are important causes of postoperative morbidity and increased costs, and include pneumonia, sepsis, and *Clostridium difficile* colitis.[42] Hospital-acquired pneumonia, and specifically ventilator-acquired pneumonia (VAP), may occur in any patient receiving continuous mechanical ventilation. Studies quote rates of hospital-acquired pneumonia of 3% to 8% for cardiac surgical patients, when assessed by criteria used by the Centers for Disease Control and Prevention (CDC), but these rates are lower when assessed by clinicians taking into account alternate explanations for new infiltrates,

BOX 39.1 CRITERIA TO BE MET BEFORE EARLY POSTOPERATIVE EXTUBATION

- *Neurologic*: Awake, neuromuscular blockade fully dissipated (head lift ≥5 s); following instructions, able to cough and protect airway
- *Cardiac*: Stable without mechanical support; cardiac index ≥2.2 L/m^2 per min; MAP ≥70 mm. Hg; no serious arrhythmias
- *Respiratory*: Acceptable CXR and ABGs (pH ≥7.35); minimal secretions, comfortable on CPAP or T-piece with spontaneous respiratory rate ≤20 breaths/min; MIP ≥25 cm H_2O; alternatively, a successful SBT defined as an RSBI <100 and a PaO_2/FIO_2 ≥200
- *Renal*: Undergoing diuresis well; urine output >0.8 mL/kg per h; not markedly fluid overloaded from operative or CPB fluid administration or SIRS
- *Hematologic*: Chest tube drainage minimal
- *Temperature*: Fully rewarmed; not actively shivering

ABG, Arterial blood gas; *CPAP*, continuous positive airway pressure; *CPB*, cardiopulmonary bypass; *CXR*, chest radiograph; *MAP*, mean arterial pressure; *MIP*, maximal inspiratory pressure; *PaO_2/FIO_2*, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; *RSBI*, rapid shallow breathing index; *SBT*, spontaneous breathing trial; *SIRS*, systemic immune response syndrome.

tachypnea, or hypoxemia.[43] The historical risk of VAP in ICU patients was approximately 1%/day of ventilation when VAP was diagnosed using protected specimen brush and quantitative culture techniques. Strategies believed to be effective at reducing the incidence of VAP include early removal of nasogastric or endotracheal tubes, formal infection control programs, hand washing, semirecumbent positioning of the patient,[44] daily sedation "vacations,"[45] avoidance of unnecessary reintubation, adequate nutritional support, avoidance of gastric overdistention, use of the oral rather than the nasal route for intubation, scheduled drainage of condensate from ventilator circuits,[46] and maintenance of adequate endotracheal tube cuff pressure.[47] Strategies that are not considered effective including routine changes of the ventilator circuit, dedicated use of disposable suction catheters, routine changes of in-line suction catheters, daily replacement of heat and moisture exchangers, and chest physiotherapy.[48] The literature supports both continuous aspiration of subglottic secretions and use of silver-coated endotracheal tubes to reduce the incidence of VAP.[49–51] A Cochrane review found no evidence of benefit from use of incentive spirometry in reducing pulmonary complications after CABG.[52]

Diagnosis of Acute Lung Injury and Acute Respiratory Distress Syndrome

ARDS may develop as a sequela of blood transfusion or CPB, or more commonly in the postoperative patient, it is associated with cardiogenic shock, sepsis, or multisystem organ failure. Components of ARDS include diffuse alveolar damage resulting from endothelial and type I epithelial cell necrosis and noncardiogenic pulmonary edema caused by breakdown of the endothelial barrier with subsequent vascular permeability. The exudative phase of ARDS occurs in the first 3 days after the precipitating event and is thought to be mediated by neutrophil activation and sequestration. Ultimately the alveolar spaces fill up with fluid as a result of increased endothelial permeability.

The clinical presentation is typically an acute onset of severe arterial hypoxemia refractory to oxygen therapy, with a ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FIO_2 or P/F ratio) of less than 200 mm Hg. ARDS is classically diagnosed only in the absence of left ventricular failure, a factor that complicates the diagnosis in the postoperative cardiac patient, who may also be in heart failure. Other findings in ARDS include decreased lung compliance (<80 mL/cm H_2O) and bilateral infiltrates on chest radiographs.[53] Murray and colleagues[54] created a Lung Injury Score that awards points for affected quadrants on chest radiographs, P/F ratio, amount of PEEP applied, and the static compliance of the lung. Scores greater than zero but less than 2.5 are considered to represent ALI, and scores greater than 2.5 meet the threshold for ARDS.

The proliferative phase of ARDS occurs on days 3 to 7 as inflammatory cells accumulate in response to chemoattractants released by the neutrophils. At this stage, the normal repair process removes debris and begin repair, but a disordered repair process may result in exuberant fibrosis, stiff lungs, and inefficient gas exchange. Evidence suggests that careful fluid and ventilator management may affect this process.[55,56] Conventional ventilator support following cardiac operations is to maintain large tidal volumes (typically 10 mL/kg) to reopen atelectatic but potentially functional alveoli. The problem is that the compromised lung is no longer homogeneous, and high pressures can further damage the remaining normal lung. Direct mechanical injury may result from overdistention (volutrauma), high pressures (barotrauma), or shear injury from repetitive opening and closing. "Biotrauma" may also result from inflammatory mediator release and impaired antibacterial barriers.[57] Thus current clinical practice in patients with known or suspected lung injury is to limit inflation pressures. The maximal "safe" inflation pressure is not known, but evidence favors keeping peak inspiratory pressures lower than 35 cm H_2O and restricting tidal volumes to less than 6 mL/kg of ideal body weight in patients at risk for ALI.[58] The landmark Acute Respiratory Distress Syndrome Network (ARDSNet) trial randomized patients to 6 mL/kg versus 12 mL/kg of ideal body weight and demonstrated a significant improvement in 28-day survival rates in the group with a low tidal volume.[59]

Ventilation with lower tidal volumes has been shown to be beneficial in critically ill patients even without ALI, as measured by plasma interleukin-6 levels and progression to lung injury,[60] but this issue has not yet been studied in the cardiac surgical population. A metaanalysis concluded that currently available data cannot confirm or refute any advantage of pressure-controlled over volume-controlled ventilation strategies.[61] A conservative strategy of fluid administration has been shown to improve oxygenation and shorten the duration of mechanical ventilation.[55]

Additional Therapy in Patients With Acute Lung Injury or Acute Respiratory Distress Syndrome

Maintaining a lung-protective ventilatory strategy involves permissive hypercapnia[62] if normal partial pressure of carbon dioxide (PCO_2) levels cannot be achieved with low tidal volumes. The acid-base changes must be monitored carefully, especially in patients with reactive pulmonary vasculature. Prone positioning can help achieve oxygenation.[63] A short daily turn to the prone position does not appear to improve outcome in ARDS, although one post hoc analysis found lower mortality rates in the sickest patients.[64] Lower tidal volumes with increasing amounts of PEEP may promote alveolar recruitment and thus improve oxygenation.[65] Taken to an extreme, patients with ALI may be ventilated with high-frequency oscillation, which is essentially high PEEP with tiny (smaller than dead space), frequently delivered tidal volumes. Other techniques for patients in whom conventional therapy is failing include extracorporeal CO_2 removal,[66] extracorporeal membrane oxygenation (ECMO),[67] inhaled nitric oxide,[68,69] and inhaled prostacyclin.[70] Inhaled nitric oxide has an established role in reducing right ventricular dysfunction when pulmonary hypertension compromises heart transplantation.[71] Although these therapies may be beneficial to other patients in extreme circumstances, prospective controlled trials are lacking. Corticosteroid rescue treatment for ARDS has a long history,[72] but a metaanalysis failed to establish a definitive role, although it did not exclude the possibility of reduced mortality rates or a reduction in ventilator days[73]

Healthy cardiac surgical patients generally do not require much PEEP.[74] Higher levels of PEEP may decrease cardiac output, unless volume loading is used to stabilize preload by maintaining transmural

filling pressures.[75] The effects of PEEP are most marked in the presence of abnormal right ventricular function, particularly if the right coronary artery is compromised.[76] PEEP neither protects against the development of ARDS[77] nor reduces the amount of mediastinal bleeding after cardiac surgical procedures involving CPB.[78] Most clinicians routinely use 5 cm H_2O of PEEP in ventilated patients. However, higher levels of PEEP (often 8–15+ cm H_2O) may be necessary to maintain adequate oxygenation with ALI or developing ARDS; application of PEEP in the postsurgical patient usually involves balancing cardiac and pulmonary goals.

Lung Recruitment

In laboratory and clinical models, an important component of a lung-protective ventilation strategy is recruitment of the lung. This is the closed chest analogy to the open chest recruitment maneuver typically done at the end of CPB to reexpand the collapsed lungs. The goal of opening the lung is to allow ventilation to occur at a point on the pressure-volume curve that avoids repetitive atelectasis (by staying above a critical closing pressure) and at the same time avoiding overinflation.[79] ARDSNet data suggest that the short-term effects of recruitment maneuvers are highly variable and that further study is needed to determine the role of recruitment maneuvers in the management of ALI and ARDS.[80] In many instances, impaired oxygenation results from atelectasis and responds quickly to brief recruitment maneuvers. These maneuvers should be performed cautiously because of the adverse impact of increased airway pressure on venous return and cardiac output if the patient is intravascularly "empty."

In patients who have been extubated, noninvasive ventilation (NIV) is often used to forestall reintubation, particularly in high-risk patients with chronic hypercapnic respiratory disorders or cardiac comorbidity.[81] NIV has been used to treat respiratory failure after extubation in other postsurgical settings, and it is also associated with faster improvement from acute cardiogenic pulmonary edema than with standard oxygen therapy.[82] In a randomized study of 100 patients undergoing CABG or valve operations, noninvasive positive-pressure ventilation with bilevel pressure for 30 minutes after extubation was associated with improved oxygenation.[83] However, a retrospective Spanish study of the use of NIV following extubation failure in the cardiac surgical population found that reintubation was required in one-half of the NIV-treated patients, and NIV was associated with higher hospital mortality rates.[84] Respiratory failure within 24 hours of extubation predicts NIV failure.

Permissive Hypercapnia

Conventional management is to maintain arterial P_{CO_2} (Pa_{CO_2}) within a normal or eucapnic range, classically between 35 and 45 mm Hg. A patient who retains CO_2 on a long-term basis would be considered eucapnic at his or her higher baseline Pa_{CO_2}. The traditional reason for maintaining eucapnia is primarily that acute deviation from a normal or acclimatized Pa_{CO_2} results in alkalemia or acidemia, to which the kidneys respond by retaining or excreting bicarbonate ion. Normal kidneys can compensate for a P_{CO_2}-induced pH change in 12 to 36 hours.[85] If high airway pressures would be required to maintain a normal status, Pa_{CO_2} values up to 60 mm Hg are acceptable as long as cardiovascular stability is present and the pH remains higher than 7.30. Investigators have hypothesized that raised P_{CO_2} levels may even be protective, and that low levels of P_{CO_2} could play a role in organ injury.[86] Permissive hypercapnia should be used judiciously in patients with pulmonary hypertension because acidosis can exacerbate pulmonary vasoconstriction and further impair right ventricular function and cardiac output.[87]

Cardiopulmonary Interactions

An understanding of cardiopulmonary interactions associated with mechanical ventilation is critical to the cardiothoracic intensivist. Hemodynamic changes may occur secondary to changes in lung volume and intrathoracic pressure even when tidal volume remains constant.[88] Pulmonary vascular resistance and mechanical heart-lung interactions play prominent roles in determining the hemodynamic response to mechanical ventilation. Because lung inflation alters pulmonary vascular resistance and right ventricular wall tension, the intrathoracic pressure that a damaged heart will tolerate is limited. High lung volumes may also mechanically limit cardiac volumes. In patients with airflow obstruction, occult PEEP (auto-PEEP) may also contribute to hypotension and low cardiac output.[89] Auto-PEEP can be detected by respiratory waveform monitoring or by pressure monitoring with the ventilator's expiratory port held closed at end-exhalation. Auto-PEEP may respond to bronchodilators and/or increased expiratory time to permit more complete exhalation.

Pulmonary Hypertension

Elevated pulmonary artery pressure results from vasoconstriction, smooth muscle cell proliferation, and endothelial cell proliferation. Collagen vascular diseases, chronic thromboembolic obstruction of the pulmonary arteries, lung diseases such as COPD, congenital heart disease, and left-sided heart failure all may be associated with pulmonary hypertension. These patients can present anesthetic and critical care challenges, especially following CPB, with complement activation, leukocyte activation, and release of inflammatory mediators.[90] Inhaled nitric oxide, prostaglandin E_1, the endothelin-1 antagonist bosentan, and phosphodiesterase inhibitors such as sildenafil and milrinone are among the available therapies.[91–93] A study of 61 high-risk adult cardiac surgical patients with pulmonary hypertension suggested that preemptive treatment, using a combination of milrinone and inhaled prostacyclin before CPB, reduces post-CPB pressures and the need for vasoactive support in the ICU.[94]

Extracorporeal Membrane Oxygenation Support

ECMO provides cardiac and/or pulmonary support for a patient temporarily without enough reserves to be self-sufficient. ECMO has been used for treating severe ARDS,[95] managing pulmonary hypertensive crisis, and as a bridge to lung transplantation.[96] The two types of ECMO are venoarterial (VA) and venovenous (VV). Both provide respiratory support, but only VA ECMO assists cardiac function. Indications for VV ECMO include hypoxemic respiratory failure, generally defined as a P/F ratio less than 100 mm Hg despite optimized ventilator settings (tidal volume, PEEP, inspiratory to expiratory ratio). It is also indicated for hypercapnic respiratory failure with an arterial pH less than 7.20. For patients with respiratory failure, ECMO may not be initiated if the patient has been mechanically ventilated for longer than 7 days because outcomes tend to be poor in this population.[97]

During VV ECMO, blood is extracted from the vena cava, oxygenated externally, and returned to the right atrium (see Chapter 33). VV ECMO provides respiratory support, but the patient is dependent on his or her own hemodynamic function. For VV ECMO, venous cannulas are usually placed in the right common femoral vein (for drainage) and the right internal jugular vein (for infusion). The tip of the femoral cannula should be maintained near the junction of the inferior vena cava and right atrium, and the tip of the internal jugular cannula should be in the right atrium. Alternatively, a double-lumen cannula[98] can be placed in the internal jugular vein, which is large enough to accommodate the necessary 4 to 5 L/minute of blood flow. These cannulas are available in a variety of sizes, with 31 Fr the largest and most appropriate for adult male patients. Ventilator settings are reduced during ECMO to avoid barotraumas and oxygen toxicity. Plateau airway pressures are generally maintained at less than 25 cm H_2O with an F_{IO_2} of less than 0.4.[99] One study suggested that protective strategies are routinely used in high-volume ECMO centers, and that higher PEEP levels during the first 3 days on ECMO support are associated with improved survival.[100]

Improvements in chest radiographic appearance, pulmonary compliance, and arterial oxyhemoglobin saturation indicate that the patient may be ready to be weaned from ECMO. VV ECMO trials are performed by discontinuing all countercurrent "sweep" gas through the oxygenator, so that the patient's native oxygenation can be assessed. Extracorporeal blood flow remains constant, but gas transfer does not occur with the sweep gas eliminated. Patients are observed for several hours, during which time the ventilator settings necessary to maintain adequate oxygenation and ventilation post-ECMO can be determined. Weaning from VA ECMO is beyond the scope of this chapter, but it also involves careful reduction in extracorporeal flow (see Chapter 33).

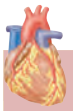
Complications of ECMO include bleeding (30%–40%) as a result of the mandatory anticoagulation, thromboembolism, vascular compromise, and heparin-induced thrombocytopenia. Future technology will include percutaneous low-flow ECMO devices for isolated CO_2 removal.

General Support Issues

Patients requiring long-term ventilation support are prone to numerous complications, including venous thromboembolism, central venous catheter–related bloodstream infections, surgical site infections, VAP, pressure ulcers, nutritional depletion, delirium, and gastrointestinal bleeding. Standard practice in patients receiving long-term ventilation includes prophylaxis against gastrointestinal bleeding with histamine blockers or proton pump inhibitors (unless the patient is receiving continuous gastric feedings), head of bed elevation to 30 degrees or more in hemodynamically stable patients,[44] a brief daily wake-up from sedation,[101] use of in-line suction catheters, glucose control,[102] and appropriate venous thromboembolism prophylaxis. Box 39.2 summarizes these risk reduction efforts. Ensuring that each of these goals is met on each patient every day requires extra work, but it can be accomplished with a daily goals form[103] or with information technology[104] (Fig. 39.1).

Impediments to Weaning and Extubation

Factors limiting the removal of mechanical ventilatory support include delirium, neurologic dysfunction, unstable hemodynamic status, respiratory muscle dysfunction, renal failure with fluid overload, and sepsis. Fig. 39.2 outlines one approach to identifying readiness to wean from ventilation and possible alternative approaches to weaning. Early mobilization including formal exercise programs, such as bedside cycling,[105] can enhance recovery from the catabolic muscle loss with critical illness.



BOX 39.2 SPECIFIC WAYS TO REDUCE INTENSIVE CARE UNIT–ASSOCIATED MORBIDITY

- Earliest possible removal of orogastric and endotracheal tubes with use of oral (not nasal) tubes
- Formal infection control program (hand washing, feedback to staff)
- Head of bed elevation to 30 degrees or more if hemodynamic status permits
- In-line suction catheters to avoid circuit contamination with repeated opening
- Scheduled drainage of condensate
- Adequate endotracheal tube cuff pressure
- Avoidance of the need for reintubation (adequate restraints, sedation)
- Glucose control protocol
- Early nutritional support, preferably by the enteral route
- Stress ulcer prophylaxis
- Deep venous thrombosis prophylaxis
- Brief daily wake-up from sedation
- Early tracheostomy if >14 days of predicted ventilator support
- Use of noninvasive ventilation (CPAP or BiPAP) to avoid reintubation
- Swallowing evaluation before oral feeding if patient is at risk for aspiration

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

Fig. 39.1 A situation awareness monitor can be populated from various sources in the electronic health record. In addition to patient identification data, the display includes current and trended laboratory values, correlation between hemodynamic parameters and infusions, fluid balance, and compliance with elements of the intensive care unit *(ICU)* safety bundle.[104]

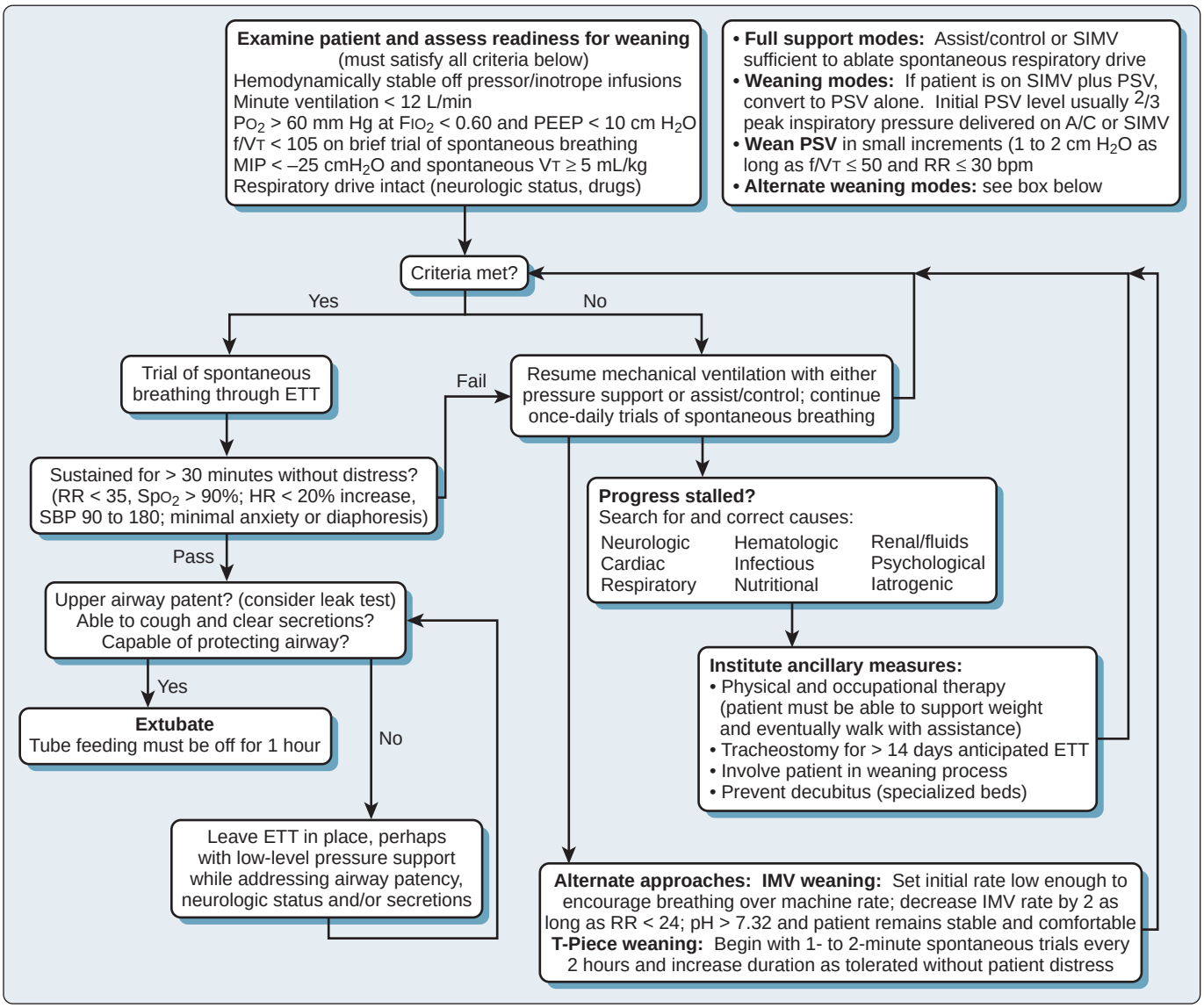


Fig. 39.2 This flow chart addresses care of patients receiving both short-term and long-term ventilatory support in the cardiothoracic intensive care unit. All patients require periodic assessment for readiness for weaning, and if they meet criteria they are eligible for spontaneous trials leading to extubation. Patients who do not meet the criteria should have mechanical ventilation maintained until criteria are met. Pressure-support ventilation *(PSV)* weaning may be possible; if not, alternative approaches include intermittent mandatory ventilation *(IMV)* weaning and T-piece weaning. Patients who stall in their weaning progress should have a comprehensive examination and an assessment of organ systems to search for correctable causes. *A/C,* Assist-control mode; *ETT,* endotracheal tube; *f/VT,* frequency-to-tidal volume ratio; *MIP,* maximal inspiratory pressure; *PEEP,* positive end-expiratory pressure; P_{O_2}, partial pressure of oxygen; *RR,* respiratory rate; *SBP,* systolic blood pressure; *SIMV,* synchronized intermittent mandatory ventilation; Sp_{O_2}, oxygen saturation measured with pulse oximetry.

Neurologic Complications

Delirium after cardiac surgical procedures is common; estimated incidence rates are approximately 30% in the general cardiac surgical population to 83% in mechanically ventilated patients.[106,107] Corticosteroids, as may be used in the treatment of ALI, increase the risk of delirium.[108] Delirium resolves spontaneously or with pharmacologic intervention in almost all patients by postoperative day 6. Evidence from a large trial of mostly medical critical care patients suggests that dexmedetomidine is associated with less delirium than midazolam.[109] Dexmedetomidine has been shown to be safe and effective in patients after CABG.[110] Alcohol or benzodiazepine withdrawal should be considered in the differential diagnosis of delirium. Ketamine may attenuate delirium in CPB-treated patients, possibly because of anti-inflammatory effects,[111] although ketamine itself can cause a dissociative state. Initial postoperative management of agitation consists of reassurance and orientation of the patient and control of pain with opioids and/or acetaminophen. Data suggest that intravenous paracetamol (acetaminophen) with tramadol provides effective pain control after cardiac operations.[112] Intravenous acetaminophen has actually been shown to be more effective than intravenous morphine in patients with acute renal colic.[113] Agitation accompanied by disorientation may be worsened by benzodiazepines, which should be restricted to treatment of oriented but anxious patients or for prophylaxis of alcohol and benzodiazepine withdrawal. If the patient remains agitated

and disoriented, haloperidol may be useful.[114] Newer agents such as risperidone, olanzapine, and quetiapine may also be useful, but they have not been well studied in the cardiothoracic ICU setting. Although some studies supported pharmacologic prophylaxis against delirium, a systematic review and metaanalysis of 13 studies suggested that the evidence is inconclusive in the post–cardiac surgical population.[115]

Diaphragmatic paralysis may complicate any procedure, but it is more common in patients undergoing reoperation, given the difficulty in identifying the phrenic nerve in fibrotic pericardial tissue. Permanent bilateral diaphragmatic paralysis is rare (<0.1% of patients after CPB), but temporary diaphragmatic weakness may occur in 4% or more. The diagnosis of diaphragmatic paralysis should be suspected whenever a patient fails to be weaned from mechanical ventilation; it should be documented by observing paradoxical movement of the diaphragm during inspiration and by comparing vital capacity and tidal volume in the supine and seated positions. Differences in supine and seated vital capacity of more than 10% to 15% should prompt fluoroscopic examination of the diaphragm ("sniff" test). Bilateral paralysis may be missed by this test because comparison of left and right diaphragmatic excursion has lower specificity when both sides of the diaphragm are involved. Transient diaphragmatic paralysis can occur secondary to cold injury to the phrenic nerve.[116] Less often, the phrenic nerve is injured or transected during dissection of the internal mammary arteries or during mobilization of the heart in patients undergoing reoperation.

Patients with respiratory failure and systemic inflammatory response syndrome (SIRS) frequently develop critical illness polyneuropathy, the first sign of which may be failure to be weaned from the ventilator.[117] Disuse atrophy[118] and steroid administration[119] also contribute to muscle weakness. Patients with severe COPD who are dependent on diaphragmatic breathing preoperatively are most likely to manifest diaphragmatic weakness as postoperative ventilator dependency. Full recovery of diaphragmatic function may take 4 months to more than 2 years, and partial recovery is apparent when the patient can lie flat without dyspnea.[120] Adjuncts to improving diaphragmatic strength include inspiratory muscle training,[7] normalizing calcium and phosphate levels, and possibly the use of aminophylline.[121]

Cardiac Complications

Acute myocardial dysfunction occurs in almost all post-CPB patients, and it reaches a nadir approximately 4 hours (range, 2–6 hours) after CPB. Patients with persistent low-output syndrome have an increased risk of cardiac death, as well as complications such as renal failure, respiratory failure, gastrointestinal bleeding, and neurologic sequelae. Regional differences in blood flow can also occur even in the presence of an adequate overall cardiac output, so a normal whole-body cardiac index does not guarantee adequate perfusion of individual organs. Multiorgan failure may be precipitated by a period of gut ischemia or hyperpermeability followed by translocation of gut bacteria and release of endotoxin and other vasoactive substances leading to generalized inflammation and organ injury.[122]

Patients maintained on long-term amiodarone therapy are prone to postoperative respiratory failure, longer intubation times, and longer ICU stays, even with only subclinical evidence of pulmonary amiodarone toxicity.[123] Rarely, patients taking amiodarone develop life-threatening pulmonary complications, including ARDS. Histologic lung examination of these patients demonstrates marked interstitial fibrosis with enlarged air spaces ("honeycomb" appearance) and hyperplasia of type II pneumocytes.[124]

Acute left ventricular dysfunction may occur in patients with COPD during the shift from mechanical to spontaneous ventilation.[125] Attention to fluid balance and aggressive diuresis or use of ultrafiltration helps with weaning. Although it is useful to compare the patient's current and preoperative body weights, catabolic states arising postoperatively, and especially during sepsis, reduce lean body weight. Patients may be "unweanable" until fluid removal reduces body weight to several kilograms lower than the preoperative value.

Patients with valvular disease have significantly higher respiratory system and lung elastances and resistances than those undergoing operations for ischemic heart disease, but these values may correct with successful surgical procedures.[126] Thus patients undergoing valve operations have less work of breathing and improved respiratory function after correction of the valvular disease, but patients undergoing CABG are less likely to show dramatic improvement postoperatively.

Utility of Echocardiography in the Intensive Care Unit Setting

Transesophageal color Doppler echocardiography (TEE), transthoracic echocardiography (TTE), and three-dimensional echocardiography[127] are commonly used preoperatively, in the operating room, and in the ICU to assess ventricular function and valvular disease.[128,129] High-quality images from TEE or TTE can be valuable diagnostic tools in the management of critically ill patients, as well as in the diagnosis and treatment of respiratory disease related to cardiopulmonary dysfunction.[130]

Pleural Effusion

Accumulation of fluid in the pleural space from bleeding or transudate can compress the lung parenchyma and cause basal atelectasis resulting in impaired gas exchange. An undetected pleural effusion may also act as a potential source of postoperative infection. The TTE probe can be used to assess the size of a pleural effusion, help mark the skin at the site that is optimal for needle insertion to drain the effusion, and verify that no lung tissue is present in the area where the operator plans to insert the needle (Fig. 39.3). TEE can also identify the pleural fluid.[131] When the patient is supine, fluid pools in the dorsal and caudal portions of the pleural space. From the four-chamber view the TEE probe is rotated counterclockwise to obtain the short-axis view of the descending aorta. In the presence of a left-sided pleural effusion a "crescent-shape linked to a tiger's claw" may be noted. To examine for a right-sided pleural effusion, the probe is rotated clockwise from the four-chamber view position. A crescent-shaped, echo-free space adjacent to the transducer is noted.

Treatment of pleural effusion is with thoracentesis or placement of a tube thoracostomy. Drainage of pleural fluid results in a significant improvement in oxygenation in acute respiratory failure patients who were refractory to treatment with mechanical ventilation and PEEP.[132]

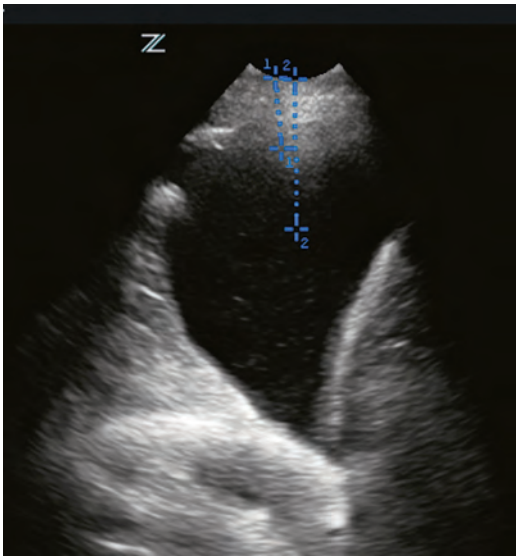


Fig. 39.3 Pleural effusion, left hemithorax: With the patient seated erect, the transducer is oriented perpendicular to the left chest wall at the skin mark. The following measurements were obtained: depth to enter the fluid collection, 1.7 cm; depth to midfluid collection, 3.7 cm.

Patent Foramen Ovale

When a mechanically ventilated patient becomes more hypoxemic despite efforts to improve ventilation, shunt-induced hypoxemia caused by a patent foramen ovale should be considered, along with other causes such as pulmonary embolism. Echocardiography can identify specific abnormalities in mechanically ventilated patients when weaning is difficult or refractory hypoxemia is not explained by pulmonary disease alone.[133] The diagnostic accuracy of TEE is superior to that of TTE in identifying cardiac causes of shock, especially in ventilated patients.[134]

Septic Shock

The treatment of critically ill patients frequently requires comprehensive evaluation of hemodynamic status. Pulmonary artery catheters have not been shown to improve survival,[135] and their use appears to be declining, although less so in surgical units than in medical units.[136] Echocardiography is increasingly used for intermittent assessment of patients with circulatory failure in the ICU and allows rapid assessment and differentiation of the cause of shock. Preliminary evidence suggests that a transoral miniaturized hemodynamic echocardiographic device (hTEE, ImaCor, Garden City, NY) can be used to guide therapy with continuous data.[137]

Assessing Preload for Fluid Management

Inadequate fluid administration can be detrimental, but avoiding inefficient and potentially deleterious volume expansion is equally important. Bedside echocardiography is one of several options for goal-directed therapy,[138] along with mixed venous O_2 saturation,[139] stroke volume variation,[140] and pulse pressure variation.[141] Passive leg-raising using esophageal Doppler imaging and respiratory variation in pulse pressure predicts fluid responsiveness.[142] However, both stroke volume and pulse pressure variability lose discrimination with an irregular rhythm such as atrial fibrillation, which is common in postoperative cardiac patients. Vieillard-Baron and Charon[143] showed that the collapsibility index (maximal diameter on expiration—minimal diameter on inspiration / maximal diameter on expiration expressed as a percentage) of the superior vena cava greater than 36% using TEE accurately distinguishes responders to a fluid challenge from nonresponders.

Pericardial Effusion

The classic Beck triad of jugular venous distention, muffled heart sounds, and hypotension manifests in less than 40% of patients with cardiac tamponade. When these signs are present, they may not appear until late in the clinical course. Echocardiography is an essential tool in making the accurate diagnosis of pericardial effusion especially in a hypotensive patient who does not respond to volume expansion or inotropic support. Findings of pericardial effusion with systolic collapse of the right atrium, diastolic collapse of the right ventricle, and mitral valve inflow decrease by 25% during inspiration (in spontaneously breathing patients), or the tricuspid valve in ventilated patients, are all consistent with cardiac tamponade. Computed tomography–guided pericardiocentesis can be highly successful in avoiding complications such as pneumothorax.[144]

Renal Failure and Fluid Overload

Significant oliguria or anuric renal failure occurs after 1% to 4% of cardiac surgical procedures, and lesser degrees of renal dysfunction, marked by elevated serum creatinine, occur in up to 30%. Univariate predictors of serious acute renal failure include low cardiac output at the end of CPB, advanced age, preoperative cardiac failure, need for postoperative circulatory support, blood transfusions, and prolonged time on CPB.[145] In patients with developing acute kidney injury, infusions of dopamine or fenoldopam do not reduce the need for renal replacement therapy or alter 30-day mortality rates.[146] Contrast-induced nephropathy is always a concern; risk factors for postoperative acute kidney injury include diabetes mellitus and cerebrovascular disease.[147] The incidence of acute kidney injury is significantly higher when the operation occurs within 24 hours of contrast injection and in patients undergoing valve surgery in addition to CABG (but not CABG alone); delaying cardiac operations beyond 24 hours of exposure to contrast agents is justified.[148] When renal failure occurs, it often follows one of three well-defined patterns.[149] Abbreviated acute renal failure occurs after an isolated insult, results in a peak in serum creatinine level around the fourth postevent day, and generally resolves if no other events occur. The second pattern initially resembles the first, except the acute insult is accompanied by prolonged circulatory failure. This pattern runs a longer course, with recovery typically occurring in the second or third week after injury, in tandem with improvements in cardiac output. In the third pattern, recovery is complicated by a second insult such as sepsis, massive gastrointestinal bleeding, or myocardial infarction, and permanent renal failure may result. Because fluid overload with renal failure may precipitate respiratory and cardiac failure, early application of continuous arteriovenous hemofiltration and related techniques to remove excess fluid can facilitate separation from ventilator support.[150]

Infectious Complications

A median sternotomy approach to cardiac surgery entails sawing through the sternum. Although rigid plate fixation has been shown to accelerate bone healing after cardiac operations,[151] most patients still have the split sternum approximated with wire closure. Mediastinitis, sternal dehiscence, or both, are complications of coronary revascularization, with an incidence of approximately 1% and a mortality rate of approximately 13% and a tendency to prolong ventilator dependency. Predisposing factors for wound complications after cardiac operations include diabetes, low cardiac output, use of bilateral internal mammary artery grafts, and reoperation for control of bleeding.[152] Keeping blood glucose lower than 200 mg/dL in the perioperative period reduces the sternal wound infection rate from 2.4% to 1.5%.[153] Tight glucose control, however, increases the risk of hypoglycemia,[154] and many clinicians have abandoned the very tight limits (keeping glucose <110 mg/dL) previously advocated. Mediastinal infection manifests as unexplained fever, an unstable sternum, and sometimes, failure to be weaned from ventilation. In addition to selective antibiotic therapy, surgical débridement and drainage of the wound are usually necessary. Polymicrobial isolates are associated with poor outcome. Additional management of mediastinitis may include primary or delayed sternal closure using pectoralis or omental flaps.

Pneumonia, tracheobronchitis, central line catheter sepsis, and urinary tract infections are frequent in the ventilator-dependent patient. Continuous lateral rotational therapy reduces the prevalence of pneumonia, but it may not affect mortality rates or the duration of mechanical support.[155] The diagnosis of VAP[156] can be difficult to confirm because upper airway organisms can contaminate the sputum specimen. Special suction catheters with a protected tip may be used for a "mini"-bronchoalveolar lavage to improve the yield of sputum cultures. Because typical perioperative antibiotic prophylaxis consists of an antistaphylococcal penicillin or cephalosporin, nosocomial pneumonia is likely to occur with organisms such as *Pseudomonas, Klebsiella, Serratia, Acinetobacter*, or methicillin-resistant *Staphylococcus aureus* (MRSA). Treatment of the secondary infection may be followed by a tertiary infection with organisms that are more difficult to eliminate, such as *Candida, Torulopsis,* or other fungal species.

Gastrointestinal Complications

Gastrointestinal complications requiring intervention occur in 1% to 3% of patients.[157] Postoperative ileus can affect diaphragmatic excursion and increase the work of breathing. Upper gastrointestinal bleeding is common. Pancreatitis, mesenteric ischemia, perforation, and bleeding elsewhere in the gastrointestinal tract are problems seen with critically ill patients, especially those with multisystem failure. Mesenteric ischemia can be the result of low perfusion or embolic atheroma from large-vessel manipulation. Gut ischemia is a potential source of bacteremia, especially problematic for patients with artificial valves. The risk

of gastrointestinal bleeding can be minimized with antacid therapy, histamine blockers, or barrier protection agents. Enteral nutritional support also appears to protect the gastric mucosa.[158]

Diarrhea can occur as the result of mesenteric ischemia, but it is also frequently caused by *C. difficile* overgrowth in patients treated with antibiotics, especially later-generation cephalosporins. Administration of proton pump inhibitors versus histamine blockers or sucralfate is associated with a higher risk for developing *C. difficile*.[159] Patients undergoing prolonged acute mechanical ventilation have a significantly higher risk of concurrent *C. difficile*–associated diarrhea, with attendant increases in hospital length of stay and costs.[160] The rapid assay for *C. difficile* can miss certain strains; culture of stool is not as rapid, but it is more reliable. Treatment of *C. difficile* colitis can be accompanied by oral or intravenous metronidazole or enteral (not intravenous) vancomycin. Toxic megacolon is a surgical emergency requiring immediate attention. Nutrition depletion is common in patients receiving long-term ventilation, and early enteral feeding should be implemented in high-risk patients unless specific contraindications such as ongoing bowel ischemia exist.

Nutritional Support and Weaning

Respiratory failure can be precipitated by high carbohydrate loads delivered during attempts to provide nutritional support, so the goals should be to institute support early before serious depletion occurs and to use an appropriate mix of fat and carbohydrate to maintain a respiratory quotient less than 1.0. Weekly monitoring of transferrin or prealbumin levels screens for changes in nutritional status; more sophisticated analysis including metabolic monitoring and nitrogen balance can identify reasons for poor response to therapy.

The adequacy of nutritional support has a strong influence on the patient's ability to be weaned from ventilation. Preoperative albumin levels lower than 2.5 g/dL are associated with increased risk of reoperation for bleeding, postoperative renal failure, and prolonged ventilatory support, ICU, and hospital length of stay.[14] Weaning success occurs in approximately 93% of patients with adequate nutritional support, but in only 50% of those with inadequate nutrition.[161] Increases in albumin and transferrin level with parenteral nutrition predict eventual ability to be weaned from ventilation.[162] Enteral and parenteral routes appear to be similar in caloric delivery, infectious complications, and mortality rates, although hypoglycemia and vomiting are more likely with enteral delivery.[163]

Modes of Ventilator Support

Positive-pressure ventilators used outside the operating room have a non-rebreathing circuit, may be volume or pressure limited, and may be triggered by changes in flow or changes in pressure. All modern ventilators contain multiple modes of ventilation support that accommodate both mandatory and patient-triggered breaths. The most common modes of positive-pressure ventilation are assist-control (A/C), synchronized intermittent mandatory ventilation (SIMV), and pressure-support ventilation (PSV). With volume modes, the inspiratory flow rate, targeted volume, and inspiratory time are set by the clinician, and inspiratory peak pressure varies depending on the patient's lung compliance and synchrony with the ventilator. Volume cycling ensures consistent delivery of a set tidal volume as long as the pressure limit is not exceeded. With nonhomogeneous lung disorders, however, delivered volume tends to flow to areas of low resistance; this may result in overdistention of healthy segments of lung and underinflation of atelectatic segments with consequent ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching. Fig. 39.4 demonstrates pressure and flow tracings with volume ventilation. Volume breaths may be triggered by a timer (control mode ventilation) or by the patient's effort between the control-mode breaths (A/C ventilation). In either case, the tidal volume delivered is determined by the ventilator settings. This situation can present a problem in a patient with tachypnea as a response to neurologic injury. If the patient breathes inappropriately in response to normal arterial levels of CO_2, significant respiratory alkalosis will result. A/C mode is most appropriate for the patient whose respiratory drive is normal but whose muscles are weak, or when neuromuscular blockade is employed, in which case A/C mode essentially becomes control-mode ventilation.

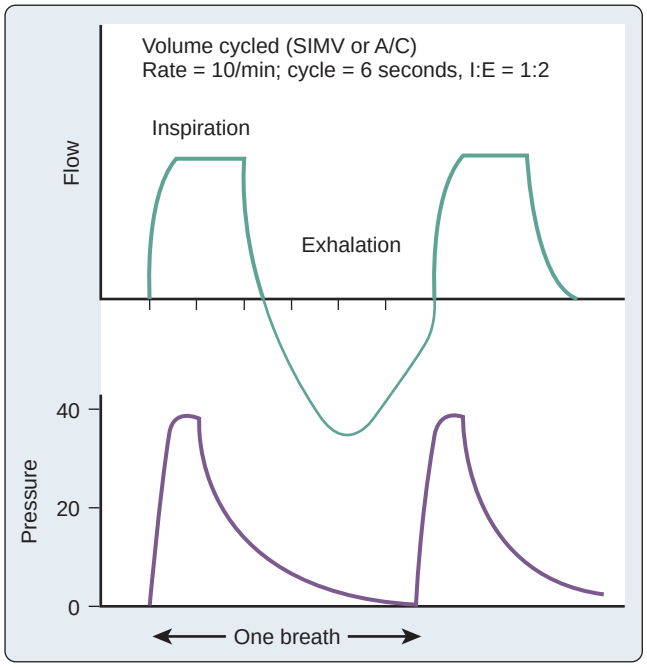


Fig. 39.4 The *top tracing* shows the inspiratory flow, which is close to a square wave. Originally this flow pattern was dictated by the function of mechanical valves, but it may now be duplicated electronically. Note that the flow waveform becomes negative (opposite direction) during the exhalation phase. The typical volume cycled breath with a square waveform results in a rapid rise to peak inspiratory pressure followed by a gradual decline. If the safety pressure limit is exceeded, the peak of the pressure waveform may be truncated. *A/C,* Assist-control mode; *I:E,* inspiration-to-expiration ratio; *SIMV,* synchronized intermittent mandatory ventilation.

Intermittent mandatory ventilation (IMV) and later SIMV were developed to facilitate weaning from mechanical ventilatory support. With either IMV modality, a basal respiratory rate is set by the clinician that may be supplemented by patient-initiated breaths. In contrast to A/C ventilation, however, the tidal volume of the patient's spontaneous breaths is determined by the patient's own respiratory strength and lung compliance rather than delivered as a preset volume. SIMV mode is appropriate for patients with normal lungs who are recovering from opioid anesthesia. Weaning is accomplished by reducing the mandatory IMV rate and allowing the patient to assume more and more of the respiratory effort over time. SIMV mode has been used for weaning in patients with complex cases, but the weaning effort may stall at very low IMV rates if the patient cannot achieve spontaneous volumes sufficient to activate the pulmonary stretch receptors. Under these circumstances, the patient is likely to become tachypneic, and weaning attempts will fail. Thus other methods of weaning support may be needed.

Pressure-Controlled Ventilation

Pressure-controlled ventilation (PCV) is available on most ventilators, and allows the clinician to specify a target inspiratory pressure; the ventilator then calculates and delivers the optimal flow rate to achieve the desired tidal volume and inspiratory-to-expiratory ratio (I:E ratio). Fig. 39.5 demonstrates the difference between PCV and volume-controlled ventilation with regard to inspiratory flow. Pressure-controlled inverse-ratio ventilation (PC-IRV) is PCV with an inspiratory time that exceeds expiratory time (I:E ratio >1.0). Consider that opening alveoli with damaged lungs sometimes requires exceeding a

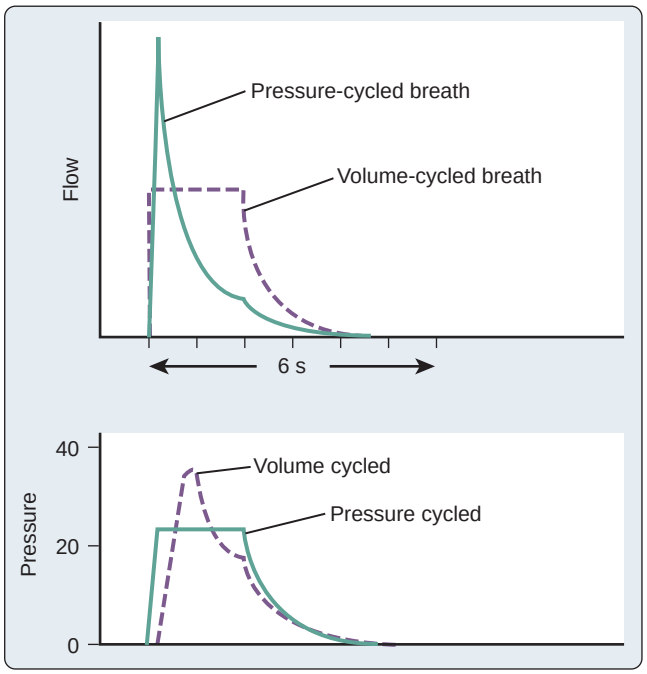


Fig. 39.5 The difference between pressure-cycled breaths and volume-cycled breaths is demonstrated. With a pressure cycle breath, the flow is titrated by a feedback mechanism to maintain a set inspiratory pressure. Thus flow is very rapid at the beginning of the inspiratory cycle and rapidly tapers, in contrast to a volume-cycled breath in which the waveform is more or less consistent throughout the inspiratory cycle. The *bottom section* shows the difference in pressure tracings. As noted before, volume-cycled ventilation reaches a peak and then falls back. In contrast, pressure-cycled ventilation reaches a lower but sustained pressure limit and holds at that level for the inspiratory time. In the absence of significant pulmonary disease, either mode of ventilation results in a rapid decrease of pressure once exhalation occurs.

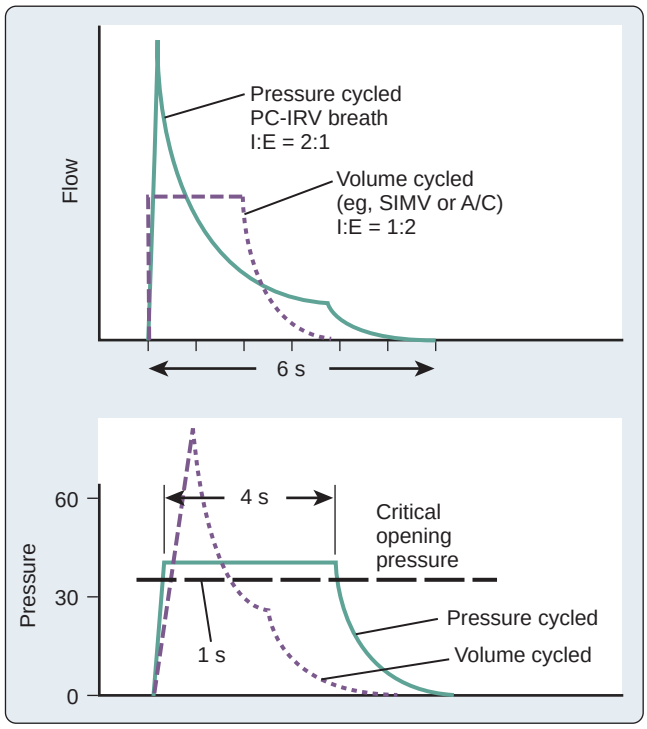


Fig. 39.6 Volume-cycled and pressure-cycled modes are compared as in Fig. 39.5. If a critical opening pressure is present to recruit atelectatic lung segments, a pressure-controlled ventilation mode, particularly if the inspiration-to-expiration ratio (I:E ratio) is inverted, is far more successful at maintaining an inspiratory pressure above the critical opening pressure for a greater length of time. Attempting to increase the volume-cycled flow would result in unacceptably high peak inspiratory pressures in an attempt to achieve more time above the critical opening pressure. Even in volume control, however, inspiratory pauses or changes to the flow rate in I:E ratio may be able to achieve longer sustained inspiratory pressures. *A/C,* Assist-control mode; PC-IRV, pressure-controlled inverse-ratio ventilation; *SIMV,* synchronized intermittent mandatory ventilation.

critical opening pressure for an adequate amount of time (Fig. 39.6). With standard ventilation, this time above the critical pressure can be lengthened only by increasing the peak inspiratory pressure, which is generally undesirable with a damaged lung. With PC-IRV, the pressure waveform is optimized to allow a long inspiratory time above the critical opening pressure while avoiding high peak pressures. The disadvantage of PC-IRV is that the increased inspiratory time necessarily reduces exhalation time, which may lead to stacking of breaths or auto-PEEP in patients with abnormal lungs. Tharratt and colleagues[164] demonstrated that PC-IRV allowed a reduction in minute ventilation and reduced peak pressures while increasing mean airway pressures in patients with ARDS. At a given plateau pressure (similar end-inspiratory distention), lower tidal volume and increased PEEP are associated with better recruitment and oxygenation.[165]

Changing a patient from convention volume-controlled ventilation to PC-IRV can be accomplished by noting the existing tidal volume, inspiratory pressures, and I:E ratio and switching to PCV mode with similar inspiratory peak pressure, rate, and inspiratory time. The level of inspiratory pressure is then titrated to deliver a tidal volume similar to what the patient was receiving with volume control ventilation. Then the inspiratory time can be lengthened to achieve better oxygenation or decreased to allow sufficient exhalation time if auto-PEEP is evident. In any patient with abnormal lungs, but particularly if an IRV mode is used, the patient must be monitored for the development of auto-PEEP, identified either by monitoring failure of the pressure waveform to return to baseline between breaths or by instituting an expiratory hold and noting the difference in pressure between the ventilator's pressure gauge and the level of PEEP that was specified. Sedation and often neuromuscular blockade are necessary if the I:E ratio is inverted. Adjusting the ventilator settings in pressure-control mode is not always intuitive. Increased rates may paradoxically decrease CO_2 elimination if tidal volumes decrease. Improvements in oxygenation may not occur until the patient is stabilized and given sufficient time (≥30 minutes) to recruit atelectatic segments. Recruitment maneuvers when initiating PCV may help to open up atelectatic segments that may remain open once recruited. Airway pressure-release ventilation is functionally similar to PC-IRV in terms of recruitment, but it can often be accomplished in spontaneously breathing patients.[166] Adaptive-support ventilation, a microprocessor-controlled mode that maintains preset minute ventilation, has also been used in cardiothoracic surgical patients.[167]

Pressure-Support Ventilation

PSV, which is primarily a weaning tool, must be distinguished from pressure-control ventilation, which is generally used during the maintenance phase of ventilation. PSV may be used in conjunction with CPAP or SIMV modes. Pressure support augments the patient's spontaneous inspiratory effort with a clinician selected level of pressure. Putative advantages include improved comfort for the patient, reduced ventilatory work, and faster weaning. The volume delivered with each PSV breath depends on the pressure set for inspiratory assist, as well as the patient's lung compliance. The utility of PSV in weaning from long-term ventilation support is that it allows the patient's ventilatory muscles to assume part of the workload while augmenting tidal volume, thus preventing atelectasis, sufficiently stretching lung receptors, and keeping the patient's spontaneous respiratory rate within

a reasonable physiologic range. With some older (and now mostly obsolete) ventilators, the inspiratory phase of PSV is terminated when flow falls to less than 25% of the initial value. In the presence of a cuff leak around the endotracheal tube, the flow rate may not fall to sufficiently low levels to terminate the breath, and the patient will struggle while trying to exhale against the inspiratory flow. This problem is rare or nonexistent with newer ventilators. Tidal volume varies markedly with the patient's lung compliance, so close clinical observation is needed with the initiation of PSV. Monitoring end-tidal CO_2 as well as pulse oximetry readings during the PSV weaning phase helps limit phlebotomy for arterial blood gas measurements.

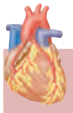
Liberation From Mechanical Support (Weaning)

An important concept to consider is that weaning from ventilator support is not synonymous with extubation. In certain conditions weaning is possible, but extubation is not (eg, upper airway edema or compression, glottic dysfunction with aspiration, neurologic dysfunction, or any other inability to protect the airway). As noted earlier, extubation to CPAP may be an option when chronic respiratory disorders or cardiac morbidity are affecting oxygenation.[81] A second important concept is that a formal weaning process is not essential in a normal postoperative patient, although SIMV or PSV weaning may be most convenient. The adaptive-support ventilation mode has been demonstrated to reduce ventilation time by more than 2 hours versus physician-directed weaning in patients undergoing fast-track cardiac valvular operations.[168] In the absence of significant cardiopulmonary dysfunction, extubation depends more on a stable clinical condition, adequate warming, elimination, and metabolism of anesthetic agents and reversal of neuromuscular blockade. Weaning strategies, however, are almost always required after more than 3 days of ventilation support.

When terminating mechanical ventilation, two phases of decision making are involved. First, resolution of the initial process for which mechanical ventilation was begun should occur. The patient cannot have sepsis, be hemodynamically unstable, or be burdened with excessive respiratory secretions. If these general criteria are met, then specific weaning criteria can be examined. These include oxygenation (typically a PaO2 >60 mm Hg on 35% inspired oxygen and low levels of PEEP), adequate oxygen transport (measurable by oxygen extraction ratio or assumed if the cardiac index is adequate and lactic acidosis is not present), adequate respiratory mechanics (tidal volume, maximal inspiratory pressure) and adequate respiratory reserve (minute ventilation at rest of <10 L/min), and a low frequency-to–tidal volume ratio (f/VT <100; see next section) indicating adequate volume at a sustainable respiratory rate.

Objective Measures of Patients' Strength and Endurance

Although clinicians may use a variety of parameters to determine readiness for extubation, few parameters have been examined carefully. Vital capacity, defined as the volume of gas exhaled after maximal inspiration, is normally greater than 70 mL/kg. A clinical readiness threshold of 10 to 15 mg/kg has been proposed, but this is neither sensitive nor specific. For patients receiving short-term ventilatory support, vital capacity is less reliable than the ability to maintain a pH value greater than 7.35 while the IMV rate is decreased to CPAP.[169] Maximal inspiratory pressure is often referred to as inspiratory force, negative inspiratory force, or peak negative pressure and quantifies inspiratory effort as a marker of respiratory muscle strength. The proper technique involves airway occlusion for up to 20 seconds starting at full exhalation by using a one-way valve that allows the patient to exhale after attempted inspiration. Normal values of maximal inspiratory pressure should exceed 100 cm H_2O in male patients and 80 cm H_2O in female patients. Values are usually expressed as an absolute to avoid confusion with "less than" or "greater than" when referring to a negative number.



BOX 39.3 NONRESPIRATORY FACTORS AFFECTING WEANING FROM MECHANICAL VENTILATION

- Cardiac function
- Nutritional status
- Renal function
- Fluid balance
- Sepsis or infection
- Hematologic status or anemia
- Metabolic disturbance
- Pharmacologic therapy and metabolites
- Neurologic compromise
- Neuropsychiatric issues or delirium
- Sleep deprivation
- Endotracheal tube size
- Patient's self-perception of breathing

The classic cutoff value of 20 to 30 cm H_2O is associated with a 26% false-positive and 100% false-negative rate in predicting extubation success. Maximal inspiratory pressure is best used for serial evaluation of patients and is more a measure of strength than endurance.

Attempts have been made to predict endurance by using the resting minute ventilation rate, but using the common value of 10 L/minute as the threshold results in a false-positive rate of 11% and a false-negative rate of 75% in predicting successful extubation. Similarly, the ability to sustain maximum voluntary ventilation twice the minute ventilation is correctly predictive in only approximately 75% of the patients. More sophisticated measurement of endurance can be accomplished using a diaphragmatic or intercostal electromyographic power spectrum, but these techniques are not practical for routine clinical use. Yang and Tobin[170] developed an index using the ratio of respiratory rate (frequency [f], measured in breaths/min) to tidal volume (VT, measured in liters). An f/VT ratio greater than 105 has a predictive value of 89% for weaning failure.[170] An issue with all measured respiratory parameters or scoring systems is that they rarely include nonrespiratory parameters affecting weaning (Box 39.3).

Weaning: The Process

The actual process of weaning from mechanical ventilatory support must be individualized. No "one size fits all" method exists. While gradually lowering the SIMV rate in increments of two breaths/minute generally works for short-term ventilatory support, patients receiving long-term ventilatory support often have difficulty making the transition from SIMV rates of two breaths/minute to CPAP. The time-honored method of weaning by maintaining a patient on full ventilatory support and alternating with increasingly longer periods of spontaneous ventilation on a T-piece is effective, but it is time consuming because it requires setting up additional equipment and also requires a nurse or respiratory therapist to be immediately available at the bedside during each weaning attempt. Diaphragmatic effort is significantly lower during a T-piece trial with a deflated tracheostomy tube cuff than with the cuff inflated.[171] Weaning trials with the cuff deflated may thus be more physiologic when attempting weaning from the ventilator in a patient for whom this process is difficult. Breath-to-breath monitoring, display of tidal volumes, and ventilator alarms are not available during a T-piece trial. More commonly, pressure support is used as an adjunct to weaning either with IMV or CPAP while the patient is still connected to the ventilator and its alarm system.

Our preference is to conduct CPAP weaning with pressure support alone (ie, no additional IMV rate) because mechanical ventilation introduces one more variables into the evaluation of a patient's progress. Sufficient CPAP is applied to maintain open alveoli (generally 5–8 cm H_2O, but often higher when recovering from ALI or ARDS), and then the pressure-support level is titrated to provide the patient

with sufficient tidal volume to achieve a respiratory rate lower than 24 breaths/minute. Rapid rates are detrimental to weaning, because diaphragmatic blood flow is limited during contraction. As the patient's exercise tolerance improves, the pressure-support level can be lowered in increments of 2 to 3 cm H_2O. It is usually necessary to address fluid overload, nutritional support, and other nonpulmonary factors to achieve the pressure-support reduction.

Regardless of which weaning method is chosen, it is important to end each weaning trial with success rather than to stress the patient to the point of fatigue. Cohen and colleagues[172] identified the clinical sequence of inspiratory muscle fatigue. The earliest sign of inspiratory muscle fatigue is a spectrum shift in the electromyographic power spectrum, which is impractical to measure in the clinical setting. However, the next most sensitive sign is an increase in respiratory rate, which occurs before respiratory alternans, abdominal paradox, increase in the $PaCO_2$ level, or acidemia. Thus respiratory rate can serve as a sensitive marker of weaning progress.

Specific Impediments to Weaning

Weaning from ventilator support affects cardiac output in response to changes in pulmonary vascular resistance. Increased pulmonary vascular resistance can lead to septal shifts and consequent changes in the efficiency of right ventricular and left ventricular function. Thus it makes little sense to attempt weaning in the hemodynamically unstable patient. Our approach has been to keep these patients on full ventilator support with sedation and neuromuscular blockade if necessary until the acute cardiac problem is resolved.

Older ventilators with demand-valve systems impose an additional work of breathing, although it would be rare to see such ventilators in clinical use today. Current ventilators use computer-assisted demand valve technology to supply a variable flow rate, unlike older ventilators, in which a fixed low gas flow rate occasionally resulted in the inability to supply peak flow on demand. Nonetheless, if the patient is demonstrating apparent air hunger during the weaning process, a quick check of the inspiratory flow rates can often solve the problem. Pulmonary effusions and pneumothorax can develop in patients in otherwise stable condition and may also manifest as stalled weaning. Stacking of breaths or auto-PEEP can occur if the expiratory time is too short for patients, particularly patients with obstructive disease, to exhale fully before the next breath is delivered.

Ventilator Dyssynchrony

Increases in intercostal muscle tone and increases in abdominal muscle tone, pressure, or contents decrease chest cage compliance. During volume-cycled ventilation, a decrease in chest cage compliance results in elevated intrathoracic pressure that may reduce venous return to the right side of the heart.[88] A patient may also actively attempt to impede flow during the inspiratory cycle, a process referred to as "fighting," being "out of phase," or "breathing against" the ventilator.

The most common reason for "fighting" the ventilator is a mismatch between ventilator support and patient demand. During the triggering phase, insensitive systems or intrinsic PEEP may cause delayed or missing triggers. During flow delivery, either inadequate flow or excessive flow can be responsible. Cycling may also be mismatched if the patient's effort continues despite termination of the machine breath or if the patient is exhaling to terminate a prolonged machine breath. These phenomena and appropriate remedies were discussed in a comprehensive review with accompanying pressure, flow, and volume tracings.[173] With sudden onset of distress, inadequate ventilation (hypercarbia), acidemia, inadequate oxygenation, central nervous system dysfunction, pain, and/or anxiety must be excluded. Endotracheal cuff leak, misplacement of the endotracheal tube, inadequate inspiratory flow rates, pneumothorax, abdominal distention, sepsis, pain, and anxiety should all be considered in the differential diagnosis.

Assisting the patient with manual ventilation or switching to assist modes for a short time with or without additional sedation often allows the patient to settle down and return to synchrony with the ventilator. Pressure and flow tracings displayed on the ventilator can narrow the differential diagnosis and confirm whether adjustments to the inspiratory flow rate are helpful. Neurally adjusted ventilator assist is emerging as a method to match ventilator assistance more closely to patients' needs by assessing diaphragmatic electrical activity through an esophageal probe.[174] As diaphragmatic activity occurs before airway flow or pressure changes, synchrony between the patient and the ventilator may be improved using neurally adjusted ventilator assist, although more clinical studies are needed.

Muscle Weakness and Critical Illness Polyneuropathy

Long-term administration of neuromuscular blocking agents, particularly drugs such as vecuronium with a steroid structure; have been associated with persistent paralysis.[175] One explanation may be the accumulation of the metabolite 3-desacetylvecuronium, which is rarely seen in patients with normal renal function but is quite common in patients with delayed recovery.[175] However, prolonged paralysis can also be seen after treatment with other drugs such as pancuronium, metocurine, and *cis*-atracurium, which do not necessarily share the same structure or have persistent metabolism. The suspicion is that neurogenic atrophy occurs with prolonged paralysis resulting in low-grade flaccid quadriplegia or more localized weakness of respiratory muscles.

Prolonged ICU stay may also precipitate psychiatric problems even in psychologically normal patients, although these problems occur more commonly in patients with an underlying psychiatric history. Light, noise, and lack of sleep can change a patient's perception of reality. Psychological dependency on the ventilator may also develop, although this is rare. Careful attention to maintaining a normal day/night sleep cycle, ensuring adequate sleep, creating a quiet ICU environment, judicious use of pharmacologic agents such as haloperidol or quetiapine,[176] and involvement of the patient and family as participants in the weaning process may be helpful when psychological impediments to weaning exist.

Tracheostomy

Prolonged endotracheal intubation results in damage to the respiratory epithelium and cilia and may lead to vocal cord damage and airway stenosis.[177,178] If mechanical ventilation is anticipated for longer than 14 days, consideration should be given to early tracheostomy.[179] Other indications for tracheostomy include copious or tenacious secretions in debilitated patients who are unable to clear secretions spontaneously. Tracheostomy is relatively contraindicated in patients with ongoing mediastinitis or local infection at the tracheostomy site because of the potential for mediastinal contamination with respiratory secretions. Tracheostomy is not a risk-free procedure, and complications include pneumothorax, pneumomediastinum, subcutaneous emphysema, incisional hemorrhage, late tracheal stenosis or tracheomalacia, stomal infections, and rarely tracheoinnominate fistula. Early tracheostomy can be accomplished at the bedside with commercially available kits.[180] Swallowing dysfunction may occur following tracheostomy or after prolonged endotracheal intubation introducing the risk of aspiration pneumonia or respiratory failure. A swallowing evaluation is indicated before allowing a patients with a tracheostomy to attempt oral feeding. This evaluation is usually accomplished with a formal speech pathology consultation, but swallowing difficulty may also be noted by the nurses during attempted feedings.

Inability to Wean

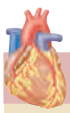
A few patients are not able to be weaned from ventilator support despite all efforts. Predictive models, however, are rarely useful for deciding which patients will not benefit from further intensive care.[5,9,17,21,181]

It is rarely a single problem, but rather the interactions among multiple morbidities that create a situation in which the patient may never be able to achieve the "escape velocity" needed to separate from the

ventilator. At this point, a discussion with the patient (if he or she has decisional capacity) or the health care proxy can be helpful in defining the benefits and burdens of further therapy and the patient's desires. Consultation with the hospital's ethics team may be very helpful. A frank assessment of which problems can be "fixed" versus those that are irreversible will define care options. Patients who remain in low–cardiac output states cannot resolve their multiple organ failure and thus their dependence on high-technology support including ventilation and hemodialysis. Unless patients are candidates for long-term ventricular assist devices or heart transplantation, they are facing a slow, technology-assisted decline that will end in an untreatable infection. Conversely, malnutrition and deconditioning in the absence of ongoing sepsis and organ system failure sometimes respond to prolonged rehabilitation, which may be better handled by a long-term ventilation facility than an acute care hospital. The critical issue is the patient's reserve because unless the patient has adequate cardiac and pulmonary reserve to tolerate stress once all remediable problems have been addressed, indefinite technologic support (ventilation, dialysis) will be required.

Conclusions

Successful postoperative respiratory care, including weaning from long-term mechanical ventilation and multisystem organ failure, requires an individualized and holistic approach to the patient. Weaning should be the first priority for the day, and all other demands should be minimized if possible. If trips to the computed tomography scanner or therapeutic interventions such as wound débridement are anticipated, weaning may not be possible for part of the day. Thus we try to minimize interruptions and to group them so as not to interrupt the weaning process. With that goal in mind, it is also essential to avoid disrupting the patient's nighttime sleep, so that the patient can be well rested and ready to participate in the weaning process. Detailed and full instructions must be given to the patient, and it is frequently helpful to include family members in the discussion so that they can serve as adjunct respiratory coaches. We try to avoid pushing the patient to the point of exhaustion or panic and use a planned, conservative approach such that weaning always ends in a sense of accomplishment for the patient rather than failure. Windows of opportunity for weaning from mechanical support are few and must often be created. Box 39.4 summarizes recommendations for the cardiac surgical patient who is difficult to wean from mechanical ventilation.



BOX 39.4 SUMMARY

1. Recognize patients at risk based on preoperative and intraoperative events (see Table 39.1).
2. Where possible, minimize the risk of adverse events (see Box 39.2).
3. Prioritize organ system support: without adequate perfusion, all other systems will fail.
4. Maintain full ventilator support during the acute phase of respiratory insufficiency or circulatory failure to avoid unnecessary fatigue.
5. Adopt a lung-protective ventilation strategy for patients with acute lung injury or acute respiratory distress syndrome.
6. Expect and defend against common problems (see Box 39.3).
7. Pay attention to general support measures and safety issues including sedation holidays and infection control.
8. Prepare the patient and family for involvement in the rehabilitation phase.
9. Have a clear weaning plan or protocol, and follow it.
10. Recognize when the burdens of treatment are disproportionate, and initiate appropriate discussions with the patient or health care proxy.

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Central Nervous System Dysfunction After Cardiopulmonary Bypass

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KEY POINTS

1. Despite a progressive decrease in cardiac surgical mortality, the incidence of postoperative neurologic complications has remained relatively unchanged over the decades. During this same interval, the age, acuity, and extent of comorbidities in cardiac surgical patients have increased.
2. The risk for stroke in patients undergoing coronary artery surgery increases progressively with increasing age, ranging from 0.5% for patients younger than 55 years to 2.3% for those older than 75 years.
3. Age-associated increased risk of stroke and adverse central nervous system (CNS) outcome appear to be powered primarily by comorbidities, particularly ascending and aortic arch atherosclerosis.
4. Neurologic events in cardiac surgical patients are associated with increased postoperative mortality, prolonged intensive care unit stay, longer hospital stay, decreased quality of life, and decreased long-term survival.
5. Neurologic complications range from coma, stroke, and visual field deficits to impairments of cognitive processes (eg, delirium, impaired memory and attention, mood alterations).
6. Mechanisms for neurologic injury in cardiac surgery include some combination of cerebral embolism, hypoperfusion, and inflammation, associated vascular disease, and altered cerebral autoregulation, rendering the brain more susceptible to injury.
7. Progression of underlying disease is a confounder in assessing late postoperative CNS complications.
8. While occlusive carotid disease is associated with increased risk of perioperative stroke, such stroke is not infrequently contralateral, and concomitant perioperative carotid endarterectomy may increase risk of stroke and other major adverse events.
9. Perioperative risk factors for neurologic complications include renal dysfunction, diabetes mellitus, hypertension, prior cerebrovascular disease, aortic atheromatosis, manipulation of ascending aorta, complex surgical procedures, bypass time longer than 2 hours, hypothermic circulatory arrest, hemodynamic instability during and after bypass, new-onset atrial fibrillation, hyperglycemia, hyperthermia, and hypoxemia.
10. Routine epiaortic scanning before instrumentation of the ascending aorta is a sensitive and specific technique used to detect nonpalpable aortic atheromatosis.
11. In patients with significant ascending aorta atheromatosis, avoidance of aortic manipulation ("no-touch technique") is associated with decreased perioperative stroke.
12. Strategies to decrease the impact of cardiopulmonary bypass (CPB) on embolization, inflammation, and coagulation will decrease neurologic complications.
13. Cerebrovascular disease renders patients who experience wide hemodynamic perturbations during CPB at greater risk for perioperative stroke.
14. Modular minimally invasive extracorporeal circulation (MiECC) is a new approach to physiologically integrated CPB and is associated with a variety of improved outcomes.
15. Minimal access (minimally invasive) surgery can produce greater physiologic derangements and risk of adverse outcomes compared with conventional CPB.
16. Cerebral near-infrared spectroscopy (cerebral oximetry) can detect cerebral ischemia and is associated with decreased incidence of stroke and improved outcomes after cardiac surgery.
17. There is a greater incidence of early postoperative cognitive dysfunction in patients exposed to conventional CPB compared with off-pump and noncardiac surgical patients.
18. The incidence of late cognitive dysfunction and stroke appears to be similar between groups undergoing conventional CPB, percutaneous coronary intervention, or medical management, implying progression of underlying disease and atrial arrhythmias as primary mechanisms of late stroke.
19. Pharmacologic management should be directed primarily toward intraoperative usage of volatile anesthetics, continuance of perioperative aspirin and statin medications, minimization of hyperglycemia, and vigilant therapy for postoperative atrial arrhythmia.

From 2001 to 2011, coronary artery bypass graft (CABG) procedures decreased by nearly 50% to 213,700 procedures, whereas percutaneous coronary intervention (PCI) decreased by more than 25% to 560,500 procedures in 2011.[1] Although these trends may reflect a variety of environmental, lifestyle, and therapeutic factors, overt and subclinical perioperative cerebral injury remains a compelling problem and continues to influence the debate over optimal strategy for coronary revascularization.

In a retrospective review of 86,244 CABG and 103,549 PCI patients undergoing revascularization for stable multivessel coronary disease from 2004 through 2008, who were identified from national registries, the 4-year composite event rate of death, myocardial infarction, and stroke favored CABG, whereas the risk of stroke alone favored PCI. This difference was primarily due to the higher 30-day stroke rate for CABG of 1.55% versus 0.37% for PCI.[2] Although a meta-analysis and a large prospective study appeared to demonstrate that the early excess risk of stroke in CABG was compensated for by a slow but progressive catch-up phenomenon in patients undergoing PCI, it has been argued that these analyses were all underpowered for stroke.[3,4] In contrast, a subsequent metaanalysis of 57 studies involving 80,314 patient records determined a significantly lower risk of stroke within 30 days and a lower cumulative stroke with PCI as compared with CABG up to year 5.[5] Importantly, in this meta-analysis the incidence of late stroke (>30 days) was similar between the two groups.[5]

As such, these and similar studies strongly affirm that it is primarily intraoperative factors associated with CABG that give rise to the increased stroke risk. Accordingly, the risk factors, causes, and potential for mitigation of perioperative stroke and neurobehavioral outcomes associated with cardiac surgery and cardiopulmonary bypass (CPB) are the topic of this chapter.

Categorization of Central Nervous System Injury

In a seminal study, Roach and colleagues[6] classified central nervous system (CNS) injury into two broad categories: type I (focal injury, stupor, or coma at discharge) and type II (deterioration in intellectual function, memory deficit, or seizures). Cerebral injury can also be broadly classified as stroke, delirium (encephalopathy), or postoperative cognitive dysfunction as outlined in the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for CABG.[7] Perioperative cognitive performance is assessed through the administration of a series of standardized psychometric tests, ideally administered before and after surgery.

Stroke is defined clinically as any new focalized sensorimotor deficit persisting longer than 24 hours, identified either on clinical grounds only or, ideally, as confirmed by magnetic resonance imaging (MRI), computed tomography, or other form of brain imaging.

Transient ischemic attack (TIA) is defined as brief neurologic dysfunction persisting for less than 24 hours. Neurologic dysfunction lasting longer than 24 hours but less than 72 hours is termed a *reversible ischemic neurologic deficit.*

Delirium is described as a transient global impairment of cognitive function, reduced level of consciousness, profound changes in sleep pattern, and attention abnormalities.

Cognitive dysfunction is defined as a decrease in score falling below some predetermined threshold, such as a decrease in postoperative score of magnitude 1 standard deviation or more derived from the preoperative performance of the study group as a whole.

Seizure is categorized as either convulsive or nonconvulsive and may be related to overt CNS injury or alternatively may reflect transient biochemical or pharmacologically mediated neuroexcitation.

The incidence of stroke or type I injury after closed-chamber cardiac procedures is generally considered to be approximately 1%.[8] For isolated single valve surgical repair or replacement, most recent data from the Society of Thoracic Surgeons (STS) database encompassing 109,759 procedures report a stroke rate of 1.6%,[9] increasing to 2.9% for combined CABG and valve surgery based on reports of 101,661 patients.[10] It is interesting that, whereas STS database is predicated upon self-reporting of outcomes incidences, a meta-analysis of 40 observational studies reporting on 8975 patients aged 80 years or older undergoing combined conventional aortic valve replacement (AVR) and CABG reported a postoperative stroke rate of 3.7% (95% confidence interval [CI], 2.8–4.8; 12 studies, 2770 patients) not inconsistent with STS database results.[11]

The incidence of cognitive dysfunction (type II) is reported as ranging in rate from 30% to 80% in the early postoperative period.[7,12–19] The difference in the incidence of cerebral injury after cardiac surgery is related to the type and complexity of the procedure, whether it is off-pump coronary artery bypass (OPCAB), CABG, open chamber, combined CABG and valvular surgery, or aortic arch and related procedures.[15,20–22] The increasing usage of minimally invasive valvular and coronary revascularization techniques, as well as the expanding role for catheter-based valve replacement, have independently impacted the risk of CNS injury and are discussed separately in this chapter.

Overall, the increased length of stay and increased mortality rates associated with any form of cerebral complication in cardiac surgical patients are striking.[7,12,19,23] Despite the relatively greater impact on mortality of stroke as opposed to cognitive dysfunction, type II injury is still associated with a fivefold increase in mortality. In their study based on data from mid-1990s, Roach and colleagues evaluated 2108 patients undergoing CABG at 24 U.S. institutions and recorded adverse cerebral outcomes in 6.1% of patients overall.[6] Of these, 3.1% experienced type I focal injury, stupor, or coma and had an associated in-hospital mortality rate of 21%, whereas 3.0% of patients experienced deterioration of intellectual function or seizures and had a mortality rate of 10%. In contrast, a significantly lower overall mortality rate of 2% was seen in those patients without adverse cerebral outcomes. In addition, patients with neurologic complications had, on average, a twofold increase in hospital length of stay and a sixfold likelihood of discharge to a nursing home. Independent risk factors were identified for both types I and II cerebral injury. Predictors of both types of cerebral complications included advanced age of older than 70 years and a history or the presence of significant hypertension. Predictors of type I deficits include the presence of proximal aortic atherosclerosis as defined by the surgeon at the time of surgery, a history of prior neurologic disease, use of the intraaortic balloon pump, diabetes, a history of hypertension, a history of unstable angina, and increasing age. Perioperative hypotension and the use of ventricular venting were also weakly associated with this type of outcome.[6]

An important caveat that must be borne in mind when interpreting Roach and colleagues' results is that type II injury as identified in their study is not necessarily equivalent to perioperative cognitive dysfunction as demonstrated in other studies. Type II injury was detected on clinical grounds alone rather than on the basis of deterioration in performance on a predefined series of specific cognitive tests. The latter are a much more sensitive measure of performance and thus detect cognitive dysfunction with a considerably greater frequency; as such, they potentially have a much different, although not necessarily benign, implication from the increased mortality rates associated with type II injury demonstrated by Roach and colleagues.[6,24]

Early, Delayed, and Late Stroke

In considering the incidence of perioperative stroke it is apparent that distinguishing stroke as early (ie, neurologic deficit apparent on emergence from anesthesia), delayed (ie, neurologic deficit developing more than 24 hours postoperatively), or late (ie, stroke developing more than 30 days postoperatively), is important in order to better discriminate causative factors and potential risk reduction strategies. Such an analysis facilitates identification of potentially causal intraoperative events (eg, hypotension, atherosclerotic aorta), from perioperative occurrences (eg, atrial fibrillation) and later progression of underlying disease (eg, cerebrovascular atherosclerosis).[25]

In an analysis of 2516 consecutive patients who underwent either CABG (n = 1399) or OPCAB (n = 1117), more than half of strokes (29 of 46; 63%) were delayed strokes.[25] Patients undergoing OPCAB had significantly lower risk of early stroke (0.1% vs 1.1%; P = .0009), whereas the incidence of delayed strokes was not different significantly (0.9% vs 1.4%; P = .3484) between patients undergoing CABG and OPCAB.[25] Similarly, in a review of more than 7839 CABG, 297 OPCAB, and 986 combined CABG and valve surgeries, an overall early stroke incidence of 1.6% and delayed stroke incidence of 1.1% was reported.[26] Univariate analysis indicated higher early stroke risk for CABG versus OPCAB (1.4% vs 0.3%; P = .011). Multivariate analysis indicated that risk factors for early stroke were advanced age, high preoperative creatinine level, extent of aortic atherosclerosis, and duration of CPB. Factors associated with delayed stroke were female gender, unstable angina, previous cerebrovascular disease, inotropic support requirement, and postoperative atrial fibrillation. Early stroke was associated with increased mortality mainly in the acute perioperative period, whereas delayed stroke was associated with increased long-term mortality.[26]

These studies strongly indicate that patient comorbidities, particularly aortic atherosclerosis, in concert with intraoperative factors, whether associated with CABG, OPCAB, or PCI, fundamentally impact the incidence of early stroke and are thus potentially modifiable, whereas late stroke reflects progression of comorbid disease and atrial arrhythmias.

Age-Associated Risk for Central Nervous System Injury

In a review of 67,764 cardiac surgical patients, of whom 4743 were octogenarians, and who underwent cardiac surgery at 22 centers in the National Cardiovascular Network, Alexander and coworkers reported that the incidence of type I cerebral injury (defined by Roach et al as stroke, TIA, or coma)[6] was 10.2% in patients older than 80 years versus 4.2% in patients younger than 80.[27] Although global mortality for cardiac surgery in octogenarians was greater than in younger patients, the researchers reported that when octogenarians without significant comorbidities were considered, their mortality rates were similar to those of younger patients.[27]

This observation has been confirmed in a recent single-center study of 418 consecutive patients older than 80 years who underwent cardiac surgery between 2000 and 2012 and who were matched according to gender, surgical procedure, and comorbidities with 426 younger patients.[28] This study identified postoperative stroke in 4.1% of octogenarian patients and in 3.5% of matched controls (P = .65). In younger patients, peripheral vascular disease and cardiac rhythm disturbances were significant risk factors, whereas factors related to intraoperative brain oxygenation (ie, preoperative anemia) were the most critical determinant of stroke in the older patients. In a recent review from the STS National Adult Cardiac Surgery Database of 774,881 patients undergoing isolated CABG between January 2002 and December 2006, the overall incidence rate of stroke was 1.4%, increasing to 2.3% in patients aged 75 years and older.[8] Stroke rate was inversely related to body surface area; this may again reflect a decrease in red cell mass and greater degree of hemodilution during CPB and was directly proportional to serum creatinine concentration, as well as presence of valvular heart disease and other comorbidities.[8]

In this respect, in addition to the age-related factor, reports from Europe and North America consistently describe previous cerebrovascular disease, diabetes mellitus, hypertension, peripheral vascular disease (including carotid disease), aortic atherosclerosis, renal dysfunction, infarction or unstable angina within 24 hours before surgery, and intraoperative and postoperative complications as being additional factors increasing the incidence of cerebral injury in cardiac surgical patients (Box 40.1) Determining the impact of age-associated cerebral injury in cardiac surgery is becoming more relevant because of the progressive increase in the average age of the general population and, in particular, of the cardiac surgical population.[6,8,20,23,29,30]

BOX 40.1 FACTORS RELATED TO CEREBRAL INJURY IN CARDIAC SURGERY

- Age[8,27,28]
- Aorta atheromatosis[160,161,163,164,166,168,391–393]
- Carotid disease[30,394]
- Diabetes mellitus[6,8,21,131,174,218,395]
- Hypertension[6,8,395,396]
- Peripheral vascular disease[6,68,165,218,395,397]
- Renal dysfunction[8,398]
- Stroke or cerebrovascular disease[6,21,30,131,399]
- Recent unstable angina or acute myocardial infarction[6,218,398,400]
- Preoperative low output/low ejection fraction[397,398]
- Combined/complex procedures[15,395]
- Redo surgery[218,395]
- Prolonged cardiopulmonary bypass time[22,68,395]
- Intraoperative hemodynamic instability[15,22,149,395]
- Postoperative atrial fibrillation[149,168,398,399]

Risk factors consistently reported for perioperative cerebral injury in cardiac surgery patients; see reference numbers and discussion in the text.

The presence of preoperative comorbidities is increasingly recognized as the primary determinant of the age-associated risk for CNS complications. As overall survival and quality of life after cardiac surgery continue to improve in older patients, advanced age alone is no longer considered a deterrent when evaluating a patient for cardiac surgery, with some centers reporting similar incidences of stroke in octogenarians independent of whether CABG or OPCAB was employed.[11,20,27,29,31] The presence and extent of comorbidities should be considered as being of equal or greater importance than age itself as a risk factor for cerebral injury in cardiac surgical patients.

Retrospective Versus Prospective Neurologic Assessment

The detection of CNS injury depends critically on the methodology used, and retrospective studies have been demonstrated as insensitive in various studies.[14,18,32,33] As Sotaniemi and colleagues demonstrated, a retrospective chart review is inadequate as an assessment of the overall incidence of postoperative neurologic dysfunction.[33] In their study of 100 patients in whom a 37% incidence rate of neurologic dysfunction had been diagnosed by careful neurologic examination, the prevalence rate of cerebral abnormalities detected by retrospective analysis of the same patient pool was only 4%. The reasons for the inability of retrospective chart audit to detect the majority of patients with neurologic dysfunction are readily apparent and include incompleteness of records, a reluctance to document apparently minor complications, and, most important, an insensitivity to subtle neurologic dysfunction. The timing, thoroughness, and reproducibility (single examiner) of the neurologic examinations, as well as the incorporation of a preoperative assessment for comparison, all determine the sensitivity and accuracy with which postoperative CNS injury can be detected.[14,18,32,34,35] Many of the types of neurologic impairment now being documented are subclinical and not readily detectable by a standard "foot-of-the-bed" assessment and have currently unknown implications for longer term patient outcomes.[36,37]

This is most clearly illustrated by a recent prospective study by Messé and colleagues in which 196 patients (mean age, 75.8 ± 6.2 years) undergoing AVR for calcific aortic stenosis were evaluated by neurologists preoperatively and postoperatively and underwent postoperative MRI.[36] Over a 4-year period, clinical strokes were detected in 17%, whereas the frequency of stroke in the STS database in a comparable cohort was less than 5%.[9] Moderate or severe stroke (National Institutes of Health Stroke Scale ≥10) occurred in 8 patients (4%)

and was strongly associated with in-hospital mortality (38% vs 4%; $P = .005$), while silent infarct was identified on postoperative MRI in 59 (54%) of the 109 stroke-free subjects but was not associated with in-hospital mortality or increased length of stay.[36]

Delirium

In a study by Bucerius and coworkers [15] assessing CNS outcomes from 16,184 patients undergoing cardiac operations with CPB ($n = 14,342$) or without CPB ($n = 1847$), the overall prevalence rate of postoperative delirium was 8.4%. Stepwise logistic regression revealed history of cerebrovascular disease, peripheral vascular disease, atrial fibrillation, diabetes mellitus, left ventricular ejection fraction of 30% or less, preoperative cardiogenic shock, urgent operation, intraoperative hemofiltration, operation time of 3 hours or more, and a high perioperative transfusion requirement as being independent predictors of delirium, whereas beating-heart surgery and younger patient age were identified as having a significant protective effect.[15] In a prospective follow-up study of 112 cardiac surgical patients, the incidence rate of postoperative delirium was 21% and was associated with significantly increased mortality and readmission to hospital, as well as significantly greater incidences of cognitive and sleep disturbances.[38] Similarly, in a prospective study of 221 patients, 31% developed delirium of whom older age, higher Charlson's comorbidity index, lower Mini-Mental State Examination (MMSE) score, length of CPB, and systemic inflammatory response syndrome in the intensive care unit (ICU) were independently associated with delirium.[39] Other studies have also identified heightened inflammatory response characterized by increased levels of interleukin (IL)-2 and tumor necrosis factor-α (TNF-α) as associated with postoperative delirium.[40] Alternatively, Hori and associates detected a lower incidence of delirium of 9.2% (42/491 patients) that was associated with high mean arterial pressures (MAPs) above the near-infrared spectroscopy (NIRS)–detected upper limit of cerebral autoregulation during CPB, as well as age, prior stroke, and mechanical ventilation more than 48 hours as causative factors.[41]

Seizures

In a recent prospective study of 101 post–cardiac surgical patients, the incidence of electroencephalographically detected seizures was 3% (2 focal and convulsive, 1 generalized and electrographic) in which all 3 patients with seizures were 65 years or older, had open-chamber procedures, and underwent CPB for a duration longer than 120 minutes.[42] Risk factors recently associated with seizures after cardiac surgery include open-chamber cardiac surgery,[43–45] deep hypothermic circulatory arrest,[43] aortic calcification or atheroma,[43] critical preoperative state[43] or high APACHE II score,[45] tranexamic acid exposure,[44–47] preoperative cardiac arrest,[45] long CPB time,[45] previous cardiac surgery,[45] poor renal function,[45,48] age 75 years or older,[44] and peripheral vascular disease.[44]

Independent of CNS injury, recent evidence has focused on seizures associated with high dosage of tranexamic acid (>30 mg/kg), an antifibrinolytic administered to decrease blood loss and transfusion requirements.[47] Studies have generally implicated open-chamber procedures associated with prolonged duration CPB and renal failure as contributory and thought to be due to increased cerebral spinal fluid concentrations of tranexamic acid–producing enhanced neuronal excitation by impairing neuronal inhibition due to direct postsynaptic receptor blockade by tranexamic acid of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[49]

Neuropsychologic Dysfunction

Compared with stroke, cognitive dysfunction (neurocognitive dysfunction) is a considerably more frequent sequela of cardiac surgery and has been demonstrated in up to 80% of patients early after surgery.[18,50,51] The pathogenesis of cognitive dysfunction after cardiac surgery is still uncertain. Variables that have been postulated to explain the development of postoperative neurocognitive decline include advanced age, concomitant cerebrovascular disease, and severity of cardiovascular disease, as well as progression of underlying disease. Various intraoperative factors such as cerebral emboli, hypoperfusion or hypoxia, activation of inflammatory processes, aortic cross-clamp or CPB time, low MAP and cerebral venous hypertension have all been implicated. In many instances, subtle signs of neuropsychological dysfunction are detectable only with sophisticated cognitive testing strategies, although depression and personality changes may be noted by family members. It should be recognized that formalized cognitive testing is reproducible and quantifiable and represents an objective outcome measure; as such, it can act as a benchmark to assess various therapeutic interventions (eg, the efficacy of putative cerebroprotectants, equipment modifications, pH management strategies). In addition, a number of studies have made correlations between early postoperative cognitive dysfunction and intraoperative cerebral oxygen desaturation, as well as new ischemic lesions on MRI.[52,53] Assessment of early cognitive dysfunction can be used to discriminate between various intraoperative treatment modalities (eg, pH management, use of cell saver, epiaortic scanning [EAS]). However, whether early postoperative cognitive dysfunction represents permanent neurologic damage remains controversial.[54]

Newman and colleagues sought to determine the course of cognitive change 5 years after CABG, reporting an incidence rate of cognitive decline of 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years.[55] Cognitive function at discharge was a significant predictor of long-term function. Their results confirmed the relatively high prevalence and persistence of cognitive decline after CABG and suggested a pattern of early improvement followed by a later decline that is predicted by the presence of early postoperative cognitive decline.[55] What is interesting is the apparent lack of association between cognitive dysfunction and aortic atherosclerosis. At least in one study of 162 CABG patients who had a perioperative neurocognitive evaluation and evaluable intraoperative transesophageal echocardiography (TEE) images, no significant relation was found between cognitive dysfunction and atheroma burden in the ascending arch or descending aorta, suggesting that aortic atherosclerosis may not be the primary factor in the pathogenesis of post-CABG cognitive changes.[56]

In the systematic review and meta-analysis in CABG patients by Van Dijk and colleagues, data from six highly comparable studies were pooled and demonstrated an incidence of cognitive deficit (defined as a decrease of at least 1 standard deviation in at least 2 of 9 or 10 neuropsychological tests) of 22.5% (95% CI, 18.7–26.4) at 2 months after surgery.[18] In a prospective study of 316 CABG patients, Murkin and colleagues reported a perioperative stroke rate of 2.8% and demonstrated that 33% of 239 patients assessed 2 months after surgery evidenced cognitive dysfunction, and that 45% experienced either neurologic or cognitive dysfunction, in comparison with their preoperative performance.[57]

One important confounder in many of the earlier studies is the absence of a nonsurgical control cohort with similar comorbidities also followed longitudinally with cognitive testing. Several more recent studies have demonstrated similar incidences of later cognitive dysfunction whether patients underwent CABG, off-pump surgery, PCIs, or were managed medically.[54,58] These results strongly imply that underlying comorbidities and progression of cerebrovascular disease are the most relevant factors in late postoperative cognitive dysfunction rather than cardiac surgery per se.

The mid- and long-term impact of neurocognitive dysfunction on quality of life after cardiac surgery has been addressed by different studies.[24,59,60] Ahlgren and investigators prospectively evaluated neurocognitive function and driving performance after CABG in 27 patients who underwent neuropsychological examination involving 12 cognitive tests, including a standardized on-road driving test and a test in an advanced driving simulator before and 4 to 6 weeks after surgery.[59] Twenty patients who underwent PCIs under local anesthesia served as a control group. After surgery, 48% of patients in the CABG group showed cognitive decline, whereas significantly fewer patients in

the PCI group, only 10%, showed cognitive decline after intervention. Of particular relevance to functional quality of life, patients demonstrating cognitive decline also tended to drop in the on-road driving scores to a larger extent than did patients without a cognitive decline.[59] Di Carlo and colleagues administered a series of cognitive tests before and 6 months after the operation to 110 patients (mean age, 64.1 years; 70.9% male sex) undergoing cardiac surgery.[60] The degree of the impairment was determined by two independent neuropsychologists in relation to its impact on everyday life activities. At 6-month assessment, 10 patients (9.1%) were ranked as having severe deterioration, 22 (20%) as having mild or moderate deterioration, and 78 (70.9%) as unchanged or improved.[60] At 5-year follow-up, Newman and coworkers also found a significant correlation between cognitive function and quality of life in patients after cardiac surgery.[24] Lower overall cognitive function scores at 5 years were associated with lower general health and a less productive working status.

Overall, it appears that underlying patient comorbidities rather than use of CPB or even surgery or PCI or medical management are most important in the genesis of long-term cognitive outcome. Although cognitive testing can be used to discriminate and optimize among various perioperative treatment modalities, the incidence of neurocognitive dysfunction between studies is potentially unreliable as an index of the absolute incidence of neurocognitive dysfunction, because of the high variability in methodologies among studies (ie, differing definitions of neurocognitive dysfunction, choice of tests, employment of relevant comparator groups), associated with a given procedure (eg, CABG surgery). Cognitive testing is best used as a comparator tool to discriminate between treatment modalities.

Neuropsychological Testing

As noted in the studies discussed, neuropsychological testing has been used increasingly in an attempt to discriminate the efficacy of various treatment modalities or as an index of cognitive functioning after CPB. In large measure, the sensitivity of this type of testing is such that very small decrements in performance can be assessed and quantified. It appears that a patient may have a consistent decrease in cognitive performance, with or without evidence of subtle neurologic abnormalities, yet may be apparently oblivious to it, whether because of denial or an absence of awareness. Commonly, such a patient's family may have noted some nonspecific alteration in mood or behavior, likely a manifestation of the same dysfunction detected on cognitive testing.

Preoperative Cognitive Function

One of the earliest prospective reports of neurobehavioral sequelae of cardiac surgery appeared in 1954, and it focused on the acute and chronic stress responses manifested as psychobehavioral syndromes in patients undergoing valvular surgery.[61] More recently, Rankin and associates used a 1-hour neuropsychological battery administered before surgery to 43 patients before prospective randomization to either CABG or OPCAB and again to 34 of those patients 2 to 3 months after surgery by an examiner blind to surgical condition.[62] Neuropsychological status did not change 2.5 months after surgery between OPCAB or CABG groups. However, both groups showed dramatic presurgical cognitive deficits in multiple domains, particularly verbal memory and psychomotor speed. This corroborates previous research suggesting that patients requiring CABG may evidence significant presurgical cognitive deficits as a result of existing vascular disease.

Neuropsychological Test Selection

Research examining cognitive functioning in patients undergoing CPB has frequently focused on the assessment of cognitive functioning within the domains of attention/concentration, psychomotor speed, motor dexterity, and verbal learning. Under the best case scenario, it might be desirable to use a complete battery of neuropsychological tests assessing the entire spectrum of cognitive functions. However, the cost of such a procedure and the time demands make such an approach unrealistic.

In perioperative cardiac surgical patients, the evaluation is necessarily limited by constraints of time and fatigue; thus, tests used should have good sensitivity to dysfunction, even if at the expense of specificity. Tests that can be administered quickly and reliably and are highly sensitive, particularly to dysfunction within cognitive domains localized to brain regions vulnerable to effects of microemboli or transient hypoxia, should be selected.

Research suggests that among the tests most appropriate under these circumstances are tests of attention/concentration, psychomotor speed, motor dexterity, and verbal learning. Research as to the behavioral consequences of hypoxia (and other conditions associated with more diffuse brain damage) suggests these domains are likely to be compromised.[63] This presumption has also been supported by research to date examining behavioral consequences of CPB. Frequently, the Grooved Pegboard Test (motor dexterity), various subtests of the Wechsler Adult Intelligence Scale-Revised (Digit Symbol [psychomotor speed]), some of the seven subtests of the Wechsler Memory Scale (Mental Control [attention], Digit Span [concentration], Paired Associates Verbal Learning [verbal learning]), as well as the Halstead Reitan Trail Making Test (Trails A and B), have been used in whole or in part for the assessment of cognitive impairment after CPB.[24,50,55,57,59,60,64–73]

Methodologic Issues in Neurobehavioral Assessment

The Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery encouraged a more standardized and comparable methodology in assessment of cognitive injury, identifying several key issues of concern in perioperative cognitive testing.[34]

1. A spectrum of postoperative CNS dysfunction, both acute and persistent, occurs in a proportion of patients after cardiac surgery, including brain death, stroke, subtle neurologic signs, and neuropsychological impairment.
2. A number of patients who will undergo cardiac surgery have preexisting CNS abnormalities. Patients' neurologic and neuropsychological states need to be assessed before surgery to provide accurate baseline information.
3. The individual change in performance from baseline to a time after surgery is essential to any evaluation of the impact of surgery or any intervention associated with it.
4. When indicated, designs should incorporate the use of a control or comparison group. This is arguably one of the most important recommendations that was made, but, as noted earlier, until recently it has not been consistently applied, resulting in discordant results in the literature.
5. Because of the time constraints and physical limitations of the patient in performing a neuropsychological assessment in the context of cardiac surgery, care must be taken to select appropriate tests. Selection of tests should take the following issues into consideration:
   - Cognitive domain of the test
   - Sensitivity and reliability of the test
   - Time taken to perform the test
   - Degree to which learning may occur in the test
   - Availability of parallel forms of the test
   - Physical effort required to perform the test
   - Overall balance of the cognitive domains assessed in the battery
6. Tests should be free from sex, race, and ethnic bias and be structured to avoid floor and ceiling effects.
7. Because of the multifocal nature of the potential lesion locations, no single test will always detect postoperative neurobehavioral dysfunction.
8. Care must be taken in performing the assessments because neurobehavioral performance can be influenced by environmental, psychiatric, physiologic, and pharmacologic factors.
9. Because the performance of neuropsychological tests may be influenced by mood state and mood state variations, it is important

that mood state assessments be performed concurrently with the neuropsychological assessments.
10. To ensure objectivity and reliability of the assessment, for each patient, the testing should be performed by the same suitably qualified and trained individual, and tests should minimize subjectivity and be performed in a standardized manner. The examiner should be blinded to any treatment.
11. A comprehensive and concise neurologic examination should be performed by a suitably qualified and trained individual.
12. Because the incidence of postoperative neurobehavioral dysfunction is greatest in the immediate postoperative period and then declines, care must be taken to perform at least one assessment when performance is more stable. Ideally, this should be at least 3 months after surgery.
13. Investigators should be aware that new events may occur in the days after surgery.
14. Cognitive testing may be associated with improvement in performance on repeated testing, recognized as "practice effect." This improvement needs to be taken into consideration in any analyses of the data. In addition, study design incorporating procedures to minimize practice effects (ie, providing sufficient practice trials on each test at each assessment period) is encouraged.[21]

Based on the proceedings of these consensus conferences,[34] the following cognitive tests were recommended as necessary but not sufficient components of any neuropsychological test battery based on their availability in multiple languages and availability of paper-and-pencil versions for use with cardiac surgical patients:

- Rey Auditory Verbal Learning Test
- Trail Making A
- Trail Making B
- Grooved Pegboard

Furthermore, in 1997 an additional statement was published in which consensus was reached that (1) individual change scores rather than group means should be used, (2) there should be consistency of setting for testing, and (3) practice effect in neurocognitive testing should be corrected for.[35]

Mechanisms of Brain Injury

Determining which factor or, more likely, which combination of factors is responsible for postoperative neurologic or behavioral dysfunction in patients undergoing cardiac surgery using CPB is problematic (Box 40.2). From the few studies in which a surgical control group has been used, it appears that elements inherent to CPB are causative, particularly in dysfunction occurring in the immediate postoperative period.[57,72] How much of this dysfunction is as a direct result of exposure to CABG and CPB or occurs as a result of underlying comorbid disease is an area of active ongoing investigation. Underlying disease such as aortic and cerebrovascular atherosclerosis, hypertension, and diabetes, which predispose such patients to CNS dysfunction as a result of nonspecific stress associated with major surgery independent of CABG clearly plays a role. Based on postmortem studies, as well as correlative analyses of intraoperative events with neurologic outcomes, two primary mechanisms appear to be responsible for brain injury in otherwise uncomplicated cardiac operations: cerebral hypoperfusion and cerebral emboli.

Intraoperative cerebral embolization of particulate and microgaseous elements has a significant role in the genesis of cerebral events in postoperative cardiac surgical patients.[51,74–83] Increasing attention is also being paid to the role of perioperative hypoperfusion, particularly in patients with intracranial and extracranial atherosclerosis, and to the effect of inflammatory processes triggered during exposure to surgery and CPB.[22,84,85]

In a prospective study of 151 consecutive Japanese patients (115 men and 36 women ranging in age from 41 to 82 years) scheduled for CABG, carotid and intracranial arteries were examined for occlusive lesions with magnetic resonance angiography.[86] Cervical carotid artery stenoses of more than 50% narrowing were detected in 16.6% of the patients, and intracranial artery stenoses of more than 50% narrowing were detected in 21.2% of the patients. In a similar study of 201 Korean patients presenting for CABG, more than 50% had evidence of either extracranial or intracranial atherosclerotic disease, whereas 13% of patients had evidence of both.[87] In this series, 25.4% of patients had single or multiple postoperative CNS complications, and intracranial atherosclerotic disease was found to have a strong independent association with the development of CNS complications. The presence of both extracranial and intracranial atherosclerotic disease was even more strongly associated with adverse perioperative CNS outcomes than was intracranial atherosclerotic disease alone.[87]

In those studies in which a control group (subjected to a noncardiac procedure) was used, the incidence of both new neurologic signs and cognitive dysfunction was significantly greater in the patients undergoing CABG in the first several postoperative days compared with the surgical cohort.[57,88]

There is also evidence of a greater stroke rate in cardiac surgery from the recently published SYNTAX trial in which 1800 patients with three-vessel or left mainstem coronary artery disease were randomized to PCI or conventional CABG surgery.[89] This study demonstrated no difference in mortality at 1 year but a significantly ($P = .002$) lower incidence of primary composite end point of major adverse cardiac or cerebrovascular event in CABG (12.4%) versus PCI (17.8%) patients. However, although the overall outcome should argue strongly in favor of CABG surgery, the stroke rate was significantly greater in CABG (2.2%) than PCI (0.6%) patients.

More recent evidence is also focusing on new-onset postoperative atrial fibrillation (POAF) as being associated with increased long-term mortality and stroke.[90,91] Formerly, POAF was thought to be relatively benign and self-limited, whereas a recent meta-analysis involving records of 69,518 patients identified new-onset POAF following CABG as associated with significantly higher risk of mortality in short- and long-term follow-up and higher rates of stroke and other complications.[90] As discussed later, such evidence is giving new impetus to surgical and pharmacologic strategies to decrease risk of POAF and attendant complications.

BOX 40.2 RISK FACTORS FOR NEUROLOGIC COMPLICATIONS IN CARDIAC SURGERY

- Hemodynamic instability
- Diabetes mellitus
- Advanced age
- Combined/complex procedures
- Prolonged cardiopulmonary bypass time
- Prior stroke/cerebrovascular disease
- Aortic atheromatosis
- Renal dysfunction
- Peripheral vascular disease

Neuropathologic Studies

In an early series from 1962 to 1970 that examined 206 patients dying after cardiac surgery or CABG and a group of 110 patients dying after non-CPB vascular surgery, Aguilar and investigators reported that there was a high correlation between the use of CPB and the incidence of brain lesions.[92] They reported that the most significant abnormalities found, in both severity and frequency of occurrence, were emboli in small cerebral vessels; acute petechial, perivascular, and focal subarachnoid hemorrhages; and acute ischemic neuronal damage (Box 40.3). They noted the virtual disappearance from the brain of nonfat emboli such as fibrin, platelet aggregates, polarizable crystalline material, xanthomatous debris, striated muscle, and calcium in cases examined after the introduction of arterial line filtration, whereas they reported that cerebral embolization of such debris was commonly

BOX 40.3 MECHANISMS AND FACTORS FOR NEUROLOGIC LESIONS

- Embolization
- Hypoperfusion
- Inflammation
- Influencing factors
- Aortic atheroma plaque
- Cerebrovascular disease
- Altered cerebral autoregulation
- Hypotension
- Intracardiac debris
- Air
- Cerebral venous obstruction on bypass
- Cardiopulmonary bypass circuit surface
- Reinfusion of unprocessed shed blood
- Cerebral hyperthermia
- Hypoxia

observed in patients dying after CPB before the introduction of arterial line filtration.[92] Other early studies showed that measures taken to decrease the duration of CPB, as well as the introduction of arterial line filtration and filtration of the cardiotomy suction return, decreased overt neurologic dysfunction.[76,79,93]

A review of autopsy findings from 221 patients dying after CABG or valve surgery between 1982 and 1989 reported a direct correlation among age, severe atherosclerosis of the ascending aorta, and presence of atheroemboli.[94] Atheroemboli were significantly more common in patients who underwent CABG versus valvular surgery, and there was a high correlation of atheroemboli with severe atherosclerosis of the ascending aorta, being present in 37.4% of patients with severe disease of the aorta versus only 2% of those without. Of all patients who had evidence of atheroemboli, 95.8% had severe atherosclerosis of the ascending aorta.[94] Doty and colleagues reviewed the records of 49,377 autopsy cases and surgical specimens from the Johns Hopkins Hospital between 1973 and 1995.[77] Three hundred twenty-seven patients (0.7%) had an identifiable atheroembolism on histologic examination. Of these patients, 29 (0.2%) had undergone a cardiac surgical procedure within 30 days of autopsy or surgical resection. Six of the 29 patients (21%) had atheroembolism to the heart, 7 patients (24%) had embolism to the CNS, 19 patients (66%) had embolism to the gastrointestinal tract, 14 patients (48%) had embolism to one or both kidneys, and 5 patients (17%) had embolism to a lower extremity. Sixteen patients (55%) had atheroembolism in two or more areas. In six patients (21%), death was directly attributable to atheroembolism, including intraoperative cardiac failure from coronary embolism (three), massive stroke (two), and extensive gastrointestinal embolization (one).[77]

In a neuropathologic study of brains from 262 patients dying after having undergone CABG, valve replacement, or heart transplantation surgery, 49% of cases demonstrated evidence of circulatory disturbances identified as macrohemorrhages and microhemorrhages, infarcts, subarachnoid hemorrhages, or hypoxemic brain damage.[95] The infarcts were caused by local arteriosclerosis of cerebral arteries, fat emboli, arterial emboli from operative sites, or foreign body emboli. These investigators concluded that histologically overt microemboli did not play a major role in their findings and that nonfatal white matter microhemorrhages were found with varying frequency, especially after valve operations.[95] These observations are not inconsistent with the apparent lack of correlation seen in several beating-heart surgery studies between differing incidences of transcranial Doppler (TCD)–detected cerebral emboli and cognitive dysfunction.[74,96]

In a postmortem study of brain histology, four of five patients dying after CPB, two patients dying after proximal aortography, and six dogs placed on CPB were all found to have small capillary and arteriolar dilations (SCADs) distributed throughout brain parenchyma, consistent with sites of gas bubbles or fat emboli (Fig. 40.1).[81] These microvascular anomalies were only found in conjunction with use of CPB or proximal aortic instrumentation. In a subsequent series of

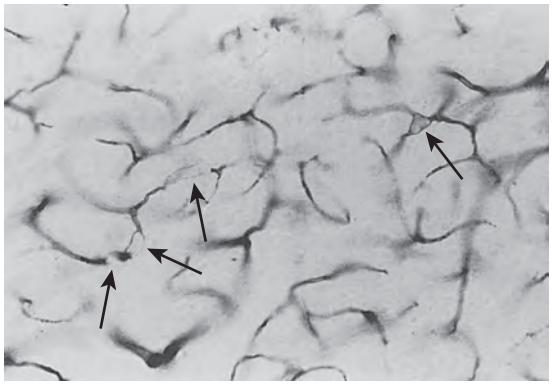


Fig. 40.1 Microemboli or small capillary and arteriolar dilatations (SCADs) in arterioles of human brain 1 day after cardiopulmonary bypass. The afferent microvessels are black. The SCADs are dilated clear areas *(arrows)*; the largest one here measures 25 μm in diameter. It is believed these represent the "footprints" of emboli that were almost completely removed by the reagents used in this histochemical staining method. Alkaline phosphatase–stained 100-μm-thick celloidin section; magnification ×300 before 50% reduction. *(Reprinted from Moody DM, Brown WR, Challa VR, et al. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study.* Ann Thorac Surg. *1995;59:1304–1307.)*

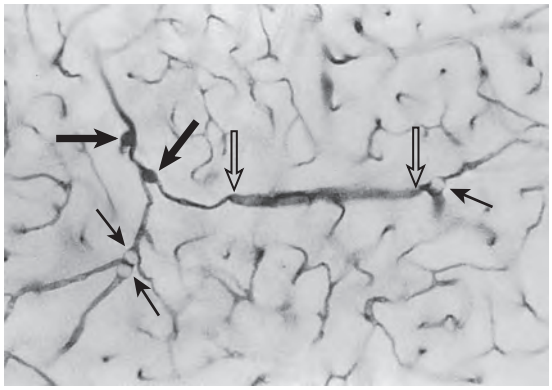


Fig. 40.2 Microemboli *(white arrows)* "bracketed in time" by sequentially injected microspheres of different colors. Clear microspheres *(small black arrows)* and black microspheres *(large black arrows)* can be seen distal to proximal order in a single arteriolar complex. In this experiment, clear spheres were injected into the carotid artery of a dog, followed in succession by injection of corn oil and then black spheres. Direction of blood flow in the arteriole is from top to bottom. Alkaline phosphatase–stained 100-μm-thick celloidin section; microspheres = 15 μm. *(Reprinted from Moody DM, Brown WR, Challa VR, et al. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study.* Ann Thorac Surg. *1995;59:1304–1307.)*

canine CPB studies by this same group of researchers, use of colored microspheres was able to "time-lock" the development of SCADs to the period associated with CPB (Fig. 40.2).[97]

Watershed Infarctions

Watershed, or boundary zone, infarcts are ischemic lesions that are situated along border zones between the territories of two major cerebral arteries (eg, the middle and posterior, or the anterior and middle cerebral arteries) where terminal arteriolar anastomoses exist (Fig. 40.3).[98–101] In a series reported by Malone and colleagues, a correlation was made between the presence of intraoperative electroencephalographic (EEG) abnormalities (virtual or complete electrical silence), usually seen in conjunction with sustained hypotensive episodes, and neuropathologic lesions found at necropsy.[99] In all nine

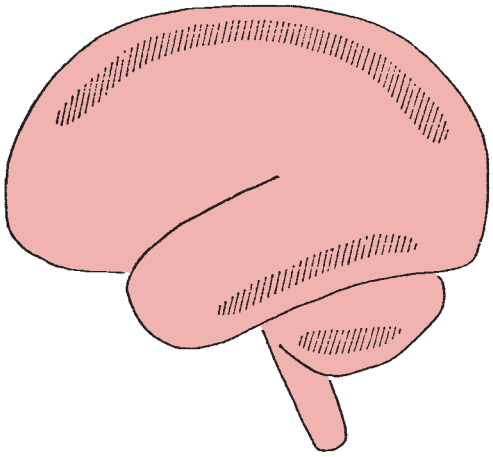


Fig. 40.3 Hatched areas showing the most frequent locations of boundary area, or watershed zone infarcts in the brain, situated between the territories of major cerebral or cerebellar arteries. *(From Torvik A. The pathogenesis of watershed infarcts in the brain.* Stroke. *1984;2:221–223.)*

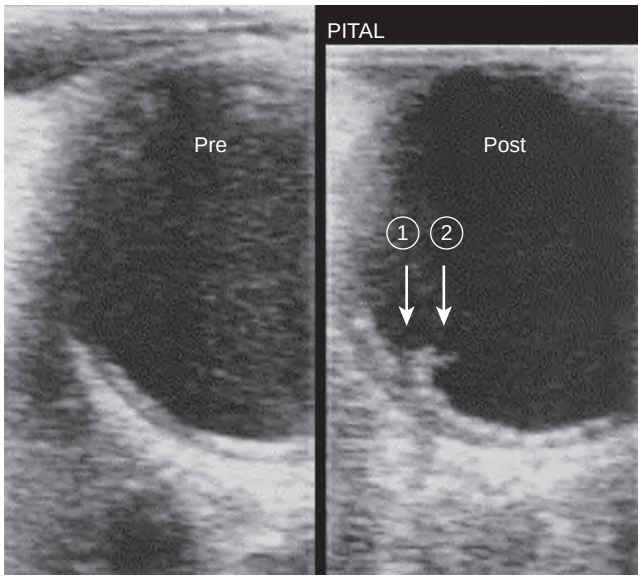


Fig. 40.4 New intimal tear *(arrow 1)* and new mobile lesions *(arrow 2)* likely to have been caused by aortic clamping. *(From Ura M, Sakata R, Nakayama Y, Goto T. Ultrasonographic demonstration of manipulation-related aortic injuries after cardiac surgery.* J Am Coll Cardiol. *2000;35:1303–1310.)*

patients with clinical evidence of brain damage, cortical boundary zone (watershed) lesions were observed in the parieto-occipital areas. Malone and colleagues suggest that this location is the most sensitive area for placement of recording EEG electrodes because it is where minimal boundary zone ischemic lesions occurred in the absence of other lesions, and it is also where ischemic lesions were found in their maximal severity and extent.[99]

A profound reduction in systemic blood pressure is the most frequent cause of watershed infarcts. These areas are thought to be more susceptible to ischemia resulting from hypotension because of their critical dependence on a single blood supply. Wityk and coworkers studied the pattern of ischemic changes on diffusion- and perfusion-weighted MRI in a case series of 14 patients and 4 patients, respectively, with neurologic complications after cardiac surgery.[102] Acute ischemic lesions were classified as having a territorial, watershed, or lacunar pattern of infarction. Patients with multiple territorial infarcts in differing vascular distributions that were not explained by occlusive vascular lesions were classified as having multiple emboli. Diffusion-weighted MRI revealed acute infarcts in 10 of 14 patients, of whom 4 had combined watershed and multiple embolic patterns of ischemia. Findings of perfusion-weighted MRI were abnormal in two of four patients, showing diffusion-perfusion mismatch. Both patients had either fluctuating deficits or TIAs, and their conditions improved with blood pressure increase.[102]

By the same rationale, however, these areas are also highly susceptible to ischemia because of end-artery embolization, and it is also recognized that although severe hypotension is the most common cause, showers of microemboli may lodge preferentially in these areas and cause infarcts in the underlying brain.[102–105] As such, although they commonly arise from profoundly hypotensive episodes, watershed lesions are not pathognomonic of a hypotensive episode and may be the result of cerebral emboli. Embolization and hypoperfusion acting together play a synergistic role and either cause or magnify the brain damage of cardiac surgical patients. The negative influence of hemodynamic instability and hypoxia has been demonstrated by several researchers, showing improved outcomes by an early and aggressive recognition and correction of hypoperfusion.[15,22,68,98,106,107]

Cerebral Emboli and Outcome

Cerebral emboli during CPB can be arbitrarily differentiated into macroemboli (eg, calcific or atherosclerotic debris) and microemboli (eg, microgaseous bubbles, microparticulate matter). Overt and focal neurologic damage likely reflects the occurrence of cerebral macroemboli (eg, calcific and atheromatous debris generated during valve tissue removal or instrumentation of an atheromatous aorta), whereas less focal neurologic dysfunction has been ascribed to cerebral microemboli.[6] Microemboli are primarily detected based on characteristic TCD signature being transient (<300 ms), high intensity (>3 decibels above spectrum), high frequency ("chirpy"), and unidirectional and appear to have some role in diffuse, subtle neurologic and cognitive disturbances, whereas macroemboli likely produce clinically apparent catastrophic strokes. Whatever the nature of the cerebral insult, however, it seems that coexistent inflammatory processes can exacerbate the magnitude of injury.

In a perioperative study of 127 patients undergoing OPCAB (n = 61) or CABG (n = 66), 35 (27.6%) showed new brain infarcts on postoperative diffusion-weighted MRI.[108] Most lesions were clinically silent, located in the cortical territory (80%), small (<1.5 cm) in diameter (89%), and not related to the underlying cerebral arterial abnormality (80%). Older age, use of CPB, a moderate to severe aortic plaque, and high levels of high-sensitivity C-reactive protein were independent predictors of new brain infarction, suggesting that a systemic inflammatory response may also contribute to the pathogenesis of post-CABG new infarcts.[108]

In a study to assess the impact of surgical manipulation of the aorta and correlations with postoperative stroke, Ura and colleagues performed EAS before aortic cannulation and after decannulation in 472 patients undergoing cardiac surgery with CPB and followed them for new type I neurologic complications.[109] Grade 2 aortic atherosclerosis was present in 73 patients (15%) and grade 3 in 28 patients (6%). Based on these results, in 63 of 472 patients the operative procedure was modified to change the cannulation site (52 patients) or avoid cross-clamping (23 patients). After aortic decannulation, a new lesion in the ascending aortal intima was identified in 16 patients (3.4%), of which 10 were severe (mobility or disruption of intima) (Fig. 40.4). Twelve were attributable to aortic clamping and four (all severe) to cannulation or decannulation. A total of 10 patients sustained neurologic complications, of whom 3 were diagnosed with severe new lesions (P < .001). The incidence rate of new lesions was directly related to extent of aortic atheroma, being 11.8% if the atheroma was approximately 3 to 4 mm thick and as high as 33.3% if the atheroma was greater than 4 mm, but only 0.8% when it was less than 3 mm.[109] Again, this underscores the need to reliably detect and ultimately avoid disruption of aortic atherosclerotic plaque.

Sylivris and investigators studied 41 consecutive patients undergoing CABG with TCD monitoring and preoperative and postoperative MRI brain scans.[110] A subgroup of 32 patients underwent neuropsychological testing the day before and 5 to 6 days after the operation, of whom 27 had TCD data. Among the subgroup of patients with reliable TCD data and neuropsychological studies, early neuropsychological deficit after CABG was found in 17 (63%) of the 27 patients. On univariate analysis, the time duration on CPB, total microembolic load during bypass, and microembolic rates during bypass were all significantly greater in the group with neuropsychological decline. Actual rates of emboli detected per minute were greatest during release of the aortic cross-clamp. Five patients had strokes, of which four had a significant decline in neuropsychological functioning. Unlike the association between microembolic signals during bypass and neuropsychological deficits, there was no relation between these factors and radiologic evidence of cerebral infarction. Not inconsistent with the findings of Ura and colleagues described earlier, there was a significantly greater microembolic load during aortic instrumentation in patients with cerebral infarction, temporally suggestive of particulate emboli, which was not apparent in comparison with patients with neuropsychological deficits alone.[109,110]

A study with a newer generation of TCD, which uses two different frequencies of insonation and purportedly discriminates between gaseous and particulate emboli, compared the number and nature of intraoperative microemboli in patients undergoing on-pump and off-pump cardiac surgical procedures in 45 patients (15 OPCAB, 15 on-pump CABG, and 15 open cardiac procedures).[74] The investigators demonstrated significantly fewer emboli in the OPCAB versus on-pump CABG and open procedure groups, averaging 40 (range, 28–80), 275 (range, 199–472), and 860 (range, 393–1321) emboli, respectively ($P < .01$). Twelve percent of microemboli in the OPCAB group were defined as solid compared with 28% and 22% in the on-pump CABG and open procedure groups, respectively. In the on-pump groups, 24% of microemboli occurred during CPB, and 56% occurred during aortic manipulation for cannulation, decannulation, application, and removal of cross-clamp or side clamp, again underscoring the importance of minimizing aortic instrumentation.[74]

Gaseous emboli are not innocuous, however. In various studies in nonheparinized animals it has been demonstrated that the effects of air emboli on the cerebral vasculature not only are due to bubble entrapment with direct blockage of cerebral vessels but also represent the effects that such bubbles have on vascular endothelial cells.[111] Ultrastructural examinations of pial vessels in rats exposed to cerebral air emboli demonstrated severe injury to endothelial plasmalemma, leading to loss of cellular integrity and endothelial cell swelling.[112] Such endothelial damage produces disruptions of vasoreactivity, as has been observed in cat pial vessels exposed to air emboli. In these capillary beds, the endothelial layer demonstrated ultrastructural abnormalities that included degradation of intercellular junctions, flattening of nuclei, and crenation of the plasmalemma. Air embolism also produces changes in blood elements leading to formation of a proteinaceous capsule around the bubbles, marked dilation of pial vessels, platelet sequestration, and damage to endothelial cells.[113–115] Air-induced mechanical trauma to the endothelium causes basement membrane disruption, thrombin production, release of P-selectin from intracellular vesicles, synthesis of platelet-activating factor, and a reperfusion-like injury with perturbations in inflammation and thrombotic processes. These phenomena likely impair nitric oxide production, causing alterations in cerebral microvascular regulation.[116,117] Whether heparin anticoagulation during CPB mitigates the impact of cerebral gas embolization as demonstrated during cerebral angiography remains speculative.[118]

Kincaid and coworkers used a cell saver to process the cardiotomy blood in dogs that underwent hypothermic CPB.[119] The brain tissue from two groups of dogs (group I, cardiotomy suction blood reinfused through arterial line filter; group II, cardiotomy suction blood collected and processed in a cell saver) was examined for the presence of SCADs. Mean SCAD density in the cell-saver group was less than that in the arterial filter group (11 ± 3 vs 24 ± 5; $P = .02$). The researchers concluded that using a cell saver to scavenge shed blood during CPB decreases cerebral lipid microembolization.[119]

This hypothesis was investigated in two separate randomized, prospective studies in cardiac surgical patients to assess the impact of cell-saver usage on cognitive dysfunction after cardiac surgery.[120,121] A series of 226 patients older than 60 years undergoing CABG surgery were randomly allocated to either processing of shed blood by cell-saver or control groups.[120] Anesthesia and surgical management were standardized. EAS of the proximal thoracic aorta was performed in all patients, and TCD was used to measure cerebral embolic rates. Cognitive dysfunction was present in 6% of patients in the cell-saver group and 15% of patients in the control group 6 weeks after surgery ($P = .038$). However, significantly ($P = .018$) more patients in the cell-saver group required transfusion of fresh frozen plasma (25%) versus the control group (12%). In a remarkably similar study from Rubens and coworkers, patients undergoing coronary and/or aortic valve surgery using CPB were randomized to receive unprocessed blood (control, $n = 134$) or cardiotomy blood that had been processed by centrifugal washing and lipid filtration (treatment, $n = 132$).[121] The treatment group received more intraoperative red blood cell transfusions (0.23 ± 0.69 vs 0.08 ± 0.34 units; $P = .004$), and both red blood cell and non–red blood cell blood product use was greater in the treatment group. Postoperative bleeding was greater in the treatment group. Patients also underwent neuropsychometric testing before surgery and at 5 days and 3 months after surgery. No difference was found in the incidence of postoperative cognitive dysfunction in the two groups. Similarly, there was no difference in the quality of life, nor was there a difference in the number of emboli detected in the two groups. These researchers concluded that processing of cardiotomy blood before reinfusion results in greater blood product use with greater postoperative bleeding in patients undergoing cardiac surgical procedures and that there was no clinical evidence of any neurologic benefit with this approach in terms of postoperative cognitive function. In summary, both of these studies showed an increase in use of allogeneic blood products and perioperative blood loss as a consequence of routine cell-saver usage, with either no or minor improvements in incidence of postoperative cognitive decline. In view of the variable impact on neurocognitive dysfunction demonstrated in these studies and the detrimental impact of perioperative allogeneic transfusion, routine usage of cell saver for processing of cardiotomy suction blood for removal of SCADs is unwarranted because of increased risk of bleeding and transfusion.[122]

An alternate approach to emboli elimination employs a modified aortic cannula incorporating a separate suction lumen for which a recent study randomized 66 patients undergoing elective AVR surgery with or without CABG surgery to the use of the emboli protection cannula or a standard aortic cannula.[123] The primary end point was the volume of new brain lesions measured by diffusion-weighted MRI performed preoperatively and postoperatively. The volume of new brain lesion assessed by diffusion-weighted MRI for the modified cannula group was 44.00 ± 64.00 versus 126.56 ± 28.74 mm^3 in the control group, and 41% of the modified cannula group demonstrated new postoperative lesions versus 66% in the control group. The incidence of clinical complications was similar in both.[123] Whether these results will be confirmed in larger trials, and, if confirmed, what the longer term impact of such a decrease in subclinical cerebral emboli and diffusion-weighted MRI–detected lesions will be on later cognitive performance and quality of life remain to be seen. However, it is a promising development and further evidence that emboli reduction is feasible and can decrease the magnitude and incidence of postoperative brain lesions.

Neurocognitive Dysfunction Unrelated to Cerebral Microgaseous Emboli

Just as calcific or atheromatous macroembolic debris from the ascending aorta or aortic arch is a prime factor in the production of clinical stroke syndromes, microembolic elements, either gaseous or

particulate, were thought to produce cognitive dysfunction. However, studies from beating-heart surgery in which CPB is avoided, appear to have a relatively similar incidence of cognitive dysfunction to CABG using conventional CPB, despite a much lower incidence of embolic events.[74,96,124] This suggests that there may be different factors operative in the production of gross neurologic damage than in the genesis of cognitive dysfunction.

A series of longitudinal studies by Selnes and others in patients undergoing off-pump cardiac surgery, as well as those treated medically, have suggested that long-term changes in cognitive function are not specific to CABG or use of CPB and may rather reflect progression of underlying disease.[54,58,125,126] Other longitudinal studies have, however, demonstrated a greater incidence of cognitive dysfunction in CABG patients in comparison with various nonsurgical control groups, though the comparability of underlying disease processes between groups remains a significant confounder in many such studies.[55,127]

However, as there is general agreement that the incidence of early postoperative cognitive dysfunction is greater in CABG patients compared with other, noncardiac surgical groups, and because correlations have been made between such early postoperative cognitive dysfunction and new ischemic lesions on MRI studies in valve surgery patients,[52] and between cerebral oxygen desaturation and early postoperative cognitive dysfunction in CABG patients,[53] it does appear as though early postoperative cognitive dysfunction is, in part, reflective of subclinical brain injury; as such, efforts to mitigate against early postoperative cognitive dysfunction are warranted.

Cerebrovascular Disease

Relatively few studies have examined the cerebrovascular responses to CPB in patients with known cerebrovascular disease. Because of the vasodilatory effects of increased carbon dioxide in patients with cerebrovascular disease, pH-stat management could theoretically induce redistribution of regional cerebral blood flow (CBF) from marginally perfused to well-perfused regions (ie, an intracerebral steal). Gravlee and associates investigated patients with cerebrovascular disease undergoing CABG and assessed the CBF responses to varying pH management, between alpha-stat and pH-stat.[128] They confirmed the responsiveness of the cerebral vasculature to changes in arterial partial pressure of carbon dioxide ($PaCO_2$) during hypothermic CPB but did not demonstrate evidence of intracerebral steal at greater $PaCO_2$ levels in any of these patients. In all patients, however, arterial perfusion pressure was greater than 65 mm Hg during CBF measurements, which may have offset any tendency for regional CBF inhomogeneities.

Using TCD monitoring of CBF velocity, 18 patients with severe carotid stenosis and 37 with no or mild stenosis were monitored during CPB.[129] Although not specified, it appears as though pH-stat management was used, because flow velocities correlated with $PaCO_2$ and arterial pressure. There were no significant differences detectable in flow velocity between patients with or without significant carotid stenosis. In a case report of a single patient with bilateral carotid stenoses, alpha-stat pH management was used and arterial pressure was varied from 35 to 85 mm Hg, whereas CBF was measured during hypothermic CPB.[130] The CBF values obtained from contralateral hemispheres were essentially equal and remained so throughout the range of different perfusion pressures used. These studies suggest that the cerebrovascular responses to CPB in patients with cerebrovascular disease do not differ significantly from those of normal patients with respect to gross measures of cerebrovascular responsiveness. Other factors, including associated aortic atherosclerosis, may be more important.

Hogue and investigators examined demographic and perioperative data prospectively collected from 2972 patients undergoing cardiac surgery.[131] Carotid artery ultrasound examination was performed before surgery for patients aged 65 years or older and in patients with a history of TIAs or prior stroke. Epiaortic ultrasound was performed at the time of surgery in all patients to assess for atherosclerosis of the ascending aorta. Strokes occurred after surgery in 30 women and 18 men ($P < .0001$). A history of stroke was the strongest predictor of new stroke for both women and men. A previous cerebrovascular event was a more important predictor of stroke for men than women.[131]

A small study of 32 patients undergoing cardiac surgical procedures with asymptomatic preoperative silent infarctions detected by diffusion-weighted MRI was unable to demonstrate any increase in risk of adverse postoperative CNS complications, although the sample size limits the generalizability of these results.[132] In a larger study of 514 consecutive patients who underwent cardiac surgery with CPB ($n = 484$) or OPCAB ($n = 30$), preoperative studies diagnosed 17% of patients as having obstructive cerebrovascular disease ($n = 88$), detected by carotid ultrasonography and/or magnetic resonance angiography. Of these 88 patients, impaired cerebral perfusion reserve was identified in 1 (1.1%) through the use of brain perfusion single-photon emission computed tomography (SPECT) and reactivity to acetazolamide.[133] Of this group no patients experienced perioperative hemodynamic ischemic stroke, suggesting it is unusual for obstructive cerebrovascular disease to affect the incidence of hemodynamic ischemic stroke during cardiac surgery.

Cerebral Perfusion Pressure

Despite the previously described findings, intraoperative hypotension during cardiac surgery has been related to postoperative neurologic dysfunction.[13,22,78] Ridderstolpe and colleagues published a retrospective study of 3282 patients of mean age of 65.6 years who underwent cardiac surgery in the period from July 1996 through June 2000.[22] Cerebral complications occurred in 107 patients (3.3%). Of these, 60 (1.8%) were early, 33 (1.0%) were delayed, and in 14 (0.4%) patients the onset was unknown. Predictors of early cerebral complications were older age, preoperative hypertension, aortic aneurysm surgery, prolonged CPB time, hypotension at CPB completion and soon after CPB, and postoperative arrhythmia and supraventricular tachyarrhythmia. Predictors of delayed cerebral complications were female sex, diabetes, previous cerebrovascular disease, combined valve surgery and CABG, postoperative supraventricular tachyarrhythmia, and prolonged ventilator support. Early cerebral complications seemed to be more serious, with more permanent deficits and a greater overall mortality rate (35.0% vs 18.2%). The results of this study suggest that aggressive antiarrhythmic treatment and blood pressure control may improve the cerebral outcome after cardiac surgery.[22]

EEG patterns consistent with ischemia—increased slow wave activity, diffuse slowing of EEG activity—have been reported to occur during CPB episodes thought to be associated with cerebral hypoperfusion.[134–136] Episodes of flow reduction during normothermia frequently produced ischemic changes, whereas similar decreases during stable hypothermia were not associated with EEG changes.[134] Indeed, ischemic EEG changes are frequently seen in association with reductions in perfusion flow rate during the initiation of CPB (see Chapters 18, 31, and 32).[134–136] Using computerized electroencephalography to quantitate episodes of low-frequency power as an index of cerebrocortical ischemia in 96 patients undergoing CABG, a correlation was made among episodes of hypotension, focal increases in low-frequency EEG power, and the occurrence of postoperative disorientation.[137]

During the transition to CPB, the brain is particularly vulnerable to ischemia, inasmuch as cerebral metabolic rate for oxygen ($CMRO_2$) is apparently unchanged, yet the brain is initially perfused with an asanguineous prime, and even after equilibration during established CPB, hematocrit is generally maintained at a range between 20% and 30%. As a result, any further decreases in cerebral perfusion, in the absence of concomitant decreases in $CMRO_2$, are poorly tolerated. During hypothermic conditions, there is a profound decrease in $CMRO_2$, exceeding 50% for a 10°C reduction in temperature.[138] Without need to postulate an extension of the lower limit of cerebral autoregulation, it is clear that under anesthesia, and particularly during hypothermic CPB, CBF is maintained at very low levels of cerebral

perfusion pressure. As discussed later, this was initially reported by Govier and coworkers and further explored by Murkin and colleagues and Prough and colleagues.[138–140]

Using radioisotope techniques for measurement of CBF, and incorporating a jugular venous catheter for calculation of $CMRO_2$, it was determined that there is a profound reduction in $CMRO_2$ during hypothermic CPB and that CBF is decreased proportionately and will autoregulate down to a cerebral perfusion pressure of 20 mm Hg, in the presence of alpha-stat pH management.[138] Low arterial pressure during the hypothermic phase of CPB is thus unlikely to result in cerebral ischemia in the absence of cerebrovascular disease. In a study of high versus low arterial pressure management during CPB in 248 patients undergoing CABG, however, an apparently lower rate of postoperative complications was reported by Gold and colleagues for those patients in the high-pressure group.[141] Although specific CNS morbidity, cognitive and functional status outcomes, and mortality rate did not differ significantly between groups, the overall complication rate for combined cardiac and neurologic complications was significantly lower in the high-pressure group, advocating for a less liberal blood pressure management during CPB. Moreover, as the average age and extent of disease in patients presenting for CABG continue to increase, the number of patients with concomitant cerebrovascular disease, and thus potentially deranged cerebral autoregulation, presents an increasingly important group. This is not inconsistent with data demonstrating a high incidence of cerebrovascular disease in coronary revascularization patients.[56,59]

Using NIRS to detect cerebral autoregulation in 450 patients undergoing CABG and/or valve surgery, the area under the curve of the product of the duration and magnitude of blood pressure below the limits of cerebral autoregulation was compared between patients with and without major postoperative morbidity or mortality (eg, stroke, renal failure, mechanical lung ventilation >48 hours, inotrope use >24 hours, or intraaortic balloon pump insertion). Eighty-three out of 450 experienced major morbidity or operative mortality, and the study demonstrated that the area under the curve below the limits of cerebral autoregulation was independently associated with major morbidity or operative mortality after cardiac surgery.[142] This is directionally similar to what had been previously reported by Murkin and coworkers in a prospective study of NIRS that demonstrated a similar association between cerebral desaturation and major morbidity or operative mortality.[143]

Cerebral Venous Obstruction

It should also be appreciated that during CPB, cerebral venous hypertension can result from partial obstruction of the superior vena cava (Fig. 40.5), particularly in the presence of a single two-stage venous cannula, and may cause cerebral edema and produce a disproportionate decline in cerebral perfusion pressure relative to arterial pressure.[144] In a study by Avraamides, surgical dislocation of the heart during CPB produced increases in proximal superior vena cava pressure and resulted in significant decreases in CBF velocity as measured with TCD,

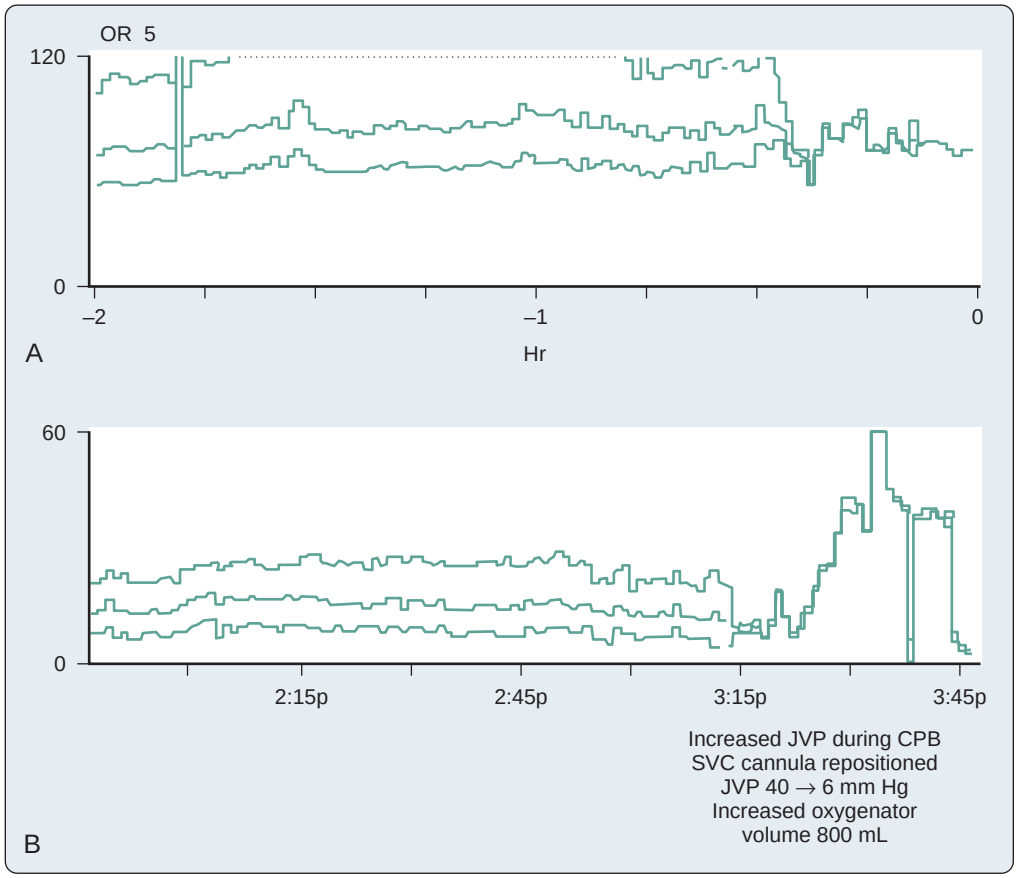


Fig. 40.5 (A) Systolic, mean, and diastolic arterial blood pressures, with commencement of cardiopulmonary bypass *(CPB)* indicated at 3:15 pm, after which mean arterial pressure (MAP) is shown. (B) Pulmonary artery systolic, mean, and diastolic pressures with proximal jugular venous pressure *(JVP)* recorded at 3:15 pm, with commencement of CPB. A single two-stage venous cannula was used for CPB. With rotation of the heart, venous return to the oxygenator decreased and JVP approached MAP values. *SVC,* Superior vena cava. *(Modified from Murkin JM. Intraoperative management. In: Estaphanous FG, Barash PG, Reves JG, eds.* Cardiac Anesthesia Principles and Clinical Practice. *Philadelphia: Lippincott; 1994:326.)*

despite stable arterial pressure and pump flow rates.[145] This strongly suggests that cerebral venous hypertension, as can occur during CPB with myocardial dislocation and impaired drainage of superior vena cava, may result in cerebral ischemia if unrecognized and untreated. It is feasible that such unrecognized cerebral venous hypertension has resulted in some of the postoperative neurologic syndromes that have been reported.[146]

In a study of 92 patients undergoing CABG, the effect of changes in jugular venous bulb pressure (JVBP) on plasma blood-brain barrier was detected by retrograde cannulation of jugular bulb to measure concentrations of plasma S-100β protein, matrix metalloproteinase 9, creatine kinase isoenzyme BB (CK-BB), and arteriovenous total and ionized magnesium as biomarkers of blood-brain barrier dysfunction. CPB increased JVBP, and that JVBP elevated above 12 mm Hg increased biomarkers of blood-brain barrier disruption.[147]

Although the association between arterial hypotension during CPB and cerebral dysfunction remains contentious, there is some evidence that certain subsets of patients may be at particular risk. Newman and associates used preoperative and postoperative cognitive testing to assess the effects of MAP and rate of rewarming on cognitive decline in 237 patients.[148] They demonstrated significant interactions between cognitive decline and MAP less than 50 mm Hg on one measure of cognitive performance and between rate of rewarming and age on another. They concluded that although MAP and rewarming were not primary determinants of cognitive decline, hypotension and rapid rewarming contributed significantly to cognitive dysfunction in older patients. Again, because older patients comprise an increasing segment of the population undergoing cardiac surgical procedures, these aspects are becoming increasingly important clinical management issues.

Hemodynamic Instability During Cardiopulmonary Bypass

Hemodynamic complications, either before, during, or after surgery, have been found to increase cerebral injury in cardiac surgical patients. In a study by Bucerius and colleagues, ejection fraction less than 30%, urgent operations, and preoperative cardiogenic shock were related to increased postoperative delirium.[15] Ridderstolpe and investigators found that hypotension and postoperative arrhythmias were related to cerebral complications, whereas Stanley and colleagues reported that POAF was related to increased cognitive decline.[22,149] Ganushchak and coworkers reported in a retrospective analysis of 1395 patients that the frequency of neurologic complications was 3.9% in the group of patients who experienced large fluctuations in hemodynamic parameters while on CPB, whereas in the group of patients with more stable values on CPB, the incidence rate of neurologic complications was 0.3%.[150] These studies indicate an increased susceptibility of the brain in cardiac surgical patients to apparently "benign" hemodynamic alterations that either produce or enhance cerebral injury, probably through hypoperfusion of the brain tissue. This is of particular importance since it has been estimated that more than 50% of CABG patients have coexisting cerebrovascular disease.[86,87]

The interaction of emboli, perfusion pressure, and the particular conditions of the regional cerebral circulation (eg, preexisting cerebral intravascular lesions) determine the final expression of brain damage in the cardiac surgical patient. In a retrospective study, Ganushchak and associates tested the hypothesis that combinations of hemodynamic events from apparently normal CPB procedures are related to the development of postoperative neurologic complications and affect the impact of common clinical risk factors.[150] A multivariate statistical procedure (cluster analysis) was applied to a data set of automatically recorded perfusions from 1395 patients who underwent CABG. The following five parameters emerged for cluster analysis: MAP, dispersion of MAP, dispersion of systemic vascular resistance, dispersion of arterial pulse pressure, and the maximum value of mixed venous saturation. Using these parameters, they found four clusters that were significantly different by CPB performance (first cluster, 389 patients; second cluster, 431 patients; third cluster and fourth cluster, 229 patients each). The researchers found that patients in cluster 4 represented procedures with high alterations of hemodynamic parameters during CPB, as compared to stable procedures in cluster 1. For example, the range of on-pump hemodynamic variables such as MAP, arterial pulse pressure, systemic vascular resistance, and rectal temperature was doubled in cluster 4 compared with cluster 1, indicating more hemodynamic instability. The frequency of postoperative neurologic complications was 0.3% in the first cluster and increased to 3.9% in the fourth cluster. Importantly, the impact of common clinical risk factors for postoperative neurologic complications was affected by the performance of the CPB procedure. For example, the frequency of neurologic complications among patients with cerebrovascular disease in their medical history was 22% in the fourth cluster, whereas it was zero in the second cluster. Patients with cerebrovascular disease who undergo CPB procedures with large fluctuations in hemodynamic parameters are at particularly increased risk for the development of postoperative neurologic complications.[150]

Aortic Atherosclerosis

Atheroembolism from an atheromatous ascending aorta and aortic arch is recognized as a major risk factor in the patient undergoing cardiac surgical procedures and is a widespread problem.[88,151–156] In a study of 298 asymptomatic members from the Framingham cohort aged 60 ± 9 years and of whom 51% were women, subjects underwent thoracoabdominal aortic cardiovascular MRI, which demonstrated aortic plaque of 1-mm radial thickness was present in 38% of the women and 41% of the men.[151] The Stroke Prevention: Assessment of Risk in the Community (SPARC) study used TEE in 581 people older than 44 years.[152] Atheroma was identified in 51.3% of patients, of whom 7.6% had severe atheroma (>4 mm thick, ulcerated or mobile). The prevalence rate of aortic arch atheroma increased with age, such that severe atheroma was seen in more than 20% of patients older than 74 years—a primary factor in the age-associated increase in risk of perioperative stroke.[88]

Atheroembolism in cardiac surgery has a broad spectrum of clinical presentations, including devastating injuries and death, yet its true incidence is probably underestimated.[77,94,157,158] Thoracic aorta atheromatosis is associated with coronary artery disease and stroke in the general population.[88,153–156] A review by Macleod and investigators concluded that the risk for stroke is four times greater in patients with severe arch atheroma.[154] Yahia and colleagues prospectively studied patients with diagnoses of TIA or stroke using TEE to assess aortic atheromatosis.[156] Thoracic aortic atheromas were present in 141 of 237 patients (59%); mild plaque (<2 mm) was present in 5%, moderate plaque (2–4 mm) in 21%, severe plaque (≥4 mm) in 33%, and complex plaque in 27%. Plaques were more frequently present in the descending aorta and the arch of the aorta than in the ascending aorta.[156] Watanabe and coworkers investigated whether thoracic aorta calcification on computed tomography and coronary risk factors had any correlation with obstructive coronary artery disease on angiography.[155] Two hundred twenty-five consecutive patients underwent both thoracic conventional helical computed tomography and coronary angiography. Thoracic aorta calcification was detected in 185 patients; 141 of 225 patients had significant obstructive coronary artery disease. All of the 13 patients without thoracic aorta calcification and no coronary risk factors had no coronary artery disease. In a recent small (N = 124) single-center study, the severity of TEE-diagnosed aortic atherosclerosis increased significantly between 2002 and 2009.[159] Significant atherosclerosis of the ascending aorta is present in 20% to 40% of cardiac surgical patients, the percentage increases with age (Fig. 40.6), and it is an independent risk factor for stroke (type I cerebral injury).[131,160–168]

Diabetes Mellitus and Hyperglycemia

The presence of diabetes is recognized as a factor related to increased morbidity and mortality in cardiac surgical patients.[169–173] The incidence

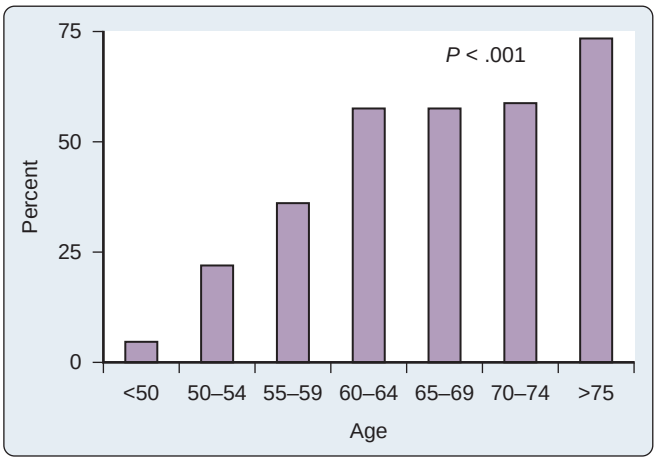


Fig. 40.6 Prevalence of severe atherosclerosis of the ascending aorta at autopsy after operations for coronary and valvular heart disease, 1982–1989. *(From Blauth CI, Cosgrove DM, Webb BW, et al. Atheroembolism from the ascending aorta. An emerging problem in cardiac surgery.* J Thorac Cardiovasc Surg. *1993;103:1104–1111.)*

of diabetes mellitus increases with age, and its presence is known to accelerate the damage caused by atherosclerosis; thus, an increasingly greater percentage of patients coming for CABG have concomitant diabetes, currently estimated as a comorbidity in approximately 30% to 40% of CABG patients. Bucerius and associates found diabetes to be associated with increased incidence of stroke and delirium and prolonged ICU and hospital stays.[174] Mortasawi and investigators[175] and Nussmeier[21] describe diabetes mellitus as associated with increased incidences of stroke and mortality. In a large study, McKhann and colleagues prospectively collected data on 2711 CABG patients and identified diabetes mellitus as an independent risk factor for both stroke and encephalopathy.[17] Part of the risk may involve cerebral hypoperfusion because increased extent and duration of cerebral oxygen desaturation during CPB has been documented in diabetic patients, with patients with insulin-dependent diabetes demonstrating the lowest values (as measured via jugular oximetry) and the poorest response to increases in MAP.[176]

Studies identify normoglycemia as a desirable perioperative goal in cardiac surgical patients regardless of whether they are diabetic.[170,172] Experimental and clinical evidence shows that hyperglycemia is associated with exacerbation of neurologic injury.[177] Approaches to maintain serum glucose values less than 150 mg/dL have shown favorable results. Furnary and coworkers reported on 3554 patients who underwent CABG from 1987 through 2001, demonstrating that the observed mortality in the group managed with tighter glucose values was lower and concluded that continuous intravenous insulin infusion added a protective effect against death.[171] Carvalho and associates used an aggressive approach to maintain serum glucose values between 80 and 110 mg/dL and reported that this is a safely attainable goal.[169] One study positively correlated average blood glucose on the first postoperative day with a variety of adverse outcomes (stroke, myocardial infarction, septic complication, or death). For each 1-mmol/L increase greater than 6.1 mmol/L (1 mmol = 18 mg/dL), risk increased by 17%.[178] The ideal value of serum glucose in cardiac surgical patients remains unknown, but the evidence available suggests that maintenance of euglycemia is related to a better prognosis.

In accordance with these data, STS guidelines for glucose control in patients undergoing cardiac surgery recommend that in both diabetic and nondiabetic patients, blood glucose levels should be maintained at less than or equal to 180 mg/dL with intravenous insulin as required.[179] However, there are concerns regarding potential adverse effects associated with hypoglycemia, including increased risk for mortality associated with even a single episode of severe hypoglycemia as seen in medical/surgical intensive care patients.[180] Furthermore, in a randomized, prospective study of 400 cardiac surgical patients managed either with tight glucose control (intravenous insulin to maintain intraoperative glucose between 80 and 100 mg/dL) or conventional management (glucose level < 200 mg/dL), a significantly greater incidence of stroke was found in the treatment group.[181] Hence, avoidance of hypoglycemia should be paramount. Accordingly, an important caveat recommending preservation of lower limit of glucose level greater than 100 mg/dL should be appended to the guidelines.[182] Overall, it would appear that maintenance of perioperative serum glucose between 100 and 180 mg/dL in both diabetic and nondiabetic patients is desirable.

Cerebral Blood Flow

In the mid-1960s, Wollman and investigators used changes in the arterial and jugular venous oxygen content differences ($A\text{-}Vd_{O_2}$) to estimate changes in CBF during alterations of MAP and arterial carbon dioxide tensions (Pa_{CO_2}) in patients undergoing CPB.[183] They observed a direct correlation between Pa_{CO_2} and $A\text{-}Vd_{O_2}$ (CBF), but no relation between $A\text{-}Vd_{O_2}$ and MAP. Although the concepts of alpha-stat and pH-stat pH management had not been formulated at that time, these authors recommended maintaining temperature-corrected Pa_{CO_2} between 30 and 40 mm Hg during hypothermic CPB (see Chapter 31).

In 1968, a Japanese investigator, using the recently developed technique of radioisotope clearance, measured CBF and CMR_{O_2} during CPB.[184] In a series of 40 patients, krypton-85 clearance, with concomitant cannulation of the superior jugular bulb, was used to measure CBF and calculate CMR_{O_2} during CPB. The influence of nonpulsatile CPB on the cerebral vasculature was also directly observed using retinal photomicrography. Although critical data such as esophageal temperatures and hematocrits were not reported, the observed 35% decrease in CBF with institution of CPB, 63% decrease in CMR_{O_2} during hypothermia, 23% decrease in CMR_{O_2} during rewarming, and retinal venous engorgement during rewarming are consistent with subsequent research findings. This report apparently also marked the first observations in humans of retinal microembolism occurring during CPB, consistent with but markedly preceding the reports of Blauth and colleagues.[75]

Few subsequent radioisotope CBF studies during CPB in humans were reported for the next 15 years. Other investigators used indirect estimates of CBF (eg, $A\text{-}Vd_{O_2}$, TCD CBF velocities, or thermodilution techniques) to estimate CBF.[185]

pH Management and Cerebral Blood Flow

Relatively little new information regarding the cerebral circulation in human beings during CPB appeared until 1983, when Henriksen and colleagues reported evidence of cerebral hyperemia occurring during CPB.[186] This report was followed in 1984 by a seminal paper from Govier and coworkers, who not only incited controversy with their observations of ischemic threshold levels of CBF during CPB, in direct contrast with the hyperperfusion reported by Henriksen, but also made preliminary observations on many of the other critical variables thought to influence CBF during CPB.[140]

Without the measurement of concomitant cerebral metabolism, these apparently discordant observations of CBF could not be reconciled. Murkin and coworkers subsequently reported their observations of both CBF and CMR_{O_2} during hypothermic CPB in humans, using a xenon-133 clearance technique for measurement of CBF, similar to techniques used by Kubota, Govier and coworkers, and Henriksen and colleagues, but with the addition of a jugular bulb catheter for sampling effluent cerebral venous blood for measurement of cerebral metabolic activity.[138] It was hypothesized that differences in pH management accounted for the divergent values previously reported for CBF during hypothermic CPB. Accordingly, patients were managed with either alpha-stat or pH-stat pH management during hypothermic CPB. A similar and pronounced reduction in CMR_{O_2} was observed in both groups during hypothermia (Fig. 40.7), and in the alpha-stat group,

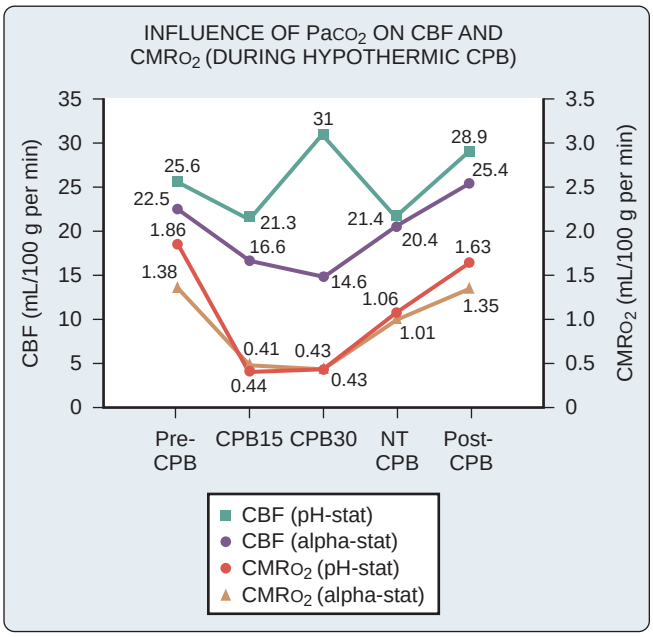


Fig. 40.7 Cerebral blood flow *(CBF)* and cerebral metabolic rate for oxygen *($CMRO_2$)* in the alpha-stat (non–temperature-corrected) and pH-stat (temperature-corrected) groups. Note the convergence of $CMRO_2$ and divergence of CBF between groups during the hypothermic phase of cardiopulmonary bypass *(CPB). (From Murkin JM. Cerebral hyperperfusion during cardiopulmonary bypass: the influence of $PaCO_2$. In: Hilberman M, ed.* Brain Injury and Protection During Heart Surgery. *Boston: Martinus Nijhoff; 1988:57.)*

global cerebral flow/metabolism coupling was preserved in comparison with the group managed with pH-stat (Fig. 40.8). Decreases in CBF and $CMRO_2$, significantly lower than similar measures before and after CPB, were still evident after rewarming during normothermic nonpulsatile CPB. These low values for CBF and $CMRO_2$ were restored to control levels shortly after separation from CPB. Alpha-stat management preserved autoregulation and the relation between CBF and metabolism and has become the standard of care for adult patients undergoing CPB with mild and moderate hypothermia.[138]

Cerebral Hyperthermia

Cerebral hyperthermia during the rewarming phase of CPB can exacerbate a preexisting injury before rewarming and may be detrimental itself. Hyperthermia can have a strong impact on cerebral oxygen transfer and neurologic outcome. Glutamate levels can increase during cerebral hyperthermia, leading to eventual cell death. Rapid rewarming decreases jugular venous hemoglobin saturation, creating a mismatch between cerebral oxygen consumption and delivery.[187,188] Okano and associates assessed the effects of normothermia and mild hypothermia (32°C) during CPB on jugular venous oxygen saturation ($SjvO_2$) in 20 patients scheduled for elective CABG.[189] The $SjvO_2$ in the normothermic group was decreased significantly at 20 and 40 minutes after the onset of CPB compared with pre-CPB, whereas there was no change in $SjvO_2$ in the mild hypothermic group during the study. The investigators concluded that cerebral oxygenation, as assessed by $SjvO_2$, was increased during mild hypothermic CPB compared with normothermic CPB. Kawahara and colleagues examined the effect of rewarming rates on $SjvO_2$ in 100 patients scheduled for elective CABG and randomly divided into two groups: a control group and a slow rewarming group.[187] Cerebral desaturation (defined as an $SjvO_2$ value < 50%) during rewarming was more frequent in the control group than in the slow group. The ratio of the cerebral desaturation time to the total CPB time in the control group differed significantly from those in the slow group (control group: 17 ± 11 minutes, 12% ± 4%; slow group: 10 ± 8 minutes, 7% ± 4%, respectively; $P < .05$).[187] Consistent with this, in a study of the impact of rate of rewarming on cognitive outcomes in 165 CABG patients randomized to two differing rewarming strategies, Grigore and colleagues demonstrated a significant association between change in cognitive function and rate of rewarming.[66]

Grocott and colleagues recorded hourly postoperative temperatures in 300 patients undergoing CABG on CPB and determined the degree of postoperative hyperthermia using peak temperature within 24 hours, as well as area under the curve for temperatures higher than 37°C.[190] Patients underwent a battery of cognitive testing both before surgery and 6 weeks after surgery. The maximum temperature within 24 hours after CABG ranged from 37.2°C to 39.3°C. Findings showed that the maximum postoperative temperature was independently associated with cognitive dysfunction at 6 weeks.[190] Accordingly, slower rewarming rate with lower peak temperatures during CPB may be an important factor in the prevention of neurocognitive decline after hypothermic CPB, and interventions to avoid postoperative hyperthermia may be warranted to improve cerebral outcome after cardiac surgery.

Cardiopulmonary Bypass Equipment

Early studies demonstrated increased microemboli in patients undergoing CPB using bubble oxygenators, with a reduction in cerebral embolization with the use of membrane oxygenators and arterial line filtration (Box 40.4).[75,76,191–193] Using intraoperative fluorescein retinal angiography, Blauth and coworkers reported retinal microembolizations occurring during CPB with much greater frequency in patients in whom bubble versus membrane oxygenators were used.[76] Using TCD for detection of cerebral emboli, Padayachee and associates demonstrated continuous generation of cerebral emboli in all patients managed using bubble oxygenators and none in patients in whom a membrane oxygenator was used.[192] They also demonstrated the efficacy of arterial line filtration to significantly decrease cerebral embolic load.[193] It is apparent that emboli may be generated continuously during CPB and that equipment modification (eg, arterial line microfiltration and preferential usage of membrane oxygenators) can decrease the generation of such emboli.[194] Membrane oxygenators are currently recommended for CPB[80] (see Chapters 31 and 32).

It is equally evident that equipment modifications, although decreasing the embolic load, cannot completely eliminate it.[192,195] Georgiadis and investigators used Doppler ultrasound and evaluated the percentage of microembolic signal (MES) reduction caused by the arterial filter and the proportion of MESs actually reaching the brain by comparing the MES counts detected before the arterial filter, after the arterial filter, and in both middle cerebral arteries.[196] Eleven patients underwent surgery using normothermic CPB, alpha-stat, a membrane oxygenator, and a 40-μm arterial filter. Evaluation of MESs was only performed during extracorporeal circulation, was initiated after cannulation and clamping of the ascending aorta, and was terminated shortly before the aortic clamp was removed. The arterial filter resulted in a 58.9% reduction of MESs, with only 4.4% (2624/59,132) of the MESs detected after the arterial filter. The proportion of MESs detected in the middle cerebral artery corresponded to the total cerebral perfusion under CPB, estimated as 5% to 10% of the total perfusion volume.[196]

Schoenburg and colleagues used a dynamic bubble trap, incorporated in the arterial line after a 40-μm filter, to reduce the number of gaseous microemboli in 50 patients undergoing CABG.[197] In 26 patients, a dynamic bubble trap was placed between the arterial filter and the aortic cannula (group 1), and in 24 patients, a placebo dynamic bubble trap was used (group 2) with TCD continuously measured on both sides during bypass, which was separated into four periods: phase 1, start of bypass until aortic clamping; phase 2, aortic clamping until rewarming; phase 3, rewarming until clamp removal; and phase 4, clamp removal until end of bypass. The bubble elimination rate during bypass was 77% in group 1 and 28% in group 2. The number of TCD-detected high-intensity signals was lower in group 1

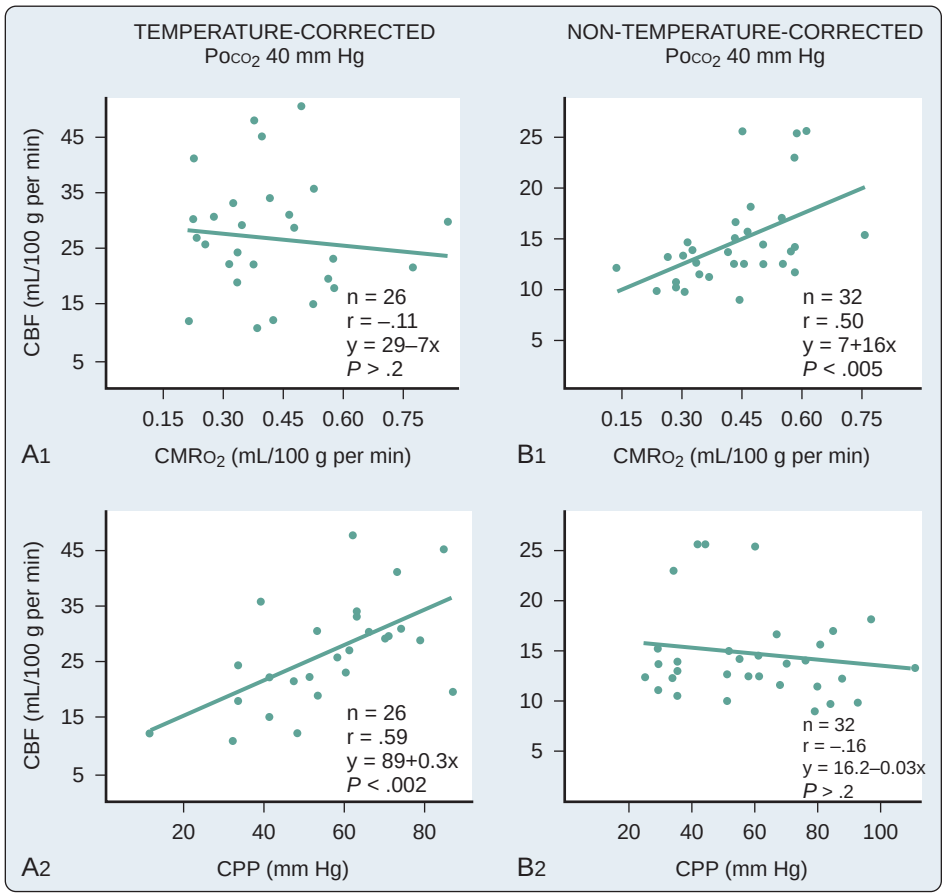
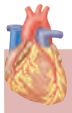


Fig. 40.8 Simple linear regression of cerebral blood flow *(CBF)* versus cerebral perfusion pressure or cerebral oxygen consumption for temperature-corrected and non–temperature-corrected groups. There is no significant correlation between CBF and cerebral metabolic rate for oxygen *($CMRO_2$)* in the temperature-corrected group *(A1)*, whereas CBF significantly correlates with $CMRO_2$ in the non–temperature-corrected group *(B1)*. CBF is significantly correlated with cerebral perfusion pressure *(CPP)* in the temperature-corrected group *(A2)*, whereas CBF is independent of CPP in the non–temperature-corrected group *(B2)*. *(From Murkin JM, Farrar JK, Tweed A, et al. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $PaCO_2$. Anesth Analg. 1987;66:825–832.)*



BOX 40.4 CLINICAL STRATEGIES THAT MAY DECREASE NEUROLOGIC COMPLICATIONS IN CARDIAC SURGERY

- Early and aggressive control of hemodynamic instability
- Perioperative euglycemia between 100 and 180 mg/dL
- Routine epiaortic scanning before manipulation of ascending aorta
- Avoidance of manipulation of ascending aorta in severe atheromatosis
- Maintenance of adequate cerebral perfusion pressure (neuromonitoring/cerebral oximetry)
- Monitoring of cerebral venous pressure via a proximal central venous pressure catheter or the introducer port of a pulmonary artery catheter
- Alpha-stat pH management during moderate hypothermic cardiopulmonary bypass (CPB)
- Avoidance of arterial inflow temperature greater than 37°C
- Use of CPB circuitry incorporating membrane oxygenator and 40-μm arterial line filter
- Use of surface-modified and reduced-area CPB circuitry
- Use of cerebral oximetry

during phase 1 (5.8 ± 7.3 vs 16 ± 15.4; $P < .05$ vs group 2) and phase 2 (6.9 ± 7.3 vs 24.2 ± 27.3; $P < .05$ vs group 2) but not during phases 3 and 4. The researchers determined that the dynamic bubble trap can remove gaseous microemboli.[197] Unfortunately, no psychometric studies were performed on either group of patients, but future research in this area might yield positive influence on neurologic outcome by decreasing gas microemboli. Other investigators have demonstrated that air within the venous line of the CPB circuit, resulting from air entrainment at the venous cannulation site, injection of drugs into the venous line, or use of cardiotomy suction can pass through the oxygenator and appear as microemboli within the arterial line, even in the presence of a venous line defoamer and with use of a membrane oxygenator. Georgiadis and coworkers used tubing systems that included an arterial line 40-μm filter.[196] They demonstrated that the arterial filter resulted in a 58.9% reduction of microemboli signals with only 4.4% of the MESs detected after the arterial filter was detected in the middle cerebral artery.

Modification of the inflammatory response to the CPB using modified surface CPB circuits and leukocyte-depleting filters has also been explored. Hamada and associates examined the combined use of heparin coating of the CPB circuit and a leukocyte-depleting arterial line filter.[198] Thirty patients were randomly allocated to equal groups with a conventional circuit and arterial line filter, a heparin-coated

circuit with a conventional filter, or a heparin-coated circuit with a leukocyte-depleting arterial line filter. Plasma IL-6 and IL-8 concentrations in the heparin bonded with leukocyte-depleting filter group were lower than in the conventional circuit group. Although a decrease in inflammatory mediator release has been observed by using leukocyte-depleting filters, the impact of these types of filters on neurologic outcome is less clear. In a meta-analysis of 28 relevant clinical studies, Whitaker and investigators concluded that conventional arterial line filtration had a definite effect in reducing post-CPB neuropsychological deficit.[199] The results of studies using the leucocyte-depleting filter were less clear-cut.

In an attempt to decrease emboli originating from the surgical field, cell savers have been used for processing cardiotomy suction blood before returning it to the CPB circuit. Jewell and colleagues reported on 20 patients prospectively randomized to either cell saver or cardiotomy suction.[200] They found that compared with cardiotomy suction, cell saver removed significantly more fat from shed blood, such that the percentage reduction in fat weight achieved by cell saver or cardiotomy suction was 87% compared with 45%. De Vries and coworkers published a study on patients randomly assigned to have a fat removal filter for the cardiotomy suction.[201] The fat filter removed 40% more fat, leukocytes, and platelets from cardiotomy suction blood during cardiac surgery compared with the control group without the filter.

In addition, various intraoperative manipulations, particularly instrumentation of the atherosclerotic aorta, are independent risks for the generation of cerebral emboli and likely produce particulate and microparticulate emboli, rather than oxygenator-generated microgaseous and microaggregate emboli.[94,160,202,203] Avoidance of manipulation of a diseased aorta seems to decrease embolization and cerebral injury.[71,204,205] An alternative approach, emboli reduction by capture using an intraaortic filter inserted through a side chamber of a modified aortic cannula, has also been assessed (Fig. 40.9).[109]

In a nonrandomized study, Schmitz and associates examined the impact of intraaortic filtration during CPB.[206] Patients undergoing cardiac surgical procedures ($n = 304$) had intraaortic filtration using a 150-μm net deployed through the aortic cannula, whereas a further 278 patients formed the control group. Patients in the filter group experienced a lower incidence of adverse neurologic outcomes than patients in the control group (4.3% vs 11.9%), with significantly fewer TIAs (0% vs 1.4%), less delirium (3.0% vs 6.5%), and less memory deficit (1.3% vs 6.2%). There were also fewer strokes in the filter group compared with the control group (0.7% vs 2.2%). Although the sample size was relatively small and the patients were not randomly assigned, the study findings suggest a protective effect of intraaortic filters on CNS injury.[206] In a large, multiinstitutional, prospective, randomized trial of 1289 patients in whom intraaortic filtration or conventional CPB cannula was used, emboli were identified in 598 (96.8%) of 618 filters successfully deployed, and their post hoc analysis indicated a reduction in postoperative renal complications.[207] In other studies, intraaortic emboli trapping devices have been used with varied results.[196,204] In a small study by Eifert and investigators in 24 patients, the use of the intraaortic filter device did not show any difference in neurologic, neuroradiographic, or neuropsychological outcomes, yet the intraaortic filter was effective in capturing particulate material.[195] Similar efficacy in capturing intraoperative material using intraaortic filters during CPB was reported by Reichenspurner and colleagues.[208] It appears as though intraaortic filters can be safely deployed and that they capture particulate emboli, the predominant origin of which is atheromatous.

In a recent study of 150 CABG patients randomized to either intraaortic filtration, dynamic bubble trap, or conventional management, no difference was found in the overall incidence of postoperative MRI-detected small ischemic brain lesions (17/143) between groups, whereas dynamic bubble trap was associated with significantly fewer TCD-detected cerebral emboli and improved cognitive performance at 3 months after surgery in comparison with control and intraaortic filtration groups.[209]

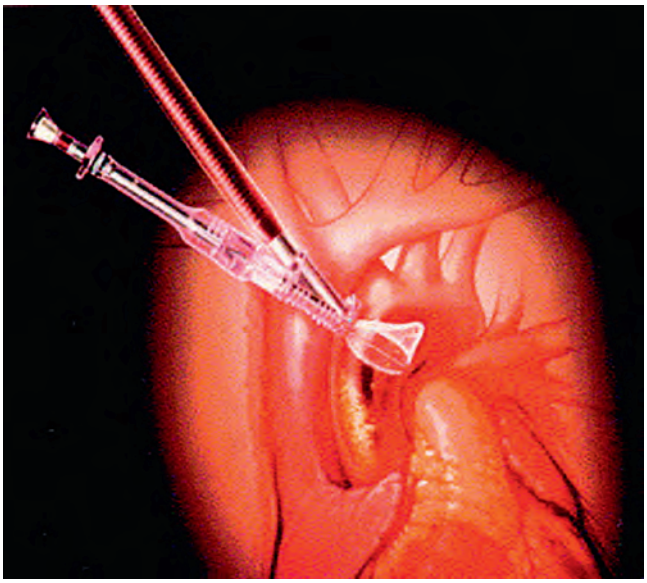


Fig. 40.9 The Embol-X intraaortic filtration system. *(From Banbury MK, Kouchoukos NT, Allen KB, et al. Emboli capture using the Embol-X intraaortic filter in cardiac surgery: a multicentered randomized trial of 1,289 patients.* Ann Thorac Surg. *2003;76:508–515.)*

Minimally Invasive Extracorporeal Circulation

A recent development in the drive for more physiologic CPB has been the advent of minimally invasive extracorporeal circulation (MiECC).[210] This system consists of a modular biocompatible closed circuit of minimal priming volume, incorporating a centrifugal pump and membrane oxygenator, and has been shown to result in significantly decreased inflammatory markers.[211] A metaanalysis of 24 studies involving 2770 patients showed an association with a significant decrease in mortality (0.5% vs 1.7%; $P = .02$), postoperative myocardial infarction (1.0% vs 3.8%; $P = .03$), and neurologic events (2.3% vs 4.0%; $P = .08$).[212] Again, MiECC was also associated with reduced systemic inflammatory response as measured by polymorphonuclear elastase, hemodilution as calculated by hematocrit drop after procedure, need for red blood cell transfusion, reduced levels of peak troponin release, incidence of low cardiac output syndrome, need for inotropic support, peak creatinine level, occurrence of POAF, duration of mechanical ventilation, and ICU stay.[212]

Because the technique of modular MiECC (Fig. 40.10) has been employed for combined CABG and valve surgery,[213] as well as in high-risk patients,[214] and shown to result in less cerebral microembolization and improved cerebral tissue oxygenation,[215] as well as improved neurocognitive outcomes,[216] there is significant potential that such an approach to CPB may well become the standard of care in the near future.[217]

Cerebroprotective Strategies

Risk Assessment

Using a risk-stratification analysis of the same database as Roach and colleagues, Newman and colleagues developed a preoperative index predicting major perioperative neurologic events of which key predictors were age, history of neurologic disease, diabetes, previous CABG, unstable angina, and history of pulmonary disease (Fig. 40.11).[6,218] The Stroke Risk Index allows neurologic risk to be estimated for each patient, thus enabling the most appropriate perioperative therapy to be used, whether surgical modification, change in perfusion management, applied neuromonitoring, or administration of putative pharmacologic cerebroprotectants. It is also useful as a scale to compare risk

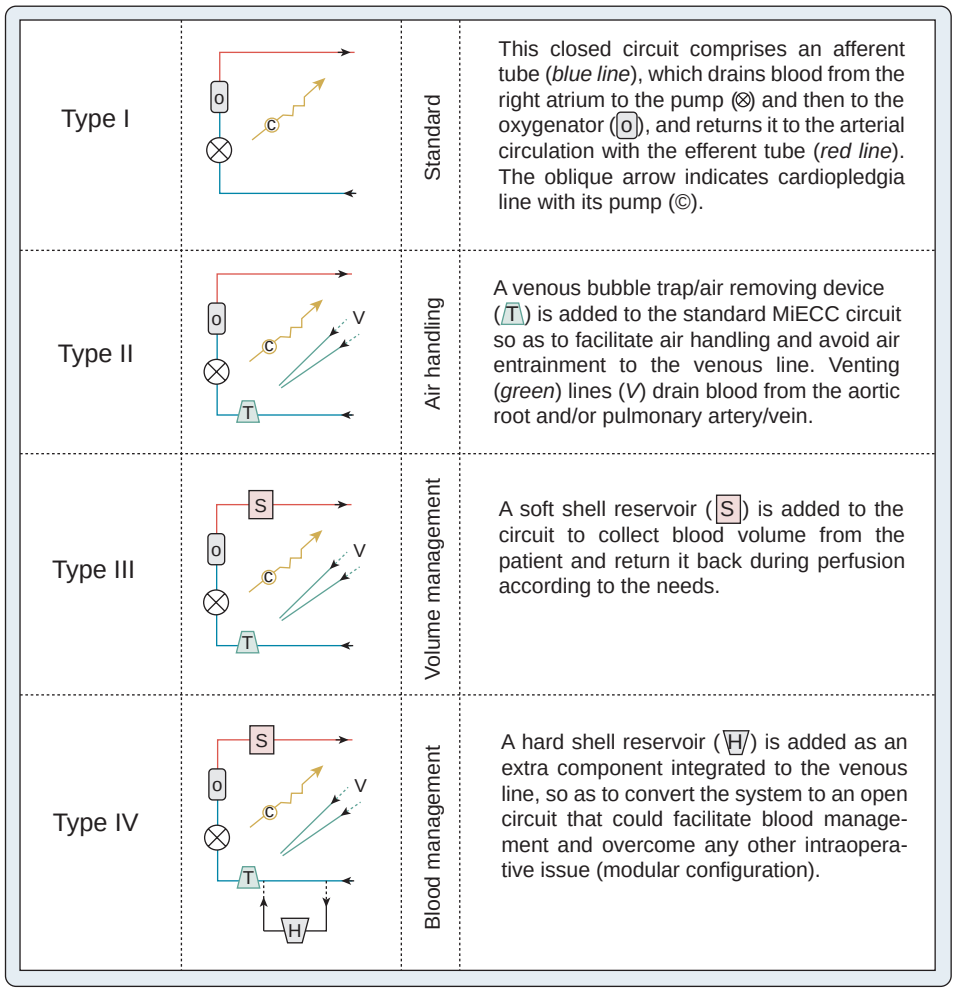


Fig. 40.10 Classification of minimally invasive extracorporeal circulation *(MiECC)* circuits. The modular type IV circuit is literally type III with a standing-by component, used only when necessary. *(From Anastasiadis K, Antonitsis P, Argiriadou H, et al. Modular minimally invasive extracorporeal circulation systems; can they become the standard practice for performing cardiac surgery?* Perfusion *2015;30:195–200.)*

indices and thus the efficacy of different interventions across clinical outcome studies.[12,162]

In a recent analysis of the incidence of the rate and predictors of long-term stroke and death up to 2 years postoperatively in a cohort of 108,711 patients who underwent cardiac surgery, 1.8% had a stroke perioperatively, and 3.6% had a stroke within the ensuing 2 years.[219] The strongest predictors of both early and late stroke were advanced age (65 years or older), combined CABG and valve surgery, a history of stroke or TIA, and peripheral vascular disease–again likely markers of aortic atherosclerosis, and valve surgery alone, whereas preoperative need for dialysis and again, new-onset POAF, were predictors of only early stroke. A CHADS2 (C, congestive heart failure; H, hypertension > 140/90; A, age >75; D, diabetes mellitus; S, prior stroke or TIA) score of 2 or higher was associated with an increased risk of stroke or death compared with a score of 0 or 1 (19.9% v. 9.3%) among patients with a history of atrial fibrillation, 16.8% versus 7.8% among those with new-onset POAF, and 14.8% versus 5.8% among those without this condition. Among other factors, this study again highlights both the acute and long-term stroke risk associated with perioperative atrial fibrillation.[219]

Reporting a negative multicenter study assessing acadesine (adenosine regulating agent) for efficacy in decreasing death, stroke, or need for mechanical cardiovascular support in 3080 patients undergoing CABG, four independent preoperative risk factors were predictive of the composite end point of major morbidity or operative mortality; these risk factors are a history of heart failure, increasing age, peripheral vascular disease, and receiving aspirin before CABG (which was protective).[220] Of note, the duration of CPB was the only intraoperative variable that contributed to adverse outcomes and suggests once again that there are intraoperative factors that contribute to adverse outcomes and may be remediable.

The role of perioperative inflammation and the importance of intraoperative hemodynamic factors was further highlighted in a retrospective study of 1046 patients who underwent OPCAB and in whom postoperative C-reactive protein elevation was shown to be associated with long-term postoperative major adverse cardiac and stroke events (which was mitigated by postoperative statin medication) and in which postoperative C-reactive protein elevation was associated with intraoperative parameters, reflecting hypoperfusion and inflammation.[221] As discussed later, this study suggests that statins may have a salutary effect on stroke incidence as well as further indicating that hemodynamic instability is associated with a heightened inflammatory response and greater stroke risk.

Carotid Endarterectomy

In the current cardiac surgical population, 17% to 22% of patients have a moderate carotid artery stenosis of 50% or more, and 6% to

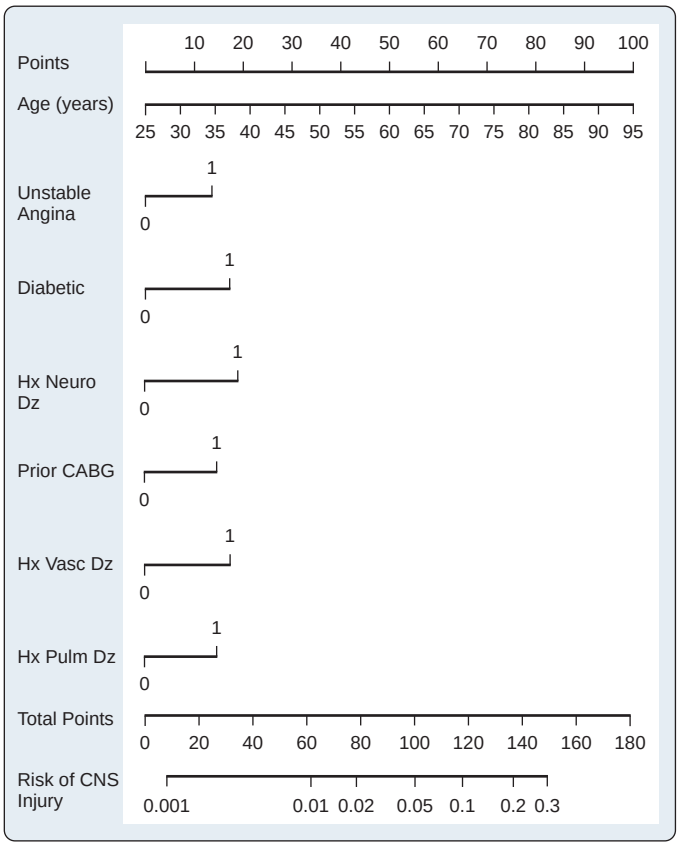


Fig. 40.11 Nomogram for computing risk of central nervous system *(CNS)* injury. Neurologic risk is determined by assigning points for age and positive history of the predictors listed. Total points for each variable are read from the points line at the top of the nomogram. After the total points for an individual patient are computed, the risk for CNS injury can be determined by plotting the total points received against the risk score at the bottom of the nomogram. For example, 100 total points predict a risk for CNS injury of 5%. *CABG,* Coronary artery bypass graft; *Hx Neuro Dz,* history of symptomatic neurologic disease; *Hx Pulm Dz,* history of emphysema, chronic bronchitis, asthma, or restrictive lung disease; *Hx Vasc Dz,* history of atherosclerotic vascular disease or previous vascular surgery. *(From Newman MF, Wolman R, Kanchuger M, et al. Multicenter preoperative stroke risk index for patients undergoing coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia [McSPI] Research Group.* Circulation. *1996;94[Suppl 9]:II74–II80.)*

12% have a severe stenosis of 80% or more.[12] The risk for postoperative stroke is 10% in patients with moderate and 11% to 19% in patients with severe stenosis, whereas it remains 2% or less in patients with a stenosis of less than 50%. Although in patients presenting for cardiac surgery, severe bilateral carotid artery disease is rare, the risk for perioperative stroke is as high as 20%.[12,222–224] However, it is not clear that carotid endarterectomy decreases this rate, because in a meta-analysis, pooled data for stroke or death did not support carotid endarterectomy for risk reduction from asymptomatic carotid stenosis during CABG (relative risk, 0.9; $P = .5$).[225] In a review, it was estimated that only about 40% of perioperative strokes (at most) could be directly attributable to ipsilateral carotid artery disease.[226] Accordingly, in a patient with asymptomatic carotid stenosis, combined surgery should not be undertaken unless the surgical team is very experienced in combined carotid endarterectomy/CABG procedures. Concomitant carotid endarterectomy is unlikely to decrease a patient's stroke risk. Rather, carotid stenosis should be regarded as indicating a high likelihood of aortic and/or concomitant intracerebral disease, and that use of EAS with appropriate modification of surgical approach and applied neuromonitoring can be of particular benefit in this high-risk group.

Transesophageal Echocardiography Versus Epiaortic Scanning

The detection of ascending aorta atheromatosis is a cornerstone of strategies to decrease the incidence of stroke during and after cardiac surgical procedures. Manual palpation of the aorta, despite its widespread utilization, has a very low sensitivity for this purpose.[71,227] The association between severe thoracic aortic plaques (defined as 5-mm-thick focal hyperechogenic zones of the aortic intima and/or lumen irregularities with mobile structures or ulcerations) and coronary artery disease is well established.[166] Identifying severe aortic disease has important clinical implications because surgical technique, including surgical procedure and siting of cannulation and anastomotic sites for proximal grafts, can be altered to avoid producing emboli and stroke. Intraoperative EAS is a helpful tool for the diagnosis of ascending aortic atherosclerosis and has revealed major insights into the nature and distribution of this disease.

Djaiani and coworkers performed TEE and EAS to assess the severity of aortic atherosclerosis in the ascending aorta and the aortic arch.[161] Patients were allocated to either low- or high-risk groups according to aorta intimal thickness. TCD was used to monitor the middle cerebral artery. Diffusion-weighted MRI was performed 3 to 7 days after surgery. The NEECHAM Confusion Scale was used to assess cognitive function and monitor patient consciousness level. In the high-risk group (intimal thickness > 2 mm), confusion was present in six (16%) patients versus five (7%) patients in the low-risk group, and there was a threefold increase in median embolic count (223.5 vs 70.0). Diffusion-weighted MRI–detected brain lesions were present only in patients from the high-risk group (61.5% vs 0%). There was significant correlation between the NEECHAM scores and embolic count in the high-risk group.[167] Multiple studies have documented that most of the significant atherosclerotic lesions in the ascending aorta are missed by intraoperative palpation by the surgeon, and intraoperative echocardiographic studies of the aorta have been recommended (Fig. 40.12).[13,71,161,164,168,195,227–230] However, the ability of TEE to reliably detect ascending aorta and aortic arch lesions is limited.

The high acoustic reflectance attributable to the air-tissue interface resulting from overlying right main bronchus and trachea limits TEE assessment of the upper ascending aorta, where cannulation is generally undertaken.[71,204,227,229] Intraoperative EAS is a helpful tool for the diagnosis of ascending aortic atherosclerosis and has revealed major insights into the nature and distribution of this disease. Konstadt and associates investigated 81 patients (57 male and 24 female, aged 32–88 years; mean age, 64 years) scheduled for elective cardiac surgical procedures.[204,230] A comprehensive examination of the entire thoracic aorta in both the longitudinal and transverse planes was performed with the aid of biplane TEE. In both echocardiographic examinations, the presence and location of protruding plaques and intimal thickening greater than 3 mm were recorded. Fourteen (17%) of the 81 patients had significant atherosclerotic disease of the ascending aorta as diagnosed by EAS echocardiography. The sensitivity of TEE was 100%, the specificity was 60%, the positive predictive value was 34%, and the negative predictive value was 100%. According to the examiners, if the complete biplane TEE examination is negative for plaque, it is highly unlikely that there is significant plaque in the ascending aorta. If the TEE examination is positive for plaque, there is a 34% chance that there is significant disease of the ascending aorta, and EAS should be considered. TEE is a sensitive but only mildly specific method of determining whether ascending aortic atherosclerosis is present.[195,204,228–230]

The standard for aortic assessment before instrumentation continues to be visual inspection and palpation by the surgeon, despite the fact that this has been shown to identify atheromatous disease in only 25% to 50% of patients and, even when identified, to significantly underestimate its severity.[71,84,227,231,232] Identification of ascending aorta atheromatous disease would prompt the surgical team for strategies to modify, decrease, or avoid aortic manipulation. Management strategies for the diseased ascending aorta range from minimally invasive aortic "no-touch" techniques (NTTs) to maximally invasive procedures,

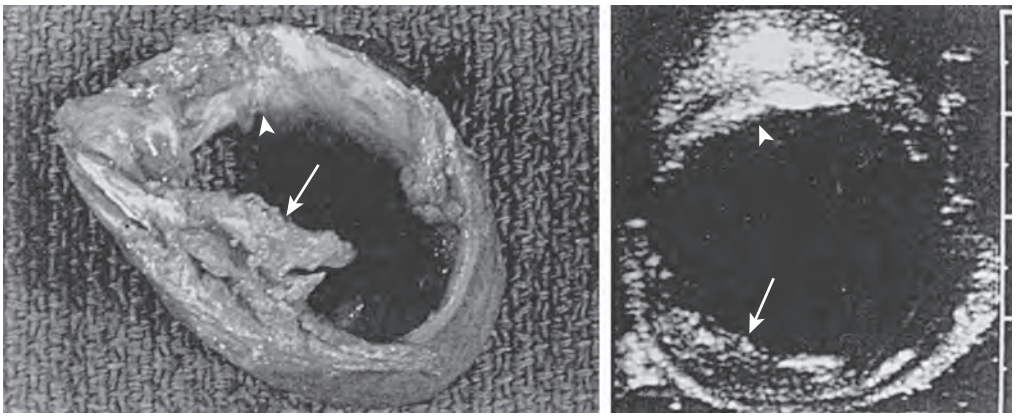


Fig. 40.12 Transverse ultrasonic image of the ascending aorta and the corresponding segment of aorta in a patient with severe atherosclerosis. Note the calcification *(arrowhead)* and the projection of atheroma *(arrow)* into the lumen. *(From Wareing TH, Davila-Roman VG, Barzilai B, et al. Management of the severely atherosclerotic ascending aorta during cardiac operations. A strategy for detection and treatment.* J Thorac Cardiovasc Surg. *1992;103:453–462.)*

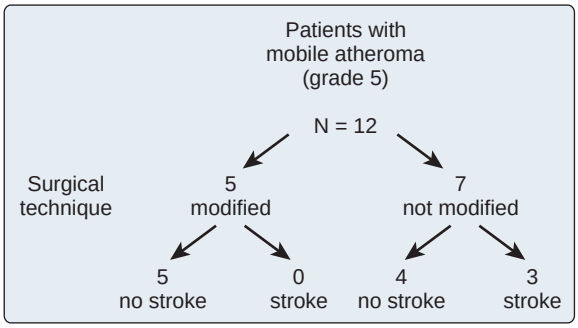


Fig. 40.13 Influence on neurologic outcome of altering operative technique on the basis of the finding of mobile aortic atheromas on transesophageal echocardiography. *(Reprinted from Katz ES, Tunick PA, Rusinek H, et al. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography.* J Am Coll Cardiol. *1992;20:70–77.)*

including ascending aorta replacement or extensive aortic debridement under deep hypothermic circulatory arrest (HCA).[233] Royce and colleagues outlined specific techniques for EAS, as well as steps to be used by the surgical team to mitigate aortic atheroemboli.[234] Operative modifications in CABG include avoidance of aortic cross-clamping, alternative sites of aortic cross-clamping, and avoidance of proximal anastomoses by usage of all arterial conduit or Y-grafts. A decreased incidence of stroke and CNS dysfunction has been associated with this approach (Fig. 40.13).[235]

In a large retrospective cohort of 2292 patients who underwent isolated OPCAB, patients were subdivided into two groups: the non-EAS group (n = 1019), who underwent OPCAB under only intraoperative TEE, and the EAS group (n = 1273), who underwent OPCAB under EAS and demonstrated an incidence of early stroke trending to favor EAS versus non-EAS groups (0.8% [10/1273] vs non-EAS 1.7% [17/1019]; P = .052) for which in the subgroups of patients with partial aorta clamping, the incidence of the early stroke was significantly lower in the EAS group (2.8% [9/317] vs 0.7% [2/301]; P = .041).[236] This study is again compelling evidence that a primary factor in early postoperative stroke is instrumentation of an atherosclerotic aorta, even during OPCAB,[237]and whether due to direct plaque fracture or secondary embolization due to intimal disruption,[109] this again underscores the necessity for EAS and/or NTTs to avoid what is a potentially remedial but otherwise devastating perioperative complication.

"No-Touch" Technique

Avoidance of instrumentation of the ascending aorta in patients with severe aortic atheromatosis has been advocated. Leacche and colleagues retrospectively reviewed data from 640 OPCAB patients and identified 84 patients in whom they adopted an NTT.[163] In these patients, revascularization was performed with single or bilateral internal thoracic arteries and by connecting additional coronary grafts (saphenous vein, radial artery) in a T or Y configuration. In the NTT group, the frequencies were greater for severe atherosclerosis of the aorta (13% vs 0%), carotid disease (25% vs 16%), and history of previous cerebrovascular accidents (17% vs 8%). In the NTT group, weak trends toward a lower incidence of postoperative delirium (8% vs 15%; P = .12), a lower incidence rate of stroke (0% vs 1%; P = .85), and a shorter ICU stay (P = .07) were observed.[163] In a review of 1993 beating-heart surgery patients, Calafiore and colleagues[104] observed that in patients with evidence of peripheral vascular disease, use of aortic partial occlusion clamp was associated with a similar stroke rate as in patients in whom conventional CPB was used.[237] They concluded that in patients with extracoronary vasculopathy, aortic manipulation must be avoided to reduce the incidence of stroke. Gaspar and coworkers used EAS and TEE in 22 patients considered to be at high risk for stroke in whom severe aortic atheroma (maximum aortic wall thickness > 5 mm or mobile plaque) was detected, and with the use of aortic NTT and beating-heart surgery, no strokes occurred.[229]

Royse and colleagues performed screening of the aorta for atheroma before aortic manipulation and used an exclusive Y-graft revascularization technique, which involves no aortic coronary anastomoses.[71] Aortic atheroma was detected using EAS and TEE. In the control group, aortic atheroma was assessed by manual palpation, whereas TCD of the right middle cerebral artery was used to detect cerebral microemboli. Neuropsychological dysfunction was assessed using a battery of 10 psychometric tests, and they demonstrated that at 60 days after surgery, dysfunction in the control group was 38.1%, whereas in the TEE/Y-graft group, it was reduced to 3.8%. Microemboli detected by TCD during periods of aortic manipulation were greater for those with late dysfunction (5.2 ± 3.0 compared with 0.5 ± 0.2), suggesting an embolic cause for cognitive dysfunction.[71]

Powerful evidence implicating aortic instrumentation comes from a 12,079-patient study of isolated coronary artery bypass surgery in which aortic manipulation was completely avoided by using in situ internal thoracic arteries for inflow in 1552 patients (no-touch), a clampless facilitating device for proximal anastomoses in 1548 patients, and aortic clamping in 8979 patients.[238] The study demonstrated an overall incidence of postoperative stroke of 1.4% (n = 165), with an

unadjusted incidence of 0.6% ($n = 10$) in the no-touch group, 1.2% ($n = 18$) in the clampless facilitating device group, and 1.5% ($n = 137$) in the clamp group ($P < .01$ for no-touch vs clamp). The ratio of observed to expected stroke rate increased as the degree of aortic manipulation increased from 0.48 in the no-touch group, to 0.61 in the clampless facilitating device group, and to 0.95 in the clamp group, demonstrating that aortic clamping was independently associated with an increase in postoperative stroke compared with a no-touch technique. Even after correcting for use of CPB, aortic clamping was an independent risk factor for postoperative stroke, since both the OPCAB partial clamp and the on-pump cross-clamp techniques increased the risk of postoperative stroke compared to no-touch.[238]

CO_2 Insufflation During Open-Chamber Procedures

A primary determinant of the number and duration of microgaseous emboli during open-chamber procedures relates to methodologies for removal of intracavitary air. Although needle aspiration and/or aortic root venting are standard techniques for air removal, use of CO_2 insufflation, either continuously or immediately before closure of ventriculotomy, has been shown to significantly increase the efficacy of de-airing, resulting in decreased systemic gaseous emboli.[85,239] However, although there has been a general expectation of improvements in neurologic and cognitive outcomes resulting from such CO_2 insufflation, it has been surprisingly difficult to demonstrate. In a recent prospective study of 80 patients undergoing valve surgery and randomized to CO_2 insufflation versus conventional de-airing, although postoperative auditory-evoked potential monitoring demonstrated shorter P-300 latency in the CO_2-insufflated group, there was no detectable difference in clinical outcomes or in the incidence of cognitive dysfunction between groups.[240] In a recent review on the role of CO_2 insufflation, the reviewers concluded that although the use of CO_2 field flooding has been observed to be associated with a significantly lower count of intracardiac air bubbles and improved survival in two small studies, so far there is no evidence of a sustained reduction of cerebrovascular complications.[241]

Temperature and Coronary Artery Bypass Grafting

How much does cerebral hyperthermia superimposed on a brain suffused with focal ischemic lesions contribute to postoperative CNS dysfunction? It is known that the vulnerability of the normothermic brain to focal ischemic insult demonstrates a surprising variability in the presence of small gradations in temperature. Busto and associates demonstrated that at 33°C, expression of cerebral ischemia was virtually eliminated compared with controls maintained at 36°C.[242] In fact, a large measure of the apparent cerebroprotective efficacy of the glutamate-receptor antagonist MK-801 in global ischemia was demonstrated by Buchan and Pulsinelli to be mediated by just such a small secondary decrease in brain temperature.[243] Conversely, small increases in brain temperature, such as to 39°C increments as may occur during CABG (Fig. 40.14), have been shown to profoundly enhance the susceptibility of the brain to focal ischemic insult and result in ischemic lesions of much greater extent in comparison with controls at 37°C.[244]

Normothermic Cardiopulmonary Bypass

The demonstration of apparently improved myocardial performance and shorter CPB and operating room times after normothermic CPB has prompted several outcome studies to assess the efficacy of this therapy, with particular focus now centered on CNS outcomes. Hypothermia reduces cerebral metabolic rate; thus, mild hypothermia might protect the brain by preferentially suppressing energy utilization to maintain cellular integrity.[245] In support of this are results from a subset of 138 patients randomized to normothermic or hypothermic CPB, in whom a detailed prospective neurologic examination and a series of cognitive tests were performed before surgery, at postoperative days 1 to 3 and 7 to 10, and again at 1 month after surgery.[246] Seven of 68 patients in the normothermic group were found to have a central

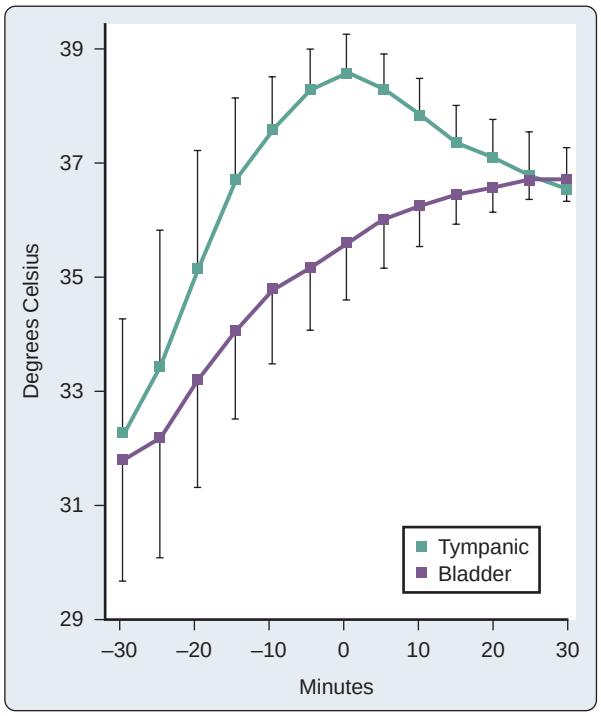


Fig. 40.14 Tympanic and bladder temperatures during rewarming. Time 0 is the maximal temperature achieved. Mean ± standard deviation values are shown. *(From Nathan JH, Lavallée G. The management of temperature during hypothermic cardiopulmonary bypass: I. Canadian survey.* Can J Anaesth. *1995;42:669–671.)*

neurologic deficit compared with none of the patients in the hypothermic group, a significantly greater incidence. In a separate study of 96 patients undergoing CABG and randomized to CPB at either 28°C, 32°C, or 37°C, patients managed at 37°C had a significantly greater incidence of deterioration on cognitive test scores than did those managed at either 28°C or 32°C.[247] No additional benefit in terms of cognitive function was conferred by cooling to 28°C versus 32°C.[199] Nathan and investigators reported on CABG patients operated under hypothermic (32°C) CPB and then randomly assigned to rewarming to 37°C (control) or 34°C (hypothermic), with no further intraoperative warming.[248] Neurocognitive testing was performed 1 week and 3 months after surgery. Eleven tests were combined into three cognitive domains: memory, attention, and psychomotor speed and dexterity. The incidence of cognitive deficits 1 week after surgery was 62% in the control group and 48% in the hypothermic group (relative risk, 0.77; $P = .048$). In the hypothermic group, the magnitude of deterioration in attention and in speed and dexterity was reduced by 55.6% ($P = .038$) and 41.3% ($P = .042$), respectively. At 3 months, the hypothermic group still performed better on one test of speed and dexterity.[248]

Other studies have demonstrated apparently different results, however. Engelman and colleagues randomized a series of 291 patients undergoing coronary revascularization to either hypothermic or tepid/normothermic perfusion.[249] Twelve intraoperative ischemic strokes occurred; six of these were in the group receiving hypothermic perfusion, and six were in the group receiving the tepid/normothermic perfusion. Measurements of the infarct volume showed that three of the strokes in each group resulted in minor or small infarcts and that three in each group were significant, major strokes. The volume of infarction, whether including all six patients in each group or only those with major strokes, was no different between the hypothermic and the tepid/normothermic groups. The researchers observed no relation between the size of a cerebral ischemic infarct and the perfusate temperature during coronary revascularization.[249] Similarly, Dworschak and coworkers found no difference in brain isoenzyme

S-100β release pattern or in clinical neurologic complications between two groups of CABG patients randomly assigned to normothermic or hypothermic (32°C) CPB.[250] In a large, prospective study, Grigore and associates randomly assigned 300 patients undergoing elective CABG to tepid/normothermic (35.5–36.5°C) or hypothermic (28–30°C) CPB and used a battery of neurocognitive tests evaluating four distinct cognitive domains administered before surgery and at 6 weeks after surgery.[66] Again, there were no differences in neurologic or neurocognitive outcomes between normothermic and hypothermic groups in multivariable models. In a separate study, Grimm and investigators found subclinical impairment of cognitive brain function to be more pronounced in CABG patients undergoing mildly hypothermic CPB compared with normothermic CPB.[251] Accordingly, a protective effect of hypothermia on neurologic outcome in CABG has not been verified in most clinical trials, possibly because of too fast and/or excessive rewarming of patients or, more likely, because the impact of only transient cooling during CPB does not extend into the postoperative interval when cerebral hyperthermia has also been demonstrated and correlated with impaired cognitive performance at 6 weeks after surgery.[12,190,252–255]

Procedural Risk

Valve Surgery Versus Coronary Artery Bypass Graft Surgery

In a large retrospective review by Alexander and colleagues of 64,467 patients who underwent CABG alone and 3297 patients who underwent CABG in conjunction with AVR or CABG in conjunction with mitral valve repair or replacement, the incidence rate of type I cerebral injury in patients younger than 80 years was 4.2% for CABG, 9.1% for CABG with AVR, and 11.2% for CABG with mitral valve repair or replacement.[27] Notably, the total CPB time was 96 minutes for CABG, 148 minutes for CABG in conjunction with AVR, and 161 minutes for CABG with mitral valve repair or replacement. It thus remains unclear whether it is the procedure itself or the prolonged duration of CPB, either acting directly or as a marker of a greater surgical difficulty and thus perioperative hemodynamic instability, that is fundamentally causative.[256]

Wolman and colleagues prospectively studied 273 patients from 24 U.S. medical centers who underwent combined intracardiac surgery and CABG.[19] Adverse cerebral outcomes occurred in 16% of patients (43/273), being nearly equally divided between type I cerebral injury (8.4%; 5 cerebral deaths, 16 nonfatal strokes, and 2 new TIAs) and type II cerebral injury (7.3%; 17 new intellectual deteriorations persisting at hospital discharge and 3 newly diagnosed seizures), rates of injury twofold to threefold greater than demonstrated after CABG alone by this same group of investigators.[19] Associated resource utilization was significantly increased according to type of CNS injury: prolonging median ICU stay from 3 days (no adverse cerebral outcome) to 8 days associated with type I injury and from 3 to 6 days in those patients with type II injury. Significant risk factors for type I cerebral injury related primarily to embolic phenomena, including proximal aortic atherosclerosis, intracardiac thrombus, and intermittent clamping of the aorta during surgery. Risk factors for type II cerebral injury included proximal aortic atherosclerosis; a preoperative history of endocarditis, alcohol abuse, perioperative arrhythmia, or poorly controlled hypertension; and the development of a low-output state after CPB.[19]

In a recent prospective cohort study, 196 patients of mean age 75.8 ± 6.2 years who underwent AVR were evaluated by neurologists preoperatively and postoperatively and underwent postoperative MRI. Clinical strokes were detected in 17%, TIAs occurred in 2%, and the in-hospital mortality rate was 5%.[36] In comparison, the frequency of stroke in the STS database is 1.4% after isolated AVR.[9] Clinical stroke was associated with increased length of stay and moderate or severe stroke (National Institutes of Health Stroke Scale score ≥10) occurred in 8 (4%) and was strongly associated with in-hospital mortality (38% vs 4%; $P = .005$). Of the 109 stroke-free patients who underwent postoperative MRI, silent infarct was identified in 59 (54%) but was not associated with in-hospital mortality or increased length of stay.

Circulatory Arrest

Retrograde and Selective Anterograde Cerebral Perfusion

During complex aortic arch repair, surgical access may require interruption of systemic perfusion for relatively protracted periods. Although moderate (25–30°C) and deep (<25°C) hypothermia remain a mainstay for cerebral and systemic protection, the duration of safe cerebral ischemia time and the nature and techniques for provision of cerebral perfusion during times of HCA have been an area of active interest.

In a nonrandomized study, Reich and colleagues performed preoperative and postoperative cognitive testing on 56 patients undergoing HCA, of whom 12 patients underwent retrograde cerebral perfusion (RCP).[257] Memory dysfunction and the overall incidence of cognitive dysfunction had strong associations with RCP even when controlling separately for age and cerebral ischemia time, suggesting worsened outcome with RCP. Okita and colleagues separately evaluated 60 patients who were nonrandomized but were sequentially stratified to receive either RCP or selective antegrade cerebral perfusion (ACP) using serial brain imaging, brain isoenzyme measurement, and limited cognitive testing.[258] They also demonstrated that the prevalence of clinically defined transient brain dysfunction was significantly greater in patients with RCP. Svensson and colleagues used cognitive testing in a subset of 30 of 139 patients undergoing HCA and prospectively randomized three groups to receive either HCA alone, HCA and RCP, or HCA and selective ACP.[259] Comparison of postoperative mean cognitive test scores showed that the HCA alone group did significantly better than either the RCP or ACP group patients.

Despite its conceptual attractiveness and relative ease of application, RCP has not been demonstrated to result in clinically significant CBF, even under conditions of hypothermia-induced decreased cerebral metabolism. In a primate study comparing HCA alone with HCA combined with RCP, less than 1% of the RCP inflow returned to the aortic arch, and histologic analysis revealed slightly more glial edema in the RCP group.[260] Similarly, during HCA in 14 pigs, use of RCP or RCP with inferior vena cava occlusion also resulted in negligible CBFs, and it was similarly observed that less than 13% of retrograde superior vena caval inflow blood returned to the aortic arch with either technique.[261]

It appears as though modified RCP may be effective in flushing emboli from the cerebral circulation, but at the cost of some mild cerebral ischemic damage. Juvonen and coworkers studied the impact on histologic and behavioral outcome of an interval of RCP with and without inferior vena cava occlusion, versus ACP control, after cerebral arterial embolization in a chronic porcine model.[262] Microsphere recovery from the brain revealed significantly fewer emboli after RCP with inferior vena cava occlusion but demonstrated that significant mild ischemic damage occurred after RCP even in nonembolized animals but not in the other groups. Behavioral scores by day 7 were considerably lower in all groups after embolization, with no significant differences between groups.

Another interesting study of Okita and colleagues is a retrospective review of 8169 patients who underwent total arch replacement between 2009 and 2012 and of whom 7038 patients had ACP and 1141 patients had HCA/ RCP, in whom the duration of CPB and cardiac ischemia was longer in the ACP group. The investigators found no significant differences between the ACP and RCP groups with regard to 30-day mortality (3.2% vs 4.0%), hospital mortality (6.0% vs 7.1%), incidence of stroke (6.7% vs 8.6%), or transient neurologic disorder (4.1% vs 4.4%). In addition, there were no significant differences between the groups in a composite outcome of hospital death, bleeding, prolonged ventilation, need for dialysis, stroke, and infection (ACP 28.4% vs HCA 30.1%).[263] However, HCA/RCP resulted in a significantly higher rate of prolonged stay in the ICU (>8 days: 24.2% vs 15.6%). The investigators concluded that ACP might be preferred as the brain protection method for complicated aortic arch procedures.

pH Management During Hypothermic Circulatory Arrest

The milieu in which HCA is conducted may well also have an important impact on CNS outcomes, but this has not yet been systematically investigated in adult patients. Clinical studies and experimental evidence point to a benefit of pH-stat management in infants and children undergoing HCA.[264] However, it should be noted that neither the clinical studies in pediatric patients nor the experimental models using nonatheromatous animals are necessarily relevant to the adult patient who invariably has substantial atheromatous disease within the ascending aorta, often with concomitant extracranial and intracranial involvement. For adults undergoing moderate hypothermic CPB at least, the weight of evidence from CNS outcomes of at least three separate, prospective, randomized, clinical trials supports alpha-stat pH management over pH-stat.[57,265,266] In this context, alpha-stat has also been associated with decreased cerebral embolization[267] and preservation of cerebral autoregulation,[138,265] factors likely of paramount importance in perioperative CNS injury in adult patients undergoing HCA.

In none of these studies were stroke rate, mortality, or other measures of morbidity influenced by treatment mode, although all were underpowered to detect such outcomes. However, Hagl and associates retrospectively analyzed outcomes in 717 survivors of ascending aortic and aortic arch surgery.[268] They determined that the method of cerebral protection did not influence the occurrence of stroke but that ACP resulted in a significant reduction in the incidence of temporary neurologic dysfunction, a result not seen after RCP. Directionally similar results demonstrating that antegrade perfusion was associated with significantly lower incidences of temporary neurologic complications, earlier extubation, shorter ICU stay, and shorter hospitalization in comparison with patients managed with RCP have been shown by Apostolakis and colleagues.[269] Halkos and investigators demonstrated that during proximal aortic surgery, selective ACP was associated with lower mortality, as well as improved resource utilization and fewer pulmonary and renal complications.[270]

It is unlikely that pH management will substantially change the results of RCP versus ACP discussed earlier; however, the study conducted by Harrington and colleagues used alpha-stat management, whereas the study done by Reich and colleagues used pH-stat management, both with similar directional results relatively unfavorable to RCP.[67,257] Whether pH management will influence the overall incidence of CNS dysfunction after HCA is unknown. A recent metaanalysis has concluded that in the absence of randomized trials, pH-stat management for infants and alpha-stat management for adults would appear to be the most appropriate strategies for patients undergoing HCA.[271] Based on the impact of pH management on CBF, a strong argument could be made to use pH-stat during the cooling phase before circulatory arrest followed by alpha-stat during rewarming, as practiced in some institutions.[272]

During HCA, meticulous clinical management with systemic hypothermia combined with topical cooling of the head, avoidance of cerebral hyperthermia during rewarming and in the immediate postoperative interval, maintenance of normal perioperative blood glucose concentrations, careful de-airing of graft and arteries, ideally with carbon dioxide flushing before reperfusion, all coupled with an expeditious surgical repair designed to minimize the duration of HCA, should be the goal.

Minimal Access Surgery and Circulatory Support

Development of Minimal Access Surgical Techniques

In the mid-1990s, efforts occurred to decrease the invasiveness of CABG in order to reduce postoperative morbidity and mortality. Research focused on trying to avoid instrumentation of the aorta (neurologic complications), avoid sternotomy (infectious complications), and avoid use of CPB (inflammation, bleeding, neurologic complications). First, the port-access endovascular technique was developed, avoiding sternotomy, right atrial manipulation (POAF), and external aortic cross-clamping.[273] Retrograde CPB was established through femoral arterial and venous cannulation. In lieu of aortic clamping, a transfemoral endoaortic balloon catheter was used for aortic occlusion, aortic-root venting, root pressure monitoring, and anterograde cardioplegia administration. The left internal mammary artery graft was placed on the left anterior descending coronary artery (LAD) through a limited left anterior thoracotomy incision. However, there were issues of balloon migration and occlusion of arch vessels, as well as intraoperative aortic dissection or iliac artery dissection. It was therefore recommended to include preoperative screening for peripheral vascular disease (a contraindication for endovascular CPB), as well as intraoperative monitoring of both right and left radial artery pressures.[274] After 1166 cases (614 CABG, 412 mitral valve procedures, and 140 other procedures), the reported 30-day stroke rate after CABG was 1.2% and after mitral valve surgery was 4.0%.[274] This was equivalent to the stroke rate of 1.4% after isolated conventional CABG of the STS database.[8] Furthermore, the STS stroke rate after mitral valve surgery is considerably lower (mitral valve replacement 2.1%, mitral valve repair 1.4%), demonstrating that minimal access surgery is not necessarily minimally invasive.[9] The main culprits are thought to be the deployment of an intravascular balloon in the ascending aorta and difficulty of retrograde de-airing leading to cerebral air embolism. Moreover, retrograde femoral arterial perfusion is thought to increase stroke risk, especially in patients with severe (grade IV or V) atherosclerosis of arch and/or ascending aorta.[275] The collaborators themselves decided to stop using port-access and performed minimally invasive direct coronary artery bypass grafting (MIDCAB) instead.[274]

The MIDCAB procedure was developed as an off-pump LAD bypass through a limited left thoracotomy, with transient occlusion of the LAD.[276] Avoiding both CPB and aortic manipulation, it could potentially protect patients from neurologic adverse events. In a series of 199 patients, 14 (7%) were converted to conventional sternotomy; all but 1 of these was due to technical difficulties. From the 185 remaining MIDCAB patients, only 1 had an undefined neurologic complication. However, since this technique is technically difficult for right coronary lesions and effectively impossible for circumflex arterial lesions, it is now used only in a hybrid approach, which incorporates percutaneous catheter–based interventions for multivessel disease.

A third approach, OPCAB, uses a full sternotomy, without CPB and aortic cross-clamping, but still makes use of aortic side clamps. This procedure is used for approximately 25% of all CABG in the United States and is associated with less perioperative morbidity.[277] The true reduction in postoperative neurologic adverse events, however, remains to be elucidated. The body of evidence on postoperative stroke is confounded by procedural differences related to use of EAS and partial aortic clamping in different study groups. For example, use of EAS in the conventional CABG study population will minimize a beneficial effect in the OPCAB group. Likewise, use of aortic side clamps in the OPCAB group in the presence of markers of vascular disease will also preclude major reduction in postoperative neurologic outcomes. Robotic surgery was introduced to further minimize the route of access to the mediastinum and was combined with OPCAB to avoid use of CPB. Robotic surgery was used initially for bypass grafting. Centers now report robot-assisted atrial septal defect and patent foramen ovale closure, as well as robot-assisted mitral valve surgery.[278,279]

Similar to CABG surgery, valvular surgery has also embraced minimal access. Aortic valve surgery is now performed via right anterior thoracotomy and right upper partial sternotomy incisions in order to reduce wound infections. More recently, percutaneous transcatheter (transfemoral or transapical) aortic valve implantation (TAVI) approaches have been introduced to avoid CPB and hence CPB-induced morbidity.[280] However, there is still concern of atherosclerotic emboli released during deployment of the valve or during transfemoral catheterization. Because the latter techniques are relatively new, there is still uncertainty regarding long-term durability and clinical results compared with open heart surgery. Potential TAVI candidates

are therefore mainly high-risk and older symptomatic patients with severe aortic stenosis.

Transcatheter mitral valve interventions or mitral clip procedures for mitral regurgitation are yet another chapter in the development of minimally invasive cardiac surgery and were first introduced in 2005. These procedures eliminate use of CPB, sternotomy, and manipulation of the aorta and are expected to reduce postoperative neurologic morbidity. Nevertheless, outcome data from these new techniques mainly focus on surgical results, and data on neurologic outcomes are currently limited.

Off-Pump Coronary Artery Bypass

In 2012, the CORONARY investigators published the 30-day outcome of 4752 patients that were randomized to compare OPCAB to conventional CABG. The reported incidence of stroke was similar in both groups (1.0% vs 1.1%).[281] At 1 year, the incidence of stroke had marginally increased, but the increase was similar between the two groups (1.5% vs 1.7%).[282] This was surprising since avoidance of aortic cannulation and cross-clamping were thought to reduce the embolic risk. This may have been because 102 patients assigned to conventional CABG crossed over to have OPCAB because of a calcified aorta, or it may have been due to lack of power.

Previously, in 2004, a meta-analysis on OPCAB versus conventional CABG also found no difference in the incidence of stroke at 30 days from 21 randomized clinical trials ([RCT]; $n = 2859$; OPCAB 0.4 vs CABG 1.0%; odds ratio [OR], 0.68; 95% CI, 0.33–1.40).[277,283] One year after surgery the stroke rate increased to OPCAB 1.1% compared with CABG 2.3% ($n = 864$, 4 RCTs; OR, 0.50; 95% CI, 0.17–1.50). As the researchers point out, the study population consisted only of patients with lesions amenable to OPCAB, with exclusions of circumflex lesions beyond the first obtuse margin, affecting generalizability. Moreover, crossover rates were higher in OPCAB versus CABG patients (8.0 vs 1.7%), introducing room for possible bias. In comparison, a large body of nonrandomized studies showed reduced stroke risk with OPCAB versus conventional CABG (40% to 45% risk reduction, respectively), possibly because of patient selection or a lack of power among RCTs.[277]

Results on early cognitive outcome or cognitive function in patients already experiencing decline preoperatively are conflicting. Two studies report that OPCAB was associated with a significant reduction in decline,[284,285] whereas another trial did not find a difference.[124] Mid-term cognitive outcome at 2 and 6 months also differs across studies from a reduction in number of patients with cognitive dysfunction after OPCAB to no difference between groups.[124,285,286] One year after surgery the number of patients experiencing cognitive decline is the same between OPCAB versus CABG.[124,284,286,287] More recently the CORONARY trial investigators studied neurocognitive outcome at discharge, 30 days and 1 year after surgery and found the same direction of effect. At discharge they found less neurocognitive decline from baseline in the OPCAB group, assessed with use of the Digit Symbol Substitution Test, but no significant between-group difference at 30 days or 1 year.[282] No differences between groups was found in change in scores on two more tests. This is in accordance with an observational study comparing 89 OPCAB with 129 conventional CABG patients that also found decreased early neuropsychological dysfunction 1 week after surgery in the OPCAB group.[288] OPCAB surgery in comparison to CABG therefore seems to impact early but not late neurocognitive outcome, probably reflecting the progression of underlying disease.

Endoscopic, Robot-Assisted Coronary Artery Bypass Graft Procedures

A systematic review of 14 studies on endoscopic, robot-assisted CABG procedures included 880 OPCAB and 360 CABG surgeries.[289] Weighted mean incidence of stroke within 1 year after endoscopic, robot-assisted OPCAB was 0.7% versus 0.8% robot-assisted CABG. However, because seven of the eight studies reporting on postoperative stroke were nonrandomized cohorts, these low incidence figures probably reflect the selection of low-risk patients for endoscopic, robot-assisted OPCAB and robot-assisted CABG.[289]

Transcatheter Aortic Valve Implantation

Only three RCTs evaluating TAVI have been conducted so far, comprising 1564 patients; of these three trials, two report on postoperative stroke (769 patients).[290–292] In the multicenter trial of Kodali and colleagues (PARTNER trial), 699 high-risk patients were assigned to surgical AVR or TAVI (transapical).[292] Patients at 25 sites were included if they had severe aortic stenosis with an aortic valve area of less than 0.8 cm^2 and were determined to be at high surgical risk because of comorbidities that were associated with an estimated 30-day mortality risk of at least 15%. The total number of strokes over the follow-up period of 36 months was the same (24 TAVI and 20 AVR; hazard ratio [HR], 1.22; 95% CI, 0.67–2.23). However, in the first 30 days, the hazard of stroke was increased in the TAVI group (4.6% with TAVI vs 2.4% with surgery).[292] This raised concern that TAVI is responsible for early strokes, possibly owing to increased liberation of atherothrombotic debris (from valve or aorta), causing embolic ischemic strokes. Nielsen and colleagues conducted a multicenter trial in patients over 75 years aiming to include 200 patients and follow them for a composite end point of 30-day all-cause mortality, major stroke, and renal failure requiring dialysis.[291] Unfortunately, the study was prematurely terminated after inclusion of 70 patients, when the primary end point was met in 5 patients in the transapical TAVI (2 deaths, 2 strokes, 1 renal failure) versus 1 patient in the surgical group (stroke).[291] In their discussion, the authors touch upon the increased early stroke risk after TAVI, emphasizing the importance of early dual anticoagulation. Furthermore they recommend preoperative computed tomography imaging improving valve sizing, possibly preventing the adverse events of paravalvular leak caused by undersizing and occlusion of LAD after TAVI.

Schymik and coworkers published results of 1000 consecutive patients undergoing transapical or transfemoral TAVI in their institution between 2008 and 2012.[293] Selection criteria for TAVI were EuroSCORE (European System for Cardiac Operation Risk Evaluation) of more than 15, irrespective of age; age older than 75 years with predisposing risk factors such as prior heart surgery, comorbidities, or frailty; and patients with known porcelain aorta. In this high-risk patient cohort with mean age of 81, female gender greater than 50%, and EuroSCORE higher than 20, the researchers found a 30-day incidence of stroke or TIA of only 1.7% after 413 transapical procedures and 2.3% after 587 transfemoral procedures. After propensity score matching, the incidences were similar: 2.0% versus 2.3%. This is in contradiction with the belief that transfemoral catheterization increases the risk of disrupting calcific plaques, especially in patient with severe (grades IV and V) aortic arch or ascending aortic atherosclerosis.[275]

Knipp and associates reported a single-center nonrandomized study on cognitive function 3 months after surgical AVR and TAVI.[294] Sixty-four patients with severe aortic stenosis were subjected to neurologic and neuropsychological testing before and after surgery, at discharge, and at 3-month follow-up. Diffusion-weighted MRI was performed before surgery and before discharge. Of the 64 patients, 27 underwent transapical TAVI and 37 had surgical AVR. Patients undergoing TAVI were significantly older, had more comorbidities, and had a higher estimated operative risk for mortality. In TAVI patients there was no statistically significant decrease in any of the six cognitive domains tested. However, the composite cognitive score suggested a clinically relevant deficit in 18% of patients at discharge and in 28% patients at 3 months. From the available MRI studies, 7 out of 12 TAVI patients had areas of new focal ischemia, all clinically silent, not unlike the results of Messé and investigators in which a 54% incidence of new lesions on MRI was noted after surgical AVR.[36] The presence of these lesions was unrelated to cognitive dysfunction.[294]

Taken together, these studies indicate the following: (1) Extensive preoperative assessment is necessary to correctly size the aortic annulus and identify severe atherosclerotic lesions in ascending aorta and arch. (2) TAVI is associated with an increased risk of early stroke, emphasizing the need for coagulation after TAVI.[295] Early studies with new cerebral filters suggest frequent capture of atherothrombotic material after TAVI; however, clinical studies are yet to be published.[296] (3) TAVI

procedures should only be performed by experienced, high-volume centers.[297] This is once more demonstrated by the high number of procedures (1000 in 4 years), yet low number of adverse neurologic outcomes (2–2.3%) presented by Schymik and colleagues.[293] (4) It is still unknown if transfemoral catheterization increases the risk of postoperative neurologic events compared with transapical TAVI.[275]

The SANITY study, a prospective, multicenter study comparing the incidence of neurologic injury associated with transapical, transaortic, or transfemoral TAVI and surgical AVR, has hypothesized that surgical AVR is associated with less neurologic injury than transcatheter valve insertion, and transapical/transaortic with less neurologic damage than transfemoral.[298] This study aims to include 150 high-risk patients with severe aortic stenosis, who are planned for either surgical or transcutaneous treatment, and who have an STS score higher than 8%, EuroSCORE higher than 20%, or EuroSCORE II higher than 10%. It is hoped that extensive preoperative evaluation of patient demographics, calcification of aorta, neurocognitive function, and functional capacity; intraoperative assessment of hemodynamics and cerebral oximetry; and postoperative follow-up for adverse events, neurocognitive change, and serologic markers; and MRI, diffusion-weighted MRI, and susceptibility-weighted MRI until 6 months after surgery will enhance the existing body of knowledge in this area once the results have been analyzed and published.

MitraClip

The MitraClip procedure is used to treat patients with moderate-to-severe and severe mitral regurgitation (MR). During this procedure a device is advanced via the femoral vein into the right atrium and then via a transseptal route antegradely into the left atrium and further into the left ventricle under two- and three-dimensional TEE and fluoroscopic guidance. In most patients general anesthesia is used, whereas use of CPB and aortic clamping or cannulation is avoided. With the clip arms opened at 160 to 180 degrees, the device is retracted against the mitral valve to grasp the anterior and posterior leaflet at the site of the maximum regurgitation jet. The clip arms are then closed to approximate the leaflets (called *edge-to-edge repair*). If reduction in MR is acceptable and appropriate leaflet insertion is ascertained, the clip device is released from the delivery system. Additional MitraClip implantations are performed if residual lateral/medial MR is present. The first study on mitral clips implantation (EVEREST I) enrolled 27 patients with moderate-to-severe or severe MR.[299] Of 24 patients receiving a clip, 1 suffered from a stroke after the procedure. The EVEREST II trial, wherein 279 patients with moderate-to-severe or severe MR were randomized to percutaneous repair or conventional surgery, found less efficacy after percutaneous repair (55% vs 73%) but also less incidence of major adverse events (15% vs 48%), mainly attributed to bleeding.[300] Major stroke occurred in two patients in each group.

Recently, Eggebrecht and colleagues published data from the multicenter German registry on MitraClip procedures,[301] which was established to assess safety and efficacy and is open to all German sites performing percutaneous mitral valve interventions. Their analysis of 828 high-risk patients (median age, 76; median EuroSCORE, 20.0%) from 15 centers demonstrated an in-hospital stroke rate of 0.9%, an in-hospital TIA rate of 1.0%, and an overall in-hospital death rate of 2.2%. The ACCESS-EU study prospectively enrolled 567 patients of (mean age, 73.7; mean EuroSCORE, 23.0%) from 15 different European sites between April 2009 and April 2011.[302] The patients were followed for 1 year for adverse events, quality of life, and 6-minute walking test and demonstrated a 30-day stroke incidence of 0.7% and a 1-year stroke rate of 1.1%.

The incidence rates of stroke from both studies are considerably lower than those reported in the STS database, in which the frequency of cerebrovascular accident after isolated surgical mitral valve replacement is 2.1%, and after surgical mitral valve repair 1.4%.[9] However, since long-term efficacy is still questioned, it is useful to look at their 12-month outcomes. The investigators reported that 78.9% were free of MR 2+ severity, 6.3% underwent mitral surgery, and 3.4% underwent a second MitraClip procedure. The Kaplan-Meier estimate of freedom from all-cause mortality at 12 months was 81.8% (95% CI, 78.1–84.8%).[302] A recent systematic review by Philip and colleagues of 21 studies in patients with a high risk of surgical mortality (EuroSCORE > 18 or STS score > 10) reports a 30-day success rate of 96.3% for MitraClip vs 98.1% for mitral valve surgery, with an urgent mitral valve surgery rate of 2.7% versus 0.6%.[303] However, with a mean death rate of 3.3% for MitraClip vs 16.2% for mitral valve surgery and a stroke rate of 1.1% and 4.5%, respectively, it seems that in high-risk patients MitraClip may be associated with significantly lower risk for neurologic morbidity and mortality.

Extracorporeal Membrane Oxygenation and Ventricular Assist Device Procedures and Cerebral Dysfunction

Venoarterial extracorporeal membrane oxygenation (ECMO) has been used successfully for cardiogenic shock and cardiac arrest refractory to usual resuscitative techniques as a form of mechanical support. Therefore, all patients on ECMO represent a very high-risk patient group who would otherwise probably die. In the absence of large clinical trials, performance of pooled analysis represents the best method for ascertaining complication rates associated with ECMO in patients who experience cardiogenic shock and cardiac arrest. However, there is an abundance of insertion techniques, with a heterogeneous risk profile. The first and major defining characteristic is site of cannulation, peripheral versus central. Central cannulation is most often used in patients who cannot be weaned from bypass. This patient group therefore has a high a priori chance of cerebral complication resulting from long CPB time and low cardiac output syndrome. Peripheral cannulation can be started intraoperatively in the same patient group to allow primary chest closure. However, most peripheral cannulation will be performed without use of CPB and aortic cross-clamping, for example in ICUs, thereby lowering the predisposing factors for adverse neurologic outcome. Still, it entails aortic manipulation by advancing the arterial cannula via the femoral or axillary artery. A recent meta-analysis on venoarterial ECMO, including all studies with more than 10 patients published after 2000, retrieved 20 studies encompassing 1866 patients.[304] The reported pooled estimate stroke rate from three studies (630 patients) was 5.9% (95% CI, 4.2–8.3%), and overall neurologic complications rate from nine studies (1019 patients) was 13.3% (95% CI, 9.9–17.7%), encompassing hemorrhage, ischemic stroke, coma, anoxic brain injury, brain death, or brain injury.[304] In summary, ECMO insertion is performed only in very high-risk patients and involves considerable risk for adverse neurologic events.

Patients receiving ventricular assist devices (VADs) represent a slightly different group. They have been screened to see that no contraindications exist for this complex surgery. Most patients receive VAD as bridge to therapy (56%) or destination therapy (43%) for heart failure. A small percentage of patients receive VAD as rescue therapy (0.3%) or bridge to recovery (1.0%).[305] The ultimate clinical goals of VAD therapy are to restore adequate blood flow, preserve end organ function, and provide effective decompression of failing ventricles. VAD insertion involves a long procedure with CPB and aortic cross-clamping. The reported rates of stroke after VAD implantation are variable and reflect differences in follow-up and patient population. Neurologic events seem to be relatively common and are associated with bad patient outcome. Consistent evidence shows that pulsatile pumps tend to lead to more complications (especially malfunction and infection) compared with continuous pumps. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Fifth Annual Report shows a twofold increase of postoperative neurologic dysfunction associated with pulsatile versus continuous flow (3.81 vs 1.83%; $P < .0001$).[306] Thus it comes as no surprise that currently less than 5% of implanted VADs are pulsatile pumps.[305] Moreover, it seems that the total burden of adverse events is slightly decreasing with greater experience using continuous-flow devices.[305]

However, although the early stroke risk after VAD insertion is low, it increases steadily over time. Outcomes in a group of 5366 adult primary continuous-flow left ventricular assist devices indicated the risk of stroke at 1 month was 3%, increasing to 11% at 12 months, 17% at 24 months, and 19% at 36 months after implantation, presumably due to the constant thrombogenic threat of artificial hardware in the main vasculature.[306] This further emphasizes the need for adherence to long-term anticoagulation regimes.

Applied Neuromonitoring

Intraoperative neurophysiologic monitoring may be of benefit to decrease CNS injury.[307] Intraoperative TCD has been demonstrated to detect embolic events in real time and allows modification of perfusion and surgical techniques. It has been shown that the numbers of emboli generated by perfusionist interventions (eg, drug injection, blood return), as well as episodes of entrainment of air from the surgical field, are rapidly identified and corrected by TCD detection of intraoperative emboli (see Chapter 18).[308]

Brain oximetry studies using noninvasive NIRS have shown promising results.[143,309–314] In Goldman and colleagues' large, nonrandomized cohort study, NIRS was used to monitor cerebral oxygen saturation in 1034 cardiac surgical patients and was compared with outcomes in 1245 patients who underwent cardiac surgery immediately before cerebral oximetry was incorporated.[313] The study group had significantly more patients in New York Heart Association (NYHA) classes III and IV than the control group, but the study group overall had fewer permanent strokes (10 [0.97%] vs 25 [2.5%]; $P = .044$) and the proportion of patients requiring prolonged ventilation was significantly smaller in the study group, as was the length of hospital stay. Murkin and coworkers reported a prospective, blinded, randomized study of NIRS cerebral oximetry in 200 cardiac surgical patients and demonstrated significantly fewer adverse clinical outcomes in NIRS versus control groups ($P = .027$).[143]

Even during beating-heart procedures, compromised cerebral perfusion can occur relatively frequently, and if unrecognized, may account for the relative lack of difference in CNS outcomes between CABG and OPCAB surgery.[315] Combined electroencephalography and cerebral oximetry identified episodes of cerebral ischemia in 15% of a series of 550 beating-heart patients; all were treated successfully by a combination of pharmacologically improved cardiac output, increased perfusion pressure, and cardiac repositioning.[315]

In a study utilizing cerebral oximetry in 265 patients undergoing primary coronary artery bypass surgery and randomized to active monitoring and a series of interventions designed to improve regional hemoglobin oxygen saturation (rSO_2) or to a control group in which blinded monitoring was used, a significant association was found between prolonged cerebral desaturation and early cognitive decline, as well as a threefold increased risk for prolonged hospital stay.[53] However, cerebral desaturation rates were similar between groups and ascribed to poor compliance with the treatment protocol, resulting in no difference in the incidence of cognitive dysfunction between groups. In a study of 103 patients undergoing valvular heart surgery in whom blinded cerebral NIRS monitoring was used, cerebral oxygen desaturation was again found to be associated with significantly longer duration of postoperative hospitalization.[316]

In a prospective, randomized, blinded study in 200 patients undergoing coronary artery grafting, Murkin and colleagues demonstrated that active treatment of declining rSO_2 values prevented prolonged cerebral desaturations and was associated with a shorter ICU length of stay and a significantly reduced incidence of major organ morbidity or mortality in comparison with a similar control group.[143] In this study, the intervention protocol undertaken to return rSO_2 to baseline resulted in a rapid improvement in rSO_2 in 84% of cases and did not add undue risk to the patient, including no increase in allogeneic blood transfusions.[317] There were also numerically fewer clinical cerebrovascular accidents in the monitored patients directionally consistent with previous studies.[313] More recently, use of an active treatment algorithm to minimize cerebral desaturation has been shown to be associated with decreased neurocognitive dysfunction and decreased markers of brain dysfunction.[318,319] As such, a physiologically derived treatment algorithm for management of perioperative cerebral oxygen desaturation has been proposed and is shown in Fig. 40.15.[320] An important aspect in using cerebral NIRS devices is the efficacious use of a treatment algorithm for management of cerebral desaturation.

Another recent development in cerebral oximetry monitoring has been the recognition that it can be used to determine the lower limit of cerebral autoregulation (LLA) and that perfusion pressures below this limit are associated with a variety of adverse outcomes, including major organ morbidity and mortality, analogous to the findings of Murkin and colleagues, as well as stroke and acute kidney injury.[142,321,322]

Some of the concerns associated with cerebral oximetry, including extracerebral signal contamination, and change in arterial/venous partitioning, have been addressed in a new generation device.[323] The incorporation of a Doppler ultrasound to focus NIRS photons has permitted the direct measurement of changes in microcirculatory CBF using ultrasound-tagged photons, and a series of preliminary studies have demonstrated the utility of this approach to assess the integrity of cerebral autoregulation and LLA.[324]

Neuromonitoring During Deep Hypothermic Circulatory Arrest

Moderate (25–30°C) and deep (<25°C) hypothermia remain a mainstay for cerebral and systemic protection during complex aortic arch repair because surgical access may require interruption of systemic perfusion for relatively protracted periods. As there is relatively little ability to monitor cerebral well-bring during such times because electroencephalography becomes progressively attenuated at less than 25°C, cerebral NIRS has been advocated as a means of monitoring and detecting onset of cerebral ischemia during deep HCA.[325,326] Although some groups monitor jugular venous oxygen saturation (SjO_2) using retrograde cannulation of the internal jugular vein as an index of cerebral metabolic suppression during cooling, correlation has not been demonstrated between SjO_2 and cerebral NIRS during deep HCA.[327] A possible explanation could be that NIRS is a highly regional measure of cerebral cortical oxygen tissue saturation, whereas SjO_2 is a measure of cerebral mixed venous oxygen saturation and thus reflective of global changes in venous oxygenation and, as such, potentially less sensitive to regional perfusion inhomogeneities.

In addition to deep HCA, some centers use RCP via the superior vena cava or, increasingly, selective anterograde cerebral perfusion (SACP) via the innominate or subclavian artery. There have been a variety of case reports of the ability of cerebral NIRS to detect onset of cerebral ischemia during aortic arch surgeries, and there is growing interest in the role of cerebral NIRS as a measure of adequacy of perfusion in this setting.[328–332] It is increasingly recognized that RCP does not provide sufficient nutritive flow to sustain cerebral integrity for an extended interval, as has been reflected in lower rSO_2 values seen during NIRS monitoring in RCP versus SACP.[328,330,333]

In a study investigating the role of NIRS monitoring during SACP, a study was undertaken in 46 consecutive patients in whom SACP was established by separate concomitant perfusion of the innominate and the left carotid arteries or by perfusion of the right subclavian artery (with or without left carotid artery perfusion) and during which bilateral regional cerebral tissue oxygen saturation index was monitored.[334] Stroke was the primary clinical end point, together with indices of diagnostic performance of the NIRS device. In this series, six patients died in the hospital and six patients (13%) in whom regional cerebral tissue oxygen saturation values were significantly lower during SACP experienced a perioperative stroke. Regional cerebral tissue oxygen saturation decreasing to 76% to 86% of baseline during SACP had a sensitivity of up to 83% and a specificity of up to 94% in identifying individuals with stroke. It was concluded that using NIRS monitoring of regional cerebral tissue oxygen saturation during SACP allows detection of clinically important cerebral desaturations and can help

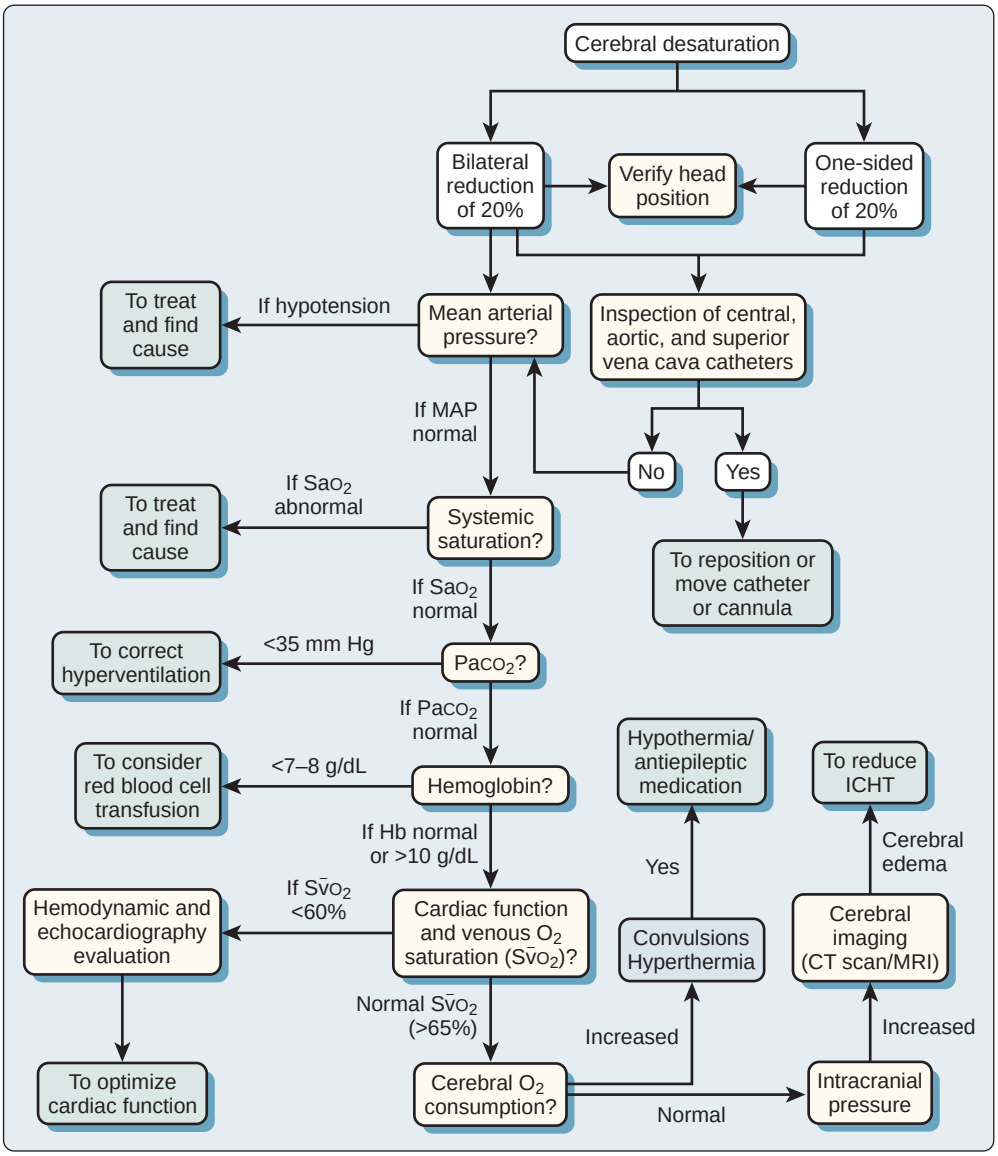


Fig. 40.15 Algorithm for the use of brain oximetry. *CT,* Computed tomography; *ICHT,* intracranial hypertension; *MAP,* mean arterial pressure; *MRI,* magnetic resonance imaging; *$Paco_2$,* arterial partial pressure of carbon dioxide; *Sa_{O_2},* arterial oxygen saturation; *$S\bar{v}o_2$,* mixed venous oxygen saturation. *(Reprinted from Denault A, Deschamps A, Murkin JM. A proposed algorithm for the intraoperative use of cerebral near-infrared spectroscopy.* Semin Cardiothorac Vasc Anesth. *2007;11:274–281.)*

predict perioperative neurologic sequelae, supporting its use as a non-invasive trend monitor of cerebral oxygenation.[334]

In adult patients, cerebral malperfusion can occur either as a consequence of ascending aortic dissection with occlusion of carotid lumen, kinking or obstruction of perfusion cannula during selective cerebral perfusion for circulatory arrest procedures, or migration of aortic endoclamp cannula during minimal-access cardiac surgery with potential compromise of cerebral perfusion.[335–337] Reports are increasing that bilateral rSo_2 monitoring can detect contralateral desaturation during unilateral selective cerebral perfusion. This can result from an incomplete circle of Willis, which, in some series, has a prevalence rate of up to 50% and has been estimated to be a factor in cerebral malperfusion in approximately 15% of patients.[338,339] In a more recent case report, cerebral rSo_2 monitoring was used during selective cerebral perfusion in the absence of systemic CPB during repair of traumatic aortic arch rupture and detected both episodes of cerebral malperfusion and, most critically, acute thrombosis of carotid artery graft leading to thrombectomy and restoration of flow.[340] In addition, a number of cases of aortic arch surgery have been reported in which cerebral oximetry has detected cerebral hypoperfusion caused by various factors, including diminished Blalock-Taussig shunt flow after pediatric cardiac surgery.[341]

Pharmacologic Cerebral Protection

Whereas multiple advances toward understanding the basic mechanisms of brain injury have led to the development of multiple pharmacologic strategies for neuroprotection, in general, pharmacologic protection from cerebral ischemia remains an elusive goal. Based on sound experimental evidence, including data from animal studies, a number of putative neuroprotective agents have been examined in cardiac surgical patients, but the results have been mostly negative.[342] Agents tested have included those that reduce brain oxygen consumption to increase tolerance to ischemia (thiopental and propofol) and

those that target established neuroprotective pathways, including the *N*-methyl-D-aspartate (NMDA) receptor, calcium channels, oxidant stress, the GABA receptor, and others. Post hoc analyses of several trials have suggested encouraging neuroprotective effects from remacemide and complement-inhibiting agents.[342] However, for the most part, there are no widely accepted pharmacologic agents with proven efficacy to reduce the extent of brain injury associated with cardiac surgery.

Although there had been one clinical study in which a significant reduction in persistent neurologic defects after open-chamber cardiac surgery was reported after administration of high-dose thiopental, this was not confirmed in closed-chamber CABG procedures.[343,344] Other data have suggested that if there is any such thiopental-derived cerebroprotective effect, the mechanism may be caused by lower cerebral metabolic rate and lower CBF due to cerebral vasoconstriction, with a concomitant reduction in the delivery of emboli into the brain, rather than occurring primarily as a result of a decrease in $CMRO_2$.[345] However, a three-center study including 225 patients undergoing mitral or aortic valve surgery and randomized to high-dose propofol with induction of burst-suppression on electroencephalography or a sufentanil control group was unable to detect any significant differences in neurologic or neuropsychological outcomes between groups.[346] These investigators concluded that neither cerebral metabolic suppression nor reduction in CBF reliably provides neuroprotection in open-chamber cardiac surgery.

Another interesting association existed between β-blocker and lowered incidences of stroke and adverse CNS events. In 2002, Amory and associates reported a retrospective review of 2575 CABG patients in which patients who had received perioperative β-blockers had a significantly lower incidence of severe neurologic outcomes versus those who did not, demonstrating a 1.9% incidence of stroke and coma versus 4.3%, and an incidence of any postoperative neurologic complication of 3.9% versus 8.2%, respectively.[347] However, concerns regarding perioperative β-blocker therapy have been raised by the results of the PeriOperative ISchemic Evaluation (POISE) trial in which 8351 patients with, or at risk for, atherosclerotic disease who were undergoing noncardiac surgery were randomized to receive extended-release metoprolol ($n = 4174$) or placebo ($n = 4177$).[348] Although significantly fewer patients in the metoprolol group than in the placebo group had a myocardial infarction, there were more deaths in the metoprolol group than in the placebo group (3.1% vs 2.3%; HR, 1.3%), more patients in the metoprolol group than in the placebo group had a stroke (1.0% vs 0.5%; HR, 2.2), and more patients died from fatal stroke (11% vs 5% of all deaths).[348] This new finding is consistent with data on increased stroke risk in patients with hypertension treated with β-blockers.[349] One explanation might be found in the nonselective β-blocking properties of metoprolol, inhibiting the β_2-induced cerebral vasodilation. A retrospective propensity matched cohort indeed found evidence for less incidence of postoperative strokes in patients on bisoprolol, as compared to those given metoprolol or atenolol.[350] In conclusion, initiating new β-blocker therapy in the preoperative setting could be unsafe and should be avoided, as should withdrawal before surgery, and if used, perhaps β_1 selective agents should be preferred over nonselective agents.

As a broad-spectrum antiinflammatory agent, the serine protease inhibitor aprotinin has been shown to positively impact coagulation and inflammatory alterations triggered by CPB and has also been associated with decreased incidences of stroke and major CNS injury in cardiac surgical patients.[351–353] However, because the clinical usage of aprotinin has been suspended indefinitely because of several reports of increased mortality and adverse events associated with aprotinin therapy in cardiac surgical patients,[354–356] the future of this drug remains controversial.[357,358]

There are some other interesting associations between certain drug therapies having antiinflammatory and antiplatelet properties and lowered incidences of stroke and adverse CNS events. In a prospective study of 5065 patients undergoing CABG conducted at 70 centers in 17 countries, the relation between early aspirin use and fatal and nonfatal outcomes was investigated.[359] Among patients who received aspirin within 48 hours after revascularization, subsequent mortality rate was 1.3% compared with 4% ($P < .001$) among those who did not receive aspirin, and aspirin therapy was also associated with a 48% reduction in the incidence of myocardial infarction (2.8% vs 5.4%; $P < .001$), a 50% reduction in the incidence of stroke (1.3% vs 2.6%; $P = .01$), a 74% reduction in the incidence of renal failure (0.9% vs 3.4%; $P < .001$), and a 62% reduction in the incidence of bowel infarction (0.3% vs 0.8%; $P = .01$). These findings are strongly supportive of perioperative aspirin therapy and suggest that platelets have a fundamental role in orchestrating the ischemic response to reperfusion injury of multiple organ systems in patients undergoing cardiac surgery.

Another promising line of investigation for cerebral protection is the role for 3-hydroxy-3-methyl-glutaryl coenzyme–A (HMG CoA) reductase inhibitors (eg, statins).With evidence accruing that statins not only have a lowering effect on LDL cholesterol but also present pleiotropic and neuroprotective effects, evidence for stroke reduction is accumulating. Currently statins are thought to possess antiatherosclerotic properties, increase plaque stability, and exert favorable effects on inflammation, vasomotor function, local fibrinolysis, and platelet activity.[360–363] A prospective single-center study to determine predictive factors for postoperative stroke in 810 CABG patients found that preoperative statins were cerebroprotective (OR, 0.24; 95% CI, 0.07–0.78).[364] A small trial combining high-dose statins with high-dose angiotensin-converting enzyme inhibitors compared with standard dosing found an intraoperative reduction in proinflammatory mediators and normalization of postoperative myocardial scintigraphic ischemia scores in comparison with preoperative scores.[365] However, a single-center retrospective cohort study of 5121 CABG patients compared incidences of stroke, diagnosed by neurologists, and encephalopathy, defined as seizures, decreased level of arousal, delirium, or mental state change after 24 hours after CABG until hospital discharge. They could not reproduce these results and found no difference in stroke/encephalopathy between statin users and nonusers (propensity adjusted OR, 0.96; 95% CI, 0.78–1.17).[366] Perhaps, there is a strong dose-effect relationship that needs further elucidation.

Another plausible mechanism for statin-induced neuroprotection could be the prevention of POAF, possibly inflammation induced, leading to less postoperative stroke. A best evidence–based report reviewed 445 papers of which 12 represented best evidence,[367] and among which was a systematic review including 91,491 patients.[368] The reviewers found that preoperative statin therapy in patients undergoing elective cardiac surgery is associated with (1) lower incidence and risk of developing POAF, (2) reduced stroke rate, (3) shorter hospital stay, and (4) reduced levels of inflammatory markers postoperatively. However, again, the optimal duration, dose, and type of statin could not be concluded from this review.[367] Another recent study performed a post hoc analysis of 1509 patients with mild to moderate aortic stenosis randomized to receive simvastatin and ezetimibe versus placebo. These researchers found that the combined statin therapy did not lower the risk of stroke before or after AVR (429 patients).[369] However, it is likely that the mechanism for perioperative stroke in AVR is different from that of CABG-induced stroke. Taken together, these studies seem to indicate that therapies associated with decreased platelet functionality and lowered inflammatory and sympathetic responses appear to be associated with decreased incidence of stroke and adverse CNS events.

A large multicenter trial on the intraoperative use of dexamethasone in 4494 cardiac surgical patients found no difference in the incidence of postoperative stroke (dexamethasone 1.3% vs placebo 1.4%).[370] A preplanned substudy of this trial followed 291 patients for postoperative cognitive decline. A 1-month POCD incidence of 13.6% in the dexamethasone group versus 7.2% in the placebo group was reported. At 12 months the incidence had declined to 7.0% versus 3.5%.[371] Another substudy on the incidence and duration of delirium in the first 4 days after surgery did not demonstrate a difference

between dexamethasone (14.2%) and placebo (14.7%).[372] Therefore, blunt systemic inhibition of inflammation does not seem to provide protection of the brain in cardiac surgery.

Several preliminary studies had suggested that intraoperative administration of lidocaine infusion during cardiac surgery was associated with a decreased incidence of postoperative cognitive dysfunction.[73,373] However, in prospective randomized trials this was not demonstrated.[374,375] In view of these divergent results, whether lidocaine infusion will have any further role as a cerebroprotectant remains uncertain.[376] Recently, Mathew and colleagues reported on the effects of magnesium infusion on postoperative neurocognitive decline in a RCT of 389 patients undergoing cardiac surgery and found no difference between intraoperative magnesium versus placebo at 6 weeks after surgery.[377]

A large trial of perioperative nimodipine in valve replacement surgery had to be terminated prematurely after enrollment of only 150 of 400 patients because of a significant increase in major bleeding and an increased mortality in the 6-month follow-up period.[378] Also, there was no beneficial effect on the incidence of new neurologic deficits. A Cochrane review on calcium antagonists in ischemic stroke also failed to find a beneficial effect.[379]

More promising is the evidence on NMDA receptor antagonists. Since focal cerebral ischemia causes release of excitatory amino acid neurotransmitters, especially glutamate, this results in overstimulation of receptors and downstream pathways, leading to irreversible ischemic damage. A prospective trial on remacemide versus placebo given 4 days prior to surgery until 5 days after surgery resulted in less neurocognitive decline and better learning ability at 8 weeks after surgery.[380] A Cochrane review studied the effect of excitatory amino acid antagonist on patients with acute stroke but failed to find a difference between treatment and control groups and even found a trend toward increased mortality with certain NMDA receptor antagonists.[381] Therefore, it seems too early to draw any firm conclusions.

Piracetam, a nootropic compound that modulates cerebral functions by directly enhancing cognitive processes, has also been subjected to three small trials in cardiac surgery. Although end points were different, they all found a beneficial effect of piracetam infusions (short-term neuroprotective effect, less neurocognitive dysfunction at 6 weeks, less early neurocognitive decline).[382] Perhaps this could be one of few medications actually improving neurologic outcome, although larger trials are needed for confirmation.

Theoretically, volatile anesthetics and nonvolatile xenon possess neuroprotective effects as well. There is experimental evidence for increased perfusion of ischemic areas, decreased cerebral metabolism, inhibition of glutamate receptor activity and neurotransmitter activity, inhibition of ion channels thereby preventing pathologic calcium or sodium influx, reduction of injurious oxidative stress, maintenance of mitochondrial function, and inhibition of apoptosis.[383] However, apart from an abundance of animal data, clinical evidence is still scarce.[384] In cardiac surgery there is some evidence for better neurocognitive outcome or organ dysfunction (sevoflurane, desflurane, isoflurane, xenon),[385–388] but other studies failed to find such differences.[389] According to clinicaltrials.gov, more trials are currently investigating the neuroprotective effects of anesthetics, and it is hoped they will provide more insight in the coming years.

Although these results suggest that there is as yet no pharmacologic magic bullet that can be used to reduce neurologic injury in patients undergoing cardiac surgery, a combination of technical and pharmacologic measures is currently available that might positively affect the CNS outcomes of these patients.[390] In patients identified as being at risk for perioperative cerebral injury, preventive measures (as outlined in Box 40.4) should be instituted with organ-targeted management to guide the whole intraoperative and postoperative period. A multidisciplinary group of physicians, epidemiologists, and perfusionists set out to develop an evidence-based review of practice of CPB in adults, focusing on neurologic injury, glycemic control, hemodilution, and inflammatory response.[390] They summarized these measures as neurologic protection by means of:

- the use of alpha-stat pH management during moderate hypothermic CPB,
- avoidance of cerebral hyperthermia by limiting arterial line temperature to 37°C,
- avoidance of direct reinfusion of unprocessed cardiotomy suction blood by use of blood cell processing and secondary filtration,
- intraoperative TEE or epiaortic ultrasonographic EAS in all patients,
- use of arterial line filters to minimize embolic load,
- maintenance of euglycemia,
- reduction of CPB circuit area and use of biocompatible surface-modified circuits, and
- reduced hemodilution to avoid subsequent allogeneic blood transfusion.

Further recommendations would include monitoring cerebral venous outflow pressure via proximal jugular venous pressure, avoidance of hypotension, and the use of tepid rather than normothermic perfusion during CPB. As the age and incidence of comorbid disease in the cardiac surgical population continue to increase, the importance of these issues becomes ever more acute. In summary, primary prevention continues to be the only effective measure to decrease the incidence of cerebral injury in patients undergoing cardiac surgical procedures.

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41

Long-Term Complications and Management

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KEY POINTS

1. After undergoing cardiac surgical procedures, patients usually follow a fairly predictable postoperative course: the hemodynamic sequelae of cardiopulmonary bypass abate; the patient is weaned from mechanical ventilation and extubated; and within 24 hours, most patients are discharged from the intensive care unit (ICU).
2. After undergoing cardiac operations, a small percentage of patients have complicated courses and prolonged stays in the ICU.
3. Patients with extended stays in the ICU have a higher-than-average mortality rate because of noncardiac organ dysfunction.
4. Anesthesiologists and intensivists caring for patients who have prolonged stays in the ICU and who have complex medical issues must take into account all organ systems when determining the correct diagnosis and prescribing appropriate treatment.
5. Meticulous attention to detail and the application of recent evidence-based treatments will result in improved survival in patients who have extended stays in the ICU.

This chapter focuses on the long-term complications and management of patients after cardiac surgery in the intensive care unit (ICU) and includes a discussion of specific infections observed in patients after surgery, the management of acute renal failure, and the role of nutritional support in the critically ill. The chapter also covers complications after newer surgical procedures such as transcatheter aortic valve replacement (TAVR), other minimally, invasive hybrid procedures, and long-term complications of ventricular assist devices (VADs) and extracorporeal membrane oxygenation (ECMO). Finally, this chapter concludes with an overview of the numerous ethical dilemmas that this technology has created for patients, families, and clinicians.

Infections After Cardiac Surgery

Device-Related Infections

Cardiac-Implanted Electronic Devices

As the number of cardiac-implanted electronic devices (CIEDs; eg, pacemakers, cardioverter defibrillators, cardiac resynchronization therapy) is gradually increasing, their complications, such as infections, are also increasing. CIED-related infections can be difficult to diagnose since echocardiography is less accurate and blood cultures are less sensitive than in endocarditis. Most of the patients exhibit nonspecific symptoms, and fewer than 10% of the patients develop septic shock.[1]

The incidence of CIED-related infections varies among studies from between 0.5% and 2.2%, with a twofold to fivefold increase in incidence after a revision.[1] One large National Hospital Discharge Survey conducted in the United States reported that CIED-related infections increased out of proportion to the number of implanted devices, probably because of the preponderance of patients with organ dysfunction and diabetes mellitus receiving CIEDs in recent years.[2] One high-volume center in the United States reported a CIED-related infection incidence of 1%; the risk factors for infection were device replacement, prior lead dislodgment, and more complex devices.[3] A large national database from Taiwan, which included more than 40,000 patients who were followed over 14 years, revealed that the incidence of CIED-related infections was 2.45 per 1000 CEID years.[4] This large study reported that CIED-related infections were more common in young men and in patients requiring replacement of the device, with the caveat that high-volume centers had a lower incidence of infection.[4] The increased number of prior complex procedures and the lack of antibiotic prophylaxis were the most consistent reported risk factors in other studies.[1] The most common pathogens identified across different studies were staphylococci and other gram-positive bacteria (68%–93%). All-cause mortality associated with CIED-related infection varied between 0% and 35%.[1]

The management of suspected CIED-related infections, including the number and sequence of blood cultures and antibiotic therapy, should be guided by the clinical severity (Table 41.1). The treatment recommendations for definite CIED-related infections include early removal of the entire system (ie, all leads and generator) along with appropriate antibiotic therapy.[1]

Ventricular Assist Devices

Left ventricular assist device (LVAD) driveline-related infections occur with an incidence up to 20% and commonly develop more than 30 days after implantation.[5] Infections in patients with LVADs are associated with increased hospitalization, frequent need for re-operation, increased risk of stroke, and delay in heart transplantation.[6] Some authors report a trend toward decreased survival in patients with an LVAD who develop infections.[7]

A multicenter study that included patients who received HeartWare VADs in the ADVANCE Bridge-to-Transplant Trial and the Continuous Access Protocol reported that driveline exit site infections occurred in 16.9% of patients and sepsis occurred in 17.2% of patients, commonly more than 30 days after implantation.[8] Patients with LVAD infections had a larger body mass index and frequently had a history of diabetes mellitus.[8] *Staphylococcus aureus* was the most common organism identified in patients with an LVAD and with sepsis complications.[8] A large multicenter study conducted in the United States revealed that risk factors for postcardiac surgery infection included postoperative red blood cell units transfused, longer duration of surgery, and

TABLE 41.1 Management of Cardiac-Implanted Electronic Devices–Related Infection With Lead or Endocarditis Involvement

Evidence of Severe Sepsis	*NO Evidence of Severe Sepsis*
Initial actions: 1. Conduct blood cultures testing twice within 1 hour. 2. Start empirical intravenous antimicrobial therapy within 1 hour, after blood cultures are tested. 3. Obtain an urgent echocardiographic scan within 24 hours.	*Initial actions:* 1. Blood cultures testing three different times (more than 6 hours apart) 2. Obtain an echocardiographic scan. 3. Follow blood culture and echocardiographic results.
Positive blood cultures and/or echocardiographic evidence of vegetations: 1. Remove system, and repeat echocardiographic scan. 2. If native cardiac structures are involved, then conduct 4 weeks of empirical antimicrobial therapy. 3. Extracardiac focus is a 6-week course of antibiotic therapy. 4. If it is a lead only infection, then consider a short course (2 weeks) of antibiotic therapy.	*NO positive blood cultures and/or echocardiographic evidence of vegetations:* 1. Review diagnosis, and repeat echocardiographic scan and blood cultures as clinically indicated. 2. If generator pocket infection signs are present, then consider 10–14 days of antibiotic treatment after the removal of the system.

Adapted from Sandoe JA, Barlow G, Chambers JB, et al. Guidelines for the diagnosis, prevention and management of implantable cardiac electronic device infection. Report of a joint Working Party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, hot organization) British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE). *J Antimicrob Chemother.* 2015;70(2):325–359.

transplant or VAD implantation.[9] The management of LVAD driveline-related infections potentially require driveline repositioning or LVAD exchange with antibiotic bead implantation and systemic antibiotic treatment.[5]

Intravascular Devices

Intravascular devices such as arterial, central venous, or pulmonary artery catheters are universally used in patients after cardiac surgery. Patients who have intravascular catheters often acquire bloodstream infections (BSIs), which are associated with prolonged hospitalization and increased risk of mortality.[10,11] Central line–associated BSI (CLABSI) is defined by the Centers for Disease Control and Prevention (CDC) as bacteremia not related to an infection at another site or two or more positive blood cultures with a common skin contaminant associated with signs and symptoms of infection. CLABSIs are prevalent worldwide, and the rate is almost fourfold higher internationally (7.6 per 1000 central-line days) than the national rate in the United States (2 per 1000 central-line days).[11,12] The CDC reported a significant reduction of CLASBI incidence in ICUs in the United States in the recent years: a 58% reduction from 2001 to 2009.[11] The risk of a BSI for arterial catheters is lower than the risk associated with noncoated, uncuffed, nontunneled short-term central vascular catheters (1.7 vs 2.7 per 1000 catheter days).[13] If arterial catheters are inserted using maximum barrier precautions, then a very low risk of BSIs (0.41 per 1000 catheter days) can be achieved.[14]

The recognized risks factors for the development of CLABSIs were prolonged hospitalization before catheter insertion, femoral and internal jugular catheterization, longer catheterization duration, neutropenia, use of total parenteral nutrition, extensive catheter manipulation, and reduced nurse-to-patient ratio.[15] A summary report by the National Healthcare Safety Network revealed that the majority of CLABSI cases were caused by gram-positive organisms (60%), including coagulase-negative staphylococci (34%), the *Enterococcus* species (16%), and *Staphylococcus aureus* (10%); approximately 18% of the reported CLABSI cases were attributable to gram-negative organisms (18%) and to the *Candida* species (12%).[16]

The prominent reduction of the CLASBI rate with the implementation of various prevention initiatives has prompted the development of many quality improvement initiatives with the goal to achieve a minimum-to-none CLABSI incidence.[11] The CDC published guidelines for the prevention of catheter-related infections (CRIs) in 2011.[17] The summary of the guidelines is presented in Box 41.1.

BOX 41.1 PREVENTION OF INTRAVASCULAR CATHETER–RELATED INFECTIONS

Central Venous Catheter Infection Prevention

- Use the subclavian site if possible, and avoid using the femoral site.
- Use ultrasound, if available, to reduce the number of imaging attempts.
- Use the catheter with the minimum number of lumens necessary.
- Use strict hand hygiene, skin preparation with an antiseptic, and full barrier precaution for insertion.
- Maintain aseptic technique through the insertion and care of the catheter.
- Regularly monitor the catheter insertion site for signs of infection.
- Use 2% chlorhexidine for daily skin cleansing.
- Do not routinely replace the catheter to prevent infection.
- Do not use guidewire to exchange the catheter in case of suspected infection.
- Remove the catheter when it is no longer necessary.

Arterial Catheters Infection Prevention

- In adults, radial, brachial, and dorsalis pedis are preferred over axillary and femoral sites.
- Use a minimum of cap, mask sterile gloves for arterial catheter insertion, and full barrier precautions for the femoral site.
- Replace the arterial catheter only when clinically indicated.
- Remove the arterial catheter when no longer necessary.

Adapted from O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control.* 2011;39(4 Suppl 1):S1–S34.

Sternal Wound Infections

The CDC classifies this surgical site infection as superficial or deep. Based on the CDC definition of a deep sternal wound infection (DSWI), this surgical site infection occurs within 30 to 90 days after a surgical procedure. The incision is dehiscent or deliberately opened, an association exists with fever or localized pain and tenderness, or an abscess has formed. The DSWI is an uncommon but serious complication after cardiac surgery that is associated with unfavorable morbidity and increased mortality.[18,19]

A large retrospective study from a single institution in Canada that included more than 30,000 patients after cardiac surgery reported an incidence of DSWI of 0.77%.[19] The mortality of the patients with DSWI (6.9%) was significantly higher than the mortality of the patients without DSWI (2.8%). The researchers identified old age, diabetes, previous stroke and transient ischemic attacks, congestive heart failure, and bilateral internal mammary artery grafts for the coronary artery bypass graft (CABG) procedure as risk factors for DSWI after cardiac surgery. Mechanical ventilation duration and ICU and hospital lengths of stay were longer in patients diagnosed with DSWI as compared with patients without DSWI. *Staphylococcus aureus* and gram-positive bacteria were the most common pathogens. A large multicenter study conducted in the United States revealed an incidence of 0.56% of DSWI.[9] Another prospective study revealed a DSWI incidence of 0.47% after CABG surgery with an associated in-hospital mortality rate of 9.1%.[20] The risk factors for DSWI after CABG surgery were female gender, hypertension, and reexploration for bleeding. A study conducted in Japan that included more than 73,000 patients revealed an incidence of DSWI of 1.8% after cardiac surgery, with an

TABLE 41.2 Modified Duke Criteria for Diagnosing Infective Endocarditis

Major Criteria	*Minor Criteria*
1. Two positive blood cultures with typical microorganisms collected at least 12 hours apart (or one positive blood culture for *Coxiella burnetii*)	1. Fever >38°C 2. Vascular phenomena (systemic emboli, Janeway lesions) 3. Immunologic phenomena (Osler nodes, Roth spots)
2. Evidence of endocardial involvement (new murmur, echocardiographic evidence of a cardiac mass, abscess, valve dehiscence)	4. Predisposition to infective endocarditis (previous infective endocarditis or intravenous drug abuse) 5. Microbiologic evidence that does not meet major criteria

Adapted from Thanavaro KL, Nixon JV. Endocarditis 2014: an update. *Heart Lung.* 2014;43(4): 334–337.

incidence of 2.8% after combined valve and CABG surgery and 3.4% after combined CABG and thoracic aortic surgery.[21] Diabetes mellitus was found to be a significant risk factor for DSWI, and the diagnosis was associated with increased mortality, especially when it coincided with reexploration and bleeding.

Another study reported that the incidence of surgical site infection after cardiac surgery decreased from over 8% to less than 2% after routine implementation of nasal mupirocin and preoperative chlorhexidine showering.[22] The recommended treatment for DSWI is adequate systemic antibiotic therapy, along with either surgical débridement with antibiotic irrigation and primary closure or sternotomy with flap reconstruction.[18]

Prosthetic Valve Endocarditis

The diagnosis of endocarditis requires a high level of clinical suspicion, considering that the clinical presentation is frequently nonspecific with fever, chills, fatigue, or weight loss. The modified Duke criteria are the gold standard for the infective endocarditis (IE) diagnosis: two major, one major and three minor, or five minor clinical criteria are required (Table 41.2).[23] Prosthetic valve IE can occur early (less than 1 year after valve replacement) or late (more than 1 year after surgery). The risk of IE was found to be 1% to 4% early after surgery, and 0.5% to 1% per patient year of prosthetic valve later after surgery.[24,25] The prosthetic valve and CIED-associated IE incidences has increased in recent years.[26,27] The reported risk was similar for mitral or aortic valve replacement (AVR), regardless of the type of prosthesis; however, it was higher if more than one valve was replaced (de Gevigney, Pop, and Delahaye, 1995).[28] *Staphylococcus aureus* was reported to be the most common pathogen in prosthetic valve IE (34%), followed by the *Streptococcus* species (23%), the *Enterococcus* species (19%), and coagulase-negative *Staphylococcus* (18%).[27] The gram-negative bacilli HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species) accounted for 5% to 10% of cases of IE, and *Candida* species represented less than 1%.

Despite the low level of evidence regarding the benefit of antibiotic prophylaxis in the prevention of IE, the current recommendation remains that all patients with prosthetic valves receive antibiotic prophylaxis before dental or surgical procedures.[23] Because echocardiography can be inconclusive in cases of prosthetic endocarditis, new evidence has revealed that a positron emission tomography/computed tomography (PET/CT) scan might be a better option for prosthetic- and CIED-related endocarditis diagnoses.[29] Evidence also suggests that antibiotic treatment decreases the risk of stroke after IE.[30] Based upon current guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA), surgery is indicated in prosthetic valve–related IE, resulting in hemodynamic instability, heart failure, or valvular complications such as dysfunction or dehiscence, obstruction or regurgitation, and abscess or fistula formation, but it is not indicated in uncomplicated cases.[31] A review of 17 studies showed that surgery improves survival and is the treatment of choice for prosthetic valve–related IE, especially if caused by *Staphylococcus aureus*.[32] The authors of the review also suggested performing surgery for prosthetic valve–related IE treatment before the development of cerebral complications (Box 41.2).[27,31]

BOX 41.2 INDICATIONS FOR SURGERY IN PROSTHETIC VALVE INFECTIVE ENDOCARDITIS

- Surgery is indicated for aortic or mitral valve infective endocarditis (IE) complicated with severe regurgitation or obstruction or heart failure or hemodynamic instability.
- Surgery is also indicated for locally uncontrolled infection (eg, abscess, false aneurysm, fistula, enlarging vegetation).
- Surgery should be considered for persistent fever and positive blood cultures for longer than 7 to 10 days or infection caused by fungi or multiresistant organisms (*Serratia marcescens, Pseudomonas* species).
- Surgery is possibly indicated for IE with large vegetation (>10 mm) after one or more embolic episodes, despite appropriate antibiotic therapy or associated with complicated clinical course (eg, heart failure, persistent infection, abscess); or for IE with very large vegetation (>15 mm).
- Surgery is commonly indicated for IE caused by *Staphylococcus* species because the clinical course might be particularly severe with perivalvular abscess and valve dehiscence formation.

Systemic Inflammatory Response Syndrome and Sepsis

Systemic inflammatory response syndrome (SIRS) and sepsis are clinical entities initially defined at the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference in 1992,[33] and the definitions were updated in 2001 at the International Sepsis Definition Conference.[34] Box 41.3 summarizes the diagnostic criteria for sepsis as described in the International Guidelines for Management of Severe Sepsis and Septic Shock published in 2013.[35]

The number of sepsis cases reported in the United States exceeds 750,000 per year, of which 50% were treated in ICUs.[36] Up to 15 and 19 million new sepsis cases per year were estimated to develop worldwide each year.[37] Most studies have reported that sepsis mortality remained high over time, and septic shock accounted for the highest mortality approaching 50%.[38–40] Recent epidemiologic evidence showed improvement in outcomes with a 57% reduction in sepsis mortality from 1988 and 1989 to 2010 through 2012.[41] Although some studies conducted in the early 2000s revealed the preponderance of gram-positive bacteria in sepsis, the most recent European Prevalence of Infection in Intensive Care (EPIC II) study reported gram-negative organisms were isolated in 62%, gram-positive bacteria in 47%, and fungi in 19% of cases.[39,42]

Some authors report that infections are the most common noncardiac complication after cardiac surgery.[43,44] Sepsis accounted for 20% of the infection cases in a large multicenter study.[44] Hospital costs, lengths of stay, and readmissions were significantly associated with hospital-acquired infections after cardiac surgery. Another large prospective study revealed that nearly 5% of the patients were diagnosed with major infections (eg, DSWI, mediastinitis, infectious myocarditis or pericarditis, endocarditis, cardiac device infection, pneumonia, empyema, *Clostridium difficile* colitis, BSI) after cardiac surgery.[43] The risk factors associated with increased infections were chronic lung disease, heart failure, long surgery, emergent surgery, prolonged mechanical ventilation, and postoperative antibiotic administration for longer than 48 hours.[43] Major infections significantly increased the mortality rate after cardiac surgery.

Considering the high mortality and morbidity risk of sepsis, a group of experts representing numerous international organizations

BOX 41.3 DIAGNOSTIC CRITERIA FOR SEPSIS

Infection Documented or Suspected With Some of the Following Criteria

General Variables
Fever
Hypothermia
Tachycardia
Tachypnea
Altered mental status
Positive fluid balance
Hyperglycemia in the absence of diabetes

Inflammatory Variables
Leukocytosis
Leucopenia
Greater than 10% immature leucocytes
Increased plasma C-reactive protein
Increase plasma procalcitonin

Hemodynamic Variables
Arterial hypotension

Organ Dysfunction Variables
Hypoxemia
Oliguria
Creatinine increase
Coagulation abnormalities
Ileus
Hyperbilirubinemia

Tissue Perfusion Variables
Increased lactic acid
Decreased capillary refill

Adapted from Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. *Crit Care Med.* 2013;41(2):580–637.

BOX 41.4 SUMMARY OF THE SURVIVING SEPSIS CAMPAIGN GUIDELINES

- Routine screening of patients who are potentially infected and seriously ill is recommended for severe sepsis.
- Protocolized resuscitation of patients with hypoperfusion should be initiated during the first 6 hours of recognizing septic shock.
- Effective intravenous antimicrobials should be administrated within the first hour of recognizing severe sepsis or septic shock, ideally after culture collection.
- Crystalloids should be the initial fluid of choice in the resuscitation of severe sepsis and septic shock. Albumin may be added when substantial amount of crystalloids are needed.
- Norepinephrine should be the first vasopressor of choice. Epinephrine may be added when an additional agent is needed.
- Hydrocortisone is not indicated if fluid therapy and vasopressor restores hemodynamic stability. If hemodynamic stability is not achievable, then 200 mg daily hydrocortisone might be beneficial.
- Empiric antibiotic combination therapy should not be administered for more than 3 to 5 days. De-escalation to the appropriate single therapy should be performed when available.
- The typical antibiotic therapy duration should be 7 to 10 days.
- Glucose management in the ICU to maintain glycemia <180 mg/dL is indicated.
- Transfusion is indicated only for hemoglobin levels less than 7 g/dL (with a goal range of 7–9 g/dL) unless severe hypoxemia, myocardial ischemia, coronary artery disease, or acute hemorrhage is present.

Adapted from Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. *Crit Care Med.* 2013;41(2):580–637.

launched the Surviving Sepsis Campaign (SSC) and published guidelines in 2003, which were updated in 2012.[35] Emerging evidence regarding sepsis management and some of the SSC guidelines have been continually challenged since their publication in 2012. A large multicenter study comparing the protocol-based early septic shock therapy with the standard of care revealed no difference in mortality.[45] Of note, the mortality in all arms ranged from 18% to 21%, substantially lower than historically reported and probably related to the overall improvement of sepsis care.[46] A recent multicenter open-label trial readdressed the question of crystalloid versus albumin use in the treatment of severe sepsis and found no difference in mortality.[47] The SSC guidelines are outlined in Box 41.4.

Pneumonia

Pneumonia is a difficult diagnosis to make in patients after cardiac surgery because the typical radiographic signs might be confused with postsurgical changes. A study that evaluated autopsy-proven pneumonia in patients who were mechanically ventilated concluded that no single radiographic sign with diagnostic accuracy greater than 68% was recognized.[48] The clinical pulmonary infections score (CPIS) is based on six clinical signs, each worth between 0 and 2 points (Table 41.3).[49] A CPIS greater than or equal to 6 was the threshold that accurately identified the patients with pneumonia in one study,[49] but other authors challenged CPIS specificity.[50] The National Nosocomial Infection Surveillance (NNIS) system was developed in the 1970s by the CDC to provide definitions suitable for interhospital comparison.[51] The NNIS system's definition of pneumonia comprises physiologic, radiologic, and laboratory data including quantitative bronchoalveolar lavage (>10^4 colony-forming units per milliliter [CFU/mL]) and protective specimen brushing (>10^3 CFU/mL). A systematic review of 159

TABLE 41.3 Clinical Pulmonary Infection Score

Criterion	*0*	*1*	*2*
Tracheal secretions	None	Not purulent	Purulent and abundant
X-ray infiltrates (*CHEST Journal: American College of Chest Physicians*)	None	diffuse	Localized
Temperature (°C)	≥36.5 or ≤38.4	≥38.5 or ≤38.9	≥39 or ≤36
Leukocytes	≥4000 and ≤11,000	<4000 or >11,000	<4000 or >11000 + immature neutrophils >50% or >500
PaO_2/FIO_2	>240 or ARDS		≤240, no ARDS
Microbiology	Negative		Positive

ARDS, Acute respiratory distress syndrome; FIO_2, fraction in inspired oxygen; PaO_2, arterial partial pressure of oxygen.

Adapted from Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis.* 1991;143(5 Pt 1):1121–1129.

articles concluded that the bacteriologic criteria did not improve the accuracy of the diagnosis of ventilator-associated pneumonia (VAP), as compared with the clinical assessment.[52]

Pneumonia is an important complication after cardiac surgery. A multicenter study revealed that pneumonia represented 48% of hospital-acquired infections in patients who underwent cardiac surgery.[44] Another large study reported an incidence of 2.38% among patients who underwent cardiac surgery.[43] A large European study revealed that the history of chronic obstructive lung disease was significantly

associated with respiratory infection after cardiac surgery.[53] One study reported that pneumonia was the most common infection in patients who required blood transfusions after cardiac surgery.[9]

Approximately 5.5% of patients require prolonged mechanical ventilation after cardiac surgery.[54] Considering the increased mortality and health care costs related to VAP, the Institute for Healthcare Improvement (IHI) recommends the use of a five-component ventilator bundle, which has been associated with a lower incidence of VAP: (1) head of the bed elevation, (2) daily sedation interruption and spontaneous breathing trials, (3) peptic ulcer disease prophylaxis, (4) deep vein thrombosis (DVT) prophylaxis, and (5) daily oral care with chlorhexidine. A single-center study revealed that the implementation of four preventative measures (some of the IHI recommended bundle along with subglottic secretion aspiration) was associated with a decreased incidence of VAP in patients after cardiac surgery.[55] A systematic review concluded that no evidence supports the contention that quantitative cultures of respiratory secretions improved outcomes when compared with qualitative cultures in patients with hospital-acquired pneumonia.[56] Another systematic review of eight studies that included 1703 patients concluded that a short course (7 or 8 days) of antibiotic treatment might be more appropriate than a prolonged course for VAP treatment not attributable to nonfermenting gram-negative bacilli.[57]

Urinary Tract Infection

Urinary tract infection (UTI) is one of the most common hospital-acquired infections and accounts for 4.4% of infections after cardiac surgery.[53,57] Diabetes mellitus and advanced age are associated with increased incidences of UTI in patients after cardiac surgery. Bacteriuria rapidly develops in patients with a urinary catheter, with an average of 3% to 10% per day of catheterization.[58] The incidence of UTI diagnosed in ICUs in a large single-center study was 9%, out of which only 0.4% developed UTI-associated bacteremia or fungemia.[57] Bacteriuria is frequently asymptomatic (approximately 90% of the cases), and therefore the diagnosis of UTI is primarily clinical.[58,59] Traditional diagnostic criteria for UTI include the presence of pyuria and great than 10^5 CFU/mL urine. UTI treatment is not indicated unless laboratory data are associated with clinical signs and symptoms of infection (eg, temperature >38°C, urgency, frequency, dysuria, suprapubic tenderness). Because 80% of UTIs are attributable to the presence of an indwelling catheter, the removal of unnecessary catheters is recommended (Nicolle, 2008).[60]

Clostridium difficile Colitis

Clostridium difficile is a gram-positive, spore-forming, anaerobic rod rarely found in healthy adults (5%–15%). Colonization with *Clostridium difficile* can occur after treatment with any antibiotic and is due to alteration of normal flora. The spread is via the fecal oral route.[61,62] The spectrum of *Clostridium difficile* infection is wide: from antibiotic-associated diarrhea to antibiotic-associated colitis or antibiotic-associated pseudomembranous colitis.[63] The clinical presentation varies from low-grade fever, leukocytosis, and watery diarrhea (10 to 15 bowel movements per day) to toxic megacolon.

The risk factors associated with *Clostridium difficile* infection are prolonged antibiotic treatment, the use of proton pump inhibitors, older age, severe underlying disease, immunosuppression, or inflammatory bowel disease.[64,65] A hypervirulent *Clostridium difficile* strain that produces high levels of toxins has been associated with very severe disease outbreaks in several hospitals in North America and Europe.[66] A large, multicenter, observational study revealed that *Clostridium difficile* infection accounted for 18% of the hospital-acquired infections after cardiac surgery.[44]

The diagnosis of *Clostridium difficile* colitis is suggested by the presence of fecal leukocytes, signs of SIRS, and persistent diarrhea, despite a discontinuation of enteral feeding with carbohydrates that might cause watery diarrhea. The enzyme immunoassay tests for toxins A and B were widely used in the past but have relatively poor sensitivity and specificity.[65] The most sensitive and specific tests for *Clostridium difficile* are nucleic acid amplification tests; for instance, the polymerase chain reaction (PCR) test detects the toxins genes, but even this test might give false-negative results.[65,67]

The treatment of *Clostridium difficile* colitis is based on its severity. For mild-to-moderate disease, metronidazole, 500 mg, taken daily three times orally for 10 days is recommended, whereas for severe disease, vancomycin, 125 mg, administered daily four times orally for 10 days is recommended.[65,68] Vancomycin orally plus metronidazole intravenously is recommended for severe and complicated disease. Vancomycin enema might be a useful alternative or an additional treatment, especially in patients with ileus or toxic megacolon. Surgical treatment should be considered in severe and complicated *Clostridium difficile* colitis with septic shock and severe sepsis.[68] For recurrent *Clostridium difficile* infection, fecal microbiota transplant might be considered as an alternative for a pulsed, prolonged vancomycin regimen.[65,68] Health care personnel and visitors entering the room of any patient with known or suspected *Clostridium difficile* infection should use hand hygiene and barrier precautions.

Acute Kidney Injury

Acute kidney injury (AKI) is a frequent and potentially devastating complication after cardiac surgery. When severe, dialysis may be necessary. Risk factors are multiple, and the etiology and pathogenesis is complex and only incompletely understood. Multiple preventative strategies have been tried. Unfortunately, the benefit is unclear, especially pharmacologic prevention. After the onset of AKI, multiple therapeutic interventions also have been tried, and these, too, have been mostly unsuccessful. The purpose of this section is to describe briefly the incidence of and risk factors for the development of AKI, as well as the pathophysiologic mechanisms underlying this complication. Additionally, preventative strategies and potential treatments of AKI and the decision-making process concerning dialysis initiation are reviewed.

Incidence of and Risk Factors for Cardiac Surgery–Associated Acute Kidney Injury

The incidence of cardiac surgery–associated AKI (CSA-AKI) is difficult to delineate, because it changes with the definition of AKI and differs for different surgical procedures. The consequences of CSA-AKI are severe. Mortality after routine CABG surgery can increase from less than 1% to 20% when moderate AKI develops. If dialysis is required, then mortality can exceed 50%. Additionally, costs dramatically increase.[69,70] Over the past several years, attempts have been made to standardize the definition of AKI, starting with the introduction of the Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Renal Disease (RIFLE) criteria in 2004.[71] The RIFLE criteria scored acute renal dysfunction according to increases in creatinine (Cr) concentration, decreases in glomerular filtration rate (GFR), or oliguria over the course of 7 days or less. Loss and failure were defined, based on the required length of renal replacement therapy (RRT) (Tables 41.4 through 41.6 compare various criteria.) Three years later the Acute Kidney Injury Network (AKIN) refined the RIFLE criteria by removing the loss of kidney function, the end-stage renal disease criteria, and the GFR criteria, and then adding the initiation of RRT to the definition of stage 3 AKI.[72] In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) criteria were published, which are similar to the AKIN criteria.[73] The incidence of CSA-AKI can vary from approximately 9% to 40%, depending on the definition used and the procedure performed. Although more carefully defining AKI is an enormous advance, Cr-based criteria are problematic. Cr typically rises approximately 48 hours after the inciting injury, cardiopulmonary bypass (CPB) prime dilution may falsely lower Cr levels, and urine output criteria can be unreliable (Gaffney and Sladen, 2015).[74] Novel biomarkers (see the following text under "Biomarkers") may help with an earlier diagnosis.

TABLE 41.4 RIFLE Criteria

	Glomerular Filtration Rate Criteria	*Urine Output Criteria*
Risk	1.5 × increase in baseline Cr or GFR decrease by 25%	UO <0.5 cc/kg/hr × 6 hours
Injury	2 × increase in baseline Cr or GFR decrease by 50%	UO <0.5 cc/kg/hr × 12 hours
Failure	3 × increase in baseline Cr or Cr >4 or GFR decrease by 75%	UO <0.3 cc/kg/hr × 24 hours or anuria
Loss	Persistent ARF: Complete loss of renal function >4 weeks	
ESRD	End-stage renal disease	

RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; *GFR,* glomerular filtration rate; *Cr,* creatinine; *UO,* urine output; *ARF,* acute renal failure; *ESRD,* end-stage renal disease.

Adpated from Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204–R212.

TABLE 41.5 Acute Kidney Injury Network Criteria

AKI Stage	*Serum Creatinine Criteria*	*Urine Output Criteria*
1	Absolute increase >0.3 mg/dL or Cr 1.5 × baseline	<0.5 cc/kg/hr × 6 hours
2	Cr 2–3 × baseline	<0.5 cc/kg/hr × >12 hours
3	3 × baseline Cr or value >4 mg/dL with absolute increase >0.5 mg/dL or receiving renal replacement therapy	<0.3 cc/kg/hr or anuria × 12 hours

AKI, Acute kidney injury; *Cr,* creatinine.

Adapted from Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2): R31.

TABLE 41.6 Kidney Disease Improving Global Outcomes Criteria

Stage	*Serum Creatinine (Cr)*	*Urine Output*
1	1.5–1.9 × baseline Cr or >0.3 mg/dL increase	<0.5 cc/kg/hr × 6 hours
2	2–2.9 × baseline Cr	<0.5 cc/kg/hr × 12 hours
3	3 × baseline Cr or Cr >4 mg/dL or initiation of RRT	<0.3 cc/kg/hr × 24 hours or anuria >12 hours

RRT, Renal replacement therapy.

From http://kdigo.org/home/guidelines/acute-kidney-injury/

Patient risk factors are well studied. They include advanced age, female gender, chronic obstructive pulmonary disease (COPD), diabetes, peripheral vascular disease, congestive heart failure (CHF), baseline renal insufficiency, cardiogenic shock, need for emergent surgery, and left main coronary artery disease. Procedural risk factors include CPB time, aortic cross-clamp time, transfusion requirements, valvular surgery, combined procedures, and on-pump versus off-pump procedures.[69,75,76]

Biomarkers

The search for early biomarkers of CSA-AKI is intense because of the problems associated with traditional clinical criteria. Multiple biomarkers have been studied and show promise. The most frequently studied are neutrophil gelatinase–associated lipocalin (NGAL) and plasma cystatin C levels. NGAL is derived from tubular epithelial cells, and gene expression is upregulated early in the course of AKI.[74] The utility of NGAL as an early biomarker for CSA-AKI has been confirmed in multiple studies. A systematic review performed by Haase-Fielitz and associates[77] confirmed quite good receiver-operating characteristics, with an area under the curve of >0.8.

Plasma cystatin C levels quickly increase after a decrease in GFR, and these levels are potentially a useful biomarker of CSA-AKI. Additionally, an elevated preoperative cystatin C level plus preoperative proteinuria are associated with multiple risk factors and the development of CSA-AKI.[74]

Etiology and Pathogenesis

Multiple perioperative insults lead to the development of CSA-AKI, and it is unlikely that one particular insult is the primary causative factor. Preoperative hemodynamic instability coupled with the administration of nephrotoxins, such as intravenous contrast dye, is an early insult. During CPB, blood loss and transfusion, atheroembolism, and further hemodynamic instability add further injury. After CPB, hemodynamic instability is not uncommon, and insults can continue if complications such as infections and sepsis occur. The renal medulla is exceptionally prone to hypoxemia and, even under normal conditions, has a very low tissue oxygen tension. The oxygen tension becomes virtually undetectable during CPB.[70] Additionally, CPB aggravates systemic inflammation, leading to cytokine-mediated renal injury.[69]

Prevention

Unfortunately, many of the risk factors for and injuries that cause CSA-AKI are not modifiable. Although some are, they are generally surgical in nature. Careful and timely surgery, with shorter CPB and cross clamp times, will lead to lower rates of renal injury. Less bleeding with fewer transfusions will also be renoprotective. The ACC/AHA Guidelines recommend potentially delaying surgery in patients with preexisting renal dysfunction until the effects of contrast can be assessed.[78]

Multiple pharmacologic agents have been studied. Some show promise, whereas others demonstrate futility. A metaanalysis of six small randomized controlled trials demonstrated some potential efficacy for fenoldopam, a selective dopamine$_1$–receptor agonist. Although the risk of AKI was lower, there was more hypotension and a greater need for a vasoactive medication was observed. The need for RRT, mortality, and length of stay were all unchanged.[79]

Natriuretic peptides show promise for potential pharmacologic renoprotection. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) create a favorable physiologic environment by decreasing renin-angiotensin-aldosterone system activation, which increases renal vasodilation, improves diuresis, and helps avoid or reduce the use of loop diuretic agents.[69] Two trials have shown efficacy for ANP infusions during cardiac surgery.[80,81]

Sodium bicarbonate has failed to show a renoprotective benefit. Two recent randomized controlled trials failed to show efficacy.[82,83] Turner and colleagues[83] randomized 120 patients to receive either a sodium chloride infusion or a sodium bicarbonate infusion starting before CPB and ending the day after surgery. The trial was stopped early after the first interim analysis showed no efficacy. A similar study was conducted by Haase and associates,[82] although the sample size was larger (350 patients). Not only did sodium bicarbonate provide no benefit, but mortality in the group that received sodium bicarbonate was significantly higher (6.3% vs 1.7%). Based on these data, bicarbonate cannot be recommended.

N-Acetylcysteine has been studied multiple times. The results are conflicting, but two metaanalyses failed to demonstrate efficacy.[84,85]

Treatment

Unfortunately, there is no treatment for CSA-AKI once it occurs. The best practice is to optimize hemodynamics, avoid nephrotoxins, and hope that renal function recovers. If renal function does not recover or if it worsens, then the patient may require dialysis. Standard indications for dialysis initiation are presented in Box 41.5.

Determining when renal replacement should be initiated is not always clear. Additionally, it is not precisely clear what determines *early* or *late* initiation, as the periods defining these terms greatly vary from study to study. Although the evidence is difficult to sort through and

BOX 41.5 INDICATIONS FOR RENAL REPLACEMENT THERAPY

Uremia
Hyperkalemia that cannot be medically managed
Significant volume overload unresponsive to diuretics
Severe metabolic acidosis
Removal of dialyzable toxins

Adapted from Liu Y, Davari-Farid S, Arora P, et al. Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth.* 2014;28(3):557–563.

remains an area of great controversy and ongoing research, it appears that initiating RRT *early* in the course of oliguric AKI not responsive to diuretic medications improves outcomes.[86]

RRT can be prescribed in two basic ways, continuous or intermittent. Each has its own advantages and disadvantages. Continuous therapy provides greater hemodynamic stability and the ability for more controlled and well-tolerated fluid removal, whereas intermittent treatment has the ability to clear blood of harmful electrolytes or toxins more quickly. No data are available that clearly demonstrates the superiority of one technique over the other. Continuous RRT can usually be changed to intermittent therapy after a period of relative hemodynamic stability and when the ability to manage volume status improves.

No evidence-based criteria exist for the cessation of RRT. Cessation depends on multiple criteria, such as the return of renal function and increased urine output, the ability to manage volume status without RRT, the risk outweighs the benefit, or potential medical futility in the moribund patient.[87]

Nutritional Support

Nutritional support is an increasingly important part of intensive care. To care for patients' nutritional needs appropriately, several questions must be answered. Who should receive nutritional support? What is their baseline nutritional status? When should nutrition start? What should be fed to them, and via which route should they be fed? How much should be fed to them, and how should that amount be determined? The questions are straightforward, as are some of the answers. However, some answers are complicated, and the literature is large and not always consistent. The purpose of this section is to briefly answer these questions and to provide information how best to provide nutritional care.

Who Should Receive Nutritional Support?

Which patient should receive nutritional support is intimately tied to his or her baseline nutritional status and illness severity, which is discussed more thoroughly in the text that follows. Both the American Society of Parenteral and Enteral Nutrition (ASPEN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend enteral nutritional support for all critically ill patients who cannot meet metabolic requirements on their own, although the level of evidence is not strong. The rationale is multifactorial (the level of recommendation is grade C in both guidelines).[88,89] Enteral nutrition maintains gut integrity and may help prevent the increased permeability associated with bacterial translocation and the potential development of multiorgan dysfunction syndrome.[90] The immune response is also modulated, decreasing the inflammatory response, and oxidative stress and insulin resistance are decreased.[91] Additionally, a nutritional deficit develops early in the course of critical illness and may be attenuated by early initiation of enteral support.[92,93]

Nutritional Assessment

Not all critically ill patients benefit to the same degree from nutritional support. Patients who are sicker with prior malnutrition and those expected to spend considerable time in the ICU will more likely benefit from early support than patients who are less sick with normal or mild nutritional derangements and who are expected to have a relatively short length of stay in the ICU.[91] Both the ASPEN and the ESPEN recommend a nutrition assessment for all patients who are hospitalized. Although the level of evidence is low (level E in the ASPEN Clinical Guidelines), the rationale is that malnutrition is frequently found and that patients who are malnourished have more complications, more infections, longer lengths of stay, and higher mortality.[88,94] Additionally, nutritional status rapidly declines in critically ill patients. Losses of body protein can be as high as 1 to 2 kg in 10 days.[92] Multiple nutritional assessment tools have been published, although many look only at nutritional status, and not disease severity, and have not been validated in the ICU.[95]

In contradistinction to many tools, the Nutrition Risk Screening (NRS) 2002 was developed to account for both baseline nutritional status and illness severity. The NRS 2002 was developed by an ESPEN working group. By analyzing data from multiple retrospective studies, they developed an assessment tool based on a relationship between clinical outcome and nutritional intervention, finding who benefitted from nutritional intervention. The tool was then validated against 128 controlled trials that demonstrated clinical benefit from nutritional intervention.[95] ESPEN now recommends nutritional assessment with the NRS 2002.[96] The score is determined by three components. First, baseline nutritional status is determined, and then, disease severity is ascertained. Both are scored from 0 to 3. The two scores are added together, and an extra point is added for age older than 70 years. If the total score is greater than 3, then the patient is at high nutritional risk, and an intervention should be developed (Table 41.7 demonstrates NRS 2002 scoring.)

Heyland and colleagues[97] developed the Nutrition Risk in the Critically Ill (NUTRIC) score specifically for patients in the ICU. They prospectively collected data about variables that measured the degree of malnutrition, illness severity, and markers of inflammation such as C-reactive protein. The addition of inflammatory markers was important. Critically ill patients are exceptionally stressed and catabolic. This state likely arises from the cytokine and hormonal milieu characteristic of critically ill patients.[98] A complex multivariable regression determined which variables were most important and developed a score based on those variables. The total score can be as high as 10; the higher the score, the greater the risk of 28 day mortality. Variables include age, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, baseline Sequential Organ Failure Assessment (SOFA) score, number of comorbidities, the number of days in the hospital before ICU admission, and interleukin 6 (IL-6) levels.[97] The NUTRIC score was internally well validated but may have limited use, as some its components (IL-6 level) are not routinely measured.

When Should Nutrition Be Initiated?

ASPEN, ESPEN, and the Canadian Critical Care Nutrition Guidelines all recommend that enteral nutrition should start within 24 hours of ICU admission. The recommendations were based on multiple clinical trials, during which the preponderance of evidence clearly suggested that overall nutrition was improved, ventilator-free days were increased, infection rate was lower, and the trend toward mortality was reduced. There were no differences in ICU lengths of stay.[89,96]

Although the reasons for initiating early enteral nutrition are well known, physicians have considered hemodynamic instability, which requires vasopressor support, a potential contraindication to early enteral nutrition because enteral nutrition increases the metabolic demand of the small intestine. An increase in splanchnic blood flow is required to meet this demand, and the demand may be greater than can be supplied by an unstable patient, causing bowel ischemia.

TABLE 41.7 Nutritional Risk Screening 2002 (ESPEN Guidelines)

Impaired Nutritional Status		*Severity of Disease (Approximate Increase in Requirements)*	
Mild Score 1	Weight loss >5% in 3 months or Food intake <50%–75% of normal requirement during the preceding week	Mild Score 1	Hip fracture Chronic illness, in particular, with acute complications, such as cirrhosis, COPD Chronic hemodialysis, diabetes, cancer
Moderate Score 2	Weight loss >5% in 2 months or BMI 18.5–20.5 + impaired general condition or Food intake 25%–50% of normal requirement during the preceding week	Moderate Score 2	Major abdominal surgery Stroke Severe pneumonia, hematologic malignancy
Severe Score 3	Weight loss >5% in 1 month (approximately >5% in 3 months) or BMI <18.5 + impaired general condition or Food intake 0%–25% of normal requirement during the preceding week	Severe Score 3	Head injury Bone marrow transplantation In intensive care unit (APACHE410)
Score: +		Score: = Total Score	

ESPEN, European Society for Clinical Nutrition and Metabolism, *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *APACHE,* Acute Physiologic Assessment and Chronic Health Evaluation.

From Kondrup J, Allison JP, Elia M, et al. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* 2003;22(4):415–421.

Additionally, even if splanchnic flow can increase, it may be at the expense of blood flow to other organs.[99,100] Khalid and associates[101] conducted an analysis of prospectively collected data from 1174 patients who were hemodynamically unstable and mechanically ventilated for longer than 2 days to test the alternate hypothesis that early enteral nutrition may improve outcome. Patients who received enteral nutrition within 48 hours had a lower ICU (22.5% vs 28%) and hospital (34% and 44%) mortality rate. The sickest patients appeared to benefit the most. Although uncontrolled, the analysis provided evidence that early enteral nutrition in patients who are hemodynamically unstable is safe and probably beneficial. The Canadian Critical Care Nutrition Guidelines noted this potential benefit in the sickest patients. The ASPEN guidelines, which recommended withholding enteral nutrition from patients who were hemodynamically unstable, were published in 2009, before the publication of the Khalid study in 2010. Until the updated ASPEN guidelines are published, it remains unknown whether the recommendation will change.

Via Which Route Should Nutritional Support Be Given?

ASPEN, ESPEN, and the Canadian Critical Care Nutrition Guidelines all state that the enteral route is the preferred course. Parenteral nutrition should be given to patients who will likely be unable to receive enteral nutrition for a considerable period.[91] Parenteral nutrition is disadvantageous; morbidity and mortality associated with parenteral nutrition is increased. The studies are problematic in that differences in the amount of energy delivered to the parenteral and enteral groups are significant.[102] Increased energy delivery may be harmful early in the course of critical illness (see the following text). Randomized prospective data are most useful, and three studies have been recently published. The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) study is the largest and demonstrated harm caused by the addition of early parenteral nutrition started on day 3, compared with late initiation on day 7.[103] Over 4000 patients were randomized. Patients in the early initiation group spent more time in the ICU, developed more new infections, spent more time on the ventilator, and had a longer duration of RRT if it was needed. Two other smaller randomized controlled trials by Heideggar and colleagues[104] and Doig and associates[105] did not show harm caused by the early use of parenteral nutrition; however, the net benefit was weak.

Gastrointestinal motility is compromised in critically ill patients, with up to 50% of patients displaying delayed gastric emptying.[106] Controversy exists as to whether the placement of a gastric or postpyloric feeding tube is superior. There are data that support the use of postpyloric feeding tubes, especially in relation to the ability to achieve nutritional goals and pneumonia rates.[107] However, postpyloric tube placement can be difficult to achieve. For these reasons, the Canadian Critical Care Nutrition Guidelines recommend placement of a postpyloric feeding tube for patients considered to be at high-risk for enteral nutrition intolerance, such as patients receiving vasoactive medications, continuous sedative medications, or neuromuscular blocking drugs, and patients with high gastric residual volumes.

What Should Nutritional Support Consist Of?

Multiple enteral formulas are available and are considered to be medical foods by the US Food and Drug Administration (FDA). As such, they are not as tightly regulated as pharmaceutical agents and are designed to meet the micronutrient and macronutrient requirements of patients.[108] The formulas may be subdivided in myriad ways, based on the macronutrient content (polymeric vs elemental or semielemental), caloric concentration, protein and electrolyte concentration, and fat content, among other factors. Choosing which formula to use depends on the patient and what is available at particular institutions.

Standard polymeric formulas are most common. They contain nonhydrolyzed carbohydrate, protein, and fat. They also contain the recommended dietary allowance (RDA) of most vitamins and minerals. Their concentration varies between 1 and 2 kcal/mL. Higher concentration formulas tend to be used when fluid restriction is important.[108] Renal formulas are similar to standard formulas but tend to contain less protein, potassium, and phosphorus. Renal formulas also are more concentrated, usually 1.5 to 2 kcal/mL. Critically ill patients requiring dialysis, especially continuous RRT, will need protein supplementation.

Fiber is frequently added to formulas, especially to prevent or treat diarrhea. The type of fiber can vary (soluble or insoluble), and the amount contained in commercial products is significantly less than the RDA for those with normal gut function. To meet the RDA, supplemental fiber needs to be added. The ASPEN guidelines make several specific recommendations regarding fiber. The guidelines recommend using soluble fiber in fully resuscitated critically ill patients with diarrhea, never using insoluble fiber in critically ill patients, and not using fiber in patients at risk for bowel ischemia.[89] The Canadian recommendations significantly differ. They concluded that available data are insufficient to make any recommendations regarding the use of fiber and specifically state that the effect of fiber on diarrhea is negligible.

Pulmonary formulas were developed with two thoughts in mind. First, having a high fat-to-carbohydrate ratio would lower the respiratory quotient (RQ) and thereby decrease carbon dioxide (CO_2) production. Second, an immunomodularity effect created by the use of fish oil–derived omega-3 fatty acids and alpha-linolenic acid, instead of the omega-6 fatty acids used in standard formulas, could theoretically

reduce the production of arachidonic metabolites. The reduction in arachidonic metabolites would then reduce the damaging inflammatory milieu observed in patients with acute respiratory distress syndrome (ARDS). The data concerning the maximum volume of oxygen (V_{O_2}), CO_2 production, and RQ are mixed. Early reports demonstrated benefit. Later reports seem to show that the improvements in these parameters were more likely related to the prevention of overfeeding.[108]

Using fish oil–derived omega-3 fatty acids and alpha-linolenic acid deserves special attention. Based on three studies, the ASPEN guidelines made a grade A recommendation that patients with ARDS should receive formulas characterized by "[A]n anti-inflammatory lipid profile."[89,109–111] The 2009 Canadian Guidelines made similar recommendations. In 2011, two studies were published that considerably changed things. The Omega trial was designed to test the hypothesis that antiinflammatory nutrition would be beneficial for patients suffering from acute lung injury (ALI) or ARDS.[112] A total of 272 patients were randomized; 143 patients received omega-3 supplementation, whereas 129 patients received an isocaloric control supplement. Ventilator-free days were the primary endpoint. After the first interim analysis, the data safety monitoring board stopped the study for futility. The patients receiving omega-3 supplementation did worse than the control patients. They had fewer ventilator-free days, ICU-free days, and nonpulmonary organ–free days, and the trend toward mortality increased. Grau-Carmona and associates[113] published a similar study, although the primary endpoint was new organ dysfunction. Secondary outcomes were mortality, nosocomial infections, ventilator-free days, and ICU lengths of stay. A total of 160 patients were randomized, and 132 were studied. No differences in any outcome variable were observed, except for ICU lengths of stay, which were slightly shorter in the antiinflammatory group (16 vs 18 days). Because of these findings, the Canadian Clinical Practice Guidelines downgraded their recommendation from recommend to should be considered.[114]

Other immunomodulatory additives have been tested, the most important of which is glutamine. Glutamine is a glutathione precursor and is potentially involved in decreasing oxidative stress. It is also potentially and relatively depleted in critically ill patients, and low plasma glutamine levels are associated with increased mortality rate.[115] The Reducing Deaths Due to Oxidative Stress (REDOXS) Study was designed to test the hypothesis that glutamine and antioxidant supplementation would decrease mortality in critically ill patients.[116] The study had a 2×2 randomized factorial design. A total of 1223 patients were randomized, 302 were assigned to the placebo group, 303 were assigned to receive glutamine, 308 were to receive antioxidants, and 310 were to receive glutamine plus antioxidants; 28-day mortality was the primary endpoint. Mortality was higher in patients who received glutamine. This study had methodologic problems involving randomization, as well as the large doses of glutamine given, which led to an unbalanced amino acid profile.[104] However, the results of the MetaPlus Study corroborate the findings of REDOXS Study.[117] The MetaPlus Study was a randomized, double-blinded, multicenter trial comparing the efficacy of high protein enteral nutrition with high protein enteral nutrition plus glutamine, omega-3 fatty acid, and antioxidants. The primary endpoint was the incidence of new infections. No differences were observed in the primary endpoint. Of note, however, medical patients receiving supplementation had a higher 6-month mortality rate (54% vs 35%). Subgroup analysis is hypothesis generating at best, but the possibility of considerable harm makes the results worrisome. The 2013 Canadian guidelines strongly recommended that glutamine not be used in critically ill patients with shock and multiorgan failure.[114]

How Much Should Patients Be Fed, and How Is This Determined?

Resting energy expenditure is difficult to estimate in critically ill patients. Equations, such as the Harris-Benedict equation, are frequently used. Alternatively, clinicians can provide approximately 20 to 30 kcal/kg/day, and protein delivery should be between 1.5 and 2 g/kg/day. However, these estimations do not agree with measurements of energy expenditure, such as those made by indirect calorimetry, and tend to underestimate energy expenditure.[118,119] Whether these differences are problematic is not clear. No available data describes outcome differences. However, avoiding overfeeding patients, especially early in the course of their illnesses, is very important, as illustrated by the EPaNIC trial and a study by Arabi and associates,[120] which demonstrated that patients who were underfed and who received approximately 60% of their caloric requirements had a lower in-hospital mortality rate than those who received near target caloric intake.[103,120]

Complications of Transcatheter Aortic Valve Replacement

TAVR has been used in many high-risk patients and, to some extent, in intermediate-risk patients with severe aortic stenosis (AS) since its introduction in Europe in 2001 (see Chapters 21 and 27). This procedure was developed to offer an alternative treatment for patients with severe AS classified as at too high risk for open surgical aortic valve replacement (SAVR). In 2011, the FDA granted the approval of this procedure for the replacement of severely stenosed aortic valves.[121]

Mortality After Transcatheter Aortic Valve Replacement

The first large, multicenter, prospectively randomized trial, the Placement of Aortic Transcatheter Valve (PARTNER) Trial, was conducted in 25 centers in the United States and comprised two cohorts: PARTNER A compared the outcomes of the high-risk patients treated with TAVR versus SAVR, and PARTNER B compared the outcomes of the inoperable patients treated with TAVR versus standard therapy.[122–124] Cohort A enrolled 699 high-risk patients and revealed that the 30-day mortality rate was 3.4% for TAVR and 6.5% for SAVR, the 1-year mortality rate was 24.2% and 26.8%, respectively, and the 2-year mortality rate remained similar between TAVR and SAVR.[122–124] Of the 348 patients treated with TAVR, 244 underwent transfemoral TAVR (TF-TAVR) and 104 underwent transapical TAVR (TA-TAVR). In high-risk patients, TA-TAVR and SAVR were associated with higher periprocedural risk of death as compared with TF-TAVR. In Cohort B, 358 inoperable patients were enrolled. The 30-day mortality rate was 5% for TF-TAVR and 2.8% for standard therapy; the 1-year mortality rate was 30.7% and 50.7%, respectively; and the 2-year mortality rate was 43.3% and 68%, respectively.[123,125,126] A Nonrandomized Continuous Access (NRCA) registry was created after the completion of the randomization of the PARTNER trial.[127] The 1-year mortality rate was significantly lower in the NRCA cohort (19%), as compared with TF-TAVR in the PARTNER trial (25.3%), with the caveat that many baseline characteristics were significantly different. Results from a multicenter registry in Europe of 697 patients revealed an in-hospital mortality rate of 7.5% post-TAVR versus 22.6% post-SAVR.[128] For reasons not yet elucidated in the PARTNER trial, the 2-year mortality among female patients tended to be lower with TAVR, especially TF-TAVR (28.2%) versus SAVR (38.2%).[123,129,130]

Stroke After Transcatheter Aortic Valve Replacement

At 30 days, the incidence of stroke in the PARTNER trial cohort A was significantly higher after TAVR (4.6%) versus SAVR (2.4%), and stroke increased the hazard of death.[122] This stroke hazard peaked early after TAVR and remained constant thereafter in relation to SAVR.[123] The overall rate of stroke was significantly higher after TAVR (13.8%), as compared with medical treatment (5.5%) in inoperable patients.[125] The rate of procedural stroke was significantly higher with TAVR (5.4%) versus SAVR (0.7%) in women, and it was similar with TAVR (4.5%) versus SAVR (4%) in men.[130] A systematic review and metaanalysis of 25 multicenter studies and 33 single-center studies

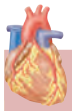
published in 2013 revealed that the risk of stroke within 30 days after TAVR is similar between TF-TAVR and TA-TAVR and the different valve types.[126]

Paravalvular Leak After Transcatheter Aortic Valve Replacement

A paravalvular leak post-TAVR could be the result of incomplete prosthesis apposition to the annulus, annular eccentricity, undersized prosthetic valve, or malposition of the implanted device (see Chapters 15, 22, and 27). Moderate-to-severe paravalvular aortic regurgitation (AR) was more frequent after TAVR at 1 and 2 years (7% and 6.9%), as compared with SAVR (1.9% and 0.9%) in the PARTNER trial cohort A and was associated with increased late mortality.[122] The effect of AR on mortality was proportional to the severity of regurgitation. In the PARTNER trial cohort B, the TAVR group and standard therapy group had similar degrees of AR at both 1 year and 2 years. The trend toward a higher mortality rate at 1 year associated with paravalvular regurgitation dissipated at 2 years follow-up in the PARTNER trial cohort B.[125] Based on the current literature, the causal relationship between mild paravalvular leak and mortality remains unclear.[127]

Vascular and Bleeding Complications After Transcatheter Aortic Valve Replacement

Major vascular complications were more frequent 1 year after TAVR (11.3%), as compared with SAVR (3.8%), whereas major bleeding was less frequent 1 year after TAVR (15.7%) than after SAVR (26.7%) in the PARTNER trial cohort A, and the differences were maintained at 2 years.[122] Major bleeding was also more common after TAVR, as compared with standard therapy in the PARTNER trial cohort B.[125] The results of a large study that included 2401 patients who underwent TAVR from a randomized and nonrandomized continuous access registry revealed that the incidence of the late major bleeding complication was 5.9%.[129] The common major bleeding complications after TAVR were gastrointestinal (40.8%), neurologic (15.5%), trauma or fall (7.8%), and genitourinary (6.3%). The occurrence of a major late bleeding complication was a strong independent predictor of mortality, and it was associated with a fourfold increase in late mortality. The association between moderate-to-severe paravalvular leak and the incidence of late major bleeding might be explained by high shear stress and flow turbulence leading to cleavage of proaggregation proteins and, subsequently, causing increased bleeding susceptibility (Box 41.6).[129,131]



BOX 41.6 SUMMARY OF COMPLICATIONS RELATED TO TRANSCATHETER AORTIC VALVE REPLACEMENT

- TAVR remains a noninferior alternative to SAVR in high-risk patients and a superior alternative to standard treatment in inoperable patients with severe aortic stenosis with regards to mortality.
- The increased early stroke incidence and the increased paravalvular leak, along with their association with mortality, portend significant concerns.
- A high-level suspicion for stroke should ensure that prompt diagnostic testing and treatment are part of the post-TAVR plan.
- Paravalvular regurgitation requires special consideration and follow-up, considering its association with worse later outcomes.

TAVR, Transcatheter aortic valve replacement; *SAVR*, surgical aortic valve replacement.
From http://content.onlinejacc.org/article.aspx?articleid=2042957&resultClick=3

Complications of Minimally Invasive Cardiac Surgery

Minimally invasive cardiac surgery has been gradually used since early 1990 with the intention of decreasing morbidity, inflammatory response, and organ dysfunction derived from surgical access, CPB, and the manipulation of the large vessels.

Minimally Invasive Coronary Artery Bypass Graft

Most of the studies comparing minimally invasive CABG surgery with on-pump standard sternotomy CABG surgery are small, and many of the studies are nonrandomized (see Chapter 20). One small study revealed that a ministernotomy offered no advantage over the standard procedure with regards to postoperative pulmonary function recovery.[132] A few nonrandomized studies reported the benefit of a minithoracotomy for respiratory function recovery in patients with chronic respiratory disease, but more postoperative pain was reported, as compared with a standard sternotomy.[133] The Sternotomy Versus Thoracotomy (STET) trial revealed that a left anterolateral thoracotomy off-pump CABG (OPCAB) surgery was associated with shorter intubation times and fewer arrhythmias, but the OPCAB surgery was also associated with longer operative time, a greater need for postoperative pain relief, and worse lung function at discharge as compared with the standard OPCAB procedure with a median sternotomy.[134] Mortality and long-term morbidity outcomes were similar after the OPCAB and on-pump revascularization; however, recurrent angina was more frequent after the OPCAB.[135] A large metaanalysis including over 13,000 patients revealed that the OPCAB was associated with a decreased incidence of stroke but with similar mortality and myocardial infarction rates, as compared with on-pump CABG surgery.[136] Importantly, patients older than 80 years of age had a lower incidence of stroke and a trend toward better survival with the use of off-pump revascularization.[137] A major concern with the OPCAB is the need for an emergent conversion to the on-pump CABG surgery, which leads to increased perioperative mortality and morbidity (Polomsky and Puskas, 2012).[137] Another controversial area with the OPCAB procedure is the ability to complete the revascularization, possibly leading to fewer grafts as compared with the on-pump CABG surgery.[136] Therefore a hybrid approach for revascularization has been advocated and has been associated with shorter lengths of stay and intubation times, less pain and blood loss, and fewer transfusions as compared with the OPCAB.[137,138] Robotic-assisted CABG surgery was also associated with lower mortality and a lower incidence of complications when a single graft was performed; however, the benefits were reduced when multiple grafts were required.[139]

Minimally Invasive Aortic Valve Replacement

Since the first report of the right thoracotomy approach for AVR in 1993, the minimally invasive AVR has been performed via right anterior thoracotomy or upper hemisternotomy.[140] A propensity-matched single-center study revealed that the minimally invasive AVR is associated with shorter mechanical ventilation duration, lower incidence of postoperative atrial fibrillation, and fewer transfusions.[141] A pooled analysis of propensity-matched data of 18 studies showed that ischemic time and CPB time were significantly longer, whereas mechanical ventilation time, and ICU and hospital lengths of stay were shorter with minimally invasive AVR, as compared with conventional AVR.[142] The pain scores, the transfusion requirements, and the incidences of stroke and atrial fibrillation were comparable between minimally invasive and conventional AVR. A single-center study also revealed that minimally invasive AVR was associated with increased survival in octogenarians requiring redo surgery, as compared with conventional AVR.[143] Another review of 13 articles concluded that minimally invasive reoperative AVR can be at least as safe as conventional full sternotomy and is associated with shorter hospital lengths of stay, less blood products, shorter mechanical

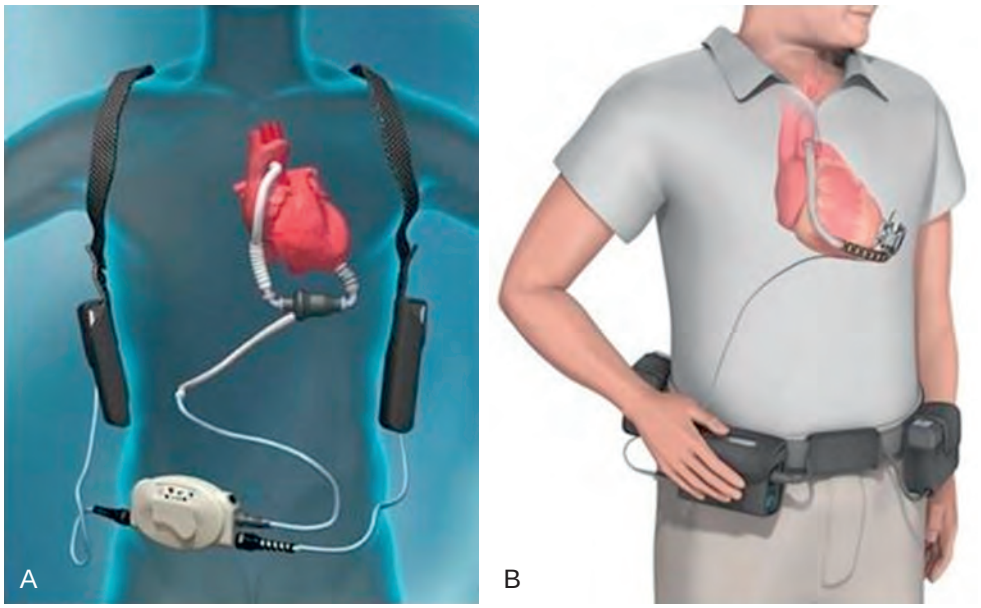


Fig. 41.1 (A) The Heartmate II ventricular assist device. *(From www.thoratec.com.)* (B) The HeartWare ventricular assist device. *(From www.heartware.com.)*

ventilation duration, and fewer sternal wound infections (see Chapters 21 and 29).[144]

Minimally Invasive Mitral Valve Surgery

To minimize surgical trauma and potentially positively affect surgical pain, length of recovery, and cosmesis, minimally invasive mitral valve surgery has been increasingly used since early 1990.[145] An observational study conducted at one institution revealed that patients who underwent cardiac reoperation via minithoracotomy for mitral or aortic valve surgery had significantly lower hospital mortality (5.6%), as compared with median sternotomy (11.3%), fewer blood transfusions, and shorter hospital lengths of stay.[146] A single-center reported their immediate and long-term results after minimally invasive mitral valve repair surgery in a large series of patients: 1.3% operative mortality, and 95% freedom from reoperation or severe recurrent mitral regurgitation.[147] At present, no randomized controlled trial has compared the safety and efficacy of these minimally invasive procedures with open surgeries for mitral valve disease, but the historical cohorts and the case series suggest that the minimally invasive approach is a feasible alternative.[148]

Complications of Mechanical Assist Devices

Long-Term Complications of Ventricular Assist Device Implantation

The landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of 2001 demonstrated that implanting LVAD improved survival and the quality of life for patients with heart failure over medical management (see Chapter 28).[149] This trial paved the way for a new paradigm in heart failure management, during which VADs are not only solely used in patients who are failing medical management as a bridge-to-transplant, but they are also used as destination therapy (DT) for patients in end-stage heart failure who are not candidates for heart transplantation.[150] Furthermore, as devices have improved, survival rates in patients who have a nonemergent VAD implant have started to approach that of heart transplant patients, with a 2-year survival for heart transplantation unchanged at approximately 80% over the last 10 years.[151] Thus VADs are increasingly chosen as DT in lieu of transplantation, even in patients who are transplant eligible.[150,152] This development could lead to a future in which a heart for transplant may not be quite in such short supply when compared with the demand.

The adverse event burden that patients with a implanted VAD experience is key to the long-term success of their implant and is increasingly critical in this new era of DT VADs. The original pulsatile-flow VADs (eg, HeartMate XVE) have been replaced by continuous-flow devices (eg, HeartMate II, HeartWare HVAD, DuraHeart II) (Fig. 41.1) for DT, as they generally show improved outcomes.[153,154] Many long-term complications of VAD use still remain, however, which are discussed in the following text.

Device Infection

Stating definitive infection rates is difficult, because they greatly vary, depending on the device, definitions used, reporting, and severity of infection.[155] Additionally, many studies that report definitive infection rates are small, single-center studies from the time when pulsatile VADs were still being used. Since rates of infection and other complications have dropped with the use of continuous-flow devices, these data are increasingly irrelevant.

Recently reported rates of all infections in patients with a VAD range up to 49%, with a range of serious infections, such as interior pump infections, occurring in less than 1%, to less serious infections such as percutaneous site infections ranging from 12% to 32%. The latest Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report states an infection rate of 9.96 per 100 patient months.[150] Overall sepsis rates are relatively high at 11% to 36%.[155–161] One recent, single-center trial reported an overall driveline infection rate of 12%.[162] The only independent characteristic predictive of infection was increased duration of support. *Staphylococcus* and *Pseudomonas* species were the most commonly cultured organisms, as in previous studies, likely attributable to these organisms' ability to create a biofilm.[163]

Although most VAD-related infections are superficial and can be treated with antibiotics and local débridement, serious infectious complications lead to 11% of device failures.[164] More aggressive treatment strategies that have been reported include vacuum-assisted wound closure and antibiotic-impregnated beads.[165,166] Curbing an infection as soon as possible is particularly important to prevent the need for

device exchange, which carries significantly lower survival rates with each exchange.[150]

Device Thrombosis

Mechanical propulsion of blood within the VAD has several consequences, including stasis and contact with the nonbiologic material, which can lead to thrombosis. Hematologic effects differ, depending on the type of device. Continuous axial flow pumps, such as the HeartMate II, spin at higher revolutions per minute and have more surface-area contact with blood, whereas centrifugal flow pumps such as the HeartWare have fewer and slower moving parts that contact the blood, resulting in less shear stress, less hemostasis, and less blood component activation. Because of this, axial flow pumps have higher rates of hemolysis than centrifugal flow models.[167] Centrifugal flow pumps may ultimately prove to have fewer hemocompatibility issues such as thrombosis as well.[158]

Device-related thrombosis is a feared complication of long-term VAD use; it requires device exchange or transplant. Furthermore, device-related thrombosis is the most common cause of device failure at 50%.[164] Rates of device-related thrombosis in the HeartMate II original studies were 2% to 4% of patients.[161] A recent increase in the incidence to approximately 8% has been blamed on changes in practice regarding anticoagulation, although this is speculative.[121,168]

Thrombosis is diagnosed by elevated lactate dehydrogenase levels, reflecting associated hemolysis attributable to increased turbulence near the thrombus, echocardiographic findings, CT angiography, and increasing pump power use.[167] Conservative treatment strategies that have been reported with success include glycoprotein IIb/IIIa inhibitors and thrombolytic therapy. If these fail or if hemodynamic compromise occurs, then the device must be exchanged.[155]

Gastrointestinal Bleeding

Many factors predispose the patient with a VAD to bleeding events. First, patients require chronic anticoagulation therapy to avoid thrombotic complications. Typical regimens include full-dose aspirin and warfarin with an international normalized ratio (INR) of 2 to 2.5.[155] Another factor predisposing patients to bleeding events is a consequence of the mechanical propulsion of blood, which causes shear stress on the blood components. This leads to acquired von Willebrand (vWB) disease attributable to cleavage of the vWB factor multimers, leading to increased rates of bleeding events.[169] The levels of the vWB factor have been shown to be preserved in centrifugal-flow devices, as compared with axial-flow devices, but this did not appear to translate into different bleeding risks.[170] One recent study with the HeartWare centrifugal-flow device showed a relatively low rate of gastrointestinal bleeding (GIB) of 5%, but it was not clear whether the low rate of GIB was associated with preserved levels of the vWB factor.[171]

GIB is the most frequently experienced bleeding event in patients with a VAD, with reported rates ranging from 10% to 40%.[156,157,172–174] Patients with continuous-flow VADS tend to form arteriovenous malformations (AVMs) in the intestines, which are thought to be the result of the low pulse-pressure state, and further increase the risk for GIB.[172] Pulsatile-flow VADS have lower rates of GIB, independent of anticoagulation status, likely attributable to the absence of AVMs.[174,175]

Management of the patient with a VAD and GIB is similar to a patient without a VAD, primarily consisting of transfusion, anticoagulation cessation, and endoscopic evaluation. Bleeding of a large number of AVMs in the small intestine may result in more capsule endoscopic studies. Aspirin should be restarted after the cessation of the bleeding and warfarin after individual patient consideration.[176]

Neurovascular Events

Between 2% and 14% of patients with a VAD will experience a stroke, and 4% to 11% will have a stroke leading to disability or death.[155–157,159–161,177] Disabling stroke is a dreaded event with possibly the greatest impact on the quality of life and the potential to complicate the course of a patient with an otherwise perfectly functioning VAD. Rates of neurologic events are less in continuous-flow devices, as compared with pulsatile-flow devices.[154] The rates of neurologic events have also declined over time in continuous-flow devices, but the explanation remains unclear. One trial found a reduction in stroke rate from 19% in the original HeartMate II DT trial to 12% in the post-FDA approval period.[177]

An important patient factor in stroke is anticoagulation status. Multiple studies have found that patients with laboratory values favoring coagulation (high platelet count, low INR and prothrombin time [PT]) correlate with ischemic stroke, and patients with values reflecting anticoagulation (high INR and PT) correlate with hemorrhagic stroke.[173,178,179] Careful monitoring of chronic anticoagulation therapy is, no doubt, critical to balance the risk of thrombotic events with hemorrhage.

Device Failure

One-year survival after nonemergent implant of a continuous-flow device is now 80%; 1-year survival drops to 65% after a second implant and 50% after a third.[150] Whether this decrease is due to underlying conditions that may have predisposed to a problem with the pump or to the device exchange itself remains unclear, but exchange is still avoided until deemed absolutely necessary. One recent review focused on device failure in original retrospective observational studies. Device failure occurred at rates of approximately 4%, with a median duration of support of around 500 days. Pump thrombosis was the most common cause of failure at 50%. Lead or cable damage was the next cause at 22%, followed by mechanical failure at 12%, and infection at 11%.[164]

Bend-relief disconnect is a recently described cause of device failure observed in the HeartMate II.[180] The purpose of the bend relief is to prevent kinking in the outflow from the pump to the aorta. A detachable ring seals the relief closed, with the purpose of being able to detach the ring should the graft need to be visualized in the future. The ring can become spontaneously detached in vivo, potentially leading to thrombosis, increased hemolysis, worsened heart failure, or severe hemorrhage.

Long-Term Complications of Extracorporeal Membrane Oxygenation

The use of ECMO outside of the surgical unit was first reported in 28 cases by Bartlett and associates[181] in 1972 (see Chapters 32 and 33). Since then, extracorporeal life support (ECLS) has been used in thousands of patients with respiratory or cardiovascular failure that have not responded to medical management. However, indications and guidelines for the use of ECLS/ECMO remain controversial.[182,183] The mortality rate in patients undergoing ECMO remains high. Mortality rates range from 21% to 50% in patients undergoing ECMO for respiratory failure, whereas in patients with heart failure, the mortality rate is in the 40% range.[184]

Complications are extremely common in patients undergoing ECMO. Combes and colleagues[185] reported that 57% of all patients undergoing ECMO for cardiac failure had at least one major complication. In an excellent review article, Esper and associates[186] divided complications into two general categories: device-related and patient-related. The ECMO circuit, itself, is complex, and failures from each component (eg, cannula, tubing, pump, oxygenator, heat exchanger, tubing and return cannula [arterial or venous]) have been reported. Fortunately, with modern cannulas, centrifugal pumps, heparin-coated circuits, and hollow-filter oxygenators, the incidence of circuit-related failures seems to be decreasing.[187] Problems with venous drainage cannulas may include partial obstruction that will increase venous pressure in the patient (an increase in venous pressure may also decrease organ perfusion pressure) and decrease flow rates

that will affect oxygenation, ventilation, and blood pressure if using venoarterial (VA) ECMO. Venous drainage may also be decreased if the pump flows are too high, which results in "suck down" where the cannula is occluded because the vein collapses around it, preventing venous drainage. When vein collapse happens, the circuit tubing often "shakes" or "chatters." The collapse can usually be treated by transiently decreasing flows, a fluid bolus, or both. Echocardiography is useful to confirm cannula position. Another cannula problem with venovenous (VV) ECMO can occur when the venous drainage cannula is too close to the venous return cannula from the oxygenator and the oxygenated blood is drained back into the ECMO circuit, which results in inadequate tissue oxygenation. This problem is usually treated by adjusting the position of the cannulas.

A newer bicaval Avalon Elite dual lumen cannula (Avalon Laboratories, Rancho Dominguez, CA) is now being used for VV-ECMO that drains blood from both the superior vena cava and the inferior vena cava and returns it to the right atrium. When properly positioned by echocardiography or fluoroscopy, femoral cannulation is avoided. However, a high rate (up to 80%) of upper extremity DVT is associated with the use of this cannula.[188] Complete or partial resolution of the DVT occurred in all patients after the cannula was removed, and no patient had a documented pulmonary embolism.

Hemolysis is also a common complication that has been reported in 10% to 67% of neonates treated with ECMO.[189] Hemolysis can lead to anemia, hyperbilirubinemia, AKI, and neurologic complications. Risk factors for hemolysis include the type of oxygenator used, mean venous inlet pressure, and mean pump speed. Hemolysis can be limited by using the largest cannula and the lowest pump speeds possible.

Thrombosis of the pump and/or oxygenator is another dreaded complication of ECMO that must be balanced against over-anticoagulation and bleeding.[186] Unfortunately, no standardized, universally accepted guidelines are available for anticoagulation or for the monitoring of adequate anticoagulation in patients on ECMO.

Cheng and colleagues[190] recently published an excellent review and metaanalysis of complications in 1866 patients undergoing ECMO for cardiac failure. They reported an overall survival rate of 35%, with a range of 21% to 65%. The complication rates are shown in Table 41.8 and are similar to complication rates reported by Ventetuolo and associates.[184]

ECMO is also incredibly expensive, costing $65,519 more in the patients randomized to the conventional ventilation or ECMO for Severe Adult Respiratory failure (CESAR) trial.[191] In this study, ECMO showed a favorable lifetime predicted cost utility of $131,000 per life year.

Finally, ECMO has created numerous ethical problems for patients, families, and clinicians. The most stressful for everyone is the so-called "bridge to nowhere" in which patients on ECMO have no long-term alternative for life support. This and other common ethical dilemmas are reviewed in detail in an excellent review article by Abrams and colleagues.[192]

In conclusion, ECMO is an expensive intervention that has a mortality rate of 20% to 50% and a morbidity rate of approximately 50%. Further studies are underway to continue to define the indications and management of ECMO to improve outcomes.

TABLE 41.8 Complications for Extracorporeal Membrane Oxygenation for Cardiac Failure

	Rate	*95% Confidence Interval*
Lower extremity ischemia	16.5	12.5–22.6
Compartment syndrome or fasciotomy	10.3	7.3–14.5
Lower extremity amputation	4.7	2.3–9.3
Stroke	5.9	4.2–8.3
Other neurologic injury	13.3	9.9–17.7
Acute kidney injury	55.6	35.5–74
Renal replacement therapy	46	36.7–55.5
Major bleeding	40.6	26.8–56.6
Reoperation for bleeding or tamponade	41.6	24.3–61.8
Infection	30.4	15.5–44

Adapted from Cheng R, Hachamovitch R, Kittleson M, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg.* 2014;97(2):610–616.

Patient and Family Support, Palliative Care, and End-of-Life Issues

Twenty percent of Americans who die each year do so during or shortly after a stay in the ICU.[193] This fact places ICU providers in a key position of helping families and patients begin to navigate a difficult process that has the potential to end in an unforeseen and undesirable way. Certainly, helping patients live with a good quality of life for as long as possible is preferable, but when the end inevitably comes, helping patients and their families experience a "good death" can also be invaluable.

Patient care in the cardiothoracic ICU is extremely technology heavy and becoming more so with time. Supporting organ vital functions is almost indefinitely possible, moving the interventions and care from what used to be "can we" questions to "should we" questions, which result in far more difficult decisions for practitioners, patients, and families.

One complexity particular to surgical ICUs is that the ongoing goals of care may differ among practitioners. A covenant of care often exists between surgeons and their patients. This covenant is described by medical anthropologist Joan Cassell, in which the surgeon's commitment to the patient is characterized as not "giving up" and defeating death at all costs. This commitment can lead to conflicts with intensivists, who more often emphasize the quality of life[194] and can create confusion for the patient and their families, who may be hearing mixed messages.

Patients in the cardiac surgical ICU tend to be older and have chronic medical conditions. These patients have often been prompted to create an advanced directive or living will. Patients and families can feel forearmed when this has already been discussed and is in place. Unfortunately, when unforeseen circumstances and questions of whether to continue curative treatment arise, the wording is often unhelpful when it comes to making practical decisions in the ICU. Typical standardized documents say something to the effect that the patient would not want to continue to receive medical intervention or "heroic procedures" if no "realistic" hope of recovery exists. Unfortunately, having no hope or no chance is extremely rare, and physicians do not know how to predict whether or when a patient will die.[195]

Prognosticating

Patients coming through the ICU are having major surgery and have underlying medical comorbidities; their chance of a poor outcome is not insignificant. A patient having CABG surgery has an overall 3.2% chance of death by 30 days. If a patient has a left ventricle ejection fraction of less than 20%, then that risk increases to 8% by 30 days.[196,197] In patients 80 years of age and older, the 30-day mortality rate for an AVR is 6.6%. Often, these patients are also approaching the end of their lives, with a 2-year mortality rate of 35%.[122] At the extreme end of the morbidity spectrum is the patient who receives VA-ECMO for a cardiac arrest, severe cardiogenic shock, or failure to wean from CPB; hospital survival is a mere 35% to 43%.[185,198,199] This scenario is not infrequently encountered in the cardiac surgical ICU.

Scoring systems can be helpful in getting a sense of a patient's likelihood of doing poorly. Several scoring systems for patients undergoing cardiac surgery have been validated.[200,201] Another system that predicts morbidity and mortality is the cardiac anesthesia risk evaluation (CARE) score (Box 41.7).[202] The CARE model incorporates severity of

cardiac disease, comorbidities, nature of the surgery, and urgency into a scale of 1 to 5 with an E that designates emergency. For example, a 4E patient would be a patient with an uncontrolled medical problem having a complex surgery that is also an emergency; the risk of hospital mortality is 17% (Table 41.9).

The troubling population in the ICU is made up of patients who become chronically critically ill, with physical and cognitive impairments. These are the patients who linger in the ICU, often malnourished and frail, and are unable to be liberated from respiratory support. Hospital mortality for these patients is between 20% and 49%. Even when these patients are able to be eventually discharged from the hospital, the 1-year mortality rate is approximately 50%.[203]

BOX 41.7 CARDIAC ANESTHESIA RISK EVALUATION SCORE

1. Patient with stable cardiac disease and no other medical problem: a noncomplex surgery is undertaken.
2. Patient with stable cardiac disease and one or more controlled medical problems[a]: a noncomplex surgery is undertaken.
3. Patient with any uncontrolled medical problem[b] *or* patient in whom a complex surgery is undertaken.[c]
4. Patient with any uncontrolled medical problem *and* in whom a complex surgery is undertaken.
5. Patient with chronic or advanced cardiac disease for whom cardiac surgery is undertaken as a last hope to save or improve life.
6. Emergency: surgery is performed as soon as the diagnosis is made and the surgical unit is available.

[a]Examples: Controlled hypertension, diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, controlled systemic diseases, and others as judged by clinicians.
[b]Examples: Unstable angina treated with intravenous heparin or nitroglycerin, preoperative intraaortic balloon pump, heart failure with pulmonary or peripheral edema, uncontrolled hypertension, renal insufficiency (creatinine level >140 µmol/L), debilitating systemic diseases, and others as judged by clinicians.
[c]Examples: Reoperation, combined valve and coronary artery surgery, multiple valve surgery, left ventricular aneurysmectomy, repair of ventricular septal defect after myocardial infarction, coronary artery bypass of diffuse or heavily calcified vessels, and other as judged by clinicians.
Adapted from Dupuis JY, Wang F, Nathan H, et al. The cardiac anesthesia risk evaluation score: a clinically useful predictor of mortality and morbidity after cardiac surgery. *Anesthesiology.* 2001; 94(2):194–204.

Palliative Care

Recognizing that palliative care does not exclude curative treatment is important. Palliative care is a concept that incorporates symptom management into medical and surgical disease therapy. It recognizes that the patient has a chronic disease that must be managed and is designed to relieve suffering and to improve the quality of life, which can enhance disease-specific therapies but need not replace them. Almost without exception, the cardiac surgery patient almost without exception has a chronic disease that must be indefinitely managed. Thus palliative care, with the goals of managing symptoms and improving the quality of life, is often appropriate to incorporate into the care plan, even if stopping therapy is not expected in the near future.[204]

Palliative care consults have been shown to increase lifespan, decrease costs, and improve patient satisfaction.[205–208] Thus early integration of a palliative care approach to a patient's care plan has no apparent drawbacks. If disease-specific therapies become ineffective or exhausted or if the goals of care change to sole palliation, then palliative therapies can be ramped up accordingly (Fig. 41.2).

Recommendations for Patient and Family Support

Some ICUs have instituted a set schedule for family meetings starting from admission, or a set time for "family rounds" when families can be

TABLE 41.9 Probabilities of Mortality, Morbidity, and Prolonged Postoperative Length of Stay in Hospital, as Predicted by the CARE Score

CARE Score	*Mortality (%)*	*Morbidity (%)*	*Prolonged LOS (days)*
1	0.5 (0.3–0.9)	5.4 (4.3–6.8)	2.9 (2.2–3.9)
2	1.1 (0.7–1.7)	10.3 (8.9–12.1)	5.1 (4.2–6.3)
3	2.2 (1.6–3.1)	19.0 (17.2–20.9)	8.8 (7.6–10.2)
3E	4.5 (3.5–5.7)	32.1 (29.3–35.0)	14.7 (12.8–16.8)
4	8.8 (6.9–11.3)	48.8 (44.1–53.6)	23.5 (20.1–27.3)
4E	16.7 (12.4–22.1)	65.8 (59.5–71.6)	35.4 (29.3–42.0)
5	29.3 (20.8–39.6)	79.6 (73.2–84.7)	49.4 (40.4–58.5)
5E	46.2 (32.4–60.5)	88.7 (83.5–92.5)	63.6 (52.5–73.4)

Values obtained from the logistic regression analysis performed in the reference population (n=2000). Numbers in parentheses are 95% confidence intervals.
CARE, Cardiac anesthesia risk evaluation; *LOS*, length of stay.
Adapted from Dupuis JY, Wang F, Nathan H, et al. The cardiac anesthesia risk evaluation score: a clinically useful predictor of mortality and morbidity after cardiac surgery. *Anesthesiology.* 2001; 94(2):194–204.

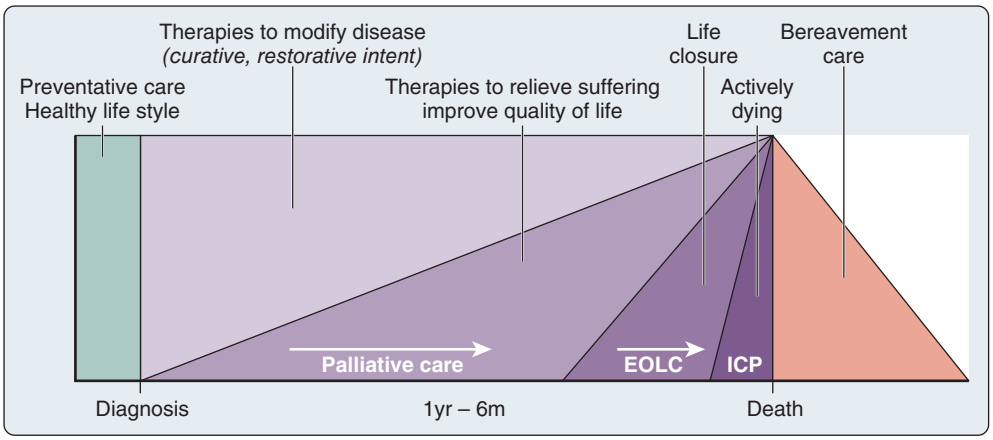
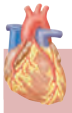


Fig. 41.2 The continuum of palliative care. *(Courtesy of the University of Washington, Seattle. From Macaden SC. Moving toward a national policy on palliative and end of life care.* Indian J Palliat Care. *2011;17[Suppl]:S42–S44.)*



BOX 41.8 BUNDLE OF MINIMAL PALLIATIVE CARE QUALITY MEASURES IN THE INTENSIVE CARE UNIT

ICU Day 1 Goals
- Identify the medical decision maker.
- Determine whether there is an advance directive.
- Determine resuscitation (DNR/DNI) status.
- Give institutional ICU information, if applicable.
- Perform regular pain assessments, strive for optimal pain management.

ICU Day 3 Goals
- Involve social work support if not already done.
- Involve spiritual support if not already done.

ICU Day 5 Goals
- Conduct an interdisciplinary family meeting in a dedicated space.

ICU, Intensive care unit; *DNR,* do not resuscitate; *DNI,* do not intubate.
Adapted from Nelson JE, Mulkerin CM, Adams LL, Pronovost PJ. Improving comfort and communication in the ICU: a practical new tool for palliative care performance measurement and feedback. *Qual Saf Health Care.* 2006;15(4):264–271. Copyright ©2015 by Elsevier. Adapted with permission.

at the bedside and expect care providers to visit. This practice has many potential benefits. It allows family members and patients to become familiar with the care providers before a potential complication or urgent situation arises, and it can improve patient and family satisfaction, in that they believe they are more regularly informed. Family meetings also provide opportunities to discuss a patient's goals of care in a nonurgent manner, while eliminating some of the anxiety that can be provoked by a hastily scheduled meeting should the patient's status unexpectedly decline. Nelson and associates[209] developed a bundle of palliative care quality measures to be used in the ICU with a recommended standard timeline of actions (Box 41.8). Patients with a statistically poor prognosis or an unexpected ICU admission should have a family meeting earlier, ideally on ICU day 1.

Facilitating a family meeting is a skill that requires practice. Extensive literature is available to provide guidance. Meetings should include members of all disciplines as appropriate, and introductions of all participants should be made. The family's understanding of the patient's condition should be assessed. A clear, coherent message should be delivered to the family about the patient's condition, including clear prognosticating as much as possible.

If decisions need to be made about further treatment, then the goal is to discover what the patient's goals of care would be in this situation. It is the surrogates' role to help interpret those wishes, based on their knowledge of the patient, not to express their own wishes for care plans. It can then be appropriate for providers to make recommendations to the decision maker about further care, taking into consideration the patient's perceived wishes and the clinical situation. As Pelligrino wrote, "The efficacy of a treatment is for clinicians to assess and comment on, but the burdens and benefits of a treatment (in terms of its quantitative or qualitative goals) [are] in the purview of the patient."[210] Thus decisions to limit or change the goals of care are a joint decision between practitioners and family members, based on the patient's perceived wishes within the clinical context.

Withdrawal of Life-Sustaining Treatments and Palliative Sedation

If the decision is made that curative treatment has been exhausted and that the goals of care are changed to palliative only, then disease-specific treatment and life-sustaining therapies can be stopped or not escalated, according to the surrogates' and providers' judgment. Excellent resources exist that can guide the mechanics of this process.[211,212]

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42

Postoperative Pain Management for the Cardiac Patient

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KEY POINTS

1. Inadequate postoperative analgesia and/or an uninhibited perioperative surgical stress response has the potential to initiate pathophysiologic changes in all major organ systems, including the cardiovascular, pulmonary, gastrointestinal, renal, endocrine, immunologic, and/or central nervous systems, all of which may lead to substantial postoperative morbidity. Adequate postoperative analgesia prevents unnecessary patient discomfort, may decrease morbidity, may decrease postoperative hospital lengths of stay, and thus may decrease costs.
2. Pain after cardiac surgery may be intense and originates from many sources, including the incision (sternotomy or thoracotomy), intraoperative tissue retraction and dissection, vascular cannulation sites, vein-harvesting sites, and chest tubes, among other sources. Achieving optimal pain relief after cardiac surgery is often difficult, yet it may be attained through a wide variety of techniques, including local anesthetic infiltration, nerve blocks, intravenous agents, intrathecal techniques, and epidural techniques.
3. Traditionally, analgesia after cardiac surgery has been obtained with intravenous opioids (specifically morphine). However, intravenous opioid use is associated with definite detrimental side effects (nausea and vomiting, pruritus, urinary retention, respiratory depression), and longer-acting opioids such as morphine may delay tracheal extubation during the immediate postoperative period via excessive sedation and/or respiratory depression. Thus in the current era of early extubation (eg, fast-tracking), cardiac anesthesiologists are exploring unique options other than traditional intravenous opioids for the control of postoperative pain in patients after cardiac surgery.
4. Although patient-controlled analgesia is a well-established technique (used for more than 2 decades) and offers potential unique benefits (eg, reliable analgesic effect, improved patient autonomy, flexible adjustment to individual needs), whether it truly offers significant clinical advantages (compared with traditional nurse-administered analgesic techniques) to patients immediately after cardiac surgery remains to be determined.
5. Cyclooxygenase-2 (COX-2) inhibitors possess analgesic (opioid-sparing) effects and lack deleterious effects on coagulation, in contrast with nonselective nonsteroidal antiinflammatory drugs (NSAIDs). However, current evidence does not suggest that COX-2 inhibitors provide major advantages over traditional NSAIDs. Furthermore, potential links between this class of drugs and cardiovascular complications, sternal wound infections, and thromboembolic complications need to be fully evaluated.
6. Administration of intrathecal morphine to patients initiates reliable postoperative analgesia after cardiac surgery, yet its effect on respiratory depression remains unpredictable, potentially delaying tracheal extubation. Intrathecal opioids or local anesthetics cannot reliably attenuate the perioperative stress response associated with cardiac surgery that persists during the immediate postoperative period. Although intrathecal local anesthetics (not opioids) may induce perioperative thoracic cardiac sympathectomy, the hemodynamic changes associated with total spinal anesthesia make the technique unpalatable in patients with cardiac disease.
7. Administration of thoracic epidural opioids or local anesthetics to patients initiates reliable postoperative analgesia after cardiac surgery. The quality of analgesia obtained with thoracic epidural anesthetic techniques is sufficient to allow cardiac surgery to be performed in "awake" patients (ie, without general endotracheal anesthesia). The administration of thoracic epidural local anesthetics (not opioids) can both reliably attenuate the perioperative stress response associated with cardiac surgery that persists during the immediate postoperative period and induce perioperative thoracic cardiac sympathectomy.
8. Use of intrathecal and epidural techniques in patients undergoing cardiac surgery remains extremely controversial. Concerns regarding the risk of hematoma formation and the fact that numerous clinical investigations regarding this topic are suboptimally designed and use a wide array of disparate techniques have prevented clinically useful conclusions.
9. For a wide variety of reasons, including the increased use of small incisions, the last decade has seen a resurgence of nerve blocks (including catheter-based techniques) in patients undergoing cardiac surgery. Recent clinical studies using intercostal, intrapleural, and paravertebral blocks indicate that these techniques may have unique clinical advantages, even when compared with traditional intrathecal and epidural techniques. The emergence of liposomal bupivacaine, which has the potential to provide clinical analgesia for 96 hours after a single injection, may revolutionize the use of single-shot nerve blocks for patients undergoing cardiac surgery.
10. As a general rule, avoiding intense, single-modality therapy for the treatment of acute postoperative

pain is best. The administration of two analgesic agents that act by different mechanisms (multimodal or balanced analgesia) provides superior analgesic efficacy with equivalent or reduced adverse effects. Analgesic therapies should be used only after thoughtful consideration is given to the risks and benefits for each individual patient. The therapy or therapies selected should reflect the individual anesthesiologist's expertise, as well as the capacity for safe application of the chosen modality in each practice setting. The choice of medication, dose, route, and duration of therapy should always be individualized.

Adequate postoperative analgesia prevents unnecessary patient discomfort, may decrease morbidity, may decrease postoperative hospital lengths of stay, and thus may decrease costs. Because postoperative pain management has been deemed important, the American Society of Anesthesiologists has published practice guidelines regarding this topic.[1] Furthermore, in recognition of the need for improved pain management, The Joint Commission has developed standards for the assessment and management of pain in accredited hospitals and other health care settings.[2] Patient satisfaction (no doubt linked to adequacy of postoperative analgesia) has become an essential element that influences clinical activity of not only anesthesiologists but all health care professionals.

Achieving optimal pain relief after cardiac surgery is often difficult. Pain may be associated with many interventions, including sternotomy, thoracotomy, leg-vein harvesting, pericardiotomy, and/or chest tube insertion, among other interventions. Inadequate analgesia and/or an uninhibited stress response during the postoperative period may increase morbidity by causing adverse hemodynamic, metabolic, immunologic, and hemostatic alterations.[3–5] Aggressive control of postoperative pain, associated with an attenuated stress response, may decrease morbidity and mortality in high-risk patients after noncardiac surgery[6,7] and may also decrease morbidity and mortality in patients after cardiac surgery.[8,9] Adequate postoperative analgesia may be attained via a wide variety of techniques (Box 42.1). Traditionally, analgesia after cardiac surgery has been obtained with intravenous opioids (specifically morphine). However, intravenous opioid use is associated with definite detrimental side effects (eg, nausea and vomiting, pruritus, urinary retention, respiratory depression), and longer-acting opioids such as morphine may delay tracheal extubation during the immediate postoperative period via excessive sedation and/or respiratory depression. Thus in the current era of early extubation (fast-tracking), cardiac anesthesiologists are exploring unique options other than traditional intravenous opioids for the control of postoperative pain in patients after cardiac surgery.[10–12] The last decade has witnessed increased use of smaller incisions by cardiac surgeons, prompting clinical investigations into the use of intercostal, intrapleural, and paravertebral blocks (with and without catheters), and the emergence of long-acting liposomal bupivacaine may revolutionize the use of these techniques. No single technique is clearly superior; each possesses distinct advantages and disadvantages. It is becoming increasingly clear that a multimodal approach and/or a combined analgesic regimen (using a variety of techniques) is the best way to approach postoperative pain in all patients after surgery to maximize analgesia and minimize side effects. When addressing postoperative analgesia in cardiac surgical patients, the choice of technique (or techniques) should be made only after a thorough analysis of the risk-benefit ratio of each technique in the specific patient in whom analgesia is desired.

BOX 42.1 TECHNIQUES AVAILABLE FOR POSTOPERATIVE ANALGESIA

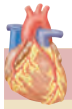
- Local anesthetic infiltration
- Nerve blocks
- Opioids
- Nonsteroidal antiinflammatory agents
- α-Adrenergic agents
- Intrathecal techniques
- Epidural techniques
- Multimodal analgesia

Pain and Cardiac Surgery

Surgical or traumatic injury initiates changes in the peripheral and central nervous systems that must be addressed therapeutically to promote postoperative analgesia and, it is hoped, positively influence clinical outcomes (Box 42.2). The physical processes of incision, traction, and cutting of tissues stimulate free nerve endings and a wide variety of specific nociceptors. Receptor activation and activity are further modified by the local release of chemical mediators of inflammation and sympathetic amines released via the perioperative surgical stress response. The perioperative surgical stress response peaks during the immediate postoperative period and exerts major effects on many physiologic processes. The potential clinical benefits of attenuating the perioperative surgical stress response (above and beyond simply attaining adequate clinical analgesia) have received significant attention during the 2000s and remain fairly controversial.[13] However, inadequate postoperative analgesia and/or an uninhibited perioperative surgical stress response clearly has the potential to initiate pathophysiologic changes in all major organ systems, including the cardiovascular, pulmonary, gastrointestinal, renal, endocrine, immunologic, and/or central nervous systems, all of which may lead to substantial postoperative morbidity.

Pain after cardiac surgery may be intense, and it originates from many sources, including the incision (eg, sternotomy, thoracotomy), intraoperative tissue retraction and dissection, vascular cannulation sites, vein-harvesting sites, and chest tubes, among other sources.[14,15] Patients in whom an internal mammary artery is surgically exposed and used as a bypass graft may have substantially more postoperative pain.[16]

A prospective clinical investigation involving 200 consecutive patients undergoing cardiac surgery via median sternotomy assessed the location, distribution, and intensity of postoperative pain.[14] All patients received 25 to 50 μg/kg of intraoperative intravenous fentanyl, were subjected to routine cardiopulmonary bypass (CPB), had their arms positioned along their body on the surgical table, had their sternum closed with five peristernal wires, and received mediastinal and thoracic drains passed through the rectus abdominis muscle just below the xiphoid. A subgroup (127 patients) also underwent long saphenous vein harvesting from either the calf (men) or thigh (women). All patients were extubated before the first postoperative



BOX 42.2 PAIN AND CARDIAC SURGERY

- Originates from many sources.
- Most commonly originates from the chest wall.
- Preoperative expectations influence postoperative satisfaction.
- Quality of postoperative analgesia may influence morbidity.

morning. Postoperative analgesic management was standardized and included intravenous morphine, oral paracetamol, oral tramadol, and subcutaneous morphine. Pain location, distribution, and intensity were documented in the morning on the first, second, third, and seventh postoperative days using a standardized picture dividing the body into 32 anatomic areas. A numerical rating scale of 0 to 10 (with 0 representing no pain and 10 representing the worst possible pain) was used to assess maximal pain intensity. These investigators found that maximal pain intensity was highest on postoperative day 1 and lowest on postoperative day 3. However, maximal pain intensity was only graded as moderate (mean pain score was approximately 3.8) and did not diminish during the first 2 postoperative days and yet started to decline between postoperative days 2 and 3. Pain distribution did not appear to vary throughout the postoperative period, yet its location did (more shoulder pain was observed on postoperative day 7). As time after surgery increased, the pain usually moved primarily from the incisional and epigastric regions to osteoarticular areas.

Another source of postoperative pain in patients after cardiac surgery is thoracic cage rib fractures, which may be common.[17,18] Furthermore, sternal retraction, causing posterior rib fracture, may lead to brachial plexus injury. In these patients, routine chest radiographs may appear normal despite the presence of fracture. Thus bone scans (better at detecting rib fractures than chest radiographic images) are recommended whenever unexplained postoperative nonincisional pain is present in a patient who has undergone sternal retraction.[18] Other studies have indicated that the most common source of pain in patients after cardiac surgery is the chest wall. Age also appears to affect pain intensity; patients younger than 60 years of age often have greater pain intensity than patients older than 60 years of age. Although maximal pain intensity after cardiac surgery is usually only moderate, ample room for clinical improvement in analgesic control to minimize pain intensity remains, especially during the first few postoperative days.

Persistent pain after cardiac surgery, although rare, can be problematic.[19–21] The cause of persistent pain after sternotomy is multifactorial, yet tissue destruction, intercostal nerve trauma, scar formation, rib fractures, sternal infection, stainless-steel wire sutures, and/or costochondral separation may all play roles.[22] Such chronic pain is often localized to the arms, shoulders, or legs. Postoperative brachial plexus neuropathies also may occur and have been attributed to rib fracture fragments, internal mammary artery dissection, suboptimal positioning of the patient during surgery, and/or central venous catheter placement. Postoperative neuralgia of the saphenous nerve has also been reported after harvesting of saphenous veins for coronary artery bypass grafting (CABG). Younger patients appear to be at greater risk for the development of chronic, long-lasting pain. The correlation of severity of acute postoperative pain and the development of chronic pain syndromes has been suggested (patients requiring more postoperative analgesics may be more likely to develop chronic pain), yet this link is still vague.

Ho and associates[19] assessed 244 patients after cardiac surgery and median sternotomy and found that persistent pain (defined as pain still present 2 or more months after surgery) was reported in almost 30% of patients. The incidence rate of persistent pain at any site was 29% (71 patients) and for sternotomy was 25% (61 patients). Other common locations of persistent pain reported to these investigators were the shoulders (17%), back (16%), and neck (6%). However, such persistent pain was usually reported as mild, with only 7% of patients reporting interference with daily living. The most common words used to describe the persistent pain were "annoying" (57%), "nagging" (33%), "dull" (30%), "sharp" (25%), "tiring" (22%), "tender" (22%), and "tight" (22%). The temporal nature of this pain was mostly reported as being transient and intermittent. Twenty patients (8%) also described symptoms of numbness, burning pain, and tenderness over the internal mammary artery–harvesting site, symptoms suggestive of internal mammary artery syndrome. Thus it was concluded that mild persistent pain after cardiac surgery and median sternotomy is common yet only infrequently substantially interferes with daily life.

Although the most common source of pain in patients after cardiac surgery remains the chest wall, leg pain from vein-graft harvesting can be problematic as well. Such pain may not become apparent until the late postoperative period, which may be related to the progression of patient mobilization and the decreasing impact of sternotomy pain (unmasking leg incisional pain). Using minimally invasive vein-graft harvesting techniques (endoscopic vein-graft harvesting) decreases the intensity and duration of postoperative leg pain, compared with conventional open techniques.[23] Although initial harvest times may be prolonged, harvest times become equivalent between the two techniques (endoscopic vs conventional) once a short learning curve is overcome. Furthermore, leg morbidity (eg, infection, dehiscence) may be less in patients undergoing endoscopic vein-graft harvesting, compared with patients undergoing conventional open techniques because of different incisional lengths.

Patient satisfaction with quality of postoperative analgesia is as much related to the comparison between anticipated and experienced pain as it is to the actual level of pain experienced. Satisfaction is related to a situation that is better than predicted, dissatisfaction to one that is worse than expected. Patients undergoing cardiac surgery remain concerned regarding the adequacy of postoperative pain relief and preoperatively tend to expect a greater amount of postoperative pain than that which is actually experienced.[15] Because of these unique preoperative expectations, patients after cardiac surgery who postoperatively receive only moderate analgesia will likely still be satisfied with their pain control. Thus patients may experience pain of moderate intensity after cardiac surgery yet still express very high satisfaction levels.[15,16]

Scientific advances have allowed a better understanding of how and why pain occurs, leading to unique and possibly clinically beneficial pain management strategies. Noxious input from an acute injury may trigger a state of central nervous system sensitization, called *wind-up.* In essence, dorsal horn neurotransmitter release via nociceptive input conditions the central nervous system in such a way that responsiveness (secondary hyperalgesia) is enhanced. Although experimental evidence indicates that enhanced responsiveness outlasts the initial provocative insult (induced sensitivity outlasts the stimulus), the exact clinical relevance remains to be determined. Advances regarding spinal cord neuropharmacology have led to research aimed at modifying or blocking *N*-methyl-D-aspartate receptors to influence pain control and the concept of preemptive analgesia, which is predicated on addressing pain before it initiates peripheral and central sensitization. However, given the redundancy in neurotransmitter receptor systems in the central nervous system, it is unlikely that blocking only one component will result in clear clinical benefits. Although the use of *N*-methyl-D-aspartate receptor antagonists and the concept of preemptive analgesia are intriguing and certain clinical investigations appear to support their utility, clear and definite clinical benefits in humans remain to be determined. Debate continues over the potential benefits of *N*-methyl-D-aspartate receptor antagonists and the utility of preemptive analgesic treatment, as well as the direction in which research and conceptual development in this exciting field needs to proceed.

Potential Clinical Benefits of Adequate Postoperative Analgesia

Inadequate analgesia (coupled with an uninhibited stress response) during the postoperative period may lead to many adverse hemodynamic (tachycardia, hypertension, vasoconstriction), metabolic (increased catabolism), immunologic (impaired immune response), and hemostatic (platelet activation) alterations (Box 42.3). In patients undergoing cardiac surgery, perioperative myocardial ischemia (diagnosed by electrocardiography and/or transesophageal echocardiography) is most commonly observed during the immediate postoperative period and appears to be related to outcome.[24,25] Intraoperatively, initiation of CPB causes substantial increases in stress response hormones (eg, norepinephrine, epinephrine) that persist into the

BOX 42.3 POTENTIAL CLINICAL BENEFITS OF ADEQUATE POSTOPERATIVE ANALGESIA

- Hemodynamic stability
- Metabolic stability
- Immunologic stability
- Hemostatic stability
- Stress-response attenuation
- Decreased morbidity

immediate postoperative period and may contribute to myocardial ischemia observed during this time.[26–28] Furthermore, postoperative myocardial ischemia may be aggravated by cardiac sympathetic nerve activation, which disrupts the balance between coronary blood flow and myocardial oxygen demand.[29] Thus during the pivotal immediate postoperative period after cardiac surgery, adequate analgesia coupled with stress-response attenuation may potentially decrease morbidity and enhance health-related quality of life.[29,30]

Existing evidence indicates that aggressive control of postoperative pain in patients after noncardiac surgery may beneficially affect outcome.[6,7] In 1987, Yeager and colleagues[7] in a small ($n = 53$ patients), randomized, controlled clinical trial involving patients undergoing major thoracic vascular surgery revealed that patients who were managed with more intense perioperative anesthesia and analgesia demonstrated decreased postoperative morbidity and improved operative outcome. In 1991, Tuman and associates[6] in another small ($n = 80$ patients), randomized, controlled clinical trial involving patients undergoing lower extremity revascularization revealed that patients who were managed with more intense perioperative anesthesia and analgesia demonstrated improved outcome compared with patients receiving routine on-demand narcotic analgesia.

Existing evidence also indicates that aggressive control of postoperative pain in patients after cardiac surgery may beneficially affect outcome. Two intriguing clinical investigations published in 1992 hint at such possibilities.[8,9] Mangano and associates[8] prospectively randomized 106 adult patients undergoing elective CABG to receive either standard postoperative analgesia or intensive analgesia during the immediate postoperative period. Standard-care patients received low-dose intermittent intravenous morphine for the first 18 postoperative hours, whereas intensive-analgesia patients received a continuous intravenous sufentanil infusion during the same time period. Patients receiving sufentanil demonstrated lesser severity of myocardial ischemia episodes (detected by continuous electrocardiographic monitoring) during the immediate postoperative period. The authors postulated that the administration of intensive analgesia during the immediate postoperative period may have more completely suppressed sympathetic nervous system activation, thereby having numerous beneficial clinical effects, including alterations in the sensitivity of platelets to epinephrine, alterations in fibrinolysis, enhanced regional left ventricular function, and decreased coronary artery vasoconstriction, all potentially leading to a reduced incidence and reduced severity of myocardial ischemia. Anand and Hickey[9] prospectively randomized 45 neonates undergoing elective cardiac surgery (mixed procedures) to receive either standard perioperative care or deep opioid anesthesia. Standard-care patients received a halothane-ketamine-morphine anesthetic with intermittent intravenous morphine for the first 24 postoperative hours, whereas deep-opioid patients received an intravenous sufentanil anesthetic with a continuous infusion of either intravenous fentanyl or intravenous sufentanil during the same postoperative period. Neonates receiving continuous postoperative opioid infusions demonstrated a reduced perioperative stress response (assessed via multiple blood mediators), less perioperative morbidity (hyperglycemia, lactic acidemia, sepsis, metabolic acidosis, disseminated intravascular coagulation), and significantly fewer deaths than the control group (0/30 vs 4/15, respectively; $p < 0.01$). The accompanying editorial accurately summarizes this clinical investigation: "What Anand and Hickey have shown is that this reluctance to treat pain adequately is not a necessary evil. It markedly contributes to a bad outcome."[31] Unfortunately, aggressive control of postoperative pain in patients after cardiac surgery with relatively large amounts of intravenous opioids in this manner does not allow tracheal extubation in the immediate postoperative period (a goal of current practice).

Techniques Available for Postoperative Analgesia

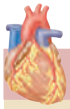
Although the mechanisms of postoperative pain and the pharmacologic actions of analgesic drugs are relatively well understood, the delivery of effective postoperative analgesia remains far from universal. Many techniques are available (see Box 42.1). In general, the American Society of Anesthesiologists Task Force on Acute Pain Management in the Perioperative Setting reports that the existing literature supports the efficacy and safety of three techniques used by anesthesiologists for perioperative pain control: (1) regional analgesic techniques, including but not limited to intercostal blocks, plexus blocks, and local anesthetic infiltration of incisions; (2) patient-controlled analgesia (PCA) with systemic opioids; and (3) intrathecal and epidural opioid analgesia.[1] Regarding regional analgesic techniques, the existing literature supports the analgesic efficacy of peripheral nerve blocks and postincisional infiltration with local anesthetics for postoperative analgesia, and yet it is equivocal regarding the analgesic benefits of preincisional infiltration. Regarding PCA with systemic opioids, the existing literature supports its efficacy compared with intramuscular techniques for postoperative pain management, yet the existing literature is equivocal regarding the efficacy of PCA techniques compared with nurse- or staff-administered intravenous analgesia. In addition, the existing literature is equivocal regarding the comparative efficacy of epidural PCA versus intravenous PCA techniques.

When background opioid infusions are included with PCA techniques, patients report better analgesia and greater morphine consumption without increased incidence of nausea, vomiting, pruritus, or sedation. Although greater morphine consumption during PCA with continuous background infusion might predispose patients to respiratory depression, the existing literature is insufficient to reveal this potential adverse effect. Finally, regarding intrathecal and epidural opioid analgesia, the existing literature supports the efficacy of epidural morphine and fentanyl for perioperative analgesia but is insufficient to characterize the spectrum of risks and benefits associated with the use of other specific opioids administered by these routes. Pruritus and urinary retention more frequently occur when morphine is given intrathecally or epidurally compared with systemic (intravenous or intramuscular) administration. Furthermore, epidural morphine provides more effective pain relief than intramuscular morphine. Similarly, epidural fentanyl provides more effective postoperative analgesia than intravenous fentanyl. The existing literature is insufficient to evaluate the effects of epidural techniques administered at different times (eg, preincisional, postincisional, postoperative).

Local Anesthetic Infiltration

Pain after cardiac surgery is often related to median sternotomy, peaking during the first 2 postoperative days. Because of problems associated with traditional intravenous opioid analgesia (nausea and vomiting, pruritus, urinary retention, respiratory depression) and with the more recently introduced nonsteroidal antiinflammatory drugs and cyclooxygenase (COX) inhibitors (gastrointestinal bleeding, renal dysfunction), alternative methods of achieving postoperative analgesia in cardiac surgical patients have been sought. One such alternative method that may hold promise is the continuous infusion of a local anesthetic (Box 42.4).

In a prospective, randomized, placebo-controlled, double-blind clinical trial, White and colleagues[32] studied 36 patients undergoing



BOX 42.4 LOCAL ANESTHETIC INFILTRATION

- Advantage: Simple, reliable analgesia
- Disadvantage: Tissue necrosis?

cardiac surgery. Intraoperative management was standardized. All patients had two indwelling infusion catheters placed at the median sternotomy incision site at the end of surgery; one was placed in the subfascial plane above the sternum and the other one was placed above the fascia in the subcutaneous tissue. Patients received 0.25% bupivacaine ($n = 12$), 0.5% bupivacaine ($n = 12$), or normal saline ($n = 12$) via a constant-rate infusion through the catheter (4 mL/hr) for 48 hours after surgery. Average times to tracheal extubation were similar in the three groups (approximately 5 to 6 hours). Compared with the control group (normal saline), a statistically significant reduction in verbal rating scale pain scores and intravenous PCA morphine use was observed in the 0.5% bupivacaine group. Patient satisfaction with pain management was also improved in the 0.5% bupivacaine group versus the control group. However, no significant differences were observed in PCA morphine use between the 0.25% bupivacaine and control groups. Although tracheal extubation time and the duration of the intensive care unit (ICU) stay (30 versus 34 hours, respectively) were not significantly altered, time to ambulation (1 vs 2 days, respectively) and the duration of hospital stay (4.2 vs 5.7 days, respectively) were lower in the 0.5% bupivacaine group than in the control group. Serum bupivacaine concentrations in patients were reasonable, yet one complication related to the local anesthetic delivery system was encountered when a catheter tip was inadvertently broken off during its removal from the incision site, which required surgical reexploration of the wound under local anesthesia. The authors conclude that continuous infusion of 0.5% bupivacaine at 4 mL/hr is effective for decreasing postoperative pain and the need for postoperative supplemental opioid analgesic medication and for improving patient satisfaction (earlier ambulation, reduced length of hospital stay) with pain management after cardiac surgery.

Another clinical investigation revealed the potential benefits of using a continuous infusion of a local anesthetic in patients after cardiac surgery. In this prospective, randomized, placebo-controlled, double-blind clinical trial, Dowling and associates[33] studied 35 healthy patients undergoing cardiac surgery. Patients undergoing elective CABG via median sternotomy were randomized to either ropivacaine or placebo groups. At the end of the surgery but before wound closure, bilateral intercostal nerve injections from T1 to T12 were performed using 20 mL of either 0.2% ropivacaine or normal saline. After sternal reapproximation with wires, two catheters with multiple side openings were placed anterior to the sternum (Fig. 42.1). These catheters were connected to a pressurized elastomeric pump containing a flow regulator, which allowed for the delivery of 0.2% ropivacaine or normal saline at approximately 4 mL/hr. The intraoperative anesthetic technique was standardized (short-acting anesthetics were used to minimize the presence of residual anesthetic agents in the postoperative period) as was postoperative pain management via intravenous PCA morphine (for 72 hours). Both groups exhibited similar postoperative extubation times (approximately 8 hours). The sternal catheters were removed in both groups after 48 hours. Total mean PCA morphine consumption during the immediate postoperative period (72 hours) was significantly decreased in the ropivacaine group compared with the placebo group (47.3 vs 78.7 mg, respectively; $p = 0.038$). Mean overall pain scores (scale ranging from 0 for no pain to 10 for maximum pain imaginable) were also significantly decreased in the ropivacaine group compared with the placebo group (1.6 vs 2.6, respectively; $p = 0.005$). Most interestingly, patients receiving ropivacaine had a mean hospital length of stay of 5.2 ± 1.3 days compared with 8.2 ± 7.9 days for patients receiving normal saline, a

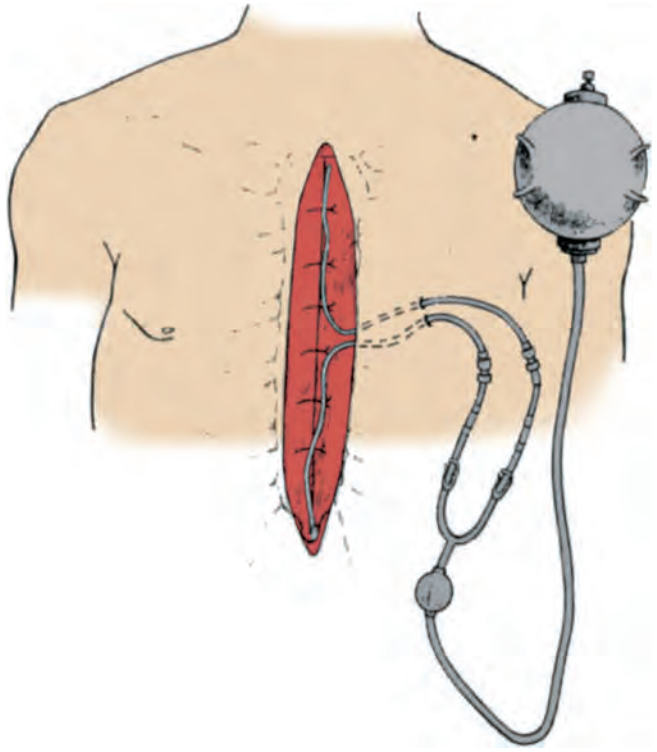


Fig. 42.1 Intraoperative placement of the pressurized elastomeric pump and catheters. *(Dowling R, Thielmeier K, Ghaly A, et al. Improved pain control after cardiac surgery: results of a randomized, double-blind, clinical trial.* J Thorac Cardiovasc Surg. *2003;126:1271–1278.)*

difference that was statistically significant ($p = 0.001$). One patient in the placebo group had an extremely long postoperative hospitalization (39 days). However, the difference between the two groups regarding the lengths of hospital stay remained statistically significant even when this outlier was removed (5.2 ± 1.3 days vs 6.3 ± 2.8 days, respectively; $p < 0.01$). Despite the differences in postoperative analgesia, postoperative pulmonary function (assessed via forced expiratory volume in 1 second and peak expiratory flow) was similar between the two groups. No difference was observed in wound infections or wound healing between the two groups during hospitalization or after hospital discharge. No complications related to placement of the sternal wound catheters or performance of the intercostal nerve blocks were encountered. The authors concluded that their analgesic technique significantly improves postoperative pain control while decreasing the amount of opioid analgesia required in patients subjected to standard median sternotomy. The significant decrease in hospital lengths of stay observed by the investigators is intriguing, may result in substantial cost reductions, and deserves further study.

The management of postoperative pain with continuous direct infusion of a local anesthetic into the surgical wound has been described after a wide variety of surgeries other than cardiac (eg, inguinal hernia repair, upper abdominal surgery, laparoscopic nephrectomy, cholecystectomy, knee arthroplasty, shoulder surgery, gynecologic operative laparoscopy).[34] The infusion pump systems used for anesthetic wound infusion are regulated by the US Food and Drug Administration (FDA) as medical devices. Thus adverse events involving these infusion pump systems during direct local anesthetic infusion into surgical wounds are reported to this organization. Complications encountered with these infusion pump systems reported to the FDA include tissue necrosis, surgical wound infection, and cellulitis after orthopedic, gastrointestinal, podiatric, and other surgeries. None of these reported adverse events involved patients undergoing cardiac surgery. The most commonly reported complication was tissue necrosis, an adverse event rarely seen after normal surgical procedures. Furthermore, the consequences of

these reported adverse events were typically severe and required intervention and additional medical and/or surgical treatment. Although these initial reports may be isolated incidents, they may also represent an early warning sign and provide a potentially important signal, suggesting the need for further investigation into the relationship between the use of these pumps for direct continuous infusion of local anesthetics and other drugs into surgical wounds and the adverse events of tissue necrosis, serious infections, or cellulitis. Neither of the two clinical investigations involving local anesthetic infusion in patients after cardiac surgery with median sternotomy reported such wound complications.[32,33] Regardless, these safety issues merit careful consideration because of the importance of sternal wound complications in this setting.

The anterior and posterior branches of the intercostal nerves innervate the sternum. Parasternal infiltration of a local anesthetic therefore is a possible means of improving postoperative analgesia. Although the use of parasternal blocks has not been extensively investigated, one small, prospective, randomized, placebo-controlled, double-blind clinical study indicated that parasternal block and local anesthetic infiltration of the sternotomy wound and mediastinal tube sites with local anesthetic may be a useful analgesic adjunct for patients who are expected to undergo early tracheal extubation after cardiac surgery.[35]

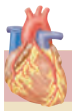
Nerve Blocks

With the increasing popularity of minimally invasive cardiac surgery, which uses nonsternotomy incisions (minithoracotomy), the use of nerve blocks for the management of postoperative pain has increased[36–43] (Box 42.5). Thoracotomy incisions (transverse anterolateral minithoracotomy, vertical anterolateral minithoracotomy), because of costal cartilage tissue trauma to ribs, muscles, or peripheral nerves, may induce more intense postoperative pain than that resulting from median sternotomy. Adequate analgesia after thoracotomy incisions is important because pain is a key component in the alteration of lung function after this type of incision. Uncontrolled pain causes a reduction in respiratory mechanics, reduced mobility, and increases in hormonal and metabolic activity. Perioperative deterioration in respiratory mechanics may lead to pulmonary complications and hypoxemia, which may in turn lead to myocardial ischemia or infarction, cerebrovascular accidents, thromboembolism, delayed wound healing, increased morbidity, and prolonged hospital stay. Various analgesic techniques have been developed to treat postoperative thoracotomy pain. The most commonly used techniques include intercostal nerve block, intrapleural administration of a local anesthetic, and thoracic paravertebral block. Intrathecal techniques and epidural techniques are also effective in controlling postthoracotomy pain and are covered in greater detail later in this chapter.

Intercostal nerve block has been extensively used for analgesia after thoracic surgery[36,38] and can be performed either intraoperatively or postoperatively. It usually provides sufficient analgesia lasting approximately 6 to 12 hours (depending on the amount and type of local anesthetic used) and may need to be repeated if additional analgesia is required. Local anesthetics may be administered as a single injection under direct vision before chest closure, as a single preoperative percutaneous injection, as multiple percutaneous serial injections, or via an indwelling intercostal catheter. Blockade of intercostal nerves interrupts C-fiber afferent transmission of impulses to the spinal cord. A single intercostal injection of a long-acting local anesthetic can provide pain relief and improve pulmonary function in patients after thoracic surgery for up to 6 hours. A continuous extrapleural intercostal nerve block technique may be used, during which a catheter is placed percutaneously into an extrapleural pocket by the surgeon to achieve longer duration of analgesia. A continuous intercostal catheter allows frequent dosing or infusions of local anesthetic agents and avoids multiple needle injections. Various clinical studies have confirmed the analgesic efficacy of this technique, and the technique compares favorably with thoracic epidural analgesic techniques.[36,38] A major concern associated with intercostal nerve block is the potentially high amount of local anesthetic systemic absorption. However, multiple clinical studies involving patients undergoing thoracic surgery have documented safe blood levels with standard techniques. Clinical investigations involving patients undergoing thoracic surgery indicate that intercostal nerve blockade by intermittent or continuous infusion of bupivacaine (0.25% to 0.5%) or ropivacaine (0.5% to 0.75%) through indwelling intercostal catheters is an effective method for supplementing systemic intravenous opioid analgesia for postthoracotomy pain.[36,38,44,45] The value of single preclosure injections remains doubtful.

Intrapleural administration of local anesthetics initiates analgesia via mechanisms that remain incompletely understood. However, the mechanism of action of extrapleural analgesia seems to depend primarily on diffusion of the local anesthetic into the paravertebral region. Local anesthetics then affect not only the ventral nerve root but also afferent fibers of the posterior primary ramus. Posterior ligaments of the posterior primary ramus innervate posterior spinal muscles and skin and are traumatized during posterolateral thoracotomy. Intrapleural administration of a local anesthetic to this region through a catheter inserted in the extrapleural space creates an analgesic region in the skin. The depth and width of this region depend on the diffusion of the local anesthetic in the extrapleural space. With this technique, local anesthetics may be administered by intermittent or continuous infusion regimens via an indwelling intrapleural catheter placed between the parietal and visceral pleura. Concerns regarding systemic absorption of a local anesthetic and toxicity are always present with this technique yet have not been substantiated in clinical studies that assayed plasma levels. A handful of clinical investigations involving patients undergoing thoracic surgery via thoracotomy incision suggests that 0.25% to 0.5% bupivacaine may improve analgesia in patients after thoracic surgery, yet its true efficacy as a postoperative analgesic in this patient population remains somewhat controversial.[39] The analgesic benefits are short in duration, and a significant overall opioid-sparing effect does not appear to occur. Furthermore, the optimal concentration and duration regimen remains undefined. However, a prospective, randomized, clinical study involving 50 patients undergoing minimally invasive direct CABG via minithoracotomy indicates that an intrapleural analgesic technique with 0.25% bupivacaine is safe, effective, and compares favorably (ie, provides superior postoperative analgesia) with a conventional thoracic epidural technique.[40] These investigators noted, however, that careful catheter positioning, chest tube clamping, and anchoring of the catheter are mandatory for postoperative intrapleural analgesia to be effective. A major factor implicated in the lack of efficacy regarding intrapleural techniques is loss of the local anesthetic solution through intercostal chest drainage tubes. Although clamping the chest tubes during the postoperative period will increase analgesic efficacy, it may not be safe to clamp chest tubes for extended periods because they provide important drainage of blood and air and allow for enhanced lung patency and expansion. Apart from proper catheter positioning (inserting the catheter under direct vision and anchoring the catheter to skin are both essential), effective analgesia with this technique also appears to depend on whether lung surgery is performed or whether the anatomic and physiologic structure of the pleura is relatively intact.

Thoracic paravertebral block involves the injection of a local anesthetic adjacent to the thoracic vertebrae close to where the spinal nerves emerge from the intervertebral foramina (Fig. 42.2). Thoracic paravertebral block, compared with thoracic epidural analgesic techniques, appears to provide equivalent analgesia, is technically easier, and may harbor less risk. Several different techniques exist for successful thoracic paravertebral block and have been extensively reviewed.[37,46]



BOX 42.5 NERVE BLOCKS

- Advantage: Simple, long-lasting analgesia
- Disadvantage: Unreliable?

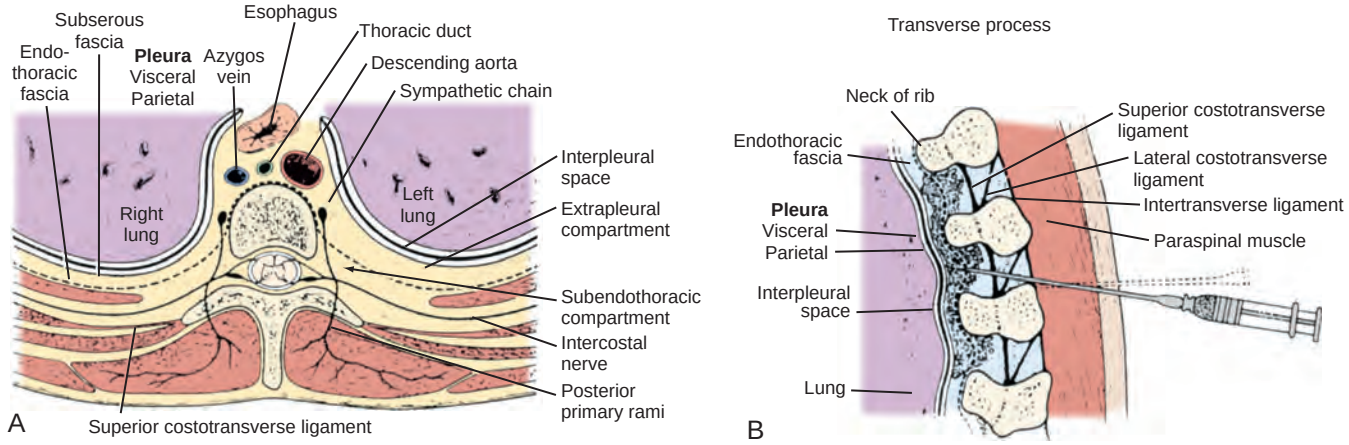


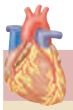
Fig. 42.2 Anatomy of the thoracic paravertebral space (A) and sagittal section through the thoracic paravertebral space showing a needle that has been advanced above the transverse process (B). *(From Karmakar MK. Thoracic paravertebral block.* Anesthesiology. *2001;95:771–780.)*

The classic technique, most commonly used, involves eliciting loss of resistance. Injection of a local anesthetic results in ipsilateral somatic and sympathetic nerve blockade in multiple contiguous thoracic dermatomes above and below the site of injection, together with the possible suppression of the neuroendocrine stress response to surgery. These blocks may be effective in alleviating acute and chronic pain of unilateral origin from the chest, abdomen, or both. Bilateral use of thoracic paravertebral block has also been described. Continuous thoracic paravertebral infusion of a local anesthetic via a catheter placed under direct vision at thoracotomy is also a safe, simple, and an effective method of providing analgesia after thoracotomy. It is usually used in conjunction with adjunct intravenous opioid or other analgesics to provide optimal relief after thoracotomy. Although supplemental intravenous analgesics are usually required, opioid requirements are substantially reduced.

Unilateral paravertebral block is useful for attaining postthoracotomy analgesia because pain after lateral thoracotomy is essentially always unilateral. The role of bilateral thoracic paravertebral block remains to be defined. The benefits of unilateral paravertebral blockade are a reduced incidence of adverse events (hypotension, urinary retention) and a decreased risk for systemic local anesthetic toxicity because less local anesthetic is used. Continuous thoracic paravertebral block as part of a balanced analgesic regimen may provide effective pain relief with few adverse effects after thoracotomy and appears to be comparable with thoracic epidural analgesia (TEA).[37,46–49]

Intercostal nerve block, intrapleural administration of local anesthetic, and thoracic paravertebral block offer the advantages of simplicity and efficacy in controlling postoperative pain in patients after thoracic surgery. However, although analgesic efficacy of these techniques may be comparable with intrathecal and epidural techniques, these methods appear to work best as part of a multimodal analgesic regimen (ie, supplementing other analgesic techniques). Complications associated with the infiltration of large quantities of local anesthetics, which is often required, is always a concern when using these analgesic techniques.

For a wide variety of reasons, including the increased use of small thoracic incisions by cardiac surgeons, the last decade has seen a resurgence of nerve blocks (usually catheter-based techniques) in patients undergoing cardiac surgery. Specifically, recent clinical studies using intercostal catheters,[50] intrapleural catheters,[51–53] and paravertebral blockade[46,54–56] indicate that these techniques may have unique advantages, even when compared with traditional intrathecal and epidural techniques.[57–63] Lastly, the emergence of liposomal bupivacaine, which has the potential to provide clinical analgesia for 96 hours after a single injection, may revolutionize the use of single-shot nerve blocks for thoracic and cardiac surgeries.[64–66]



BOX 42.6 OPIOIDS

- Advantages
  - Time-tested analgesia
  - Reliable
- Disadvantages
  - Pruritus
  - Nausea and vomiting
  - Urinary retention
  - Respiratory depression

Opioids

Beginning in the 1960s and continuing for essentially 30 years, large doses of intravenous opioids (starting with morphine) have been administered to patients undergoing cardiac surgery[67,68] (Box 42.6). Because even very large amounts of intravenous opioids do not initiate "complete" anesthesia (eg, amnesia, analgesia, muscle relaxation), other intravenous and inhalation agents must be administered during the intraoperative period.[69] Analgesia is the best known and most extensively investigated opioid effect, yet opioids are also involved in a diverse array of other physiologic functions including the control of pituitary and adrenal medulla hormone release and activity, the control of cardiovascular and gastrointestinal function, and the regulation of respiration, mood, appetite, thirst, cell growth, and the immune system.[70] A number of well-known and potential side effects of opioids (eg, nausea and vomiting, pruritus, urinary retention, respiratory depression) may limit postoperative recovery when they are used for postoperative analgesia.

Opioids interact with specific receptors that are widely distributed within the central nervous system to produce a variety of pharmacologic effects. Currently, three major distinct opioid-receptor types are recognized: μ, κ, and δ. The μ receptor has two subtypes: a high-affinity μ_1 receptor and a low-affinity μ_2 receptor. The supraspinal mechanisms of analgesia are thought to involve μ_1 receptors, whereas spinal analgesia, respiratory depression, and gastrointestinal effects are associated with the μ_2 receptor. Other subtypes of the μ receptor have been isolated, yet their clinical relevance remains to be elucidated. Likewise, subtypes of the κ and δ receptors have also been isolated. Selective κ agonists may have therapeutic potential as analgesics, lacking the adverse side effects produced by the current μ-receptor agonists. δ_1 Receptors appear to mediate spinal analgesia, whereas δ_2 receptors appear to mediate supraspinal analgesia. Unfortunately, despite

extensive pharmacologic and functional studies of the wide variety of opioid receptors, understanding the structural basis of their actions remains quite limited.

The classic pharmacologic effect of opioids is analgesia, and these drugs have traditionally been the initial choice when a potent postoperative analgesic is required. Two anatomically distinct sites exist for opioid receptor–mediated analgesia: supraspinal and spinal. Systemically administered opioids produce analgesia at both sites. Supraspinally, the μ_1 receptor is primarily involved in analgesia, whereas the μ_2 receptor is the receptor predominantly involved in the spinal modulation of nociceptive processing. κ Receptors are important in mediating spinal and supraspinal analgesia as well. δ Ligands may have a modulatory rather than a primary analgesic role. All three types of opioid receptors (μ, κ, and δ) have been demonstrated in peripheral terminals of sensory nerves. Activation of these receptors seems to require an inflammatory reaction because locally applied opioids do not produce analgesia in healthy tissue. The inflammatory process also may activate previously inactive opioid receptors.

Although nausea and vomiting, pruritus, and urinary retention are more commonly encountered, respiratory depression remains the most feared complication associated with use of opioids.[71] All μ receptor agonist opioids produce dose-related respiratory depression that appears to be mediated via μ_2 receptors. Pure κ agonists have little effect on respiration, and the role of δ receptors in respiratory control remains to be elucidated. The primary respiratory effect of opioids is a reduction in the sensitivity of the respiratory center to carbon dioxide (together with depression of both medullary and peripheral chemoreceptors). Initially, respiratory rate is affected more than tidal volume, which may actually increase. With increasing doses of opioids, respiratory rhythmicity is disturbed, resulting in the irregular gasping breathing characteristic of opioid overdose. In addition to the retention of carbon dioxide, respiratory depression may also result in hypoxia (the hypoxic drive to ventilation is depressed by the opioids as well). Older adult patients seem to be more sensitive to the respiratory depressant effects of opioids than younger patients, and the dose used needs to be adjusted accordingly. The realization that all other central nervous system depressants, such as benzodiazepines, barbiturates, and/or inhalation anesthetics, will potentiate the respiratory depressant effects of the opioids is also important to keep in mind. Furthermore, in addition to the parent opioid drug, metabolites may contribute to respiratory depression in some circumstances. For instance, metabolites of morphine (morphine-6-β-glucuronide) may occur in substantial quantities after intravenous administration and may be responsible for a considerable proportion of the clinical effects of intravenous morphine.

Morphine is the prototype opioid agonist with which all opioids are compared and is perhaps the most popular analgesic used in patients after cardiac surgery. Many semisynthetic derivatives are made by simple modifications of the morphine molecule. Morphine is a poorly lipid soluble and binds approximately 35% to plasma proteins, particularly albumin. Morphine is primarily metabolized in the liver, principally by conjugation to water-soluble glucuronides. The liver is the predominant site for morphine biotransformation, although extrahepatic metabolism also occurs in the kidney, brain, and possibly the gut. Extrahepatic clearance accounts for approximately 30% of the total body clearance. The terminal elimination half-life of morphine is 2 to 3 hours. In patients with liver cirrhosis, morphine pharmacokinetic actions are variable, probably reflecting the variability of liver disease in patients. Morphine's terminal elimination half-life in patients with renal disease is comparable with that of patients without renal disease. Although morphine is perhaps the most popular intravenous analgesic used in patients after cardiac surgery, other synthetically derived opioids have been developed and may be used as well. These include fentanyl, alfentanil, sufentanil, and remifentanil.

Fentanyl is considerably more potent (60 to 80 times) than morphine. However, at the opioid receptor, the intrinsic affinities of fentanyl and morphine differ by only a factor of 2 to 3. The differences between receptor affinities and clinical potency ratios arise from differing physiochemical and pharmacokinetic properties of the drugs, in particular the differences in lipid solubility. Fentanyl is highly lipid soluble, which influences the rate of entry and exit to and from organs and tissues, especially the central nervous system, which has a high lipid content.

Fentanyl is rapidly transferred across the blood-brain barrier, resulting in a rapid onset of action after intravenous injection. The relative potential for entering the central nervous system is approximately 150 times greater for fentanyl than for morphine. However, the large quantities of fentanyl taken up by adipose tissues may act as a reservoir (depending on dosage amounts) that slowly releases fentanyl back into the systemic circulation when plasma concentrations decline to less than that in fat. This slow reentry may serve to maintain the plasma concentration and is one factor in the relatively long plasma terminal elimination half-life of fentanyl. The drug is rapidly and extensively metabolized by the liver to inactive metabolites. After a bolus intravenous injection, plasma fentanyl concentrations decrease rapidly because of the distribution from the plasma to tissues; consequently, fentanyl has a short duration of action after moderate (10 μg/kg) doses (see Chapter 10).

Larger doses convert fentanyl from a short-acting to a long-acting drug. With increased doses, the distribution phase is completed before the fentanyl concentration declines to threshold levels; therefore duration of action becomes dependent on the decrease in concentration during the much slower elimination phase. Thus to avoid an accumulation of fentanyl, successive doses at regular intervals should be progressively reduced in amount or the interval between doses of the same size should be progressively lengthened. When fentanyl is administered by continuous intravenous infusion, the rate of decline of fentanyl plasma concentration is significantly dependent on the duration of the infusion. Fentanyl undergoes substantial first-pass uptake in the lungs (approximately 80% of the injected dose). Hepatic extraction of fentanyl is also high, making its clearance dependent on liver blood flow. Thus factors that reduce liver blood flow also will decrease fentanyl clearance. Fentanyl metabolites will likely accumulate in patients with impaired renal function, yet this accumulation is unlikely to have clinical consequences because the metabolites are pharmacologically inactive. Because the liver is the principal organ for fentanyl biotransformation, decreases in hepatic function caused by liver disease will be expected to alter fentanyl pharmacokinetics.

The popularity of fentanyl as an intraoperative analgesic agent relates directly to the cardiovascular stability it provides, even in critically ill patients. Additionally, its analgesic efficacy relative to the intensity of side effects has prompted much interest in its use as an analgesic after surgery and/or in critically ill patients.[72] Fentanyl, as well as any opioid, can be administered intravenously for postoperative analgesia in many ways: using a loading dose with a continuous fixed or variable infusion, a fixed background infusion with PCA, or PCA alone. An intravenous bolus of 1 to 2 μg/kg is usually administered before initiating an infusion. If variable, the infusion rate is usually 1 to 2 μg/kg/hr and may be adjusted upward or downward as required by fluctuations in analgesic requirements or the appearance of side effects. Before the infusion rate is increased, small intravenous bolus doses of fentanyl may be administered. Infusion rates of 1.5 to 2.5 μg/kg/hr usually provide good-to-excellent postoperative analgesia. At rest, the quality of analgesia remains stable; however, with movement, analgesia may not be sufficient, even with greater infusion rates.

A background low-dose intravenous infusion of fentanyl may be combined with PCA to provide satisfactory analgesia with potentially fewer adverse effects. PCA bolus doses typically range from 5 to 50 μg, and background infusion rates may be fixed (ranging from 5 to 50 μg/hr) or variable (adjusted up and down according to clinical criteria). Generally, the larger the background infusion rate, the smaller the PCA bolus dose. Lockout intervals (ie, minimum time between doses) range from "on demand" (no lockout interval) to 15 minutes with the most common lockout interval being 1 to 5 minutes. The technique of using a background infusion plus PCA produces excellent postoperative analgesia. Fentanyl is rarely used alone for PCA because of

its brief duration of action. Morphine remains the most commonly administered opioid used alone in PCA.

Transdermal delivery of fentanyl has also been investigated extensively. This modality is simple, noninvasive, and allows continuous release of fentanyl into the systemic circulation. However, the steady release of fentanyl in such a manner does not allow flexibility in dose adjustment, which may result in inadequate treatment of postoperative pain during rapidly changing intensity. Thus intravenous opioids are often necessary to supplement analgesia when transdermal fentanyl is used to manage acute postoperative pain.

Alfentanil is approximately 5 to 10 times less potent than fentanyl. The drug acts rapidly; its peak effect is reached within minutes after intravenous administration. Its duration of action after bolus administration is also shorter than fentanyl. Alfentanil is highly lipid soluble (approximately 100 times more lipid soluble than morphine) and rapidly crosses the blood-brain barrier. Alfentanil pharmacokinetics is minimally affected by renal disease, and hepatic extraction is more a function of intrinsic hepatic enzyme capacity and protein binding than liver blood flow.

The performance of a patient-demand, target-controlled alfentanil infusion system has compared favorably with traditional morphine PCA in patients after cardiac surgery. Checketts and associates[73] prospectively randomized 120 patients undergoing elective cardiac surgery to receive either morphine PCA or alfentanil PCA for postoperative analgesia (nonblinded study). All patients received a similar standardized intraoperative anesthetic technique and were extubated during the immediate postoperative period. Overall median visual analogue pain scores were significantly lower in patients receiving alfentanil, yet both alfentanil and morphine delivered high-quality postoperative analgesia (Fig. 42.3). Although the clinical impression of these investigators was that alfentanil patients were less sedated in the immediate postoperative period, this clinical observation was not substantiated after statistical analysis of sedation scores. The two groups did not differ with respect to overall sedation scores, frequency of nausea and vomiting, hemodynamic instability, myocardial ischemia, or hypoxemia during the immediate postoperative period.

Sufentanil is approximately 10 times more potent than fentanyl. The drug is extremely lipid soluble and highly bound to plasma proteins. Because of its high potency, conventional clinical doses of sufentanil result in plasma concentrations that rapidly decline to less than the sensitivity of most assayed methods, making it difficult to determine accurate pharmacokinetic parameters. However, sufentanil pharmacokinetic actions appear not to be altered in patients with renal disease. Because hepatic sufentanil clearance approaches liver blood flow, the drug's pharmacokinetic properties are expected to change with hepatic disease yet the clinical relevance remains undetermined. Sufentanil undergoes substantial (approximately 60%) first-pass uptake in the lungs.

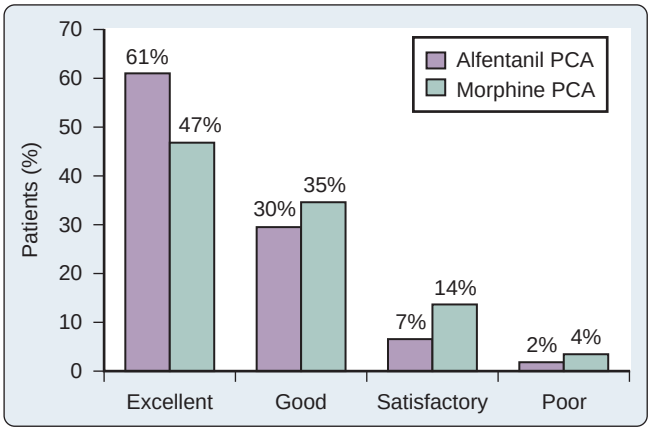


Fig. 42.3 Overall patient satisfaction with postoperative analgesia. Ninety-one percent of patients using alfentanil rated their postoperative analgesia as excellent or good, whereas 82% of patients using morphine rated their postoperative analgesia similarly (differences not statistically significant). *PCA,* Patient-controlled analgesia. *(From Checketts MR, Gilhooly CJ, Kenny GN. Patient-maintained analgesia with target-controlled alfentanil infusion after cardiac surgery: a comparison with morphine PCA.* Br J Anaesth. *1998;80:748–751.)*

Remifentanil has a very fast onset and an ultrashort duration of action; it is unique in that it is readily susceptible to rapid hydrolysis by nonspecific esterases in the blood and tissues. The drug is moderately lipophilic and is half as potent as fentanyl when blood concentrations causing equivalent analgesia are compared. Remifentanil has an elimination half-life of 10 to 20 minutes, and the time required for a 50% reduction in blood concentration after discontinuation of an infusion that has attained a steady state is approximately 3 minutes and does not increase with the duration of infusion. Available evidence suggests that neither the pharmacokinetics nor the pharmacodynamics of remifentanil is significantly altered in patients with severe hepatic or renal disease. These properties should confer ease of titration to changing analgesic conditions. However, the quick offset of action, although desirable, may result in inadequate postoperative analgesia. Because of the rapid offset of analgesic effect of remifentanil, the continued requirement for postoperative analgesia needs to be considered before the remifentanil is discontinued. A transition must be made from remifentanil to some other longer-acting analgesic agent for the initiation of substantial postoperative analgesia. Although the transition to postoperative pain management can be made using a remifentanil infusion alone, this appears to be associated with a high incidence of adverse respiratory effects.

Bowdle and colleagues[74] evaluated the use of a remifentanil infusion to provide postoperative analgesia during recovery from total intravenous anesthesia with remifentanil and propofol from a wide variety of noncardiac surgeries (eg, abdominal, spine, joint replacement, thoracic). This multiinstitutional study involving 157 patients had a detailed protocol that specified doses and method of administration of all anesthetic drugs. Total intraoperative intravenous anesthesia consisted of midazolam (premedication only), remifentanil, propofol, and vecuronium. Propofol was stopped immediately before intraoperative extubation, and the remifentanil infusion was continued for postoperative analgesia. During the immediate postoperative period, intravenous morphine was administered during tapering of remifentanil infusion. Adverse respiratory events that included oxygen saturation via pulse oximetry less than 90%, respiratory rate less than 12 per minute, and apnea, affected 45 patients (29%; 2 required naloxone). Apnea occurred in 11 patients (7% treated with mask ventilation and downward titration of remifentanil infusion; 1 required naloxone). The administration of a bolus of remifentanil preceded the onset of adverse respiratory events in 19 of 45 cases and in 9 of 11 cases of apnea.

These data suggest that remifentanil boluses plus an infusion are particularly likely to produce clinically significant adverse respiratory events. The authors of this open, dose-ranging study concluded that although remifentanil certainly initiates analgesia, its use in the immediate postoperative period may pose dangers.[74] Additional studies are needed to investigate the transition from remifentanil to longer-lasting analgesics and to refine strategies that minimize respiratory depression while optimizing pain control. The administration of a potent, rapid-acting opioid such as remifentanil by continuous infusion for postoperative analgesia must be performed with meticulous attention to detail and constant vigilance. Extreme caution should be exercised in the postoperative administration of bolus doses of remifentanil because substantial respiratory depression (including apnea) may develop. Furthermore, the remifentanil infusion should be inserted into the intravenous line as close as possible to the patient to minimize dead space, and the rate of the main intravenous infusion should be controlled at a rate that is high enough to continuously flush remifentanil from the tubing. A more dilute remifentanil solution that runs at greater rates (on a volume-per-time basis) helps minimize the effect of variations in flow rate of the main intravenous tubing on

delivery of remifentanil to the patient. Remifentanil also may possess detrimental cardiovascular effects via bradycardia and decreases in systemic vascular resistance, leading to decreased cardiac output and hypotension.[75] Such changes may occur during clinically used doses for cardiac surgery (0.1 to 1.0 µg/kg/min), inducing significant cardiovascular disturbances that are potentially deleterious to patients with cardiac disease.[75]

Patient-Controlled Analgesia

When intravenous opioids are used for controlling postoperative pain (most commonly morphine and fentanyl), PCA technology is generally used. Essentials in the successful use of PCA technology include loading the patient with intravenous opioids to the point of patient comfort before initiating PCA, ensuring that the patient wants to control analgesic treatment, using an appropriate PCA dose and lockout interval, and considering the use of a basal rate infusion. Focused guidance of PCA dosing by a dedicated acute pain service, compared with surgeon-directed PCA, may result in more effective analgesia with fewer adverse effects. Patient-controlled epidural analgesic techniques with opioids and/or local anesthetic agents also have been proved reliable, effective, and safe.[76,77]

Although PCA is a well-established technique that has been used for more than 2 decades and offers potential unique benefits (eg, reliable analgesic effect, improved patient autonomy, flexible adjustment to individual needs), whether it truly offers significant clinical advantages compared with traditional nurse-administrated analgesic techniques to patients immediately after cardiac surgery remains to be determined.[78–83] A clinical investigation by Gust and associates[79] indicates that PCA techniques provide a higher quality of postoperative analgesia, which may lead to a reduction in postoperative respiratory complications. In this prospective, randomized, clinical investigation involving 120 healthy patients, following extubation after elective CABG, patients received intravenous PCA piritramide, intravenous PCA piritramide plus rectal indomethacin, or conventional nurse-controlled analgesia with intravenous piritramide and/or rectal indomethacin for 3 days. Postoperative assessment included daily visual analog pain scores and chest radiographs graded for the extent of atelectasis by a radiologist blinded to treatment. Perioperative management (surgical treatment, intraoperative anesthetic management) was standardized. Although chest radiography atelectasis scores and visual analog pain score values were similar among the three groups on the first and second postoperative days, chest radiography atelectasis scores and visual analog pain score values were significantly better on the third postoperative day in the two PCA groups compared with the control (nurse-controlled analgesia) group. At the end of the study, all patients retrospectively graded their postoperative pain management on average as good but significantly more patients in the two PCA groups assessed their pain management as excellent compared with the control group. These investigators concluded that treatment with PCA may reduce respiratory complications in patients after CABG. However, no difference was observed regarding perioperative oxygenation values among the three groups during the entire study period, and not a single patient in any group prospectively met the defined criteria for a diagnosis of pneumonia. Other clinical investigations also have indicated that PCA techniques, compared with standard nurse-based pain therapy, may provide higher quality analgesia leading to reduced cardiopulmonary morbidity after cardiac surgery.[80,83]

Despite the popularity of PCA techniques and the results of the previously quoted studies, other clinical investigations have demonstrated no major benefits offered.[78,81,82] Tsang and Brush[78] prospectively evaluated 69 patients after cardiac surgery via median sternotomy. Thirty-nine patients were randomized to receive PCA morphine after surgery, whereas 30 were randomized to receive nurse-administered morphine after surgery. Perioperative care was standardized, visual analog pain scores were used for pain assessment, and pulmonary function tests were performed before surgery and every 6 hours after surgery until discharge from the ICU. These clinical investigators found

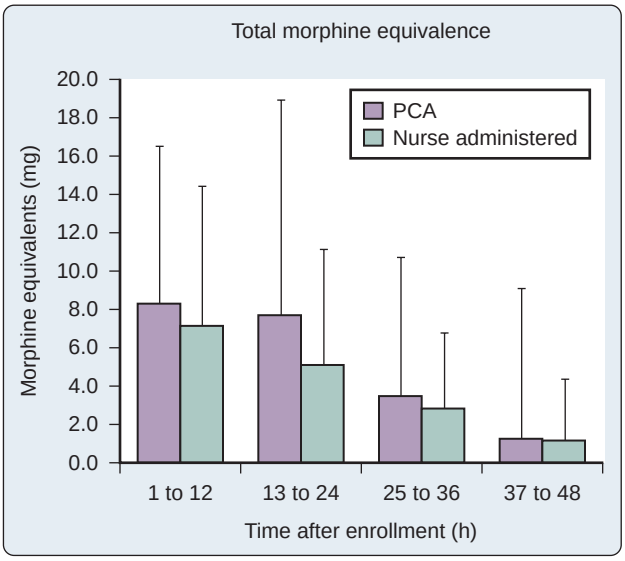


Fig. 42.4 Total Morphine Equivalents. Dosages of morphine equivalents in the patient-controlled analgesia *(PCA)* and nurse-administered groups during each observation period. No differences existed between the two groups at any observation period. *(From Tsang J, Brush B. Patient-controlled analgesia in postoperative cardiac surgery.* Anaesth Intensive Care. *1999;27:464–470.)*

no differences between the two groups regarding postoperative morphine consumption (Fig. 42.4), postoperative visual analog pain scores, postoperative sedation scores, and postoperative pulmonary function (Fig. 42.5). These investigators concluded that no significant advantages were achieved when routinely using PCA in patients after cardiac surgery. Interestingly, in this study, opinions expressed by the nursing staff on the use of PCA were not as positive as expected. Repeating the instructions to patients on PCA was often required during the study period. Potential reasons for the need to repeat instructions on PCA included poor retention of preoperative learning because of anxiety after hospital admission, incomplete recovery of higher cognitive function after prolonged general anesthesia and CPB, and/or ICU-induced disorientation.

These results suggested that additional patient limitations to the effective use of PCA may exist immediately after cardiac surgery, even though patients can obey simple commands and acknowledge discomfort. Munro and colleagues,[81] when comparing intravenous PCA morphine and nurse-administered subcutaneous morphine, detail similar findings. They prospectively randomized 92 patients undergoing elective cardiac surgery to receive either intravenous PCA morphine or nurse-administered subcutaneous morphine during the postoperative period. They found no differences between the two groups regarding many postoperative variables, including total postoperative morphine requirements, postoperative visual analog pain scores at rest and with movement, daily verbal pain relief scores, side effect profiles, and physiotherapists' evaluation of effectiveness of analgesia for chest physiotherapic treatments. Subcutaneous techniques are attractive because they have low equipment and disposable costs, eliminate the need for bulky pumps in ambulating patients, and may be more effective for older adults or the postoperative patient who is mildly confused.

Myles and associates[82] were also unable to find any specific clinical benefits during the use of PCA techniques in patients after cardiac surgery. In their prospective clinical investigation, 72 patients undergoing elective cardiac surgery were randomized to receive either intravenous PCA morphine or intravenous nurse-titrated morphine during the immediate postoperative period. The investigators of this study found no differences between the two groups regarding many postoperative variables, including postoperative morphine consumption, pain scores, nausea scores, and serum cortisol levels (Fig. 42.6). Similar to Munro and associates,[81] they noted that patients also had variable

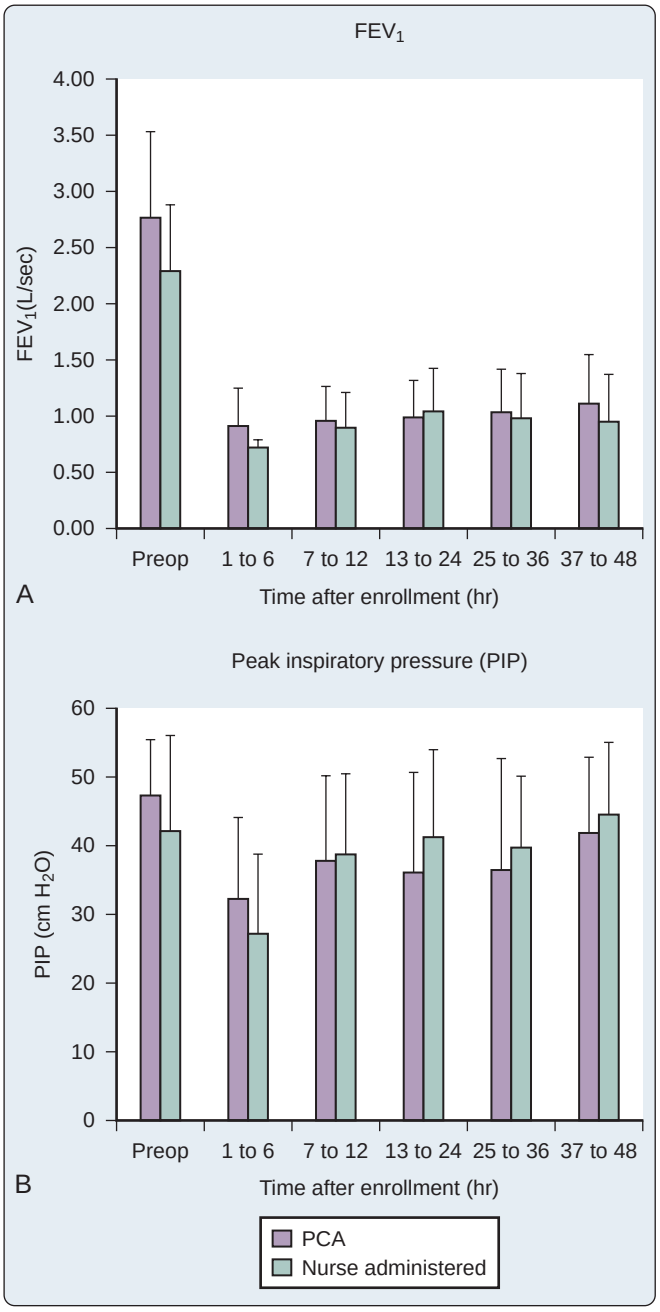


Fig. 42.5 Postoperative Pulmonary Function. Postoperative pulmonary function tests in the patient-controlled analgesia *(PCA)* and nurse-administered groups during each observation period. A significant decrease in forced expiratory volume in 1 second *(FEV_1)* in both groups was observed immediately after surgery, lasting 48 hours. No differences existed between the two groups at any observation period. *(From Tsang J, Brush B: Patient-controlled analgesia in postoperative cardiac surgery.* Anaesth Intensive Care *1999;27:464–470.)*

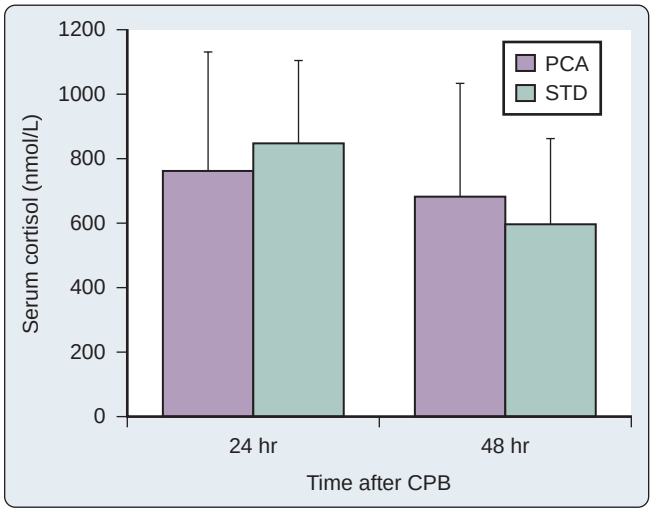


Fig. 42.6 Postoperative Serum Cortisol. Mean serum cortisol level at 24 and 48 hours after cardiopulmonary bypass *(CPB)* for patients receiving intravenous patient-controlled analgesia *(PCA)* morphine or intravenous nurse-titrated morphine *(STD). (From Myles PS, Buckland MR, Cannon GB, et al. Comparison of patient-controlled analgesia and nurse-controlled infusion analgesia after cardiac surgery.* Anaesth Intensive Care. *1994;22:672–678.)*

BOX 42.7 NONSTEROIDAL ANTIINFLAMMATORY AGENTS

- Advantages
  - Opioid-sparing analgesia
  - Reliable
- Disadvantages
  - Gastric mucosal dysfunction?
  - Renal tubular dysfunction?
  - Inhibition of platelet aggregation?
  - Sternal wound infection?
  - Thromboembolic complications?

ability and understanding of the requirements of PCA, particularly in the early postoperative period when they were either confused or too weak to operate the demand button. These investigators also noted that the patients who received experienced one-to-one nursing care reported improved overall pain management. Other studies evaluating PCA have also found that nurse-administered techniques may provide the highest quality analgesia. It could therefore be argued that these studies support increased staff education and involvement to optimize postoperative analgesia. The nurses in these clinical investigations all raised concerns regarding the time required for PCA setup and the inability of patients to cope with the demands of PCA in the early stages of their recovery, particularly if the patients were older adults, confused, or both. However, PCA was well received later in the recovery process and was found to be less demanding on nursing time.

Nonsteroidal Antiinflammatory Agents

Nonsteroidal antiinflammatory drugs (NSAIDs), in contrast with the opioids' central nervous system mechanism of action, primarily exert their analgesic, antipyretic, and antiinflammatory effects peripherally by interfering with prostaglandin synthesis after tissue injury[84,85] (Box 42.7). NSAIDs inhibit COX, the enzyme responsible for the conversion of arachidonic acid to prostaglandin (Fig. 42.7). Combining NSAIDs with traditional intravenous opioids may allow a patient to achieve an adequate level of analgesia with fewer side effects than if a similar level of analgesia was obtained with intravenous opioids alone. Numerous clinical investigations reveal the potential value (opioid-sparing effects) of NSAIDs when combined with traditional intravenous opioids during the postoperative period after noncardiac surgery. In fact, the administration of NSAIDs is one of the most common nonopioid analgesic techniques currently used for postoperative pain management. The efficacy of NSAIDs for the management of postoperative pain has been repeatedly demonstrated in many analgesic

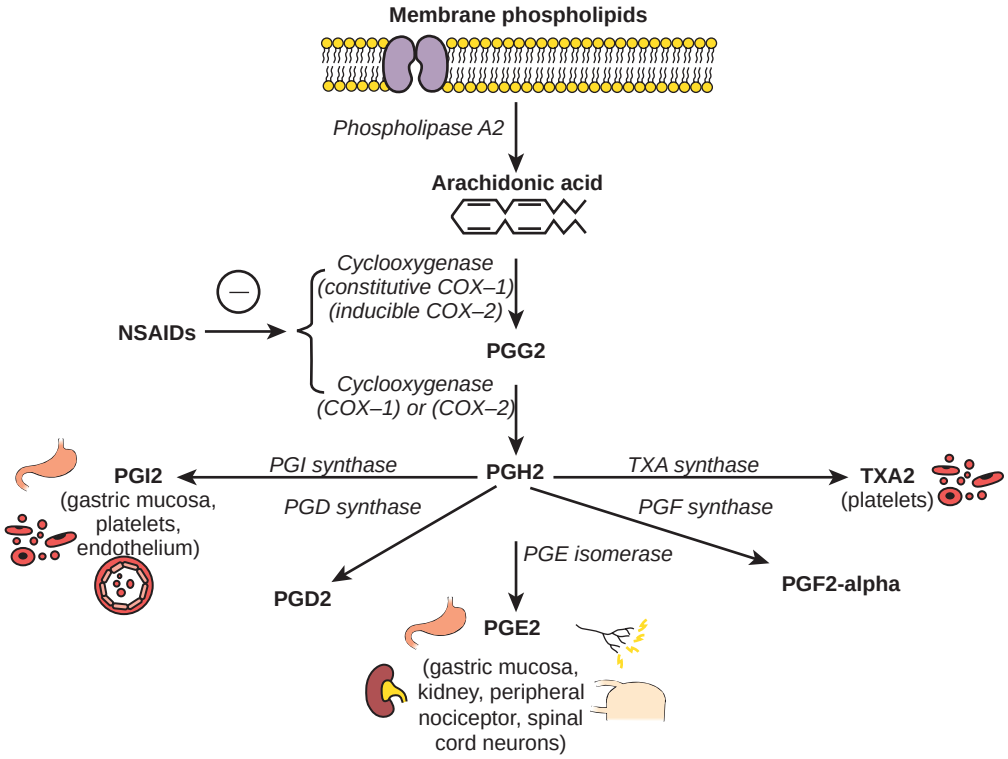


Fig. 42.7 The Role of Cyclooxygenase in Prostaglandin Synthesis. Prostaglandin *(PG)* and thromboxanes *(TX)*, which are important in inflammation and homeostasis, are products of a biochemical cascade during which membrane phospholipids are converted to arachidonic acid, then to intermediate prostaglandins by cyclooxygenase, and to their final products by a series of synthases. *COX,* Cyclooxygenase; *NSAIDs,* nonsteroidal antiinflammatory drugs. *(From Gilron I, Milne B, Hong M. Cyclooxygenase-2 inhibitors in postoperative pain management: current evidence and future directions.* Anesthesiology. *2003;99:1198–1208.)*

clinical trials. Unlike opioids, which preferentially reduce spontaneous postoperative pain, NSAIDs have comparable efficacy for both spontaneous and movement-evoked pain, the latter of which may be more important in causing postoperative physiologic impairment. Certainly, NSAIDs reduce postoperative opioid consumption, accelerate postoperative recovery, and represent an integral component of balanced postoperative analgesic regimens after noncardiac surgery. However, little is known regarding NSAID use in the management of pain after cardiac surgery. Concerns regarding NSAID side effects, including alterations in the gastric mucosal barrier, renal tubular function, and inhibition of platelet aggregation, have likely made clinicians reluctant to use NSAIDs in patients undergoing cardiac surgery. Other rare adverse effects of NSAIDs (from COX inhibition) include hepatocellular injury, asthma exacerbation, anaphylactoid reactions, tinnitus, and urticaria. Despite these fears, a small number of clinical investigations seem to indicate that NSAIDs may provide analgesia in patients after cardiac surgery without untoward effects (eg, gastrointestinal ulceration, renal dysfunction, excessive bleeding). Although NSAIDs have been associated with reports of increased postoperative blood loss, other studies have failed to corroborate this blood loss.

NSAIDs are not a homogenous group and vary considerably in analgesic efficacy as a result of differences in pharmacodynamic and pharmacokinetic parameters. NSAIDs are nonspecific inhibitors of COX, which is the rate-limiting enzyme involved in the synthesis of prostaglandins. COX exists in multiple forms. Most importantly, a constitutive form, cyclooxygenase-1 (COX-1), is present in normal conditions in healthy cells, and an inducible form (COX-2) exists, which is the major isozyme induced by and associated with inflammation. Simplistically, COX-1 is ubiquitously and constitutively expressed and has a homeostatic role in platelet aggregation, gastrointestinal mucosal integrity, and renal function, whereas COX-2 is inducible and primarily expressed at the sites of injury (and in the kidney and brain) and mediates pain and inflammation. NSAIDs are nonspecific inhibitors of both forms of COX yet vary in their ratio of COX-1 to COX-2 inhibition. Molecular studies distinguishing between constitutive COX-1 and inflammation-inducible COX-2 enzymes have led to the exciting hypothesis that the therapeutic and adverse effects of NSAIDs could be uncoupled[86–91] (Fig. 42.8). Subsequently, clinicians have witnessed an exponential increase in publications and the growing use of COX-2 inhibitors in the perioperative period after noncardiac surgery. A compelling body of evidence now exists that COX-2 inhibitors, similar to their predecessors, the nonselective NSAIDs, generally provide postoperative analgesia, decrease intravenous opioid requirements, and greater patient satisfaction compared with placebo. Some evidence also suggests that opioid-sparing by COX-2 inhibitors also spares opioid side effects. The primary advantage of COX-2 inhibitors, compared with NSAIDs, is their lack of effect on platelet function and bleeding, hence the opportunity for perioperative administration.

Only a handful of clinical studies have investigated the potential of NSAIDs in the management of pain after cardiac surgery.[92–95] One well-designed clinical investigation revealed that a combination of NSAIDs and intravenous opioids may provide superior analgesia after cardiac surgery without untoward effects. Rapanos and colleagues[94] prospectively randomized 57 patients to receive either indomethacin suppositories or placebo suppositories in a double-blinded fashion during the immediate postoperative period after elective CABG. Patients receiving indomethacin suppositories demonstrated significantly less ($p = 0.019$) morphine consumption (assessed via PCA morphine) and significantly lower ($p = 0.006$) pain scores (assessed via visual analog pain scores) during the immediate postoperative period compared with those in the control placebo group. Postoperative morphine use during the first 24 postoperative hours was 22 ± 13 mg in the indomethacin group

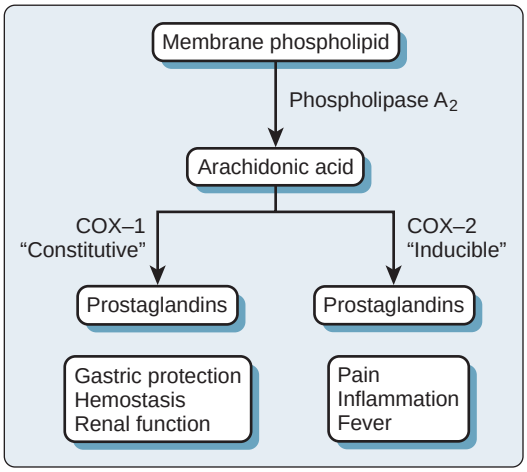


Fig. 42.8 Cyclooxygenase *(COX)* Pathways. Molecular studies distinguishing between COX-1 and COX-2 enzymes have led to the exciting hypothesis that the therapeutic and adverse effects of the nonspecific inhibitors (nonsteroidal antiinflammatory drugs) could be uncoupled. *(From Gajraj NM. Cyclooxygenase-2 inhibitors.* Anesth Analg. *2003;96: 1720–1738.)*

and 36 ± 26 mg in the placebo group. No differences were observed between groups regarding tracheal extubation time or postoperative blood loss (assessed via chest tube output). None of the study subjects in either group developed postoperative renal dysfunction. In fact, a moderate reduction in serum creatinine concentration was observed in both groups. These investigators concluded that the combination of indomethacin suppositories with morphine after cardiac surgery results in reduced postoperative pain scores and opioid consumption without an increase in side effects.

However, two well-designed clinical investigations demonstrate that the use of NSAIDs or NSAID-like drugs (acetaminophen) in patients after cardiac surgery may not offer any substantial clinical benefits.[92,95] Hynninen and associates[92] in a prospective, double-blind, placebo-controlled study, randomized patients to receive diclofenac ($n = 28$ patients), ketoprofen ($n = 28$ patients), indomethacin ($n = 27$ patients), or placebo ($n = 31$ patients) for postoperative analgesia after elective CABG via a median sternotomy. All patients received standardized fast-track cardiac anesthesia and standardized postoperative analgesia treatment. Mean morphine consumption in the immediate postoperative period was significantly reduced in only the diclofenac group when compared with the placebo group (12 mg vs 19 mg, respectively; $p < 0.05$). Total analgesic consumption calculated as morphine equivalents was also significantly lower in only the diclofenac group compared with the placebo group (18 mg vs 27 mg, respectively; $p < 0.05$). No additional important differences were observed when doses of other analgesics were compared. The visual analogue pain scores at rest were comparable among the four groups at all times. Additionally, no postoperative differences were observed among the four groups regarding creatinine concentration, percentage of patients with 20% or greater increases in the creatinine level after surgery, and 24-hour blood loss. Although some NSAIDs may offer opioid-sparing effects, these findings indicated that others may not.

Lahtinen and colleagues[95] in a prospective, double-blind, placebo-controlled study, patients were randomized to receive either propacetamol, a prodrug of acetaminophen ($n = 40$ patients), or placebo ($n = 39$ patients) for postoperative analgesia after elective CABG via a median sternotomy. Acetaminophen (not an NSAID) might be a safer nonopioid analgesic in cardiac surgery because it does not depress platelet function or renal function as much as traditional NSAIDs. The mechanism behind the analgesic action of acetaminophen remains unclear. Acetaminophen has only a weak inhibitory influence on peripheral COX pathways and has no substantial antiinflammatory activity. Acetaminophen-induced analgesia may be partially centrally mediated, and the peak cerebrospinal fluid concentrations may reflect analgesic action. Intravenous propacetamol is quickly hydrolyzed to acetaminophen in the bloodstream. In the clinical investigation by Lahtinen and colleagues,[95] a standardized intraoperative anesthetic technique was used for all patients, and extubation times were identical between the two groups (approximately 5 hours). From the time of extubation, all patients had access to PCA oxycodone using a standardized protocol. The variation of oxycodone consumption was large in both groups. Although postoperative cumulative oxycodone consumption (combined amount administered via PCA and given as rescue doses) was less in the propacetamol group compared with the placebo group, the difference was not statistically significant (124 ± 51 mg vs 142 ± 58 mg, respectively; $p = 0.15$). Postoperative visual analog pain scores obtained at rest and during a deep breath were similar, as well as patients' satisfaction with analgesia between the two groups. Furthermore, no differences existed between the two groups regarding postoperative pulmonary function tests (eg, forced expiratory volume in 1 second, peak expiratory volume, forced vital capacity), blood gas analysis, bleeding, renal function tests, and liver function tests. Postoperative nausea and vomiting were the most common adverse events, which occurred with identical frequency in both groups. These investigators conclude that propacetamol neither enhances postoperative opioid-based analgesia in patients after CABG nor does it decrease cumulative opioid consumption or reduce adverse effects.

One prospective, randomized clinical study investigated the potential advantages and disadvantages of using COX inhibitors in patients after cardiac surgery. Immer and associates[96] prospectively randomized 69 patients scheduled for elective CABG with conventional sternotomy to receive either a COX-2 inhibitor (etodolac), a nonselective COX inhibitor (diclofenac), or a weak opioid (tramadol) for postoperative analgesia. Postoperative pain was assessed via a visual analogue scale, perioperative blood samples were obtained for serum creatinine and urea levels, and creatinine clearance was determined on postoperative day 1 (before starting the study medication) and on postoperative day 4 (after receiving the study medication). In patients with insufficient postoperative analgesia (defined via predetermined visual analog scale score), supplemental subcutaneous morphine was administered. Total morphine consumption and occurrence of nausea were recorded daily. At the doses analyzed by these investigators, etodolac and diclofenac produced slightly better postoperative analgesia (assessed via visual analog scale scores and morphine consumption) with fewer adverse effects (assessed via antiemetic therapy) than tramadol. However, a short-lasting impairment of renal function was found in patients treated with etodolac and diclofenac (assessed via serum creatinine and urea levels; Figs. 42.9 and 42.10). However, at hospital discharge, no significant differences existed among the three groups regarding serum creatinine and urea levels (see Figs. 42.9 and 42.10). Lastly, all three groups experienced similar decreases in postoperative creatinine clearance.

Another clinical investigation of patients after CABG suggested a proportionately, but not significantly, greater incidence of serious cardiac and cerebrovascular adverse events in patients taking COX-2 inhibitors. In this multicenter (58 institutions), prospective, randomized, double-blind, parallel-group trial performed by Ott and associates,[97] 462 patients undergoing CABG were allocated at a ratio of 2:1 to parecoxib (prodrug of valdecoxib) group (311 patients) or standard care control group (151 patients;). Patients in the parecoxib/valdecoxib group required significantly less morphine or morphine equivalents than patients in the control group during the postoperative period (up to 6 days). Both patients and physicians evaluated the study medication (parecoxib/valdecoxib) as significantly better than control therapy. Pain questionnaires detected significant improvements in the parecoxib/valdecoxib group beginning on day 4 and continuing for at least 4 days. However, although no differences were observed between the groups in overall adverse events, serious adverse events occurred twice as frequently in parecoxib/valdecoxib–treated patients than in control patients (19% vs 10%, respectively; $p = 0.015$). Regarding individual serious adverse events, a greater incidence rate in sternal

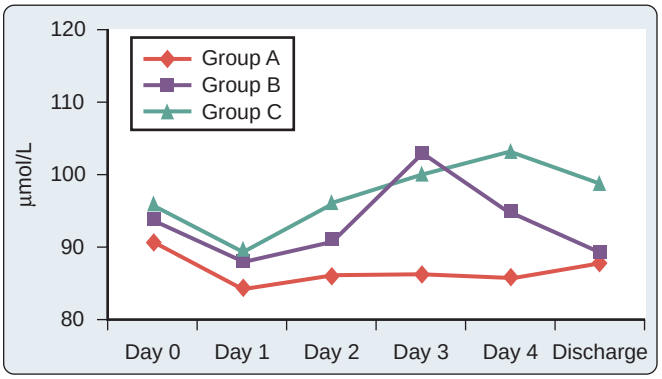


Fig. 42.9 Serum Creatinine Values. Serum creatinine values for groups A (tramadol), B (diclofenac), and C (etodolac) on postoperative days 1 to 4 and at discharge. Results are displayed as mean values. Serum creatinine levels were significantly greater on postoperative days 3 and 4 in groups B and C compared with group A ($p < 0.05$). However, at discharge, no significant differences were found among the three groups. *(From Immer FF, Immer-Bansi AS, Trachsel N, et al. Pain treatment with a COX-2 inhibitor after coronary artery bypass operation: a randomized trial.* Ann Thorac Surg. *2003;75:490–495.)*

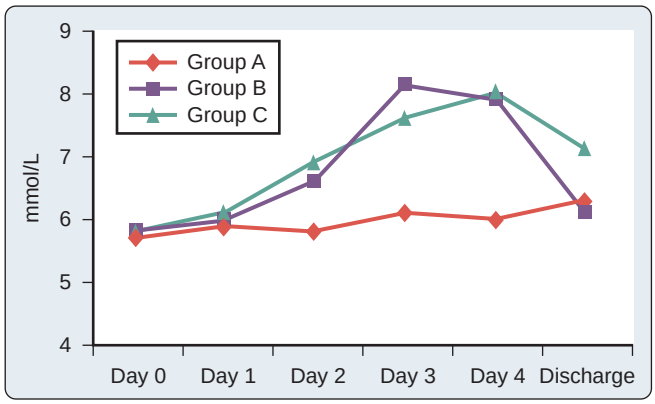


Fig. 42.10 Serum Urea Values. Serum urea values for groups A (tramadol), B (diclofenac), and C (etodolac) on postoperative days 1 to 4 and at discharge. Results are displayed as mean values. Serum urea levels were significantly greater on postoperative days 3 and 4 in groups B and C compared with group A ($p < 0.05$). However, at discharge, no significant differences were found among the three groups. *(From Immer FF, Immer-Bansi AS, Trachsel N, et al. Pain treatment with a COX-2 inhibitor after coronary artery bypass operation: a randomized trial.* Ann Thorac Surg. *2003;75:490–495.)*

wound infection was found in the parecoxib/valdecoxib patients (3%) versus control patients (0%) ($p = 0.035$). The effects of NSAIDs on sternal wound complications had not been previously reported. The COX-2 enzyme enables prostaglandin release and the inflammatory response. Inhibition of this enzyme by nonspecific COX inhibitors (NSAIDs), as well as specific COX-2 inhibitors, might impede reparative inflammatory responses and increase susceptibility to sternal wound infections. An alternative hypothesis is that reduced fever and tachycardia in NSAID/COX-2 inhibitor–treated patients may delay detection of infection, resulting in further progression and greater consequence. Regardless of the mechanism, these safety issues merit careful consideration because of the importance of sternal wound complications in this setting. The incidence of other individual serious adverse events, including cerebrovascular complications, myocardial infarction, and renal dysfunction, were proportionally greater in the parecoxib/valdecoxib group but not significantly different between the two groups. Specifically, when the groups were compared, more patients in the treatment group (parecoxib/valdecoxib) experienced cerebrovascular disorders (3% vs 1%; $p = 0.177$), myocardial infarction (2% vs 1%; $p = 0.669$), and renal dysfunction (2% vs 0%; $p = 0.184$) when compared with control patients.

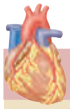
Such thrombosis-mediated complications merit careful consideration. In cardiac surgery patients who are exposed to CPB, the delicate balance among platelets, endothelial cells, and serum clotting factors is disturbed, with consequent thrombosis and clot lysis disparately and unpredictably occurring throughout the vascular system. Given that COX-2 inhibitors are platelet sparing, these drugs might tip the balance toward thrombosis during periods of platelet activation. In addition, because COX-1 is unaffected, consequent release of thromboxane A_2 may further promote platelet activation and thrombosis. Of note, some analyses addressing these issues in chronically treated patients with arthritis indicate a potential association between COX-2 inhibition and thrombogenic events (eg, myocardial infarction, stroke, vascular death).[98] Ott and associates[97] concluded that in patients undergoing CABG, the COX-2 inhibitor combination of parecoxib/valdecoxib is effective in controlling postoperative analgesia, yet the treatment regimen may be associated with an increased incidence of serious adverse events overall and sternal wound infections in particular. Their study therefore raised important concerns requiring a comprehensive evaluation of the potential link between this class of drugs and perioperative complications in a large-scale clinical trial before the COX-2 inhibitors are routinely used in patients undergoing cardiac surgery.

Over time, significantly more will be learned about COX-2 inhibitors. Their analgesic (opioid-sparing) effects and lack of deleterious effects on coagulation (in contrast with nonselective NSAIDs) are certainly desirable. The evidence to date does not suggest that COX-2 inhibitors provide major advantages over traditional NSAIDs. Their continued development will possibly lead to specific drugs with a superior therapeutic profile. Many important questions regarding their safety remain unanswered, such as effects on central nervous system sensitization, perioperative renal function, preemptive analgesia, clinically significant blood loss, the gastrointestinal system, the cardiovascular system, chronic postsurgical pain, bone and wound healing, blood pressure, and peripheral edema, among others. Specifically regarding patients undergoing cardiac surgery, the potential links between this class of drugs and sternal wound infections and thromboembolic complications need to be fully evaluated. Lastly, the recent and unprecedented retraction of numerous peer-reviewed articles and abstracts (spanning 15 years) published by a leading investigator in the perioperative use of NSAIDs and COX-2 inhibitors raises important questions as to the potential adverse impact of this investigator's fraudulent work on the practice of acute postoperative pain management.[99] Simply put, such unprecedented retraction forces clinicians to question all that was previously known (and assumed true) of the advantages and disadvantages of using NSAIDs and COX-2 inhibitors, prompting the need for future clinical analysis studies to address these important issues.

Alpha$_2$-Adrenergic Agonists

The α_2-adrenergic agonists provide analgesia, sedation, and sympatholysis (Box 42.8).[100] The initial impetus for the use of α_2 agonists in anesthesia resulted from astute clinical observations made in patients during intraoperative anesthesia who were receiving clonidine therapy. Soon thereafter, investigators revealed that clonidine substantially reduced anesthetic requirements (minimal alveolar concentration). More recently, dexmedetomidine has undergone extensive clinical evaluation for perioperative use. Dexmedetomidine exerts profound effects on cardiovascular parameters and thus appears to affect its own pharmacokinetics. At high doses, there is significant vasoconstriction, which probably reduces the drug's volume of distribution. The elimination half-life of dexmedetomidine is 2 to 3 hours.

α_2-Adrenergic agonists produce clinically sedative effects via stimulation of α_2 receptors in the locus ceruleus and clinically analgesic effects via stimulation of α_2 receptors within the locus ceruleus and spinal cord.[101] Existing evidence indicates that α_2 agonists enhance the



BOX 42.8 ALPHA$_2$-ADRENERGIC AGONISTS

- Advantage
  - Cardiovascular stability?
- Disadvantages
  - Sedation
  - Hypotension

analgesic effects of the opioids via an unknown mechanism of action. Several mechanisms of action have been postulated for the analgesia noted with α_2-adrenergic agonists including supraspinal, ganglionic, spinal, and peripheral mechanisms. Clinically, systemic administration of these agents produces antinociception and sedation, whereas intrathecal administration usually produces only antinociception. Similar to other adrenergic receptors, the α_2-adrenergic agonists demonstrate tolerance after prolonged administration.

As with all clinically used analgesics, the α_2-adrenergic agonists possess clinically important side effects that may limit their usefulness. The effects of dexmedetomidine on the respiratory system include a decrease in tidal volume, minimal changes in respiratory rate, and a rightward shift and depression of slope of the carbon dioxide response curve, all of which may cause hypercarbia. However, respiratory depression associated with the drug is usually clinically unimportant, even during profound levels of sedation. The effects of dexmedetomidine on the cardiovascular system are many and, in contrast with the respiratory effects, may become clinically important. Physiologic changes include decreased heart rate, decreased systemic vascular resistance, and possibly indirectly decreased myocardial contractility, all potentially leading to decreased cardiac output and decreased blood pressure in susceptible patients. By developing more highly selective α_2-adrenergic agonists, it is hoped that these detrimental cardiovascular effects will be minimized while maximizing the desired analgesic and sedative properties. Currently, the clinical role of these drugs includes preoperative sedation, an intraoperative adjuvant during anesthesia to reduce sedative and analgesic requirements, and postoperative sedation and analgesia. The potential ability of the α_2-adrenergic agonists to reduce and/or prevent perioperative myocardial ischemia, although intriguing, remains to be determined.[102]

The potential perioperative analgesic benefits of α_2 agonists when administered to patients undergoing cardiac surgery were demonstrated 30 years ago. In 1987, Flacke and associates[103] in prospective, nonblinded fashion, randomized patients undergoing elective CABG to receive either perioperative oral clonidine supplementation (10 patients) or serve as control patients (10 patients). Outside of oral clonidine supplementation, management of the two study groups was identical. Patients receiving oral clonidine required significantly less preinduction diazepam and significantly less intraoperative sufentanil (Fig. 42.11) and isoflurane to maintain intraoperative normotension (clearly establishing clonidine's sedative and analgesic properties). Furthermore, patients receiving oral clonidine were extubated earlier during the postoperative period, compared with control patients (approximately 11 vs 16 hours, respectively; $p < 0.05$). However, 4 of 10 patients receiving oral clonidine required atropine for treatment of intraoperative bradycardia. Unfortunately, postoperative analgesia was not assessed in this clinical investigation.

Although the analgesic properties of α_2-adrenergic agonists are undisputed, most of the clinical investigations regarding perioperative use of this class of drugs remain focused on exploiting the sedative effects and beneficial cardiovascular effects (decreasing hypertension and tachycardia) associated with their use.[104–107] α_2-Adrenergic agonists have been used perioperatively in patients undergoing cardiac surgery. However, the focus of such clinical investigations has been on the intraoperative period and the potential for enhanced postoperative hemodynamic stability, potentially leading to reduced postoperative myocardial ischemia (but not specifically to enhance postoperative analgesia).[108–111] Taken together, these clinical investigations indicate that perioperative administration of α_2-adrenergic agonists to patients undergoing cardiac surgery decreases intraoperative anesthetic requirements, may enhance perioperative hemodynamic stability, and may decrease perioperative myocardial ischemia. α_2-Adrenergic agonists may also cause excessive postoperative sedation and initiate postoperative hemodynamic instability via bradycardia and/or decreased systemic vascular resistance, leading to hypotension and increased pacing requirements in susceptible patients. The potential ability of this class of drugs to initiate reliable postoperative analgesia awaits definitive investigation.

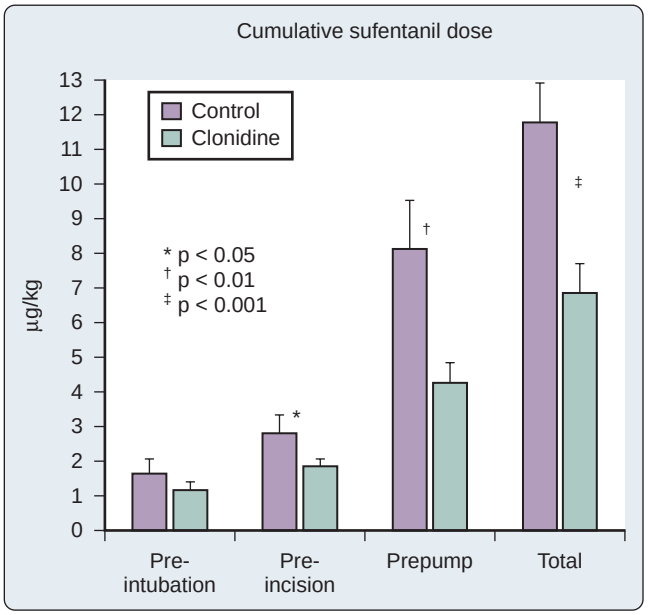


Fig. 42.11 Cumulative Sufentanil Dose. Mean cumulative sufentanil doses are shown for the periods before intubation, before incision, before cardiopulmonary bypass (CPB) surgery, and for the entire anesthetic period. *(From Flacke JW, Bloor BC, Flacke WE, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery.* Anesthesiology. *1987;67:11–19.)*

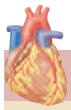
Intrathecal and Epidural Techniques

Numerous clinical investigations clearly indicate that intrathecal and/or epidural techniques (using opioids and/or local anesthetics) initiate reliable postoperative analgesia in patients after cardiac surgery[112] (Boxes 42.9 and 42.10). Traditional additional potential advantages of using intrathecal and/or epidural techniques in patients undergoing cardiac surgery include stress-response attenuation and thoracic cardiac sympathectomy. Recent animal investigations seem to indicate that intrathecal morphine may also confer protection against myocardial ischemia and reperfusion injury through the activation of spinal cord opioid receptors.[113–115] Although the signaling pathway of this form of remote cardioprotection has not yet been elucidated, it does not seem to require peripheral opioid–receptor involvement.

An uninhibited stress response during the postoperative period may lead to many adverse hemodynamic (tachycardia, hypertension, vasoconstriction), metabolic (increased catabolism), immunologic (impaired immune response), and hemostatic (platelet activation) alterations. Intrathecal or epidural anesthesia and analgesia (with local anesthetics or opioids) can effectively inhibit the stress response associated with surgical procedures.[29] Local anesthetics appear to possess greater efficacy than opioids in perioperative stress-response attenuation, perhaps because of their unique mechanism of action. Although still a matter of some debate, perioperative stress-response attenuation

BOX 42.9 INTRATHECAL TECHNIQUES

- Advantages
  - Simple, reliable analgesia
  - Stress-response attenuation
  - Less hematoma risk than epidural techniques
- Disadvantages
  - No cardiac sympathectomy
  - Hematoma risk increased
  - Side effects of intrathecal opioids



BOX 42.10 EPIDURAL TECHNIQUES

- Advantages
  - Reliable analgesia
  - Stress-response attenuation
  - Cardiac sympathectomy
- Disadvantages
  - Labor intensive
  - Hematoma formation risk increased
  - Side effects of epidural opioids

with epidural local anesthetics and/or opioids in high-risk patients after major noncardiac surgery may decrease morbidity and mortality.[6,7,29] In patients undergoing cardiac surgery, initiation of CPB causes significant increases in stress-response hormones that persist into the immediate postoperative period.[26–28] Attenuation of this component of the perioperative stress response with intravenous opioids also may decrease morbidity and mortality in these patients.[8,9] Unfortunately, perioperative stress-response attenuation in patients undergoing cardiac surgery with intravenous opioids in this manner does not allow tracheal extubation to occur in the immediate postoperative period. Intrathecal or epidural anesthesia and analgesia techniques (particularly with local anesthetics) are attractive alternatives to intravenous opioids in this setting because of their potential to attenuate the perioperative stress response yet still allow tracheal extubation to occur in the immediate postoperative period.

The myocardium and coronary vasculature are densely innervated by sympathetic nerve fibers that arise from T1 to T5 and profoundly influence total coronary blood flow and distribution.[116] Cardiac sympathetic nerve activation initiates coronary artery vasoconstriction[117] and paradoxic coronary vasoconstriction in response to intrinsic vasodilators.[118] In patients with coronary artery disease, cardiac sympathetic nerve activation disrupts the normal matching of coronary blood flow and myocardial oxygen demand.[119,120] Animal models have revealed an intense poststenotic coronary vasoconstrictive mechanism mediated by cardiac sympathetic nerve activation that attenuates local metabolic coronary vasodilation in response to myocardial ischemia.[121,122] Furthermore, myocardial ischemia initiates a cardiocardiac reflex mediated by sympathetic nerve fibers, which augments the ischemic process.[123] Cardiac sympathetic nerve activation likely plays a central role in initiating postoperative myocardial ischemia by decreasing myocardial oxygen supply via the mechanisms previously listed.[29,124]

Thoracic epidural anesthesia (TEA) with local anesthetics effectively blocks cardiac sympathetic nerve afferent and efferent fibers.[29] Opioids, similarly administered, are unable to effectively block such cardiac sympathetic nerve activity.[29] Patients with symptomatic coronary artery disease benefit clinically from cardiac sympathectomy, and the application of thoracic sympathetic blockade in the management of angina pectoris was described as early as 1965.[125] TEA with local anesthetics increases the diameter of stenotic epicardial coronary artery segments without causing dilation of coronary arterioles,[119] decreases determinants of myocardial oxygen demand,[120] improves left ventricular function,[126] and decreases anginal symptoms.[120,127] Furthermore, cardiac sympathectomy increases the endocardial-to-epicardial blood flow ratio,[128,129] beneficially affects collateral blood flow during myocardial ischemia,[120] decreases poststenotic coronary vasoconstriction,[122] and attenuates the myocardial ischemia-induced cardiocardiac reflex.[122] In an animal model, TEA with local anesthetics actually decreased the size of the myocardial infarction after coronary artery occlusion.[128] Of note, systemic absorption of the local anesthetic does not cause these beneficial effects.[128] In short, TEA with local anesthetics may benefit patients undergoing cardiac surgery by effectively blocking cardiac sympathetic nerve activity and improving the balance of the myocardial oxygen supply and demand.

Intrathecal Techniques

The application of intrathecal analgesia to patients undergoing cardiac surgery was initially reported by Mathews and Abrams in 1980[130] who described the administration of intrathecal morphine (1.5 to 4.0 mg) to 40 adults after the induction of general anesthesia for cardiac surgery. Somewhat remarkably, all 40 patients awakened free from pain at the end of surgery (before leaving the surgical unit), and 36 patients were tracheally extubated before being transferred to the ICU. All 40 patients were entirely pain free for the first 28 postoperative hours, and 17 did not require any supplemental analgesics before being discharged from the hospital. Of the 17 patients who received 4 mg intrathecal morphine, 11 did not require any postoperative analgesic drugs. Mathews and Abrams[130] summarized, "The benefits of recovering from surgery free from pain have been impressive. This has been particularly appreciated by patients who have had previous operations with conventional anesthesia and postoperative analgesic drugs. The patients have been remarkably comfortable, able to move more easily in bed, and more cooperative, thus greatly helping their nursing care." After this impressive clinical display, other investigators have subsequently applied intrathecal anesthesia and analgesia techniques to patients undergoing cardiac surgery.[131–171]

Most clinical investigators have used intrathecal morphine in hopes of providing prolonged postoperative analgesia. Some clinical investigators have used intrathecal fentanyl, sufentanil, and/or local anesthetics for intraoperative anesthesia and analgesia (with stress-response attenuation) and/or thoracic cardiac sympathectomy. An anonymous survey of members of the Society of Cardiovascular Anesthesiologists published in 2001 indicated that almost 8% of practicing anesthesiologists incorporate intrathecal techniques into their anesthetic management of adults undergoing cardiac surgery.[172] Of these anesthesiologists, 75% practice in the United States, 72% perform the intrathecal injection before the induction of anesthesia, 97% use morphine, 13% use fentanyl, 2% use sufentanil, 10% use lidocaine, and 3% use tetracaine.[172]

Two randomized, blinded, placebo-controlled clinical studies reveal the ability of intrathecal morphine to induce significant postoperative analgesia after cardiac surgery.[143,150] In 1988, Vanstrum and colleagues[150] prospectively randomized 30 patients to receive either intrathecal morphine (0.5 mg) or intrathecal placebo before the induction of anesthesia. Intraoperative anesthetic management was standardized; after surgery, all patients received only intravenous morphine administered by a nurse who attempted to keep the linear analog pain score at less than 4 (a score of 1 represented no pain, 10 represented the worst pain imaginable; the scale was 25 cm long). Although pain scores between groups were not significantly different at any postoperative time interval tested, patients who received intrathecal morphine required significantly less intravenous morphine than placebo controls (2 vs 8 mg, respectively; $p < 0.02$) during the initial 30 hours after intrathecal injection (Fig. 42.12). Associated with this enhanced analgesia in patients receiving intrathecal morphine was a substantially decreased need for antihypertensive medications (eg, sodium nitroprusside, nitroglycerin, hydralazine) during the immediate postoperative period. The use of

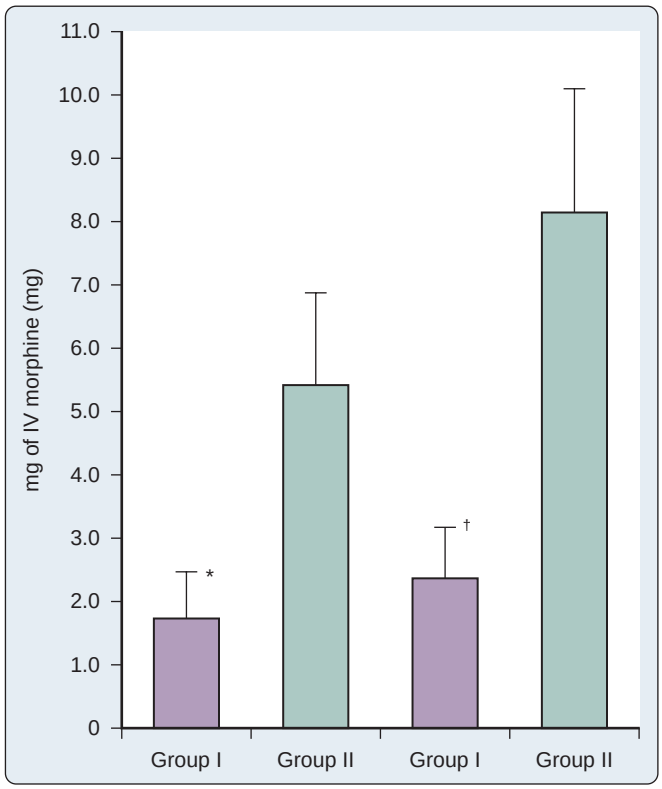


Fig. 42.12 Postoperative Supplemental Intravenous (IV) Morphine Requirements. Patients receiving intrathecal morphine (Group I) required significantly less supplemental intravenous morphine during the initial 24 postoperative hours (*, $p < 0.048$) and during the initial 30 postoperative hours (†, $p < 0.02$) compared with patients receiving intrathecal placebo (Group II). *(From Vanstrum GS, Bjornson KM, Ilko R. Postoperative effects of intrathecal morphine in coronary artery bypass surgery.* Anesth Analg. *1988;67:261–267.)*

intrathecal morphine did not significantly affect the time to tracheal extubation (approximately 20 hours) and postoperative arterial blood gas tensions after anesthesia. In 1996, Chaney and associates[143] prospectively randomized 60 patients to receive either intrathecal morphine (4 mg) or intrathecal placebo before the induction of anesthesia for elective CABG. Intraoperative anesthetic management was standardized, and all patients received intravenous morphine via PCA after tracheal extubation exclusively. The mean time from ICU arrival to tracheal extubation was similar in all patients (approximately 20 hours). However, patients who received intrathecal morphine required significantly less intravenous morphine than placebo controls (33 mg vs 51 mg, respectively; $p < 0.05$) during the initial postoperative period (Table 42.1). Despite enhanced analgesia, no clinical differences were observed between the groups regarding postoperative morbidity (eg, pruritus, nausea, vomiting, urinary retention, prolonged somnolence, atrial fibrillation, ventricular tachycardia, myocardial infarction, stroke), mortality, or duration of postoperative hospital stay (approximately 9 days in each group).

The mid-1990s saw the emergence of fast-track cardiac surgery, with the goal being tracheal extubation in the immediate postoperative period. Chaney and colleagues[142] in 1997 were the first to study the potential clinical benefits of intrathecal morphine when used in patients undergoing cardiac surgery and early tracheal extubation. They prospectively randomized 40 patients to receive either intrathecal morphine (10 μg/kg) or intrathecal placebo before the induction of anesthesia for elective CABG. Intraoperative anesthetic management was standardized (intravenous fentanyl, 20 μg/kg; intravenous midazolam, 10 mg); after surgery, all patients received intravenous morphine via PCA exclusively. Of the patients who were

TABLE 42.1 Postoperative Supplemental Intravenous Midazolam and Morphine Requirements

	Group MS (n = 27)	*Group NS (n = 29)*
Midazolam use from ICU arrival to extubation, mg (range)	8.7 ± 15.8 (0–80)	8.3 ± 15.4 (0–66)
Morphine use from ICU arrival to 8:00 AM POD 2, mg (range)	33.2 ± 15.8 (4–74)	51.1 ± 45.7 (4–254)
Morphine use from 8:00 AM POD 2 to 8:00 AM POD 3, mg (range)	14.2 ± 16.4 (0–68)	12.1 ± 12.6 (0–42)

Patients receiving intrathecal morphine (group MS) required significantly less supplemental intravenous morphine during the immediate postoperative period compared with patients receiving intrathecal placebo (group NS; 33.2 vs 51.1 mg, respectively; $p < 0.05$).

ICU, Intensive care unit; *POD,* postoperative day.

From Chaney MA, Smith KR, Barclay JC, Slogoff S. Large-dose intrathecal morphine for coronary artery bypass grafting. *Anesth Analg.* 1996;83:215–222.

tracheally extubated during the immediate postoperative period, the mean time from ICU arrival to tracheal extubation was significantly ($p = 0.02$) prolonged in patients who received intrathecal morphine (11 ± 4 hours) compared with placebo controls (8 ± 3 hours). Three patients who received intrathecal morphine had tracheal extubation substantially delayed (12 to 24 hours) because of prolonged ventilatory depression (likely secondary to intrathecal morphine). Although the mean postoperative intravenous morphine use for 48 hours was less in patients who received intrathecal morphine (43 mg) compared with patients who received intrathecal placebo (55 mg), the difference between groups was not statistically significant. No clinical differences existed between groups regarding postoperative morbidity, mortality, or duration of postoperative hospital stay (approximately 9 days in each group).

These somewhat discouraging findings (eg, absence of enhanced analgesia, prolongation of tracheal extubation time) stimulated the same group of investigators in 1999 to try again, this time decreasing the amount of intraoperative intravenous fentanyl that the patients received in hopes of decreasing the effect of fentanyl on augmenting postoperative respiratory depression associated with intrathecal morphine.[140] Forty patients were prospectively randomized to receive either intrathecal morphine (10 μg/kg) or intrathecal placebo before the induction of anesthesia for elective CABG. Intraoperative anesthetic management was standardized (intravenous fentanyl, 10 μg/kg; intravenous midazolam, 200 μg/kg); after surgery, all patients received intravenous morphine exclusively via PCA. Of the patients tracheally extubated during the immediate postoperative period, mean time to tracheal extubation was similar in patients who received intrathecal morphine (7 ± 3 hours) compared with intrathecal placebo patients (6 ± 3 hours). However, once again, four patients who received intrathecal morphine had tracheal extubation substantially delayed (14, 14, 18, and 19 hours) because of prolonged respiratory depression (likely secondary to intrathecal morphine). The mean postoperative use of intravenous morphine during the immediate postoperative period was actually greater in patients receiving intrathecal morphine (50 mg) compared with patients receiving intrathecal placebo (36 mg), yet the difference between groups was not statistically significant. No clinical differences existed between groups regarding postoperative morbidity, mortality, or duration of postoperative hospital stay (approximately 6 days in each group). Thus Chaney and associates,[140,142,143] from their three prospective, randomized, double-blind, placebo-controlled, clinical investigations in the late 1990s involving 140 healthy adults undergoing elective CABG, concluded that although intrathecal morphine can certainly initiate reliable postoperative analgesia, its use in the setting of fast-track cardiac surgery and early tracheal extubation may be detrimental by potentially delaying tracheal extubation in the immediate postoperative period.

Since this time, however, other clinical investigators have revealed that certain combinations of intraoperative anesthetic techniques

TABLE 42.2 Analysis of Outcome Measures After Elective Cardiopulmonary Bypass Surgery[a]

	Placebo (n = 19)	*250 µg (n = 16)*	*500 µg (n = 15)*	P
Ventilatory time (min)	441 ± 207	325 ± 187	409 ± 245	0.270
Morphine (mg)	21.3 ± 6.2	13.6 ± 7.8	11.7 ± 7.4	0.001
Midazolam (mg)	2.3 ± 3.5	0.9 ± 1.8	1.5 ± 2.7	0.346
Nitroglycerin (mg)	52.5 ± 37.6	55.0 ± 38.4	52.8 ± 43.0	0.982
Nitroprusside (mg)	7.9 ± 22.7	0.1 ± 0.4	1.4 ± 4.0	0.230

[a]Adult patients received placebo, intrathecal morphine (250 µg), or intrathecal morphine (500 µg) during the postoperative period.

From Alhashemi JA, Sharpe MD, Harris CL, et al. Effect of subarachnoid morphine administration on extubation time after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth.* 2000;14:639–644.

coupled with appropriate doses of intrathecal morphine will allow tracheal extubation after cardiac surgery within the immediate postoperative period to co-exist with enhanced analgesia. Alhashemi and colleagues[132] prospectively randomized 50 adults undergoing elective CABG to receive either one of two doses of intrathecal morphine (250 µg or 500 µg) or intrathecal placebo. Intraoperative anesthetic management was standardized (fentanyl, midazolam), and all patients received intermittent morphine by a blinded practitioner during the postoperative period. Tracheal extubation times were similar in the placebo group, 250 µg intrathecal morphine group, and 500 µg intrathecal morphine group (7, 5, and 7 hours, respectively; $p = 0.270$). However, postoperative morphine requirements in the placebo group (21 ± 6 mg), 250 µg intrathecal morphine group (14 ± 8 mg), and the 500 µg intrathecal morphine group (12 ± 7 mg) were substantially different. At least a 36% reduction in postoperative intravenous morphine requirements was observed among those patients who received intrathecal morphine. Although no differences in postoperative intravenous morphine requirements were observed among patients randomized to receive either 250 or 500 µg intrathecal morphine, both groups required significantly less intravenous morphine during the immediate postoperative period compared with control patients ($p = 0.001$). However, despite enhanced analgesia, no differences existed among the study groups with regards to midazolam, nitroglycerin, and sodium nitroprusside requirements in the postoperative period (Table 42.2). Furthermore, postextubation blood gas analysis, use of supplemental inspired oxygen, and ICU lengths of stay (approximately 22 hours in all groups) were comparable among the three groups.

These investigators, as well as others, reveal that the use of intrathecal morphine in patients undergoing fast-track cardiac surgery and early tracheal extubation may, if used appropriately, provide enhanced postoperative analgesia without delaying tracheal extubation. The authors also interestingly postulated that limiting the amounts of intraoperative intravenous opioids and intravenous sedatives and applying a postoperative tracheal extubation protocol may be more important in achieving the goal of early tracheal extubation after cardiac surgery than adequate pain control during the immediate postoperative period.

Many other suboptimally designed clinical investigations (eg, retrospective, observational) attest to the ability of intrathecal morphine to induce substantial postoperative analgesia in patients after cardiac surgery (Table 42.3). Intrathecal doses of 0.5 mg to 10.0 mg administered before CPB initiates reliable postoperative analgesia, the quality of which depends not only on the intrathecal dose administered but also on the type and amount of intravenous analgesics and sedatives used for the intraoperative baseline anesthetic. The optimal dose of intrathecal morphine for achieving maximum postoperative analgesia with minimum undesirable drug effects is uncertain. Naturally, when larger doses of intrathecal morphine are used, more intense and prolonged postoperative analgesia is obtained at the expense of more undesirable drug effects (nausea and vomiting, pruritus, urinary retention, respiratory depression).

Because of morphine's low lipid solubility, analgesic effects after intrathecal injection are delayed. Consequently, even large doses of intrathecal morphine administered to patients before cardiac surgery will not initiate reliable intraoperative analgesia[150–152,155] and therefore would not be expected to potentially attenuate the intraoperative stress response associated with CPB. Only an extremely large dose of intrathecal morphine (10 mg) may initiate reliable intraoperative analgesia in this setting.[154] One clinical investigation has examined the ability of intrathecal morphine to potentially attenuate the intraoperative stress response associated with CPB as measured by blood catecholamine levels.[143] In Chaney and associates'[143] clinical investigation, patients were prospectively randomized to receive either intrathecal morphine (4 mg) or intrathecal placebo before the induction of anesthesia for elective CABG with CPB. Intraoperative anesthetic management was standardized and multiple arterial blood samples were perioperatively obtained to ascertain norepinephrine and epinephrine levels. Patients who were administered intrathecal morphine experienced similar perioperative increases in blood catecholamine levels when compared with placebo controls. Thus intrathecal morphine (even in relatively large doses) appeared to be unable to reliably attenuate the perioperative stress response associated with cardiac surgery and CPB.

Although intrathecal morphine cannot reliably prevent the perioperative stress response associated with CPB, it may potentially attenuate the stress response during the immediate postoperative period by initiating postoperative analgesia. Vanstrum and colleagues[150] revealed that patients who were administered 0.5 mg intrathecal morphine before the induction of anesthesia not only required significantly less intravenous morphine after surgery compared with placebo control patients, but they also required significantly less intravenous nitroprusside (58 vs 89 mg, respectively; $p < 0.05$) during the initial 24 postoperative hours to control hypertension, which suggests partial postoperative stress-response attenuation.

Some clinical investigators have used intrathecal fentanyl, sufentanil, and/or local anesthetics for patients undergoing cardiac surgery, hoping to provide intraoperative anesthesia and analgesia (and stress-response attenuation), with mixed results (see Table 42.3). The administration of intrathecal local anesthetics to patients after the induction of anesthesia for cardiac surgery may help promote intraoperative hemodynamic stability,[144,146] whereas intrathecal sufentanil (50 µg) administered before the induction of anesthesia for cardiac surgery can reduce volatile anesthetic requirements during mediastinal dissection but is unable to reliably block intraoperative hemodynamic responses to laryngoscopy and intubation.[147] The addition of intrathecal clonidine in various amounts (100 µg, 1 µg/kg) may potentiate intrathecal morphine-induced postoperative analagesia.[157,159,163,170]

Most clinical attempts at inducing thoracic cardiac sympathectomy in patients undergoing cardiac surgery have used TEA with local anesthetics. However, a small number of clinical investigators have attempted cardiac sympathectomy in this setting with an intrathecal injection of local anesthetic. In 1994, as retrospectively reviewed, 18 adult patients were administered lumbar intrathecal hyperbaric bupivacaine (23 mg to 30 mg) and/or hyperbaric lidocaine (150 mg) mixed with morphine (0.5 mg to 1.0 mg) after the induction of anesthesia.[146] In an attempt to produce total spinal anesthesia and thus thoracic cardiac sympathectomy, the Trendelenburg position was maintained for at least 10 minutes after intrathecal injection. Heart rate decreased significantly (baseline mean 67 beats per minute [bpm] to postinjection mean 52 bpm) after intrathecal injection, indicating cardiac sympathectomy was obtained. Not a single patient exhibited electrocardiographic evidence of myocardial ischemia before CPB. Although these authors reported that the technique provided stable perioperative hemodynamics, 17 of 18 patients intraoperatively required intravenous phenylephrine to increase blood pressure. In 1996, the same group of investigators reported similar hemodynamic changes in a case report involving a 10-year-old child with Kawasaki disease who underwent CABG and received intrathecal hyperbaric bupivacaine mixed with morphine via a lumbar puncture after the induction of anesthesia.[144] Although Kowalewski's group reported that these patients experienced enhanced postoperative analgesia, definite conclusions cannot

TABLE 42.3 Reports of Intrathecal Anesthesia and Analgesia for Cardiac Surgery

First Author	Year	Study Design	Total Patients	Drugs: Dose	Intraoperative Management	Remarks
Nader[157]	2009	Prospective, observational	85	Morphine: 0.5 mg Clonidine: 100 µg	Not standardized	Clonidine enhances morphine-induced analgesia and may facilitate early extubation
dos Santos[158]	2009	Prospective, randomized	42	Morphine: 400 µg	Standardized	Reliable postoperative analgesia No pulmonary benefits
Lena[159]	2008	Prospective, randomized	83	Morphine: 4 µg/kg Clonidine: 1 µg/kg	Standardized	Reliable postoperative analgesia Facilitated early extubation Enhanced quality of recovery?
Yapici[160]	2008	Prospective, randomized	23	Morphine: 7 µg/kg	Standardized	Reliable postoperative analgesia Facilitated early extubation Decreased ICU length of stay?
Roediger[161]	2006	Prospective, randomized, blind, placebo-controlled	30	Morphine: 0.5 mg	Standardized	Reliable postoperative analgesia Mild pulmonary benefits Decreased catecholamine release
Parlow[162]	2005	Retrospective	131	Morphine: <5 µg/kg	Not standardized	Reliable postoperative analgesia Facilitated early extubation
Lena[163]	2005	Prospective, randomized, blind	40	Morphine: 4 µg/kg	Standardized	Reliable postoperative analgesia Facilitated early extubation?
Zisman[164]	2005	Retrospective	22	Morphine: 7 µg/kg	Not standardized	Reliable postoperative analgesia
Hammer[165]	2005	Prospective, randomized	45	Morphine: 7 µg/kg Tetracaine: 0.5–2.0 mg/kg	Standardized	Reliable postoperative analgesia
Turker[166]	2005	Prospective, randomized, blind	46	Morphine: 10 µg/kg	Standardized	Reliable postoperative analgesia
Jacobsohn[167]	2005	Prospective, randomized, blind, placebo-controlled	43	Morphine: 6 µg/kg	Standardized	Reliable postoperative analgesia Mild pulmonary benefits
Metz[168]	2004	Retrospective	112	Morphine: 0.3–1.6 mg	Not standardized	Facilitated intraoperative extubation? Increased respiratory depression?
Mehta[169]	2004	Prospective, randomized, blind, placebo-controlled	100	Morphine: 8 µg/kg	Standardized	Reliable postoperative analgesia Facilitated early extubation Mild pulmonary benefits
Lena[170]	2003	Prospective, randomized	45	Morphine: 4 µg/kg Clonidine: 1 µg/kg	Not standardized	Reliable postoperative analgesia Facilitated early extubation
Lee[173]	2003	Prospective, randomized, blind, placebo-controlled	38	Bupivacaine: 37.5 mg	Standardized	Potential stress-response attenuation
Boulanger[171]	2002	Prospective, randomized	62	Morphine: 20 µg/kg–1.0 mg	Standardized	No benefit May hinder early extubation
Bowler[131]	2002	Prospective, randomized	24	Morphine: 2.0 mg	Not standardized	No benefit
Bettex[156]	2002	Prospective, randomized	24	Morphine: 0.5 mg Sufentanil: 50 µg	Not standardized	Reliable postoperative analgesia Facilitated early extubation
Alhashemi[132]	2000	Prospective, randomized, blind, placebo-controlled	50	Morphine: 250 or 500 µg	Standardized	Significant postoperative analgesia
Latham[133]	2000	Prospective, randomized	40	Morphine: 8 µg/kg	Standardized	No benefit
Zarate[134]	2000	Prospective, randomized	40	Morphine: 8µg/kg	Standardized	Reliable postoperative analgesia
Peterson[137]	2000	Retrospective	18	Morphine: 5–10 µg/kg Tetracaine: 1–2 mg/kg	Not standardized	No benefit
Hammer[138]	2000	Retrospective	25	Morphine: 7–20 µg/kg Tetracaine: 0.5–2 mg/kg	Not standardized	No benefit
Chaney[140]	1999	Prospective, randomized, blind, placebo-controlled	40	Morphine: 10 µg/kg	Standardized	No benefit
Shroff[141]	1997	Prospective, randomized	21	Morphine: 10 µg/kg	Not standardized	Reliable postoperative analgesia Facilitated early extubation
Chaney[142]	1997	Prospective, randomized, blind, placebo-controlled	40	Morphine: 10 µg/kg	Standardized	Hindered early extubation
Chaney[143]	1996	Prospective, randomized, blind, placebo-controlled	60	Morphine: 4.0 mg	Standardized	Significant postoperative analgesia No stress-response attenuation
Taylor[145]	1996	Retrospective	152	Morphine: 30 µg/kg	Not standardized	Reliable postoperative analgesia
Kowalewski[146]	1994	Retrospective	18	Morphine: 0.5–1.0 mg Bupivacaine: 23–30 mg Lidocaine: 150 mg	Not standardized	Reliable postoperative analgesia Possible thoracic cardiac sympathectomy
Swenson[147]	1994	Retrospective	10	Morphine: 0.5 mg	Not standardized	Reliable postoperative analgesia Facilitated early extubation
Fitzpatrick[149]	1988	Prospective, randomized	44	Morphine: 1.0–2.0 mg	Not standardized	Significant postoperative analgesia
Vanstrum[150]	1988	Prospective, randomized, blind, placebo-controlled	30	Morphine: 0.5 mg	Standardized	Significant postoperative analgesia Possible stress-response attenuation
Casey[151]	1987	Prospective, randomized, blind, placebo-controlled	40	Morphine: 20 µg/kg	Standardized	No benefit
Cheun[152]	1987	Prospective, observational	180	Morphine: 0.1 mg/kg	Not standardized	Reliable postoperative analgesia
Aun[153]	1985	Prospective, randomized	60	Meperidine: 1.5 mg/kg Morphine: 2.0–4.0 mg	Not standardized	Significant postoperative analgesia
Jones[155]	1984	Prospective, observational	56	Morphine: 20–30 µg/kg	Not standardized	Reliable postoperative analgesia
Mathews[130]	1980	Retrospective	40	Morphine: 1.5–4.0 mg	Not standardized	Reliable postoperative analgesia

be reached regarding this technique because of study design formats (retrospective review, case report).

A small ($n = 38$ patients), prospective, randomized, blinded clinical investigation showed that large doses of intrathecal bupivacaine (37.5 mg) administered to patients immediately before the induction of general anesthesia (19 patients received intrathecal bupivacaine, 19 patients served as controls) for elective CABG may potentially initiate intraoperative stress-response attenuation (assessed via serum mediator levels, hemodynamics, and qualitative and quantitative alterations in myocardial β receptors).[173] However, no effect on clinical outcome parameters (eg, tracheal extubation times, respiratory function, perioperative spirometry) was observed. Mean tracheal extubation time measured from the time of sternotomy dressing application was extremely short in both groups (11 to 19 minutes). Specifically regarding postoperative analgesia, postoperative pain scores, and morphine use via PCA did not differ between the two groups. Not surprisingly, phenylephrine use was more common in patients who received intrathecal bupivacaine compared with control patients.

Many clinical investigations involving the use of intrathecal analgesic techniques in patients undergoing cardiac surgery indicate that the administration of intrathecal morphine to patients before CPB initiates reliable postoperative analgesia after cardiac surgery. Intrathecal opioids or local anesthetics cannot reliably attenuate the perioperative stress response associated with CPB that persists during the immediate postoperative period. Although intrathecal local anesthetics (not opioids) may induce perioperative thoracic cardiac sympathectomy, the hemodynamic changes associated with total spinal anesthesia make the technique unpalatable in patients with cardiac disease. A recently published metaanalysis of randomized, controlled trials (25 randomized trials, 1106 patients) concluded that spinal analgesia does not improve clinically relevant outcomes in patients undergoing cardiac surgery.[174] Additional large reviews came to the same conclusion.[175,176] Meylan and associates[176] concluded that "this analgesic intervention that reduces postoperative morphine consumption but not morphine-related adverse effects, that only slightly improves postoperative pain intensity, that significantly increases the risk of pruritus, and that is associated with a finite risk of respiratory depression should be abandoned." The most recently published clinical investigation involving intrathecal morphine for cardiac surgery dates back to 2009,[157] indicating perhaps that intrathecal morphine has become "The Forgotten Child" (see Table 42.3)[177]

Epidural Techniques

The initial description of TEA applied to a cardiac surgical patient occurred in 1954, during the formative years of CPB. Clowes and colleagues[178] described their presurgical anesthetic technique in a 55-year-old man with severe cardiac failure: "An endotracheal tube was passed with topical anesthesia. Under extradural block of the upper thorax, hypotension developed but responded to the administration of a vasopressor drug. At this time the patient became comatose" (Fig. 42.13). The patient eventually died. The application of TEA to patients undergoing cardiac surgery during the modern surgical era was initially reported by Hoar and associates[179] in 1976. They described the intraoperative insertion of thoracic epidural catheters in 12 patients after CABG and intravenous protamine but before transfer to ICU. The epidural catheters were injected with lidocaine and bupivacaine during the immediate postoperative period to promote analgesia and control hypertension effectively. The administration of epidural local anesthetics to these patients significantly decreased postoperative blood pressure in hypertensive and normotensive patients, and not a single patient required cardiac or peripheral vascular stimulants during the immediate postoperative study period. The 1987 report by El-Baz and Goldin[180] was the first to describe the insertion of thoracic

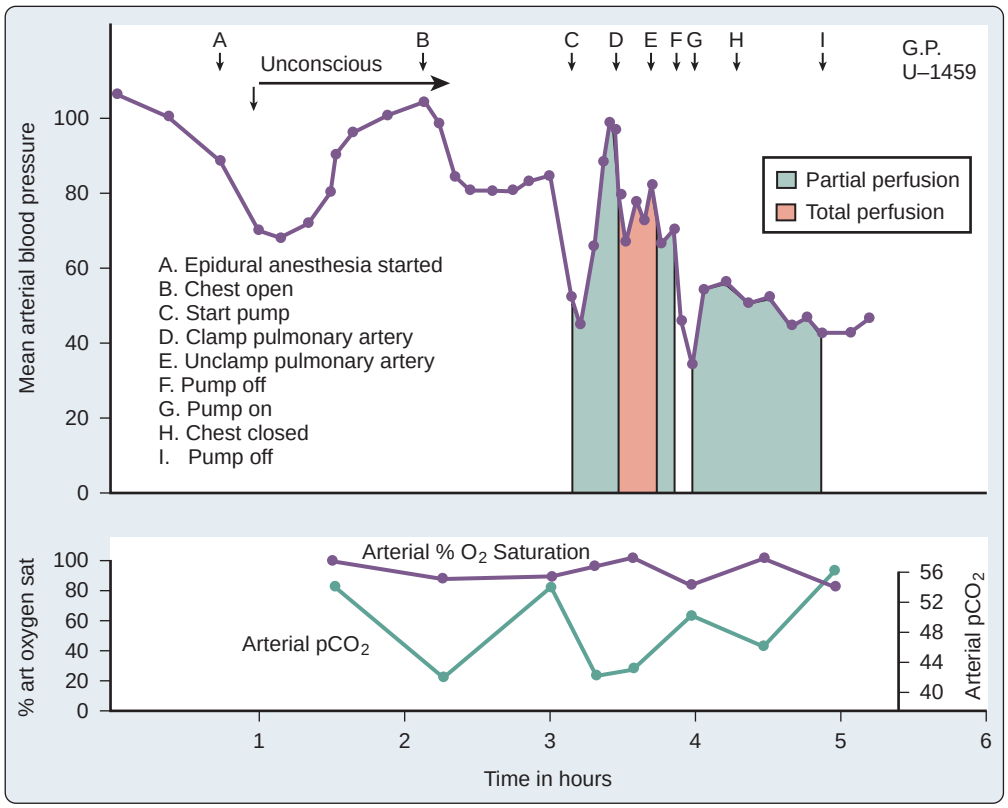


Fig. 42.13 Graph of clinical course of a patient is severe cardiac failure receiving presurgical epidural anesthesia in 1954. pCO_2, Carbon dioxide partial pressure. *(From Clowes GH Jr, Neville WE, Hopkins A, et al. Factors contributing to success or failure in the use of a pump oxygenator for complete by-pass of the heart and lung, experimental and clinical.* Surgery. *1954;36:557–579.)*

epidural catheters in patients before performing cardiac surgery. In prospective, randomized fashion, patients undergoing elective CABG received either routine treatment for postoperative pain (n = 30 patients, intravenous morphine) or a continuous infusion of morphine (0.1 mg/hr) via a thoracic epidural catheter (n = 30 patients). Thoracic epidural catheters were inserted at T3 to T4 immediately before the induction of anesthesia on the day of surgery. The intraoperative anesthetic technique was standardized, and the mean postoperative tracheal extubation time was significantly shorter in patients receiving TEA compared with control patients (9 ± 3 hours vs 18 ± 5 hours, respectively; $p < 0.01$). Continuous thoracic epidural infusion of morphine also achieved more effective postoperative pain relief than intravenous morphine (significantly better pain scores and significantly less supplemental intravenous morphine). Furthermore, in a subgroup of 20 patients (10 per group), postoperative stress was assessed via serum cortisol and β-endorphin levels. Patients receiving TEA had significantly lower postoperative levels of these mediators compared with control patients, indicating potential postoperative stress-response attenuation. Continuous thoracic epidural infusion of morphine (compared with control patients) was also associated with a lower incidence of opioid-related side effects during the immediate postoperative period. The insertion of the thoracic epidural catheter immediately before administering systemic heparin was not associated with any neurologic problems.

Since this initial impressive display of potential benefits (eg, reliable postoperative analgesia, stress-response attenuation, facilitation of early tracheal extubation), other clinical investigators have subsequently applied TEA to patients undergoing cardiac surgery.[181–216] Most clinical investigators have used thoracic epidural local anesthetics in hopes of providing perioperative stress-response attenuation and/or perioperative thoracic cardiac sympathectomy. Some clinical investigators have used thoracic epidural opioids to provide intraoperative and/or postoperative analgesia. An anonymous survey of members of the Society of Cardiovascular Anesthesiologists published in 2001 indicated that 7% of practicing anesthesiologists incorporate thoracic epidural techniques into their anesthetic management of adults undergoing cardiac surgery.[172] Of these anesthesiologists, 58% practice in the United States. Regarding the timing of epidural instrumentation, 40% perform instrumentation before the induction of general anesthesia, 12% perform instrumentation after the induction of general anesthesia, 33% perform instrumentation at the end of surgery, and 15% perform instrumentation on postoperative day 1.[172]

TEA with local anesthetics and/or opioids induces significant postoperative analgesia in patients after cardiac surgery. Patients randomized to receive a continuous thoracic epidural morphine infusion (0.1 mg/hr) after cardiac surgery required significantly less postoperative supplemental intravenous morphine compared with patients without thoracic epidural catheters (5 vs 18 mg/day per patient, respectively; $p < 0.05$) during the initial 3 postoperative days.[180] Children (aged 2 to 12 years) randomized to receive caudal epidural morphine (75 μg/kg) intraoperatively after cardiac surgery required significantly less postoperative supplemental intravenous morphine compared with patients who did not receive epidural morphine (0.3 vs 0.7 mg/kg, respectively; $p < 0.01$) during the initial 24 postoperative hours.[200] Numerous additional clinical studies further attest to the ability of TEA with local anesthetics and/or opioids to induce substantial postoperative analgesia in patients after cardiac surgery (Table 42.4).

One unique clinical investigation directly compared TEA and intravenous clonidine in patients undergoing cardiac surgery. Loick and colleagues[184] prospectively randomized 70 patients undergoing elective CABG to receive TEA supplementation (bupivacaine, sufentanil continuous infusion) perioperatively to general anesthesia (n = 25 patients), to receive intravenous clonidine supplementation (continuous infusion) perioperatively to general anesthesia (n = 24 patients), or to receive only general anesthesia (n = 21 control patients). Hemodynamics, plasma epinephrine and norepinephrine levels, plasma cortisol levels, the myocardium-specific contractile protein troponin T levels, and other plasma cardiac enzymes were perioperatively assessed. Both the TEA and intravenous clonidine groups experienced postoperative decreases in heart rate compared with the control group (without jeopardizing cardiac output or perfusion pressure). The effects on stress-response mediators were unpredictable and variable. Electrocardiographic evidence of ischemia (ST-segment elevation, ST-segment depression) occurred in 70% of control patients, 50% of TEA patients, and 40% of intravenous clonidine patients. The release of troponin T was attenuated (compared with control patients) in the TEA group only (no effect in the intravenous clonidine group). Interestingly enough, the highest quality of postoperative analgesia was found in the patients receiving intravenous clonidine. In the intravenous clonidine group, visual analogue pain scores were nearly halved when compared with the other two groups. Sedation scores were similar among the three groups with the exception of the 24-hour value in the intravenous clonidine group, which was greater than that in the TEA group. The postoperative comfort scores (rated between excellent and good) did not differ among the three groups.

Many clinical investigations have proved that TEA with local anesthetics also significantly attenuates the perioperative stress response in patients undergoing cardiac surgery. Patients randomized to receive intermittent boluses of thoracic epidural bupivacaine intraoperatively, followed by continuous infusion postoperatively, exhibited significantly decreased blood levels of norepinephrine and epinephrine perioperatively when compared with patients similarly managed without thoracic epidural catheters.[194] Furthermore, increased blood catecholamine levels in these patients were associated with increased systemic vascular resistance.[194] Patients randomized to receive continuous thoracic epidural bupivacaine infusion perioperatively exhibited significantly decreased blood levels of norepinephrine and cortisol perioperatively when compared with patients similarly managed without thoracic epidural catheters.[191] Patients randomized to receive a continuous thoracic epidural bupivacaine and sufentanil infusion perioperatively exhibited significantly decreased blood levels of norepinephrine after sternotomy when compared with patients similarly managed without thoracic epidural catheters.[197]

Other clinical studies further attest to the ability of TEA with local anesthetics to promote perioperative hemodynamic stability in patients undergoing cardiac surgery, which suggests perioperative stress-response attenuation.[179,193,194,197] Although most clinical attempts at stress-response attenuation involve thoracic epidural administration of local anesthetics, one investigation indicated that TEA with opioids may significantly attenuate the perioperative stress response in patients undergoing cardiac surgery. In this clinical investigation, patients who were randomized to receive a continuous thoracic epidural morphine infusion after surgery exhibited significantly decreased blood levels of cortisol and β-endorphin postoperatively when compared with patients similarly managed without thoracic epidural catheters.[180]

Two provocative clinical studies demonstrated the ability of TEA to induce significant thoracic cardiac sympathectomy in patients undergoing cardiac surgery.[192,193] In the first study, patients undergoing CABG were evaluated with reverse thermodilution catheters that had been inserted into the midcoronary sinus under fluoroscopic guidance before the induction of anesthesia.[192] Intraoperative anesthetic management was standardized. Coronary sinus blood flow was measured by a constant-infusion technique, and coronary vascular resistance was calculated using coronary perfusion pressure (arterial diastolic pressure minus pulmonary capillary wedge pressure) and coronary sinus blood flow. Patients who had been randomized to receive intermittent boluses of thoracic epidural bupivacaine intraoperatively, followed by a continuous infusion after surgery, exhibited significant decreases in coronary vascular resistance after CPB when compared with pre-CPB values. Patients similarly managed but without thoracic epidural catheters exhibited significant increases in coronary vascular resistance after CPB. In the second study, patients undergoing CABG were evaluated with catheters that had been inserted into the coronary sinus under fluoroscopic guidance and continuous pressure monitoring before the induction of anesthesia.[193] Intraoperative anesthetic management was standardized, and all patients received a continuous

TABLE 42.4 Reports of Epidural Anesthesia and Analgesia for Cardiac Surgery

First Author	Year	Study Design	Total Patients	Drugs: Dosage	Intraoperative Management	Remarks
Rajakaruna[224]	2013	Prospective, randomized	226	Bupivacaine: bolus plus infusion Clonidine: infusion	Standardized	May promote intraoperative hemodynamic stability
Gurses[225]	2013	Prospective, randomized	64	Levobupivacaine: bolus plus infusion Fentanyl: bolus plus infusion	Standardized	Reliable postoperative analgesia Facilitated early extubation Decreased ICU and/or hospital stay
Onan[226]	2013	Prospective, randomized	40	Bupivacaine: bolus plus infusion	Standardized	Reliable postoperative analgesia Facilitated early extubation Decreased ICU and/or hospital stay
Monaco[227]	2013	Retrospective	66	Lidocaine: bolus Ropivacaine: infusion Sufentanil: infusion	Not Standardized	Decreased adverse events?
Stenger[228]	2013	Retrospective	1016	Lidocaine: bolus Bupivacaine: bolus plus infusion Sufentanil: infusion	Not standardized	Decreased postoperative renal failure?
Jakobsen[229]	2012	Prospective, randomized	60	Bupivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Not standardized	Improved cardiac performance?
Nielsen[230]	2012	Prospective, randomized	60	Bupivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Not standardized	No benefit
Onan[231]	2011	Prospective, randomized	30	Bupivacaine: bolus plus infusion	Standardized	Increased internal thoracic artery free blood flow
Caputo[232]	2011	Prospective, randomized	226	Bupivacaine: bolus plus infusion Clonidine: infusion	Standardized	Reliable postoperative analgesia Facilitated early extubation Decreased postoperative arrhythmias Decreased hospital stay
Svircevic[233]	2011	Prospective, randomized	654	Bupivacaine: bolus plus infusion Morphine: bolus plus infusion	Standardized	No benefit
Caputo[234]	2009	Prospective, randomized	74	Bupivacaine: bolus plus infusion Clonidine: infusion	Standardized	No benefit
Crescenzi[235]	2009	Prospective, observational	92	Lidocaine: bolus Ropivacaine: infusion Sufentanil: infusion	Not standardized	Stress-response attenuation? Decreased ICU stay?
Tenebein[236]	2008	Prospective, randomized	50	Ropivacaine: bolus plus infusion Hydromorphone: bolus	Standardized	Reliable postoperative analgesia Improved pulmonary function
Royse[237]	2007	Prospective, randomized	61	Ropivacaine: infusion Fentanyl: infusion	Not standardized	Decreased postoperative depression?
Bakhtiary[238]	2007	Prospective, randomized	132	Ropivacaine: bolus plus infusion	Standardized	Decreased perioperative arrhythmias Stress-response attenuation
Heijmans[239]	2007	Prospective, randomized	60	Bupivacaine: bolus plus infusion Morphine: infusion	Standardized	Reliable postoperative analgesia Facilitated early extubation
Salvi[240]	2007	Retrospective	1473	Ropivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Not standardized	Facilitated early extubation
Lagunilla[241]	2006	Prospective, randomized, double-blind	50	Ropivacaine: bolus	Standardized	Increased myocardial oxygen availability
Hansdottir[223]	2006	Prospective, randomized	113	Bupivacaine: bolus plus infusion Fentanyl: bolus plus infusion Adrenalin: bolus plus infusion	Standardized	Facilitated early extubation
Anderson[242]	2005	Prospective, observational	104	Bupivacaine: bolus plus infusion Sufentanil: infusion	Not standardized	No benefit
Kessler[243]	2005	Prospective, observational	90	Ropivacaine: infusion Sufentanil: infusion	Standardized	Reliable perioperative analgesia
Lundstrom[244]	2005	Prospective, randomized	50	Bupivacaine: bolus plus infusion Morphine: infusion	Standardized	No benefit
Hemmerling[245]	2005	Prospective audit	45	Bupivacaine: bolus plus infusion	Standardized	Reliable postoperative analgesia
Salvi[246]	2004	Retrospective	106	Ropivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Not standardized	Reliable postoperative analgesia
Hemmerling[247]	2004	Prospective audit	100	Bupivacaine: bolus plus infusion	Standardized	Reliable postoperative analgesia
Berendes[248]	2003	Prospective, randomized	73	Bupivacaine: bolus plus infusion Sufentanil: bolus	Standardized	Thoracic cardiac sympathectomy
Royse[221]	2003	Prospective, randomized	80	Ropivacaine: infusion Fentanyl: infusion	Not Standardized	Reliable postoperative analgesia
Pastor[203]	2003	Prospective, observational	714	Bupivacaine: bolus plus infusion Ropivacaine: bolus plus infusion	Not Standardized	No hematoma formation
Bach[249]	2002	Prospective, randomized	40	Bupivacaine: bolus plus infusion	Standardized	Stress-response attenuation
Priestley[222]	2002	Prospective, randomized	100	Ropivacaine: infusion Fentanyl: infusion	Not Standardized	Reliable postoperative analgesia
de Vries[207]	2002	Prospective, randomized	90	Bupivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Standardized	Reliable postoperative analgesia Facilitated early extubation Possible decreased hospital stay
Canto[208]	2002	Prospective , observational	305	Ropivacaine: bolus plus infusion	Not Standardized	No hematoma formation

TABLE 42.4 Reports of Epidural Anesthesia and Analgesia for Cardiac Surgery—cont'd

First Author	Year	Study Design	Total Patients	Drugs: Dosage	Intraoperative Management	Remarks
Fillinger[209]	2002	Prospective, randomized	60	Bupivacaine: bolus plus infusion Morphine: bolus plus infusion	Not Standardized	No benefit
Jideus[181]	2001	Prospective, randomized	41	Bupivacaine: bolus plus infusion Sufentanil: infusion	Not Standardized	Stress-response attenuation Thoracic cardiac sympathectomy
Scott[182]	2001	Prospective, randomized	206	Bupivacaine: bolus plus infusion Clonidine: infusion	Standardized	Decreased postoperative arrhythmias Improved postoperative pulmonary function Decreased postoperative renal failure Decreased postoperative confusion
Dhole[210]	2001	Prospective, randomized	41	Bupivacaine: bolus plus infusion	Not Standardized	No benefit
Djaiani[211]	2001	Retrospective	37	Bupivacaine: bolus plus infusion	Not Standardized	Facilitated early extubation
Warters[183]	2000	Retrospective	278	Not specified	Not Standardized	No hematoma formation
Loick[184]	1999	Prospective, randomized	25	Bupivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Standardized	Stress-response attenuation Thoracic cardiac sympathectomy Facilitated early extubation
Tenling[185]	1999	Prospective, randomized	14	Bupivacaine: bolus plus infusion	Not Standardized	Reliable postoperative analgesia Facilitated early extubation
Sanchez[186]	1998	Prospective, observational	571	Bupivacaine: boluses	Not Standardized	No hematoma formation
Fawcett[214]	1997	Prospective, randomized	16	Bupivacaine: bolus plus infusion	Standardized	Reliable postoperative analgesia Improved pulmonary function Stress-response attenuation
Turfrey[215]	1997	Retrospective	218	Bupivacaine: bolus plus infusion Clonidine: infusion	Not Standardized	Facilitated early extubation Possible thoracic cardiac sympathectomy
Shayevitz[189]	1996	Retrospective	54	Morphine: bolus plus infusion	Not Standardized	Reliable postoperative analgesia Facilitated early extubation
Stenseth[216]	1996	Prospective, randomized	54	Bupivacaine: bolus plus infusion	Not Standardized	Facilitated early extubation Possible thoracic cardiac sympathectomy
Moore[191]	1995	Prospective, randomized	17	Bupivacaine: bolus plus infusion	Standardized	Stress-response attenuation Possible thoracic cardiac sympathectomy
Stenseth[192]	1995	Prospective, randomized	30	Bupivacaine: bolus plus infusion	Standardized	Thoracic cardiac sympathectomy
Kirno[193]	1994	Prospective, randomized	20	Mepivacaine: bolus	Standardized	Stress-response attenuation Thoracic cardiac sympathectomy
Stenseth[194,195]	1994	Prospective, randomized	30	Bupivacaine: bolus plus infusion	Standardized	Stress-response attenuation Possible thoracic cardiac sympathectomy
Liem[197–199]	1992	Prospective, randomized	54	Bupivacaine: bolus plus infusion Sufentanil: bolus plus infusion	Not Standardized	Reliable postoperative analgesia Stress-response attenuation Possible thoracic cardiac sympathectomy
Rein[250]	1989	Prospective, randomized	16	Bupivacaine: bolus plus infusion	Not standardized	Decreased interstitial fluid accumulation
Rosen[200]	1989	Prospective, randomized	32	Morphine: bolus	Not Standardized	Reliable postoperative analgesia Facilitated early extubation
Joachimsson[201]	1989	Observational	28	Bupivacaine: boluses	Not Standardized	Reliable postoperative analgesia
El-Baz[180]	1987	Prospective, randomized	60	Morphine: infusion	Standardized	Reliable postoperative analgesia Stress-response attenuation Facilitated early extubation
Robinson[202]	1986	Prospective, observational	10	Meperidine: bolus	Standardized	Reliable postoperative analgesia
Hoar[179]	1976	Prospective, observational	12	Lidocaine: boluses Bupivacaine: boluses	Not Standardized	Reliable postoperative analgesia Possible stress-response attenuation

intravenous infusion of tritiated norepinephrine, which allowed the assessment of cardiac norepinephrine spillover to plasma via isotope dilution technique. Blood samples were obtained from the coronary sinus and radial artery, and the rate of norepinephrine spillover from the heart was calculated according to the Fick principle to assess cardiac sympathetic activity. Patients who were randomized to receive a single bolus of thoracic epidural mepivacaine immediately after the induction of anesthesia exhibited significantly decreased cardiac norepinephrine spillover after sternotomy when compared with patients similarly managed without thoracic epidural catheters. Furthermore, 20% of patients managed without thoracic epidural catheters exhibited electrocardiographic evidence of myocardial ischemia after sternotomy, whereas no patient managed with a thoracic epidural catheter exhibited myocardial ischemia during this time.

Perioperative cardiac sympathectomy induced via TEA with local anesthetics may clinically benefit patients undergoing cardiac surgery by increasing myocardial oxygen supply.[119,128,129] However, such a cardiac sympathectomy may offer additional benefits to patients undergoing cardiac surgery. Multiple clinical studies have demonstrated that TEA with local anesthetics significantly decreases heart rate before[197] and after[191,197] the initiation of CPB and significantly decreases the need to administer β-blockers after CPB.[194] Multiple clinical studies have also demonstrated that TEA with local anesthetics significantly decreases systemic vascular resistance before[193,194] and after[197,201] the initiation of CPB. Furthermore, patients undergoing cardiac surgery who receive TEA with local anesthetics not only exhibit significant decreases in postoperative heart rate and systemic vascular resistance, but they also exhibit significant decreases in postoperative electrocardiographic evidence of myocardial ischemia when compared with patients similarly managed without thoracic epidural catheters.[197]

A relatively large clinical investigation highlighted the potential clinical benefits of TEA in cardiac surgical patients. Scott and associates[182]

TABLE 42.5 Various Outcomes of Patients

Outcome	*TEA (n = 206),* n *(%)*	*GA (n = 202),* n *(%)*
Supraventricular arrhythmia	21 (10.2)	45 (22.3)
Lower respiratory tract infection	31 (15.3)	59 (29.2)
Renal failure	4 (2.0)	14 (6.9)
Cerebrovascular accident	2 (1.0)	6 (3.0)
Acute confusion	3 (1.5)	1 (5.5)
Significant bleeding	35	23
Any complications	84	108

Significant (unadjusted) differences existed among groups regarding supraventricular arrhythmia ($p = 0.0012$), lower respiratory tract infection ($p = 0.0007$), renal failure ($p = 0.016$), acute confusion ($p = 0.031$), and any complications ($p = 0.011$).
GA, General anesthesia; *TEA*, thoracic epidural analgesia.
From Scott NB, Turfrey DJ, Ray DA, et al. A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. *Anesth Analg.* 2001;93:528–535.

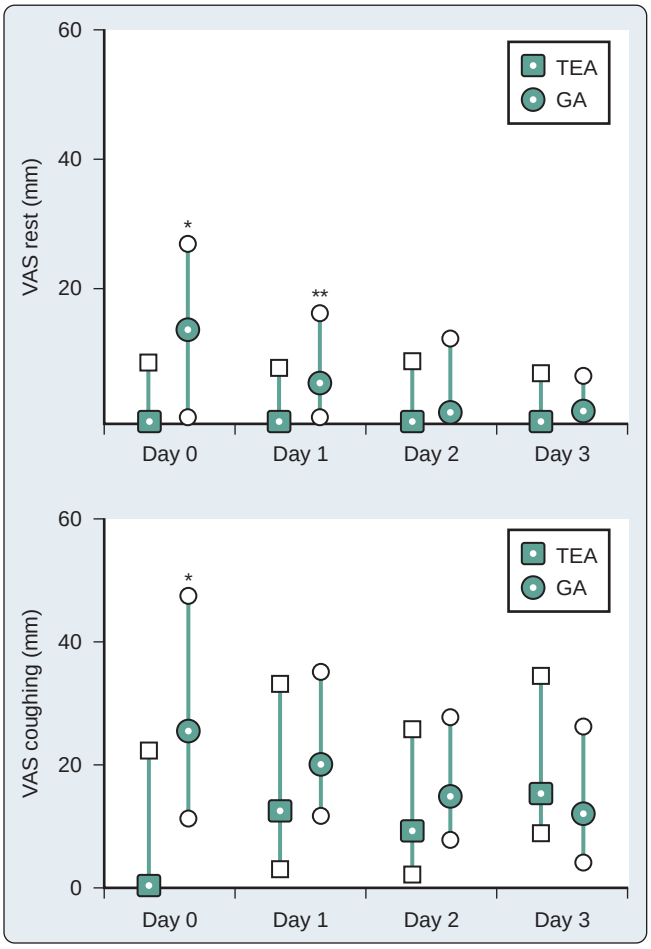


Fig. 42.14 Visual Analogue Scale (VAS) Scores. VAS scores for pain at rest (*top*) and with coughing (*bottom*) on the day of surgery and the first 3 postoperative days. Significant differences ($p < 0.03$) existed between the two groups only on postoperative day 0 (rest and coughing) and on postoperative day 1 (rest only). *GA*, General anesthesia; *TEA*, thoracic epidural analgesia. *(From Priestley MC, Cope L, Halliwell R, et al. Thoracic epidural anesthesia for cardiac surgery: the effects on tracheal intubation time and length of hospital stay.* Anesth Analg. *2002;94:275–282.)*

prospectively randomized (nonblinded) 420 patients undergoing elective CABG to receive either TEA (bupivacaine/clonidine) and general anesthesia or general anesthesia alone (control group). The two groups received similar intraoperative anesthetic techniques. In TEA patients, the thoracic epidural infusion was continued for 96 hours after surgery (titrated according to need). In control patients, target-controlled infusion of alfentanil was used for the first 24 postoperative hours, followed by PCA morphine for the next 48 hours. After surgery, striking clinical differences were observed between the two groups (Table 42.5). Postoperative incidence of supraventricular arrhythmia, lower respiratory tract infection, renal failure, and acute confusion all were significantly lower in patients receiving TEA compared with control patients. However, data from this clinical investigation must be viewed with caution. The clinical protocol dictated that β-adrenergic blocker therapy could not be intraoperatively or postoperatively used for the 5 days of the study period (except in those patients who developed a new arrhythmia requiring additional therapy). Because approximately 90% of this study's patients were taking β-adrenergic blockers before surgery, this unique perioperative management clouds the interpretation of postoperative supraventricular arrhythmia data. Despite prospective randomization, substantially fewer patients receiving TEA were current active smokers before surgery compared with control patients (6% vs 13%, respectively), which clouds the interpretation of postoperative lower respiratory tract infection data. These investigators also found that postoperative preextubation maximal expiratory lung volumes were increased in TEA patients (compared with control patients) and postoperative tracheal extubation was facilitated via TEA as well, yet TEA patients and control patients were managed somewhat differently during the immediate postoperative period. Although postoperative analgesia was not definitively assessed in this clinical investigation, 12% of control patients were converted to TEA during the first 24 postoperative hours because of suboptimal postoperative analgesia, whereas only 3% of TEA patients were converted to target-controlled infusion alfentanil or PCA morphine because of suboptimal postoperative analgesia. The results of this clinical investigation are certainly intriguing, yet definitive conclusions regarding the use of TEA techniques in patients undergoing cardiac surgery cannot be drawn because of the study's substantial limitations, highlighted by an accompanying editorial[217] and three subsequent letters to the editor.[218–220]

In contrast with the encouraging findings of Scott and associates'[182] clinical investigation, two prospective, randomized, nonblinded clinical investigations revealed that using TEA techniques in patients undergoing cardiac surgery may not offer substantial clinical benefits.[221,222] In 2002, Priestley and associates[222] prospectively randomized 100 patients undergoing elective CABG to receive either TEA (ropivacaine/fentanyl) and general anesthesia or general anesthesia alone (control group). The two groups received significantly different intraoperative anesthetic techniques. Before surgery, TEA patients received epidural ropivacaine/fentanyl for 48 hours (supplemental analgesics were available if needed), whereas control patients received nurse-administered intravenous morphine followed by PCA morphine. Patients receiving TEA were extubated sooner than control patients (3 vs 7 hours, respectively; $p < 0.001$), yet this difference may have been secondary to the different amounts of intraoperative intravenous opioid administered to the two groups (intraoperative intravenous anesthetic technique not standardized). Postoperative pain scores at rest were significantly lower in patients receiving TEA only on postoperative days 0 and 1 (equivalent on days 2 and 3). Postoperative pain scores during coughing were significantly lower in patients receiving TEA only on postoperative day 0 (equivalent on days 1, 2, and 3; Fig. 42.14). No significant differences were observed between the two groups in postoperative oxygen saturation on room air, chest radiograph changes, or spirometry (Table 42.6). Furthermore, no clinical differences were detected between the two groups regarding postoperative mobilization goals, atrial fibrillation, postoperative hospital discharge eligibility, or actual postoperative hospital discharge. In short, this clinical investigation revealed that TEA may provide enhanced postoperative analgesia (although brief) and enhance early postoperative tracheal extubation, yet it has no effect on important clinical parameters such as morbidity and hospital length of stay.

TABLE 42.6 Spirometry Results

	Mean FEV_1 (SD)		Mean FVC (SD)	
Variable	TEA (L)	GA (L)	TEA (L)	GA (L)
Predicted	2.9 (0.4)	2.9 (0.5)	3.9 (0.5)	3.9 (0.6)
Preoperative	2.5 (0.4)	2.6 (0.8)	3.3 (0.8)	3.4 (0.9)
Postoperative day 1	1.0 (0.3)	1.0 (0.4)	1.2 (0.4)	1.4 (0.5)
Postoperative day 2	1.1 (0.3)	1.1 (0.4)	1.4 (0.4)	1.5 (0.5)
Postoperative day 4	1.4 (0.4)	1.3 (0.5)	1.8 (0.6)	1.7 (0.6)

No significant differences existed between patients receiving thoracic epidural analgesia (TEA) and control patients receiving general anesthesia (GA).

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *SD*, standard deviation.

From Priestley MC, Cope L, Halliwell R, et al. Thoracic epidural anesthesia for cardiac surgery: the effects on tracheal intubation time and length of hospital stay. *Anesth Analg.* 2002;94:275–282.

TABLE 42.7 Visual Analog Scale Scores

Pain Score	High Thoracic Epidural Analgesia (mean ± SD)	Control (mean ± SD)
Rest day 1	0.02 ± 0.2	0.8 ± 1.8
Cough day 1	1.2 ± 1.7	4.4 ± 3.1
Rest day 2	0.1 ± 0.4	1.2 ± 2.7
Cough day 2	1.5 ± 2.0	3.6 ± 3.1
Rest day 3	0.2 ± 1.0	0.3 ± 1.1
Cough day 3	1.7 ± 2.3	2.7 ± 3.0

Mean pain scores at rest and with cough for postoperative days 1, 2, and 3. Significant differences ($p < 0.05$) existed between groups on postoperative days 1 and 2 (at rest and with cough) yet not on day 3.

SD, Standard deviation.

From Royse C, Royse A, Soeding P, et al. Prospective randomized trial of high thoracic epidural analgesia for coronary artery bypass surgery. *Ann Thorac Surg.* 2003;75:93–100.

In 2003, Royse and associates[221] prospectively randomized 80 patients undergoing elective CABG to receive either TEA (ropivacaine/fentanyl) and general anesthesia or general anesthesia alone (control group). The two groups received very different intraoperative anesthetic techniques. After surgery, TEA patients received epidural ropivacaine/fentanyl until postoperative day 3, whereas control patients received nurse-administered intravenous morphine followed by PCA morphine. Patients receiving TEA were tracheally extubated sooner during the immediate postoperative period than control subjects (3 vs 5 hours, respectively; $p < 0.001$), yet this difference may have been secondary to the administration of different amounts of intraoperative intravenous anesthetics (intraoperative anesthetic technique was not standardized). Postoperative pain scores at rest and with cough were significantly lower in patients receiving TEA on postoperative days 1 and 2 only (equivalent on postoperative day 3; Table 42.7). Similar to the investigation conducted by Priestley and associates,[222], no substantial differences were observed between the two groups regarding important postoperative clinical parameters such as respiratory function, renal function, atrial fibrillation, ICU length of stay, and hospital length of stay.

In 2006, Hansdottir and associates[223] provided additional evidence that TEA techniques offer no real clinical benefits to patients undergoing cardiac surgery. This relatively large (113 patients) prospective trial randomized patients undergoing elective cardiac surgery to receive either patient-controlled TEA (catheter inserted the day before surgery; using bupivacaine, fentanyl, and epinephrine) or patient-controlled intravenous morphine analgesia during the immediate postoperative period. Perioperative care was standardized (all patients underwent general anesthesia and received a median sternotomy). When the two groups were compared, the only difference was a shorter time to postoperative tracheal extubation in patients receiving TEA (2 vs 7 hours). No differences were observed regarding postoperative analgesia (at rest and during cough), degree of sedation, lung volumes (forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow), degree of ambulation, global quality of recovery score (including all five domains studied), cardiac morbidity (myocardial infarction, atrial fibrillation), renal morbidity (peak serum creatinine), neurologic outcome (stroke, confusion), ICU stay, or hospital length of stay. Furthermore, this group of experienced investigators reported a very high failure rate (17%) for the use of thoracic epidural catheters in these patients.

Numerous other clinical investigations have demonstrated varying degrees of mild clinical benefits (see Table 42.4).[224–250] For instance, Lagunilla and colleagues[241] found that high thoracic epidural blockade with ropivacaine increased myocardial oxygen availability in patients before surgical revascularization without deleterious hemodynamic disturbances, and Tenenbein and associates[236] found that high TEA decreased postoperative pain and atelectasis and improved pulmonary function in patients undergoing myocardial revascularization. Lastly, Bakhtiary and colleagues[238] revealed that high TEA in combination with general anesthesia significantly reduced the incidence of perioperative arrhythmias such as atrial fibrillation and significantly reduced serum epinephrine levels. However, the vast amount of clinical investigations continues to reveal no clinical benefits above and beyond the initiation of reliable postoperative analgesia (see Table 42.4).

The February 2011 issue of *Anesthesiology* highlights the controversial nature of this topic as two clinical studies with opposite conclusions were published. Caputo and associates[232] randomized 226 patients undergoing off-pump CABG to receive general anesthesia plus epidural ($n = 109$) or general anesthesia alone ($n = 117$). The primary outcome was the length of postoperative stay, and secondary outcomes were arrhythmia, inotropic support, intubation time, perioperative myocardial infarction, neurologic events, intensive care stay, pain scores, and analgesia requirement. They found that the addition of TEA to general anesthesia significantly reduced the incidence of postoperative arrhythmias and improved pain control and overall quality of recovery, allowing earlier extubation and hospital discharge. In contrast, Svircevic and colleagues[233] randomized 654 patients undergoing elective on-pump and off-pump cardiac surgery to combined general anesthesia and TEA ($n = 325$) versus general anesthesia alone ($n = 329$). Follow-up was at 30 days and 1 year after surgery. The primary endpoint was 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. They were unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications. These authors concluded, "Given the potentially devastating complications of epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization." These two clinical studies were accompanied by an editorial that stated that "… we continue to try and show that regional anesthesia and analgesia can substantially alter surgical outcomes without success … perhaps it is time to move away from trying to prove that anesthetic interventions will reduce morbidity or mortality and to focus on tangible benefits to patients or their families."[251]

Despite enhanced postoperative analgesia offered via TEA techniques, such analgesia does not appear to decrease the incidence of persistent pain after cardiac surgery. Ho and associates[19] assessed 244 patients after cardiac surgery with median sternotomy. One hundred and fifty patients received perioperative supplementation of general anesthesia with TEA (ropivacaine-fentanyl infusion initiated before the induction of anesthesia and continued after surgery for 2 to 3 days). Ninety four patients received general anesthesia and routine postoperative nurse-controlled intravenous morphine infusion for analgesia, together with intraoperative wound infiltration with ropivacaine at chest wall closure. Persistent pain, defined as pain still present 2 or more months after surgery, was similar in the two cohorts (reported in almost 30% of patients). However, persistent pain reported by these patients was mild in most cases, infrequently interfering with daily life.

The quality of analgesia obtained with TEA techniques is sufficient to allow cardiac surgery to be performed in awake patients without general endotracheal anesthesia. The initial report of awake cardiac

surgery was published in the *Annals of Thoracic Surgery* in 2000. Karagoz and associates[252] described the perioperative course of five patients who underwent elective off-pump single-vessel CABG via minithoracotomy with only TEA (spontaneous ventilation throughout). All five patients did well, and none had to be converted to general endotracheal anesthesia. Soon thereafter, Aybek and colleagues[253] described the perioperative course of 12 patients who underwent elective off-pump multivessel CABG via complete sternotomy with only TEA. All patients did well, yet two patients required conversion to general endotracheal anesthesia (one for incomplete analgesia, one for pneumothorax). Also in 2002, Souto and associates[254] revealed that "outpatient" CABG (discharge to home within 24 hours of hospital admission) was possible in a small ($n = 20$) group of patients undergoing cardiac surgery solely via TEA. Since these initial small clinical reports appeared, larger series of patients have been published, demonstrating that awake cardiac surgery is feasible and safe.[255–265] In 2003, the first case report of awake cardiac surgery requiring CPB was published.[266] In this astonishing case report from Austria, a 70-year-old man with aortic stenosis underwent aortic valve replacement with the assistance of normothermic CPB (total time: 123 minutes; cross-clamp time: 82 minutes) solely via TEA. Verbal communication with the patient was possible on demand throughout the CPB surgery. The patient did well and experienced an unremarkable postoperative course.

The many clinical investigations involving the use of TEA techniques in patients undergoing cardiac surgery indicate that the administration of thoracic epidural opioids or local anesthetics before and/or after CPB initiates reliable postoperative analgesia. The administration of TEAs (not opioids) can both reliably attenuate the perioperative stress response associated with CPB (that persists during the immediate postoperative period) and induce perioperative thoracic cardiac sympathectomy. Enhanced postoperative analgesia likely facilitates early tracheal extubation after cardiac surgery, yet patients may be extubated after cardiac surgery (with or without CPB) in the surgical unit without the assistance of TEA techniques.[267]

All clinical reports involving the use of intrathecal anesthesia and TEA and analgesia techniques for cardiac surgery involve small numbers of patients, and few (if any) are well designed (see Tables 42.2 and 42.3). Only a handful of clinical studies involving intrathecal analgesia are prospective, randomized, blinded, and placebo-controlled (see Table 42.3). No blinded, placebo-controlled clinical studies involving epidural techniques (see Table 42.4) have been reported. Furthermore, very few of the existing clinical studies involving intrathecal anesthesia and TEA techniques for cardiac surgery use the clinical outcome as a primary endpoint. Thus clear deficiencies in the literature prohibit a definitive analysis of the risk-benefit ratio of intrathecal anesthesia and TEA techniques as applied to patients undergoing cardiac surgery.

A 2004 metaanalysis by Liu and colleagues[268] assessed the effects of perioperative central neuraxial analgesia on outcome after CABG. These authors, via MEDLINE and other databases, searched for randomized, controlled trials in patients undergoing CABG with CPB. Fifteen trials enrolling 1178 patients were included for TEA analysis, and 17 trials enrolling 668 patients were included for intrathecal analysis. Although TEA techniques did not affect the incidences of mortality or myocardial infarction, they reduced the risk for arrhythmias (atrial fibrillation and tachycardia) and pulmonary complications (pneumonia and atelectasis), reduced the time to tracheal extubation, and reduced analog pain scores. Intrathecal techniques did not affect incidences of mortality, myocardial infarction, arrhythmias, or time to tracheal extubation and only modestly decreased systemic morphine use and pain scores, while increasing the incidence of pruritus. These authors concluded that central neuraxial analgesia does not affect rates of mortality or myocardial infarction after CABG, yet its use is associated with improvements in faster time to tracheal extubation, decreased pulmonary complications and cardiac arrhythmias, and reduced pain scores. However, the authors also noted that the majority of potential clinical benefits offered by central neuraxial analgesia (earlier extubation, decreased arrhythmias, enhanced analgesia) may be reduced and/or eliminated with changing cardiac anesthesia practice using fast-track techniques, using β-adrenergic blockers or amiodarone, and/or using NSAIDs or COX-2 inhibitors. These authors also noted that the risk for spinal hematoma (addressed later in this chapter) associated with regional techniques in patients undergoing full anticoagulation for CPB remains uncertain. Subsequent metaanalyses by Bignami and associates[269] in 2010 (33 randomized trials, 2366 patients) and Svircevic and associates[270] in 2011 (28 randomized trials, 2731 patients) reached somewhat different conclusions. The Bignami study[269] suggested that epidural techniques may decrease renal failure, time on mechanical ventilation, and composite endpoint of mortality and myocardial infarction, whereas the Svircevic[270] study suggested that epidural techniques may decrease the incidence of supraventricular arrhythmias and respiratory complications, yet have no beneficial effects on myocardial infarction, stroke, or mortality.

The use of intrathecal and/or epidural techniques in patients undergoing full thoracotomy incisions (rare during cardiac surgery, yet sometimes used in certain circumstances) deserves brief mention.[271] Many factors are involved in the occurrence of pulmonary dysfunction after full thoracotomy. Postoperative changes in pulmonary function result from lung resection, atelectasis, and/or volume loss caused by pneumothorax and inspiratory muscle dysfunction. Pain after full thoracotomy can be intense, which may produce pulmonary complications after surgery. Somewhat surprisingly, patients undergoing a "clamshell" incision (transverse thoracosternotomy) for bilateral lung transplantation do not experience more postoperative pain than patients undergoing a standard full thoracotomy for single-lung transplantation, and lung transplant recipients undergoing full thoracotomy have a lower incidence of adequate pain relief than patients undergoing full thoracotomy for other indications.[272] These clinical observations emphasize that the condition of the patient may play a major role (together with the type of incision) regarding the adequacy of postoperative pain control. Clearly, compared with full thoracotomy incisions, patients receiving minithoracotomy incisions experience less postoperative pain and consume fewer supplemental analgesics during the immediate postoperative period. Furthermore, up to one half of all patients undergoing full thoracotomy incision will experience chronic pain related to the surgical site.

Adequate postoperative pain control after full thoracotomy may help prevent the development of chronic postoperative thoracotomy pain. Therefore an effective postoperative analgesic plan must be developed for these patients. In contrast with median sternotomy incisions and minithoracotomy incisions, some clinical evidence indicates that the use of regional anesthetic techniques may decrease postoperative complications after full thoracotomy incisions. Specifically, Ballantyne and colleagues[273] and Licker and associates[274] provided evidence that postoperative pain control with epidural techniques after full thoracotomy incision may reduce pulmonary morbidity and overall patient mortality. However, although existing evidence suggests that TEA offers superior postoperative analgesia (superiority of thoracic over lumbar routes has recently been called into question), not all clinical studies have shown that such techniques truly improve postoperative pulmonary function and reduce postoperative pulmonary complications.

Side Effects of Intrathecal and Epidural Local Anesthetics

Hypotension is the most troubling and undesirable drug effect of intrathecal and epidural local anesthetics. Spinal anesthesia to upper thoracic dermatomes produces a decrease in mean arterial blood pressure that is accompanied by a parallel decrease in coronary blood flow.[275,276] Exactly what percentage of blood pressure decrease is acceptable remains speculative, especially in patients with coronary artery disease. Disturbances in myocardial oxygenation appear to occur in patients with coronary artery disease if coronary perfusion pressure is allowed to decrease by more than 50% during the induction of TEA with local anesthetics.[277] Furthermore, if α-adrenergic agonists are used to increase blood pressure during this time, then there may be detrimental effects (vasoconstriction) on the native coronary arteries

and bypass grafts.[278,279] Of the 19 patients who received intrathecal local anesthetics to produce total spinal anesthesia for cardiac surgery, 18 required intravenous phenylephrine intraoperatively to increase blood pressure, indicating that hypotension is a substantial problem with this technique.[144,146] Hypotension also appears to be relatively common when TEA with local anesthetics are used in this setting. Volume replacement, β-adrenergic agonists, and/or α-adrenergic agonists are required in a fair proportion of patients, and coronary perfusion pressure may decrease in susceptible patients after CPB.

After epidural administration, local anesthetics can produce blood concentrations of drug that may initiate detrimental cardiac electrophysiologic effects and myocardial depression.[280] In fact, myocardial depression has been detected in patients receiving TEA with bupivacaine, a clinical effect that is at least partially caused by increased blood concentrations of the drug.[281] Concomitant use of β-adrenergic blockers may further decrease myocardial contractility in this setting.[282,283] Patients undergoing cardiac surgery who were randomized to receive intermittent boluses of thoracic epidural bupivacaine intraoperatively, followed by continuous infusion after surgery, exhibited significantly increased pulmonary capillary wedge pressures after CPB when compared with patients similarly managed without epidural catheters (11 vs 6 mm Hg, respectively; $p < 0.001$), which suggests myocardial depression.[194]

Two case reports also indicated that the use of epidural anesthesia and analgesia may either mask myocardial ischemia or initiate myocardial ischemia.[284,285] Oden and Karagianes[285] described the perioperative course of an older patient who had a history of exertional angina and underwent uneventful cholecystectomy. After surgery, analgesia was achieved with continuous lumbar epidural fentanyl. On postoperative day 2, with continuous lumbar epidural fentanyl being administered, ST-segment depression was noted on the electrocardiogram. The patient was awake, alert, and did not experience angina. Initiation of intravenous nitroglycerin at this time resulted in normalization of ischemic electrocardiographic changes. The authors of this report thought that epidural fentanyl-induced analgesia masked the patient's typical anginal pain. Easley and colleagues[284] describe the perioperative course of a middle-aged patient without cardiovascular symptoms (borderline hypertension) who was scheduled for exploratory laparotomy. Before surgery, a low thoracic epidural catheter was inserted and local anesthetic was administered (sensory level peaked by pinprick at T2). The patient at this time began complaining of left-sided jaw pain, and substantial ST-segment depression was noted on the electrocardiogram. Surgery was canceled, and the patient was treated with aspirin and nitroglycerin. The electrocardiogram normalized; yet, based on electrocardiographic changes, troponin levels, and creatine kinase-MB fractions, the patient was diagnosed with a non–Q-wave myocardial infarction. Coronary angiography on the following day was unremarkable, and a presumptive diagnosis of coronary artery spasm was made. These authors thought that low thoracic epidural-induced sympathectomy led to alterations in the sympathetic-parasympathetic balance (vasoconstriction above the level of block) leading to coronary artery spasm.

Side Effects of Intrathecal and Epidural Opioids

Although many have been described, the four clinically relevant undesirable drug effects of intrathecal and epidural opioids are pruritus, nausea and vomiting, urinary retention, and respiratory depression.[286] After the administration of intrathecal or epidural opioids, the most common side effect is pruritus. The incidence rate varies widely (from 0% to 100%) and is often identified only after direct questioning of the patient. Severe pruritus is rare, occurring in only approximately 1% of patients. The incidence of nausea and vomiting is approximately 30%. The incidence of urinary retention also varies widely (from 0% to 80%) and occurs most frequently in young male patients. When intrathecal or epidural opioids are used in patients undergoing cardiac surgery, the incidences of pruritus, nausea and vomiting, and urinary retention are similar to that described earlier. Of note, if a large dose (4 mg) of intrathecal morphine is administered, then prolonged postoperative urinary retention may occur.[143]

The most important undesirable drug effect of intrathecal and epidural opioids is respiratory depression. Only 4 months after the initial use of intrathecal[287] and epidural[288] opioids in humans, life-threatening respiratory depression was reported.[289–291] The incidence of respiratory depression that requires intervention after conventional doses of intrathecal and epidural opioids is approximately 1%, the same as that after conventional doses of intramuscular and intravenous opioids. Early respiratory depression occurs within minutes of opioid injection and is associated with the administration of intrathecal or epidural fentanyl or sufentanil. Delayed respiratory depression occurs hours after opioid injection and is associated with the administration of intrathecal or epidural morphine. Delayed respiratory depression results from cephalad migration of morphine in the cerebrospinal fluid and the subsequent stimulation of opioid receptors located in the ventral medulla.[292] Factors that increase the risk for respiratory depression include large and/or repeated doses of opioids, intrathecal use, advanced age, and concomitant use of intravenous sedatives.[286] The magnitude of postoperative respiratory depression is profoundly influenced by the dose of intrathecal or epidural morphine administered and the type and amount of intravenous analgesics and amnestics used for the intraoperative baseline anesthetic. Prolonged postoperative respiratory depression may delay tracheal extubation, and naloxone may be required in some patients. Children may be more susceptible to developing postoperative respiratory depression when intrathecal morphine is used. Of 56 children (aged 1 to 17 years) administered either 20 or 30 μg/kg intrathecal morphine before surgical incision for cardiac surgery, 3 of 29 who received 20 μg/kg and 6 of 27 who received 30 μg/kg required naloxone after surgery for respiratory depression.[155]

One clinical study indicates that the administration of intrathecal morphine to patients undergoing cardiac surgery may be contraindicated if early extubation is planned.[142] Patients were randomized to receive either intrathecal morphine (10 μg/kg) or intrathecal placebo before the induction of anesthesia. Intraoperative anesthetic management was standardized and consisted of intravenous fentanyl (20 μg/kg) and intravenous midazolam (10 mg total) together with inhaled isoflurane and/or intravenous nitroglycerin, if required. Regarding patients extubated during the immediate postoperative period, the mean time from ICU arrival to extubation was significantly increased in those who received intrathecal morphine compared with those who received intrathecal placebo (11 vs 8 hours, respectively; $p = 0.02$). However, other clinical studies indicate that intrathecal or epidural morphine may yet prove to be a useful adjunct for cardiac surgery and early extubation. The optimal dose of intrathecal or epidural morphine in this setting, together with the optimal intraoperative baseline anesthetic that will provide significant postoperative analgesia yet not delay tracheal extubation in the immediate postoperative period, remains to be elucidated. In contrast with intrathecal and epidural opioids, epidural local anesthetics, which initiate no respiratory depression, should not delay tracheal extubation in the immediate postoperative period.

Risk for Hematoma Formation

Intrathecal or epidural instrumentation entails risk, the most feared complication being epidural hematoma formation. The estimated incidence of hematoma formation is approximately 1:220,000 after intrathecal instrumentation.[293] Hematoma formation is more common (approximately 1:150,000) after epidural instrumentation because larger needles are used, catheters are inserted, and the venous plexus in the epidural space is prominent.[293] Furthermore, hematoma formation does not exclusively occur during epidural catheter insertion; almost one half of all cases develop after catheter removal.[293]

Although spontaneous hematoma can occur in the absence of intrathecal or epidural instrumentation,[294] most occur when instrumentation is performed in a patient with a coagulopathy (from any cause) or when instrumentation is difficult or traumatic.[293] Paradoxically, intrathecal or epidural instrumentation has been safely performed in

patients with known clinical coagulopathy.[295,296] Of 1000 epidural catheterizations performed in 950 patients receiving oral anticoagulants at the time of catheter insertion, none experienced signs or symptoms of hematoma formation.[296] Of 336 epidural injections performed in 36 patients with chronic cancer pain either fully anticoagulated (oral anticoagulants or intravenous heparin) or profoundly thrombocytopenic (platelet count < 50,000/mm^3) at the time of instrumentation, none had signs or symptoms of hematoma formation.[295]

Risk is increased when intrathecal or epidural instrumentation is performed before systemic heparinization, and hematoma formation has occurred in patients when diagnostic or therapeutic lumbar puncture has been followed by systemic heparinization.[297–300] When lumbar puncture is followed by systemic heparinization, concurrent use of aspirin, difficult or traumatic instrumentation, and the administration of intravenous heparin within 1 hour of instrumentation increase the risk for hematoma formation.[299] However, by observing certain precautions, intrathecal or epidural instrumentation can be safely performed in patients who will subsequently receive intravenous heparin.[301,302] By delaying surgery 24 hours in the event of a traumatic tap, by delaying heparinization 60 minutes after catheter insertion, and by maintaining tight perioperative control of anticoagulation, more than 4000 intrathecal or epidural catheterizations were safely performed in patients undergoing peripheral vascular surgery who received intravenous heparin after catheter insertion.[302] A retrospective review involving 912 patients further indicates that epidural catheterization before systemic heparinization for peripheral vascular surgery is safe.[301] However, the magnitude of anticoagulation in these two studies (activated partial thromboplastin time of approximately 100 seconds[301] and activated coagulation time approximately twice the baseline value[302]) involving patients undergoing peripheral vascular surgery was substantially less than the degree of anticoagulation required in patients subjected to CPB.

Most clinical studies investigating the use of intrathecal or epidural anesthesia and analgesia techniques in patients undergoing cardiac surgery include precautions to decrease the risk for hematoma formation. Some used the technique only after the demonstration of laboratory evidence of normal coagulation parameters, delayed surgery 24 hours in the event of traumatic tap, or required that the time from instrumentation to systemic heparinization exceed 60 minutes. Although most clinicians investigating the use of epidural anesthesia and analgesia techniques in patients undergoing cardiac surgery insert the catheters the day before scheduled surgery, investigators have performed instrumentation on the same day of surgery. Institutional practice (same-day admit surgery) may eliminate the option of epidural catheter insertion on the day before scheduled surgery. An alternative is to perform epidural instrumentation postoperatively (before or after tracheal extubation) after laboratory evidence demonstrates normal coagulation parameters.

Although most investigators agree that the risk for hematoma formation is likely increased when intrathecal or epidural instrumentation is performed in patients before systemic heparinization required for CPB, the absolute degree of increased risk is somewhat controversial; some believe the risk rate may be as high as 0.35%.[297] An extensive mathematical analysis by Ho and associates[303] of the approximately 10,840 intrathecal injections in patients subjected to systemic heparinization required for CPB (without a single episode of hematoma formation) reported in the literature as of 2000, the minimum risk was estimated at 1:220,000 and the maximum risk for hematoma formation was 1:3600; however, the maximum risk may be as high as 1:2400. Similarly, of approximately 4583 epidural instrumentations in patients subjected to systemic heparinization required for CPB (without a single episode of hematoma formation) reported in the literature as of 2000, the minimum risk for hematoma formation was 1:150,000 and the maximum risk for hematoma formation was 1:1500; however, the maximum risk may be as high as 1:1000.[303]

Certain precautions, however, may decrease risk.[293,297] The technique should not be used in a patient with known coagulopathy from any cause. Surgery should be delayed 24 hours in the event of a traumatic tap, and time from instrumentation to systemic heparinization should exceed 60 minutes. In addition, systemic heparin effect and reversal should be tightly controlled (smallest amount of heparin used for the shortest duration compatible with therapeutic objectives), and patients should be closely monitored after surgery for signs and symptoms of hematoma formation. An obvious economic disadvantage of intrathecal or epidural instrumentation in patients before cardiac surgery is the possible delay in surgery in the event of a traumatic tap. However, one study involving more than 4000 intrathecal or epidural catheterizations via a 17-gauge Tuohy needle indicated that the incidence of traumatic tap (blood freely aspirated) is quite rare (< 0.1%).[302]

In 2004, the first case report of an epidural hematoma associated with a thoracic epidural catheter inserted in a patient before cardiac surgery was published.[304] This 18-year-old man had a thoracic (T9 to T10) epidural catheter uneventfully inserted after induction of general anesthesia (the patient had intense fear of needles) immediately before the initiation of CPB for aortic valve replacement surgery. Three hours elapsed from instrumentation to systemic heparinization. The entire intraoperative course and immediate postoperative course were uneventful (tracheally extubated soon after surgery, ambulating without difficulty on postoperative day 1). At 49 hours after surgery, intravenous heparin therapy was initiated (prosthetic valve thromboprophylaxis). At 53 hours after surgery, alteplase (thrombolytic drug) was used to flush a dysfunctional intravenous catheter. Within 2 hours of intravenous alteplase administration, the patient reported intense back pain while ambulating. At this point, the epidural catheter was removed. The activated partial thromboplastin time assessed at this time (during catheter removal) was 87 seconds (reference range, 25 to 37 seconds). The patient also was thrombocytopenic at this time. On catheter removal, the patient experienced sudden onset of numbness and weakness distal to T9. Intravenous heparin was discontinued, a computed tomographic scan was inconclusive, requiring a magnetic resonance imaging scan, which revealed an epidural hematoma. Within 5 hours from the onset of neurologic symptoms, the patient underwent surgical evacuation of the hematoma, which extended from the T8 to T11 levels. Intraoperatively, intravenous methylprednisolone (30 mg/kg) was administered, followed by an infusion (5.4 mg/kg/hr) that was continued for 72 hours. Twenty-four hours after laminectomy, the patient demonstrated mild residual lower extremity motor and sensory deficits. Six weeks later, his neurologic examination returned to normal. The authors noted the factors (eg, heparin, alteplase, thrombocytopenia) affecting coagulation in this patient that likely led to hematoma formation and theorized that removing the catheter may have increased bleeding, further compounding the problem.

Since 2004, additional such accounts reporting catastrophic consequences such as permanent paralysis have appeared in the literature.[305–307] In addition, thromboembolic complications (neurologic stroke) may occur during the postoperative period when normalization of coagulation parameters (in a patient requiring anticoagulation) is achieved to safely remove the epidural catheter.[308] Thus bleeding and/or thromboembolic complications associated with these techniques in this setting are very real and potentially catastrophic.

The use of regional anesthetic techniques in patients undergoing cardiac surgery remains extremely controversial, prompting numerous editorials by recognized experts in the field of cardiac anesthesia.[309–313] One of the primary reasons such controversy exists (and likely will continue for some time) is that the numerous clinical investigations regarding this topic are suboptimally designed and use a wide array of disparate techniques, preventing clinically useful conclusions on which all can agree.[314–318]

Multimodal Analgesia

The possibility of synergism among analgesic drugs is a concept that is nearly a century old.[319,320] Although subsequent research has demonstrated the difference between additivity and synergy, the fundamental strategy behind such combinations (multimodal or balanced analgesia) remains unchanged—enhanced analgesia with the minimization

of adverse physiologic effects. The use of analgesic combinations during the postoperative period, specifically the combination of traditional intravenous opioids with other analgesics (eg, NSAIDs, COX-2 inhibitors, ketamine), has been proven clinically effective in noncardiac patients for decades. Early clinical investigations simply reported analgesic efficacy, whereas more recent clinical investigations have additionally evaluated and described specific opioid-sparing effects, which should lead to a reduction in side effects. For example, in the late 1980s, initial clinical studies involving ketorolac (the first parenteral NSAID available in the United States) revealed significant opioid-sparing effects (analgesia) together with a reduction in respiratory depression. Subsequently, substantial clinical research has clearly established the perioperative analgesic efficacy and opioid-sparing effects of NSAIDs (together with a reduction of side effects).

The American Society of Anesthesiologists Task Force on Acute Pain Management in the Perioperative Setting reports that the literature supports the administration of two analgesic agents that act by different mechanisms via a single route for providing superior analgesic efficacy with equivalent or reduced adverse effects.[1] Potential examples include epidural opioids administered in combination with epidural local anesthetics or clonidine and intravenous opioids in combination with ketorolac or ketamine. Dose-dependent adverse effects reported with the administration of a medication occur whether it is given alone or in combination with other medications (opioids may cause nausea, vomiting, pruritus, or urinary retention, and local anesthetics may produce motor block). The literature is insufficient to evaluate the postoperative analgesic effects of oral opioids combined with NSAIDs, COX-2 inhibitors, or acetaminophen compared with oral opioids alone. The Task Force believes that NSAIDs, COX-2 inhibitors, or acetaminophen administration has a dose-sparing effect for systemically administered opioids. The literature also suggests that two routes of administration when compared with a single route may be more effective in providing perioperative analgesia. Examples include intrathecal or epidural opioids combined with intravenous, intramuscular, oral, transdermal, or subcutaneous analgesics versus intrathecal or epidural opioids alone. Another example is intravenous opioids combined with oral NSAIDs, COX-2 inhibitors, or acetaminophen versus intravenous opioids alone. The literature is insufficient to evaluate the efficacy of pharmacologic pain management combined with nonpharmacologic, alternative, or complementary pain management compared with pharmacologic pain management alone.

How Important Is Postoperative Pain After Cardiac Surgery?

Cardiac surgery is unique; because of this, it involves unique risks not routinely associated with noncardiac surgery.[321] Furthermore, as all are aware, for a wide variety of reasons, patients who are undergoing cardiac surgery continue to get older and sicker (more comorbidities: neurologic dysfunction, myocardial dysfunction, renal dysfunction). Multiple factors interact in a complicated manner during the perioperative period that affect the outcome and quality of life after cardiac surgery including the type and quality of surgical intervention, extent of postoperative neurologic dysfunction, extent of postoperative myocardial dysfunction, extent of postoperative pulmonary dysfunction, extent of postoperative renal dysfunction, extent of postoperative coagulation abnormalities, extent of systemic inflammatory response, and quality of postoperative analgesia. Obviously, depending on specific clinical situations, certain factors are more important than others. The potential clinical value of preventive (preemptive) analgesia remains extremely controversial.[322,323] Determining, exactly, how important attaining adequate or high-quality postoperative analgesia truly is in relation to all these important clinical factors surrounding a patient undergoing cardiac surgery is extremely difficult (if not impossible). For example, how important is it to obtain high-quality postoperative analgesia in an 80-year-old patient with preoperative myocardial dysfunction, renal dysfunction, and a heavily calcified aorta after double-valve replacement? It could be argued that factors other than quality of postoperative analgesia will determine the clinical outcome in this patient. On the other hand, how important is it to obtain high-quality postoperative analgesia in an otherwise healthy 50-year-old patient after routine CABG? It is likely that this patient's clinical outcome will be satisfactory even if postoperative analgesia is suboptimal. In essence, for cardiac and noncardiac surgery patients alike, evidence is insufficient to confirm or deny the ability of postoperative analgesic techniques to truly affect postoperative morbidity or mortality.[324–332]

BOX 42.11 FACTORS AFFECTING OUTCOME AFTER CARDIAC SURGERY

- Type and quality of surgical intervention
- Extent of postoperative neurologic dysfunction
- Extent of postoperative myocardial dysfunction
- Extent of postoperative pulmonary dysfunction
- Extent of postoperative renal dysfunction
- Extent of postoperative coagulation abnormalities
- Extent of systemic inflammatory response
- Quality of postoperative analgesia

Conclusions

Multiple factors are important during the perioperative period that potentially affect outcome and quality of life after cardiac surgery; these factors include the type and quality of surgical intervention; the extent of postoperative neurologic dysfunction, myocardial dysfunction, pulmonary dysfunction, renal dysfunction, coagulation abnormalities, and extent of systemic inflammatory response; and/or the quality of postoperative analgesia, among other factors[333] (Box 42.11). This list is presented in no particular order. Obviously, depending on specific clinical situations, such as the surgical procedure and patient comorbidity, among others, certain factors will be more important than others. Determining exactly how important attaining adequate postoperative analgesia truly is in relation to all of these clinical factors surrounding a patient undergoing cardiac surgery is extremely difficult (if not impossible). A clear link between adequate or high-quality postoperative analgesia and clinical outcome in patients after cardiac surgery has yet to be established.[333–336]

However, despite the absence of substantiating scientific evidence, most clinicians intuitively believe that attaining high-quality postoperative analgesia is important because it may prevent adverse hemodynamic, metabolic, immunologic, and hemostatic alterations, all of which may potentially increase postoperative morbidity. Although many analgesic techniques are available, intravenous systemic opioids form the cornerstone of postcardiac surgery analgesia. Opioids have been used with good results for many years in the treatment of postoperative pain in patients after cardiac surgery. Although NSAIDs (specifically COX-2 inhibitors) have recently received considerable attention, important clinical issues regarding their safety (eg, gastrointestinal effects, renal effects, hemostatic effects, immunologic effects) need to be resolved. Although PCA techniques are commonly used, their clear superiority over traditional nurse-controlled analgesic techniques remains unproven. The use of intrathecal and epidural techniques in patients undergoing cardiac surgery will likely remain extremely controversial. With the increased use of smaller incisions by cardiac surgeons, increased use of nerve blocks (intercostal, intrapleural, paravertebral) deserves further clinical study, and the emergence of liposomal bupivacaine may revolutionize these techniques in this setting. As a general rule, avoiding intense, single-modality therapy for the treatment of acute postoperative pain is best. Clinicians should strive for an approach that uses a number of different therapies (multimodal therapy), each counteracting pain through different

mechanisms. Preemptive analgesia, although intriguing, needs further study to determine its role in affecting postoperative analgesia and outcome.[337–340]

Finally, the American Society of Anesthesiologists Task Force on Acute Pain Management in the Perioperative Setting offers sound advice.[1] It recommends that anesthesiologists who manage perioperative pain use analgesic therapeutic options only after thoughtfully considering the risks and benefits for the individual patient. The therapy or therapies selected should reflect the individual anesthesiologist's expertise, as well as the capacity for safe application of the chosen modality in each practice setting. This expertise includes the ability to recognize and treat adverse effects that emerge after the initiation of therapy. Whenever possible, anesthesiologists should use multimodal pain management therapy. Dosing regimens should be administered to optimize efficacy while minimizing the risk for adverse events. The choice of medication, dose, route, and duration of therapy should always be individualized.

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Perioperative Cardiovascular Evaluation and Management for Noncardiac Surgery

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KEY POINTS

1. Preoperative assessment of the cardiac patient undergoing noncardiac surgery includes categorizing the risk of a major adverse cardiac event (MACE) in order to optimize perioperative care.
2. The risk of MACE depends on patient risk factors including the noncardiac procedure, age of the patient, emergent status of the procedure, preexisting organ dysfunction, and independence in daily activities.
3. Cardiac risk model calculators such as the Revised Cardiac Risk Index (RCRI), the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP), and the Gupta model used to estimate the risk of perioperative myocardial infarction or cardiac arrest (MICA) exist to facilitate quantification of risk and to aid the perioperative physician in optimizing patient care.
4. The 2014 American College of Cardiology (ACC) and American Heart Association (AHA) guideline document, *Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery*, discusses new and updated recommendations in a stepwise approach to care of the patient with cardiovascular disease presenting for noncardiac surgery.
5. The applicability of the various recommendations within the 2014 ACC/AHA guideline document is determined by the patient's risk for development of MACE.
6. Within the 2014 ACC/AHA guideline document are important updates related to the perioperative administration of various cardiac-related medications, including β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), α_2-adrenergic agents (eg, clonidine), aspirin, and dual-antiplatelet therapy with thienopyridines, vitamin K antagonists, and novel oral anticoagulants.
7. A clear understanding of antiplatelet therapy and the temporal relationship between percutaneous coronary interventions and scheduled surgery are important in determining the timing and perioperative management of noncardiac surgery.
8. Transfusion is an important part of perioperative management in the setting of hemodynamic instability, evidence of MACE, or surgical hemorrhage. In the case of hemodynamic stability with MACE, no specific recommendations are available; the decision to transfuse and the hemoglobin goal for transfusion are decided by the perioperative team.
9. Pulmonary arterial hypertension and subsequent right ventricular (RV) dysfunction are a major cause of poor perioperative outcomes in this patient population. Every effort should be made to optimize ventilation/perfusion matching and to reduce pulmonary vascular resistance preoperatively in order to avoid hemodynamic collapse due to RV failure.

Patients undergoing surgery experience a well-described stress response of sympathetic nervous system activation, insulin resistance, cytokine production, leukocyte proliferation, and pituitary hormone secretion.[1,2] These physiologic changes in the setting of preexisting patient comorbidities, surgical complexity including breaches of visceral and vascular containment, and postoperative complications and recovery may contribute to the occurrence of perioperative cardiovascular events in patients undergoing noncardiac surgery. As part of a perioperative team approach, every patient should undergo an individualized risk assessment to delineate the risks, benefits, and alternatives of surgical intervention. Interventions for optimizing cardiovascular health should be performed or alternative approaches considered to ensure the maximal benefit with minimal risk to the patient. This chapter reviews the initial preoperative cardiac evaluation, including a discussion of common risk calculators, to assist the clinician with risk assessment and surgical planning.

The 2014 American College of Cardiology (ACC) and American Heart Association (AHA) clinical practice guideline, *Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery,* is also reviewed.[3,4] The European Society of Cardiology (ESC), in collaboration with the European Society of Anaesthesiology (ESA), also published guidelines on the cardiovascular assessment and management of patients undergoing noncardiac surgery in 2014.[5] The ACC/AHA and the ESC/ESA coordinated to ensure that their recommendations were consistent and to provide rationales in clinical areas where their recommendations diverged.

The recommendations of these professional societies regarding specific and frequently encountered perioperative challenges are discussed in this chapter, including significant updates since the previous guidelines were published in 2007.[6,7] Medical therapy with β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), α_2-agonists, aspirin (including dual-antiplatelet therapy [DAPT]), vitamin K antagonists (VKAs), and novel oral anticoagulants (NOACs) are also addressed. Perioperative management of anemia, pulmonary vascular disease, and right ventricular (RV) dysfunction is also discussed.

Preoperative Cardiac Assessment: Categorizing Risk

Patients with underlying cardiovascular disease have an increased risk of perioperative cardiac complications compared with their healthier counterparts.[3–5] This results in part from the presence of coronary artery disease (CAD) leading to impaired left ventricular ejection fraction (LVEF) and in part from the aforementioned physiologic factors associated with surgery that predispose patients to myocardial ischemia.[1,2] Hemodynamic instability, including acute blood loss, results in reduction of oxygen delivery to metabolically active tissue. Increased myocardial oxygen demand secondary to tachycardia or acute hypertension may occur related to anesthetic administration and surgical stimulation. Perioperative disturbance of the balance between myocardial oxygen supply and demand can result in significant mismatch and can precipitate myocardial ischemia when demand critically exceeds supply.

Validated algorithms have been developed to determine the cardiovascular risk of mortality and morbidity encountered by a patient for each noncardiac operation. Stratification is performed to objectively determine and categorize patients as being at low, intermediate, or high risk. High-risk patients include those with recent myocardial infarction (MI) or unstable angina, decompensated heart failure (HF), high-grade arrhythmias, or hemodynamically important valvular heart disease (eg, aortic stenosis).[3–5] These patients are at increased risk for perioperative cardiovascular events including MI, HF, cardiac arrest, conduction abnormalities, and death.[3–5] Certainly, the emergent or urgent status of the surgery significantly influences perioperative cardiovascular risk because of summation of the effects of the acute illness, the nature of the emergent operation, and the lost opportunities for risk assessment and elective modification.[3–5] However, patients with the conditions listed are at increased risk for a perioperative cardiovascular event compared with normal, age-matched controls. In most emergent cases, the benefit of proceeding with surgery outweighs the risk of waiting to perform additional testing.[3–5] The physician-anesthesiologist should be prepared to manage cardiovascular events encountered during the intraoperative period related to the emergent status of the surgery.[3–5]

The initial preoperative evaluation and risk assessment are typically performed by either a primary care physician or an anesthesiologist. Referral to a cardiologist is warranted if specialized procedures are indicated for life-threatening conditions. Intermediate- and high-risk patients may have overt evidence of cardiovascular disease such as angina, dyspnea, syncope, and palpitations during evaluation or a history positive for heart disease, hypertension, diabetes, chronic kidney disease, cerebrovascular events, or peripheral arterial disease.[3,4] Cardiac functional status (peak work capacity) may be expressed in metabolic equivalents (METs), as initially determined by the Duke Activity Status Index (Table 43.1).[8,9] One MET is equivalent to oxygen utilization by an adult at rest.[8] One important indicator for major adverse cardiac events (MACE) after major noncardiac surgery is preoperative inability to climb two flights of stairs or walk four city blocks.[10,11] However, ambulatory limitations due to orthopedic or pulmonary conditions may confound the true assessment of cardiac functional status, and alternative testing may be required for at-risk patients.[3–5] The decision to pursue cardiovascular or pulmonary testing should be considered only if the results would affect surgical decision making (eg, pursuing a less invasive route, opting for no treatment intervention) or would likely identify an immediately life-threatening condition requiring treatment.[3,4]

TABLE 43.1 Duke Activity Status Index

Activity	*Energy Expenditure (in METs)*
Can You…	
1. Take care of yourself—that is, eating, dressing, bathing, or using the toilet?	2.75
2. Walk indoors, such as around your house?	1.75
3. Walk a block or two on level ground?	2.75
4. Climb a flight of stairs or walk up a hill?	5.50
5. Run a short distance?	8.00
6. Do light work around the house such as dusting or washing dishes?	2.70
7. Do moderate work around the house such as vacuuming, sweeping floors, or carrying groceries?	3.50
8. Do heavy work around the house such as scrubbing floors or lifting or moving heavy furniture?	8.00
9. Do yardwork such as raking leaves, weeding, or pushing a power mower?	4.50
10. Have sexual relations?	5.25
11. Participate in moderate recreational activities such as golf, bowling, dancing, doubles tennis, or throwing a baseball or football?	6.00

METs, Metabolic equivalents (1 MET is the equivalent of resting oxygen consumption).
From Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol.* 1989;64:651–654.

Preoperative Cardiac Assessment: Risk Model Calculators

Risk model calculators estimate the probability of a perioperative event based on information obtained from the history, physical examination, and type of surgery. These risk models are more applicable for patients at intermediate to high perioperative cardiac risk during noncardiac surgery. Patients at low risk for MACE should proceed to surgery without further evaluation.

In order to appropriately identify individualized risk using a risk calculator, specific information pertaining to both the patient and the surgery must be provided. Information is entered into one or both of two commonly used perioperative risk indices: the Revised Cardiac Risk Index (RCRI)[12] and the American College of Surgeons' National Surgical Quality Improvement Program (ACS-NSQIP) surgical risk calculator (www.facs.org).[13] The RCRI determines preoperative risk based on the following criteria: type of surgery, history of ischemic heart disease, congestive HF, cerebrovascular disease, preoperative treatment with insulin, and creatinine level greater than 2.0 mg/dL (Fig. 43.1). The RCRI for an individual patient can be quantified readily with an online calculator (www.mdcalc.com). The ACS-NSQIP calculator incorporates 20 patient risk factors in addition to the surgical procedure (Fig. 43.2). The surgery-specific estimates from the RCRI and ACS-NSQIP calculators report the risk of myocardial infarction or cardiac arrest (MICA), typically categorized as less than 5% in high-risk procedures, 1% to 5% in intermediate-risk procedures, and less than 1% in low-risk procedures.[14] As a rule, emergency surgery is associated with 2 to 5 times the risk of MACE compared with elective procedures.[15]

The results of risk calculation can be applied in several ways. Once patient risk is estimated, perioperative physicians and the patient can proceed with the planned operation, modify the treatment plan, or postpone the procedure. On the day of surgery, the options for consideration include proceeding directly with the operative plan, delaying surgery to allow further diagnostic evaluation (eg, myocardial stress testing, echocardiography, 24-hour ambulatory monitoring), and changing the planned surgery. This last option may involve performing a surgical procedure with less risk, selecting a nonsurgical alternative such as palliation, or cancelling the operation so that cardiac interventions such as coronary revascularization or heart valve intervention can be performed. In addition to risk-assessment models such as the RCRI[12] and the ACS-NSQIP calculator, the Gupta Perioperative Risk Calculator, which is used to estimate the risk of MICA, also includes high-risk patients who have been managed with current medical practices and surgical techniques.[16] The Gupta index was derived and validated from large data sets within the ACS-NSQIP database (2007

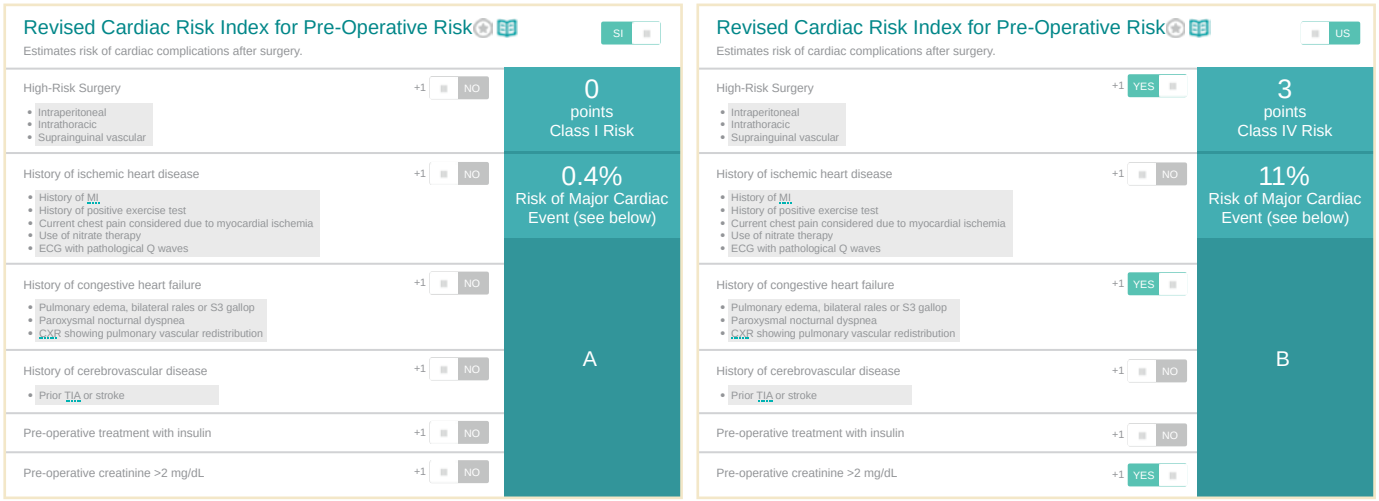


Fig. 43.1 Revised Cardiac Risk Index calculator results are depicted for two patients. (A) Patient A has no risk factors and a calculated risk for major adverse cardiac events equal to 0.4%. (B) Patient B has several risk factors and a calculated risk for major adverse cardiac events equal to 11%. *(From* http://www.mdcalc.com/revised-cardiac-risk-index-for-pre-operative-risk/*.)*

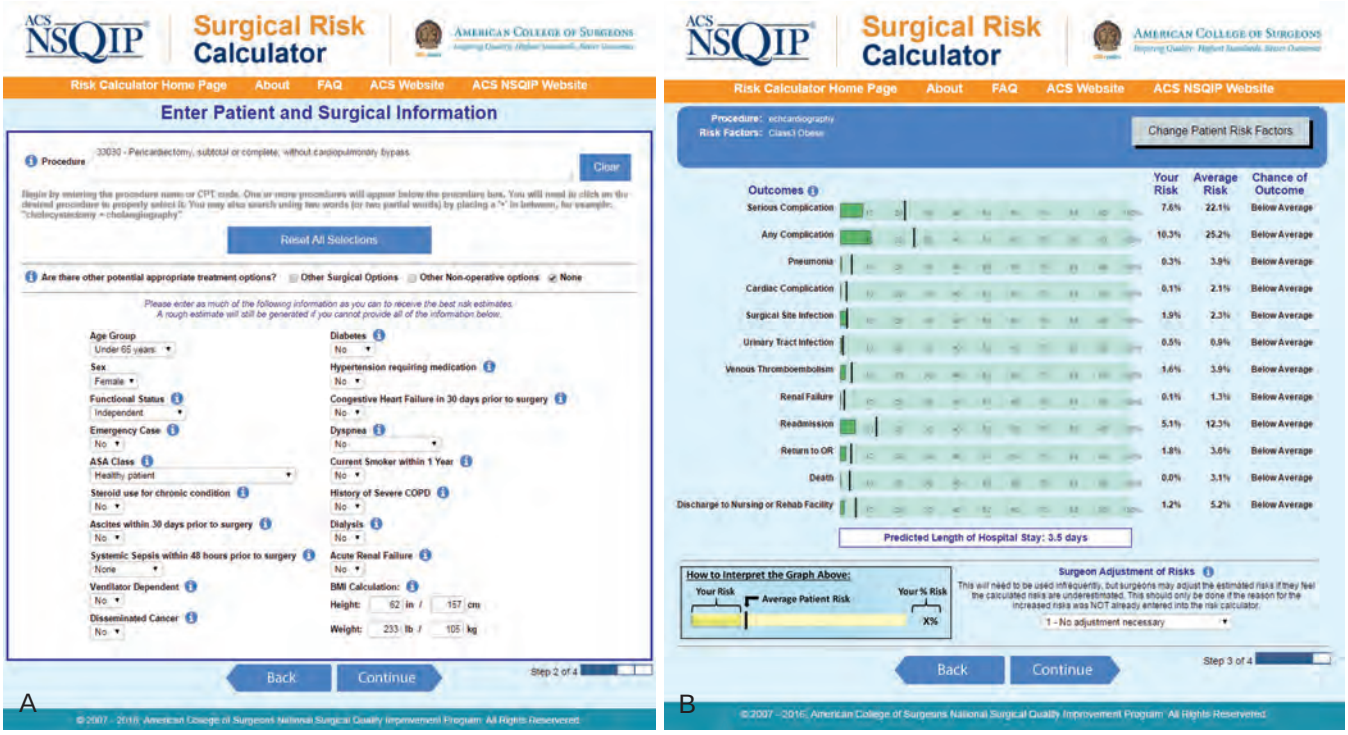


Fig. 43.2 National Surgical Quality Improvement Program (NSQIP) risk calculator. (A) The online site display where patient and surgical features may be put into the data calculator. (B) As an example, the surgical risk calculation has been performed for a patient undergoing a pneumonectomy with specific risk factors. The resulting surgical risk calculation, including negative outcomes, estimated risk of each outcome, and the chance of the outcome (eg, average, above average) are displayed. Notice in the lower right corner that the surgeon may adjust the risk calculation; in this example, no adjustment has been made. *(From* http://riskcalculator.facs.org/RiskCalculator/*.)*

derivation cohort, $N = 211{,}410$; 2008 validation cohort, $N = 257{,}385$).[16] The Gupta index has the same discriminative ability and predictive accuracy as the larger ACS-NSQUIP variable model and outperforms the RCRI, likely due in part to the evolution of surgical procedures that have tended to lower operative risk in the almost 20 years since the RCRI was formulated.[10] Because the ACS-NSQIP and Gupta surgical risk calculators are more comprehensive and procedure specific, they have largely replaced older models for risk stratification.[17–22] The risk calculation models are discussed individually in the following sections.

Revised Cardiac Risk Index

The RCRI is sometimes referred to as the Lee index, after the primary author of the original 1999 article.[12] In the derivation of the index, 2893 patients undergoing elective major noncardiac operations were monitored for major cardiac complications (ie, death, acute MI, pulmonary edema, ventricular fibrillation/cardiac arrest, and complete heart block). The index was validated in a cohort of 1422 similar individuals. The Lee index is based on six independent predictors for perioperative complications (see Fig. 43.1). The predictive value was significant in all types of major noncardiac surgery except for abdominal aortic aneurysm surgery. A systematic review evaluated the ability of the RCRI to predict cardiac complications and mortality after major noncardiac surgery in various populations and settings.[23] The RCRI performed well in distinguishing patients at low risk versus high risk for all types of noncardiac surgery, the area under the receiver operating characteristic curve (AUC), also called the C statistic, being 0.75 and the 95% confidence interval (CI) being 0.72–0.79. However, it was somewhat less accurate in patients undergoing vascular noncardiac surgery (AUC, 0.64; 95% CI, 0.61–0.66).[23] In addition, the RCRI did not predict all-cause mortality well—a flaw that is inherent to a risk predictor that does not capture risk factors for noncardiac causes of perioperative mortality. Moreover, only one third of the perioperative deaths were from cardiac causes.[23]

ACS-NSQIP Universal Surgical Risk Calculator

A universal surgical risk calculator model was developed from the ACS-NSQUIP database using a Web-based tool consisting of 20 patient factors plus the surgical procedure (see Fig. 43.2). This model has excellent performance in regard to mortality (C statistic, 0.944) and morbidity (C statistic, 0.816).[24] Although it is more comprehensive than the other risk calculators, it has not been validated through external studies, and it may be more cumbersome, limiting its use.

Gupta MICA ACS-NSQIP Database Risk Model

The NSQIP database was used by Gupta and colleagues[16] to determine risk factors associated with perioperative MICA. A simplified online calculator using only the greatest risk variables was developed, as outlined in Fig. 43.3 (www.qxmd.com). Among the more than 200,000 patients who underwent surgery in 2007, 0.65% developed perioperative MICA. On multivariate logistic regression analysis, five factors were identified as predictors: (1) type of surgery, (2) dependent functional status, (3) elevated creatinine, (4) American Society of Anesthesiologists' physical status score, and (5) increased age (see Fig. 43.3). The risk model was developed using these five factors and subsequently validated on a 2008 data set (n = 257,385). The risk model had a relatively high predictive accuracy (C statistic, 0.874) and outperformed the RCRI (C statistic, 0.747).[16]

In summary, risk calculators are important tools that are used to quantify the perioperative risk of a cardiac event. Once a patient is deemed to be at intermediate or high risk, the 2014 ACC/AHA guideline may be used to guide further perioperative optimization and management.

Perioperative Cardiac Assessment: Algorithmic Approach

The 2014 ACC/AHA perioperative guideline proposed a stepwise approach to perioperative cardiac assessment, incorporating both the physician's role in managing risk and providing informed consent and the patient's perspective in weighing risks, benefits, and alternatives to invasive testing or preventive therapies.[3,4] The emphasis placed on sharing information contextually with other perioperative physicians and with the patient highlights the importance of providing patient-centered care while minimizing risk for each intervention. The algorithmic flow chart begins with determination of surgical urgency, followed by assessment of the presence or absence of a preoperative acute coronary event, and concludes with a perioperative risk calculation for MACE (Fig. 43.4)[3,4] (see Chapter 1). For patients at low risk of MACE, no further testing is needed, and the patient may proceed to surgery without further evaluation. For patients at significant risk for MACE, an objective determination of the functional capacity of the patient is recommended. If a patient at elevated risk for MACE has 4 METs or greater functional capacity, no further evaluation is required

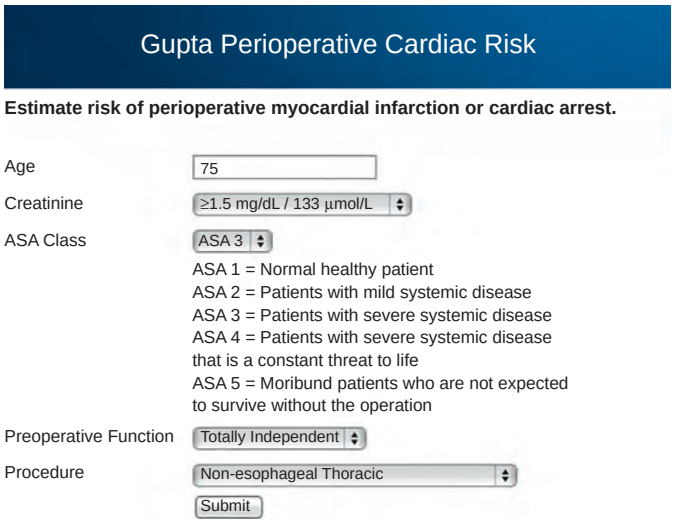
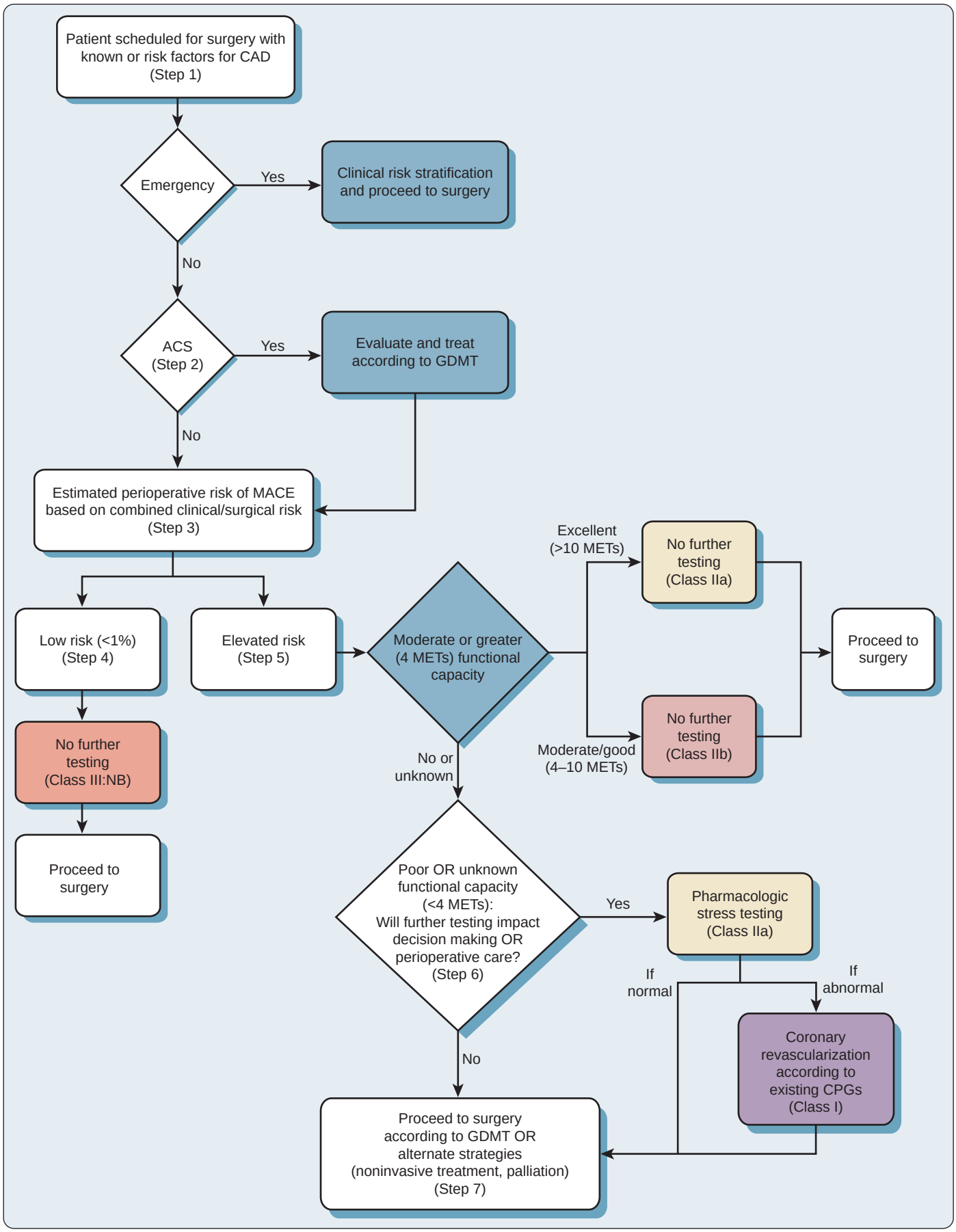


Fig. 43.3 Gupta Perioperative Risk Calculator for estimating the risk of MICA is designed to receive input on the patient's age, creatinine level, ASA score, preoperative ability to manage ADLs, and procedure category. As an example, information and risk factors have been entered for a patient undergoing a nonesophageal thoracic procedure. The resulting Gupta perioperative cardiac risk score is calculated at the bottom. *ASA*, American Society of Anesthesiologists, *ADLs*, activities of daily living, *MICA*, myocardial infarction or cardiac arrest. *(From* https://www.qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk.*)*

Fig. 43.4 The 2014 ACC/AHA guideline algorithm depicting the stepwise approach to perioperative cardiac assessment for CAD. *ACS*, Acute coronary syndrome; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CPG*, clinical practice guideline; *DASI*, Duke Activity Status Index; *GDMT*, guideline-directed medical therapy; *HF*, heart failure; *MACE*, major adverse cardiac event; *MET*, metabolic equivalent; *NB*, no benefit; *NSQIP*, National Surgical Quality Improvement Program; *PCI*, percutaneous coronary intervention; *RCRI*, Revised Cardiac Risk Index; *STEMI*, ST-elevation myocardial infarction; *UA/NSTEMI*, unstable angina/non–ST elevation myocardial infarction; *VHD*, valvular heart disease. *(From Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* Circulation. *2014;130:2354–2394.)*


Patient scheduled for surgery with known or risk factors for CAD (Step 1)
Emergency
Yes
Clinical risk stratification and proceed to surgery
No
ACS (Step 2)
Yes
Evaluate and treat according to GDMT
No
Estimated perioperative risk of MACE based on combined clinical/surgical risk (Step 3)
Low risk (<1%) (Step 4)
Elevated risk (Step 5)
Moderate or greater (4 METs) functional capacity
Excellent (>10 METs)
No further testing (Class IIa)
Moderate/good (4–10 METs)
No further testing (Class IIb)
Proceed to surgery
No further testing (Class III:NB)
Proceed to surgery
No or unknown
Poor OR unknown functional capacity (<4 METs): Will further testing impact decision making OR perioperative care? (Step 6)
Yes
Pharmacologic stress testing (Class IIa)
If normal
If abnormal
Coronary revascularization according to existing CPGs (Class I)
No
Proceed to surgery according to GDMT OR alternate strategies (noninvasive treatment, palliation) (Step 7)

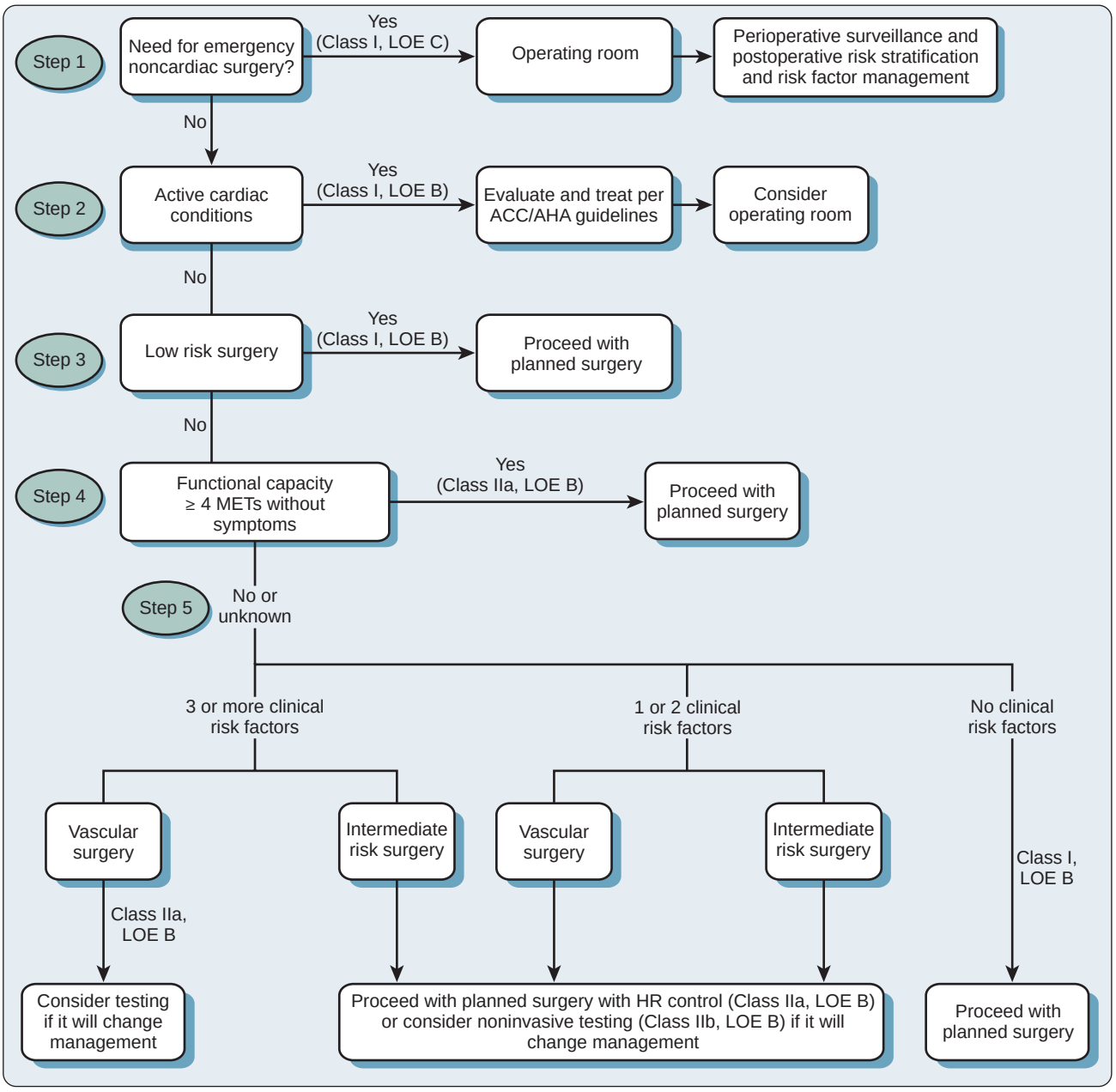


Fig. 43.5 The 2007 ACC/AHA guideline algorithm depicting the stepwise approach to perioperative cardiac assessment for coronary artery disease. *HR*, heart rate; *LOE*, level of evidence; *METs*, metabolic equivalents. *(From Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery.* Circulation. *2007;116:e418–e499.)*

(see Table 43.1).[8] For elevated risk with poor (<4 METs) or indeterminate functional capacity, further testing is advised only if it will affect the decision making for surgical timing and cardiac intervention (eg, pharmacologic stress testing, coronary revascularization).

The management options should be discussed not only among the perioperative physicians but also with the patient. The patient's informed opinion and the clinical impact of further perioperative testing have been incorporated into the 2014 ACC/AHA algorithm (see Fig. 43.4).[3,4] This algorithm differs from the 2007 version (Fig. 43.5) in that it incorporates a clinical "pause" when patients with poor to indeterminate functional capacity are identified.[6,7] As a result, high-risk patients with limited functional capacity do not automatically undergo further testing; instead, the perioperative team and patient can discuss whether the test results will affect either surgical

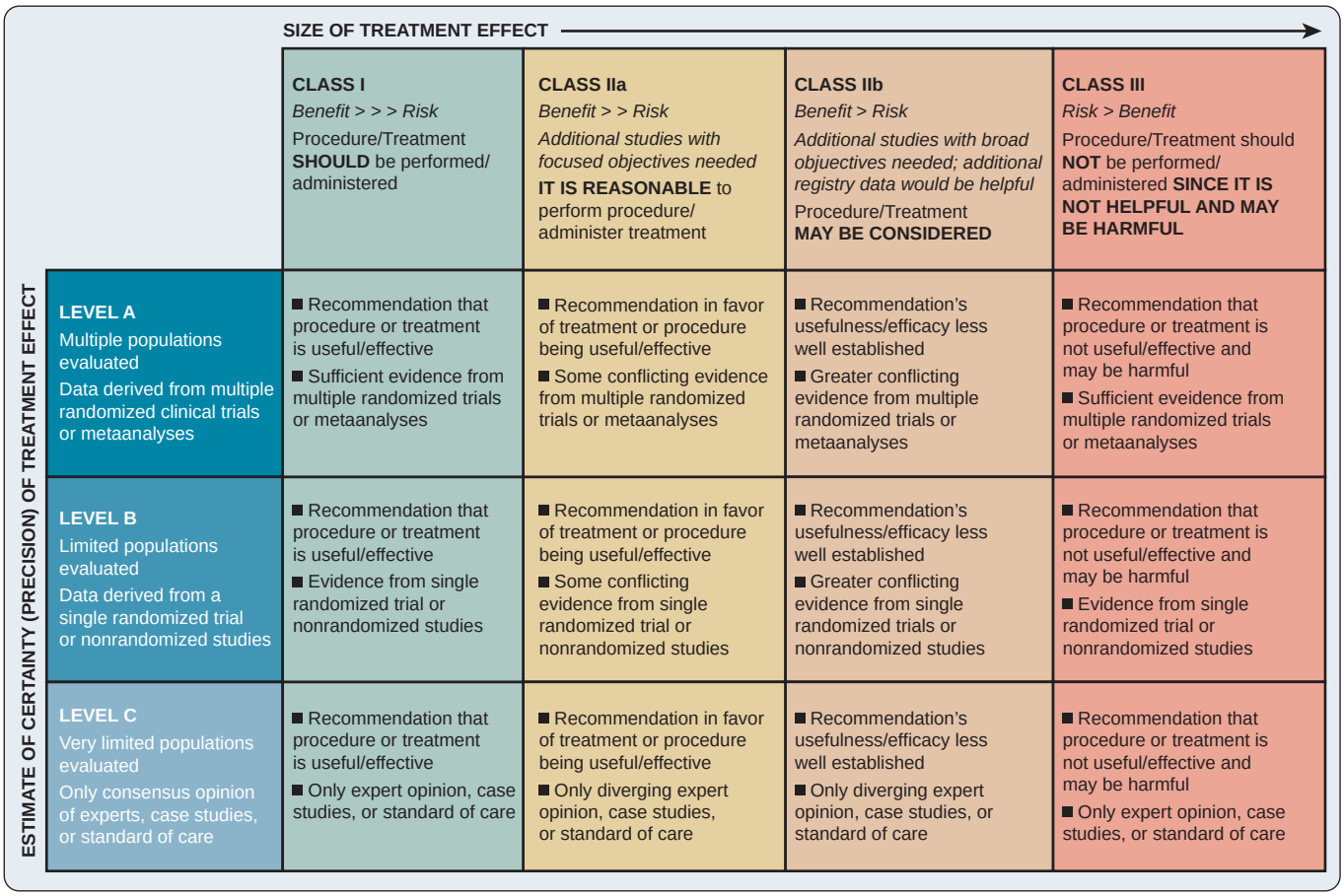


Fig. 43.6 Classification of recommendations and level of evidence. *(From Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery.* Circulation. *2007;116:e418–e499.)*

or perioperative management. If further testing will not impact the surgical plan or perioperative care, then the high-risk patient should either proceed directly to surgery or consider noninvasive treatment and palliation strategies.

The 2014 ACC/AHA guideline features important information extracted from the critical analysis of almost 500 referenced articles that are summarized and appended to the document.[3,4] Important perioperative updates in the evaluation of myocardial ischemia, management of medical therapy in patients with cardiovascular disease, and options for patients after percutaneous coronary interventions are discussed in remaining sections of this chapter. Perioperative recommendations for medical therapy, including β-blockers, ACEI, and α_2-agonists (e.g., clonidine), are also discussed. The perioperative management of antiplatelet therapy in patients with and without coronary stents is highlighted because it is commonly used and important (see Chapter 44).

Classification of Recommendations

The 2014 ACC/AHA guideline includes a comprehensive evaluation of the best available evidence. For specific topics requiring intensive review of data, a formalized systematic review by a separate Evidence Review Committee was undertaken to summarize findings pertaining to the improvement of perioperative care in patients with cardiovascular disease undergoing noncardiac surgery.[25] The guideline provides an organized framework of generalized perioperative management by applying scientific evidence to clinical practice. The recommendations were developed from an evidence base that included randomized controlled trials (RCTs), registries, metaanalyses, nonrandomized studies, case series, and expert opinion (Fig. 43.6). Each recommendation was assigned a class and a level of evidence (LOE) determined by the guideline writing committee to provide information to the clinician regarding the likelihood that the recommendations are well supported by the evidence (see Fig. 43.6).[3,4] Understanding the class and evidence level for a particular recommendation is important when one is considering either implementing or forgoing a particular treatment intervention.

The 2014 ACC/AHA perioperative guideline includes classes of recommendation (I through III) and levels of evidence (A through C) (see Fig. 43.6). A class I recommendation suggests that the benefits clearly outweigh the risks of a particular intervention and that the procedure or treatment *should* be performed or administered. Class IIa suggests that it is reasonable to perform a particular intervention; class IIb indicates that an intervention may be considered; and class

III indicates that the intervention will be of no benefit and may even be harmful. The evidence level encompasses the extent to which the population of interest has been evaluated regarding the measure of interest. For example, evidence level A implies that multiple populations have been evaluated in RCTs. On the other hand, evidence level C suggests that a very limited population of patients has been evaluated in case series, case reports, and expert opinion.

The ACC/AHA guideline writing committee also incorporated clinical practice guidelines produced after 2007 as a further evidence update. The 2014 recommendations aim to convey to perioperative practitioners the significance of each intervention as it pertains to the reduction of MACE.

Screening for Myocardial Ischemia: The Electrocardiogram and Troponins

The 2014 ACC/AHA guideline on perioperative evaluation and management of the cardiac patient undergoing noncardiac surgery recommended a 12-lead electrocardiogram (ECG) for patients with CAD, arrhythmias, structural cardiac disease, cerebrovascular disease, or peripheral arterial disease, unless they are undergoing low-risk surgery (class IIa, LOE B).[3,4] This recommendation underscores the idea that even high-risk patients undergoing low-risk surgeries do not require a routine ECG before surgery. A routine preoperative ECG is not helpful in managing patients undergoing low-risk surgery regardless of cardiovascular disease burden or risk factors. However, a postoperative ECG is recommended if there is a clinical suspicion for postoperative myocardial ischemia, infarction, or arrhythmia after noncardiac surgery. A routine postoperative ECG in asymptomatic patients is not useful regardless of risk factors. The decision to perform a postoperative ECG should be guided by patient symptoms and clinical evaluation.

The measurement of laboratory markers of myocardial injury (eg, troponins) is recommended for patients at high risk of MACE who may benefit from an intervention (class II, LOE B).[3,4] Routine measurement of troponins is not recommended without patient selection (class II, LOE B). The clinical utility of screening with troponin for perioperative MI in at-risk patients who may be asymptomatic remains uncertain in the absence of a defined management strategy. Although perioperative screening with troponin does assess risk, this approach still lacks specificity. RCTs are in progress to evaluate whether interventions based on troponin surveillance reduce the risk of MACE in the perioperative period.[3,4]

Management of Cardiac Medications

β-Receptor Antagonists

The 2014 ACC/AHA guideline provides recommendations for perioperative β-blockade based on multiple trials, including a metaanalysis by Wijeysundera and associates.[25] The key findings of this metaanalysis were not affected by the exclusion of trials with questionable scientific integrity.[26,27] Although this comprehensive report was incorporated into the 2014 ACC/AHA perioperative guideline, two recommendations are of particular interest. First, β-blockade should be continued in patients undergoing noncardiac surgery who have been prescribed these medications chronically (class I, LOE B). This recommendation emphasizes the importance of continuing chronic β-blockade, not only for the continued clinical benefit but also to prevent the negative cardiovascular consequences of acute withdrawal.[3,4] Second, it is recommended that β-blockers not be initiated within 1 day of noncardiac surgery. Although β-blockers given immediately before surgery may prevent nonfatal MI, the benefit of MI prevention is offset by increases in hypotension, stroke, and death (class III, LOE B)[2,4,28] (see Chapter 11).

Angiotensin Blockers

ACEI and ARBs are among the most commonly prescribed antihypertensives.[29,30] Both have cardiovascular and metabolic effects beyond their antihypertensive properties. Their prescription frequency partially relates to their demonstrated outcome and mortality benefit in patients with MI who have residual left ventricular dysfunction, in patients with HF, and in diabetics with kidney disease. In diabetics with renal dysfunction, these agents may delay progression to end-stage renal disease.[31–33] A very large retrospective study of 79,000 patients undergoing noncardiac surgery compared patients taking ACEI with patients not taking ACEI.[34] An analysis of a matched, nested cohort of the study demonstrated increased transient intraoperative hypotension among patients taking ACEI but failed to show any difference in other outcomes. Of note, current clinical practice guidelines recommend continuing ACEI in the setting of acute HF or hypertension.[35,36] A recent metaanalysis (18 trials, $N = 54,528$) demonstrated that in cardiac surgery, ACEI and ARBs did not reduce MACE overall but did significantly reduce mortality in diabetics ($P = .03$).[37] Based on the available data, it is reasonable to continue ACEI or ARBs perioperatively (class IIa, LOE B).[3,4] However, if ACEI or ARBs are withheld before surgery, it is recommended that they be restarted as soon as clinically feasible in the postoperative period (class IIa, LOE C). These agents are associated with intraoperative hypotension.[38,39] This hypotension can be ameliorated by withholding these agents for about 24 hours before surgery and/or using titrated vasopressor therapy during the intraoperative period, including vasopressin in refractory cases.[30,38]

Risk of MACE and α_2-Agonists

α_2-Agonists, such as clonidine, should be avoided when attempting to prevent MACE in patients undergoing noncardiac surgery (class III, LOE B). A prospective RCT (135 centers, $N = 10,010$) evaluated clonidine (0.2 mg/day) in patients with cardiovascular disease after they had undergone noncardiac surgery.[40] Clonidine was initiated preoperatively and continued postoperatively for 72 hours. Clonidine failed to reduce the 30-day incidence of death or nonfatal MI after surgery (hazard ratio [HR], 1.08; 95% CI, 0.03–1.26; $P = .29$). Clonidine administration did, however, increase the risks of nonfatal cardiac arrest (HR, 3.20; 95% CI, 1.17–8.73; $P = 0.02$) and clinically significant hypotension (HR, 1.32; 95% CI, 1.24–1.40; $P < .001$).[40] Further analysis from this large RCT demonstrated that acute perioperative clonidine exposure did not reduce the risk of acute renal injury (relative risk [RR], 1.03; 95% CI, 0.90–1.18).[41] Furthermore, the increased risk of clinically important hypotension associated with clonidine significantly increased the risk of acute renal injury (HR, 1.34; 95% CI, 1.14–1.58). Despite earlier promising evidence that clonidine may reduce perioperative mortality, its perioperative role for myocardial protection in noncardiac surgery has largely been suspended in response to the findings of this landmark trial.[42] However, the role of acute clonidine for reduction of perioperative cardiac risk in patients on chronic β-blockade was explored in a pilot RCT that confirmed its feasibility, safety, and tolerability.[43] Adequately powered RCTs are needed to evaluate perioperative clonidine for this indication in this perioperative population.

Aspirin Therapy in Patients Without Coronary Stent Implantation

The effects of aspirin were evaluated by the Perioperative Ischemia Evaluation (POISE-2) investigators in patients undergoing noncardiac surgery who were without a recent history of coronary stent placement.[44] Patients at risk for MACE were separated into those taking and not taking preoperative aspirin. Patients who were not previously on aspirin ($N = 5628$) were randomized to receive aspirin (initial dose, 200 mg; followed by 100 mg daily) or placebo on the day of surgery and for 30 days after surgery. Patients previously on aspirin ($N = 4382$) were randomized to receive aspirin (with similar dosing) or placebo beginning on the day of surgery and for 7 days postoperatively, after which they resumed their preoperative dosing regimen. Aspirin administration did not decrease the incidence of death or nonfatal MI at 30 days after surgery (HR, 0.99; 95% CI, 0.86–1.15; $P = .92$).[44] Aspirin exposure did, however, increase the risk of clinically significant bleeding (HR, 1.23; 95% CI, 1.01–1.49; $P = .04$). Based on

these recent high-quality data, the 2014 ACC/AHA guideline strongly recommended against routine aspirin therapy without previous coronary stent implantation (class III, LOE B) unless the risks of myocardial ischemia exceed the risks of surgical bleeding (class III, LOE C). It recommended only that consideration be given to the administration of aspirin for elective noncardiac surgery in the absence of recent percutaneous coronary intervention and stenting (class IIb, LOE B).[45]

Dual-Antiplatelet Therapy After Coronary Stent Implantation

Patients with a history of coronary stent implantation require special attention to maximize the chance of maintaining stent patency and minimize the risk of perioperative stent thrombosis.[46,47] DAPT with aspirin and a P2Y12 platelet inhibitor (eg, clopidogrel, prasugrel, ticagrelor) should be continued for urgent noncardiac surgery occurring within 6 weeks after percutaneous coronary intervention regardless of stent type (ie, bare metal stent [BMS] or drug-eluting stent [DES]) (class I, LOE C)[3,4] (see Chapter 44). Elective noncardiac surgery after DES placement may be considered after 180 days (approximately 6 months) if the health risk of delaying the surgery exceeds the risks of ischemia from stent thrombosis due to cessation of antiplatelet agents (class IIb, LOE B).[3,4] This recommendation is based in part on a large, retrospective, cohort study of noncardiac surgical patients ($N = 41,989$; 1980 with MACE and 40,009 with no MACE).[48] The time from stent placement to surgery was related to MACE within the first 6 months after stent implantation, but not if it exceeded 6 months (odds ratio [OR], 0.92; 95% CI, 0.82–1.05). These findings were supported in further large cohort studies (cumulative $N > 65,000$).[49,50]

Most importantly, the 2014 guideline recommends that *elective* noncardiac surgery should *not* be performed within 6 weeks after BMS or 12 months after DES placement if discontinuation of DAPT will be required before surgery, because the chance of harm outweighs the benefits of cessation (class III, LOE B).[3,4] Aspirin should be continued in the postoperative period, and the P2Y12 platelet inhibitor should be restarted as soon as is reasonable after surgery in patients undergoing procedures that require preoperative discontinuation of DAPT (class I, LOE C).[3,4] Discussion among the clinicians caring for a patient with coronary stents should address the balance between the risk of perioperative coagulopathy due to continuation of antiplatelet agents and the risk of stent thrombosis as a result of discontinuation (class I, LOE C). A summary of the recommendations related to the timing of elective noncardiac surgery after percutaneous coronary interventions is provided in Table 43.2.[51] This important, still controversial, and evolving area is discussed further in Chapter 44.

Anticoagulants: Vitamin K Antagonists and Novel Oral Anticoagulants

VKAs are prescribed for stroke prevention in patients with atrial fibrillation (AF), for prevention of thrombotic or thromboembolic complications in patients with prosthetic valves, and for patients who require deep venous thrombosis prophylaxis and treatment. NOACs such as oral thrombin inhibitors and factor Xa inhibitors are prescribed for prevention of stroke in the management of AF but are not currently recommended for long-term anticoagulation of prosthetic valves because of an increased risk of thrombosis when compared with warfarin.[52–54] The risk of bleeding with any surgical procedure must be weighed against the benefit of remaining on anticoagulants. For example, an office-based procedure for minor dermatologic surgery may not require reversal of the anticoagulant.

Although prothrombin complex concentrates (PCCs) have been used to provide acute reversal in patients taking VKAs who require surgery, the current evidence base is less definitive about reversal of NOACs with PCCs.[55–59] Acute perioperative reversal of these agents may also require dialysis for dabigatran and titrated factor VII administration.[53,54] Specific parenteral antidotes for these agents are in clinical development and may offer the possibility of acute neutralization in urgent operative settings.[60–62] In elective surgical procedures that require adequate coagulation, discontinuation of NOACs for at least 48 hours is recommended, depending on factors such as the drug half-life, route of elimination, renal function, and hepatic function (see Chapter 35).[63] A current limitation of these agents is that conventional anticoagulation tests (eg, activated partial thromboplastin time, prothrombin time) do not adequately monitor the effects of NOACs. Certain tertiary care centers, however, develop nomograms for each agent in order to report specific serum levels of each drug.

TABLE 43.2 Percutaneous Coronary Intervention and Recommendations for Timing of Noncardiac Surgery

Percutaneous Coronary Intervention	*Recommended Delay of Elective Noncardiac Surgery (Days)*
Angioplasty	14
Bare metal stent	30
Drug-eluting stent	365

From Ghadimi K, Thompson A. Update on perioperative care of the cardiac patient for noncardiac surgery. *Curr Opin Anaesthesiol.* 2015;28:342–348.

Management of Perioperative Anemia

Anemia is an important topic of discussion, especially because it may contribute to myocardial ischemia (see Chapter 34). Hemoglobin is a potent oxygen carrier, and ischemia may be triggered by both lack of oxygen delivery to poststenotic myocardium and demand for increased cardiac output to supply oxygen to other vascular beds. A common misconception among practitioners is that red blood cell (RBC) transfusions, assuming an appropriate increase in red cell mass, result in an immediate increase in the oxygen-carrying capacity of the blood and improve oxygen delivery to otherwise ischemic tissues. The exact amount of time during which the transfused RBCs replete intracellular 2,3-diphosphoglycerate (2,3-DPG) and adenosine triphosphate (ATP) is unclear, but this phenomenon certainly contributes to the necessary risk/benefit analysis of perioperative blood transfusion. Previous retrospective evidence suggested that the age of packed RBCs transfused may contribute to morbidity and mortality,[64] but this was later refuted by multicenter prospective data.[64,65]

Irrespective of the age of stored RBCs, blood transfusions increase morbidity and mortality as well as increase health care costs, and the hemoglobin transfusion thresholds needed to appropriately balance risk and benefit remain a moving target.[66] Carson and coworkers studied 2000 patients undergoing hip surgery who had either CAD or known risk factors for CAD and hemoglobin levels lower than 10 g/dL; they were treated with either a liberal transfusion strategy (threshold for treatment: hemoglobin <10 g/dL) or a conservative transfusion strategy (hemoglobin <8 g/dL).[67] There were no differences between groups in the 60-day end points of death or inability to walk, but the study was not sufficiently powered to show a difference between these two groups. In 2012, the American Association of Blood Banks recommended a restricted transfusion strategy (hemoglobin <7–8 g/dL) in asymptomatic, hemodynamically stable patients without CAD; a relatively restricted transfusion strategy in hospitalized patients with cardiovascular disease; and consideration of transfusion for patients with symptoms or hemoglobin levels lower than 8 g/dL.[68] In postoperative patients, the recommended maintenance hemoglobin concentration is 8 g/dL or greater unless the patient is symptomatic (eg, angina pectoris, HF). There are no specific recommendations for hemodynamically stable patients with acute coronary syndrome because of the lack of high-quality evidence for either a liberal or a restrictive transfusion strategy in these patients. Expert consensus has recommended a symptom-guided approach to evaluating the hemoglobin level when determining whether to transfuse an anemic patient.[68] In the perioperative setting, recent guidelines from the American Society of Anesthesiologists have recommended a restrictive transfusion strategy with strong consideration given to multimodal techniques to augment red cell mass, preserve hemostasis, and limit blood loss.[69]

Pulmonary Vascular Disease and Right Ventricular Dysfunction

Patients with pulmonary hypertension undergoing noncardiac surgery are at increased perioperative risk.[70] Perioperative events including hypoxia, hypercarbia, systemic hypotension, and positive-pressure ventilation may worsen pulmonary vascular resistance and RV systolic function.[71,72] In addition to the urgency of the surgery and the surgical risk category, perioperative risk factors for MACE in patients with pulmonary hypertension include the functional class, degree of RV dysfunction, and absence of specialized care.[73,74] Patients with significant pulmonary hypertension should undergo a thorough preoperative evaluation including determination of functional capacity, hemodynamics, and echocardiography to assess risk, severity, and RV function. In selected cases, right-sided heart catheterization may be indicated to complete the assessment.[75] Optimization of pulmonary hypertension and RV function is necessary to minimize cardiovascular risk throughout the perioperative period.[76]

Summary

Risk stratification of the cardiac patient undergoing noncardiac surgery is of paramount importance for the overall clinical outcome.[77] Perioperative risk calculators have been designed to help the perioperative team appropriately quantify the risk associated with a designated noncardiac procedure for a specific patient, although they have their limitations. These validated calculators are available online to make this determination of perioperative risk for MACE.

The 2014 ACC/AHA clinical practice guideline, *Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery*, addresses many management dilemmas in an evidence-based fashion with expert consensus where necessary. In addition, a multidisciplinary approach is advocated to develop perioperative consensus for the individual patient to minimize risk. Finally, establishing the patient's understanding of the risk and desire to proceed with surgery is at the heart of the overall assessment and development of a comprehensive perioperative care plan.

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44

The Patient With Coronary Stents Undergoing Noncardiac Surgery

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KEY POINTS

1. Percutaneous coronary intervention (PCI) with stent placement is frequently performed, and a substantial number of patients who undergo PCI require subsequent noncardiac surgery.
2. The two types of stents currently available for clinical use are bare metal stents (BMSs) and drug-eluting stents (DESs).
3. The two main stent-related complications are restenosis and thrombosis.
4. The risk of restenosis peaks within the first year after PCI and more commonly occurs in patients with BMSs.
5. The risk of stent thrombosis is highest within the first 30 days regardless of stent type. It decreases subsequently but remains higher with DESs compared to BMSs, at least for the first year. Newer generations of DESs appear to be less thrombogenic than first-generation DESs.
6. Prolonged treatment with dual antiplatelet therapy (DAPT) is necessary to prevent stent thrombosis, yet the optimal duration with particular types of stents is unknown.
7. Several clinical, procedural, and angiographic risk factors for stent thrombosis are recognized. The most important is premature discontinuation of DAPT; yet many cases of stent thrombosis occur in the presence of platelet inhibitors.
8. The standard combination for long-term DAPT consists of acetylsalicylic acid (ASA) and clopidogrel; however, there is significant variability in patient response to each drug. The more potent drugs, prasugrel and ticagrelor, exhibit more predictable antiplatelet effects but are associated with a higher risk of bleeding.
9. The use of platelet function tests to individualize antiplatelet therapy has not proven superior in medical patients, but it has shown effectiveness prior to cardiac surgical procedures and may hold promise for noncardiac surgical procedures.
10. The incidence of perioperative stent thrombosis is low, but it is associated with major morbidity and mortality.
11. The two most important decisions for patients undergoing noncardiac surgery are timing of the procedure and management of antiplatelet therapy.
12. Most recommendations are not very well defined and are based on low-quality evidence and expert opinion. Management should balance each patient's specific thrombotic risk against a particular surgical procedure's specific hemorrhagic risk.
13. Elective surgery should be delayed 6 to 12 weeks after BMS placement and at least 6 months (and, preferably, 12 months) after DES placement, with ASA continued for most procedures. If surgery cannot be postponed, decisions on antiplatelet therapy should be based on the patient's individual thrombotic/hemorrhagic risk.
14. Selected patients may benefit from bridging therapy with intravenous platelet inhibitors, but such an approach is not without risks and is associated with increased hospitalization and cost.
15. The frequency and complexity of performing noncardiac surgical procedures in patients with coronary stents requires an interdisciplinary structured approach with input from the different specialties involved in the care of these patients.

Percutaneous coronary intervention (PCI) is one of the most common procedures worldwide, with approximately 600,000 PCIs performed annually in the United States alone.[1] The term includes balloon angioplasty, as well as coronary stent placement, with the overwhelming majority of individuals undergoing the latter because of its superior results in preserving vessel patency.

Despite the obvious advantages over balloon angioplasty, the long-term care of patients with coronary stents is haunted by the risk of restenosis and stent thrombosis.[2,3] Refinements in stent technology, implantation technique, and antiplatelet therapy have increased stent safety profiles[4]; however, long-term management still involves significant challenges in aiming to achieve an optimal balance of maintaining vascular integrity while minimizing thrombotic and bleeding risks (see Chapters 1, 3, and 20).

The reported incidence of noncardiac surgery (NCS) after PCI ranges from 4% to 11% at 12 months and from 7% to 34% by 2 years.[5,6] One of the greatest causes for clinical concern is how to best manage these patients, because the presence of coronary artery stents is a recognized risk for perioperative cardiac morbidity and mortality.[7–9]

The issue is further complicated by a frequent lack of consensus among perioperative providers, either due to unawareness or personal preferences, as a result of which patients may remain uninformed of potential risks.[10,11] Because of the magnitude of the problem, professional societies have provided guidelines for perioperative

physicians to assist in their evaluation and management, but these are mostly grounded on low-quality evidence and expert opinion.[12–14] Furthermore, they frequently disagree and/or are vague and ambiguous.[15] Additionally, rapid improvements in stent technology and new pharmacologic agents find their way into clinical use before long-term outcome from clinical trials are published, adding to the confusion about the best way to manage these patients in the perioperative period.

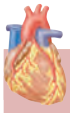
As part of a multidisciplinary team, anesthesiologists are in a unique position to provide important critical input, as they are frequently sought by perioperative providers for their expertise. It is therefore necessary to have a thorough understanding and familiarity with the basic concepts of coronary stenting, pharmacologic long-term management, and perioperative risks associated with this patient population.

Optimal Stenting Technique

Most stents are implanted following predilation of an atheromatous lesion with a high pressure balloon, but in some instances direct stenting may be considered (eg, absence of calcification, proximal lesions, or during ST-segment elevation myocardial infarction [STEMI]).[16] Regardless of technique, the single most important goal is to achieve full expansion of the arterial lumen, thus minimizing the risk of stent restenosis and thrombosis. Successful expansion should leave a minimal diameter stenosis of less than 10% and adequate blood flow without the presence of a thrombus, associated dissection, distal embolization, or occlusion of a side branch[17] (Box 44.1).

Failure to achieve maximum vessel dilatation may be caused by inadequate balloon expansion related to poor technique, location of the lesion, features of the atheroma, or stent design.[18] Suboptimal stent deployment is associated with a higher risk of periprocedural myocardial infarction and increased incidence of late cardiac events such as non–ST-segment elevation myocardial infarction (NSTEMI) and target vessel revascularization.[19–21]

Evaluation of stent expansion is commonly performed with angiography. Other techniques such as intravascular ultrasound, optical coherence tomography, and measurement of fractional flow reserve are also useful to predict optimal stenting results but are not employed routinely because most operators rely primarily on angiographic appearance[22–25] (see Chapter 3).



BOX 44.1 PERCUTANEOUS CORONARY INTERVENTION CRITERIA FOR SUCCESSFUL STENT DEPLOYMENT

Vessel diameter stenosis <10%
Adequate flow (TIMI 3)
Absence of thrombus, dissection, embolization, or vessel occlusion

TIMI 3, Thrombolysis in Myocardial Infarction Study Group grade 3 flow.

Types of Stents

The basic concept of a stent is that of a solid scaffold that prevents vessel closure due to elastic recoil or vessel contracture. In general, stents can be categorized according to material composition, durability, thickness of struts, and the presence of eluting drugs for local delivery[26–30] (Table 44.1).

Bare Metal Stents

Current bare metal stents (BMSs) are made of stainless steel, cobalt chromium, or platinum chromium. Stainless steel BMSs were the first devices used for coronary stenting.[31] They successfully reduced the incidence of abrupt vessel closure and restenosis compared with balloon angioplasty, thereby decreasing the rate of target lesion revascularization.[32–34] One advantage of BMSs is that on average, endothelial stent coverage is completed in approximately 12 weeks, which decreases the risk of stent thrombosis.[35] Nevertheless, despite refinements in stent design, significant restenosis within the stented segment develops in approximately 20% to 30% of lesions.[36–38]

Current accepted indications for placing a BMS include patients who are likely to be noncompliant with long-term dual antiplatelet therapy (DAPT); patients at a higher risk of bleeding, including individuals taking oral anticoagulants; and patients who are scheduled for NCS requiring cessation of antiplatelet therapy within 1 year after PCI.[17]

Drug-Eluting Stents

Drug-eluting stents (DESs) consist of a metallic stent platform coated with a polymer carrier vehicle that stores an antiproliferative agent.

TABLE 44.1 Types of Stents

Bare Metal Stents

Name	*Manufacturer*	*Stent Generation*	*Stent Platform*
Veri-FLEX	Boston Scientific	First	Stainless steel
Vision	Abbott Vascular	Second	Cobalt chromium
Integrity	Medtronic	Second	Cobalt chromium
REBEL	Boston Scientific	Third	Platinum chromium

Drug-Eluting Stents

Name	*Manufacturer*	*Stent Generation*	*Stent Platform*	*Polymer*	*Anti-Restenotic Drug*	*Elution Kinetics*
Cypher[a]	Cordis/J&J	First	Stainless steel	PEVA/PBMA	Sirolimus	80% at 4 weeks
Taxus[a]	Boston Scientific	First	Stainless steel	SIBBS	Paclitaxel	10% at 4 weeks
Xience	Abbott Vascular	Second	Cobalt chromium	PBMA/PVDF-HFP	Everolimus	80% at 4 weeks
Promus	Boston Scientific	Second	Cobalt chromium	PBMA/PVDF-HFP	Everolimus	80% at 4 weeks
Endeavor	Medtronic	Second	Cobalt chromium	PPChol	Zotarolimus	95% at 2 weeks
Resolute	Medtronic	3nd	Cobalt chromium	Biolynx	Zotarolimus	85% at 8 weeks
Promus Element	Boston Scientific	Third	Platinum chromium	PBMA/PVDF-HFP	Everolimus	80% at 4 weeks
Taxus Ion	Boston Scientific	Third	Platinum chromium	SIBBS	Paclitaxel	10% at 2 weeks
Nobori[b]	Terumo (Japan)	BP-DES	Stainless steel	PLA (biodegradable)	Biolimus	80% at 4 weeks
Biomatrix[b]	Biosensors (Singapore)	BP-DES	Stainless steel	PLA (biodegradable)	Biolimus	80% at 4 weeks

[a]No longer used (Cypher was discontinued in 2011).
[b]Not approved for use in the United States.
PBMA, Poly n-butyl methacrylate; *PEVA,* polyethylene vinyl acetate; *PLA,* polylactic acid; *PPChol,* phosphorylcholine; *PVDF-HFP,* poly vinylidene fluoride–hexafluoropropylene; *SIBBS,* styrene-b-isobutylene-b-styrene.

The carrier releases the drug in a gradual and controlled fashion (elution), allowing local diffusion into the vascular tissue, thus preventing excessive cell growth (neointimal hyperplasia) and encroachment into the lumen in response to device implantation.[39] DESs have been shown to outperform BMSs with respect to the rates of restenosis and target lesion revascularization, particularly within the first year after implantation.[40–44] Thereafter, it appears that the restenosis rate is similar between DESs and BMSs.[45–47]

Stent Platform

Stent design plays an important role in drug distribution into the vessel wall.[48] The configuration of the stent's struts directly determines the pattern and degree of drug delivery.[49,50] Also, the symmetric expansion of stents is essential to optimize drug diffusion. A large number of stent platform designs have been developed, but all of them can be categorized into those with closed or open cell configurations[51] (Fig. 44.1).

A closed cell stent achieves a more even expansion, and the constant cell spacing leads to more uniform drug distribution.[52] An open cell system has better conformability because of greater variation in the surface coverage between the inner and outer curvatures but at the expense of less uniform distribution.[52,53] Improvement in stent flexibility and decreased strut thickness have been shown to lessen arterial injury and decrease neointimal response[54–56] (Fig. 44.2). The optimal stent design for drug delivery should have a large stent surface area and a small cell gap, while maintaining conformability, radial support, and flexibility to reach complex coronary lesions.

Polymer Matrix

The function of a polymer matrix is that of a reservoir containing the antiproliferative drug during stent deployment, followed by gradual release of the agent into the local vessel wall.[57] The elution kinetics over a period of weeks or months following implantation are dictated by the type, composition, and design of the stent coating material.[58] Polymers can be broadly described as organic versus inorganic, bioabsorbable versus durable, and synthetic versus natural. Differences in polymer composition directly influence the length and extent of the inflammatory reaction on the vessel wall and, thus, the timing for re-endothelialization of the stent surface.[59–61]

Older DESs (so-called first-generation DESs) are composed of stainless steel platforms and durable polymers. These have been shown to produce long-term inflammatory reactions, resulting in delayed vascular healing and endothelial stent coverage.[62,63] Newer DESs (second and third generations) consist of cobalt or platinum chromium scaffolds and are coated with polymers that cause less local inflammation and less interference with re-endothelialization[64–66] (Box 44.2).

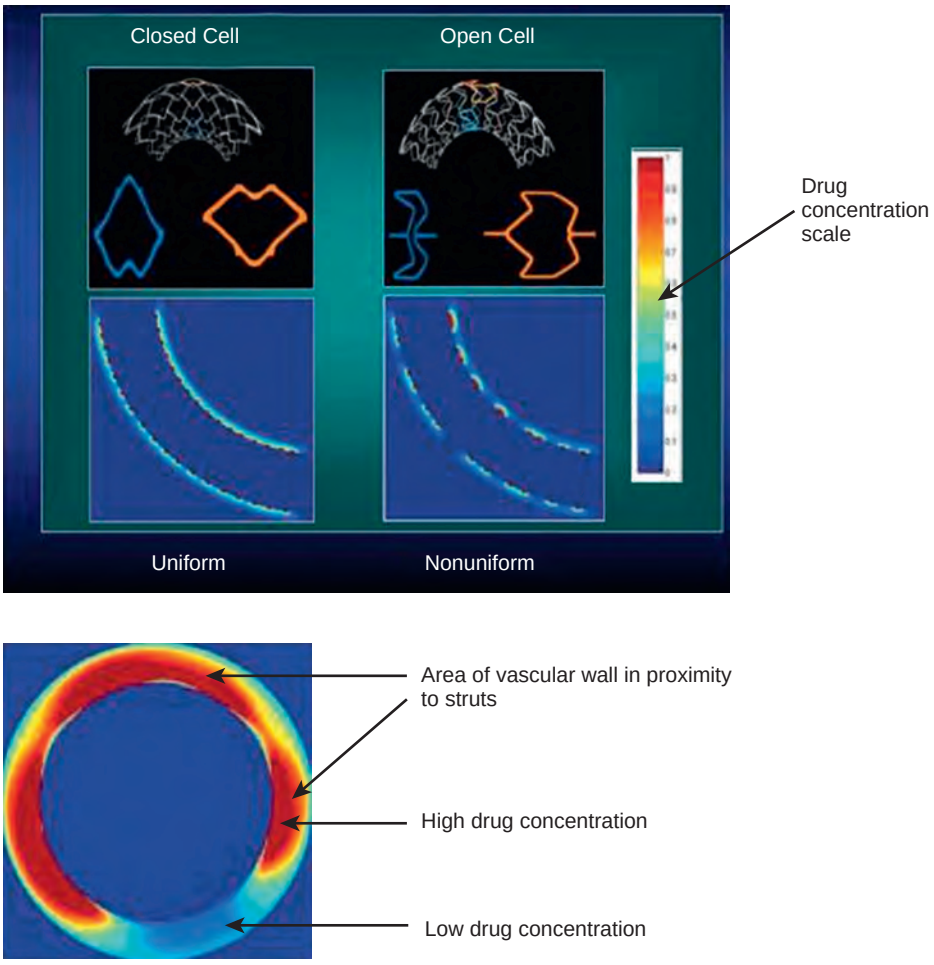


Fig. 44.1 *Upper panel,* Closed cell versus open cell configuration in a drug-eluting stent. Closed cell configuration *(left)* provides more scaffold support and more uniform drug distribution into the adjacent vascular wall than an open cell system *(right)* but at the expense of decreased flexibility. Drug concentration is shown by the color intensity in the column from highest *(red-brown)* to lowest *(blue). Lower panel,* Cross-section of a vessel after deployment of a drug-eluting stent showing nonuniform strut spacing resulting in uneven drug distribution. *(Reproduced with permission from Htay T, Liu MW. Drug-eluting stent: a review and update.* Vasc Health Risk Manag. *2005;1:263–276. Copyright Dove Medical Press.)*

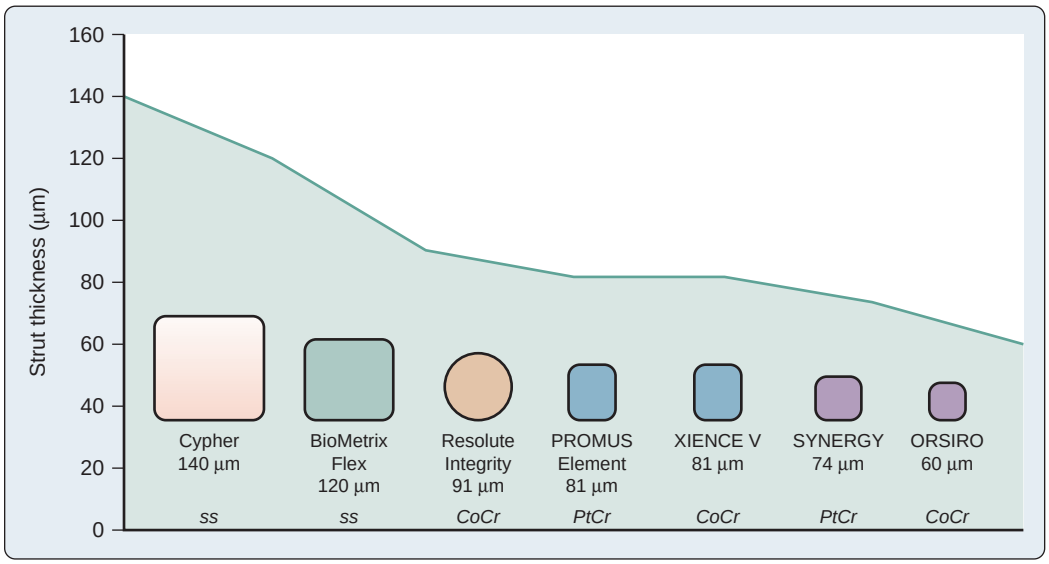


Fig. 44.2 Evolution of strut thickness in drug-eluting stent platforms. Thinner struts are made mainly from cobalt chromium *(CoCr)* or platinum chromium *(PtCr)* alloys, which have a higher mechanical strength than stainless steel. *(Modified with permission from Foin N, Lee RD, Torii R, et al. Impact of stent strut design in metallic stents and biodegradable scaffolds.* Int J Cardiol. *2014;177:800–808. Copyright Elsevier.)*

BOX 44.2 ADVANTAGES OF SECOND- AND THIRD-GENERATION DRUG-ELUTING STENTS

Improved flexibility
Thinner struts
Enhanced polymer biocompatibility
Better elution kinetics

Antiproliferative Agents

During DES design and manufacturing, multiple agents with the ability to prevent cell replication are tested; however, only five antirestenotic drugs are currently used in the clinical setting.

1. Sirolimus (also known as rapamycin) is a fermentation product of *Streptomyces hygroscopicus*. It functions as an antifungal macrolide with potent cytostatic properties. Sirolimus is a highly lipophilic molecule that readily diffuses across the membranes of vascular smooth muscle cells. In the cytoplasm, it binds to a specific intracellular protein. The resulting complex inhibits a regulatory enzyme called target of rapamycin (TOR), blocking cell progression from the G1 to S phase, thereby limiting smooth muscle cell replication and proliferation.[67,68]
2. Everolimus is a semisynthetic sirolimus derivative. It is slightly more lipophilic and more rapidly absorbed in the arterial wall.[69]
3. Zotarolimus is an equipotent analogue of sirolimus but with a shorter circulating half-life. It is also highly lipophilic.[70]
4. Biolimus is a lipophilic lactone, semisynthetic analogue of sirolimus. It is used primarily as the eluting agent in certain biodegradable polymer stents.[71]
5. Paclitaxel is an antineoplastic agent isolated from the bark of the Pacific yew tree *Taxus Brevifolia*, originally used to treat breast and ovarian cancer. It is also a lipophilic molecule that readily defuses across cell membranes. Paclitaxel acts by stabilizing cellular microtubules prior to cell division, thus preventing their disassembly, which is essential for the progression of the G2 to M phase in the mitotic cell cycle.[72] The end result is inhibition of smooth cell replication and migration.

First Generation Drug-Eluting Stents

Although widely used since first introduced in 2003,[52] first-generation DESs are rarely used today and have been largely replaced by more refined stents. First-generation DESs are comprised of a metallic stent platform, typically stainless steel, coated with a nonbiodegradable polymer that elutes either sirolimus (Cypher, no longer manufactured) or paclitaxel (Taxus).[73,74] Several trials demonstrated the superiority of DESs over BMSs in decreasing the rates of restenosis and target lesion revascularization, with the Taxus stent seemingly associated with a slight increase in stent thrombosis over the Cypher stent.[75,76] The majority of the existing body of literature regarding perioperative risk and management of surgical patients is based on first-generation DESs rather than the newer, safer, stents.

Second- and Third-Generation Drug-Eluting Stents

Second- and third-generation DESs offer numerous improvements that increase their safety profile over their first-generation counterparts.[77–80] They have decreased strut thickness, improved flexibility, enhanced polymer biocompatibility and drug elusion profiles, and superior re-endothelialization kinetics.[81] These devices are now the predominant coronary stents implanted worldwide.

Taxus Ion

This stent uses paclitaxel but with a unique polymer designed to maximize early release so most of the drug is eluted by 12 weeks. In addition, the system uses a platinum chromium strut system providing thinner struts, which are associated with lower levels of vessel wall inflammation.[82]

Zotarolimus Drug-Eluting Stents

Currently two of these stents are available. The Endeavor stent has a stronger cobalt chromium platform with improved flexibility. It also uses a phosphoryl choline polymer coating designed to maximize biocompatibility and minimize inflammation associated with previous polymers.[83] This shortens the drug elution time, so that 95% of the drug is eluted within 2 weeks, thereby allowing normal arterial repair to occur faster.

The Endeavor Resolute represents a refinement over the Endeavor stent. The main difference is the presence of a trilayered polymer made

up of three main components: (1) a hydrophilic polymer for biocompatibility, (2) a hydrophobic polymer for drug-elution control, and (3) a polyvinyl polymer that releases an initial surge of the drug immediately after implantation.[84] The net effect is suppression of the initial inflammatory response followed by 85% of the drug being eluded over the next 8 weeks.

Everolimus Drug-Eluting Stents

Two versions of the Everolimus DES exist. The Xience stent uses a cobalt chromium platform with a polymer (*N*-butyl-methacrylate) that allows 80% of the drug to be eluted within 4 weeks.[85] The Promus DES uses an identical polymer profile and drug elusion but offers improved drug delivery due to a mobile platinum-chromium scaffold.[86]

DESs are indicated for most coronary lesions, whereas BMSs are currently reserved for selective situations. In general, patients more likely to benefit from a DES are those with a high risk of restenosis that may lead to poor outcome. These include patients with left main coronary artery disease, ostial lesions, small vessels, previous in-stent restenosis, bifurcation lesions, long or multiple lesions or those in saphenous vein grafts, and patients with acute coronary syndromes (ACSs), diabetes, or chronic kidney disease.[86–90]

Differences Between Drug-Eluting Stents

All DESs are superior to BMSs by reducing the incidence of restenosis and target lesion revascularization at 12 months.[91] First-generation DESs are inferior to newer DESs regarding target lesion revascularization and late thrombosis.[91–93] With respect to second- and third-generation DESs, very little difference in outcomes are apparent between zotarolimus and everolimus DESs, although a slight decrease in stent thrombosis may be associated with the cobalt chromium everolimus stents.[94–96]

Biodegradable Coronary Stents

Although the newer generation stents have a lower incidence of stent thrombosis when compared to first-generation DESs, the stent platform and polymer matrix are permanent. A potential method to decrease stent thrombosis even further would be to shorten the length of exposure to either the polymer or the scaffold with the use of bioabsorbable stents, where either the polymer or the scaffold can degrade over time.[97–99] The main rationale for using a bioabsorbable polymer is based on the expectation of decreased chronic inflammation and improved vascular healing. The principle behind a bioabsorbable stent platform is grounded on the fact that restenosis is uncommonly seen after 12 months following a procedure[37,38]; thus, the clinical need for stent scaffolding is likely to be very limited.

Although these stents currently are not approved for clinical use in the United States, stents with bioabsorbable polymers have been extensively studied elsewhere.[100–103] Two recent meta-analyses compared bioabsorbable polymer stents against durable polymer DESs and BMSs.[104,105] The analyses demonstrated that such stents are superior to first-generation DESs and perhaps BMSs, and they are comparable to some of the second-generation DESs. Presently they are considered a reasonable alternative to second- and third-generation DESs.

Vascular and Biologic Response to Stent Placement

Most clinical decisions surrounding the perioperative evaluation and management of patients with coronary stents are based on the body's natural responses to the presence of a foreign body in the coronary lumen; therefore, it is important to review the associated pathophysiology as well as the therapeutic interventions aimed to counteract such reactions.

Balloon dilatation of an atheromatous lesion with concomitant stretching of the vascular wall initiates three sequentially distinct responses[106]:

1. Immediate vessel recoil
2. Negative arterial remodeling
3. Neointimal hyperplasia

Elastic recoil represents the immediate shrinkage of the vessel following PCI due to the elastic properties of the arterial wall, which usually occurs within 24 hours after the procedure. This is followed by negative remodeling, which is the process of local contraction of the arterial wall and narrowing of the lumen of the injured vascular segment. The cause of negative remodeling is not well established but may be related to the healing process as well as interactions between the vascular endothelium and laminar flow.[107] Neointimal hyperplasia constitutes a delayed healing response. This is represented by proliferation and migration of smooth muscle cells from the media and perhaps circulating endothelial progenitor cells from the bone marrow into the intima.[108,109]

Placement of an intracoronary stent eliminates the first two processes, leaving only that of neointimal hyperplasia playing a role in normal healing, as well as the exaggerated response responsible for restenosis. In addition, unlike plain balloon angioplasty, the permanent presence of a foreign body serves as a constant stimulus for thrombus formation due to activation of platelet function and coagulation mechanisms, which persist until complete endothelial stent coverage occurs.[110–113]

The cellular cascade initiated by stent deployment can be divided into three phases[114] (Fig. 44.3):

1. Early phase: Endothelial injury, platelet activation and inflammation with leukocyte recruitment, release of cytokines and growth factors. This response is followed by re-endothelialization and generation of neo-endothelium. In the presence of antiplatelet therapy, endothelial destruction stimulates the formation of a thin layer of thrombus consisting mainly of platelets covering the vascular and stent surfaces; in the absence of cytotoxic agents, complete coverage of neointima by endothelial cells is present after several weeks.[115]
2. Granulation phase: Replacement of the fibrin clot in injured areas by macrophages that are responsible for digesting cell debris and secretion of several growth factors, thus stimulating endothelial cell proliferation and smooth muscle cell migration.[116]
3. Tissue remodeling phase: Modification of muscle cells activated by growth factors and cytokines released by damaged endothelial cells and platelets as well as compressive vascular forces generated by the stent and low shear stress along the struts.[117,118] Smooth muscle cells undergo complex changes leading to migration and proliferation from the media toward the intima. This process is accomplished by a transformational change from a contractile to a synthetic phenotype, which enables smooth muscle cells to deposit an extracellular matrix.[119] This protein-rich matrix plays an important role as it interacts with cells and influences further cell adhesion, migration, and proliferation. Some individuals exhibit an exaggerated response, which seems to correlate with the extent and severity of vascular injury. In these circumstances, excessive neointimal growth will further encroach into the vessel lumen, leading to in-stent restenosis. The presence of antiproliferative agents blunts this response, thereby maintaining lumen patency. The trade-off is delayed endothelial stent coverage, which increases the risk of stent thrombosis (Fig. 44.4)

In-Stent Restenosis

This process involves a gradual renarrowing of the stented segment, or immediately proximal or distal to it, that is caused by excessive neointimal growth. Restenosis occurs as a result of peak neointimal thickening mostly between 4 and 12 months following stent placement.[120–122]

Clinical intervention is considered when the reduction in vessel diameter is 50% or greater in the presence of associated symptoms or signs of ischemia, or if there is a 70% or greater reduction in lumen diameter regardless of the presence of symptomatology.[123] *Target*

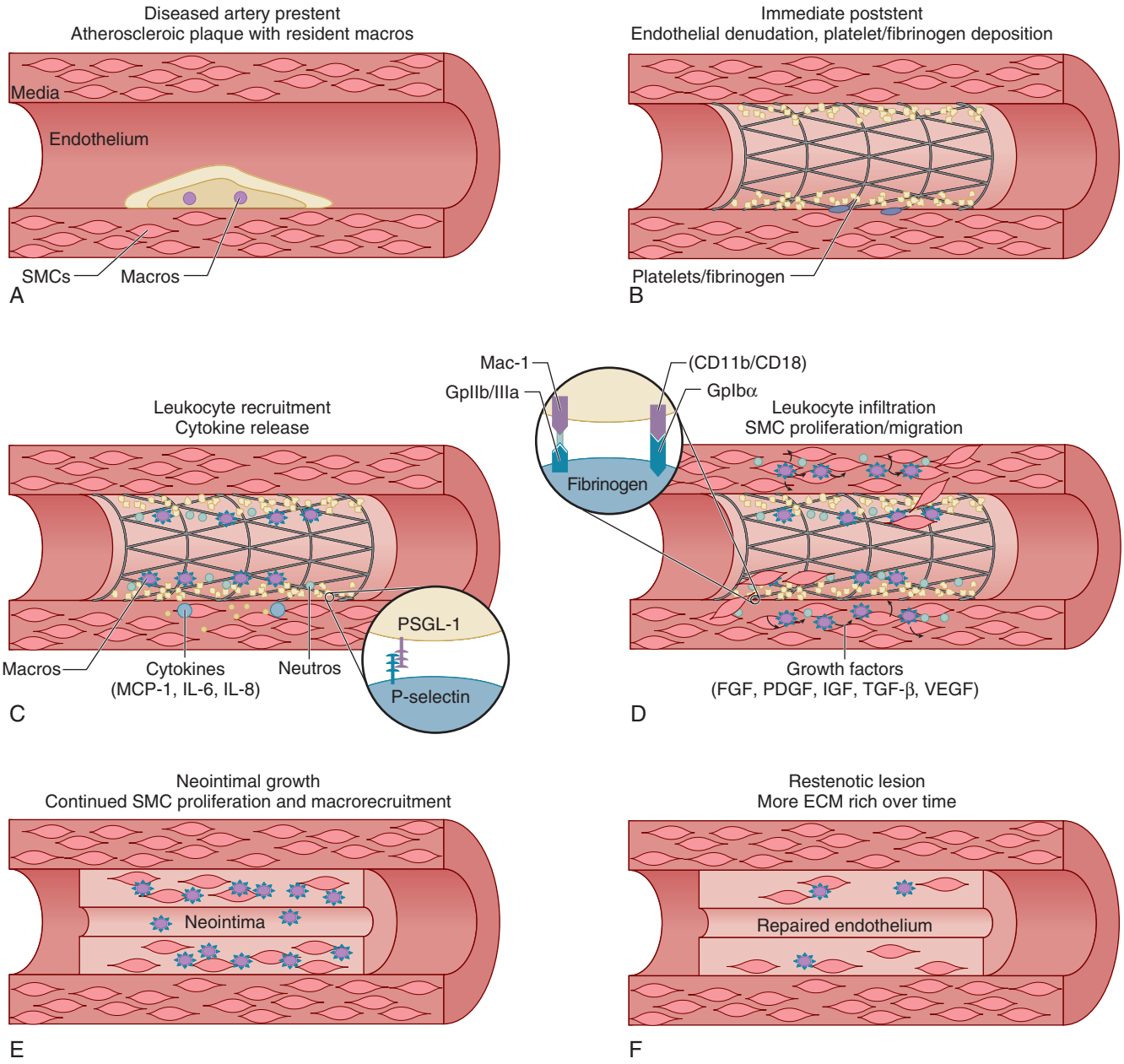


Fig. 44.3 (A) Mature atherosclerotic plaque before intervention. (B) Immediate result of stent placement with endothelial denudation and platelet and fibrinogen deposition. (C) and (D) Leukocyte recruitment, infiltration, and smooth muscle cell *(SMC)* proliferation and migration in the days after injury. (E) Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment. (F) Long-term (weeks to months) change from a predominantly cellular to a less cellular plaque, rich on extracellular matrix. *(Reproduced with permission from Bhatia V, Bhatia R, Dhindsa M. Drug-eluting stents: new era and new concerns.* Postgrad Med J. *2004;80:13–18. Copyright BMJ Publishing Group Ltd.)*

vessel revascularization refers to any reintervention along the side of the stented vessel, whereas the term *target lesion revascularization* is defined by reintervention within the lesion itself. Types of restenotic lesions are shown in Fig. 44.5.[124]

The incidence of restenosis within the first year after PCI in patients with BMSs is approximately 20% to 30%.[125] Thereafter, myocardial ischemia, if present, occurs mostly from progression of native vessel disease.[126] DESs consistently reduce the incidence of in-stent restenosis and the rate of target lesion revascularization by about 75% with the benefits seen across all subgroups of patients.[127–130]

Types of Lesions

Management of discrete concentric lesions, with little or no calcification and without branch involvement, is associated with a high success rate. More challenging lesions conferring a higher risk for restenosis are those that are diffuse, more than 20 mm long, excessively tortuous, angulated, ostial, and involving vein grafts.[131] Additional predictors include small vessel size (<2.5 mm), multiple stents, stent strut thickness, stent underexpansion, and clinical comorbidities such as diabetes mellitus (particularly insulin dependent), metabolic syndrome, and hypertension[132,133] (Box 44.3).

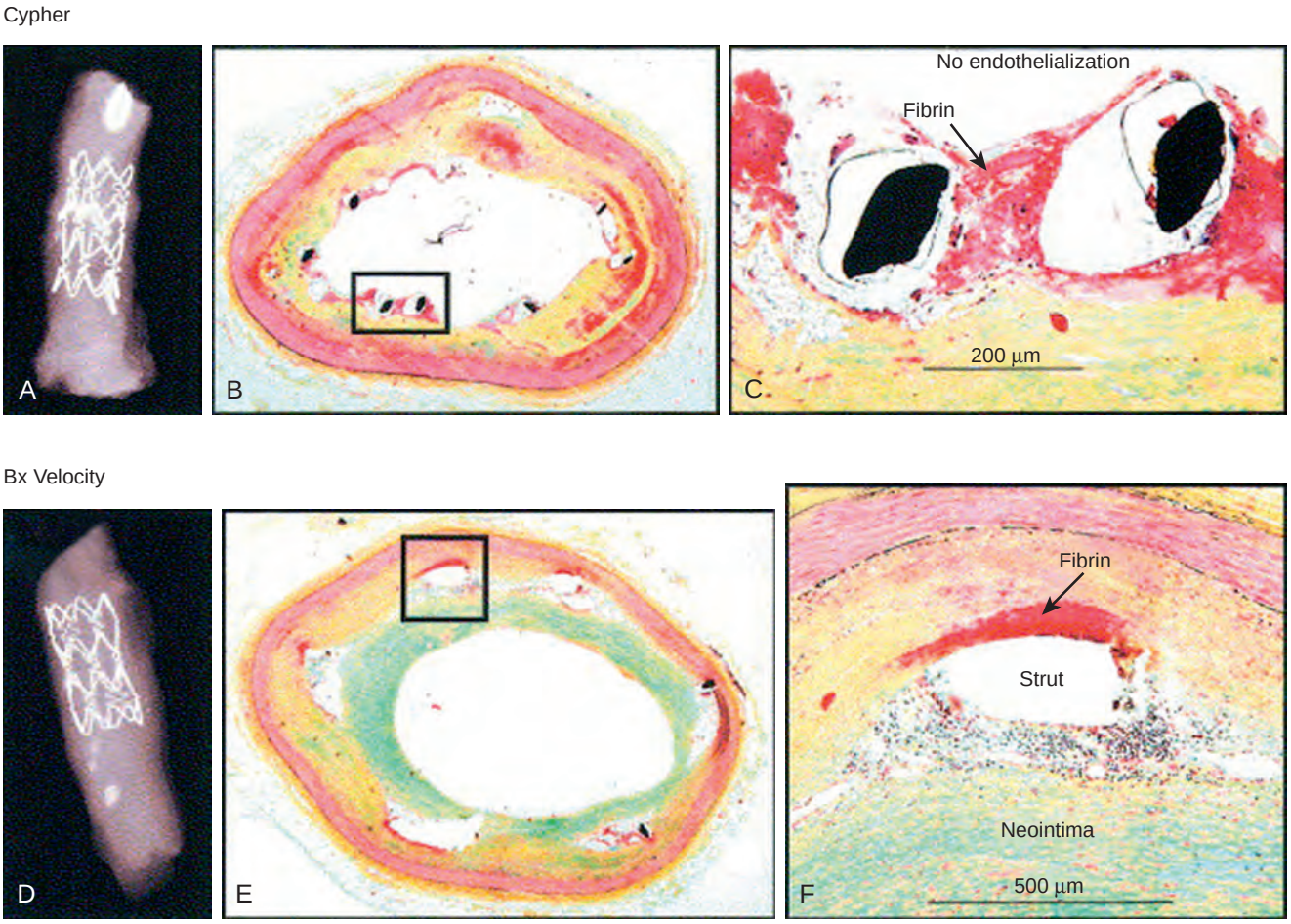


Fig. 44.4 A 65-year-old man who died from head trauma. The patient had received a proximal sirolimus drug-eluting stent (DES; Cypher) and a distal bare metal stent (BMS; Bx Velocity) in his left anterior descending coronary artery (LAD) 15 months before his death. (A) Radiograph of the stented LAD segments. (B) Histologic section of the DES showing minimal neointimal coverage of the struts. (C) High-powered magnification showing fibrin around the strut, rare endothelial cells, and no luminal thrombus. (D) Radiograph of the stented LAD segments. (E) Abundant neointimal tissue within the BMS *(green)* consisting of smooth muscle cells, extracellular matrix, and overlying endothelium. (F) Magnified section showing minimal fibrin underneath the strut, which is surrounded by lymphocytes; the luminal surface of the stent is covered by smooth muscle cells in a proteoglycan-collagen–rich matrix. All sections shown are stained with Movat pentachrome. *(Reproduced with permission from Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk.* J Am Coll Cardiol. *2006;48:193–202. Copyright Elsevier.)*

Although less frequent with DESs, restenosis still occurs depending on periprocedural challenges and the complexity of the initial lesions.[134,135] Thus, unlike with BMSs, it seems that most predictors of restenosis with DESs relate more to lesion characteristics and technical aspects of stent deployment rather than to the clinical status of the patient.[136]

Clinical Presentation

Stent restenosis is primarily suspected by recurrent symptoms of myocardial ischemia. The most common syndrome is that of stable or progressive angina, but up to 10% of patients present with acute myocardial infarction.[137] The diagnosis of in-stent restenosis is confirmed by coronary angiography.

Treatment

In patients who are symptomatic and/or fulfill anatomic criteria, repeat PCI is frequently required. Most experts recommend balloon dilatation of the lesion and insertion of a DES because of the favorable profile against restenosis. Placement of a DES for the treatment of restenosis will require prolonged DAPT to minimize the risk of stent thrombosis. Patients for whom repeat PCI is not likely to be successful should be considered candidates for surgical myocardial revascularization. In those patients, placement of arterial grafts is preferable because of a higher long-term patency rate compared to saphenous vein grafts (see Chapter 20).

Stent Thrombosis

Definition

Thrombosis of a coronary stent is one of the most serious complications of PCI and is associated with major morbidity and mortality.[138] It is defined as an abrupt occlusion at the site of the stent resulting from a platelet-rich thrombus, which can occur anytime from the moment of stent placement to years after PCI.[139–141]

Clinicians in the past have used various definitions of stent thrombosis, which made interpretation of events very difficult. Since 2006, the Academic Research Consortium has proposed criteria for the diagnosis of stent thrombosis and timing of events in relation with the

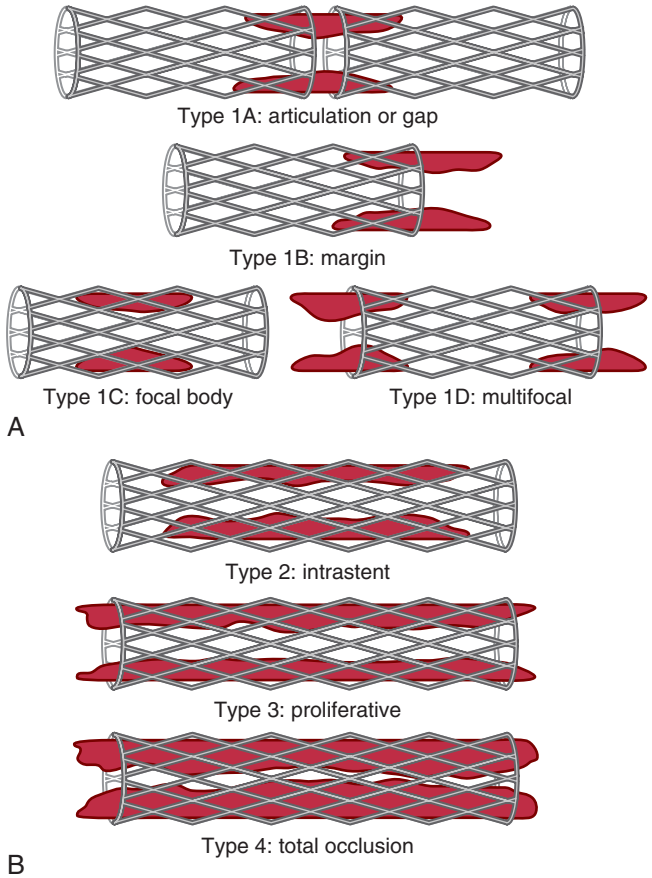


Fig. 44.5 Different angiographic patterns of in-stent restenosis. (A) Type 1: focal lesions (and subtypes) 10 mm or shorter. (B) Type 2: diffuse lesions 10 mm or greater; type 3: proliferative lesions 10 mm or greater, extending beyond the stent margins up to 5 mm; type 4: total occlusion. *(Modified with permission from Merhan R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long term outcome.* Circulation. *1999;100:1872–1878. Copyright Wolters Kluwer Health.)*

BOX 44.3 RISK FACTORS FOR STENT RESTENOSIS

Lesion Characteristics
- Long
- Diffuse
- Ostial
- Small vessel (<2.5 mm)
- Tortuous
- Angulated
- Saphenous vein graft
- Stent underexpansion
- Multiple stents

Clinical Comorbidities
- Diabetes mellitus
- Obesity
- Hypertension

index procedure[142] (Tables 44.2 and 44.3). These criteria, although imperfect, have allowed fairly consistent interpretations in comparing outcomes between different trials of DES.

The common denominator is heightened platelet activation and aggregation by one or more of the following mechanisms (Box 44.4):

TABLE 44.2 Timing of Stent Thrombosis

Acute	Within 24 hours of stent implantation
Subacute	From 24 hours to 30 days
Late	From 30 days to 12 months
Very late	More than 1 year

Modified from Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344–2351.

TABLE 44.3 Diagnosis of Stent Thrombosis

Definite	Angiographic evidence of stent thrombosis and chest pain with new ECG or echocardiographic changes, or cardiac biomarker elevation Pathologic evidence on autopsy
Probable	Unexplained death within 30 days of percutaneous coronary intervention (PCI) Myocardial infarction in the location supplied by the stented vessel
Possible	Unexplained death more than 30 days after PCI

Modified from Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344–2351.

BOX 44.4 MECHANISMS OF STENT THROMBOSIS

Slow blood flow around stent
Exposure of platelets to nonendothelial surface
Absence or low response to platelet inhibition
Local hypersensitivity or inflammation of the vascular wall
Presence of neoatherosclerotic plaques

- Persistent slow coronary flow, which may occur with wall dissection or hypoperfusion
- Exposure of blood elements to prothrombotic constituents in the vasculature (eg, tissue factor, collagen) or to the stent itself before re-endothelial stent coverage
- Failure to suppress platelet aggregation during the period of high thrombotic risk, such as premature cessation of antiplatelet therapy or drug resistance

In some patients (particularly with DESs) who develop very late stent thrombosis (VLST), other factors such as hypersensitivity reactions, excessive fibrin deposits, and ruptured neoatherosclerotic plaques within the stent struts play an important role.[143]

Timing

Most cases of stent thrombosis occur within 30 days after placement irrespective of stent type, ranging from 0.5% in low-risk patients to 2.5 % in high-risk subjects.[144–146] Episodes of stent thrombosis during this period are commonly related to periprocedural complications or abrupt interruption of DAPT, such as major bleeding or emergency high-risk surgery.

Stent thrombosis with BMSs occurs much less often after 4 to 6 weeks.[147] This observation is consistent with angioscopic studies that have shown complete re-endothelialization by 3 to 6 months.[148] VLST is even more uncommon with BMSs, and it occurs most often after a repeat procedure performed in the stented segment.[47]

Similar to BMS, most episodes of stent thrombosis associated with DESs occur in the first year, with the majority of these occurring within the first 30 days after PCI.[149,150] The cumulative incidence of stent thrombosis with DES at 1 year is approximately 0.5% to 1%.[151] Events thereafter continue at a rate between 0.4% and 0.6% per year with higher rates occurring with first-generation DESs.[152,153]

TABLE 44.4 Risk Factors for Stent Thrombosis

Stent Type	*Procedure*	*Lesions*	*Clinical*
First-generation drug-eluting stent (DES) > second- and third-generation DES ≈ bare metal stent	Stent underexpansion or malposition Vessel dissection Incomplete strut coverage Prestent or poststent vessel stenosis Stent deployed on necrotic plaques	Ostial, long, bifurcations, multiple stents Small vessel diameter (<2.5 mm) Overlapping stents Saphenous grafts Prior brachytherapy	Premature discontinuation of dual antiplatelet therapy Prior stent thrombosis Percutaneous coronary intervention for acute coronary syndrome Documented high on-treatment platelet reactivity Diabetes mellitus Chronic kidney disease Heart failure with low left ventricular ejection fraction Cancer Systemic inflammatory conditions Cigarette smoking Cocaine use

Risk Factors for Stent Thrombosis

The complex interaction between the presence of a stent, blood elements, and vascular wall is a strong stimulus for thrombus formation. Thus, it is not surprising that multiple factors have been shown to predispose patients for LST and VLST[154–156] (Table 44.4).

Stent Type

The rates of LST and VLST are highest with first-generation DESs, whereas the risk is similar between BMSs and second and third generations of DESs.[157,158] Besides the slower rate of drug elution (eg, Taxus), thicker struts and localized hypersensitivity to the durable polymer are factors that increase the propensity of first-generation DESs toward LST and VLST, when compared to BMSs and newer DESs, due to delayed endothelial coverage. Biodegradable stents have a similar safety profile to that of BMSs, but they seem to be slightly inferior to cobalt chromium everolimus stents.

Procedure-Related Factors

Features that have been correlated with higher rates for stent thrombosis include incomplete stent apposition, which leads to static blood flow between the struts and the vascular wall; persistent vessel dissection; and incomplete strut coverage.[19,20,159] These factors highlight the importance of achieving optimal results via appropriate stent selection, as well as the right technique, determined by the clinical circumstance, location, and characteristics of the lesion.

Lesion-Related Factors

Lesion characteristics may present a risk for stent thrombosis, for example, plaques with a necrotic filling lipid core during ACS, in which struts have demonstrated reduced neointimal coverage.[160] Other factors (so-called off-label indications) include complex anatomy such as multiple lesions, small vessel size, lesions larger than 3 cm, ostial and bifurcation lesions, total occlusions, saphenous vein graft stenosis, previous stent thrombosis, and prior brachytherapy.[161–163] Patients with one or more of these conditions represent approximately 50% of the total number of PCIs performed.[164]

Treatment-Related Factors

Undoubtedly the single most important predictor of early and late thrombosis is premature discontinuation of DAPT (one or both drugs), presumably during the period when vascular healing is incomplete.[165] This change is commonly related to the need to perform surgery or invasive procedures, poor patient compliance, side effects from treatment (eg, bleeding), or economic hardship. Although the duration of such a period is still a matter of controversy, it is longer with DESs when compared to BMSs.[166–168] With any stent, the highest risk period is the first 30 days after implantation, which correlates with the highest intensity of the inflammatory/thrombotic response within the vascular wall.[169]

Between 1 and 6 months the risk for stent thrombosis decreases but still remains high, particularly in patients with other risk factors and those with first-generation DESs.[170,171] After 6 months, no difference was found in one study in the rates of stent thrombosis between DES patients who underwent temporary discontinuation of antiplatelet therapy under the direction of a physician and patients who did not undergo this therapy.[172] The risk of stent thrombosis, however, was significantly higher for those who discontinued DAPT abruptly because of either noncompliance or bleeding. With current generation stents it appears that temporary discontinuation of the adenosine receptor blocker after 6 months may be relatively safe in selected patients, as long as acetylsalicylic acid (ASA) is continued.[168,173] The timing of LST or VLST during discontinuation of DAPT ranges from a few days to several months, depending on the agent discontinued and additional risk factors contributing to a prothrombotic state (eg, surgery).[174]

Medical Comorbidities

Patients shown to be at increased risk for stent thrombosis include those with diabetes mellitus[175] (particularly those with insulin deficiency),[176] chronic kidney disease,[177] heart failure with systolic dysfunction,[146] malignancy,[146] low response to platelet inhibitors,[178] cigarette smoking,[179] and cocaine use.[180] The cause is multifactorial; mechanisms include increased platelet turnover, vascular inflammation, decreased endothelial nitric oxide production, overexpression of platelet receptors, deficient antithrombotic pathways, bypass of pathways blocked by antiplatelet agents, impaired fibrinolysis, and vascular constriction.

Management

Management of patients with stent thrombosis requires the immediate recanalization of the occluded artery by aspiration of the mural thrombus and restenting the vessel.[181] With emergency surgical intervention reserved for those in whom successful PCI may be unlikely, many practitioners will perform intravascular ultrasound–guided stent sizing and confirm complete stent apposition. Patients with stent thrombosis while taking clopidogrel are at increased risk for recurrent events. Often this drug is exchanged for a different agent such as prasugrel or ticagrelor.

Outcome

The consequences of stent thrombosis can be devastating, thus highlighting the importance of timely intervention. Reported acute mortality of patients with coronary stent thrombosis presenting as STEMI is higher than 50%,[182,183] and for survivors it is 20% to 25% at 6 months.[184] Furthermore, the incidence of recurrent stent thrombosis is approximately 10% to 12%.[185,186] Compared to treatment of patients with native lesions, treatment of patients with stent thrombosis seems to be associated with less procedural long-term success.[187,188]

Antiplatelet Therapy

Platelet Physiology

Platelets play a key role in normal hemostasis as well as thrombus formation. In an inactive state, platelets appear discoid in shape and do not adhere to the vascular endothelial wall or to each other. Once

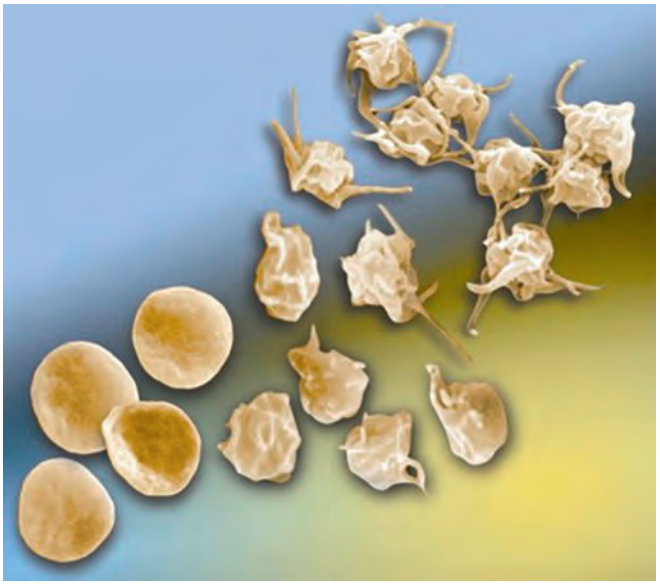


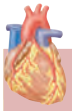
Fig. 44.6 Platelet shape change and aggregation. Scanned electron micrograph of resting *(lower left)*, partially activated *(center)*, and fully activated platelets *(upper right)*, showing the accompanying shape changes. Cytoplasmic projections are rich in activated fibrinogen (glycoprotein IIb/IIIa) receptors. *(Reproduced with permission from Michelson AD. Methods for the measurement of platelet function.* Am J Cardiol. *2009;103(suppl 2):20A–26A. Copyright Elsevier.)*

an endothelial injury occurs, platelets initially attach themselves to collagen or von Willebrand factor via glycoprotein membrane receptors (GpIb).[189] This initial phase (adhesion) is followed by subsequent activation. The activated platelet undergoes conformational changes, developing cytoplasmic projections (Fig. 44.6) rich in fibrinogen receptors (GpIIb/IIIa integrins).[189] In addition, procoagulants stored in alpha granules (thromboxane A2 [TXA2], adenosine) and dense granules (thrombin, CD4L ligand, CD6P) are released that serve to amplify the response via a positive feedback loop.[189–191] Platelet activation is followed by the phase of platelet aggregation in which activated GpIIb/IIIa receptors bind circulating fibrinogen, which acts as a bridge between neighboring platelets, binding them together.[191] Thrombin, generated from the action of tissue factor and released from platelet granules, cleaves fibrinogen into a mesh of fibrin that serves to stabilize the thrombus[192] (see Chapter 35).

Numerous pathways and platelet membrane receptors play important roles in the activation phase, thus providing pharmacologic targets for antiplatelet therapy[193,194] (Fig. 44.7). Currently, those available for platelet inhibition in patients with coronary stents include (1) activation of cyclooxygenase 1 (COX1) responsible for the production of TXA2; (2) adenosine-induced activation of membrane purinergic receptors P2X1, P2Y1, and P2Y12; (3) activation of protease-activated receptors by thrombin; and (4) active expression of membrane GpIIb/IIIa receptors (Box 44.5). Agents targeting other platelet receptors or pathways have been synthesized, but they have been found ineffective (eg, dipyridamole) or are at an early stage of development (eg, picotamide, terutroban).[193]

COX1-induced TXA2 production follows traumatic injury to the vessel wall during stent deployment whereby the eicosanoid arachidonic acid (AA) is synthesized from membrane phospholipids. COX1 acts on AA, inducing the production of prostaglandin H2, which then is transformed into TXA2.[193,194] The effects of TXA2 include changes in platelet shape, release of granular contents, and intense vasoconstriction.

Among other soluble agents, adenosine is released from neighboring red cells. In turn, adenosine attaches to its own purinergic receptors in the platelet membranes known as P2Y1, P2Y12, and P2X1.[195]



BOX 44.5 MECHANISM OF ACTION OF ANTIPLATELET AGENTS USED WITH CORONARY STENTS

ASA/aspirin: irreversible inhibition of cyclooxygenase 1
Clopidogrel and prasugrel: irreversible binding of P2Y12 receptors via active metabolite
Ticagrelor and cangrelor: reversible binding of P2Y12 receptors
Abciximab, tirofiban, eptifibatide: reversible binding of GpIIb/IIIa receptors

ASA, Acetylsalicylic acid.

Stimulation of the P2X1 receptor initiates platelet change, but alone it is not sufficient to amplify platelet activation and initiate platelet aggregation. This process depends mostly on activation of the P2Y12 receptor, which is primarily responsible for further procoagulant release (including TXA2) and expression of GpIIb/IIIa receptors.[194,195] The P2X1 receptor is involved in platelet shape change and activation from exposure to collagen under high-shear conditions.[195] A unique feature of purinergic receptors is their ability to block the intracellular production of vasodilator-stimulated phosphoprotein (VASP) via inhibition of adenylyl cyclase.[196] This is currently utilized as a laboratory test to check the effectiveness of adenosine antagonists.

Thrombin, the most potent platelet activator, binds to specific membrane proteins called *protease-activated receptors* (PARs).[197] Although four types have been described, only two, PAR-1 and PAR-4, are expressed on the platelet surface.[198] PAR-1 is the main receptor for thrombin and is activated at very low concentrations (100-fold lower than those required to activate PAR-4).[198,199] Stimulation of these receptors further increases granular content release and changes in platelet shape. In addition, the platelet membrane serves as a template for further thrombin production via the prothrombinase-tenase complex, which serves to amplify the coagulation cascade.[200] Currently, several platelet inhibitors are used in the management of coronary stents (Table 44.5).

Oral Antiplatelet Agents

Aspirin

Aspirin (ASA) exerts its effects through irreversible inhibition of platelet COX1 and COX2 with a 170-fold greater affinity for COX1.[201] Such enzymes, expressed in most cells, regulate the production of TXA2 in platelets, by the action of thromboxane synthetase. COX2 is present in the vascular endothelium, white cells, and immature platelets.[202] Endothelium-derived COX2 is associated with the synthesis of prostacyclin, which causes platelet inhibition and vasodilation; importantly, COX2 contained in monocytes and immature platelets can activate thromboxane synthetase during inflammatory response and conditions of high platelet turnover.[202]

ASA specifically and irreversibly inhibits platelet COX1 through acetylation of the amino acid serine in position 529, thereby blocking AA access to the COX1 catalytic site.[203] By inactivating COX1, ASA blocks the production of TXA2 through this pathway, rendering platelets incapable of functioning normally. At higher doses, aspirin also inhibits COX2-dependent prostacyclin synthesis in the endothelial cell. Other effects of ASA include enhanced fibrinolysis, as well as antioxidant, antiinflammatory, and antiatherosclerotic effects on endothelial cells and leukocytes.[204]

In normal subjects, a single dose of 30 mg of ASA is enough to produce complete and irreversible inactivation of COX1, with a ceiling effect observed on platelet activity with doses beyond 300 mg.[205] The current recommended dose to exert a fully antithrombotic effect is between 75 and 150 mg a day.

Plain ASA is rapidly absorbed through the gastric and enteric mucosa; peak plasma levels are seen within 30 or 40 minutes with a

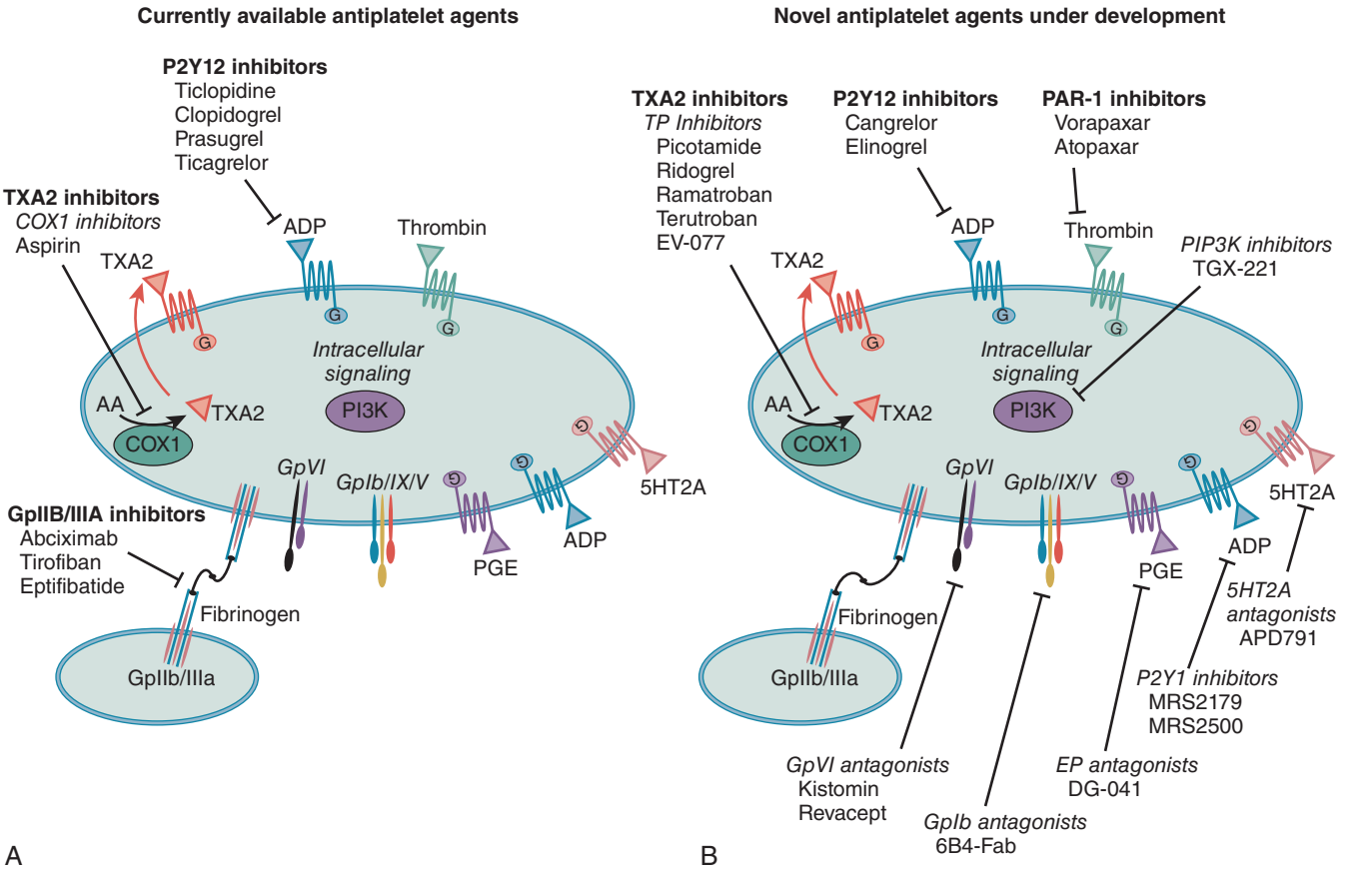


Fig. 44.7 Sites of action of antiplatelet agents. (A) Currently available agents for acute coronary syndromes or percutaneous coronary intervention. (B) Novel antiplatelet agents under development. Vorapaxar is now available for clinical use, whereas cangrelor has not yet received approval from the U.S. Food and Drug Administration. *AA*, Arachidonic acid; *ADP*, adenosine diphosphate; *COX1*, cyclooxygenase 1; *EP*, prostaglandin *E* receptor; *5HT2A*, serotonin; *G*, G-protein; *Gp*, glycoprotein; *PGE*, prostaglandin E; *PAR-1*, protease-activated receptor 1; *PI3K*, phosphatidylinositol 3-kinase; *TP*, thromboxane receptor; *TXA2*, thromboxane A2. *(Reproduced with permission from Ferreiro JL, Angiolillo DM. New directions in antiplatelet therapy.* Circ Cardiovasc Interv. *2012;5:433–445. Copyright Wolters Kluwer Health.)*

TABLE 44.5 Antiplatelet Agents

Drug	*Target*	*Mechanism*	*Loading Dose*	*Time to Maximum IPA (%)*	*Maintenance Dose*	*Plasma Half-Life*	*Time to Platelet Recovery for Adequate Hemostasis on Drug Cessation*
Oral							
ASA	COX1	Irreversible inhibition	325 mg	30 min	80–325 mg/day	15–30 min	5–7 days
Clopidogrel	P2Y12 receptor	Irreversible binding	300–600 mg	6 h (37%)	75–150 mg/day	6–8 h	5 days
Prasugrel	P2Y12 receptor	Irreversible binding	60 mg	4 h (85%)	5–10 mg/day	7–9 h	5–7 days
Ticagrelor	P2Y12 receptor	Reversible binding	180 mg	2 h (88%)	90 mg BID	8 h	5 days
Vorapaxar	PAR-1	Reversible binding	40 mg	2 h (80%)	2.5 mg/day	4–13 days	>4 weeks
Intravenous							
Abciximab	GpIIb/IIIa receptor	Reversible binding	250 μg/kg	Immediate (80%)	125 μg/kg per min	10–15 min	12 h
Eptifibatide	GpIIb/IIIa receptor	Reversible binding	180 μg/kg	15 min (80%)	2 μg/kg per min	2½ h	4–8h
Tirofiban	GpIIb/IIIa receptor	Reversible binding	0.4 μg/kg	5 min (80%)	0.1–0.15 μg/kg per min	1½ –2 h	4–6h
Cangrelor	P2Y12 receptor	Reversible binding	30 μg/kg	<5 min (80%)	2 μg/kg per min	5 min	60–90 min

COX1, Cyclooxygenase 1; *GpIIb/IIIa*, glycoprotein IIb/IIIa; *IPA*, inhibition of platelet aggregation; *PAR-1*, protease-activated receptor.

serum half-life of 15 to 20 minutes.[205,206] Because the effects of ASA are irreversible, they last for the life of the platelet (approximately 7–10 days); thus, once-a-day dosing is sufficient to sustain platelet inhibition. Enteric coated preparations are associated with longer absorption time, reaching peak plasma levels 2 to 4 hours after ingestion.[207]

After a single dose of ASA, platelet production begins to recover. Approximately 10% of new platelets are released from the bone marrow each day, with full replacement of ASA-free platelets within 10 days after discontinuing the drug. Such platelets tend to exhibit a "rebound effect" characterized by an exaggerated response to procoagulant

stimuli.[208] This phenomenon has been demonstrated experimentally and may in fact increase thrombotic risk in certain populations. Moreover, it is not necessary to wait for full platelet turnover, because normal hemostasis can be seen with as little as 20% of platelets maintaining normal COX1 activity.[209] Many subjects have 80% normalized platelet function after 72 hours from their last ASA dose.[210]

When compared to other platelet antagonists, ASA is comparatively weak, because it has no effects on other receptor-mediated pathways triggered by adenosine diphosphate (ADP), thrombin, or collagen. Nevertheless, its benefits in risk reduction against myocardial infarction in patients with established coronary artery disease are undeniable.[211] Currently, the strongest indications for chronic ASA include secondary prevention of coronary artery disease and post-PCI patients. The latter is the cornerstone for DAPT and for lifelong monotherapy in most patients, unless contraindicated.

Adenosine Receptor Antagonists

Currently available drugs for clinical use are the thienopyridines clopidogrel and prasugrel and the nucleoside analogue ticagrelor. All three share a common mechanism of action (binding to the P2Y12 platelet receptor), yet there is major pharmacokinetic variability among them[212] (Fig. 44.8). These differences translate into significant clinical differences regarding efficacy and bleeding risk.

Clopidogrel

Clopidogrel is a second-generation thienopyridine (the first-generation thienopyridine ticlopidine is no longer used because of toxicity concerns). Ingested clopidogrel acts as a prodrug whose active thiol metabolite binds permanently to the P2Y12 platelet receptor, thus preventing ADP-mediated activation of the GpIIb/IIIa complex.[213] Platelets blocked by clopidogrel remain so for the remainder of their 7- to 10-day life span.

Following a loading dose of 300 to 600 mg, the time to maximum inhibition of platelet aggregation (IPA) (37% inhibition) is 6 hours.[214] The parent compound is absorbed in the intestine, after which it is carried to the liver where 85% is hydrolyzed to an inactive metabolite by liver esterases. The other 15% must undergo a two-step enzymatic process via the actions of several isoenzymes of cytochrome P450. First it is converted to 2-oxoclopidogrel (predominantly by the action of CYP2C19), and then to the active thiol metabolite (mainly by the actions of CYP3A4 and CYP2C19).[215] Elimination of the parent drug is in 6 hours and of the active metabolite about 30 minutes. Approximately 50% of the drug is eliminated in urine and 45% in feces.

Disadvantages of clopidogrel include the many possible interactions, which can interfere with the drug's antiplatelet ability. Different genetic polymorphisms involved in clopidogrel biotransformation or the platelet receptor's response, and interactions with commonly prescribed drugs, yield a certain degree of unpredictability resulting in either an increased risk for thrombosis or bleeding.[215] Despite its inherent limitations and modest antiplatelet effects, clopidogrel is the P2Y12 receptor antagonist of choice in most patients because of its proven efficacy in many clinical studies.[216–218] It is considered the standard component with ASA as part of DAPT.

On discontinuation of clopidogrel, complete platelet recovery is expected within 7 days, but appreciable platelet aggregation is already noticed by 72 hours.[219] A phenomenon of platelet rebound has been described associated with an increased prothrombotic state. The cause is likely multifactorial and its clinical significance is unclear, but an increased risk for ischemic syndromes has been reported.[220]

Prasugrel

Prasugrel is a third-generation thienopyridine. Like clopidogrel, prasugrel must be biotransformed into an active metabolite to achieve its antiplatelet effect. The inhibition of the P2Y12 receptor is also irreversible and thus lasts for the life span of the platelet.

Prasugrel undergoes hydrolysis in the liver, and CYP elements assist in biotransformation to the active metabolite.[212] However, this drug is less subject to interference with other agents, and important genetic polymorphisms that seriously affect its metabolism are less frequent. The end result is a more predictable and potent antiplatelet effect. The time to maximum IPA (85% inhibition) achieved after a loading dose of 60 mg is approximately 4 hours.[221] The maintenance dose is 10 mg/day. To decrease bleeding risk, certain groups of patients, such as those older than 65 years and those weighing less than 60 kg, require reduced doses of 5 mg/day. Prasugrel is eliminated primarily by the kidneys. On discontinuation of the drug, platelets fully recover within 7 to 10 days, reflecting new platelet production.

The most common side effect is bleeding. This drug is contraindicated in patients with a history of transient ischemic attack or stroke or active bleeding. Although less common than with clopidogrel, poor platelet responsiveness has been described in some patients receiving maintenance doses of prasugrel.[221]

Several studies have shown the superiority of prasugrel over clopidogrel in reducing the incidence of LST and VLST; however, this improvement occurs at the expense of increased bleeding, which may necessitate discontinuation of the drug.[222–224]

Ticagrelor

This drug represents a nonthienopyridine class of ADP receptor antagonist.[225] Ticagrelor does not require conversion to an active metabolite to produce inhibition of platelet aggregation, although an active metabolite is also generated by the action of hepatic CYP3A4.[212] Ticagrelor acts by an allosteric reversible binding to the P2Y12 receptor. Its effects are more potent than those exerted by the thienopyridines. Because of its reversible interaction with the P2Y12 receptor, recovery of platelet function is likely with decreased serum concentrations of the drug or metabolites.

Following a 180-mg loading dose of ticagrelor, the time to maximum IPA (88% inhibition) is 2 hours, which may be maintained up to 8 hours.[226] The maintenance dose is 90 mg twice a day. Less than 10% IPA is seen 5 days following discontinuation of the drug. The main route of elimination is enteric with a lower percentage via the urine.

In clinical trials, ticagrelor has been shown to be superior to clopidogrel or prasugrel in the prevention of stent thrombosis, at the expense of a higher risk for bleeding.[227,228] This drug is contraindicated in patients with a history of active bleeding or intracranial hemorrhage. Patients may also experience dyspnea due to an apparent mild autoimmune response. When given in combination with ASA as part of DAPT, the dose of ASA should not exceed 100 mg; higher doses are associated with decreased effectiveness.[227] The mechanism of this blunted response is currently unknown.

Protease-Activated Receptor 1 Antagonists

The importance of thrombin in platelet aggregation via interaction with PARs has led to efforts to synthesize inhibitors in order to provide additional benefits over standard antiplatelet therapy. Although multiple compounds have been synthesized, only one, vorapaxar, has recently been approved for clinical use.

Vorapaxar is a synthetic 3-fenyl-pyridine structurally derived from himbacine (a natural alkaloid present in the bark of Australian magnolia).[229] Its mechanism of action is by high affinity yet reversible attachment to the PAR-1 platelet receptor. This action prevents granule procoagulant release and further platelet expression of fibrinogen receptors, without interfering with thrombin-induced fibrin formation.[230]

Unlike thienopyridines, vorapaxar does not require biotransformation into an active metabolite. A full inhibitor effect (>80% IPA) is reached following a loading dose of 40 mg.[231] When a maintenance dose of 2.5 mg is administered for several days, platelets are effectively inhibited for 4 weeks.

Vorapaxar is rapidly absorbed through the intestine and undergoes biotransformation by CYP3A4 mainly into an inactive metabolite. However, with prolonged dosing an active metabolite (M20) becomes relevant, representing up to 25% of the parent compound.[229] The drug

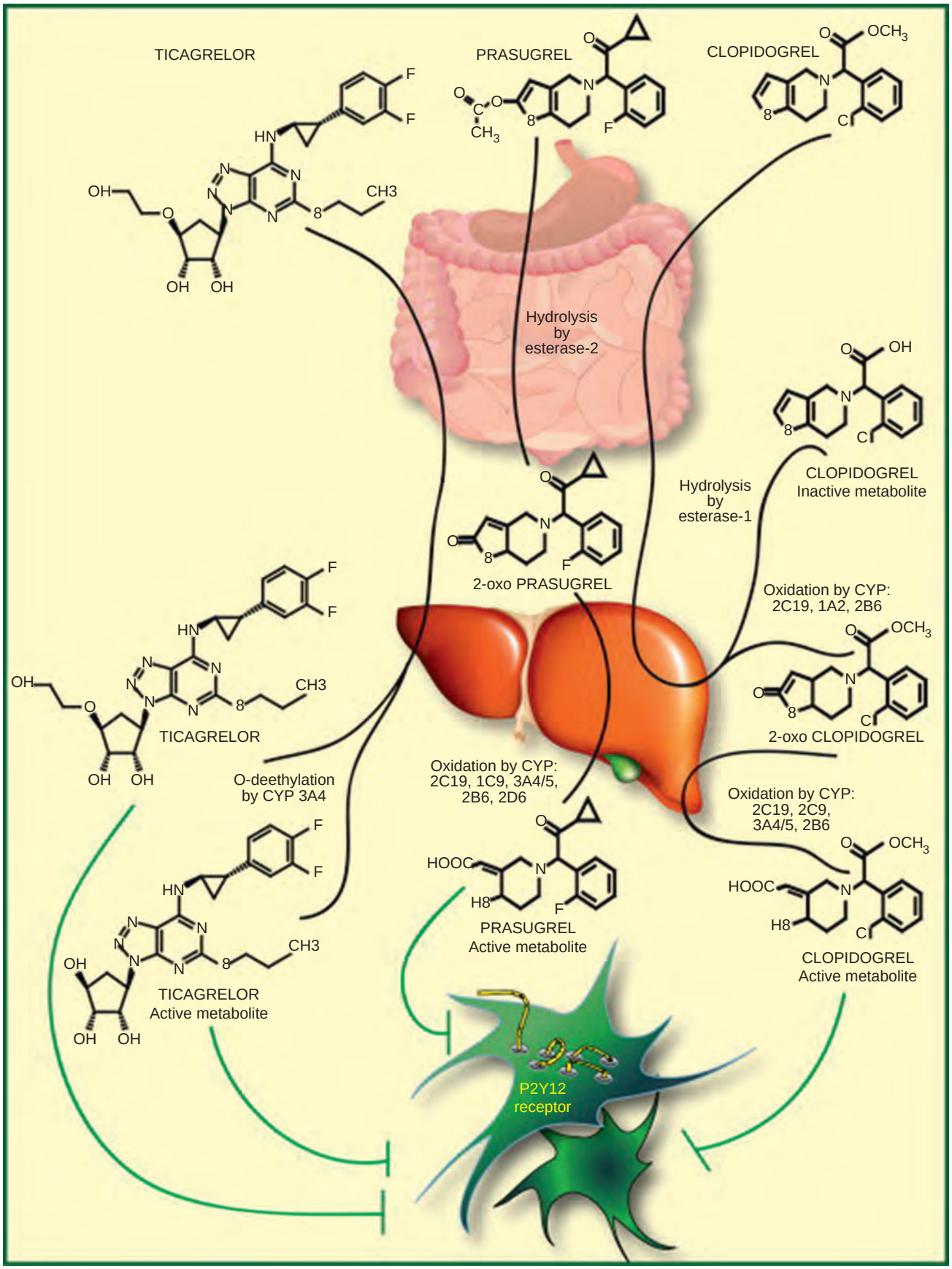


Fig. 44.8 Metabolic pathways of adenosine diphosphate receptor blockers. The actions of clopidogrel and prasugrel depend on hepatic biotransformation to an active metabolite, which binds irreversibly to the platelet P2Y12 receptor. In contrast, both ticagrelor and its active metabolite bind to the P2Y12 receptor in a reversible fashion. *CYP,* Cytochrome P450. *(Reproduced with permission from Siller-Matula JM, Trenk D, Schror K, et al. Response variability to P2Y12 receptor inhibitor: expectations and reality.* JACC Cardiovasc Interv. *2013;6:1111–1128. Copyright Elsevier.)*

is primarily eliminated as the inactive metabolite and has a plasma half-life of 5-13 days with no significant accumulation in the presence of kidney or liver disease. The concomitant administration of CYP3A4 inducers or inhibitors can exert significant influence on the antiplatelet effects of vorapaxar.[229]

When added to a preexisting regimen of aspirin and clopidogrel, vorapaxar reduces the risk of thrombotic events, albeit at the risk of significant bleeding (particularly intracerebral hemorrhage) in certain populations.[232] A recent analysis of patients after PCI and stenting showed that the net clinical outcome analysis favored the use of vorapaxar in patients with no history of stroke.[233]

Its long half-life may represent a challenge in management for patients undergoing NCS, because it may require discontinuing the drug several weeks prior to the procedure. Vorapaxar is currently approved for use during ACS and in patients with peripheral vascular disease but not as standard therapy for patients with coronary stents.

Intravenous Antiplatelet Agents

Glycoprotein IIb/IIIa Inhibitors

The GpIIb/IIIa integrin is the most abundant and only platelet-specific receptor found on the platelet surface. Fibrinogen is the main receptor's ligand, and its attachment constitutes the common pathway toward platelet aggregation. GpIIb/IIIa inhibitors bind to the receptor, thus impairing platelet-dependent thrombogenesis due to cross linkage between neighboring platelets.[234] Currently, three molecularly distinct agents are approved for clinical use as adjunctive therapy during PCI or ACS; these agents are abciximab, eptifibatide, and tirofiban.

Abciximab

Abciximab is a monoclonal Fab molecule that binds with high affinity to the GpIIb/IIIa receptor. When given as a bolus dose of 0.25 mg/kg or as a continuous infusion of 0.125 μg/kg per minute, maximum IPA (80% inhibition) is achieved almost immediately. The serum half-life of the drug is 10-15 minutes, but recovery of platelet function is not seen until 48 hours because of slow dissociation of the drug from platelets.[235] In the presence of ADP antagonists the effects can last up to 15 days after the drug is discontinued.[236] Because very little free drug is present in the blood, platelet inhibition can rapidly be reversed with platelet transfusion.

Eptifibatide

A cyclic peptide, eptifibatide produces selective inhibition. With a loading dose of 180 μg/kg and a continuous infusion of 2 μg/kg per minute, the time to maximum IPA (80% inhibition) is about 15 minutes. The serum half-life is approximately 2.5 hours and it undergoes renal elimination. Eptifibatide dissociates rapidly from platelets; thus free drug is likely to be present for several hours following its discontinuation.[237] Transfusion of platelets is unlikely to be helpful in reversing platelet inhibition, because free circulating drug will rapidly bind to the new platelets. Drug reversal in this case is achieved primarily by stopping the medication and may take several hours.

Tirofiban

Tirofiban is a small, nonpeptide antagonist that causes rapid (5 minutes) selective blockade of GpIIb/IIIa receptors. The usual loading dose is 0.4 μg/kg followed by a continuous infusion of 0.1 to 0.15 μg/kg per minute. The serum half-life is 1.5 to 2 hours, and the primary elimination route is by the kidney. Four hours after discontinuation, less than 20% platelet inhibition remains.[238] Tirofiban also dissociates rapidly from platelets, so the main approach for return of platelet function is stopping the drug.

Adenosine Diphosphate Antagonists

Cangrelor

This drug is an intravenous analogue of ticagrelor and produces selective and reversible inhibition of the P2Y12 receptor.[239] Its major advantage is its rapid onset and short duration of action, both of which are desirable properties during acute interventions. With a loading dose of 30 μg/kg followed by a steady state infusion of 2 to 4 μg/kg per minute, it produces 80% platelet inhibition within less than 5 minutes. On discontinuation, cangrelor is rapidly deactivated by serum ectonucleotidases, resulting in a serum half-life of 2 to 5 minutes. Complete platelet recovery occurs within 60 to 90 minutes.[240]

Cangrelor during PCI has not proven superior to oral interruption of chronic therapy. In cardiac surgical patients, a study showed a positive association between preoperative use of cangrelor and decreased postoperative chest tube drainage.[241] No studies have been performed in patients undergoing NCS, although its use is theoretically appealing for high-risk patients.

Long-Term Antiplatelet Management

Dual Antiplatelet Therapy

The majority of patients undergoing coronary stenting require DAPT to protect the stented vascular segment from stent thrombosis while vascular healing occurs. Evidence shows adverse outcomes, including stent thrombosis, when DAPT is discontinued during the period of time when incomplete endothelialization is likely. This period is longer with DESs than with BMSs.[165,166]

Unlike the incidence of restenosis, which peaks several months post-PCI, the long-term cumulative incidence of stent thrombosis seems to be similar whether BMSs or DESs are employed, as long as patients are treated with DAPT for the recommended duration of therapy[242–244] (Fig. 44.9). In addition, prolonged DAPT might also confer protection from atherothrombotic events occurring outside the stented segment. In general, DAPT for most patients refers to the combination of ASA and clopidogrel. With first-generation DESs, initial recommendations were for 3 months with sirolimus stents and 6 months with paclitaxel stents, respectively. In 2006, reports of stent thrombosis beyond 6 months after discontinuation of clopidogrel prompted the U.S. Food and Drug Administration (FDA) to reexamine the duration of antiplatelet therapy in patients with DESs. New guidelines were issued recommending 12 months of DAPT with reevaluation at the end of 1 year. Current recommendations are for ASA to be taken indefinitely after PCI regardless of stent type. For P2Y12 inhibitors, a minimum of 1 year is recommended for all patients after PCI to treat ACS. For non-ACS indications, patients with a BMS should receive DAPT at least for 1 month (minimum of 2 weeks with high bleeding risk) and ideally for 12 months. Patients with DESs must remain on DAPT for 1 year or even longer if tolerated.[245] If the risk of bleeding outweighs the benefit of the recommended duration of DAPT, it may be reasonable to discontinue the P2Y12 inhibitor before 12 months has passed.[245]

Newer stents with less prothrombotic tendencies prompted trials of short versus long-term DAPT with positive results, but these studies had limited statistical power.[246] A recent large randomized controlled trial added to the controversy by demonstrating that a prolonged period up to 30 months of DAPT with aspirin and clopidogrel was associated with decreased rates of stent thrombosis compared to 12 months of DAPT.[247] This advantage was seen regardless of the type of DES. A subsequent meta-analysis concluded that long DAPT (30 months) is associated with a lower risk of definite and probable stent thrombosis and myocardial infarction, when compared with short DAPT (12 months). This benefit, however, is tempered by a higher risk of bleeding and an apparent increase in noncardiac mortality.[248] In the absence of prolonged DAPT beyond 1 year, the stent thrombosis risk is lower with second-generation DESs.[249]

Certain groups that are more likely to benefit from prolonged DAPT include those with high-risk clinical factors for stent thrombosis and patients undergoing complex PCI. Most experts recommend clopidogrel as the initial drug in stable patients, with prasugrel and ticagrelor reserved for patients with ACS and patients deemed nonresponsive to clopidogrel.

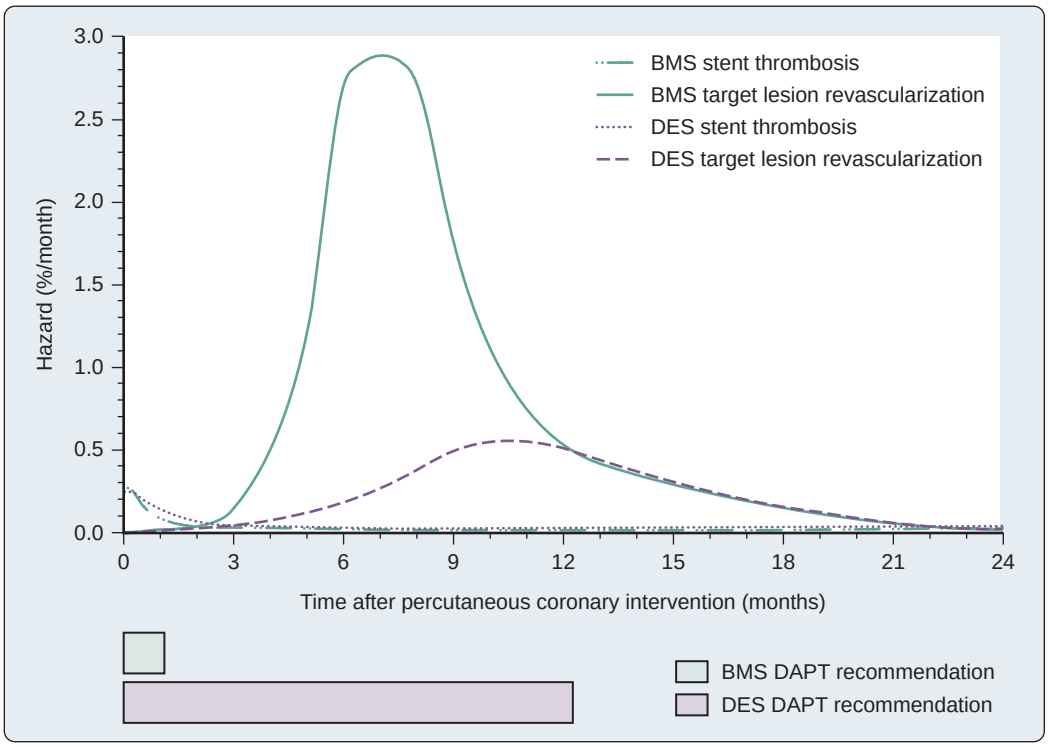


Fig. 44.9 Hazard of stent thrombosis and target lesion revascularization over time according to type of stent. *BMS,* Bare metal stent; *DAPT,* dual antiplatelet therapy; *DES,* drug-eluting stent. *(Reproduced with permission from Mathew A, Mauri L. Optimal timing of noncardiac surgery after stents.* Circulation. *2012;126:1322–1324. Copyright Wolters Kluwer Health.)*

Triple Antithrombotic Therapy

Current estimates are that 5% to 10% of patients undergoing coronary stent placement are or will require oral anticoagulant therapy.[250] The three most common indications are stroke prevention in patients with atrial fibrillation, prevention of recurrent deep venous thrombosis or pulmonary embolism, and mechanical heart valves. Management of these patients is extremely challenging and largely based on scarce evidence and expert opinion, with most experts preferring placement of BMSs.

Current recommendations are that for elective procedures in patients with low/intermediate risk of bleeding, triple antithrombotic therapy (DAPT plus oral anticoagulant) is recommended for 1 month if the patient is undergoing BMS implantation, followed by up to 12 months with a single antiplatelet agent plus the oral anticoagulant. For patients undergoing DES implantation, triple antithrombotic therapy is recommended for 3 to 6 months, followed by 12 months of anticoagulant therapy with either clopidogrel or ASA.[251] In general, oral anticoagulants plus one single antiplatelet agent with careful monitoring of international normalized ratio is preferable to DAPT. After 12 months in patients requiring lifetime oral anticoagulant therapy, low-dose ASA is preferred over an ADP antagonist.[249]

Variability in Patient Response to Antiplatelet Therapy

Optimal use of DAPT with ASA and clopidogrel does not ensure that the patient will not experience stent thrombosis. In a large study, 86% of cases of early or subacute stent thrombosis and 57% of patients with late stent thrombosis occurred while on DAPT.[252] Atherothrombotic events also have been described during NCS despite continued use of DAPT throughout the perioperative period.[253] In these patients it is likely that the presence of a high prothrombotic environment made it difficult for DAPT to be fully effective. Some patients, however, may also exhibit what has been termed *high on-treatment platelet reactivity* (HTPR),[254] due to variable efficacy of the antiplatelet drugs, leading to clinical treatment failure (Box 44.6). Evidence from numerous studies has emerged demonstrating a strong association between HTPR and post-PCI ischemic events such as stent thrombosis.[255–258] On the other hand, certain patients exhibit an exaggerated response to ADP antagonists (particularly prasugrel and ticagrelor) and are found to have low platelet reactivity (LPR).[259] These patients frequently exhibit bleeding complications (perhaps excessive surgical bleeding) with standard doses of platelet inhibitors.

BOX 44.6 CAUSES OF HIGH ON-TREATMENT PLATELET REACTIVITY

Noncompliance with antiplatelet agents
Drug interactions (NSAIDs, PPIs)
Pharmacokinetic variants (eg, CYP2C19)
Platelet receptor and enzyme polymorphisms
Clinical conditions:
- Diabetes mellitus
- Obesity
- Congestive heart failure
- Chronic kidney dysfunction
- Old age
- Chronic smoking
- Cocaine use

NSAIDs, Nonsteroidal antiinflammatory drugs; *PPIs,* proton pump inhibitors.

Response to Aspirin

Variability in the response to ASA, in cases in which thrombotic events occur despite the use of the drug, has been known for many years.[260,261]

In the past, the term was labeled *ASA resistance*. When defined by clinical events, the incidence of ASA resistance has been estimated to be approximately 13%,[262] but when based on laboratory tests it ranges between 5.5% and 60%, depending on the assay used.[263] A strict definition of *resistance* consists of the inability of ASA to inhibit platelet COX1, thus preventing TXA2 production measured directly by laboratory methods. *Nonresponsive* or *treatment failures* are more accurate terms used to refer to these patients. Evidence from real-world experience has demonstrated that the most common cause of nonresponsiveness to ASA is poor patient compliance.[264] Consequently, when compliance is ensured, the occurrence of this phenomenon is significantly reduced.

In patients known to be compliant, several reasons can explain why they might be at risk for stent thrombosis. The presence of multiple pathways for platelet aggregation independent of COX1-induced TXA2 production (eg, ADP and PAR activation) can override the effects of ASA despite effective inhibition of COX1, particularly in a prothrombotic environment such as surgery. In addition, many chronic clinical conditions are associated with HTPR independent of ASA therapy (see Box 44.6). Mechanisms include endothelial dysfunction, accelerated platelet turnover, F2 isoprostanoid production, and non-COX1 pathways of TXA2 production.[265–267]

While on ASA, failure to inhibit COX1 function can be due to either pharmacokinetic or pharmacodynamic factors. Pharmacokinetic elements limit drug bioavailability due to poor absorption of the drug as with enteric preparations,[268] increased inactivation by gastrointestinal esterases by proton pump inhibitors (PPIs),[269] increased volume of distribution (eg, obesity), or interaction with other COX1 inhibitors such as ibuprofen and other nonsteroidal antiinflammatory drugs (NSAIDs), which compete with ASA for the COX1 binding site.[270,271] Pharmacodynamic resistance is related to genetic polymorphisms of COX1, which decrease the inhibitory response to ASA.[272]

The first steps in management of a patient with apparent nonresponse to aspirin are to address issues of compliance, avoid PPIs if possible, and delay the intake of NSAIDs. In addition, better control of comorbidities, weight loss, and cessation of smoking decrease platelet activity.[273] Use of nonenteric preparations and a higher dose of ASA may increase effectiveness in some patients (eg, those who are obese or have chronic inflammation), whereas twice-a-day dosing may prove more efficacious in conditions of high platelet turnover such as in patients with diabetes.[274] Lastly, the addition of another antiplatelet agent may be indicated.

Response to Adenosine Antagonists

Between 25% and 50% of individuals taking clopidogrel exhibit HTPR.[273] A reduced response to these drugs has a strong association with ischemic events, thus confirming the importance of ADP-induced platelet aggregation as the best marker for prediction of stent thrombosis in these patients.[212]

When issues of noncompliance are excluded, poor response to these agents is more often due to abnormal absorption, biotransformation, or interaction with other drugs.[274] This issue occurs more commonly with clopidogrel, since multiple variants of polymorphisms associated with the generation of the active metabolite have been identified.[274,275]

As with ASA, clinical factors such as diabetes, obesity, renal failure, age, hyperlipidemia, heart failure, and ACS can trigger platelet reactivity independent of the ADP pathway. Additionally, variable generation of clopidogrel's active metabolite can be due to genetic variants of the intestinal transport mechanism for clopidogrel coded in the *ABCB1* gene, which may result in decreased absorption of the parent compound.[276] Of the different isoenzymes of cytochrome P450 involved in the hepatic metabolism of clopidogrel, CYP2C19 is most important because it is involved in both transformative steps. Several genetic polymorphisms of CYP2C19 have been identified; the two most frequent variants associated with decreased function are CYP2C19*2 and CYP2C19*3.[275,277] Approximately 15% of Caucasians and up to 30% of Asians are carriers of at least one of these alleles.[212] The variant CYP2C19*17 is associated with increased enzyme function and greater response to clopidogrel, which may increase the risk of bleeding.[278,279] Because identification of these polymorphisms can predict clopidogrel responsiveness, two current commercial assays for CYP2C19 genotype are available as point-of-care devices. The Spartan RX system uses a buccal swab and produces results in 1 hour. The Verigene system detects more CYP2C19 variants; it uses blood sampling, and results are obtained in 3 hours.[212]

Interaction with certain drugs also plays an important role in clopidogrel's metabolism, which can either enhance or compete as substrates for CYP activity. Statins and PPIs are two commonly prescribed agents that have been shown to decrease the activity of clopidogrel. With statins, the clinical significance is unclear, with no specific evidence demonstrated against a particular statin.[280] In the case of PPIs, reduced antiplatelet effects and increased ischemic events have been suggested, particularly with omeprazole and esomeprazole[281]; however, the only prospective trial showed no difference in cardiovascular outcomes.[282] Nevertheless, the FDA labeling for clopidogrel includes a black box warning to avoid these two PPIs, opting instead for the use of pantoprazole because it has minimal effects on CYP2C19. Of interest, cigarette smokers exhibit a mildly exaggerated antiplatelet response due to enhanced activity of CYP1A2, which also participates in clopidogrel's metabolism.[283] Similarly, CYP3A4 inducers such as St John's Wort or rifampin may result in LPR as a result of much greater availability of the active compound.

Management of patients exhibiting thrombotic events while on clopidogrel usually consists of switching to a more potent drug such as prasugrel or ticagrelor. Some clinicians test for HTPR and decide on treatment accordingly. Hyporesponsiveness in the absence of ACS may sometimes be reversed by removing adverse drug interactions or increasing the maintenance dose of clopidogrel, although this approach seems to be effective in only some patients. Prasugrel also must undergo metabolic activation; however, polymorphisms of ABCB1 and CYPC19 do not seem to affect the antiplatelet response.[212] In addition, the risk of interactions with statins and PPIs is minimized. Some patients will exhibit HTPR to prasugrel, possibly because of multiple clinical risk factors or platelet receptor polymorphisms rather than abnormal pharmacokinetics. A recent meta-analysis comparing HTPR between the three available P2Y12 inhibitors, demonstrated the lowest platelet reactivity with standard maintenance doses of ticagrelor, followed by prasugrel, with clopidogrel being the least effective at either standard or high maintenance doses.[284]

Platelet Function Tests

Because response to antiplatelet drugs varies from one patient to another, platelet function tests represent an attractive strategy to optimize antiplatelet therapy. A host of platelet function tests of varying specificity and sensitivity are available, each with its own advantages and disadvantages[285–288] (Table 44.6).

Light transmission aggregometry is considered the gold standard to measure platelet aggregation. This technique measures changes in light transmission as a result of GpIIb/IIIa receptor–dependent (final common pathway) platelet aggregation in response to a specific agonist. Based on this test, the degree of change or in baseline platelet function/responsiveness has been categorized into various degrees: nonresponsiveness is defined as less than 10% change in platelet aggregation; hyporesponsiveness reflects a change between 10% and 30%; and responsiveness is when a more than 30% difference is seen. The routine use of light transmission aggregometry in real-world experience is impractical because it is not available as a point-of-care test. Additional disadvantages are that blood needs to be separated from plasma, the test is time consuming, and a high sample volume is required.

Platelet function tests more commonly used to evaluate antiplatelet agents during clinical trials of coronary stents include (1) the VerifyNow system, (2) thromboelastography with platelet mapping, (3) Multiplate analyzer, and (4) vasodilator-stimulated protein phosphorylation.[289]

TABLE 44.6 Tests to Measure Platelet Function in Patients

Test	*Measurement*	*Advantages*	*Disadvantages*
Light transmission aggregometry	Platelet aggregation	Gold standard	Needs plasma, time consuming, high sample volume
Impedance aggregometry	Platelet aggregation	Measures smaller platelet aggregates than with light transmission	Time consuming, high sample volume
VerifyNow	Platelet aggregation	Point of care	Limited hematocrit and platelet count range
Plateletworks	Platelet aggregation	Minimal sample prep	Not enough experience
TEG Platelet Mapping system	Platelet contribution to clot strength	Clot information	Limited studies
Impact cone and plate analyzer	Shear-induced platelet adhesion	Point of care	Not widely used
PFA-100	High shear blood cessation by platelet plug	Point of care	Depends on hematocrit, von Willebrand factor Lack of correlation with thienopyridines
VASP	Platelet P2Y12 receptor activation signaling	Specific for ADP antagonists	Requires flow cytometer and experienced technician
Serum thromboxane B2	Activation-dependent release from platelets	Relates to ASA inhibition of COX1	Indirect measure, not platelet specific
Urinary 11-dehydro-thromboxane B2	Urinary metabolite of thromboxane B2	Relates to ASA inhibition of COX1	Indirect measure, not platelet specific

ADP, Adenosine diphosphate; *ASA,* acetylsalicylic acid; *COX1,* cyclooxygenase 1; *TEG,* thromboelastography; *VASP,* vasodilator-stimulated phosphoprotein.
Modified with permission from Michelson AD. Methods for the measurement of platelet function. *Am J Cardiol.* 2009;103(suppl 2):20A–26A. Copyright Elsevier.

1. VerifyNow (Accumetrics, San Diego, Calif). This point-of-care device is based on GpIIb/IIIa receptor–dependent platelet aggregation, augmented by the presence of fibrinogen-coated beads. It requires only a small sample of anticoagulated whole blood and it can be performed rapidly. Results are expressed as platelet reactive units (PRUs). ASA response is measured with the use of a cartridge containing AA, whereas an ADP cartridge is used to test the effects of ADP antagonists. Values greater than 550 PRUs with ASA and greater than 208 PRUs with P2Y12 inhibitors are considered diagnostic of HTPR. A response of less than 85 PRUs with ADP suggest LPR.

2. Thromboelastography (TEG) analyzer with platelet mapping system (Haemoscope, Niles, Ill). Updated to a more platelet-specific test in the form of the thromboelastographic platelet mapping system, this test has been used to evaluate the effects of antiplatelet therapy and it requires whole blood. A particular advantage is that it measures platelet function and also the platelet contribution to clot strength. Its disadvantages are that it is not a true point-of-care instrument and experience with it is limited. Within a thromboelastographic trace the maximum amplitude reflects platelet function. HTPR to ADP antagonists is said to occur if the MA ADP is greater than 47 mm and LPR is less than 30 mm.

3. Multiplate analyzer (Roche Diagnostics, Manheim, Germany). This is a point-of-care method that measures GpIIb/IIIa integrin–dependent platelet aggregation by changes in electrical impedance, as platelets attach to electrodes in plates containing different agonists (collagen, AA, ADP). The increase in impedance is measured by arbitrary aggregation units (AUs) plotted against time; a value of more than 46 AUs is associated with HTPR and less than 19 AUs with LPR.

4. Phosphorylation of vasodilator-stimulated phosphoprotein (VASP-P; BioCytex, Marseille, France). This test uses prostaglandin E, which binds to its platelet membrane receptor, thus triggering the production of cyclic AMP (cAMP) by activation of adenylyl cyclase, which, through protein kinase A, converts VASP to phosphorylated VASP (VASP-P). Binding of ADP to the P2Y12 receptor inhibits adenylyl cyclase, decreasing intracellular cAMP, thus preventing the formation of VASP-P. In the presence of a P2Y12 receptor inhibitor, the level of VASP-P will increase as measured by whole blood flow cytometry. Results are expressed in terms of platelet reactivity index (PRI). The platelet reactivity cutoff of more than 50% implies HTPR and lower than 16% suggests LPR. The principal advantage of this test is that it is the most sensitive assay for P2Y12 receptor signaling. The disadvantages include the number of steps involved and requirements for flow cytometry equipment and experienced technicians.

BOX 44.7 CUTOFF VALUES OF HIGH AND LOW PLATELET REACTIVITY WITH COMMONLY USED PLATELET FUNCTION TESTS

VerifyNow: ASA > 550 PRUs; P2Y12 inhibitors > 208 PRUs or < 85 PRUs
TEG: MA > 47 mm or < 30 mm
Multiplate analyzer: >46 AUs or <19 AUs
VASP-P: >50% PRI or <16% PRI

ASA, Acetylsalicylic acid; *AUs,* aggregation units; *MA,* maximum amplitude; *PRI,* platelet reactivity index; *PRUs,* platelet reactivity units; *TEG,* thromboelastography; *VASP-P,* vasodilator-stimulated phosphoprotein phosphorylation.

Use of Platelet Function Tests

Current recommendations are against the routine use of platelet function tests in post-PCI patients, as a result of prospective randomized trials showing the lack of benefit of personalized therapy based on results of platelet function.[290–292] Similarly, the routine use of genetic testing for CYP2C19 variants discovered up to now is not recommended, because it explains only a small part of the pharmacodynamic effect of clopidogrel.[292] However, a large number of observational studies have demonstrated that HTPR during clopidogrel treatment represents a strong and independent risk factor for stent thrombosis.[293–297] Platelet function tests may be considered in selective patients thought to exhibit HTPR (such as patients with insulin-dependent diabetes mellitus or prior stent thrombosis), thus allowing a switch to more potent agents like prasugrel or ticagrelor.

Another potential advantage of platelet function tests is the capability to tailor antiplatelet management in the perioperative period, thereby reducing preoperative waiting time, compared to recommended guidelines.[298] Although currently no studies evaluating such an approach in NCS are available, a few small studies have shown that testing for platelet reactivity before coronary artery surgery led to improved times to surgery and less postoperative transfusion.[299,300] Platelet function tests are currently endorsed for selected patients by the Society of Thoracic and Cardiovascular Surgeons.[301]

Studies using receiver operating characteristic (ROC) analysis to define a threshold or cutoff value largely depend on the patients studied (Box 44.7). Reported indicators of HTPR have a very negative

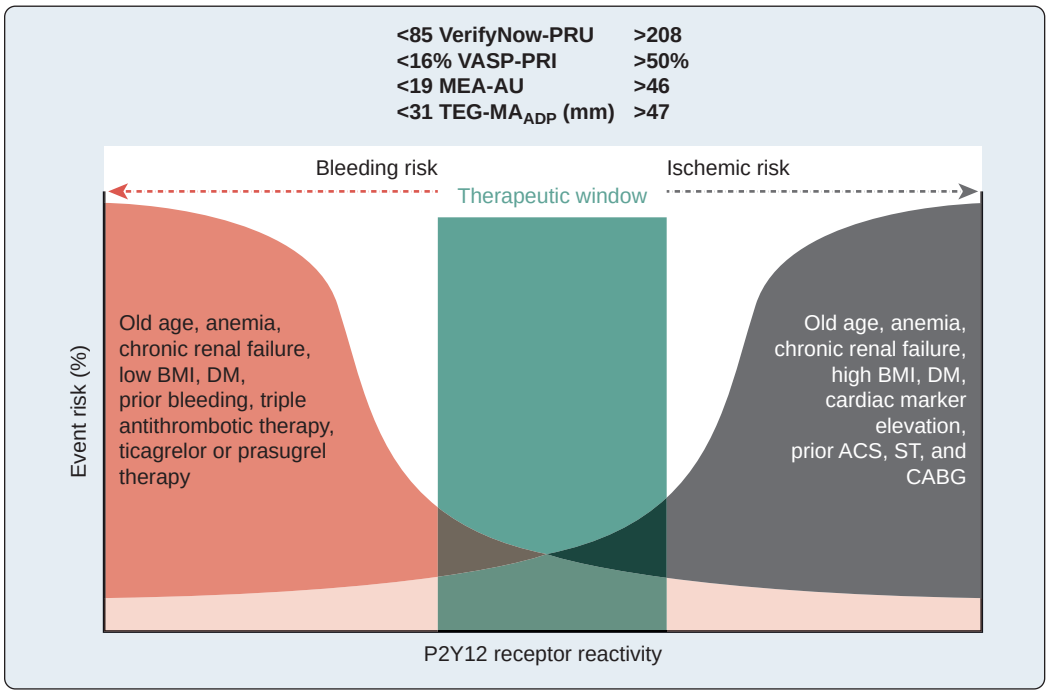


Fig. 44.10 Evidence for P2Y12 receptor reactivity associated with either post-PCI ischemic *(gray)* and bleeding *(red)* events. Cutoff values from platelet function tests showing associations with either ischemic or bleeding events. Although yet untested, the concept of a therapeutic window for optimal on-treatment platelet reactivity to prevent either bleeding or thrombotic events is suggested. *ACS,* Acute coronary syndromes; *AU,* aggregation units; *BMI,* body mass index; *CABG,* coronary artery bypass grafting; *DM,* diabetes mellitus; *MA,* maximum amplitude; *MEA,* Multiplate analyzer; *PRI,* platelet reactivity index; *PRU,* P2Y12 reaction units; *ST,* stent thrombosis; *TEG,* thromboelastography; *VASP,* vasodilator-stimulated phosphoprotein (phosphorylation). *(Reproduced with permission from Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemic and bleeding.* J Am Coll Cardiol. *2013;62:2261–2273. Copyright Elsevier.)*

predictive value for thrombotic events, yet their positive predicted value is low.[289] This observation is consistent with the fact that HTPR, although an important determinant, is not the sole factor responsible for thrombotic events. Moreover, current evidence suggests that there may be a ceiling effect in decreasing the incidence of stent thrombosis, whereas the risk of bleeding may be heightened.[302,303] Thus, the focus has shifted to finding strategies that can avoid excessive bleeding while maintaining the benefit of reduced ischemic thrombotic events. Accordingly, a model of a therapeutic window of platelet reactivity has been suggested in which an optimal balance between the risk of bleeding and stent thrombosis is achieved. This approach, in theory, should help to design better antiplatelet therapy[289] (Fig. 44.10).

Noncardiac Surgery and Coronary Stents

Surgery as a Prothrombotic State

One of the major challenges in the care of patients with coronary stents is caring for those undergoing NCS. It is well recognized that surgery constitutes a risk factor for myocardial ischemic events, including stent thrombosis, which may be triggered by the physiologic response to surgical stress.[304–307] Enhanced sympathetic response increases catecholamines, cortisol, and renin, leading to increased myocardial stress and heightened platelet activation.[308] These increases are accompanied by concomitant increases in procoagulant factors (fibrinogen and plasminogen activator inhibitor), with simultaneous inhibition of fibrinolysis.[309–311] Thus, the cumulative result is a prothrombotic, proinflammatory, and catabolic state, the magnitude of which correlates with the severity of surgical trauma and preexisting inflammatory state.

BOX 44.8 MAJOR ADVERSE CARDIAC EVENTS

Perioperative myocardial ischemia or infarction
Ischemia-related acute heart failure
Target vessel revascularization
Stent thrombosis (uncommon)
Death

The risk for thrombosis in the presence of a foreign body such as a stent is enhanced, particularly in the setting of incomplete endothelial strut coverage. However, it is important to recognize that perioperative myocardial ischemic syndromes other than stent thrombosis can also occur as a result of stent restenosis or progression of native disease elsewhere in the coronary circulation.[312] In fact, the frequency of documented perioperative stent thrombosis in published series is low, with most researchers reporting major adverse cardiac events (MACEs) as a composite outcome[313–315] (Box 44.8). Consequences of perioperative stent thrombosis, however, can be devastating because it is associated with a 50% to 70% incidence of STEMI and up to 40% mortality.[316,317] Additionally, performing a PCI in the perioperative period is particularly challenging because of the added risk of major bleeding from the use of antithrombotic agents.

Limitations of Current Guidelines and Physician Knowledge

There is general agreement that elective PCI and stent placement should not be performed as a preoperative revascularization strategy aiming at risk reduction prior to NCS.[12,13] This concept is largely reinforced by the results of two trials in which preoperative revascularization was ineffective when performed for the sole purpose of reducing perioperative cardiac events.[318,319]

Nevertheless, a recent report from a large administrative database showed that approximately 4% of elective PCIs were performed with the explicit purpose of reducing perioperative NCS risk, despite evidence to the contrary and against published guidelines.[320] Not surprisingly, the incidence of MACE was higher in those undergoing NCS when compared to those who had PCI for other reasons. Thus, despite being performed infrequently, preoperative elective PCI is still viewed by some providers as a beneficial strategy in selected patients, when in fact it does not improve perioperative risk, and at a minimum it may delay the operative procedure.

In selected high-risk surgical patients, preoperative revascularization may be indicated based on preoperative risk assessment (eg, left main or proximal LAD lesion). In this circumstance, the decision to perform PCI versus myocardial revascularization must be reached after considering the risk/benefit ratio of the cardiac procedure and the risk associated with the planned surgery.

For patients with preexisting coronary stents, several societies[12–14] have guidelines available to assist providers with decision making, but the guidelines focus primarily on timing of elective surgery and management of antiplatelet agents according to stent type. Because all of the guidelines are based on poor quality evidence and expert opinion, the recommendations vary. This situation is highlighted by a recent review of 11 clinical practice guidelines in which different recommendations were issued.[5] Moreover, such recommendations address primarily the first 12 months after PCI. Very little guidance is provided beyond 12 months, although the risk of VLST and MACE is well described up to several years after PCI.[153,321]

The recently updated guidelines from the American Heart Association (AHA) and European Society of Cardiology/ European Society of Anaesthesiology (ESC/ESA),[12,13] although an improvement over their predecessors, are limited by the lack of incorporation of specific clinical risk factors for stent thrombosis (eg, diabetes, chronic renal failure, PCI during ACS) and a standard classification of surgical hemorrhagic risk. Instead, they provide a broad statement encouraging practitioners to gauge the risk of thrombosis versus bleeding. In addition, they offer very little assistance on the management of antiplatelet therapy when surgery cannot be deferred, or on reinstitution of DAPT in patients who discontinued it preoperatively.

Despite their limitations, there is evidence of a reduction of perioperative MACEs when NCS is delayed according to guideline recommendations, mainly in DES patients.[322] Yet, variable success has been encountered when translated to local practice among individuals, in particular with the management of antiplatelet agents. The reasons are likely multifactorial, such as lack of guideline awareness, disagreement with the recommendations, emphasis on long-standing practice, and personal bias.[323,324] Among specialists, surveys have demonstrated a high degree of agreement in following guideline recommendations among most cardiologists[325] and between cardiologists and anesthesiologists when compared to surgeons.[326] This observation can be explained largely by the fact that cardiologists and anesthesiologists are mainly concerned with ischemic and thrombotic phenomena, whereas surgeons are concerned primarily with hemorrhagic risk, having little to no experience with coronary thrombosis. Within the surgical specialties, vascular surgeons are more likely to follow current guidelines than are nonvascular surgeons.[327]

Minimizing perioperative risk requires the incorporation of several patient and surgical-related factors in decision making, besides the well-described importance of timing of PCI and a particular antiplatelet regimen. Although specific angiographic and procedural data may not be available, the presence of recognized clinical risk factors (eg, diabetes, chronic heart failure, obesity, chronic kidney disease, ACS, prior stent thrombosis) can be identified. Additional data such as stent type, number and coronary location of the stents, and clinical indication for stent placement can be obtained for many patients. Although the individual risk associated with each factor is unknown, it is reasonable to believe that perioperative risk of stent thrombosis and MACE will be related to the number of risk factors in each individual patient, with some (eg, previous stent thrombosis) having perhaps greater predictive value than others (Box 44.9). Similarly, although evidence for surgery-specific thrombotic risk is not widely available, it is reasonable to expect more complex surgeries to carry a higher risk of stent thrombosis and perioperative MACE than more superficial procedures.[328]

Once an estimation of perioperative risk is made, the main decisions for elective NCS are timing of the surgery and perioperative management of antiplatelet therapy. Additional considerations include the anesthetic technique, perioperative surveillance for myocardial ischemia, and whether to perform the procedure in a facility without on-site PCI capability[329] (Box 44.10). For urgent or emergent procedures which cannot be delayed, attention should be focused primarily on the management of antihemostatic agents, minimizing the severity of bleeding, and close perioperative surveillance for ischemic/thrombotic events.

BOX 44.9 INFORMATION USUALLY AVAILABLE DURING PREOPERATIVE EVALUATION

Clinical
Diabetes
Heart failure
Kidney dysfunction
Prior myocardial infarction
Prior stent thrombosis
Cocaine use
Cigarette smoking
Type and duration of antiplatelet therapy

PCI Data
Stent type
Number of stents
Date(s) and clinical indications for PCI
Anatomic location of the stent(s)

PCI, Percutaneous coronary intervention.

BOX 44.10 KEY DECISION POINTS FOR NONCARDIAC SURGERY

Timing of surgery
Perioperative management of antiplatelet therapy
Impact on anesthetic techniques
Perioperative surveillance
Surgical venue with access to PCI capabilities

PCI, Percutaneous coronary intervention.

Timing of Surgery

This refers to the period between coronary stent placement and occurrence of the surgical procedure. For elective cases the correct timing of surgery is strongly dependent on the clinical indication for antiplatelet therapy.[330] The main concern is primarily the risk for stent thrombosis due to the presence of HTPR after PCI and the time course for endothelial stent coverage.

Cardiologists encountering candidates for elective PCI who are also scheduled for subsequent surgery have several alternatives. They first must consider whether to delay coronary stent placement and to manage the patient medically until after the surgical procedure takes place. In certain patients this option might not be possible (patients with severe ischemia, ACS, high-risk lesions, or high-risk NCS). They traditionally will follow a particular path if a future surgery date is known. For example, if surgery is required within 2 to 4 weeks, more often a balloon angioplasty will be recommended, because it is relatively safe.[331] If surgery is contemplated beyond 6 weeks, placement of a BMS will be entertained, reserving a DES for those patients who will require surgery after 12 months. This approach, however, has been called into question because many patients, particularly those with several risk factors for restenosis, will benefit from placement of a DES. Furthermore, second- and third-generation DESs have a greater safety profile against LST than do first-generation DESs, challenging the current paradigm of automatically placing a BMS in patients known to require surgery less than 12 months after PCI.[332–334]

More commonly, patients present for previously unplanned surgery following PCI and stent placement. Evidence from multiple observational studies demonstrates that NCS during the first 6 weeks after coronary stenting constitutes the highest risk period for stent thrombosis and MACE, regardless of stent type and whether antiplatelet therapy is continued.[335–340] Thus, unanimous agreement exists to withhold elective surgery during this period. Nonelective surgery must be performed at an institution with on-site PCI capability, while maintaining DAPT or bridging therapy with intravenous platelet inhibitors and aggressively monitoring for thrombotic events.

It is important to emphasize that NCS after this waiting period is predominantly based on patients undergoing elective noncomplex PCI and does not necessarily extend to patients with PCI for ACS. Indeed, retrospective data show the risk for perioperative MACEs for this population to be highest within 3 months following PCI.[341] For high-risk ACS patients, as well as for those undergoing complex PCI, it is reasonable to withhold elective surgery for 12 months, if possible. Other patients who may require increased waiting times include individuals with poorly controlled clinical risk factors or those shown to exhibit HTPR.

BMSs have traditionally been touted as safer than DESs for patients requiring surgery within 1 year after PCI. Because endothelial stent coverage in most patients appears to be complete within weeks and the incidence of restenosis peaks between 4 to 12 months, some experts have advocated a safe window in which surgery should ideally be performed between 6 weeks post–elective PCI and before restenosis becomes likely.[244] Current guidelines recommend that NCS can be performed 4 to 6 weeks or more after BMS implantation. Recent studies, however, have shown that the risk of perioperative MACE with BMS is similar to or even greater than DES,[332,342] with clinical factors such as a cardiac risk index score higher than 2, emergency surgery, and myocardial infarction 6 months preceding NCS having a greater predictive value than stent type.[343] These observations can be partially explained by selection bias—with sicker patients or those identified as having future NCS undergoing BMS placement in accordance with current practice—and widespread use of safer newer generation DES. Thus, the higher rates of MACEs with BMS are more likely explained by the individual patient's underlying disease rather than the influence of stent type on the surgical procedure.

In patients with DESs, the risk for perioperative MACEs, although lower after the first 6 to 8 weeks after PCI, remains elevated between 6 weeks and 6 months, particularly in high-risk patients undergoing complex procedures.[344] Thereafter, the risk of stent thrombosis seems to stabilize beyond 12 months, with very little difference between BMSs or any DES.[345,346] Current recommendations are to wait 12 months before elective NCS, with a minimum of 6 months if the risk of delaying surgery is higher than the potential risk of ischemic or thrombotic events. Although recent evidence suggests minimal incremental risk of NCS after 6 months,[6] further studies are needed, particularly with newer generation stents, in patients with complex PCI and other risk factors for stent thrombosis [347] (Box 44.11).

BOX 44.11 MINIMAL WAITING TIME AND DURATION OF DUAL ANTIPLATELET THERAPY BEFORE ELECTIVE NONCARDIAC SURGERY

BMS (elective PCI): >6 weeks
BMS (PCI for ACS): >12 weeks
DES: >6 months

ACS, Acute coronary syndrome; *BMS*, bare metal stent; *DES*, drug-eluting stent; *PCI*, percutaneous coronary intervention.

For time-sensitive NCS an attempt should be made to defer the procedure for at least 6 months whenever possible. If such delay is impossible, every effort should be made to maintain DAPT, fully recognizing that the increase of bleeding may also lead to increased cardiac complications. Additionally, most studies address primarily major- or intermediate-risk surgery with very little information for patients undergoing low-risk procedures.[348] Current available data suggest that performing ambulatory low-risk procedures 4 to 6 weeks or more after patients have been implanted with a BMS and more than 3 to 6 months after patients have undergone DES implantation may be relatively safe.[348,349]

Management of Antiplatelet Therapy

Perioperative management of antiplatelet therapy during NCS is one of the most important and controversial issues in patients who have coronary stent. For patients taking DAPT, a surgical or interventional procedure is considered the most common reason for temporary cessation of DAPT, thereby increasing the risk for perioperative MACEs.[350,351] Alternatively, continuation of DAPT increases the perioperative risk and severity of bleeding, thus leading to additional complications including increased risk for cardiac events.[253]

Most controversies and guideline recommendations on perioperative DAPT have been centered primarily on the first 12 months following PCI, while being conspicuously absent beyond this time frame. As a result, many surgeons and interventional physicians indiscriminately withhold DAPT after 12 months even for low bleeding risk procedures. New evidence, however, shows additional benefits of 30 months of DAPT against ischemic or thrombotic syndromes in DES patients.[247,352] This protection seems to extend to native coronaries, as well, and may require a reexamination of DAPT management in selected subjects undergoing NCS beyond 1 year.

Current guidelines provide a broad framework to guide clinicians in relation to the time of surgery. Thus, a minimum of 4 to 6 weeks of DAPT is required for BMS patients and 6 months (ideally 12 months) for patients with DESs, with continuation of ASA monotherapy in most cases, unless contraindicated by the hemorrhagic risk.[12] It is important to emphasize that most published studies are based on patients taking ASA and clopidogrel; very little evidence is available on NCS patients taking newer and more potent antiplatelet agents.

In the absence of well-designed randomized trials assessing the risk/benefit ratio of perioperative DAPT, most decisions should be based on the balance between thrombotic and hemorrhagic risks associated with each patient and surgical procedure[353] (Fig. 44.11). Thrombotic risk is related to several procedural and clinical factors as well as the time from PCI to surgery, stent type, and degree of surgical trauma[146–148,345] (Table 44.7). Hemorrhagic risk is based on the type of surgical intervention (Table 44.8), plus the patient's inherent bleeding tendencies from additional comorbidities. It is important to recognize the lack of standard definition of surgery-specific degree of hemorrhage, with most classifications based largely on expert consensus.[353] More recently, the Academic Research Consortium has proposed a

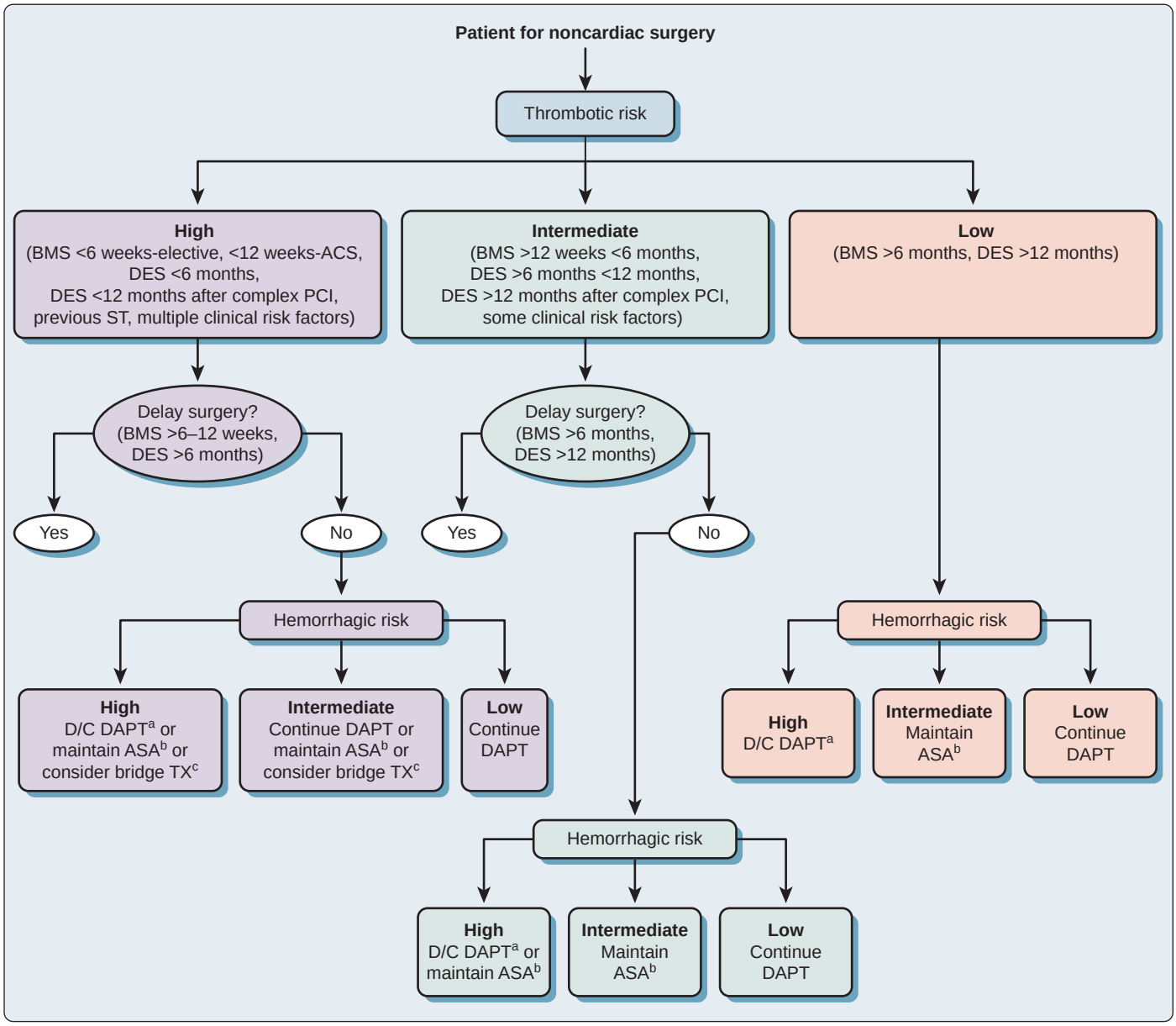


Fig. 44.11 Algorithm for management of patients with coronary stents and noncardiac surgery. Clinical and angiographic risk factors (complex percutaneous coronary intervention [PCI]) are shown in Table 44.4 Surgery-specific hemorrhagic risk is shown in Table 44.8.[a] Discontinue both antiplatelet agents preoperatively: clopidogrel and ticagrelor 5 days before surgery, ASA and prasugrel 7 days before surgery.[b]Discontinue only adenosine antagonist.[c]Discontinue DAPT followed by continuous infusion of tirofiban, eptifibatide, or cangrelor.*ASA,* Acetylsalicylic acid; *BMS,* bare metal stent; *DAPT,* dual antiplatelet therapy; *D/C,* discontinue; *DES,* drug-eluting stent; TX, therapy. *(Based on references 12, 37, 353, 381–383.)*

standardized grading system for patients on DAPT and those with post-PCI bleeding[354] (Table 44.9). Although not originally designed for NCS patients, this scoring method may prove useful in evaluating perioperative bleeding with platelet inhibitors.

Interruption of Antiplatelet Therapy

Interruption of DAPT (particularly both drugs) is associated with an increased risk of perioperative stent thrombosis and other myocardial ischemic syndromes for several reasons. First, in many patients, stent struts might not be completely covered with endothelium. This property has been demonstrated to be much more frequent with first-generation DESs and those that incorporate a durable polymer that can cause a localized chronic inflammatory vessel response. Second, abrupt interruption of either ASA or a thienopyridine may be associated with a rebound phenomenon in which newer platelets generated by the bone marrow exhibit increased activation and aggregation to thrombotic stimuli. Multiple clinical studies have demonstrated unequivocally a peak in ischemic and/or thrombotic phenomena on abrupt discontinuation of either ASA or clopidogrel.[355–360] Whether this is due to platelet rebound or simply loss of the protective effect from antiplatelet therapy is unclear.[361,362] Third, some patients exhibit variable degrees of chronic HTPR that may become fully expressed when DAPT is discontinued and may suffer from thrombotic events in stented areas or native atherosclerotic vessels.

Whereas there is unanimous agreement against interrupting oral DAPT in the first 6 weeks after PCI, studies evaluating the impact

TABLE 44.7 Perioperative Thrombotic Risk

High risk	BMS <6 weeks after elective PCI or <12 weeks after PCI for ACS DES <6 months or <12 months after complex PCI <2 weeks after balloon angioplasty Multiple clinical risk factors for stent thrombosis Left main or proximal LAD stent Previous stent thrombosis
Intermediate risk	BMS >6 weeks <6 months DES >6 months <12 months DES >12 months with complex PCI Some clinical risk factors (except prior stent thrombosis)
Low risk	BMS >6 months DES >12 months Few clinical risk factors

ACS, Acute coronary syndrome; *BMS,* bare metal stent; *DES,* drug-eluting stent; LAD, left anterior descending (coronary artery); *PCI,* percutaneous intervention.

TABLE 44.8 Hemorrhagic Risk

Surgery Related	*Types of Procedures*
Low risk: minimal morbidity/mortality risk from bleeding; transfusion from procedure is not likely	Minor plastic, orthopedic, general, gynecologic Ear, nose, and throat (ENT) procedures, endovascular aortic repair, limb amputations Closed reductions of facial fractures Flexible cystoscopy/ureteroscopy Cataract surgery and intravitreal injections Tooth extractions, endodontic therapy Gastrointestinal endoscopy and biopsy, polypectomy (<1 cm) Endoscopic retrograde cholangio-pancreatography stent without sphincterotomy
Intermediate risk: moderate morbidity/mortality risk from bleeding; perioperative transfusion is likely	Intrathoracic (lobectomy, mediastinoscopy), intraabdominal, hemorrhoidectomy, obesity surgery, major orthopedic, urology, ENT, reconstructive surgery, gastrointestinal polypectomy (>1 cm), esophageal dilatation, percutaneous endoscopic gastrostomy, variceal sclerotherapy, vitrectomy, trabeculectomy, ventriculoperitoneal shunt, multilevel spinal laminectomy
High risk: major risk of morbidity/mortality due to substantial blood loss (acutely or protracted); high likelihood of major transfusion or surgical reintervention.	Open thoracic or thoracoabdominal aortic surgery Esophagectomy, hepatic resection, transurethral resection of the prostate, transurethral resection of bladder tumor, percutaneous lithotripsy, major femoral fractures, radical or debulking pelvic tumor surgery, multiple traumatic injuries, extensive burns, major spine surgery
High risk: bleeding into an enclosed space	Intracranial surgery, spinal canal surgery

TABLE 44.9 Bleeding Definition According to Academic Research Consortium

Type 0	No bleeding
Type 1	Non actionable; patient does not seek studies, hospitalization, or treatment
Type 2	Overt sign of hemorrhage requiring nonsurgical intervention or hospitalization or increased level of care
Type 3a Type 3b	Overt bleeding with a 3–5 g/dL decrease in hemoglobin or requiring transfusion
Type 3c	Overt bleeding with >5 g/dL decrease in hemoglobin or requiring surgical intervention or vasoactive drugs Intracranial hemorrhage, intraocular bleeding compromising vision
Type 4	CABG-related bleeding
Type 5	Fatal bleeding

CABG, Coronary artery bypass graft.
Modified from Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736–2747.

TABLE 44.10 Preoperative Interruption and Resumption of Antiplatelet Therapy

Agent	*Stop Before Surgery*	*Resume After Surgery*[a]	*Dose*
Oral			
ASA	7 days	24 h	80–160 mg daily
Clopidogrel	5 days	24 h	Load with 300–600 mg followed by 75 mg/day
Prasugrel	7 days	24 h	Load with 60 mg, then 10 mg/day
Ticagrelor	5 days	24 h	Load with 180 mg, followed by 90 mg bid
Intravenous			
Tirofiban	4–8 h	4–6 h	0.1–0.15 μg/kg per min
Eptifibatide	4–6 h	4–6 h	2.0 μg/kg per min
Cangrelor	60–90 min	4–6 h	0.75 μg/kg per min

[a]Absent clinically significant bleeding. Intravenous agents can be discontinued on reinstitution of oral dual antiplatelet therapy. Oral agents can be administered by nasogastric tube if patients have not resumed oral intake.

of preoperative discontinuation of DAPT between 6 weeks and 12 months show inconsistent results. Some show a high incidence of MACE, whereas others suggest that temporary suspension of DAPT under medical supervision is safe.[172,363,364] At this time, the optimal period to perform NCS if surgical bleeding risk requires discontinuing DAPT is unknown. This is not surprising, because every patient's thrombotic and hemorrhagic risk is different. Because wide variability to antiplatelet therapy exists, future use of platelet function tests may prove advantageous by providing a tailored approach to DAPT before surgery, potentially minimizing bleeding and thrombotic risk.[365]

For most patients, discontinuing DPAT means interruption of the adenosine antagonist while maintaining perioperative ASA, because most elective and interventional procedures can safely be performed in patients receiving ASA.[366] Certain operations (eg, certain types of neurosurgery, urologic procedures, complex gastrointestinal endoscopy, or surgeries within an enclosed space) may require withholding both agents because even minimal bleeding might cause significant complications. Discontinuation of DAPT (ADP antagonist) a week before surgery is necessary if a regional anesthetic or neuraxial technique is planned per current guidelines,[367] but maintenance of ASA alone is generally considered safe. Selected patients probably can undergo peripheral nerve blocks while on clopidogrel, but published experience is limited.[368,369]

If one or both antiplatelet agents are discontinued, it is recommended that clopidogrel and ticagrelor be stopped 5 days before surgery, whereas prasugrel and ASA should be stopped seven days before surgery.[370] Limited evidence shows that when an ischemic or thrombotic event occurs after DAPT is interrupted, it most commonly occurs 1 to 30 days after surgery as a result of persistence of a prothrombotic state.[371] Thus, it is imperative that DAPT be resumed as soon as possible, preferably within the first 24 hours. Reinstitution of the P2Y12 inhibitor requires a loading dose, whereas ASA can be restarted with a normal maintenance dose (Table 44.10).

Continuation of Antiplatelet Therapy and Risk of Hemorrhage

In NCS, perioperative DAPT increases the likelihood of surgical blood loss requiring transfusion or reintervention by as much as 50%.[372] Published reports give conflicting results, suggesting that the risk for major bleeding may be rather surgery specific.[373] For example, a large registry of patients undergoing vascular surgery showed no difference in bleeding complications based on the antiplatelet regimen,[373] whereas in patients undergoing elective joint replacement or Mohs procedures, major bleeding complications were significantly higher.[374,375] In general, there is agreement that DAPT should be continued in patients undergoing procedures that have a low risk of bleeding. Nevertheless, it is

important to recognize that most of the published evidence addresses patients on DAPT with clopidogrel, with very little information available regarding prasugrel or ticagrelor.

The use of ASA monotherapy is also associated with increased surgical blood loss, although less than with DAPT.[376,377] Previous studies, including a meta-analysis of 50,000 patients, showed more bleeding with ASA and no differences in outcome except in transurethral prostatectomy and intracranial surgery.[378] A recent large randomized trial in NCS demonstrated a greater number of major bleeding events without reduction in thrombotic or ischemic events.[379] In this study, only a minority (<5%) of patients had coronary stents, so the results may not be representative of this patient population. Current recommendations support continuing ASA, with decisions primarily centered on management of the P2Y12 inhibitor, unless the hemorrhagic risk far exceeds the thrombotic risk.

Several management algorithms have been published.[380–383] with the most comprehensive document put forth by combined Italian medical societies.[354] These algorithms are based primarily on expert consensus. Ultimately, treatment recommendations should center on the careful individual evaluation of each patient's ischemic and thrombotic risk.

Bridging Therapy

This approach is reserved for selected patients who have a high thrombotic profile undergoing a procedure associated with high hemorrhagic risk, in whom DAPT must be suspended and surgery cannot be delayed. Antiplatelet agents are preferred, because therapy is aimed at prevention of a platelet-rich thrombus.[384] Although heparin has been advocated as a bridging agent, it is less than optimal because its beneficial effects on platelets are minimal or may even induce a prothrombotic effect.[385]

Current agents available for bridging therapy are the short acting GpIIb/IIIa inhibitors tirofiban and eptifibatide and the P2Y12 antagonist cangrelor. This therapy calls for discontinuation of the P2Y12 inhibitor 5 to 7 days before the surgical procedure. Patients are then admitted to the hospital and started on a continuous intravenous infusion (without a bolus) of either tirofiban or eptifibatide until 4 to 6 hours (tirofiban) or 4 to 8 hours (eptifibatide) before the planned procedure.[386] The infusion is restarted postoperatively until oral DAPT can be reinstituted. The drug cangrelor represents an attractive alternative. Because of its very short half-life, an infusion of 0.75 μg/kg per minute can be continued until shortly before surgery. However, the use of cangrelor as a potential bridging agent has only been tested on patients undergoing cardiac surgery, with no published experience in NCS. Although bridging therapy is relatively safe, stent thrombosis can still occur and there is an increased risk of bleeding.[387] Furthermore, it is associated with increased hospitalization and costs.

Patients Undergoing Ambulatory Surgery

Patients with coronary stents undergoing ambulatory surgery raise the issue of safety in locations without an on-site cardiac catheterization laboratory. Although few data exist, current literature suggests that the incidence of MACEs is very low, although the risk of stent thrombosis is still present. Some cardiologists have advocated that all surgical procedures be performed in facilities with immediate access to PCI capabilities.[388] Such recommendations are impractical and economically burdensome because of the large number of patients undergoing ambulatory procedures. Currently, no official position has been promulgated by the various professional societies, with most decisions driven by local and individual practice. A satellite center without PCI capabilities may be appropriate for patients who have undergone elective PCI, lack significant risk factors for stent thrombosis, and have exceeded the minimal duration of DAPT, who undergo procedures that do not require interruption of any antiplatelet therapy (eg, low bleeding risk endoscopic intervention).[389] More importantly, it is essential that practitioners establish protocols for treatment of STEMI and expeditious referral (less than 90 minutes) to a PCI center for immediate revascularization in the event of an ACS.

An Integrated Approach

When treating NCS patients with coronary stents, clinicians face a potentially complex clinical conundrum that offers many challenges in efforts to find the optimal balance between thrombotic/ischemic and bleeding risk. This problem is compounded because interventional cardiology is undergoing rapid advances in stent technology and availability of newer antiplatelet drugs. This explosion of innovations frequently finds its way into clinical use, and many patients receive new devices and drugs with which most perioperative physicians are relatively unfamiliar.

Inevitably a significant percentage of individuals will require a surgical or interventional procedure, thus placing practitioners at a disadvantage, because published evidence frequently lags behind clinical use. Current recommendations contained in expert reviews and society guidelines rely in large part on studies that frequently involve outdated or obsolete devices (eg, Cypher stents), forcing clinicians to extrapolate from the nonsurgical population. Moreover, techniques with significant potential for use in NCS (eg, platelet function tests) remain unexplored. The complexities of this issue highlight the importance of a multidisciplinary and regimented approach that is incorporated into an evidence-based comprehensive framework addressing surgery specific risks, PCI and clinical risk factors, the pharmacologic profile of various antiplatelet agents, and the surgical venue. Only in this manner can the care of these patients be truly optimized.

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45

Ventricular Assist Devices, Cardiac Transplants, and Implanted Electrical Devices in Noncardiac Surgery

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KEY POINTS

1. Modern left ventricular assist devices (LVADs) are increasingly used for long-term support. They feature a small footprint, durability, and pulsatile flow.
2. Right ventricular failure, infection, and bleeding (especially from the gastrointestinal tract) are complications in patients with LVADs that can be life-threatening.
3. Anticoagulation modulation, monitoring strategy, and hemodynamic management are key features of anesthesia care for patients with LVADs.
4. Advances in surgical techniques and immunosuppression have increased the longevity of cardiac transplant recipients.
5. The transplanted heart undergoes various degrees of reinnervation after a period of denervation. Responses to pressors and inotropes can be unpredictable, and the transplanted heart requires a higher preload for optimal function.
6. Rejection (primarily within the first year) and coronary allograft vasculopathy (ie, form of coronary occlusion in the graft) are complications that must be excluded because the presentation can be nonspecific and the consequences can be lethal.
7. Immunosuppression can have widespread side effects on various organ systems that can affect safe delivery of anesthesia.
8. Active rate modulation in cardiac implantable electrical devices (CIEDs) may result in heart rate alterations intraoperatively related to changes such as hyperventilation.
9. ST-segment elevation of 5 mm or more in leads without QRS concordance may be a sign of myocardial ischemia in patients who are ventricularly paced.
10. The potential for electromagnetic interference with CIEDs is markedly reduced with reduction in the burst of cautery to less than 5 seconds and when the distance from the electrocautery current to the CIED generator or leads is greater than 6 inches.
11. External defibrillator pads should be placed perpendicular to the major axis of the CIED (eg, anterior to posterior) to minimize current through the device or leads.
12. The use of a magnet or programming to an asynchronous mode in a pacemaker with a ventricular lead can result in an R-on-T phenomenon and significant ventricular arrhythmias.

With an almost 1% incidence among patients older than 65 years of age, heart failure (HF) continues to plague the population. The rising incidence is posing a growing burden on health care systems as life expectancy increases and the elderly form a larger portion of society. The total cost of caring for these patients was approximately $40 billion in 2010, and it has continued to increase.

Despite significant improvements in management, the 5-year mortality rate remains a staggering 40% to 50% for people with HF between 65 and 74 years of age.[1] Although surgical cure in the form of transplantation is effective, with a 1-year survival rate greater than 90%, it is not without limitations. Shortage of transplant organs, age restrictions (usually <65 years), and restrictive comorbidities mandate the need for other therapies.[2]

Although left ventricular assist devices (LVADs) were originally developed for temporary cardiovascular support, they are now used for increasingly longer periods. The REMATCH trial ushered in a new era for long-term mechanical circulatory support with improved 1-year survival rates with ventricular assist devices (VADs) compared with medical therapy alone for patients with advanced HF.[3] Almost 9000 VADs have been implanted since 2006, and the number continues to increase (see Chapter 28). With good survival rates reported after Heartmate II LVAD implantation, it is reasonable to assume that anesthesiologists will increasingly encounter patients with these devices who are undergoing noncardiac surgery.[4] General surgical problems occur in almost one-third of patients with VADs, and these patients often undergo elective surgery.[5]

The expanding indications for LVADs also extend to organ donation.[6] LVADs are used to support patients with severe HF as a bridge to transplantation or as destination therapy. The first-generation VADs were designed to replicate pulsatile flow and consequently were large. Their design made them susceptible to wear and tear, and the need for a large pumping chamber precluded implantation within the body. Second-generation devices abandoned pulsatile flow for continuous flow in favor of a smaller footprint and the ability to be implanted in the thoracic or preperitoneal space. The second-generation devices improved survival, reduced complications, and improved quality of life.[7] The latest VADs, including some in development, use novel technologies such as magnetic levitation and are designed for long-term use (Box 45.1).[2]

Ventricular Assist Devices

A few devices are available for long-term therapy, and the most commonly used is the HeartMate II (Thoratec Corporation, Pleasanton, CA) (Fig. 45.1). Thoratec reports that more than 20,000 of these units have been implanted, and many have been in for many years. It is a second-generation device with an axial flow pump that draws blood in through an inlet cannula placed into the left ventricle and ejects blood into the aorta through an outlet cannula. A power driveline connects the unit with the external power source and exits the body in the right upper quadrant of the abdomen.

BOX 45.1 LEFT VENTRICULAR ASSIST DEVICES

- Transplantable hearts are in short supply.
- Heart failure continues to increase.
- Left ventricular assist device (LVAD) technology continues to expand and is used as a bridge to transplantation or as destination therapy.
- Patients with LVADs have more noncardiac surgery than other groups.
- A coordinated team approach is recommended for patient care.

Fig. 45.1 The Thoratec HeartMate II. The device is intrathoracic, with a driveline that attaches to an external module. *(Courtesy Thoratec, Inc., Pleasanton, CA.)*

The speed of the pump in rotations per minute (rpm) is adjustable, with a range of 6000 to 15,000 rpm. The display panel on the control unit shows speed (in rpm), power (in watts), calculated flow (in L/min), and pulsatility or pulse index (PI). The PI (average range, 4–6) is a reflection of the left ventricular (LV) contribution to flow, resulting in changes to flow coinciding with the cardiac cycle. It varies inversely with the contribution of the LVAD to the cardiac output (CO); the higher the PI, the more the left ventricle is working. Parameters influencing the PI are shown in Table 45.1. Pump power (average range, 5.6–8 W) indicates the power needed to drive the VAD. Pump flow (average range, 4.7–6.5 L/min) is a calculated output derived from the other parameters such as power and speed, and it is prone to inaccuracies, necessitating other measures of CO.[8,9] The patients are anticoagulated only mildly (aspirin, 81 mg/day, and warfarin to an international normalized ratio [INR] of 1.5–2.5) because of the relatively low risk of thrombosis and embolism with the newer devices (Box 45.2).[10,11]

Complications of Ventricular Assist Devices

The postimplantation period can be subdivided into early (<30 days after placement) and late (>30 days) periods, and the types of complications can be correspondingly divided. The major complications of

BOX 45.2 LEFT VENTRICULAR ASSIST DEVICE PATIENTS

- Pulsatility of the arterial pressure is proportional to the native heart work and inversely proportional to the flow from the left ventricular assist device (LVAD).
- Flow becomes less pulsatile as the LVAD takes over.
- Some pulsatility is desired because it is physiologic.

TABLE 45.1 Cardiovascular Parameters and Pump Output Effects on Arterial Pulsatility

Cardiovascular Parameter	*Pulsatility Index*[a]
Preload	Increases with increasing preload
Contractility	Increases with increasing contractility
Pump Output	Decreases with increasing pump output

[a]The pulsatility index is equal to the difference between the peak systolic velocity and the minimum diastolic velocity divided by the mean velocity during the cardiac cycle. The value decreases with distance from the heart.

TABLE 45.2 Postdischarge Complications of Left Ventricular Assist Devices

Left Ventricular Assist Device Complication	*Incidence (%)*
Infection	22–50
Arrhythmias	20–30
Gastrointestinal bleeding	14–31
Other bleeding	11
Thromboembolism	6
Pump thrombosis	2–9
Neurologic events	10–20
Right ventricular failure	2–3
Renal failure	2–7
Device failure	Rare
Hemolysis	0–2

LVAD placement are coagulation disorders (both bleeding and thrombosis), right ventricular failure, and infection (Table 45.2).

Infection

Infection is a complication of hardware implanted anywhere, and VADs are no exception. The REMATCH trial reported an infection rate of 53.7% per patient-year in 2001. The continuous-flow devices have a lower rate of infectious complications (11–36%).[12] In a prospective study of 150 patients, 22% had an infection, with a median time to infection after implantation of 68 days. The driveline was most commonly affected, and depressed and elevated creatinine levels emerged as risk factors.[13] Driveline infections negatively affect outcome,[14] and bloodstream infections increase stroke risk.[15] The infections are notoriously difficult to eradicate and can be a cause of sepsis in the perioperative period.

Bleeding

Bleeding is a concern for all implanted LVADs, and many mechanisms have been postulated and tested to define this process.[16] Reduction in the effects from the VAD–blood component interaction (ie, hemocompatibility augmentation) has been a goal of VAD design from the start. Acquired von Willebrand factor deficiency, platelet activation and damage from shear stress and trauma, heparin-induced thrombocytopenia (HIT), and microparticle shedding from cell surfaces contribute to abnormalities in coagulation.[17] The continuous-flow LVADs require

anticoagulation, mostly with aspirin and warfarin, further increasing the risk of bleeding.

In one trial, more than one-half of the patients studied required a transfusion, and many needed reoperation for bleeding.[18] Between 17% and 40% of patients with VADs have gastrointestinal bleeding that is thought to be related to angiodysplasias, and some patients require endoscopic treatment.[19,20] Increased incidence of sensitization, emergence of antibodies, right ventricular (RV) dysfunction from pulmonary hypertension (PH) over time, and infections are complications possibly related to bleeding that affect noncardiac surgery in this patient population.[17]

Thrombosis

Despite lower thromboembolic risks with the newer continuous-flow devices, there still exists the possibility of catastrophic device thrombosis and embolism. Pump thrombosis manifests as poor output with high pump power, hemolysis, and HF. The rate of pump thrombosis is between 1% and 4%.[20–22] Aortic root thrombosis, embolic cerebrovascular accidents, and thrombotic events related to HIT occur and must be carefully monitored for in the perioperative period because surgery can result in a prothrombotic state, precipitating any or all of these events.[17]

Right Ventricular Failure

Development of right ventricular failure (RVF) after LVAD implantation can negate all of the benefit derived from the device because it puts the patient back in HF. Although some degree of RVF accompanies all cases of left-sided failure, a small subset of patients manifests RVF after LVAD implantation that requires inotropic support or a right-sided VAD (RVAD). The reported incidence of RVF is between 10% and 50%.[22–24]

Development of RVF correlates with increased intensive care unit (ICU) stay, mortality rates, and end-organ failure resulting in significant burdens for the patient and the health care delivery system.[25,26] Low RV output, female gender, high central venous pressure and pulmonary vascular disease can predict development of postimplantation RVF. After LVAD implantation, alteration of LV-RV relationships resulting from changes in LV geometry in conjunction with increased RV preload are largely responsible for RVF.[27–29]

Prevention of RVF after LVAD implantation is possible and useful. It involves maintenance of sinus rhythm, optimization of volume and nutritional status, normocarbia, and judicious reduction in RV afterload.[27] Clinicians must be vigilant to promptly diagnose and treat RVF in the perioperative period because of its high incidence, the multiorgan effects, and the limited therapeutic options available.

Noncardiac Surgery in Patients With Left Ventricular Assist Devices

During the early postimplantation period, noncardiac surgical procedures related to bleeding or infection and airway operations such as tracheostomy may be performed. As the duration after the implantation increases, the pathology becomes more varied. The median times to noncardiac surgery after LVAD implantation range between 285 and 500 days, underscoring the longevity of the devices.[30–32]

An LVAD team model consisting of surgeons, anesthesiologists, perfusionists, nurses, and engineers has been suggested to care for these complex patients.[33] It forms a resource for information and support for management in centers caring for patients with VADs. Because patients may be admitted to centers not involved in prior care or without such a team, anesthesiologists must be prepared to care for them with little background information.

Physiologic Changes After Left Ventricular Assist Device Placement

The restoration of systemic CO with an LVAD has profound effects on end-organ perfusion, especially the kidneys and the liver, as assessed by normalizing serum levels of creatinine, bilirubin, liver enzymes, and other markers. Improvements in organ function are sustained for months to years.[7,34] VAD use seems not to significantly affect cerebral autoregulation, although this is based only on a small, preliminary trial.[35]

LVAD implantation results in pressure and volume unloading of the left ventricle. This reduces LV size, with some improvement in function at a global level as measured by improved ejection fraction (EF) and at a microscopic level as evidenced by a reduction in myocyte size, collagen content, and myocyte tumor necrosis factor-α level.[36] There are reductions in circulating levels of catecholamines and neuroendocrine hormones that reflect improved hemodynamics.[37] QRS shortening seen on the electrocardiogram (ECG) can contribute to improvement in function, likely related to better synchronization of depolarization.[38]

The optimal duration and intensity of LV unloading is unknown. Previous work suggests that prolonged unloading can restore the EF to pre-LVAD values,[36] although with loss of contractile function[39] and expression of fetal genes in the heart.[40] This suggests that an optimal amount of load and strain is essential for normal cardiac function; Unloading the heart completely provides optimal functional restoration for only a short period, after which cardiac function does not improve further and may deteriorate.

HF results in downregulation of β-adrenergic receptors in response to an adrenergic overload. This results in reduced responsiveness to exogenously administered β- and α-adrenergic agonists to patients with advanced HF. LVAD implantation can restore β-adrenergic receptor density and reverse the downregulation.[41–43]

Calcium and its release from the sarcoplasmic reticulum is an integral part of myocyte contraction. After LVAD implantation, cardiac myocytes tend to have more sarcoplasmic calcium, faster calcium release into the cell, and shorter action potential duration, with biochemical and electrical profiles similar to those of nonfailing hearts.[44–47] Regression of stress-induced proteins, reduction in apoptosis, DNA degradation, and autophagy is seen after LVAD implantation.[48–50] Why some patients recover better cardiac function than others is being studied.[51]

Whereas most patients getting an LVAD are in biventricular failure, with up to one-third manifesting some degree of RV failure after LVAD implantation, only about 10% require RV support.[52–54] Unloading of the left ventricle results in an RV afterload reduction, and improvements in diastolic ventricular interdependence favoring the right ventricle.[55–57] However, the degree of macroscopic and microscopic improvement in the left ventricle cannot be replicated to the same degree in the right ventricle.[58] This means that the right ventricle remains susceptible to ischemia, injury, and failure after LVAD implantation and needs careful handling during anesthesia to maintain flow to the LVAD (Box 45.3).

Preoperative Evaluation

In addition to the evaluation of end-organ dysfunction, medications, and functional status of the patient, certain aspects of preoperative preparation of patients with LVADs deserve attention. This starts with clear and effective communication among the team members regarding timing, urgency, and procedural aspects of surgery. Clear discussion about the procedure can help to avoid damage to the driveline or the device in thoracic and abdominal procedures.

Another aspect of the preoperative discussion is assessment of electromagnetic interference (EMI) during the procedure, particularly

BOX 45.3 RIGHT VENTRICULAR FAILURE WITH A LEFT VENTRICULAR ASSIST DEVICE

- Right ventricular (RV) failure is always a risk with left ventricular assist device (LVAD) support.
- LVAD output increases the preload to the right heart.
- Susceptibility to RV failure and ischemia must always be considered.

with regard to defibrillation and electrocautery.[59] Most of the newer continuous-flow VADs have extensive electrical shielding and are minimally affected by electrocautery.[33] Older devices, however, may produce erratic output. Care should be taken with the placement of the return pad to avoid the path of electricity crossing the device. Defibrillation can similarly disrupt VAD electronics, leading to malfunction, and manufacturer's recommendations should be followed. This information should be available before the start of surgery so an appropriate plan can be instituted if there is interference related to the cautery or emergency defibrillation is required.

Anticoagulation management of patients can be challenging and needs to start early. The LVAD team needs to decide on an individual basis whether it requires hospital admission and inpatient care. For elective surgery, lowering of INR (ie, goal of 1.5) using warfarin adjustment and aspirin discontinuation may be all that is required for patients with a low risk of bleeding and low risk of thrombosis. However, higher surgical bleeding risk may require warfarin discontinuation in conjunction with heparin, depending on the risk of thrombosis. The risk of thrombosis with a VAD increases significantly with risk factors such as mechanical valves, deep venous thromboses, or other hypercoagulable states, including surgical stress.[30]

Reversal of anticoagulation may be considered for emergent cases. This requires a fine balance between the goals of reducing perioperative bleeding and avoidance of thromboembolic events. Fresh frozen plasma, vitamin K, and blood products must be used judiciously and often in consultation with a hematologist and guided by point-of-care testing such as a thromboelastogram.[31] It is often wise to avoid complete reversal or overcorrection of the coagulopathy.

Many investigators have analyzed the need for blood and product transfusion for patients with LVADs undergoing noncardiac surgery and found wide variation in the reported percentage of patients receiving transfusion (0–100%).[31,59–61] Most of these patients are likely to have required blood product transfusions because of prior cardiac surgery and ongoing anticoagulation. The possibility of allosensitization and presence of antibodies should be considered when arranging for the availability of blood products.

The infectious risk is substantial and carries significant outcome implications. These patients are considered at high risk for infectious endocarditis due to prosthetic cardiac material implantation.[62] In the absence of clear guidelines for this unique subpopulation, the investigators recommend using broad-spectrum antibiotics alone or in combination and consideration of the usual flora that cause infections such as staphylococci and gram-negative bacteria.[13] The addition of antifungals should be individualized and depends on risk. Strict aseptic technique during procedures is imperative.

During surgery, the VAD must be plugged into a power source, even for brief cases.[9,63,64] The battery life on the portable power packs is in the range of a few hours, but using the base power console is recommended. The console usually has a display screen with the VAD parameters on it, and it should be easily visible to all practitioners in the operating room. An alternative power source in the form a fully charged battery pack should be readily available. Defibrillator and tachycardia detection therapies should be turned off, and external pads should be used. In case there is pacemaker dependence, conversion to asynchronous pacing should be carried out as indicated, along with device interrogation (Box 45.4).

Monitoring

The application of usual American Society of Anesthesiologists (ASA) monitoring poses unique challenges in treating patients with continuous-flow LVADs. The sphygmomanometer or the noninvasive blood pressure (NIBP) cuff relies on pulsatile flow for blood pressure measurement. Although most patients with LVADs have some degree of pulsatility related to the contraction of the native heart, NIBP cuff measurements are not possible in about one-half of patients. For them, Doppler-guided estimation of the mean arterial pressure (MAP) is reliable and correlates well with invasive arterial measurements.[65,66]

BOX 45.4 ELECTRICAL ISSUES WITH LEFT VENTRICULAR ASSIST DEVICES

- Left ventricular assist devices (LVADs) must always be plugged in and have a backup battery available.
- Electromagnetic interference may compromise LVAD function.
- Defibrillation using external pads may be needed.

Arterial catheter insertion should be based on the condition of the patient, complexity of the procedure, and the comfort level of the anesthesiologist. Most practitioners lean toward invasive arterial monitoring for all but the shortest procedures because it is reliable and provides access for blood gas sampling.[61] Arterial access may require the use of Doppler or ultrasound to aid in locating the vessel.

The pulse oximeter can give accurate readings without the need for as much pulsatility as the for the NIBP cuff, although its function also needs pulsatile flow. In the absence of an accurate pulse oximeter plethysmograph and pulsatile flow, serial measurement of arterial blood gases and cerebral oximetry can be used to monitor oxygenation and tissue perfusion.[67] End-tidal carbon dioxide (CO_2) measurement can provide surrogate information about ventilation, CO, and pulmonary blood flow.[9]

Most minor procedures in stable patients can be carried out without central venous catheters.[31] In complicated cases with anticipated hemodynamic instability, blood loss, massive fluid shifts, or need for pressor support, their use can be invaluable. The debate about utility of pulmonary artery catheters (PACs) extends to patients with LVADs, with the risks and the benefits weighed for each patient. The PAC has some advantages in patients with RV dysfunction, ischemia, and PH because it can differentiate between increased RV afterload and RV contractility issues.[68]

The CO calculated by the VAD console is based on the power used by the pump, and the resistance against which it works. It is prone to error because the algorithm makes certain assumptions in the calculations that may not always be appropriate. To add to the inaccuracy, the total output is a sum of the VAD flow and the native heart output, and the latter in certain cases may be significant.[69] Continuous CO by thermodilution measurements and pulse contour analysis is likely to be unreliable; the Fick CO measurement provides a more accurate assessment of total CO.[63,69]

Intraoperative Management

The question of who should administer anesthesia for procedures in patients with LVADs often arises. Nonsubspecialist anesthesiologists have treated patients with LVADs for noncardiac procedures successfully with minimal or no support from cardiac anesthesiologists.[31,70] A survey of members of the Society of Cardiovascular Anesthesiologists, however, found that most of these anesthesias are still being performed by cardiac anesthesiologists.[61] Another trend was that care is resource intensive, requiring high staffing ratios and postoperative care in the ICU. In the same report, a higher institutional volume was associated with lower use of invasive monitoring. This probably reflects the familiarity of the clinicians with the devices, the associated conditions and complications, and the relative comfort in managing them.

The availability of an LVAD team promotes caring for LVAD recipients by general anesthesiologists because it provides a layer of safety with significant specialist resources available in case of queries or to help when unexpected clinical situations arise.[31] Our preference at our institution focuses on education and encouragement of general practitioners to undertake anesthesia responsibility for noncardiac surgery in patients with LVADs. Cardiac anesthesiologists usually provide care in thoracic or vascular operations if large fluid shifts or hemodynamic instability is expected or if transesophageal echocardiography (TEE) is required.

Regional anesthesia is seldom a choice for patients with LVADs. Perioperative anticoagulation is the main reason for this, although difficulty in patient positioning, infectious risk, and presence of the device and driveline in the needle trajectory are also factors. Local anesthetic toxicity and arrhythmias can be catastrophic in these patients. The use of regional anesthesia is usually restricted to infiltration and ultrasound-guided peripheral nerve blocks that use low amounts of local anesthetics.

Patients with LVADs have poor cardiopulmonary reserve with abnormal physiology. Irrespective of the drug combinations used, induction of anesthesia and the resultant decrease in preload and contractility may result in unpredictable decreases in CO that are not easily reversible.[2,71] Preload to the left heart in these patients is essential and is influenced negatively by hypovolemia, patient position (eg, reverse Trendelenburg), RVF, anesthetic-induced venodilation, and laparoscopic insufflation of the abdomen. Responses to laryngoscopy and intubation, with the resultant increase in afterload, need to be blunted.[63] Continuous-flow devices respond to increased afterload with sustained rotation speed but decreased CO. This can be difficult to detect because the calculated pump flow may not reflect the true systemic output.

It has been suggested that these patients be treated as "full stomachs" and aspiration precautions undertaken because the device pocket in the preperitoneal space can alter abdominal mechanics and pressure-volume relationships.[31,70,71] Almost any combination of drugs can be use to maintain anesthesia if the factors affecting their pharmacokinetics and pharmacodynamics are kept in mind. Circulation times may be prolonged, and volume of distribution may be altered depending on volume status. Liver or kidney abnormalities from hypoperfusion can result in prolonged activity of the drugs administered.

The goals for intraoperative hemodynamic management focus on maintenance of volume status and RV forward flow, avoidance of sudden changes in afterload, and maintenance of stable cardiac rhythm and rate.[63] Fluid management needs to achieve a difficult balance between ensuring adequate filling of the right ventricle and overloading it, and the margin for error is small. Ventilatory strategy should ensure that there is adequate exhalation time and reduction of intrathoracic pressures to promote venous return.[71,72] Effective and adequate ventilation is essential because hypoxia, hypercarbia, and acidosis can increase pulmonary arterial resistance, increasing RV work against a higher afterload.[9] Positioning should be done carefully and gradually to minimize fluid shifts and changes in preload (see Chapter 28).

There is no clear consensus regarding the choice of inotropes and vasopressors in these clinical situations.[32] The choice of agent should be dictated by hemodynamic need, although with an understanding of the implications on the right ventricle. Milrinone, vasopressin, and norepinephrine may be useful drugs with favorable profiles.[9] Slininger and colleagues proposed a useful clinical algorithm based on the PI in the HeartMate II and central venous pressure (Table 45.3).[63]

Hypothermia increases afterload and myocardial oxygen demand from vasoconstriction and shivering, respectively. Hypothermia may cause decompensation in patients with LVADs. It also causes disorders in coagulation and platelet function, leading to increased perioperative blood loss.[73] Resultant bleeding can be substantial because hypothermic effects on coagulation are superimposed on the pharmacologic anticoagulation necessary with the device.

Despite its potential neuroprotetective and cardioprotective effects, efforts must be made to avoid hypothermia perioperatively. Extubation of these patients is a high-risk event because of the possibility of sympathetic stimulation with decreased VAD output. The risk of aspiration persists, and tracheal extubation should be undertaken only when the patient's airway reflexes and muscular strength have been confirmed to be adequate.

Laparoscopic Surgery

Laparoscopic surgery is significantly more difficult in patients with LVADs. Trocar and port placement must avoid the VAD and driveline in the upper abdomen.[60] CO_2 insufflation for visualization can decrease preload due to compression of the inferior vena cava, especially in a reverse Trendelenburg position. When combined with increases in afterload, which accompany laparoscopy, CO_2 insufflation can be deleterious to forward flow. Absorption of CO_2, acidosis, and higher ventilatory pressures can increase pulmonary vascular resistance (PVR) and the risk of RVF.

Laparoscopic surgery has been carried out successfully with careful compensation for these factors.[9,74] Intravascular volume repletion and gentle inotropy can be used to augment forward flow. Intraabdominal insufflation should be carried out gradually, and insufflation pressures should be held below 12 mm Hg.[75] This allows control of hemodynamic perturbations and gradual equilibration, providing a time window to institute interventions.

TABLE 45.3 Guide for Using the Pulse Index of the HeartMate II and Central Venous Pressure

Parameter	*Pulse Index*	*Central Venous Pressure (mm Hg)*	*Management*
Normal, goal	4–5	10–12	—
Hypovolemia	<3	<12	Fluids Ensure venous return
Right ventricular dysfunction	<3	>12	Inotropes Rule out hypoxia, hypercarbia, acidosis Inhaled nitric oxide
High afterload	>5.5	<8	Vasodilators Ensure adequate flow in the ventricular assist device

From Slininger KA, Haddadin AS, Mangi AA. Perioperative management of patients with left ventricular assist devices undergoing noncardiac surgery. *J Cardiothorac Vasc Anesth*. 2013;27:752–759.

Cardiopulmonary Resuscitation

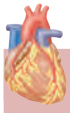
Cardiac arrest is cessation of perfusion to end organs due to a loss of forward flow from the device and the native heart. In continuous-flow devices, this can be difficult to diagnose rapidly because the fall in MAP may be gradual and pulse oximetry usually is unreliable. Sudden decreases in or loss of the capnometric waveform can provide important clues to this catastrophe. The onset of nonperfusing rhythms in patients can be compatible with life and a stable mental status for significant periods.[76] More commonly, loss of RV function leads to nonfilling of the LVAD and loss of systemic flow.

Implanted defibrillators are electronic instruments, and like any other machine, they are not immune to failure.[76] Attention must be paid to alternative means of restoring flow. In most non-LVAD patients, this is provided by external cardiac compressions. Unfortunately, in patients with LVADs, cardiac compression carries the risk of device dislodgment, air embolism, bleeding and trauma, and it usually is not advisable.[32,70] The European Association for Cardiothoracic Surgery (EACTS) recommends against use of cardiac compressions, acknowledging the complexity of this clinical scenario. There is no clear comment on this issue in the guidelines from the American Heart Association released in 2010.[77,78] There has been reported use of abdominal-only CPR in an isolated case,[79] but strong recommendations cannot be made for or against it.

TEE can provide valuable information, and it should be used as soon as possible when severe hemodynamic instability occurs. Empiric epinephrine and other aspects of the guidelines for cardiopulmonary resuscitation (eg, intubation, ventilation) should be followed (Box 45.5).[80]

Anesthesia for Noncardiac Surgery After Heart Transplantation

Cardiac transplantation is no longer a rare entity. With more than 100,000 transplantations reported and more than 4000 procedures



BOX 45.5 CARDIOPULMONARY RESUSCITATION WITH A LEFT VENTRICULAR ASSIST DEVICE

- Standard cardiopulmonary resuscitation (CPR) may be detrimental for patients with a left ventricular assist device.
- CPR may cause bleeding, device damage, air emboli, or trauma.
- Pharmacologic treatment is preferable to CPR.
- Transesophageal echocardiography may help in diagnosing the hemodynamic problem.

being performed yearly, thousands of people have hearts that were once in other persons.[81] The 5-year survival rate of more than 70% and the median survival time of more than 10 years are a testament to the strides forward in care.[82] With an increasing number of patients surviving and remaining functional long after heart transplantation (HT), it is no longer economically feasible to have specialized teams and centers perform noncardiac procedures in transplant recipients (see Chapter 25).

Anesthesiologists must have a comprehensive knowledge of the physiology of the transplanted heart, the pharmacologic implications of immunosuppressive therapy, and optimal means of anesthesia delivery for the HT population. Consultation with specialists for advice and titration of immunosuppressive therapy in the perioperative period is an essential part of the management plan.[83]

Physiology of the Transplanted Heart

Donor heart connection to the native circulation is carried out in one of two ways. Biatrial anastomosis with suturing of the native atria to the donor atria was practiced originally, but it has given way to the bicaval technique. The anastomosis occurs at the cavae, the great vessels, and along a line of atrial tissue surrounding the pulmonary veins. The bicaval technique has been associated with less sinus node dysfunction, less tricuspid regurgitation, and lower atrial size after HT.[84] The sinus node is preserved, but it is probably nonfunctional due to denervation and disruption of the blood supply. The risk of atrial fibrillation is thought to be less with this approach.[85] With the biatrial technique, dual P waves may be seen on the ECG due to activation of native atrial tissue, and it can sometimes mimic atrial flutter.[86]

There is debate about the extent, duration, and impact of reinnervation after cardiac surgery. Without question, in the early postoperative period, the transplanted heart is without any innervation, responding only to humoral catecholamines. Sympathetic stimulation and chronotropic responses to exercise, stress, and hypovolemia are not seen. This includes blunting of baroreceptor responses and those to laryngoscopy and intubation.[87] Parasympathetic denervation dominates, and most recipients have a high resting heart rate (HR) with low variability. Afferent denervation impedes vasoregulatory response by means of renin-angiotensin axis activation; and the perception of pain on ischemia (angina) is lost.[88] Eventually, nerve sprouting occurs, with both parasympathetic and sympathetic reinnervation. However, this is unpredictable. Innervation occurs more in patients with previous ischemic heart disease than in patients who received transplants for dilated cardiomyopathy.[89]

The transplanted heart significantly depends on preload for augmentation of output in response to demand. This results in a mild rightward shift on the Frank-Starling curve during rest.[88] Circulating brain natriuretic peptide (BNP) levels are elevated even with normal hemodynamic parameters, suggesting atrial stretch and the need for elevated filling pressures.[90] Myocardial metabolism appears to remain normal. The filling pressures, which are significantly elevated immediately after HT, never fully return to normal, suggesting restrictive physiology. Donor-recipient size mismatch, increased afterload in the form of hypertension, and rejection can be contributory.[91]

The result often is an abrupt rise in LV filling pressure in response to fluid challenge, making these patients prone to pulmonary and systemic venous congestion.[92] During exercise, the initial increase in CO results from increased preload and stroke volume, whereas later during exercise, contractility and HR augmentation from circulating catecholamines take over. Peak exercise capacity remains lower than that of comparable controls.[91,93] Mild rejection does not affect function significantly, although systolic and diastolic parameters are adversely affected by significant rejection.[94]

Resting coronary blood flow increases due to an absence of sympathetic tone. Serotonin hypersensitivity, likely related to endothelial damage, causes decreased flow reserve in the transplanted heart.[95] Abnormalities of response to endothelium-derived vasodilators such as substance P and acetylcholine have been described, although the response to non–endothelium-derived vasodilators such as adenosine and dipyridamole is preserved.[96] Because coronary demand-supply mismatch does not result in ischemic pain or angina in HT patients, surveillance is required to identify coronary vasculopathy in the absence of symptoms.[88]

Complications After Transplantation

Rejection, infection, and cancer are common complications. Other conditions such as diabetes, hypertension, and cardiac vasculopathy occur and are related to immunosuppression. Preeclampsia is a risk in transplant recipients who become pregnant.[83]

Rejection

With the advent of improved techniques of immunosuppression, rejection rates have been dropping. Development of a cytotoxic crossmatch (using recipient antibodies) to stratify and reduce the risk of rejection has been helpful. The risk of allograft rejection remains highest within the first 3 to 6 months of transplantation and drops significantly after the first year.[97]

These episodes, which can be difficult to detect, are often related to poor medication compliance. Acute rejection is seen on histologic examination as an inflammatory response mounted by the host against the grafted organ. On a functional level, it results in gradual failure and dysfunction of the transplanted heart. Cell-mediated immunity has been recognized as the primary offender in rejection; although antibody-mediated rejection is increasingly recognized as playing an equally important role.

The onset of symptoms can be nonspecific, such as fatigue, unexplained weight gain, edema, and atrial fibrillation. Diagnosis of rejection requires an alert treating physician. Endomyocardial biopsy carried out by the internal jugular or femoral route remains the standard for the diagnosis of rejection. It is performed with decreasing frequency after transplantation (ie, weekly for the first month, two times in the next month, and monthly for the next 4 months) according to guidelines from the International Society of Heart and Lung Transplantation. The results can help differentiate between cellular and antibody-mediated rejection, although it has the disadvantage of being invasive and sometimes requiring general anesthesia. Patch inflammatory infiltrate may be missed on random biopsy sampling, and a histologic diagnosis often means that significant myocardial damage has already occurred.[97]

Echocardiography can detect rejection using tissue Doppler imaging and by the finding of diastolic dysfunction.[98] However, it is not specific and has limited utility in the early detection of rejection. Cardiac magnetic resonance imaging (MRI) using myocardial contrast enhancement has shown some promise as a noninvasive method for detecting rejection early.[99]

Serum markers such as troponin and BNP are not specific in the low to positive range and are not elevated until later in the disease. The only US Food and Drug Administration–approved, noninvasive test used in routine clinical practice uses identification of genetic markers

TABLE 45.4 Treatment of Cardiac Transplant Rejection

Immune Response	*No Symptoms*	*Reduced Ejection Fraction*	*Failure or Shock*
Cellular	Increase CNI; oral steroid bolus with taper	Oral steroid bolus with taper *or* IV pulse steroid	IV pulse steroid; cytolytic therapy; plasmapheresis; IVIG; inotropic support; IABP/ECMO; retransplantation
Humoral	No treatment (?)	Oral steroid bolus with taper *or* IV pulse steroid ± IVIG	

CNI, Calcineurin inhibitor; *ECMO*, extracorporeal membrane oxygenation; *IABP*, intraaortic balloon pump; *IV*, intravenous; *IVIG*, intravenous gamma globulin.
From Patel JK, Kittleson M, Kobashigawa JA. Cardiac allograft rejection. *Surgeon*. 2011;9:160–167.

to create a genetic profile that suggests susceptibility to rejection. In one trial, it was shown to be comparable with endomyocardial biopsy in monitoring for rejection.[100]

Treatment of rejection depends on whether the patient is symptomatic and the nature of the rejection response (ie, whether it is primarily cellular or antibody mediated). A detailed description of the therapy is beyond the scope of this chapter, but the principles are summarized in Table 45.4.

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a unique form of atherosclerosis in patients who undergo HT with delayed graft failure. It is characterized by early intimal proliferation, followed by luminal stenosis in the epicardial branches in the later stages. More than one-half of the arteries in transplanted hearts demonstrate intimal thickening within 1 year of transplantation.[101] CAV and malignancy are the most important causes of death after this period.[102]

The lesions in CAV are diffuse and hyperplastic, affecting the entire coronary tree, and the proliferation tends to be concentric. This contrasts with native coronary atherosclerosis, in which the lesions are eccentric and distributed in a patchy manner. Calcification, which is common with native disease, is uncommon with CAV. Because angina is uncommon due to denervation at transplantation, CAV manifests in much more sinister forms as HF, arrhythmias, or sudden death. The usual cardiac risk factors such as obesity, hypertension, smoking, and diabetes influence the risk of CAV. CAV development is also closely related to the degree of human leukocyte antigen (HLA) incompatibility and the amount of rejection.[101] There is growing recognition that viral infections, particularly cytomegalovirus (CMV) infections, may have a causal role in the development of CAV.[103]

Because treatment of CAV is difficult, it must be recognized early. Intravascular ultrasound is the most sensitive tool to detect CAV, quantify intimal thickness, and provide prognostic information.[104] An increase of 0.5 mm or more in intimal thickness within the first year after transplantation is a powerful predictor of all-cause mortality, myocardial infarction, and angiographic abnormalities.[105] Management of CAV involves aggressive risk modification, optimization of blood pressure control and lipids, and the use of inhibitors of proliferation signaling such as sirolimus. The use of statins has also been associated with a reduction in the CAV burden.[106] Due to the diffuse and hyperplastic nature of the disease, percutaneous coronary intervention for stenosis is neither easy nor very successful.[101,107] Retransplantation remains the definitive treatment for this difficult condition, although it carries with it significant technical and ethical challenges.

Infection

Immunosuppression brings with it the risks of malignancy and infection. The risk of infection decreases with time since transplantation, likely reflecting alterations in immune suppression. In the immediate postoperative period, nosocomial or iatrogenic infections predominate. Between 1 and 6 months, opportunistic infections and activation of latent infection occur, and after 6 months, community-acquired infections are more common.[108]

Improved bacterial and viral prophylaxis has decreased infections with *Pneumocystis*, CMV, *Listeria*, *Nocardia*, and *Toxoplasma*. Prophylactic therapy usually includes sulfamethoxazole and trimethoprim for *Pneumocystis jirovecii*, ganciclovir for CMV, acyclovir for herpes simplex virus, pyrimethamine for toxoplasmosis, and nystatin for *Candida*.[108] These drugs should continue perioperatively, and clinicians should be aware of drug interaction issues that may occur with their use. Antifungal prophylaxis and treatments have improved, resulting in improved survival despite the emergence of resistant *Candida* and *Aspergillus* strains.[109]

Strict asepsis is essential in the perioperative care of HT patients, particularly for catheter placement, urinary catheterization, and other invasive procedures. Antibiotic prophylaxis should be individualized, with attention to the patient, the procedure, and the bacterial spectrum. Because fever and leukocytosis do not usually accompany infection in transplant recipients, vigilance is required to avoid progression to catastrophic sepsis (Box 45.6).[110]

BOX 45.6 LONG-TERM TRANSPLANTATION COMPLICATIONS

- Chronic diastolic dysfunction
- Mild to moderate heart failure
- Infection
- Immunosuppression effects

Immunosuppression

Since its inception in the 1960s, the long-term success of HT has largely resulted from development of efficacious immunosuppressive regimens.[111] Immunosuppression involves induction (ie, initiation of high-intensity therapy), maintenance, and reversal of rejection (if needed). Native and memory T lymphocytes are involved in the process of alloimmunity, especially lymphocytes sensitized to HLA antigens. sensitivity is thought to reflect previous infection with viral agents that show some cross-reactivity with the HLA antigen domains.

After activation and transformation in the lymphoid tissue around the graft, effector T cells emerge and orchestrate an inflammatory response.[82,112] This is carried out in conjunction with B lymphocytes, which mediate the humoral antibody response. It has a characteristic histopathologic appearance, with deposition of complement C4a. Antibody-mediated rejection is associated with more severe hemodynamic compromise and worse outcome; the primary site for damage is the capillary endothelium.[113] The process of rejection can take a few days to reach its peak, even after the patient has been discharged after the initial procedure.

The function of immunosuppressive drugs is to prevent or ameliorate rejection while minimally affecting normal physiology. Immunosuppressant medication has three main effects: therapy (ie, suppression of rejection), unwanted results of immunosuppression (ie, infection and cancer), and nonimmune cytotoxicity. Most drugs act by depleting lymphocytes, diverting the traffic of the ones that exist, or blocking response pathways for activated lymphocytes.[112]

The efficacy of induction therapy (ie, intensive beginning of immunosuppression) has been argued and debated; and it is currently recommended only for selected patients.[111] It is carried out using two types of drugs:

1. Drugs that deplete protein (eg, OKT3, antithymocyte globulin): They act by destroying T cells or B cells, or both. They cause cytokine release, producing severe systemic symptoms. Use is also

associated with an increased incidence of lymphoproliferative disorders.[114] Suppression of humoral immunity is better tolerated than suppression of cell-mediated immunity due to the absence of cytokine release.

2. Drugs that do not deplete protein (eg, monoclonal antibodies such as basiliximab, fusion proteins): They introduce immunosuppression without destruction of lymphocytes. These drugs have limited efficacy but much better side effect profiles.

Maintenance therapy targets graft-host adaptation while trying to minimize complications. The usual combination consists of a corticosteroid, a calcineurin inhibitor (ie, cyclosporine or tacrolimus), and an antiproliferative agent (eg, mycophenolate). Steroids are used for a limited period, with an effort to keep the duration between 1 and 5 years.[82] Tacrolimus is the preferred calcineurin inhibitor,[81] and it is used in cases with higher chances of rejection, hypertension, and hyperlipidemia; whereas cyclosporine is used more commonly for patients with diabetes mellitus. Sirolimus, an inhibitor of the mammalian rapamycin receptor, has shown promise reducing nephrotoxicity, CAV, and cardiac morbidity.[115,116]

Acute rejection, when it is cellular and associated with significant hemodynamic compromise, is treated with high-dose steroids or antithymocyte globulin. Severe humoral rejection that causes hemodynamic compromise is usually managed with high-dose corticosteroids and plasmapheresis followed by intravenous immunoglobulin or rituximab, a B-cell–depleting monoclonal anti-CD20 antibody.[82]

Interaction of Immunosuppressants With Anesthetics

It is not surprising that immunosuppressants affect the pharmacokinetics and pharmacodynamics of anesthetic drugs, and vice versa. It is surprising that there is very little information about these effects in humans; most data come from animal studies.[88]

At the simplest level, massive perioperative fluid resuscitation or cardiopulmonary bypass can result in drug level decreases from dilution.[117] Monitoring drug levels is essential because dose adjustment may be needed to maintain therapeutic levels. Many drugs, including commonly used immunosuppressants, antifungal agents, and lipid-lowering medications, are metabolized by the cytochrome P450 (CYP450) enzyme system and extruded from cells by the multidrug-resistance transporter protein 1, P-glycoprotein. Both systems show genetic polymorphism, which significantly influence drug metabolism.[118] Hypothermia during or after surgery can result in reduced clearance of and higher levels of drugs metabolized by the P450 system.[119] Tables 45.5 and 45.6 and Box 45.7 outline the drugs that affect immunosuppressant levels, immunosuppressants with an impact on perioperative management, and drugs that can cause renal dysfunction when administered with immunosuppressants, respectively.

Because tacrolimus and cyclosporine may reduce the seizure threshold, hyperventilation under anesthesia should be avoided.[120] Due to reduced gastric emptying, levels of cyclosporine and other oral medications may be subtherapeutic if oral administration occurred just before induction.[121] Cyclosporine also can prolong the effect of muscle relaxants.[88] Extrahepatic glucuronidation pathways appear to be similar for propofol and mycophenolate and may result in decreased elimination in cases of coadministration.[122] Drugs such as midazolam, verapamil, and erythromycin are inhibitors of the P-glycoprotein system and can enhance the effects and toxicity of the immunosuppressants that are substrates for it. Anaizi described the drug interactions that can occur with immunosuppressants.[123]

Perioperative Management

When patients with transplants undergo another operation, the transplantation team should be contacted about details of the procedure

BOX 45.7 DRUGS THAT IMPAIR RENAL DYSFUNCTION WHEN GIVEN WITH CYCLOSPORINE OR TACROLIMUS

- Amphotericin
- Cimetidine
- Ranitidine
- Melphalan
- Nonsteroidal antiinflammatory drugs
- Cotrimoxazole
- Vancomycin
- Tobramycin
- Gentamycin

Modified from Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, et al. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. *Anesth Analg.* 1999;89:613–622.

TABLE 45.5 Drugs That Affect Immunosuppressive Drug Levels

Drugs That Increase Levels	*Drugs That Decrease Levels*
Bromocryptine	Carbamazepine
Chloroquine	Octreotide
Cimetidine	Phenobarbital
Clarithromycin	Phenytoin
Cotrimoxazole	Rifampicin
Danazol	Ticlopidine
Diltiazem	
Erythromycin	
Fluconazole, itraconazole	
Metoclopramide	
Nicardipine	
Verapamil	

Modified from Kostopanagiotou G, Smyrniotis V, Arkadopoulos N, et al. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. *Anesth Analg,* 1999;89:613–622.

TABLE 45.6 Side Effects of Immunosuppressives That Affect Anesthesia Management

Side Effects	*CyA*	*Tacrolimus*	*Aza*	*Steroids*	*MMF*	*ATG*	*OKT3*
Anemia	–	–	+	–	+	–	–
Leukopenia	–	–	+	–	+	+	+
Thrombocytopenia	–	–	+	–	+	–	–
Hypertension	++	+	–	+	–	–	–
Diabetes	+	++	–	++	–	–	–
Neurotoxicity	+	+	–	+	–	–	–
Renal insufficiency	+	++	–	–	–	–	–
Anaphylaxis	–	–	–	–	–	+	+
Fever	–	–	–	–	–	+	+

ATG, Antithymocyte globulin, *Aza*, azathioprine, *CyA*, cyclosporine, *MMF*, mycophenolate mofetil, *OKT3*, monoclonal antibodies against CD3 antigen; –, no effect; +, mild effect; ++, significant effect.

Modified from Kostopanagiotou G, Smyrniotis V, et al. Anesthetic and perioperative management of adult transplant recipients in nontransplant surgery. *Anesth Analg.* 1999;89:613–622.

and patient status. They can provide the latest diagnostic information and study results relevant to the anesthesia. The preoperative assessment evaluates graft function (eg, echocardiography), rejection status (eg, endomyocardial biopsy), CAV (eg, intravascular ultrasound, angiography), functional status, and end-organ involvement.[124]

Complications should be carefully sought and ruled out. It is important to communicate the patient's CMV status with the blood bank because CMV-seronegative recipients require products from CMV-negative donors. Perioperative consultation with a transplantation microbiologist can help to screen for infection and devise an individual antimicrobial prophylaxis plan according to the patient's infection profile, the proposed procedure, and the duration since transplantation. Health care providers must be sensitive to the fact that these patients can suffer from subtle mental and psychiatric ailments such as depression despite improved physical status and indices.[125]

The preoperative ECG may show dual P waves or pacing spikes from an implanted device. To obtain information about the patient's dependence on the device and recent arrhythmia episodes, all cardiovascular implantable electrical devices (CIEDs) should be interrogated before surgery. Depending on the type of electrical interference anticipated, pacing might be converted to an asynchronous mode and antitachycardia therapies disabled. If this is the case, continuous monitoring with easy access to external pacing or defibrillation is required, as is the need to reprogram the device at the end of the procedure.[126]

Preoperative echocardiography can provide valuable information about systolic and diastolic function and valvular competence. Diastolic dysfunction may signal rejection, whereas systolic dysfunction may be a sign of CAV.[127] Pertinent laboratory tests include hematology, chemistry, coagulation, and liver enzyme studies, which can assist in the detection of end-organ dysfunction due to hypoperfusion or immunosuppressant toxicity.

The transplantation service should be consulted about immunosuppressants; they usually should be continued perioperatively. However, steroid administration for patients previously receiving them is a controversial issue. It has been suggested that patients receiving immunosuppressive doses of steroids do not need additional doses of steroids for surgery, and hypotension under anesthesia is often related to hypovolemia rather than adrenal insufficiency.[128,129] Excessive steroid administration is associated with gastric erosions, hyperglycemia, and psychological disturbances. We do not routinely administer steroids to patients who are on steroid therapy if they have received their daily dose of steroids on the day of surgery. If hypotension refractory to fluids and pressor administration occurs, 25 mg of hydrocortisone may be administered. A lower threshold for steroid administration should be used when steroid therapy was recently discontinued, there is coexisting infection, or the operation is major and invasive.

Patients are aware of the increased risk they face as transplant recipients, and judicious premedication can help alleviate anxiety and improve their experience. Electrocardiographic monitoring is essential for these patients. Myocardial ischemia detection is critical, as is detection of changes in HR and atrioventricular nodal conduction caused by anesthetics and other drugs used perioperatively. Specialized monitoring should be based on the patient's condition, the procedure and its timing, blood loss, and anticipated fluid shifts.[88,120] The PAC can be useful if large fluid shifts are expected, especially if there is preexisting cardiac dysfunction. TEE is a useful, minimally invasive method to guide fluid therapy, monitor global cardiac function, and titrate vasoactive and cardioactive medications.[83] Strict aseptic precautions and infection prevention during placement of invasive monitors cannot be overemphasized for this particularly vulnerable population.[120] Catheters, drains, and airways should be removed as early in the postoperative period as is safe and feasible.

The choice of anesthesia technique requires individualization. There is no clear contraindication to any type; sedation, regional, and general techniques have all been successfully used.[130] The anesthesia goals include maintenance of preload, preservation of sinus rhythm, avoidance of sudden changes in afterload, and careful monitoring for intraoperative complications.

The use of a laryngeal mask airway is acceptable.[124] Oral intubation of the trachea is preferable to the nasal route to reduce infection risk. Gingival hyperplasia related to cyclosporine and alteration of airway anatomy due to lymphoproliferative disorders can occur in transplant recipients.[83] Laparoscopic procedures can be carried out safely if sudden fluctuation in preload and afterload (as can occur with insufflation and desufflation) are detected and managed expeditiously.[131] Regional anesthesia administration may be contraindicated by coagulopathy because thrombocytopenia can accompany immunosuppression. The more gradual, controlled establishment of a regional block with an epidural may be better than spinal anesthesia in patients with a compromised ability to compensate with a sympathetic chronotropic response.

Hemodynamic management principles should take into account the altered physiology of a transplanted heart. Drugs using the sympathetic nervous system are ineffective, and drugs with direct and indirect effects (eg, ephedrine) manifest only the direct effects. Table 45.7 summarizes the effects of some medications.

Normal responses should be expected from epinephrine, norepinephrine, glucagon, isoproterenol, and metaraminol. Levosimendan, a calcium sensitizer, improves cardiac function in the graft and can reduce inotrope requirements.[132] Neostigmine causes bradycardia and can cause cardiac arrest when used for reversing neuromuscular blockade, although the exact mechanism is unclear. Preadministration of glycopyrrolate and availability of direct chronotropic agents are essential when administering neostigmine to these patients.[133] Sugammadex is a good alternative to neostigmine because it appears to be devoid of significant cardiac effects.

Patients on immunosuppressants are at increased risk for renal injury, and the use of nephrotoxic drugs such as nonsteroidal antiinflammatory agents should be avoided. Caution also should be exercised when using β-blockers or vasodilators. In the absence of organ dysfunction, the choice of opiates or muscle relaxants is based on the operation and anticipated recovery. Patient positioning should take into account the easy bruisability and osteoporosis that accompany steroid therapy.

Postoperative care is similar to that for other patients. Adequate analgesia, normothermia, and hydration are essential. Thromboprophylaxis should be started when safe because the deep vein thrombosis risk is increased.[120]

With appreciation of their unique physiologic aspects, HT recipients can be safely managed during noncardiac surgery. Organ transplantation is often described as the exchange of one disease state for another, although with modern medicine, that exchange is fast becoming a more propitious one.

TABLE 45.7 Cardiovascular Effects of Drugs on Normal and Transplanted Hearts

		Heart Rate		Blood Pressure	
Drugs	*Type of Action*	*Normal*	*Transplanted*	*Normal*	*Transplanted*
Atropine	Indirect	Increase	None	None	None
Ephedrine	Direct and indirect	Increase	Small Increase	Increase	Small increase
Epinephrine	Direct	Increase	Increase	Increase	Increase
Phenylephrine	Direct	Decrease	None	Increase	Increase

Modified from Ashary N, Kaye AD, Hegazi AR, Frost EAM. Anesthetic considerations in the patient with a heart transplant. *Heart Dis.* 2002;4:191–198.

Cardiovascular Implantable Electronic Device Management in Noncardiac Surgery

Unfortunately, avoidance and complete reliance on a magnet are no longer effective strategies for the management of CIEDs in patents undergoing noncardiac surgery. The increasing number of indications for implantation and an aging population have made it impossible to avoid these patients. Their care is made challenging by the many types of devices, programming modes, and magnet responses in use. CIED variation makes a thorough knowledge of every device impractical for the average anesthesiologist and precludes the development of a universally applicable perioperative management algorithm.

Expecting every anesthesiologist to become a CIED programmer or memorize the specifications of all CIEDs on the market is unrealistic, but anesthesiologists should have a basic understanding of CIEDs and the general perioperative management strategies available. The goal of this section is not to create a universally applicable perioperative management algorithm or present all CIED models in detail, but rather to supplement Chapter 5 by reviewing some basic concepts, potential adverse outcomes, and current recommendations for noncardiac surgery.

Pacemakers

Pacemaker configurations include devices with leads in a single chamber, two chambers, or multiple chambers (eg, biventricular pacing), which is denoted by the North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology (NASPE/BPEG) Group generic (NBG) code (Table 45.8). Pacing and sensing can occur in the atrium, the ventricle, or both chambers (Fig. 45.2), depending on the configuration and pacemaker programming. More complicated multichamber pacing and sensing schemes (eg, dual-chamber pacing) may pose clinical challenges for the anesthesiologist, but they also provide atrial-ventricular synchronicity and increase CO for the patient.[134] The indication for and patient reliance on the pacemaker should be ascertained before making perioperative management decisions.

Because the first position of the NBG code denotes the pacing chambers, the fifth position may seem redundant, but it is used to denote multiple leads in a single chamber. Examples of multisite pacing are multiple atrial leads to suppress atrial fibrillation and biventricular pacing for cardiac resynchronization therapy (CRT). Rate modulation is also denoted by the NBG code, but additional information such as magnet response, battery life, pacemaker dependence, and mode switching can be determined only by communicating with the device company or by device interrogation.

Rate Modulation

Rate modulation and *rate adaptation*, denoted by an R in the fourth column of the NBG code (see Table 45.8), are terms used to describe a pacemaker's ability to automatically change the rate in response to certain monitored parameters. Because an estimated 85% of pacemakers implanted in the United States are rate responsive and 99% have this capability, anesthesiologists should be familiar with rate modulation in case an experienced programmer is not available preoperatively.[135,136]

The parameters that can induce rate modulation include acceleration due to motion; patient movement; QT interval; central venous temperature, oxygen saturation, and pH; RV pressure, minute ventilation determined by thoracic impedance; and a combination of acceleration and minute ventilation.[137,138] When required, the pacemaker with rate modulation can alter HR and CO to meet metabolic demands through atrial, ventricular, or atrial and ventricular leads.[139]

In their 2011 ASA practice advisory, the ASA and Heart Rhythm Society (HRS) provided an equivocal recommendation that rate-adaptive therapy should be disabled preoperatively if advantageous.[140] Intraoperative rate changes, which result from elective continuation of rate modulation or a lack of CIED programming resources, are usually benign. However, an increase in HR may be hemodynamically significant, unfavorable for certain comorbidities (eg, coronary disease), or misinterpreted as patient discomfort.[141] Changes in rate due to active rate modulation can result from succinylcholine-induced muscle fasciculations, an oscillating saw, myoclonic jerks, postoperative shivering, electroconvulsive therapy, and QT alterations (eg, medications, pH, electrolytes). The most commonly encountered stimuli for rate changes in the operating room are electrocautery and mechanical hyperventilation.

If active rate modulation results in an intolerable or undesirable increase in HR, there are several treatment options. The eliciting stimulus (eg, hyperventilation, electrocautery) can be withdrawn, a magnet can place the pacemaker into an asynchronous mode, or a CIED programmer can disable rate modulation.[138]

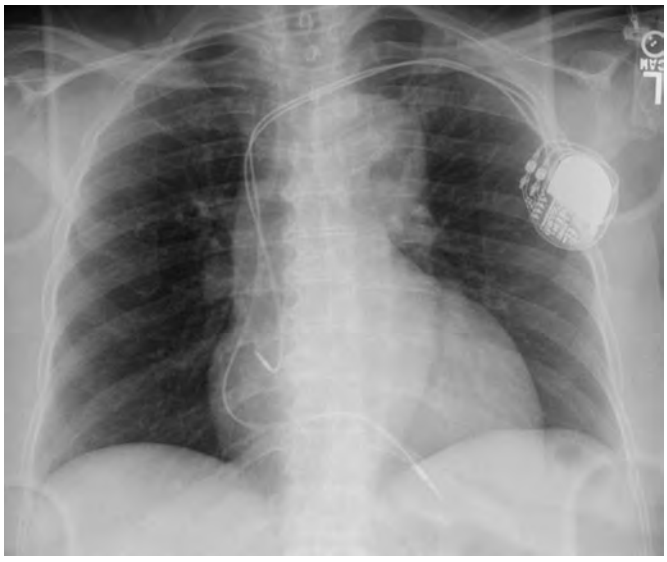


Fig. 45.2 Supine frontal chest radiograph shows an example of a dual-chamber pacemaker with leads in the right atrium and right ventricle. Notice the difference between the pacing leads shown in this example and the shock coils of an implantable cardioverter-defibrillator located in the right atrium and right ventricle in Fig. 45.4.

TABLE 45.8 2002 Revised NASPE/BPEG Generic Pacemaker Code

Pacing Chamber	*Sensing Chamber*	*Response*	*Rate Modulation*	*Multisite Pacing*
O = none	O = none	O = none	O = none	O = none
A = atrium	A = atrium	I = inhibited	R = rate modulation	A = atrium
V = ventricle	V = ventricle	T = triggered	—	V = ventricle
D = dual	D = dual	D = dual	—	D = dual

BPEG, British Pacing and Electrophysiology Group; *NASPE*, North American Society of Pacing and Electrophysiology.

From Berstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate and multi-site pacing. *Pacing Clin Electrophysiol.* 2002;25:260–264.

Automatic Mode Switching

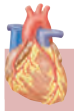
Automatic mode switching (AMS) enables identification of atrial tachyarrhythmias and automatic conversion of pacemaker settings to prevent pacemaker-mediated tachycardia (PMT). The new mode typically does not track the atrial activity, but rather paces the ventricle at a fixed, slower rate. *PMT* is a term used to describe any undesirable pacemaker generated tachycardia.[142] For example, atrial fibrillation can result in ventricular tachycardia in patients with a dual-chamber pacemaker. Without AMS, the ventricle can track the high atrial rate in atrial fibrillation and inappropriately pace to an undesirable rate. Although mode switching does not usually present significant challenges in the perioperative period, it can be used to a clinician's advantage by determining the past atrial arrhythmia burden.[143]

Electrocardiographic Diagnosis of Myocardial Ischemia in Ventricular Paced Rhythms

Ventricular pacing, specifically that originating from the RV apex, often elicits an ECG with a negative QRS followed by an elevated ST segment and positive T wave. This electrocardiographic pattern can be confused for myocardial ischemia, a diagnosis that may not be incorrect given the prevalence of coronary artery disease (CAD) in the patient population into which CIEDs are increasingly implanted. However, the classic criteria for electrocardiographic detection of myocardial ischemia may not apply to the ventricularly paced patient.

Although a pacemaker can be inhibited to analyze the underlying rhythm, this may not be feasible or even diagnostic. Comparison with a previous 12-lead ECG is an alternative approach, but an ECG is not always readily available. Sgarbossa and colleagues[144] proposed criteria for electrocardiographic detection of acute myocardial infarction in the setting of ventricular pacing (Box 45.8). Of the criteria studied, ST-segment elevation of 5 mm or more in leads without QRS concordance was the only criterion with high specificity and statistical significance.[144] An example of ST segment and QRS discordance is shown in Fig. 45.3. Although the suggested criteria are less applicable when depolarization is generated from locations other than the RV apex (eg, RV outflow tract, left ventricle), are based on a relatively small study, and their specificity questioned, they are nonetheless used to identify myocardial ischemia in the setting of a ventricularly paced rhythm. Normalization of the ST-segment elevation for the corresponding QRS amplitude and QRS prolongation have been proposed as additional electrocardiographic markers of myocardial ischemia.[145,146]

Electrocardiographic detection of myocardial ischemia in this patient population can be extremely challenging, but the ASA/HRS guidelines in addition to the clinical context can aid in identifying individuals who require further testing (eg, cardiac enzymes, echocardiography, angiography).[147] When clinical suspicion is high, additional means of diagnosing myocardial ischemia or damage such as echocardiography or serum troponin levels should be pursued.



BOX 45.8 SGARBOSSA CRITERIA FOR MYOCARDIAL ISCHEMIA IN PATIENTS WITH VENTRICULAR PACING

- ST-segment elevation ≥1 mm in a lead with QRS concordance
- ST-segment depression ≥1 mm in leads V_1 through V_3
- ST-segment elevation ≥5 mm in a lead with negative QRS concordance

Data from Sgarbossa EB, Pinski SL, Gates KB, et al. Early electrocardiographic diagnosis of acute myocardial infarction in the presence of ventricular paced rhythm. *Am J Cardiol*. 1996;77:423–424.

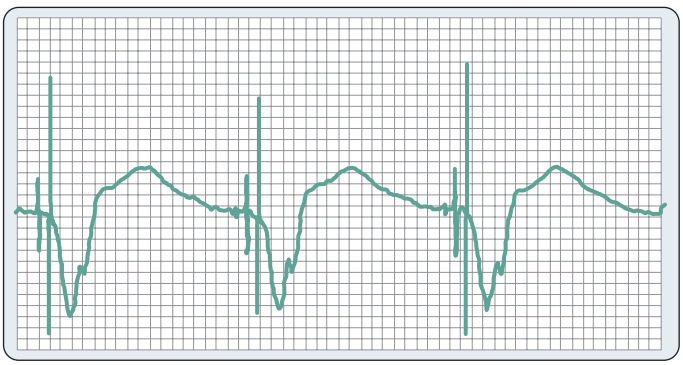


Fig. 45.3 Tracing from lead V– of the electrocardiogram shows a QRS *(negative deflection)* and ST segment *(positive deflection)* discordance in a dual-chamber pacemaker–dependent patient.

Automatic Implantable Cardioverter-Defibrillators

An automatic implantable cardioverter-defibrillator (AICD) is a CIED that can detect and treat arrhythmias with a defibrillatory shock through leads in the right ventricle and occasionally in the right atrium. The addition of a right atrial lead, which is denoted by the NASPE/BPEG Group generic defibrillator (NBD) code (Table 45.9), can be advantageous in differentiating supraventricular tachycardia from ventricular tachyarrhythmias (Fig. 45.4).[159] Treatment of identified ventricular tachyarrhythmias entails overdrive pacing or defibrillation, depending on the diagnosis of ventricular tachycardia or fibrillation. In addition

TABLE 45.9 NASPE/BPEG Generic Defibrillator Code

Shock Chamber	*Antitachycardia Pacing Chamber*	*Tachycardia Detection*	*Antibradycardia Pacing Chamber*
O = none	O = none	E = electrogram	O = none
A = atrium	A = atrium	H = hemodynamic	A = atrium
V = ventricle	V = ventricle	—	V = ventricle
D = dual	D = dual	—	D = dual

BPEG, British Pacing and Electrophysiology Group; *NASPE*, North American Society of Pacing and Electrophysiology.

From Berstein AD, Camm AJ, Fisher JD, et al. North American Society of Pacing and Electrophysiology policy statement. The NASPE/BPEG defibrillator code. *Pacing Clin Electrophysiol.* 1993;16:1776–1780.

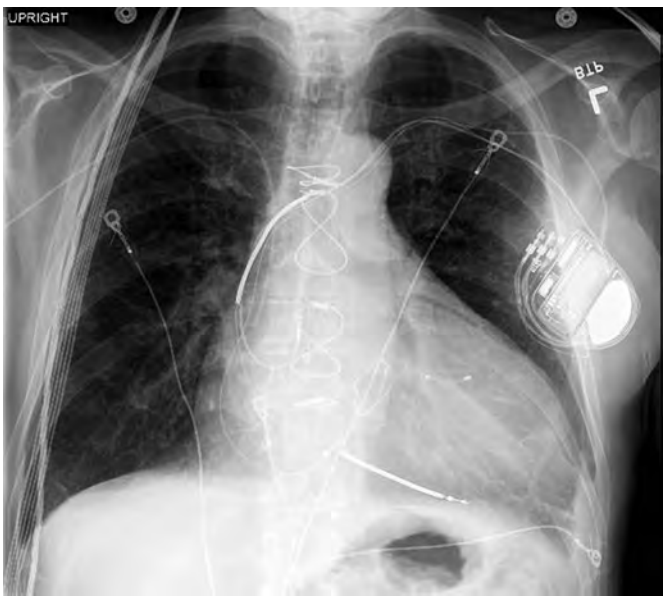


Fig. 45.4 Upright frontal chest radiograph shows a cardiac implantable electrical device with atrial and ventricular implantable cardioverter-defibrillator leads and multisite pacing for biventricular pacing (ie, cardiosynchronous therapy).

to tachyarrhythmia therapies, all AICDs are equipped with pacing capabilities. Although this feature is advantageous when defibrillation results in bradycardia or asystole, it also mandates perioperative programming in pacemaker-dependent patients.

The application of a magnet to an AICD is expected to disable tachyarrhythmia therapies. However, the typical magnet response may be disabled or ineffective.[148] Application of a magnet may not be a benign, immediately reversible process because there are reports of magnet application permanently deactivating tachyarrhythmia therapy.[149] Additional intraoperative concerns include the unrecognized displacement of the magnet and its lack of effect on the pacing function of the device. Although appropriate magnet application typically disables tachyarrhythmia therapies, it cannot change the pacing function to an asynchronous mode in an AICD. Pacemaker-dependent patients with an AICD and an increased risk of perioperative EMI require reprogramming.

Electromagnetic Interference

Although the myriad CIED options present a challenge for anesthesiologists, technologic advancements have also made the devices more resistant to EMI. Newer CIEDs use noise-protection algorithms, filters (ie, bandpass), and circuit shields to help minimize EMI. An additional explanation for the reduction in EMI is the trend to implant pacemakers with bipolar rather than unipolar leads. Bipolar leads are more resistant to EMI because the anode and cathode are contained within the lead itself. In contrast, unipolar leads are more susceptible to EMI because the distance between the anode (ie, pulse generator) and cathode (ie, tip of the lead) is much greater.[139]

Despite these improvements, EMI can still occur, and the crux of any perioperative management plan is determining the likelihood of encountering interference (Fig. 45.5). EMI can result from any device that emits radiofrequency (RF) waves between 0 and 10^9 Hertz. The

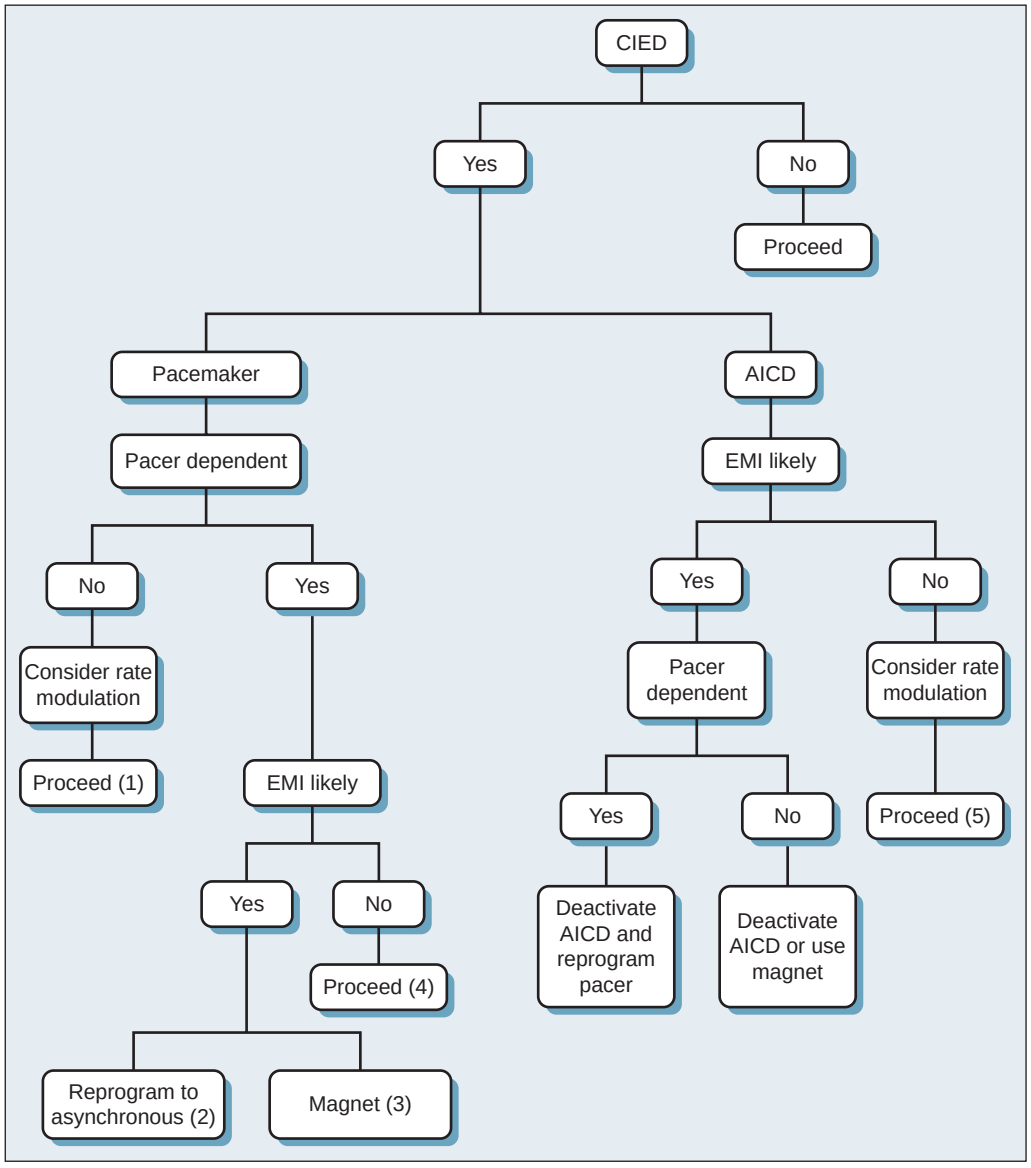


Fig. 45.5 Perioperative implantable cardiovascular electronic device *(CIED)* management. Additional considerations: *(1)* have a magnet available; *(2)* be aware of potential R-on-T phenomenon if applicable; *(3)* consider the magnet mode settings, patient comorbidities, and potential R-on-T phenomenon; *(4)* complete preoperative CIED assessment and have a magnet available; and *(5)* consider rate modulation and have a magnet available. *AICD*, Automatic implantable cardioverter-defibrillator; *EMI*, electromagnetic interference.

extensive list of potential EMI sources includes electrocautery, external defibrillation, electroconvulsive therapy, and RF waves used in ablation procedures.[137]

Although a potential source of EMI may exist, EMI may still be unlikely. For example, the potential for interaction is considered to be markedly reduced if the distance from the electrocautery current to the CIED generator and leads is greater than 6 inches.[150] One protocol further defines a *critical zone* of increased risk of EMI to include the area from the mandible to the xiphoid.[151] For operative procedures below the umbilicus, electrocautery is not thought to interfere with a generator and leads that are located in upper chest.[152]

Techniques other than absolute distance can reduce the possibility or effect of EMI, such as the use of bipolar rather than monopolar electrocautery, short bursts of electrocautery (<5 seconds), lower electrocautery power settings, and proper positioning of the electrocautery return pad to minimize return current interaction with the CIED.[140]

Potential Adverse Outcomes

Aside from preoperative preparation (eg, knowledge regarding the model type, dependency, magnet mode, EMI potential) and a careful perioperative management plan, a thorough understanding of the potential complications or adverse outcomes is paramount to the successful perioperative management of a patient with a CIED. Early recognition and action by the anesthesiologist can be facilitated by reviewing the published experience of others and known EMI interactions.

The list of potential complications with CIEDs is extensive. EMI from monopolar electrocautery or RF ablation can result in oversensing and inhibition of pacemakers, inappropriate tachyarrhythmia therapy from AICDs, device reset, pulse generator damage, lead damage, lead displacement, inappropriate rate-adaptive HR changes, inappropriate mode switching, impedance changes, and tissue damage by conduction through device leads.[152–154] One study identified a trend toward alterations in threshold and sensing in devices that required reprogramming postoperatively. One proposed explanation is changes in lead tissue interaction from intraoperative EMI.[151] However, other studies offer contrary evidence and suggest that these interactions are uncommon.[152,155]

External cardioversion or defibrillation can also result in tissue damage by conduction through leads and device reset.[154] Tachyarrhythmia therapies should be reenabled by removing a magnet or reprogramming to allow device-delivered therapy. If this is not feasible or effective, emergency guidelines must be followed. In an effort to minimize current through the device or leads, the pads should be placed as far away from the generator as possible and perpendicular to the axis of the CIED (eg, anterior to posterior).[140]

Although therapeutic irradiation in patients with CIEDs is not contraindicated, ionizing radiation can result in damage to the pulse generator or lead insulation. Evidence suggests that modern AICDs may be more susceptible to radiation damage than pacemakers. The damage incurred can result in electrical resets or AICDs unable to deliver a high voltage shock.[156,157] It is recommended that the device be shielded or relocated and interrogation be completed during and at the completion of radiation treatment.[140]

Current Recommendations

It is challenging to develop a perioperative CIED management algorithm that is universally applicable. Current recommendations from the ASA and HRS focus on an individualized, multidisciplinary approach with less reliance on direction from industry-employed allied health professionals and increased involvement of the primary CIED management team.[137,140,154] Although these recommendations excel at optimizing patient safety, strict adherence to them may not always be feasible because of the clinical situation or limited resources.

Alternative protocols for device management such as the pacing and cardioverting electronic device perioperative (PACED-OP) protocol (Table 45.10) advocate for more selective criteria for CIED reprogramming in an effort to operate within the confines of restricted resources and avoid reprogramming errors.[151] In response to high rates of reprogramming and interrogation, which require resources and personnel and create the potential for programming errors before and after surgery, the PACED-OP protocol provides a simplified perioperative management algorithm. The PACEP-OP protocol requires device reprogramming only when EMI was expected within a *critical zone* (ie, area between the mandible and the xiphoid) and the patient is pacemaker dependent or has an AICD. *Pacemaker dependency* was also simplified to encompass individuals who have a preoperative ECG displaying a paced rhythm.

TABLE 45.10 PACED-OP Protocol Summary for Perioperative Management of Automatic Implantable Cardioverter-Defibrillators

Clinical Situation	*Management*
Pacemaker-dependent patient or AICD + EMI in critical zone	Reprogram preoperatively and interrogate postoperatively
AICD + EMI outside the critical zone	Apply magnet (exception: devices with a reed switch)
Pacemaker-dependent patient + EMI outside the critical zone + bradycardia postoperatively	Interrogate postoperatively

AICD, Automatic implantable cardioverter-defibrillator; *EMI*, electromagnetic interference; *PACED-OP protocol*, pacing and cardioverting electronic device perioperative protocol.

AICDs are managed with a magnet if EMI is anticipated outside of the critical zone. Exceptions are AICDs that contain a reed switch, which are reprogrammed. Postoperatively, additional CIED interrogation is recommended only if an ECG-identified bradycardia occurred in a pacemaker-dependent patient who had electrocautery outside the critical zone. Implementation of the PACED-OP protocol resulted in a further decline in the rates of interrogation and reprogramming of CIEDs and produced no statistical difference in the rate of complications in the investigators' institution.[151]

Despite the fact that many organizations have released recommendations that call for increased involvement of the primary CIED management team and perioperative interrogation and reprogramming, anecdotes suggest these devices are frequently managed by magnet application or EMI avoidance. A few considerations regarding magnet application merit attention. Placing a pacemaker in an asynchronous mode may not be benign. The use of a magnet or programming to an asynchronous mode in a pacemaker with a ventricular lead can result in an R-on-T phenomenon and significant arrhythmia. The use of a magnet may result in atrial-ventricular dyssynchrony or a set rate that is disadvantageous in the setting of certain comorbidities (eg, CAD). There are also reports of magnet application permanently deactivating AICD tachyarrhythmia therapy. The perioperative use of a magnet should not be taken lightly or without careful consideration.

It is assumed that an overextension of the available programming resources and personnel and perioperative time constraints are reasons for the difference between the recommendations and clinical practice. In a movement similar to the evolution of intraoperative TEE, groups of specially trained anesthesiologists have taken on the responsibility of perioperative CIED management. In an effort to decrease perioperative programming delays, anesthesiologists at institutions such as the University of Washington interrogate devices preoperatively, reprogram if necessary, and restore the settings postoperatively.[158] Although the anesthesiologists' role in perioperative CIED interrogation is evolving, it is not unreasonable to expect anesthesiologists to play an increasing role in the future.[159]

Although not applicable to every situation, a general approach to perioperative CIED management is shown in Fig. 45.5. Perioperative management largely relies on determining the patient's CIED dependence and EMI potential. Based on the risk assessment, CIED management may require a magnet to be available, the use of a magnet, or interrogation and reprogramming.

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46 Echocardiography in Noncardiac Surgery

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KEY POINTS

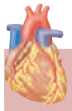
1. The portability, ease of use, and rapid diagnostic capability of transesophageal echocardiography (TEE) makes it the diagnostic modality of choice during acute hemodynamic instability.
2. Qualitative analysis of a condensed TEE examination aids in efficiency during the rapid diagnostic demands required in the emergency setting.
3. Rescue echocardiography is a process, not an event, and thus requires continuous reevaluation when treating hemodynamic instability.
4. Acute valvular insufficiency is evaluated in the same manner as chronic insufficiency with a focus on new-onset regurgitation or a large change in chronic regurgitation.
5. An intimal flap visualized on TEE is the best method of determining the presence of aortic dissection.
6. TEE findings in cardiac tamponade include hypoechoic fluid around the heart, systolic collapse of the right atrium, and exaggerated respiratory variation in right and left ventricular (LV) inflow and outflow.
7. The complex geometry of the right ventricle makes quantitative assessment of function difficult. Qualitative evaluation of right ventricular free wall thickening, tricuspid annular excursion, and interventricular septal shape aid in diagnosis of dysfunction.
8. Although echocardiography is not the tool of choice for diagnosing pulmonary embolism, it can help to guide management. The primary echocardiographic manifestations of pulmonary embolism are secondary to right heart failure.
9. LV dysfunction has multiple possible causes beyond ischemia. Qualitative assessment of function primarily through the LV short-axis view is a well-validated method of diagnosing dysfunction.
10. A hypercontractile left ventricle can lead to a dynamic outflow obstruction that is diagnosed by a "dagger"-shaped LV outflow pattern on Doppler imaging.
11. Alterations in the end-diastolic and end-systolic areas of the LV short-axis help determine whether hemodynamic instability is caused by hypovolemia or low afterload.
12. Pulsed-wave Doppler interrogation of the LV outflow tract can yield a stroke distance from which the stroke volume can be calculated.
13. The ability to assess multiple cardiac parameters, including contractility, valvular function, and loading conditions, makes TEE a valuable tool in general hemodynamic monitoring and goal-directed therapy.
14. In conjunction with echocardiographic assessments of stroke volume and contractility, Doppler-derived estimates of left atrial pressure can be used to evaluate the effectiveness of an intervention.
15. Transthoracic echocardiography can be very useful in the perioperative management of patients undergoing noncardiac surgical procedures. It can be substituted for TEE in many situations.

This chapter focuses on the applications of echocardiography to noncardiac surgical procedures. Echocardiography performed in the emergency setting, also known as rescue echocardiography, is discussed in detail. In addition, the utility of echocardiography as a hemodynamic monitor in general and the use of echocardiography in goal-directed fluid therapy are reviewed. Finally, the perioperative applications of transthoracic echocardiography (TTE) and instructions for performing a basic TTE examination are discussed.

Rescue Echocardiography

Echocardiography in general and transesophageal echocardiography (TEE) in particular are well suited for the rapid diagnostic demands of acute hemodynamic instability. The American Society of Echocardiography (ASE) recommends the use of TEE for acute, persistent, unexplained hypotension.[1] Unexplained hypotension has multiple possible causes that potentially require a wide range of diagnostic modalities. Echocardiography encapsulates these modalities through its ability to reveal disturbances in contractility, valvular function, volume, and intracardiac and extracardiac pressures (see Chapters 14–16). Echocardiography not only provides a detailed, quantitative analysis but also allows for qualitative monitoring through rapid visual assessment. The ease and speed with which echocardiography can reveal diagnoses make it an ideal diagnostic modality in the emergency setting and one that is easily teachable.[2]

Prospective data on the use of echocardiography in the emergency perioperative setting are sparse. Shillcutt and colleagues[3] looked retrospectively at 31 patients undergoing various types of noncardiac procedures who were evaluated by echocardiography (using both TEE and TTE modalities) during hemodynamic instability in the perioperative period. A diagnosis by echocardiography explained the hemodynamic instability in all patients. Of the 60% of patients who had a



BOX 46.1 RECOMMENDED LIMITED TRANSESOPHAGEAL ECHOCARDIOGRAPHY EXAMINATION

1. High esophageal AV SAX view
2. High esophageal AV LAX view
   - Measurement of LVOT diameter
3. High esophageal bicaval view
4. High esophageal RV inflow-outflow view
5. Midesophageal four-chamber view
   - With and without CFD on the TV and MV
6. Midesophageal two-chamber view
7. Midesophageal LV LAX view
8. Transgastric LV SAX view
9. Deep transgastric view
   - PWD of LVOT
   - Calculation of stroke volume
10. Descending aorta SAX view

AV, Aortic valve; *CFD,* color-flow Doppler; *LAX,* long-axis; LV, left ventricular; *LVOT,* left ventricular outflow tract; *MV,* mitral valve; *PWD,* pulsed-wave Doppler; *RV,* right ventricular; *SAX,* short-axis; *TG,* transgastric; *TV,* tricuspid valve.

preoperative TTE examination, two-thirds had a new cardiovascular (CV) abnormality to help explain the hemodynamic instability, thus highlighting the importance of reevaluation as hemodynamic values change. In addition, more than one-half of the patients had a change in their CV support regimen, and 13% underwent additional surgical procedures based on the echocardiographic findings. Markin and associates[4] retrospectively looked at 364 perioperative rescue echocardiograms also using both TEE and TTE modalities. In this study, evaluation of hemodynamic instability was performed throughout the perioperative period. A change in management occurred in 59% of the patients studied, including a change in surgical management in 7% (see Chapter 15).

Inherent in the assessment of hemodynamic instability is urgency. The cause of the instability must be rapidly diagnosed and managed. To aid in efficiency, rescue echocardiography is best performed through a qualitative analysis of a condensed examination. The value of focusing on visual estimation of hemodynamic parameters instead of a detailed quantitative analysis is recognized by the ASE and the Society of Cardiovascular Anesthesiologists (SCA), which created training pathways for basic TEE certification.[5] The echocardiography literature is replete with examples of practitioners with limited training who accurately perform and evaluate echocardiographic examinations by using primarily qualitative analyses.[6–9,9] The comprehensive TEE examination is effective but time consuming (see Chapter 14). A condensed examination focusing only on the essential views significantly improves efficiency. The limited examination (Box 46.1) is a modification of the 11 cross-sectional views recommended by the ASE and SCA for the basic TEE examination and covers most clinically relevant disorders. Cardiac disturbances found on the limited examination can be further analyzed by using appropriate additional views. In agreement with the ASE and SCA,[5] we suggest performing and storing the examination in its entirety before focusing on segments specific to the area of interest. Similar protocols have been studied and used effectively.[4,10,11]

Rescue echocardiography is a process, not an event. The CV system is complex and dynamic, changing frequently based on loading conditions. What may be considered an appropriate intervention one minute may not be the next. In the report by Markin and colleagues,[4] 14% of the patients reviewed had no findings to explain their hemodynamic instability. It is often difficult to discern the precise cause of the CV abnormality, particularly with regard to low afterload, hypovolemia, and right ventricular (RV) and left ventricular (LV) dysfunction. In addition, multiple abnormalities are often present. Markin and associates[4] suggested a "best guess" of the abnormality, followed by reevaluation after the proposed intervention. If parameters improve, the intervention should be continued. If they do not improve or worsen, an alternate diagnosis should be sought.

The most common causes of hemodynamic instability are acute valvular and aortic disease, cardiac tamponade, RV dysfunction, pulmonary embolism (PE), and LV hypocontractility and hypercontractility.

TABLE 46.1 Causes of Acute Valvular Dysfunction

AV Insufficiency	*MV Insufficiency*
Endocarditis	Endocarditis
Aortic dissection	Chordal rupture
Chest trauma	Papillary muscle rupture
Iatrogenic causes	Ischemic cardiomyopathy Iatrogenic causes

AV, Aortic valve; *MV,* mitral valve.

Acute Valvular Dysfunction

Although it must be considered in the differential diagnosis, acute valvular insufficiency is an unlikely cause of hemodynamic instability. If it occurs, it is more likely to occur on left-sided valvular structures.[11] Potential causes of acute aortic valve (AV) and mitral valve (MV) insufficiencies are listed in Table 46.1. The echocardiographic evaluation of valvular dysfunction is similar regardless of the acuity of the dysfunction. Assessment of valvular regurgitation with rescue echocardiography should be limited to a rapid, qualitative assessment. Quantitative measures such as effective regurgitant orifice area and regurgitant volume may be inaccurate in acute regurgitation.[12] Visual assessment of the regurgitant jet with color-flow Doppler (CFD) focusing primarily on the vena contracta is the preferred approach. It is unlikely that any regurgitation that is less than moderate to severe would cause significant hemodynamic instability. Because chronic regurgitation leads to myocardial remodeling, moderate-to-severe regurgitation in the setting of a normal ventricular size should alert the clinician to the high probability of new-onset dysfunction. Noting new-onset regurgitation or a large change in chronic regurgitation is more important than grading the severity of the regurgitation. Acute or subacute regurgitation in the setting of hemodynamic instability may be either the cause or a manifestation of changes in ventricular function and loading induced by another cardiac abnormality. Treatment of the underlying abnormality may improve the regurgitation.

Acute Aortic Disease

The echocardiographic assessment of aortic dissection and traumatic aortic rupture is discussed in Chapter 23 and is mentioned only briefly here. The mortality rate is high in acute dissection of the thoracic aortic and increases with a delay in diagnosis.[13] Helical computed tomography, magnetic resonance imaging, and TEE are equally reliable for diagnosing or ruling out a dissection,[14] but TEE has the advantage of portability. The diagnosis of dissection is based on the detection of an intimal flap that divides the aorta into true and false lumina[15] (Video 46.1). Color-flow interrogation of the aorta helps to discern the true lumen from the false lumen. TEE is also valuable in assessing for intimal tears, intramural hematomas,[16] and penetrating ulcers.[17] Equally important as identifying dissection is identification of associated complications such as acute aortic regurgitation and pericardial effusions with or without tamponade.

Cardiac Tamponade

Proper identification of pericardial tamponade is vital because the hemodynamic consequences can be devastating and the treatment is specific: maintain contractility and preload, and drain the pericardial fluid. The pericardium consists of two layers: visceral and parietal. The visceral layer adheres to the epicardium, and the parietal layer is the

BOX 46.2 CAUSES OF PERICARDIAL EFFUSIONS

Trauma
Inflammation
Infection
Malignant disease
Renal or hepatic failure
Post–myocardial infarction status

BOX 46.3 NORMAL RESPIRATORY VARIATION

RV inflow <25%
LV inflow <15%
RV outflow <10%
LV outflow <10%

LV, Left ventricular; *RV,* right ventricular.

TABLE 46.2 Respiratory Variation in Right and Left Ventricular Inflow in the Setting of Tamponade

	Mechanical Ventilation		Spontaneous Ventilation	
	Inspiration	*Expiration*	*Inspiration*	*Expiration*
RV inflow-outflow	↓	↑	↑	↓
LV inflow-outflow	↑	↓	↓	↑

LV, Left ventricular; *RV,* right ventricular; ↑, increased; ↓, decreased.

TABLE 46.3 Suggested Views for Doppler Interrogation of Ventricular Inflows and Outflows

	View	*PWD Placement*
RV inflow	Modified bicaval	TV leaflet tips
RV outflow	TG RV inflow/outflow	RVOT
LV inflow	ME 4-chamber	MV leaflet tips
LV outflow	Deep TG	LVOT

LV, left ventricular; *LVOT,* left ventricular outflow tract; *ME,* midesophageal; *MV,* mitral valve; *PWD,* pulsed-wave Doppler; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *TG,* transgastric; *TV,* tricuspid valve.

fibrous sac surrounding it. Five to 10 mL of fluid is normally found between the layers. Potential causes of pathologic fluid accumulation are listed in Box 46.2. The pericardium is of limited size and distensibility, thereby restraining the four chambers and dampening the effects of changes in intrathoracic pressure. Acute effusions are most likely secondary to trauma (including surgical) or myocardial infarction. Pericardial tissue affected by chronic effusion tends to be more distensible and thus causes less hemodynamic instability. The effusion can envelop the space in a free-flowing fashion or may be loculated, affecting only a portion of the heart. Free-flowing effusions tend to accumulate in the dependent portion of the space. Pericardial fat is a relatively common finding in the anterior space and should not be confused with fluid accumulation (see Chapter 24).

Pressures within the pericardium and cardiac chambers during fluid accumulation follow a recognized pattern.[18] Initially, fluid accumulation in the pericardial space compresses the right ventricle and causes the filling pressures to rise with little effect on the stroke volume (SV) of either ventricle. As the pericardial pressures rise, the right ventricle begins to collapse, but the thicker-walled left ventricle is unaffected. In the final stage, both the RV and LV SVs are significantly affected as the pericardial pressure determines passive flow. The external pressure on the cardiac chambers also exaggerates the normal respiratory variation in RV and LV SVs.. In mechanically ventilated patients, elevated intrathoracic pressure compresses the superior vena cava (SVC) and inferior vena cava and thus reduces RV preload and SV. At the same time, LV preload and SV are enhanced by increasing return from the inflated lungs. Intrathoracic and pericardial pressures decrease on expiration, augment flow into the right ventricle, and push the interventricular septum into the left ventricle. Diastolic filling and LV SV are thus reduced. In the physiologically normal patient, these hemodynamic swings are minimal. Box 46.3 lists the values for normal respiratory variation in the right and left ventricles, and Table 46.2 summarizes the changes in SV associated with cardiac tamponade.

The limited TEE examination should be performed in its entirety because some hemodynamically significant effusions may be difficult to visualize. Pericardial effusions are viewed as darkened areas between the heart and the parietal pericardium. No universally accepted rule exists for quantification, but effusions measuring less than 1 cm are considered small, effusions of 1 to 2 cm are considered moderate, and those larger than 2 cm are considered large. Echogenic "standing" in the pericardial space alerts the examiner to the possibility that the effusion is inflammatory or hemorrhagic. In the case of extreme hemodynamic instability, a large pericardial effusion should be considered to cause cardiac tamponade regardless of the results of the continuing study.

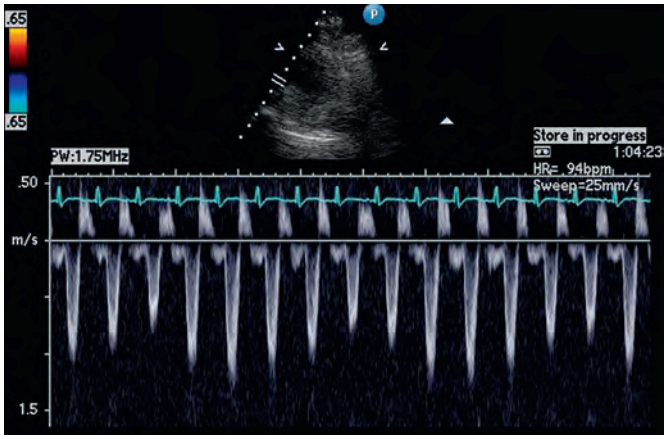


Fig. 46.1 Pulsed-wave echocardiographic interrogation of the left ventricular outflow tract by using the deep transgastric view in a patient with tamponade physiology showing respiratory variability. *HR,* Heart rate.

Pulsed-wave Doppler (PWD) interrogation of RV inflow or outflow may reveal exaggerated respiratory variations. These changes are the earliest signs of tamponade physiology and are followed by exaggerated variations in LV inflow and outflow. Because of the position and variable anatomy of the right ventricle, Doppler assessment of RV inflow and outflow can prove difficult, particularly within the time constraints of rescue echocardiography. LV inflow is best assessed in the midesophageal (ME) four-chamber view with the PWD cursor placed at the MV leaflet tips (Table 46.3). LV outflow is best assessed by placing the PWD cursor in the LV outflow tract (LVOT) seen in the deep transgastric (TG) view (Fig. 46.1). The sweep speed should be 25 to 50 mm/second to view the variability most clearly. With increasing fluid accumulation the pericardial pressure starts to exceed the right atrial (RA) pressure, thereby causing exaggerated atrial systolic (ie, ventricular diastolic) contraction that extends into atrial diastole (ie, ventricular systole). Assessment of this collapse is best performed in the ME RV inflow-outflow view or the ME four-chamber view (Videos 46.2 and 46.3). As the pericardial pressure increases further, the right ventricle begins to collapse in diastole. The RV outflow tract is most likely to collapse, and thus the preferred view is the RV inflow-outflow view (Box 46.4). A similar collapse of the thicker left-sided structures would indicate very high pericardial pressures. Once the diagnosis is

BOX 46.4 SUMMARY OF ECHOCARDIOGRAPHIC FINDINGS IN PERICARDIAL TAMPONADE

Pericardial effusion
Late diastolic or early systolic right atrial collapse
Diastolic right ventricular collapse
Increased respiratory variation in mitral inflow and left ventricular outflow tract

BOX 46.5 ECHOCARDIOGRAPHIC PARAMETERS OF RIGHT VENTRICULAR DYSFUNCTION

Dilated right ventricle
- Basal RVEDD >4.2 cm
- Mid-RVEDD >3.5 cm
- RVOT EDD >2.7 cm

Dilated right atrium
- RA area >18 cm^2
- RA length >5.3 cm
- RA diameter >4.4 cm
- Bowing into left atrium

Decreased RV contraction
- TAPSE <16 mm
- RV FAC <35%

Evidence of elevated PA pressures
- Pulmonary artery diameter >21 mm
- "D-shaped" ventricular septum

Worsening TV regurgitation

EDD, End-diastolic diameter; *FAC*, fractional area change; *PA*, pulmonary artery; *RA*, right atrial; *RV*, right ventricular; *RVEDD*, right ventricular end-diastolic diameter; *RVOT*, right ventricular outflow tract; *TAPSE*, tricuspid annular-plane systolic excursion; *TV*, tricuspid valve.

established, echocardiography can be a useful adjunct to guide needle placement during pericardiocentesis.[19]

Right Ventricular Dysfunction

RV failure, defined as the inability of the right ventricle to provide adequate blood flow to the left ventricle in the setting of normal central venous pressure, is associated with a high mortality rate in both cardiac and noncardiac surgical procedures.[20] Potential causes of RV failure are numerous and include the following: RV contractile dysfunction as seen in ischemia, volume overload, sepsis, and nonischemic cardiomyopathy; and the acute elevations in pulmonary artery pressures seen in hypoxia, acute respiratory distress syndrome,, LV dysfunction, and PE.[21] Abrupt, catastrophic RV dysfunction can result once the contractile reserve is reduced secondary to a feedback loop involving RV dysfunction, reduced cardiac output (CO), and decreased coronary perfusion causing worsening RV dysfunction (see Chapter 26).

Because the anatomy and function of the right ventricle are complex, geometric modeling and quantitative analysis are very difficult.[22] For this reason, the echocardiographic assessment of RV function in the emergency setting should be qualitative, and this approach is as good as magnetic resonance imaging at detecting dysfunction.[23] Box 46.5 summarizes the echocardiographic manifestations of RV dysfunction.[24] Visual assessment begins with inspection of right-sided chamber sizes to look for dilation of the right ventricle and right atrium. Encroachment into the left side with right-to-left bowing of the intraatrial septum (seen best in the four-chamber and bicaval views) and a "D-shaped" intraventricular septum (seen best in the LV short-axis [SAX] view) indicates elevated right-sided pressures (Videos 46.4 and 46.5). RV contractility can then be assessed by the fractional

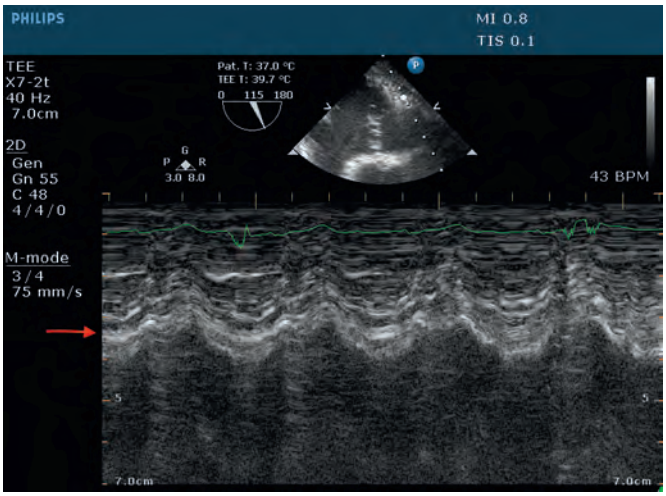


Fig. 46.2 An example of tricuspid annular plane excursion using M-mode echocardiography on the tricuspid annulus. The red arrow points to the tricuspid annulus. A visual estimation of the annular movement suggests good right ventricular function. *TEE*, Transesophageal echocardiography.

area change (FAC) and/or the tricuspid annular-plane systolic excursion (TAPSE). The RV FAC is calculated by measuring the RV end-systolic and end-diastolic areas (RVESA and RVEDA, respectively) in the four-chamber view and using the following equation: [RVEDA—RVESA] / RVEDA. A reduced FAC has significant prognostic value in myocardial ischemia and PE.[24] TAPSE is best measured by placing the M-mode cursor on the tricuspid annulus in the modified bicaval or TG RV inflow-outflow views and measuring the distance the annulus moves from systole to diastole (Video 46.6 and Fig. 46.2). A distance of less than 1.5 cm is considered abnormal.[25] For purposes of rescue echocardiography, a qualitative assessment of the TAPSE and the RV free wall in the ME RV inflow-outflow and four-chamber views is preferred.

Pulmonary Embolism

The immobility and hypercoagulability associated with surgical procedures increase the risk of PE fivefold. This risk is only partially mitigated by prophylactic measures.[26] Early diagnosis and treatment can reduce the overall mortality 10-fold.[27] The examiner should have a high suspicion for PE in hemodynamically unstable patients with malignant disease, prolonged immobilization, obesity, and/or tobacco use, as well as in patients who use oral contraceptives, hormone replacement therapy, or antipsychotic drugs. The surgical procedures with the highest risks of PE are those associated with hip fractures, acute spinal cord injuries, and general trauma. The pathophysiology of PE begins with an abrupt increase in pulmonary artery pressures. Hypoxia and vasoconstriction worsen pulmonary vascular resistance. RV wall tension and oxygen demand increase, leading to subendocardial ischemia, RV dilation, and regional wall motion abnormalities (RWMAs). The intraventricular septum shifts left, and this shift reduces LV diastolic filling and SV. Overall, the cardiac pathophysiology of PE is complex, involving the interplay of wall tension, ischemia, structural damage, and inflammation[28] (see Chapters 26 and 51).

Although TEE can help guide both diagnosis and management, it is not the gold standard. Echocardiography has high specificity and low sensitivity (90% and 56%, respectively).[29] In fact, end-tidal carbon dioxide is a significantly better diagnostic tool.[30] Although visualization of a clot, which can be found anywhere on the right side from the venae cavae to the pulmonary artery, is pathognomonic of PE and can be seen in more than 80% of cases, the presence of a thrombus does not predict death[30] (Video 46.7). The ideal views to assess for thrombus include the ME bicaval, RV inflow-outflow, and ascending

aorta SAX views. The main and right pulmonary arteries can be seen by withdrawal of the probe to the high esophagus until a cross-section of the ascending aorta is obtained. The left pulmonary artery is often obscured by the trachea. The most clinically useful echocardiographic findings in the setting of PE are those associated with acute RA and RV failure. Bowing of the intraatrial septum to the left indicates high RA pressures, which can be particularly problematic in the setting of a patent foramen ovale. A patent foramen ovale in a patient with PE doubles the mortality rate and quintuples the rate of ischemic stroke, and aggressive thrombolytic treatment is therefore warranted.[31] RV wall motion abnormalities are the most common echocardiographic findings in patients with PE.[30] The extent of RV dysfunction correlates with the overall clot burden, with perfusion defects larger than 20% to 25% more likely to cause dysfunction and dilation.[32,33] A reduced TAPSE correlates with mortality rates,[34] and it can predict the extent of the clot burden as well as residual perfusion defects when the RV dilation has resolved.[35]

RV dysfunction in the setting of PE predicts mortality rates,[36] even in normotensive patients.[37] McConnell and colleagues[38] suggested that RV dysfunction in the setting of PE had a distinct pattern of RWMAs consisting of a hypokinetic free wall and a normal to hyperdynamic apex (Video 46.8), with a sensitivity of 77% and a specificity of 94% in predicting PE. Subsequent studies, however, found reduced sensitivity and specificity,[39] and they even suggested a "reverse" McConnell sign as an indication of PE.[40] RV pressure overload also "flattens" the interventricular septum, thus reducing left-sided filling and CO. The subsequent reduction of coronary perfusion as well as the structural and inflammatory changes in the myocardium can lead to LV dysfunction. A low ejection fraction (EF) is an independent predictor of death.[34] In addition to the diagnosis of PE, echocardiography can aid in assessing the effectiveness of treatment. If a thrombus is visualized at presentation, continuous assessment of the thrombus during thrombolytic administration can show resolution of the clot and return of normal RV function.[41] Echocardiography can also be useful in following the return of RV function over longer periods of time.[35]

Left Ventricular Hypocontractility

Although LV dysfunction has many potential causes, the echocardiographic manifestations are similar. The SCA recommended a qualitative estimation of the LVEF when assessing candidates who may benefit from inotropic therapy.[5] Visual estimation, or "eyeballing," has been validated with Simpson's biplane method,[42] three-dimensional echocardiography,[43] and radionuclide angiography[4–46] In addition, visual estimation of LV function can be accurately performed by noncardiologists[47,48] and clinicians with only limited training.[9,49] The primary method of visual estimation of LV contractility is through the FAC as seen in the LV SAX view. The LV FAC is calculated by measuring the LV end-systolic and end-diastolic areas (LVESA and LVEDA, respectively) in the LV SAX view and using the following equation: [LVEDA – LVESA] / LVEDA (Videos 46.9 and 46.10). The normal values are similar to the normal values for EF.[50] Initially, the calculation should be performed to assess contractile function. However, with more experience (≈≥20 studies[51]), a visual estimate is reliable. However, in patients with regional dysfunction the LV SAX view may miss some pathologic features.[52] A brief, qualitative assessment of the left ventricle in the four-chamber, two-chamber, and long-axis (LAX) views to look for hypokinetic walls aids in the diagnosis. Particular attention should be paid to the apex because it contributes a significant portion of the overall EF (Video 46.11).

When LV dysfunction is encountered, it is important to identify myocardial ischemia as the mechanism quickly because early revascularization improves outcomes.[53] The echocardiographic manifestations of myocardial ischemia occur earlier and are more sensitive than the electrocardiogram,[54,55] even in anesthetized patients.[56] Segmental wall thickening of less than 30% suggests ischemia and can manifest within seconds.[54] Distinguishing between new-onset RWMAs and hypokinesis from chronic ischemia can be difficult. Intraoperative pharmacologic stress testing is ideal,[57] but it is often not practical in the urgent setting. Acute ischemia therefore must be diagnosed by a change in RWMA from baseline by two grades (ie, from normal to severe hypokinesis) in two or more segments.[58] Infarcted myocardium often appears thinner and brighter than surrounding tissue and is therefore easily distinguished from myocardium with acute ischemia. Complications of ischemia such as acute diastolic dysfunction, mitral regurgitation, and papillary muscle rupture can also aid in the diagnosis.

In addition to LV ischemia, the stress, inflammation, and catecholamine excess associated with acute illness can reduce LV contractility. Potentially reversible secondary cardiomyopathies can develop in patients with numerous noncardiac critical illnesses.[59] Sepsis-induced cardiomyopathy, for example, may occur in more than one-half of patients with sepsis as a result of inflammatory mediators, bacterial endotoxins, catecholamines, and microcirculatory dysfunction.[60,61] LV and RV dysfunction ensues, with global and RWMAs, as well as worsening measures of diastolic function[59] (Video 46.12). The myocardial toxicity from excess catecholamines, whether through septic shock, drug administration,[62] or stress,[63] can also induce LV dysfunction. Stress-induced cardiomyopathy, also known as takotsubo cardiomyopathy, is a form of catecholamine-mediated ventricular dysfunction induced by physical or emotional stress.[61] Takotsubo cardiomyopathy most often manifests with normal to hyperkinetic basal function and hypokinesis of the apex,[64] likely secondary to an increased density of β-adrenergic receptors in the apex. The LV apex often appears to "balloon" out,[65] and this is the most prominent feature found on echocardiography.

Left Ventricular Hypercontractility and Left Ventricular Outflow Tract Obstruction

An often overlooked consequence of a hyperdynamic left ventricle, whether secondary to low afterload, hypovolemia, or inotropic support, is dynamic LVOT obstruction (LVOTO). Although often associated with hypertrophic cardiomyopathy, LVOTO has been reported in the setting of hypertension,[66] type 1 diabetes,[67] myocardial ischemia,[68,69] pheochromocytomas,[70] takotsubo cardiomyopathy,[71,72] valvular replacements and repairs[73,74] and catecholamine administration.[75,76] The mechanism of LVOTO remains unclear and varies by cause.[66] The primary mechanism likely results from localized increases in flow velocity during ejection that results from a narrow LVOT from LV thickening and/or hypovolemia. This change causes the anterior mitral leaflet and chordae to be drawn toward the septum through both a Venturi effect and a hydrodynamic "drag."[77,78] This process distorts the mitral leaflet coaptation and results in middle- to late-systolic mitral regurgitation. Precipitating factors that further narrow the LVOT include hypovolemia, sepsis, inotropic agents, and diuretic agents. LVOTO should be considered in any hemodynamically unstable patient with risk factors for LVOT narrowing whose hemodynamic status worsens with inotropic support.

On echocardiographic examination, the left ventricle likely appears underfilled and hypercontractile. LV hypertrophy of varying degrees and morphologic features may be present. It is often possible to see movement of the anterior leaflet of the MV toward the upper septum in the ME LAX view (Video 46.13). CFD may show mitral regurgitation with an anteriorly directed jet that begins in middle- to late-systole. CFD may also show turbulent flow in the LVOT (Video 46.14). This finding is often the initial indicator of altered ejection dynamics in LVOTO. The hallmarks of LVOTO are a "dagger"-shaped spectral Doppler pattern in the LVOT and midsystolic closure of the AV. Early systolic ejection is usually normal because it takes time for the flow velocity to build. Obstruction occurs late in ventricular contraction, thus causing flow to diminish transiently and resulting in partial closure of the AV. M-mode interrogation of the AV in the ME LAX view shows a "notch" indicating midsystolic partial closure of the AV with a secondary opening. In addition, this dynamic property of the obstruction yields a late-peaking continuous-wave Doppler pattern as the gradient tends to develop in middle- to end-systole producing

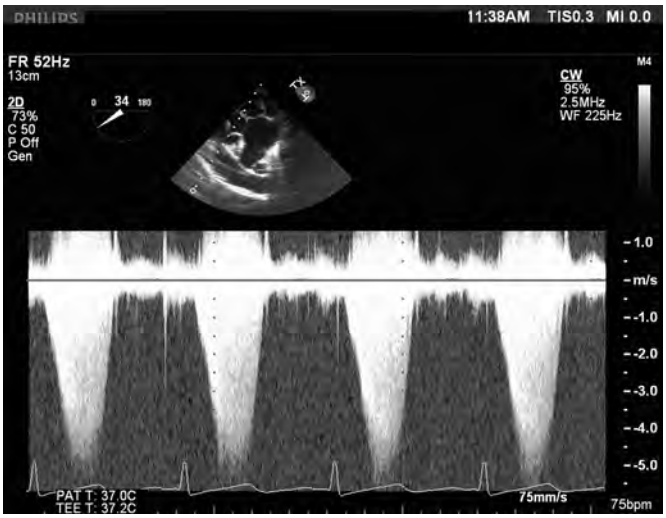


Fig. 46.3 Continuous-wave Doppler echocardiography in the left ventricular outflow tract of a patient with dynamic left ventricular outflow tract obstruction reveals a "dagger"-shaped waveform. *CW,* Continuous-wave; *FR,* frequency.

TABLE 46.4 Example of the Effects of Hypovolemia and Low Afterload on End-Diastolic and End-Systolic Volumes[a]

	EDV (mL)	*SVR*	*EF (%)*	*ESV (mL)*
Patient A	100	Normal	50	50
Patient B (hypovolemia)	50	Normal	50	25
Patient C (low afterload)	100	Low	75	25

[a]End-diastolic and end-systolic areas in the left ventricular short-axis view should reflect the changes in volumes.

EDV, End-diastolic volume; *EF,* ejection fraction; *ESV,* end-systolic volume; *SVR,* systemic vascular resistance.

a "dagger" shape (Fig. 46.3). The peak velocity of the wave is high, consistent with an elevated pressure gradient. The gradient can be measured by tracing the waveform.

Hypovolemia and Low Afterload

Cardiac tamponade, PE, and severe LV and RV dysfunction are relatively infrequent causes of hemodynamic instability. More commonly, reduced afterload or preload is encountered. A qualitative assessment of volume and afterload begins with LV end-diastolic and end-systolic areas (LVEDA and LVESA, respectively) in the TG SAX view, as well as Doppler quantification of SV. The LVEDA reflects the amount of fluid in the left ventricle. A euvolemic patient usually has a normal LVEDA. If the same patient also has reduced systemic vascular resistance, the LVEDA usually remains normal because the preload is unchanged. Conversely, the LVEDA of a hypovolemic patient is often reduced. The LVESA, in contrast, should reflect the end point of the LVEF. A hypovolemic patient who starts off with a reduced LV diastolic volume (reduced LVEDA), ends with a reduced systolic volume (reduced LVESA). Alternatively, a patient with a normal LV diastolic volume (normal LVEDA) but an elevated EF secondary to reduced afterload also ends with a reduced end-systolic volume (reduced LVESA). As examples, consider the patients with varying LV end-diastolic volumes, EF, and systemic vascular resistance in Table 46.4. Video 46.15 shows an example of a patient with hypovolemia compared with a patient with low afterload.

Normal values for LVEDA are 8 to 14 cm^2.[79] These values may vary depending on multiple factors,[80] including age, sex, FAC,[81] and even the anesthetized state.[49] LV SAX assessment by TEE has been shown to

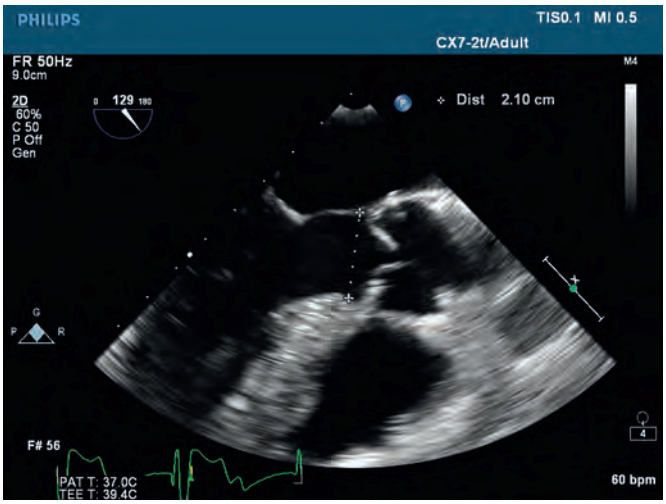


Fig. 46.4 Measurement of the left ventricular outflow diameter in the echocardiographic left ventricular long-axis view. *FR,* Frequency.

be a reasonable method of assessing ventricular volumes,[82–84] and it is more accurate than pulmonary artery occlusion pressures.[85] In addition, evidence indicates a correlation between LV volume and LVEDA in animals,[86,87] pediatric patients after congenital heart defect repair,[88] and anesthetized cardiac patients.[89] Cheung and associates[89] found the LVEDA to decrease linearly at 0.3 cm^2 per reduction in 1% of the estimated blood volume in cardiac patients. Several other studies confirmed the correlation between LV volume and LVEDA,[90–92] although at varying strengths of correlation. A correlation between a reduced LVESA and hypovolemia has also been established.[93] A direct relationship between a low LVESA and low afterload, however, has not been well established in the literature.[93,94] A qualitative assessment of the LVEDA and LVESA can therefore suggest hypovolemia, low afterload, or both, but it may require further evaluation through an estimation of SV to confirm the diagnosis.

Stroke Volume Assessment

A reduced LVESA likely represents either hypovolemia or low afterload. Hypovolemia results in a reduction in SV, whereas low afterload results in a high-CO state. SV can be calculated using the LVOT area and stroke distance.[95] The LVOT diameter is usually measured in the LV ME LAX view (Fig. 46.4), but it can be measured in any image that allows for an unobstructed view of the LVOT. The measurement should be obtained at the same level as the PWD cursor, usually approximately 5 mm proximal to the AV, measured from endocardium to endocardium.[95] Because the radius is squared, small inaccuracies in this measurement can introduce significant errors in the overall calculations. For this reason, it is important to use the baseline annular measurement for all calculations when performing serial SV measurements. The stroke distance, which is the average distance a red blood cell travels during systolic ejection, can be calculated by measuring the red blood cell velocities in the LVOT with PWD. This parameter is best measured in the deep TG or TG LAX views because of the parallel alignment between the flow and the transducer. The PWD cursor should be placed just proximal to the insertion of the AV leaflets. The image obtained is of the velocities (ie, speed and direction) of the red blood cells in the LVOT over time (Fig. 46.5). The machine can then calculate the velocity-time integral (VTI) after tracing the outer border of one of the waveforms. The VTI is the calculated stroke distance. To understand this concept better, consider a car traveling 70 miles an hour for 2 hours. Fig. 46.6 shows this plotted on a graph with velocity on the y-axis and time on the x-axis. The area of the rectangle created by these measurements would yield a distance (ie, 70 mph × 2 h = 140 miles). The VTI is similar to this calculation in that it is the area under the curve of red blood cell velocities over time. In this case,

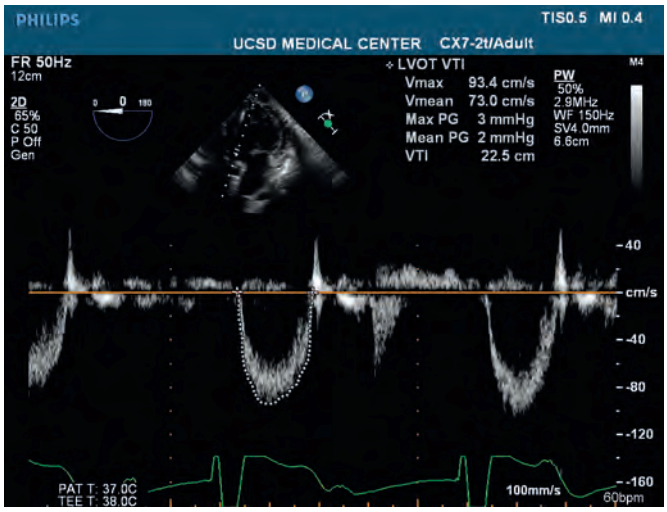


Fig. 46.5 Left ventricular outflow tract *(LVOT)* velocity waveforms obtained in the echocardiographic deep transgastric view. *FR,* Frequency, *PG,* pressure gradient; *PW,* pulsed-wave; *Vmax,* maximum velocity; *Vmean,* mean velocity; *VTI,* velocity-time integral. *(Courtesy University of California San Diego, La Jolla, Calif.)*

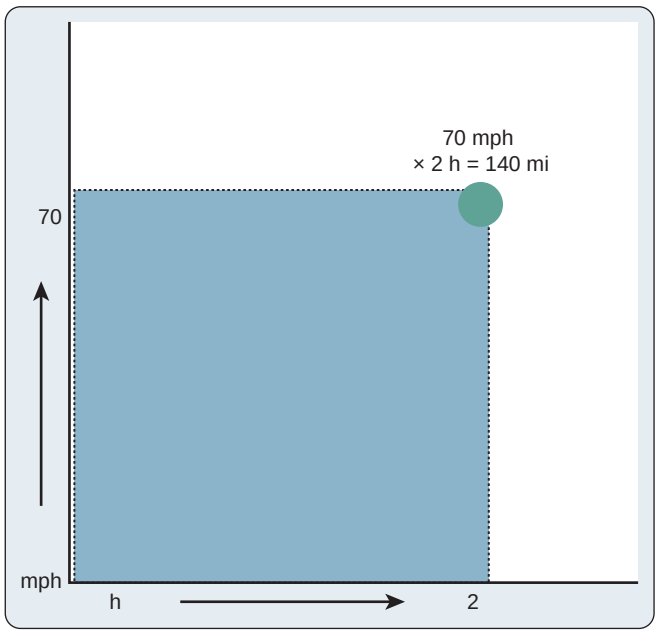


Fig. 46.6 Area under the curve for a velocity-time graph. If a car is going 70 miles per hour for 2 hours, one can calculate the distance traveled (ie, 140 miles) by calculating the shaded area. The same principle applies to the velocity-time graph obtained through spectral Doppler echocardiography. The area under a curve obtained in the left ventricular outflow tract using pulsed-wave Doppler yields a distance (centimeters). This is called the velocity-time integral.

the velocities are represented by centimeters per second, the time by seconds, and the VTI by centimeters (see Chapters 14 and 15).

The calculation of SV assumes a cylindrical LVOT with the volume being the product of the area and the length. The area of a circle is π × radius^2 or diameter^2 (D^2) × 0.785. The length is represented by the VTI. SV is expressed in milliliters and can be calculated using the following equation:

$$SV = D^2 \times 0.785 \times VTI$$

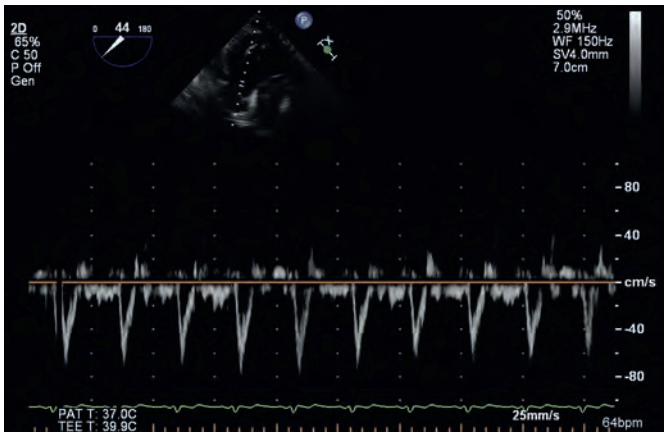


Fig. 46.7 Deep transgastric echocardiographic view with the pulsed-wave Doppler probe placed in the left ventricular outflow tract. The respiratory changes seen in the peak velocities indicate fluid responsiveness.

CO can then be calculated by multiplying SV by the HR. This method of SV calculation has been validated when compared with thermodilution,[96,97] and it is the ASE-recommended method for determining CO.[95]

Dynamic Indicators of Hypovolemia

Although changes in LVEDA and LVESA show that the cardiac chambers fill with volume administration, they do not predict whether volume administration improves SV[98] (ie, volume responsive). Dynamic indices, conversely, assess the effects of a change in preload on SV or its surrogate.[99] Positive-pressure ventilation increases pleural and transpulmonary pressures, which reduce RV preload and increase RV afterload, respectively. This process reduces overall RV SV. At the same time, insufflation pushes blood out of the lungs into the left ventricle, thus augmenting LV SV. After several beats, the reduced RV SV results in reduced LV preload and hence reduced SV, which can be seen at end-expiration. These changes are exaggerated when the ventricles are on the steep part of the Frank-Starling curve. The magnitude of the variation has been shown to predict fluid responsiveness (see Chapter 47). Euvolemia puts the ventricles on the flatter portion of the curve and limits respiratory variability. PWD interrogation of the LVOT has been shown to assess these changes in SV accurately and thus predict fluid responsiveness[100–102] (Fig. 46.7). Feissel and colleagues[11] derived the following equation in which V_{min} represents the minimum velocity in the LVOT, and V_{max} the maximum velocity, and Δ represents change:

$$\Delta V_{peak}(\%) = 100 \times (V_{max} - V_{min})/[(V_{max} - V_{min})/2]$$

A ΔV_{peak} of 12% or greater indicates volume responsiveness with a sensitivity of 100% and a specificity of 89% (as indicated by an increase in cardiac index by ≥15%). ΔV_{peak} was found to decrease after fluid administration. In addition, with a negative predictive value of 100%, these data suggest that no patient with a ΔV_{peak} of less than 12% responds to fluid administration. Volume responsiveness can also be measured by M-mode interrogation of the SVC in the LAX view (ie, in the ME bicaval view) or the SAX view (ie, in the ascending aorta SAX view) to look for collapsibility during respiration (Fig. 46.8). Vieillard-Baron and associates[103] derived the following equation in which D_{min} represents the minimum diameter and D_{max} the maximum diameter:

$$\text{SVC collapsibility index} = (D_{max} - D_{min})/D_{max}$$

An SVC collapsibility index greater than 36% discriminated between responders (an increase of 11% in cardiac index with a 10 mL/kg fluid bolus) and nonresponders with a sensitivity of 90% and a specificity

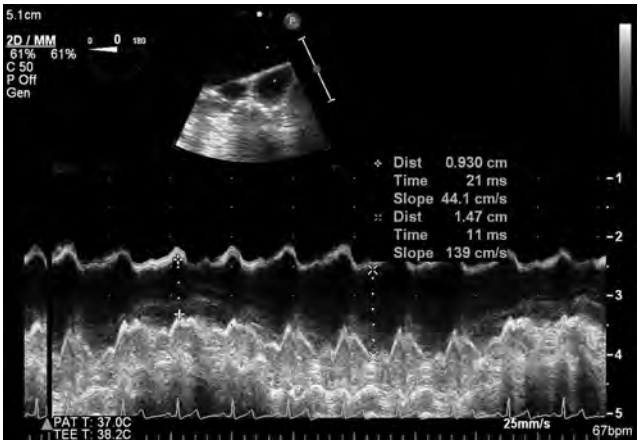


Fig. 46.8 Ascending aorta short-axis echocardiographic view. The right pulmonary artery is at the top of the screen. The superior vena cava is in the short axis beneath it. Note the collapsibility with positive-pressure ventilation.

of 100%. Spontaneous ventilation, cardiac arrhythmias, and low tidal volumes limit the accuracy of both these measurements.

Transesophageal Echocardiography as a Monitor in Noncardiac Surgical Procedures

An Argument for Use as a Monitor in Noncardiac Cases

The hemodynamic status of the intraoperative patient need not be acutely unstable for TEE monitoring to be effective. Although distinct entities such as PE and tamponade have been discussed, it is the effect of these processes on preload, afterload, contractility, and thus SV that is most important to diagnosis and treatment. It is well known that general anesthesia affects all these parameters.[104] TEE is well suited to assess the more moderate changes in hemodynamic values that occur with surgical procedures and general anesthesia. Although evidence of the outcome benefits of intraoperative TEE as a monitor is currently lacking, evidence does indicate that echocardiography can change perioperative morbidity.[105] In addition, a significant number of data indicate that the information gained from echocardiography can change perioperative management[106–111] and management in the intensive care unit.[47,112–15] As an example, Denault and associates[116] showed that intraoperative TEE in noncardiac surgical procedures not only changed management in those patients with category I indications (67% change in management) but also changed management 20% to 30% of the time in patients with category II and III indications. The benefits are clear, and the complication rate is low, with an overall morbidity rate of 0.2% and a 0% mortality rate.[117,118] The ASE and SCA currently recommend a noncomprehensive examination for intraoperative monitoring and cite that it can "dramatically influence a patient's intraoperative management."[5]

The data supporting the use of TEE as a monitor in noncardiac surgical procedures also apply to specific clinical situations. In addition to its use as a monitor for ischemia and volume in the high-risk vascular surgical patient,[119,120] TEE is valuable in assessing ventricular changes during aortic cross-clamping,[121,122] as well as to guide endovascular stent placement and monitor for complications.[123–125] In fact, TEE is more sensitive and specific than angiography in detecting leaks and thrombi,[123,126] and it can change the surgical procedure a significant amount of the time.[127] Echocardiography is also useful in identifying traumatic cardiac and vascular injuries, including cardiac contusion,[128–130] valvular disruption,[128] and traumatic aortic injuries.[131,132] Plummer and colleagues[133] showed that information derived from echocardiography reduced mortality rates in patients with penetrating cardiac injuries by more than 40%. The literature on hepatic resection and transplantation shows that TEE can have a major impact on intraoperative management,[108] particularly when it is used to assess for PE and RV dysfunction,[134] as well as changes in LV function.[135,137] Regarding orthopedic procedures, Loxdale and associates[137] showed that more than one-third of patients presenting with a hip fracture had aortic stenosis. Not only can echocardiography aid in the diagnosis and management of this and similar coexisting cardiac diseases in orthopedic patients, but it can also aid in identifying and treating emboli associated with total hip arthroplasty with cement[138,139] and without cement,[140] as well as guide resuscitation in prone spine surgical procedures.[141] TEE is also valuable as a guide in patient positioning for neurosurgical procedures,[142] identifying gas emboli and acute valvular dysfunction in laparoscopic procedures,[143,144] monitoring diastolic dysfunction in pneumonectomies,[145] and identifying and monitoring renal cell carcinoma extension into the right atrium.[146,147]

Given that one of the primary arguments against using echocardiography as a routine monitor is that outcome data are lacking, it is important to assess whether the monitors traditionally used have the same issues. Positive outcome data with the use of pulmonary artery catheters and central venous pressure monitoring are lacking. Pulmonary artery catheters do not affect outcome in several different patient groups, including high-risk surgical patients,[148] patients with sepsis,[149] cardiothoracic surgical patients,[150–152] and vascular surgical patients.[153] These data were confirmed in several systematic reviews.[154–156] Moreover, neither central venous pressure nor pulmonary artery occlusion pressure correlates with ventricular preload.[157] Evidence to support improved outcomes with the use of arterial catheters[158] and pulse oximetry[159,160] is similarly lacking (see Chapter 13). This observation is not meant as an indictment of traditional intraoperative monitors, nor does it suggest that seeking further outcome data on intraoperative echocardiography as a monitor is superfluous. This is simply to suggest that intraoperative echocardiography in noncardiac surgical procedures should not be discounted because of a lack of outcome data.

Transesophageal Echocardiography Goal-Directed Therapy

TEE is clearly a safe and valuable monitor in a multitude of intraoperative situations. The wide-ranging utility of TEE as a monitor is not solely the result of its accuracy in detecting singular cardiac events, but it also reflects the ability of TEE to provide a global view of cardiac function and the overall physiologic context within which the event occurs. This makes echocardiography the ideal monitor for goal-directed therapy (GDT). GDT is the optimization of a hemodynamic goal through fluid administration and/or inotropic or vasoactive support with the expectation that this will treatment optimize end-organ perfusion and oxygen delivery[161] (see Chapter 47). Optimization involves assessment of the hemodynamic parameter before and after the intervention and then basing further intervention on the results. Such a concept is not foreign to anesthesiologists, who tend to use normal blood pressure and heart rate as standard hemodynamic goals. Unfortunately, these parameters are poor markers of end-organ perfusion, particularly when considering volume status.[162] The hemodynamic parameters used for GDT are generally SV and CO or their surrogates. Although it remains controversial,[163] a growing body of evidence indicates that in high-risk patients undergoing noncardiac surgical procedures, GDT reduces hospital length of stay,[164] improves postoperative gastrointestinal function,[165] decreases postoperative renal dysfunction,[166] and improves short-term[167] and long-term survival.[168]

The most obvious advantage of echocardiography over other monitors, such as the esophageal Doppler or pulse contour analyzer, is the ability monitor contractility. LV systolic function is extremely complex, with multiple elements beyond EF.[169,170] A normal preoperative EF

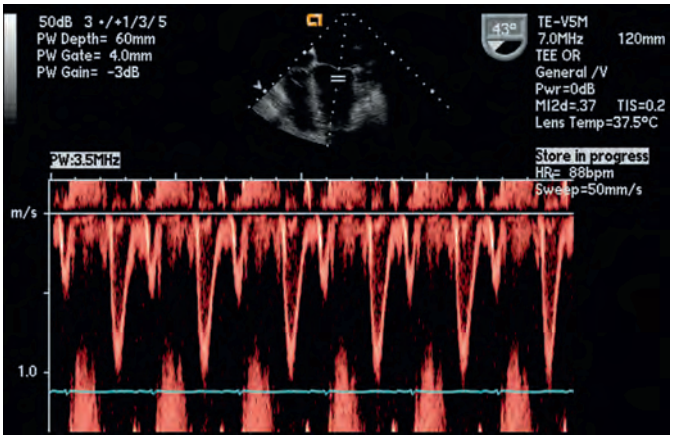


Fig. 46.9 Mitral inflow Doppler echocardiography with E and A waves. *HR,* Heart rate; *PW,* pulsed wave; *TEE,* transesophageal echocardiography.

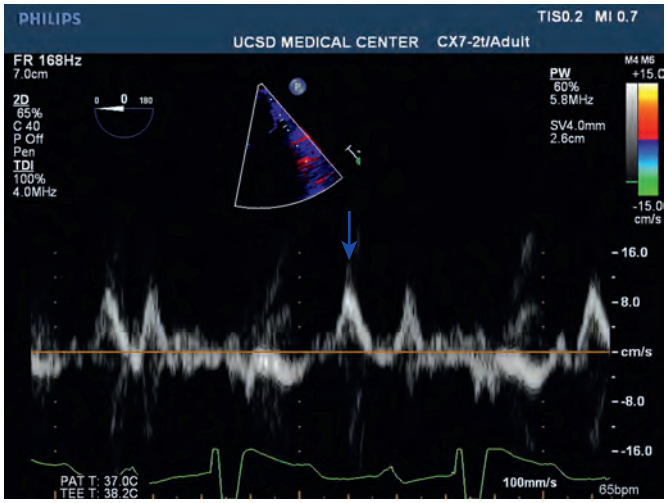


Fig. 46.10 Tissue Doppler echocardiographic imaging of the lateral side of mitral annulus in the four-chamber view. The blue arrow points to the E′ wave. *FR,* Frequency, *PW,* pulsed-wave; *TDI,* tissue Doppler image. *(Courtesy University of California San Diego, La Jolla, Calif.)*

may not predict intraoperative contractile performance, particularly as loading conditions change.[171] Subtle systolic dysfunction can be unmasked by anesthesia, surgical procedures, or some other hemodynamic disturbance. Thus hypocontractility must remain on the differential diagnosis for hemodynamic instability regardless of initial assumptions. The LV SAX view is an easy and effective way to estimate LV function qualitatively. In addition, it provides simultaneous information on contractile performance and loading conditions, which are interdependent. Frequent assessment of the LV SAX allows for both a rapid estimation of preload, afterload, and contractility in the setting of hemodynamic instability, as well as the effects of any intervention performed to alleviate the disturbance.

Volume therapy in GDT focuses on changes in SV after volume administration. The method used to assess this change is similar to that used to monitor dynamic changes in SV with positive-pressure ventilation. Baseline values are obtained for LVOT, VTI, and LV SV. Volume is then administered, and these parameters are reassessed. An increase in SV of more than 10%[172,173] indicates *volume responsiveness,* which warrants further volume loading and reassessment. An increase of less than 10% suggests that the patient will not benefit from further volume loading, and an alternate method to improve hemodynamics should be sought. Large volumes of fluid are not necessary. As little as 100 mL of colloid can be used, with a sensitivity of 95% and a specificity of 78%.[172] Alternatively, passive leg raise can be used to test volume responsiveness[174] by placing the bed at 45 degrees of semirecumbency and then tilting the bed so that the upper body is horizontal and the legs are at a 45-degree angle.[175] Passive leg raise can achieve the same SV increase as a 300-mL volume bolus in fluid responders,[176] with the advantage of being reversible.[177]

TEE is not only able to identify improvements in forward flow, but it also can monitor intracardiac pressures, particularly left atrial pressure (LAP), to aid in preventing elevated filling pressures and pulmonary edema.[178,179] Although an LAP measurement may not reflect intravascular volume status, a large increase in LAP during fluid administration warns of impending edema that may be hastened by further volume. The echocardiographic assessment of LAP involves the use of spectral Doppler to assess diastolic compliance. Placement of the PWD cursor at the mitral leaflet tips during diastole yields two waves, E and A (Fig. 46.9). The E wave represents early diastolic filling as a result of a pressure gradient between the left atrium and the left ventricle. The A wave represents the gradient between the left atrium and left ventricle generated by atrial contraction. Simplifying the diastolic physiology for the sake of clarity, the pressure gradient during the E wave can be produced in one of two ways: (1) a normal LAP in the setting of a low LV end-diastolic pressure (LVEDP) in a compliant myocardium, or (2) a high LAP generated by compensatory mechanisms to overcome a high LVEDP in a noncompliant myocardium. Because both mechanisms can generate the same pressure gradient, the E waves for both may look the same.

The velocity with which the mitral annulus ascends in diastole can help determine how the pressure gradient is established. PWD interrogation of the mitral annulus in the four-chamber view yields early and late diastolic waves termed E′ and A′ (Fig. 46.10). These waves are brighter (because of the high-density tissue) and slower compared with the mitral inflow and require an adjustment of the gain and scale. The tissue Doppler function on the machine optimizes these parameters automatically (see Chapter 15). A relatively fast E′ is a marker for normal diastolic compliance, whereas a slow E′ indicates poor diastolic compliance. Because the E wave is approximately the same for both low and high LVEDP and the E′ wave is reduced with a high LVEDP, the ratio of E to E′ increases as the LVEDP (and the LAP) increases. An elevated E/E′ ratio correlates with LAP in septic shock,[180] heart failure,[181] and ventilated patients in the intensive care unit,[182] and it may be a better marker of high pressures than brain natriuretic peptide.[183] No universally accepted values for E/E′ and LAP have been established. Based on the available data, an E/E′ ratio greater than 18 is most likely associated with an elevated LAP, whereas an E/E′ ratio of less than 12 most likely rule outs elevated pressures.[181] In addition, Bouhemad and associates[180] showed a statistical correlation between pulmonary capillary wedge pressure (PCWP) and E/E′ by using the following formula: $PCWP = 0.97 \times E/E' + 4.34$.

PWD interrogation of the pulmonary venous inflow is another method to assess diastolic compliance and LAP. In a left ventricle with normal compliance, the LAP is lowest during systole because of the descent of the mitral annulus. The pressure gradient between the pulmonary vein (PV) and the left atrium is greatest during this period and generates the most blood flow. As the left atrium fills, the gradient decreases and blood flow slows. The MV then opens, releasing the pressure in the left atrium and reestablishing a gradient between the PV and the left atrium. Blood flow from the PV to the left atrium resumes, although at a lower velocity and flow distance (ie, VTI) as a result of a smaller gradient. PWD interrogation of a PV throughout the cardiac cycle yields waves in systole (PVs) and diastole (PVd), with the maximum velocity and VTI in systole greater in normal LAP (Fig. 46.11). In a left ventricle with poor diastolic compliance, the gradient between the PV and the left atrium is reduced in systole. The majority of blood flow therefore occurs in diastole after the MV opens, to yield a PVs with a lower maximum velocity and VTI than

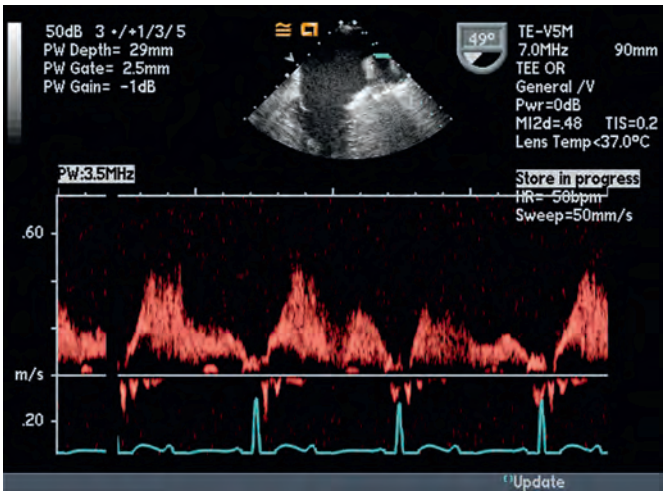


Fig. 46.11 Pulsed-wave Doppler echocardiography of the left upper pulmonary vein found in the midesophageal two-chamber view. *HR,* Heart rate; *PW,* pulsed wave; *TEE,* transesophageal echocardiography.

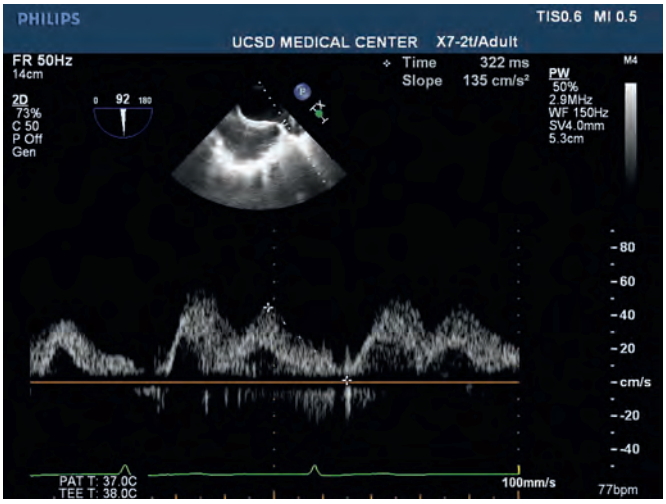


Fig. 46.12 Pulsed-wave Doppler echocardiographic S and D waves from the right upper pulmonary vein in a patient with normal left atrial pressures. Deceleration time of the D wave is 322 milliseconds in this example. *FR,* Frequency, *PW,* pulsed-wave. *(Courtesy University of California San Diego, La Jolla, Calif.)*

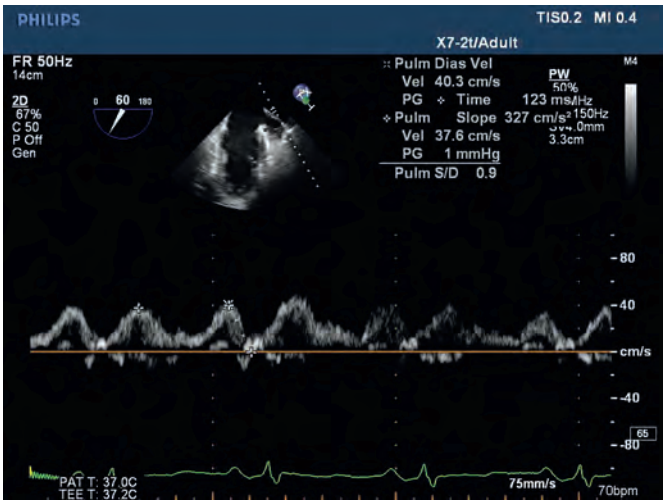


Fig. 46.13 Pulsed-wave Doppler echocardiographic S and D waves from the left upper pulmonary vein in a patient with abnormal left atrial pressures. Deceleration time of the D wave is 123 milliseconds in this example. *Diast,* diastolic; *FR,* frequency, *PG,* pressure gradient; *Pulm,* pulmonary; *PW,* pulsed-wave; *Vel,* velocity.

BOX 46.6 RECOMMENDED LIMITED EXAMINATION FOR GENERAL HEMODYNAMIC MONITORING AND GOAL-DIRECTED THERAPY USING TRANSESOPHAGEAL ECHOCARDIOGRAPHY

1. High esophageal AV SAX view
2. High esophageal AV LAX view
   - Measurement of LVOT diameter
3. High esophageal bicaval view
   - PWD of right upper PV
   - Measurement of PVs, PVd, and DTd
4. High esophageal RV inflow-outflow view
5. Midesophageal four-chamber view
   - With and without CFD on the TV and MV
   - Mitral inflow PWD for E wave
   - Mitral annulus tissue Doppler for E′ wave
   - Estimation of LAP (~ E / E′ + 4)
6. Midesophageal two-chamber view
7. Midesophageal LV LAX view
8. Transgastric LV SAX view
9. Deep transgastric view
   - PWD of LVOT
   - Calculation of stroke volume

AV, Aortic valve; *CFD,* color-flow Doppler; *DTd,* deceleration time of the pulmonary vein in diastole; *LAP,* left atrial pressure; *LAX,* long-axis; *LV,* left ventricular; *LVOT,* left ventricular outflow tract; *MV,* mitral valve; *PV,* pulmonary vein; *PVd,* pulmonary vein in diastole; *PVs,* pulmonary vein in systole; *PWD,* pulsed-wave Doppler; *RV,* right ventricular; *SAX,* short-axis; *TG,* transgastric; *TV,* tricuspid valve.

the PVd. The PV systolic fraction ($PVs_{VTI}/[PVs_{VTI} + PVd_{VTI}]$) correlates well with the mean LAP,[184] with a value of less than 0.4 predicting a PCWP greater than 12 mm Hg with a positive predictive value of 100%.[185] Additionally, the deceleration time (ie, the time from peak velocity to baseline) of the PVd wave (DTd) correlates very well with LAP (Figs. 46.12 and 46.13). A DTd of less than 175 milliseconds has a 100% sensitivity and 94% specificity for a mean LAP of greater than 17 mm Hg, and a DTd greater than 275 milliseconds predicts a mean LAP of 6 mm Hg or less with a sensitivity and specificity of 88% and 95%, respectively.[186]

Suggested Method

For the purposes of general intraoperative hemodynamic monitoring and GDT, use of the limited examination mentioned earlier with the addition of spectral Doppler assessments of mitral inflow, mitral annular, and pulmonary venous inflow velocities is suggested (Box 46.6). At the start of the monitoring period, the entire limited examination should be performed. This should include baseline values for E, E, PVs, PVd, and DTd, as well as an estimation of the LAP using an approximation of the equation noted in the report by Bouhemad and colleagues[180]:

$$PCWP = 0.97 \times E/E' + 4.34 \approx E/E' + 4$$

After this assessment, the focus of continued monitoring should be on the following views:

1. Four-chamber view for RV and LV systolic function and calculation of LAP

TABLE 46.5 Echocardiographic Findings in the Most Commonly Encountered Hemodynamic Abnormalities

Abnormality	*SV*	*Potential Other Findings*
↓ Contractility	↓	↓ Ejection fraction ↓ Segmental or global wall thickening
↓ Volume	↓	↓ End-diastolic area ↓ End-systolic area ↑ SV variability
↓ Afterload	↑	Hyperdynamic systolic function ↓ End-systolic area Normal end-diastolic area
↑ Afterload	↓	↑ End-systolic area ↓ Ejection fraction ↓ Segmental or global wall thickening ↑ Mitral or aortic valve regurgitation
Sinus bradycardia	↓	Bradycardia Normal end-diastolic area
Sinus tachycardia	↓	Tachycardia ↓ End-diastolic and end-systolic areas

SV, Stroke volume; ↑, increased; ↓, decreased.

TABLE 46.6 Echocardiographic Changes Following a Hemodynamic Intervention That Indicate the Success of the Intervention

Intervention	*Successful*	*Consider Alternative*
Inotrope	↑ SV, CO ↑ EF ↑ RV, LV contractility	No change in SV or CO Arrhythmia, ischemia[a] ↑ LAP[b]
Volume	↑ SV, CO ↓ SV variation ↑ EDA, ESA	No change in SV or CO ↑ LAP[b] ↓ EF
Pressor	↑ ESA Normalized left ventricle	↓↓ SV, CO[c] ↑ LAP[b]
Vasodilator	↑ SV, CO ↓ ESA ↑ EF, contractility ↓ LAP[b]	No change in SV or CO Hyperdynamic right ventricle, left ventricle
(+) Chronotrope	↑ SV, CO	↓ SV, CO ↑ LAP ↓ EDA Arrhythmia, ischemia[a]
(−) Chronotrope	↑ SV, CO	↓ CO ↑ LAP[b]

[a]For echocardiographic signs of ischemia, please see above.
[b]Echocardiographic parameters of ↑ LAP consist of ↑ E/E′ wave ratio, ↓ pulmonary vein in systole velocity-time integral, and/or ↓ deceleration time of the pulmonary vein in diastole. Echocardiographic parameters of ↓ LAP would be the opposite.
[c]A reduction in SV is an appropriate response to pressor administration in the setting of low afterload. An excessive reduction, however, may mean that the increase in SVR with the pressor is too much for this particular contractile state.
CO, Cardiac output; *EDA,* end-diastolic area; *EF,* ejection fraction; *ESA,* end-systolic area; *LAP,* left atrial pressure; *LV,* left ventricular; *RV,* right ventricular; *SV,* stroke volume; ↑, increased; ↓, decreased.

2. Transgastric SAX view for estimation of LV contractility, volume, and afterload
3. Deep transgastric view for spectral Doppler evaluation of the LVOT for SV and SV variation

Interventions to optimize SV should then be based on the TEE findings. For general hemodynamic monitoring, the main hemodynamic abnormalities encountered are poor contractility, hypovolemia, or low afterload. However, arrhythmias and high afterload must also be considered. Malignant arrhythmias obviously require emergency intervention to reestablish CO. Less acute arrhythmias, particularly sinus bradycardia and tachycardia, are far more common and can significantly compromise CO. Elevated afterload can also affect CO, even in the setting of high normal or only slightly elevated blood pressures. This finding highlights the interdependency of contractility and loading conditions. Mildly elevated afterload in a patient with normal systolic function may have little effect on CO, but it may have a significant effect in a patient with compromised systolic function. Table 46.5 lists the echocardiographic findings in the most commonly seen hemodynamic abnormalities.

The appropriate intervention should then be performed, and the foregoing parameters should be reevaluated by TEE. With the exception of pressor administration, all interventions should lead to an increase in SV. Although pressor administration reduces SV in a hyperdynamic left ventricle, a large reduction in SV may indicate that pharmacologic vasoconstriction is not the appropriate response. Echocardiographic parameters of LAP should also be assessed, particularly when volume or pressors have been given. An increase in E/E′ ratio, a reduction in PV systolic fraction, and a reduction in DTd suggest an acute increase in LAP. Further volume or pressor administration may result in pulmonary edema. RV and LV contractility, LV SAX assessment of preload and afterload, SV and SV variation, and LAP should be continuously monitored. Interventions should be tailored to the acute cardiac physiologic features with the goals of maintaining perfusion pressure, improving SV, and preventing pulmonary edema. Additional TEE parameters suggesting that an intervention is appropriate or potentially inappropriate are listed in Table 46.6.

Transthoracic Echocardiography

The preceding discussion focuses on the application of TEE to the noncardiac surgical patient. TEE is safe and has repeatedly been shown to add value to intraoperative management. However, as noted by Markin and associates,[4] cardiac assessment does not begin and end in the operating room, even in the emergency setting. The utility of TEE in the awake patient is obviously limited. TTE provides the anesthesiologist with additional noninvasive windows to aid in cardiac diagnosis and monitoring. The images acquired from TTE are the same as those in TEE, but at a different angle. Technically speaking, the "window" differs, but the "view" does not. The information and interpretation are the same. All the hemodynamic assessments listed earlier can be performed with TTE using similar views. The following discussion reviews the value and application of TTE by anesthesiologists, including how to perform a basic examination.

Value of Perioperative Transthoracic Echocardiography

The American College of Cardiology guidelines give a class I recommendation to preoperative echocardiography in patients "with clinically suspected moderate or greater degrees of valvular stenosis or regurgitation" and a class IIa recommendation in patients with dyspnea of unknown origin.[187] Although these recommendations apply to a significant number of preoperative patients, the ASE also encourages the use of echocardiography in the following situations[188]:

- When symptoms or conditions are potentially related to a cardiac disease
- When results from previous testing (electrocardiogram, chest radiograph, biomarkers) are concerning for heart disease
- To reevaluate known structural heart disease with a change in clinical status
- When pulmonary hypertension is suspected
- With diagnoses of atrial fibrillation
- When hypertensive heart disease is suspected

Given that preoperative patients frequently meet these criteria and the information obtained from TTE is recognized to add value to the long-term care of these patients, it seems reasonable to apply these broader criteria to preoperative echocardiography when feasible.

Preoperative cardiac assessment involves diagnosing CV dysfunction, predicting the effects of anesthesia on CV function, and attempting to mitigate the risks through preoperative optimization. Resting preoperative TTE predicts postoperative cardiac complications[189] better than does clinical risk assessment alone,[190] and it is as sensitive as but more specific than dipyridamole thallium scanning.[191,192]

Equally important is how the information on cardiac pathophysiology obtained through echocardiographic studies can guide anesthetic care. Anesthesia encapsulates a wide range of care options, and perioperative CV risk cannot be assumed to be the same across all potential anesthetic cases. Physiologic optimization is an ongoing process that carries through the preoperative, intraoperative, and postoperative periods. In the immediate perioperative period, acute cardiac physiologic status guides this care. Cardiac physiology, from systolic and diastolic function to valvular regurgitation, depends on loading conditions that can quickly vary. A preoperative TTE examination is well suited to define the *current* CV state and allows the anesthesiologist to adjust care appropriately. Numerous studies have shown that point-of-care TTE in the hands of anesthesiologists alters intraoperative care.[193–197] Preoperative point-of-care TTE has also been linked to improved outcomes including a reduction in mortality rates.[105] The information obtained through echocardiography is beneficial above and beyond the history and physical examination. The sensitivity of symptoms of heart failure (including orthopnea, paroxysmal nocturnal dyspnea, and dyspnea with 4 metabolic equivalents of activity) is less than 35%, and even including physical findings of lower extremity edema, jugular venous distention, and an S_3 gallop, the sensitivity is still only approximately 50%.[198]

The utility of TTE is not limited to the preoperative period. The advantages of TTE over TEE in the awake postoperative patient are obvious. TTE also plays an important role intraoperatively. Twenty percent of the TTE examinations performed to assess hemodynamic instability in the perioperative patients in the report by Markin and associates[4] were performed in the operating room. In the report by Shillcut and colleagues,[3] more than 80% of the TTE examinations were performed intraoperatively. Intraoperative TTE is most commonly used when TEE is contraindicated, when a TEE probe cannot physically be placed, or when TEE images are not adequate as a result of technical difficulties.

How to Perform a Basic Transthoracic Echocardiography Examination

Investigators have repeatedly shown that noncardiologist providers can successfully be trained in bedside TTE. This group of providers includes medical students,[199,200] internal medicine residents,[201] emergency medicine physicians,[202] critical care physicians,[47] internists,[203] and anesthesiology residents.[6] Kobal and associates[9] showed that first-year medical students using bedside ultrasound to diagnose cardiac disease were significantly more likely to reach accurate diagnoses than were attending cardiologists who were not using ultrasound. The teachability of point-of-care TTE is likely related to a paradigm shift with regard to image acquisition and interpretation. Because of the size and complexity of the original ultrasound machines, there use was limited to practitioners with specialized training. Current technology, conversely, has yielded small, easily portable units geared toward decision making in real time. A detailed analysis of the images is not required to make immediate decisions on prognosis and hemodynamic management. Similar to the echocardiographic assessment of hemodynamic emergencies with TEE, perioperative TTE requires only a qualitative analysis, thus reducing the training required for competency.

With adequate training an anesthesiologist can be credentialed to perform TTE and potentially bill for their studies. Although currently no standard exists for training or credentialing anesthesiologists to perform TTE, guidelines are in place for other specialties. The American College of Cardiology guidelines on training in echocardiography suggest that cardiologists with level II training in TTE who want to incorporate TEE into their practice should perform at least 50 examinations before being considered competent.[204] An argument could be made that similar criteria should apply to anesthesiologists with level II training in TEE when seeking proficiency in TTE. With training in basic image acquisition and interpretation and 50 supervised studies, an anesthesiologist should be considered competent to perform a TTE examination.

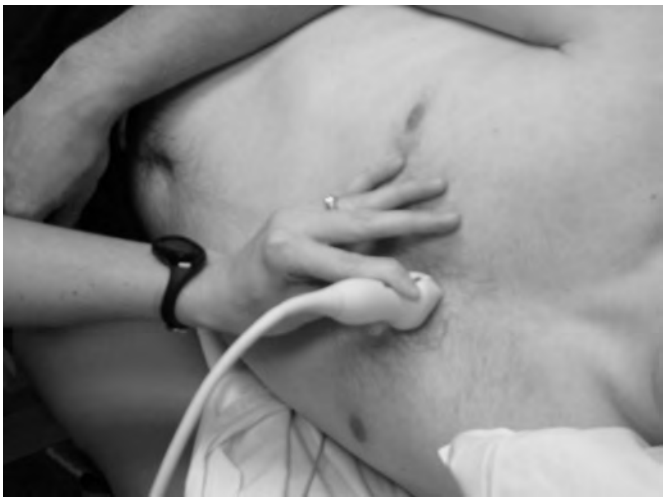


Fig. 46.14 How to obtain the parasternal long-axis echocardiographic view. The patient is in the left lateral decubitus position to position the heart on the chest wall. The probe is placed in the third or fourth intercostal space with the marker toward the right shoulder.

The following are instructions for acquiring TTE images. As noted by Shillcutt and associates[3] and Markin and colleagues,[4] a limited examination should be performed, focusing of the pertinent images that aid in perioperative care.

1. Equipment: A phased-array probe is necessary for this examination. Any machine that is used to perform TEE should also have TTE capabilities. Point-of-care devices can also acquire adequate images for qualitative analysis.
2. Positioning: When imaging is done from the parasternal and apical windows, the patient should be in the full left lateral decubitus position with the left arm resting under the head to help spread the ribs. To access the LV apex, it is necessary to move the patient to the very edge of the bed or stretcher or to tilt the patient slightly back from a true left lateral position. Although the left lateral position is preferred, it is also possible to perform the entire examination with the patient supine. The subcostal window is accessed with the patient supine and the legs slightly bent to relax the abdominal muscles.
3. Basic technique and assessment
   a. Parasternal LAX view (Video 46.16):
      i. Technique: The probe should be positioned at the third or fourth intercostal space, just to the left of the sternum, with the "indicator" pointing toward the left shoulder (Fig. 46.14).
      ii. Assessment: This view is one of the easiest to perform, even in supine or morbidly obese patients. It provides information on RV size and function, AV function, left trial size, and LV function, size, and thickness.
   b. Parasternal SAX view (Video 46.17):
      i. Technique: From the LAX, the probe is rotated approximately 90 degrees clockwise until the indicator points toward the patient's right shoulder (Fig. 46.15). The probe should then be tilted until the appropriate LV cross-section is obtained.
      ii. Assessment: With angulation of the probe, the basal, middle, and apical cross-sections showing the 16 LV segments can be assessed for wall motion abnormalities. Global LV function and filling can be assessed as well. By angling the probe to look more anteriorly (angling the "tail" toward the apex), an SAX view of the AV can be seen.
   c. Apical four-chamber (Video 46.18):
      i. Technique: The apical window can be found by placing the probe at the point of maximal impulse (Fig. 46.16). The indicator should point toward 5 o'clock. The apex

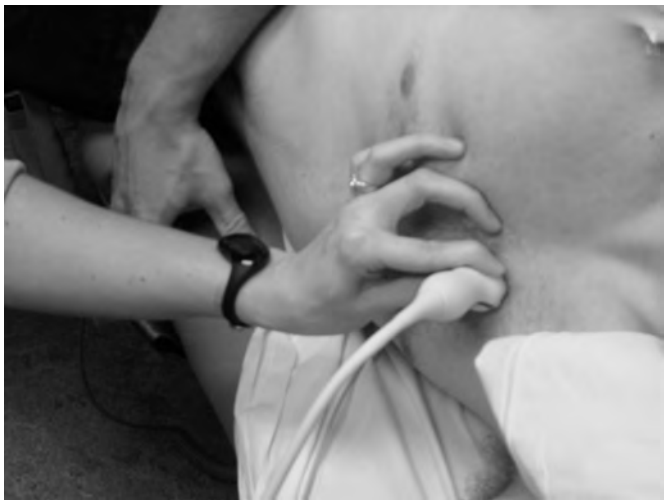


Fig. 46.15 How to obtain the parasternal left ventricular short-axis echocardiographic view. The probe is turned clockwise approximately 90 degrees.

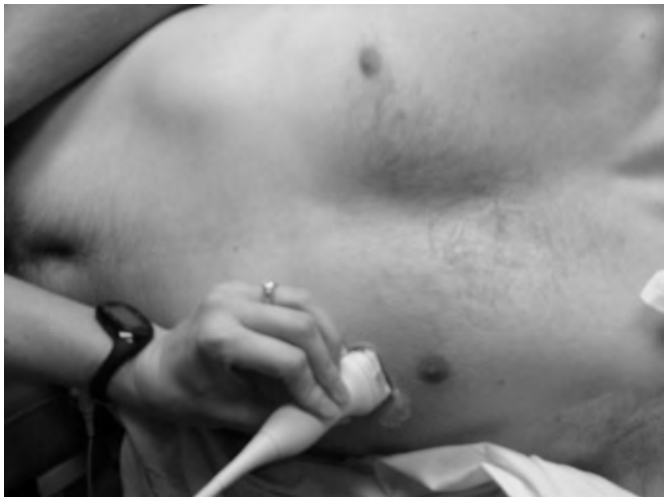


Fig. 46.16 How to obtain an apical four-chamber echocardiographic view. Ideally the probe would be placed at the point of maximal impulse in the axilla with the marker pointing toward the floor. This placement is often difficult with the beds used in the preoperative period. Placement of the probe under or near the nipple often produces adequate images.

of the left ventricle will appear directly under the probe with minimal foreshortening and without showing the coronary sinus or LVOT.

ii. Assessment: This view shows global and regional LV and RV function, chamber sizes, and mitral and tricuspid valve function. The valves can be interrogated with CFD. Spectral Doppler can be used to assess right-sided pressures with continuous-wave Doppler through any tricuspid regurgitation. Assessment of diastolic function can be performed with a combination of PWD interrogation of mitral inflow and tissue Doppler evaluation of septal and lateral mitral annulus motion in diastole. Slight angling of the tail of the probe toward the feet will reveal the five-chamber view. PWD interrogation of the LVOT yields LVOT VTI and thus allows for SV calculation.

d. Subcostal four-chamber (Video 46.19):

i. Technique: The patient should be placed supine for these images. It is useful to have the patient bend the knees or place a pillow under the knees to relax the abdominal musculature. The probe is placed just below or slightly left of the xiphoid process, with the indicator pointed to the patient's left and with the probe nearly horizontal (Fig. 46.17).

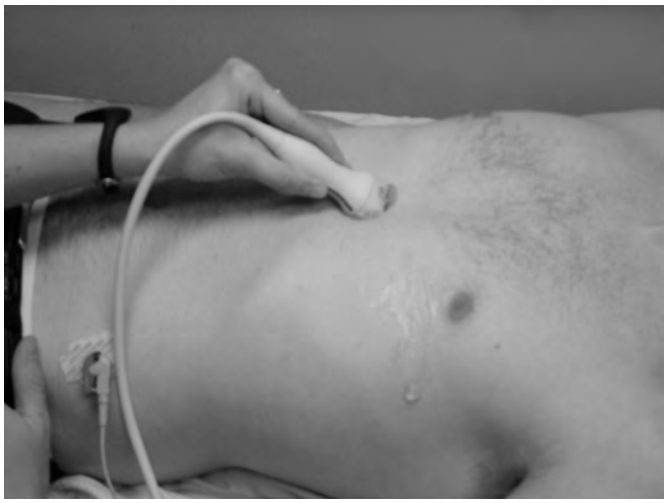


Fig. 46.17 How to obtain a subcostal four-chamber echocardiographic view. The probe should be positioned near the xyphoid process with the marker toward the right side of the patient's body.

ii. Assessment: The right ventricle is seen very well, allowing for evaluation of thickness, function, and size. Pericardial effusions can be seen here, as well as evidence of tamponade (ie, compression of the right atrium or right ventricle). The left ventricle and atrioventricular valves can also be evaluated.

Conclusion

Echocardiography, using either TTE or TEE modalities, is extremely useful to the perioperative physician by aiding in both diagnosis and management. Because of its portability and ease of use, it is the diagnostic tool of choice in the setting of hemodynamic instability. Echocardiography is not limited to emergencies; it provides a significant amount of information as a general hemodynamic monitor. With numerous complementary tools at the examiner's disposal, echocardiography is also the ideal monitor for goal-directed therapy. Finally, limited preoperative echocardiographic assessment, even in the hands of noncardiologists, significantly alters intraoperative and postoperative anesthetic management and may even reduce perioperative mortality rates.

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Goal-Directed Fluid Therapy, Enhanced Recovery, and the Perioperative Surgical Home for Cardiac Patients in Noncardiac Surgery

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TEACHING POINTS

1. The costs of health care are escalating, and the increase is unsustainable. Goal-directed fluid therapy, enhanced recovery programs, and the perioperative surgical home are ways to control costs while improving quality.
2. Goal-directed fluid therapy is an integral part of enhanced recovery programs, and both fall under the general umbrella of the perioperative surgical home.
3. The traditional approach to perioperative fluid management has no sound evidence base and causes perioperative fluid and salt overload. *Zero fluid balance* is recommended, using a goal-directed approach. Enhanced recovery programs emphasize the avoidance of salt and water overload.
4. Administering goal-directed fluid therapy involves cardiovascular monitoring such as minimally invasive cardiac output and the application of an algorithm or guidelines specific to fluid and hemodynamic management.
5. Goal-directed fluid therapy and enhanced recovery programs increase quality by decreasing variability in practice with evidence-based management. Decreased cost results from less perioperative morbidity and streamlined care delivery.
6. Various monitors may be used for goal-directed fluid therapy, ranging from invasive (pulmonary artery catheter) to noninvasive (finger cuff cardiac output). The choice of monitor is based on the clinical situation and the individual or institutional preference. The most common monitors used are esophageal Doppler and arterial pulse wave analysis systems.
7. Goal-directed fluid therapy algorithms may be based on cardiovascular performance (eg, cardiac output) or preload responsiveness (eg, stroke volume variation). Algorithms that incorporate both are likely to be the most effective.
8. Enhanced recovery programs are multidisciplinary, multifactorial care pathways. They incorporate optimal preoperative preparation, careful intraoperative management of fluid status, temperature, antibiotic administration, minimally invasive surgery, multimodal pain relief, postoperative nausea and vomiting control, and early mobilization.
9. Perioperative surgical homes are becoming popular constructs for delivering streamlined, coordinated care.
10. Anesthesiologists can enhance their value to their health systems by becoming involved in the development, implementation, and management of perioperative surgical homes.

With recent advances in expensive diagnostic and treatment modalities, the costs of health care have skyrocketed.[1] The need to care for increasing numbers of patients undergoing diagnostic and therapeutic procedures while controlling the cost has pushed health care systems to devise increasingly efficient ways to deliver care. The *throughput* of patients is often stymied by prolonged hospital stays and readmission after procedures. Inefficient systems, inconsistent care, and perioperative complications cause delays, poor patient and provider satisfaction, and high costs.

Goal-directed fluid therapy (GDT), enhanced recovery programs (ERPs), and the perioperative surgical home (PSH) are three related approaches to patient care that have emerged to provide optimal outcomes for patients undergoing surgery. GDT refers to fluid and hemodynamic management targeting optimal cardiovascular performance and using monitoring beyond standard noninvasive monitors. ERPs are designed to incorporate patient management processes, such as preoperative optimization, multimodal pain management, and early mobilization after surgery so as to facilitate recovery. PSH is a construct consisting of a coordinated, multidisciplinary team using best-evidence guidelines and protocols to guide patients through the entire perioperative experience as seamlessly as possible. Fig. 47.1 shows GDT as a component of enhanced recovery, and both are under the PSH umbrella.

Goal-Directed Fluid Therapy

Traditional, liberal fluid management of patients undergoing major surgery has entailed a type of *cookbook* approach (Box 47.1). This methodology involves the calculation of maintenance fluid requirement based on body weight, calculation of a deficit based on the period

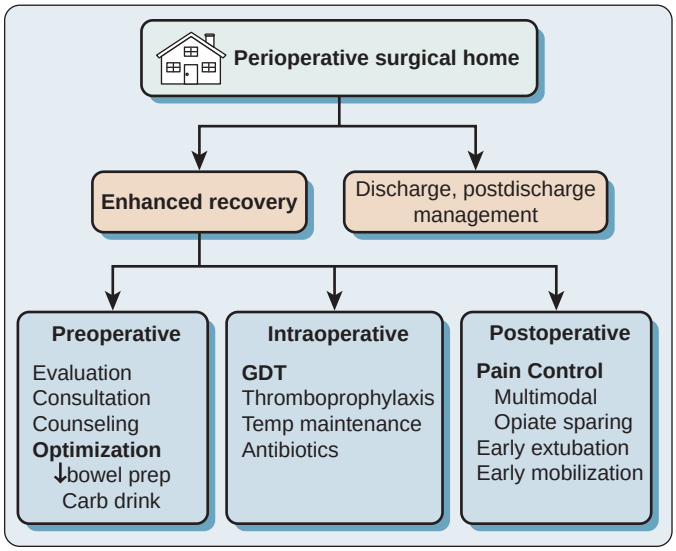
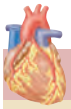


Fig. 47.1 Goal-directed fluid therapy (GDT) is part of enhanced recovery programs that are under the perioperative surgical home umbrella.



BOX 47.1 GOAL-DIRECTED FLUID THERAPY

- Standardizes fluid and hemodynamic management.
- Aims to avoid fluid and salt overload while avoiding hypovolemia.
- Is based on parameters beyond heart rate and blood pressure, such as:
  - Minimally invasive or invasive cardiac output
  - Stroke volume variation (SVV)
  - Pulse pressure variation (PPV)
  - Doppler corrected flow time (FTc)
  - Central venous oxygen saturation
- Many algorithms have been used successfully.
- Algorithm should have physiologic basis and be easy to use.

during which the patient has not had any fluid by mouth, presumed effects of a bowel preparation, and the estimation of *third space* losses based on the invasiveness of the surgery. Typically, for major abdominal surgery, 6, 8, 10, or even 12 mL of crystalloid/kg per hour would be administered to replace insensible losses and a loss to the third space. The concept of the third space grew out of a radionuclide study by Shires and associates,[2] and the massive amounts of fluid to replace losses were suggested by Jenkins and colleagues.[3] Subsequently, the methodology and clinical ramifications of this work have been called into question—specifically, if the third space exists at all.[4,5] It is highly likely that what has been referred to as fluid loss to the third space represents translocation of administered fluid out of the vascular space, resulting in intracellular and extracellular edema.

Excess salt and fluid in the perioperative period is now generally accepted as harmful. Lowell and associates[6] studied postoperative critical care patients and found that perioperative weight gain (fluid excess) was associated with a dramatic increase in mortality. Fluid and salt excess can lead to airway edema, increased lung water, tissue edema, and cardiac failure. Improved outcomes associated with relative fluid restriction (as compared with the traditional approach) have been found in prospective studies of general surgical patients published in the surgery[7] and anesthesiology[8] literature. Shorter hospital lengths of stay, improved wound healing, fewer surgical infections, and fewer cardiovascular and pulmonary complications have all been associated with relative fluid restriction and are supported by a metaanalysis.[9] It could be argued that excess perioperative fluid and salt are acceptable

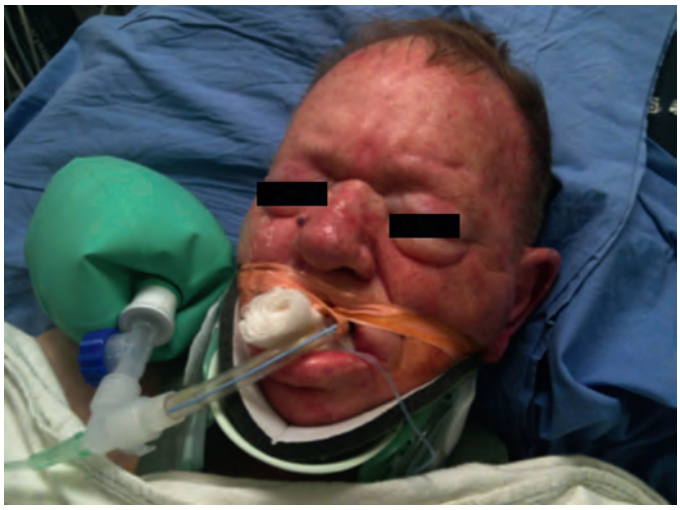


Fig. 47.2 Fluid and salt overload can cause airway problems, increased lung water, congestive heart failure, renal failure, skin breakdown, and vision problems.

because, with time, the patient will mobilize the fluid. However, the potential pulmonary problems, prolonged ventilation, increased complication rate, and extra time in recovery associated with excess fluid and salt administration are no longer necessary or acceptable (Fig. 47.2). The avoidance of fluid and salt overload in major surgery is now a standard component of ERPs (Fig. 47.3).

Over-aggressive fluid restriction can have negative consequences as well, with hypovolemia leading to hypotension, tachycardia, organ ischemia, and vital organ failure. Morbidity rates are higher in the setting of either hypovolemia or hypervolemia (Fig. 47.4).[10] Targeting no perioperative change in body weight, *fluid restriction* protocols do allow modest fluid administration with a background rate (eg, 1–4 mL/kg per hour)[8] and fluid boluses to maintain hemodynamic stability.[7] Likewise, blood products are used as needed to maintain adequate hemoglobin concentration and coagulation.

History, Development, and Outcomes of Goal-Directed Fluid Therapy

A goal-directed, protocol-based approach to fluid and hemodynamic management has grown out of accumulating evidence that optimizing hemodynamic status improves outcome and that accurate assessment of volume and hemodynamic status using only standard, noninvasive monitors is often impossible. Certainly, for example, tachycardia, hypotension, and oliguria can result from either hypovolemia or hypervolemia (heart failure). GDT adoption has also resulted from the recognition that decreasing variability of practice using a best-evidence approach improves outcome. Decreasing process variability is essential to creating high-performance systems.[11]

Shoemaker and colleagues[12] used pulmonary artery catheter data to provide *supranormal* hemodynamics in high-risk surgical patients, reporting improved outcomes. Rivers and associates[13] applied early, aggressive fluid and hemodynamic management to septic patients admitted to the emergency department, showing dramatic improvements in mortality rate. This work, published in 2001, revolutionized the initial management of sepsis, such that the vast majority of tertiary care centers now have a sepsis protocol that incorporates an early goal-directed approach.

In 2002, Gan and colleagues[14] studied 100 patients undergoing major elective surgery, randomly assigning them to receive either standard therapy or GDT, based on esophageal Doppler parameters. The goal-directed group experienced shorter hospital stays (5 ± 3 days vs 7 ± 3 days), less nausea and vomiting, and earlier return of bowel function. The algorithm, based on corrected flow time (FTc) and

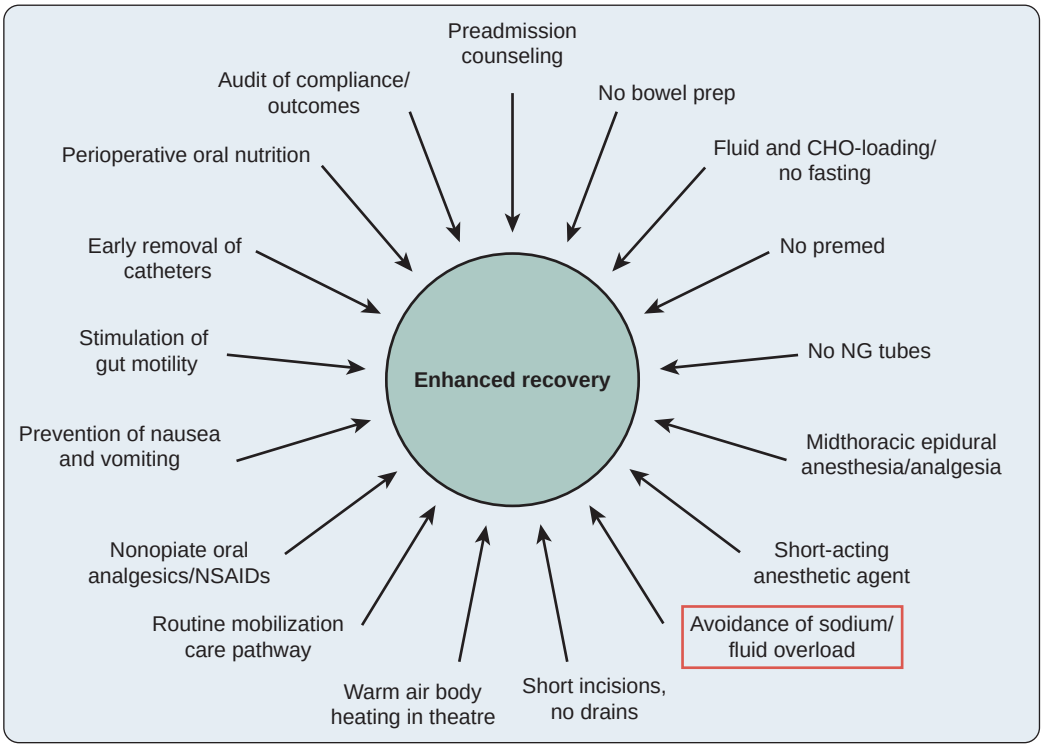


Fig. 47.3 The major components of enhanced recovery programs. *CHO,* Carbohydrate; *NG,* nasogastric; *NSAIDs,* nonsteroidal antiinflammatory drugs.

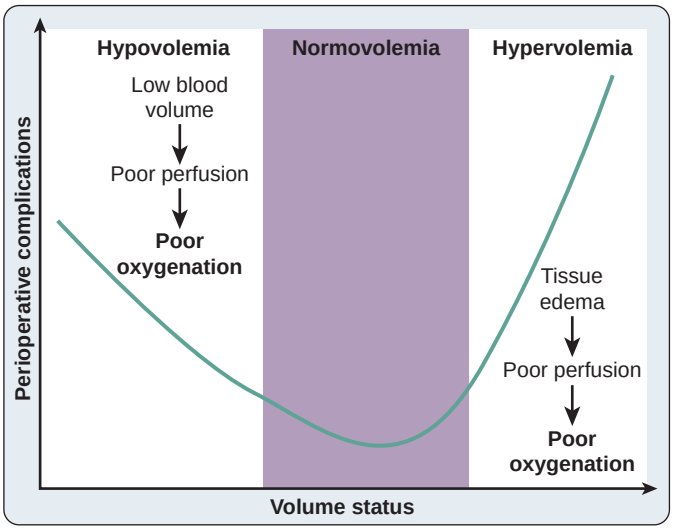


Fig. 47.4 Either hypervolemia or hypovolemia may cause impaired tissue perfusion and poor outcome. *(From Bellamy MC. Wet, dry or something else?* Br J Anaesth. *2006;97:755–757. Used with permission.)*

increases in stroke volume (SV) from colloid fluid boluses, is shown in Fig. 47.5. Numerous studies of a wide variety of surgical populations using various GDT algorithms and monitors showed benefits for the vast majority of patients.[15–21] Hamilton and associates[22] in 2011 performed a metaanalysis of 29 studies over the previous 30-year period, revealing reductions in mortality and morbidity associated with a goal-directed approach. The odds ratio for mortality was 0.48 (95% CI 0.33–0.78), and the odds ratio for surgical complications was 0.43 (95% CI 0.34–0.53). Corcoran and associates[9] performed a meta-analysis in 2012 comparing traditional with goal-directed approaches, showing improved outcomes associated with GDT. In a 2014 multi-institutional study of 734 high-risk gastrointestinal surgery patients (OPTIMISE Trial) conducted by Pearse and colleagues[23] survival and major complication benefit did not reach statistical significance. However, when this study data were included with a 38-study meta-analysis, decreased perioperative morbidity was observed (relative risk 0.77; 95% CI 0.71–0.83).[23]

Goal-Directed Fluid Therapy and Cost Reduction

With its decreased morbidity and hospital lengths of stay, it is anticipated that GDT will reduce costs. Financial benefits have been demonstrated with GDT, although the available studies are not recent and the pulmonary artery catheter was used.[24,25] Relatively little recent research in this area has been reported. Perioperative complications, in addition to being distressing to patients and health care delivery teams, dramatically increase health care costs. This increased cost results from an increased use of expensive resources (intensive care unit [ICU] and hospital beds, diagnostic tests, medical and surgical therapies), and the loss of opportunity (fewer patients can be cared for in the system). Volanthen and associates,[26] studying abdominal surgery, showed that patients with an uneventful course had a mean cost per case of $27,946, whereas patients with one or more complications had an *added* cost of $34,446. Boltz and colleagues,[27] who studied abdominal and vascular surgery, showed that for patients with one, two, or three perioperative complications the excess costs were $6,358, $12,802, and $42,790, respectively. In this large study, the average cost difference among patients who did and did not suffer complications was $22,398.

A recent study of the University HealthSystem Consortium (UHC) database, consisting of 120 academic medical centers and 300 of their affiliated hospitals, projected cost savings associated with GDT by applying the odds ratio of complications in high-risk surgeries from a recent metaanalysis to the actual costs of complications recorded in the UHC database.[28] The conservative projected direct cost savings per patient treated was $569 to $970, and $43 to $73 thousand for the entire UHC system per year. The mortality rate, hospital lengths of stay, and direct costs for patients with at least one complication versus those with no complications is presented in Table 47.1.

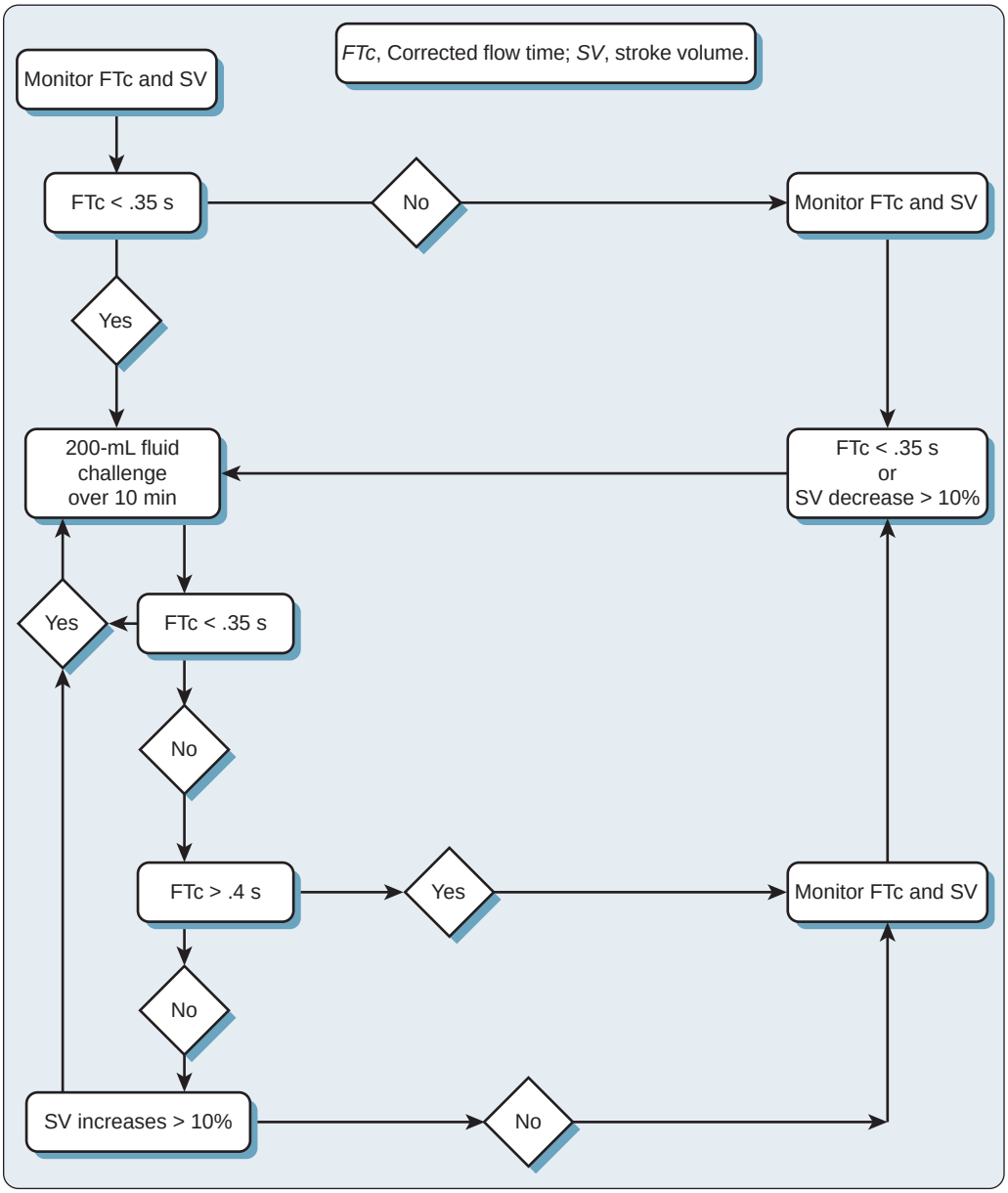


Fig. 47.5 Goal-directed fluid therapy algorithm. *(From Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002;97:820–826. Used with permission.)*

TABLE 47.1 Mortality Rate, Hospital Length of Stay, and Direct Costs of Patients With No Surgical Complications Versus One or More Complications

	No Complications	*≥1 Complication*	*P Value*
Mortality rate	1.4%	12.4%	<0.001
Hospital LOS (days)	8.1 ± 7.1	20.5 ± 20.1	<0.001
Direct Costs (mean)	$17,408 ± $15,612	$47,284 ± $49,170	<0.001

LOS, Length of stay.

Adapted from Manecke GR, Asemota A, Michard F. Tackling the economic burden of postsurgical complications: would perioperative goal-directed fluid therapy help? *Crit Care.* 2014;18:566. Used with permission.

Monitoring for Goal-Directed Fluid Therapy

Various monitors have been used successfully in GDT, ranging from invasive (pulmonary artery catheter)[12] to noninvasive (finger plethysmographic waveform).[29] The data provided complement standard monitoring (heart rate, blood pressure) with parameters tracking overall cardiac performance such as cardiac output and SV, and/or indices of potential fluid responsiveness such as stroke volume variation (SVV), pulse pressure variation (PPV), arterial pulse wave analysis systems), and FTc esophageal Doppler. Monitoring of central venous oxygenation has been used to assess adequacy of the circulation.[13] Assessment of tissue perfusion by means of gastric tonometry has been used in GDT,[30] and attempts at evaluating tissue oxygenation (near-infrared spectroscopy) have been made as well[31] (see Chapter 13).

Each monitoring system has strengths and weaknesses, and their use should be tailored to individual situations and institutional preference. Although the accuracy of minimally invasive cardiac output monitors such as arterial waveform systems and esophageal Doppler has been questioned, the ability of the systems to assess and trend cardiovascular performance appears to be adequate for perioperative GDT. Of course, in critically ill or unstable patients, invasive monitors such as a pulmonary artery catheter and transesophageal echocardiography should be considered. Monitors used for GDT are presented in Table 47.2.

TABLE 47.2 Monitors for Goal-Directed Fluid Therapy (GDT)

Invasiveness	*Technology*	*Device*	*Parameters for GDT*	*Strengths*	*Weaknesses*
Invasive	Thermodilution cardiac output Pulmonary artery Central venous pressure	Pulmonary artery catheter	Cardiac output	Clinical gold standard for measuring cardiac output Vast amount of potentially useful data, including RV function	Is invasive Requires central venous access
	Transpulmonary thermodilution	PiCCO (PULSION Medical Systems) Central arterial catheter	Pulmonary artery and central venous pressure	Vast amount of potentially useful data, including thoracic blood volume and extravascular lung water	Is invasive Requires central arterial access
	Fiberoptic oximetry	Precep Catheter (Edwards Lifesciences)	Mixed venous and venous oxygen saturation	Assessment of global oxygen balance and extraction ratio	No direct information concerning cardiac performance or fluid responsiveness
Minimally Invasive	Doppler flow measurement Descending aorta	CardioQ (Deltex Medical)	Cardiac output	Most common monitor successfully used for GDT	Requires skill (placement)
	—	—	Corrected flow time (preload, afterload)	Newer systems incorporate arterial pressure wave	Inaccurate information concerning aortic cross-clamping, aortic aneurysm, aortic regurgitation
	Pressure wave pulsatility	Vigileo/FloTrac (Edwards Lifesciences)	Cardiac output Stroke volume variation (fluid responsiveness)	Easy to use Stroke volume variation be a powerful parameter combined with cardiac output	Inaccurate information concerning aortic cross-clamping, aortic regurgitation, cirrhosis, sepsis
Noninvasive	Finger cuff	ClearSight system (Edwards Lifesciences)	Cardiac output Stroke volume variation (fluid responsiveness)	Noninvasive	Potential accuracy issues Relatively unstudied in GDT
	Finger plethysmography	Pulse oximetry	Waveform variation	Noninvasive	Potential accuracy issues Relatively unstudied in GDT No cardiac output data
	Thoracic electrical impedance Bioreactance Velocimetry	NICOM (Cheetah Medical) ICON (Cardiotronics)	Cardiac output	Noninvasive	Potential accuracy issues Relatively unstudied in GDT

RV, Right ventricular.

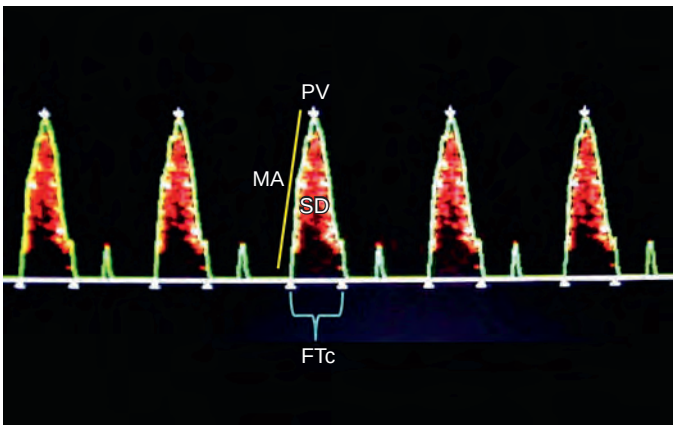


Fig. 47.6 Esophageal Doppler velocity-time waveform. *FTc*, Corrected flow time; *MA*, mean acceleration, *PV*. peak velocity.

The esophageal Doppler (CardioQ, Deltex Medical, Greenville, SC) is the most studied monitor for GCT. This system consists of a small probe placed in the esophagus that insonates the descending thoracic aorta. An estimation of the cross-sectional area of the aorta is made based on patient characteristics (age, height, gender, and weight) and the area under the velocity-time is calculated, with the terms velocity-time integral (VTI) and stroke distance (SD) used interchangeably. SD is multiplied by the aortic cross-sectional area to obtain SV:

$$SV = SD \times \text{Aortic cross-sectional area} \qquad \text{Eq 47.1}$$

Because of its common use (particularly in the United Kingdom) and its track record of utility in GDT, a number of algorithms have been developed for use with the esophageal Doppler monitor. These may use SV and FTc for volume responsiveness and afterload (see Fig. 47.5). Other potentially useful parameters include peak velocity and mean acceleration (contractility assessment) (Fig. 47.6).[32] Experienced

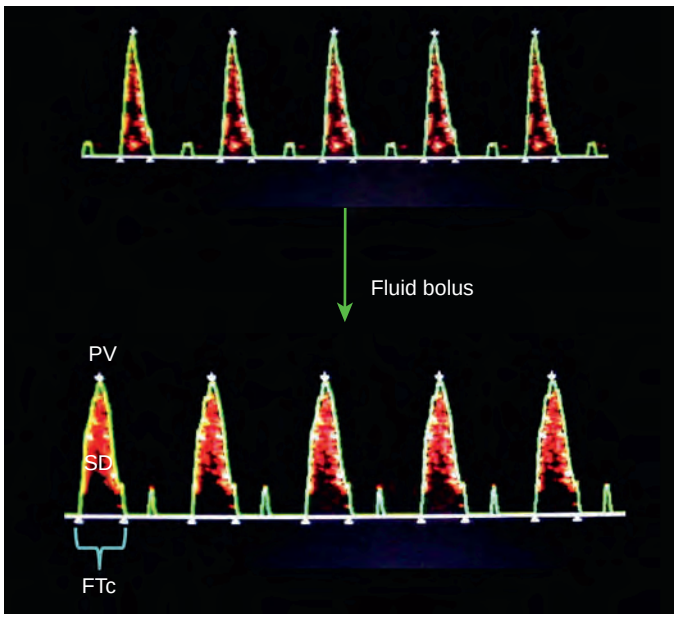


Fig. 47.7 Visual waveform inspection reveals a positive response to a fluid bolus, with increases in peak velocity (PV), corrected flow time (FTc), and stroke distance (SD).

users are able to recognize waveform changes that reflect changes in hemodynamics (Fig. 47.7). Newer esophageal Doppler systems can incorporate arterial pressure waveform analysis when an arterial catheter is used, allowing the added assessment of SVV and PPV. Proper placement and use of the esophageal Doppler system requires some practice, particularly in optimizing the velocity-time waveform. Approximately 15 practice sessions are required to gain facility.

The FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA) sensor-monitor system is the most commonly used arterial pressure–based system used for GDT. An arterial catheter is required, and the arterial wave is digitized by a proprietary transducer. The SV is determined by the pulsatility of the wave (standard deviation of the arterial wave), and a *resistance-compliance* factor, K, is calculated using patient characteristics and characteristics of the waveform:

$$SV = K \times Pulsatility \qquad \text{Eq 47.2}$$

A list of potential monitors for GDT is presented in Table 47.2.

Noninvasive cardiac output monitoring systems are also available, using pressure waveform analysis from either the finger or the wrist.[33,34] A promising concept, these systems do not involve intravascular catheters or esophageal probes. Electrical impedance and cardiometry devices are available as well. Their use for GDT has yet to be firmly established, but it is likely that they will undergo further development.

In certain situations, particularly in critically ill patients, minimally invasive systems are inadequate to provide the detailed information that invasive methods such as pulmonary artery catheterization with thermodilution, transpulmonary thermodilution, and transesophageal echocardiography can provide. These advanced monitors provide the necessary information for GDT and allow for complex hemodynamic and cardiac problem-solving solutions as well (see Chapters 13 through 16).

Patient Selection for Goal-Directed Fluid Therapy

GDT is recommended for major procedures during which substantial blood loss or fluid shifts are anticipated. These may include major general, vascular, urologic, or orthopedic surgeries such as pancreatectomy, open colectomy, radical cystectomy (Box 47.2). Major patient comorbidities such as cardiac disease or a debilitated state may prompt the use of GDT as well. GDT has been studied in cardiac surgery with some positive results. Certainly cardiac anesthesiologists and surgeons apply goals, hemodynamic monitoring, and interventions in managing their patients perioperatively, but GDT as discussed in this chapter has not been widely adopted.

Algorithms in Goal-Directed Fluid Therapy

Numerous algorithms have been used successfully in GDT, with application of SV and preload responsiveness parameters such as PPV, SVV, and FTc. An algorithm based solely on the patient's SV response to fluid bolus is attractive because of its simplicity (Fig. 47.8) but has been associated with fluid overload in aerobically fit patients.[35] Algorithms based solely on SVV have been used, but application of SVV as a primary parameter are limited to patients without significant arrhythmias, receiving controlled positive-pressure ventilation.[36] Likewise, Doppler FTc has been used successfully as a primary parameter.[14] A synthesis of these approaches, with the use of blood pressure as an additional parameter to facilitate hemodynamic problem solving, is currently under study (Fig. 47.9).

A physiologic approach to GDT and hemodynamic problem solving can be achieved using a four-quadrant plot of blood flow (*x*-axis) versus blood pressure (*y* axis) with chosen target hemodynamics in the center of the plot. Deviations from the target zone, depending on the quadrant, are associated with a differential diagnosis and recommended management. This approach facilitates understanding of the hemodynamics leading to accurate, prompt diagnosis and management (Fig. 47.10).[37]

With all the effective algorithms available, the most important conclusion from the GDT literature is that using a logical, physiologically sound algorithm in a thoughtful way results in better outcomes than not using one at all. The choice of algorithm depends on the monitors available, the clinical situation, and the practitioner and institutional preferences. Evidence strongly suggests that using a systematic approach to fluid and hemodynamic management, with particular emphasis on avoiding fluid and salt overload, is indicated for patients undergoing major surgery.

Enhanced Recovery

Enhanced recovery after surgery (ERAS) programs have gained acceptance as a multifactorial, evidence-driven multidisciplinary way of managing patients undergoing surgery (Box 47.3). The primary goal of these programs is to facilitate rapid, complete, and comfortable recovery after procedures by minimizing physiologic perturbations and stress response. *Care pathways* for a variety of surgeries, primarily general and orthopedic, have been shown to achieve this goal, and emphasis is placed on minimizing the invasiveness of the surgery such as laparoscopic or small incision surgery. ERAS programs not only decrease complications but facilitate the return to baseline function even in the absence of complications. The primary components of ERAS programs are careful preoperative optimization; improvements in intraoperative management, particularly with regard to fluid and temperature management; multimodal opiate-sparing pain management; and early mobilization (see Fig. 47.3).

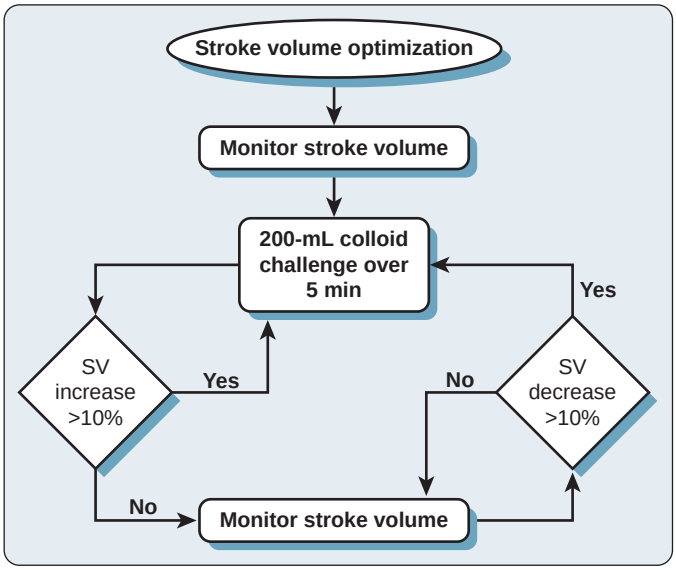


Fig. 47.8 A simple goal-directed fluid therapy algorithm based on responses to fluid bolus. *SV*, Stroke volume.

BOX 47.2 SURGERIES DURING WHICH GOAL-DIRECTED FLUID THERAPY IS RECOMMENDED[28]

- Exploratory laparotomy
- Resection bowel large; colectomy
- Whipple pancreatoduodenectomy
- Hepatectomy
- Splenectomy
- Kidney transplant
- Dissection of radical neck
- Aortofemoral, popliteal, or axillary bypass
- Total open abdominal hysterectomy or bilateral salpingo-oophorectomy
- Hyperthermic intraperitoneal chemotherapy
- Laminectomy fusion with instrumentation (>3 levels)
- Arthroplasty hip, knee, or elbow
- Excision burn
- Cystoprostatectomy with ileal conduit
- Radical cystectomy

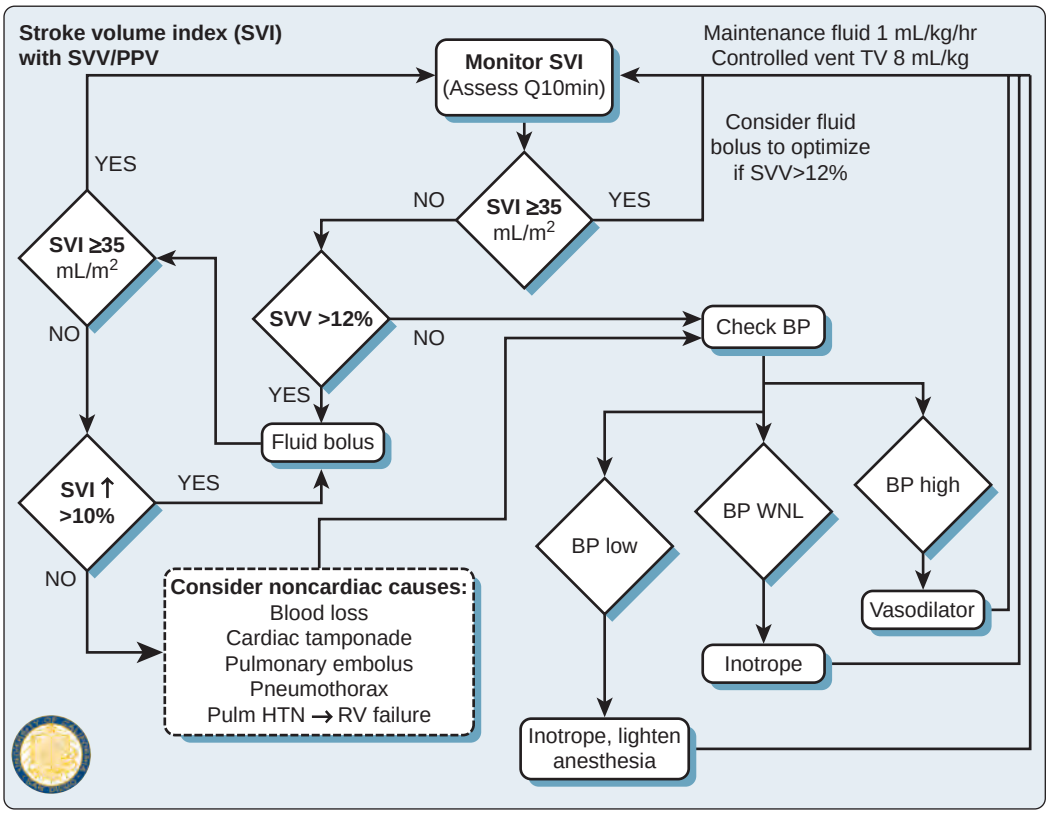


Fig. 47.9 Goal-directed therapy algorithm used at the University of California, San Diego. Stroke volume index (SVI) is the primary parameter, and the values of the targets can be adjusted according to clinical circumstances. Corrected flow time (FTc) can be substituted for stroke volume variation (SVV) for esophageal Doppler use, and an algorithm for use when SVV or FTc cannot be applied is available as well. *BP*, Blood pressure; *HTN*, hypertension; *RV*, right ventricular; *TV*, tidal volume; *WNL*, within normal limits.

BOX 47.3 ENHANCED RECOVERY PROGRAMS

- Preoperative optimization
- Minimally invasive surgery
- Avoidance of fluid and salt overload, goal-directed fluid therapy
- Careful temperature management
- Avoidance of perioperative nausea and vomiting
- Multimodal, opiate-sparing pain relief
- Early removal of catheters and drains
- Early mobilization

BOX 47.4 PERIOPERATIVE SURGICAL HOME REQUIREMENTS

- Multidisciplinary, coordinated effort
- Team leader
- Understanding and navigation of organizational complexities and politics
- Understanding the surgical and medical aspects of care
- Integration of enhanced recovery pathways
- Maintenance and close quality monitoring

ERP preoperative fasting guidelines call for fasting periods of 2 hours for clear liquids, 6 hours for a light meal, and a preoperative carbohydrate drink shortly before surgery. These feedings, along with reduced bowel preparation, result in improved volume and metabolic status at the time of surgery. Multimodal analgesia can be achieved with infiltration of the wound with a local anesthetic, regional techniques, intravenous (IV) or oral acetaminophen, nonsteroidal anti-inflammatory medications, dexmedetomidine, intravenous lidocaine infusion, gabapentinoids agents, and steroid administration. Although opiates should be available for break-through pain, their use should be minimized to facilitate a return of bowel function, decrease nausea and vomiting, and reduce the risk of respiratory depression.

Significant evidence suggests that ERPs decrease complication rates and the lengths of hospital stay. A recent metaanalysis of 16 randomized trials of ERP in colorectal surgery revealed a reduction in morbidity (relative risk, 0.60; 95% CI 0.46–0.76) and shortened hospital stays by 2.28 days, 95% CI 1.47–3.09.[38] Enhanced recovery quality improvement projects at institutional and national levels are now common, with the National Health Service Enhanced Recovery Partnership in the United Kingdom being an example.[39]

Perioperative Surgical Home

The PSH is an organizational umbrella under which ERPs may function (Box 47.4). Emphasizing the continuum that is required in ERPs and seamless care before, during, and after surgery, PSHs are now being formed as part of quality improvement and cost containment strategies. PSH has the strong backing and support of national organizations such as the American Society of Anesthesiologists, with large national meetings held on the subject.[40] Challenges in creating PSHs

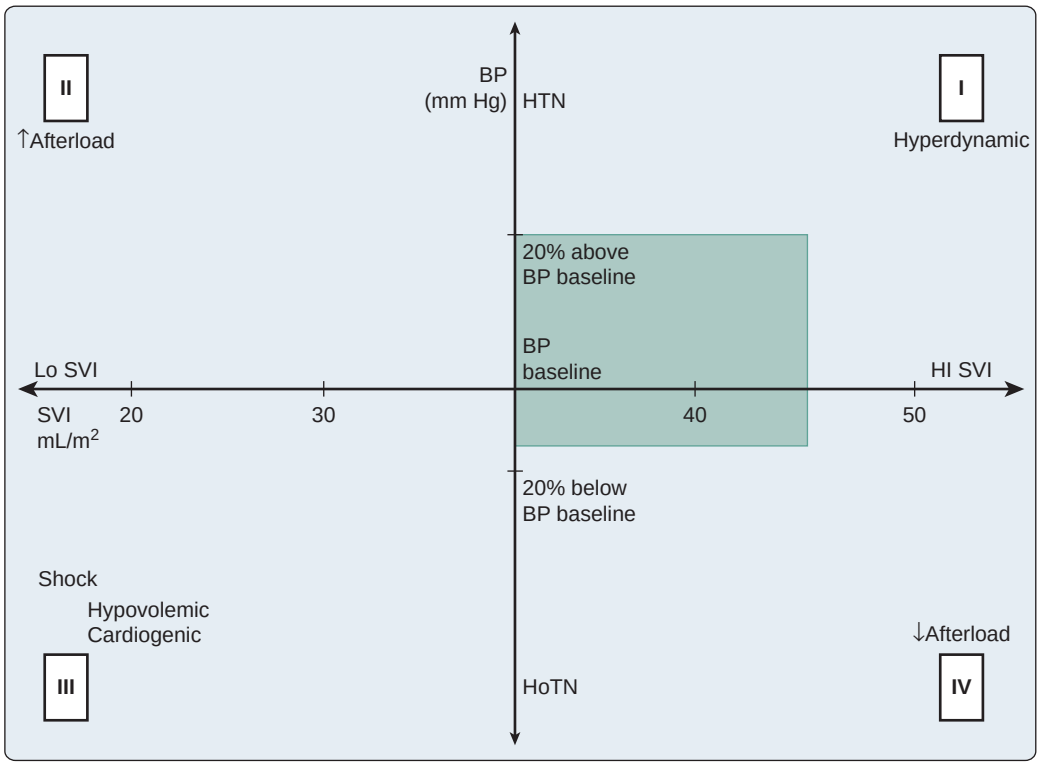


Fig. 47.10 A four-quadrant plot can be created by plotting the stroke volume index (SVI) on the *X* axis and mean arterial pressure (MAP) on the *Y* axis. A target zone (dark area) can be created, and deviations from the target zone are associated with hemodynamic aberrations specific to each quadrant. Point-of-care guidance for each quadrant can be provided. *BP*, Blood pressure; *HoTN*, hypotension; *HTN*, hypertension.

include the complexity of the perioperative care, communication and coordination between many team members, and institutional resistance to change. Anesthesiologists, with their wide scope of influence and organizational skills, will likely enhance their value to their health systems by increasing their involvement in the implementation and management of ERPs and PSHs.[41]

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48

Vascular Surgery: Endovascular and Open Surgery

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KEY POINTS

1. Patients who present for cerebrovascular, aortic, or peripheral arterial interventions are at elevated risk for concomitant coronary artery disease.
2. A thorough preoperative assessment for cardiovascular disease and medical optimization of any comorbid conditions is essential prior to elective vascular surgery. This preoperative process is typically not possible for emergency vascular procedures.
3. The most significant risk factor for future stroke in the setting of carotid stenosis is the presence of recent symptomatic neurologic symptoms. Symptomatic high-grade carotid stenosis should undergo repair. The benefit of intervention for patients with symptomatic but moderate stenosis, or in asymptomatic patients with high-grade stenosis, is statistically significant although less robust.
4. Because of the high rates of mortality and morbidity associated with emergent repair, abdominal aortic aneurysms should be repaired if increasingly symptomatic, if rapidly expanding, or the aneurysm diameter exceeds 5 cm.
5. With aggressive medical management and lifestyle modifications, the natural history of claudication related to peripheral arterial disease is generally indolent and relatively benign. A small subset will progress to critical disease. In general, critical limb ischemia mandates surgical intervention. Timing for intervention in intermittent claudication should take into account severity and tolerability of the symptoms as well as patient-specific risk factors.
6. Endovascular interventions have become a mainstay of treatment for vascular disease. In general, short-term morbidity and mortality are improved with endovascular repair, although the early preoperative benefit is not always maintained in long-term follow-up.
7. Endovascular interventions have unique complication profiles and often warrant repeat intervention and life-time surveillance.

Cardiovascular disease (CVD) is common and clinically important. It is the leading cause of death both in the United States and worldwide.[1,2] Based on data from the Framingham Heart Study, the lifetime risk of developing CVD has been estimated to be greater than 50% in men and nearly 40% in women.[3] A metaanalysis of 18 cohorts across a larger patient demographic found similar results.[4] Although the total number of deaths attributable to cardiovascular events has declined over the past decade, CVD still accounts for nearly one in every three deaths in the United States.[5]

Among the various disease processes that can lead to CVD, atherosclerosis is the most common. (CVD is discussed in detail in Chapter 7.) The process of atherosclerotic plaque formation is both complex and dynamic, involving lipid deposition, smooth muscle proliferation, and an inflammatory milieu (Fig. 48.1). Autopsy studies have demonstrated fatty streaks visible to the naked eye first evident in childhood; the severity of disease increases with age and risk factors.[6] In adulthood, these lesions progress into fibrous plaques prone to rupture, erosion, and hemorrhage. The end result is a narrowed intravascular lumen that creates the potential for downstream ischemia due to mismatch between oxygen supply and demand.

CVD can be grouped into four major categories: coronary artery disease (CAD), cerebrovascular disease, aortic disease, and peripheral arterial disease (PAD). Depending on the location of the lesion, this can result in ischemia or infarction of the heart, brain, abdominal viscera, or limbs. Noncoronary atherosclerotic disease is considered a CAD equivalent and confers a risk of a major adverse cardiac event equivalent to CAD.[7] The 10-year risk of developing CAD in this patient population is greater than 20%.

Some risk factors for CVD, such as age, gender, ethnicity, and family history, are not modifiable. Others are controllable by lifestyle and pharmacologic measures. A large, international study identified nine potentially modifiable risk factors that contributed to greater than 90% of the patient attributable risk of a cardiovascular event: hypertension, dyslipidemia, diabetes, smoking, abdominal obesity, regular physical activity, daily consumption of fruits and vegetables, regular alcohol consumption, and psychosocial factors.[8] These associations were found across both sexes, at all ages, in all regions. Many of the risk factors for CAD and noncoronary atherosclerotic disease overlap, and patients with atherosclerotic disease in one area are at increased risk of vascular disease in other major vascular beds (Table 48.1). Thus, it is common to see significant CAD in patients undergoing major noncardiac vascular surgery, and vice versa.

General Considerations in Perioperative Management for Vascular Surgery

The goal of the preoperative assessment of the patient is to delineate the extent of underlying cardiac and noncardiac disease and medically optimize any underlying conditions. It is vital for the anesthesiologist to assess each organ system for underlying pathophysiology and the subsequent likelihood of leading to perioperative complications. Perioperative management must be tailored to the individual patient to protect any at-risk organ system. Because of the significant association of CAD, cerebrovascular disease, aortic degenerative disease, and PAD, a major focus of the preoperative assessment is to detect, evaluate, and optimize preexisting vascular comorbidities.

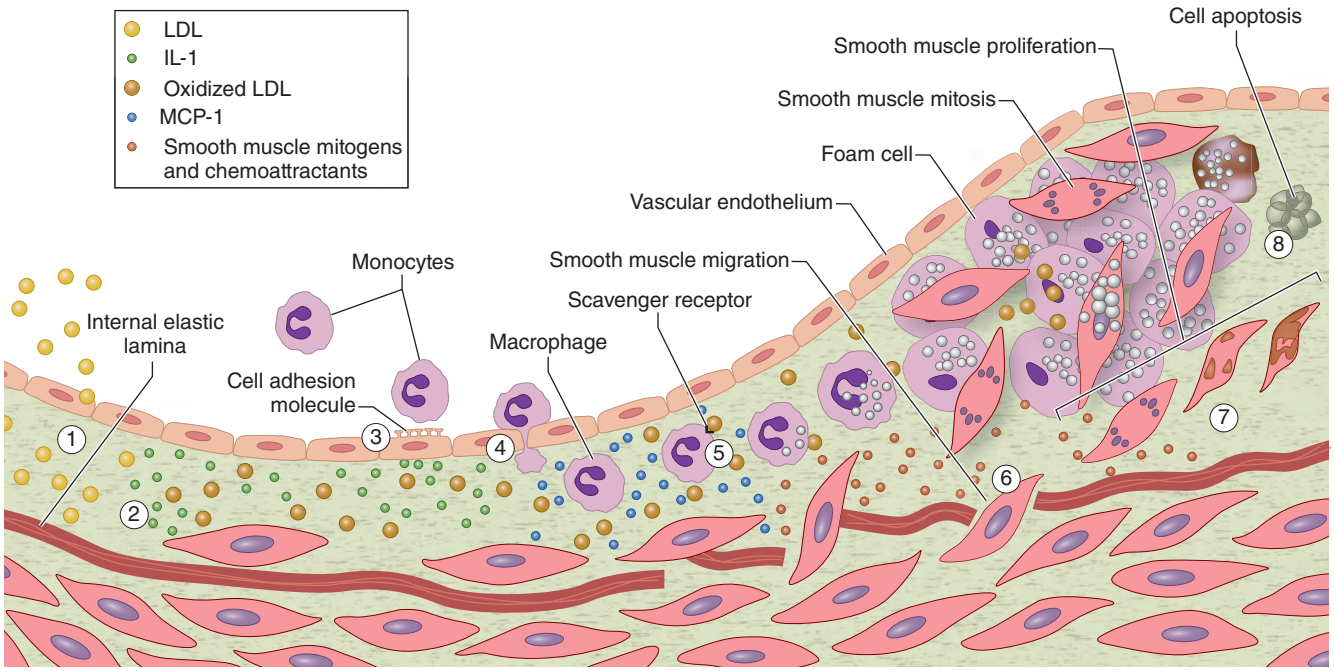


Fig. 48.1 Evolution of atherosclerotic plaque formation. *1,* Accumulation of lipoprotein in the intimal layer; *2,* oxidative stress; *3,* cytokine induction with expression of adhesion molecules; *4,* infiltration of inflammatory cells; *5,* development of foam cells and propagation of inflammatory mediators; *6,* smooth muscle migration; *7,* smooth muscle proliferation; *8,* calcification. apoptosis, and fibrosis. *IL-1,* Interleukin 1; *LDL,* low-density lipoprotein; *MCP-1,* monocyte chemoattractant protein 1. *(Redrawn from Libby P. The vascular biology of atherosclerosis. In: Mann DL, Zipes DP, Libby P, et al, eds.* Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. *10th ed. Philadelphia: Saunders; 2015:873–890.)*

TABLE 48.1 Concomitant Rates of Atherosclerotic Disease in Major Vascular Beds

	Cerebrovascular Disease	*Abdominal Aortic Disease*	*Peripheral Artery Disease*
Coronary artery disease	8–40%	30–40%	4–40%
Cerebrovascular disease	—	9–13%	17–50%
Abdominal aortic disease	—	—	7–12%

Significant overlap exists in risk factors for coronary, cerebrovascular, aortic, and peripheral arterial disease. As many as 50% of patients with atherosclerotic disease in one vascular bed will have concomitant disease present in at least one other vascular distribution.

Data from references 195, 199, 249.

Preoperative Assessment

The preoperative assessment should evaluate for coronary and noncoronary atherosclerotic disease or risk factors. Because of the risk of anemia, as well as a significant risk for blood loss, a complete blood count to assess preoperative levels of hemoglobin and hematocrit should be obtained. A metabolic panel to assess baseline renal function is reasonable because of the likelihood of underlying renal insufficiency as well as risk for postoperative renal dysfunction. Coagulation studies should be considered for any patient who has been on anticoagulation and are mandatory if considering neuraxial manipulation either for anesthesia (eg, spinal or epidural) or therapeutic intervention (spinal drain—see Chapter 23). A preoperative electrocardiogram (ECG) is often useful to serve as a baseline for evaluation of a perioperative insult. A preoperative echocardiogram is reasonable to assess baseline function for any patient with cardiovascular risk factors undergoing vascular surgery, particularly if the patient has new or worsening symptoms.

The American College of Cardiology (ACC) and American Heart Association (AHA), in collaboration with the American Society of Anesthesiologists (ASA), Society of Cardiovascular Anesthesiologists (SCA), American College of Surgeons, and Society for Vascular Medicine, have released well-known guidelines regarding the perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery (see Chapters 1 and 43).[9] The most recent recommendations from these guidelines simplify previous risk stratification prior to elective surgery (see Fig. 43.4). The first step is to evaluate whether a clinical emergency exists; if so, the patient should proceed to surgery without delay with best medical optimization. The second step evaluates whether the patient has an acute coronary syndrome, which should be evaluated and optimized according to guideline-directed medical therapy before nonemergent surgery is performed. Subsequent steps rely on a combination of surgical risk calculators,[10,11] patient functional capacity,[12,13] and clinical decision making to determine if further cardiac evaluation is warranted prior to surgery. In general, patients undergoing vascular surgery represent at least an intermediate (>1%) risk for an adverse perioperative cardiac event and may benefit from additional testing if it will change perioperative management (see Chapter 43 for further details).

Several observational studies previously suggested that preoperative cardiac revascularization improves the outcomes of patients undergoing high-risk noncardiac surgery.[14,15] The Coronary Artery Revascularization Prophylaxis (CARP) study was the first and only randomized controlled trial to evaluate outcomes following prophylactic cardiac revascularization prior to major vascular surgery.[16] This study found no difference in outcomes in patients undergoing major vascular surgery who underwent routine revascularization by either coronary artery bypass grafting or percutaneous coronary intervention. A subsequent analysis found that patients with unprotected left main coronary artery disease may be the only subset of patients who benefits from prophylactic revascularization.[17] Subset analyses found

that of the cohort randomized to prevascular surgical intervention, patients who underwent coronary artery bypass grafting had a lower incidence of perioperative myocardial infarction (MI) and shorter length of stay (LOS) than those that underwent percutaneous coronary intervention.[18] This difference was attributed to better overall revascularization. In large part because of the results of the CARP trial, cardiac revascularization is not typically recommended before surgery unless otherwise indicated according to current practice guidelines.[19,20]

Preoperative Medication Management

It is incumbent on the anesthesiologist to work with the patient's surgical and medical teams to ensure medical optimization prior to surgery, including appropriate management of preoperative medications. As such, it is critical that the anesthesiologist recognize the potential benefits and risks of maintaining, stopping, or initiating medications in the perioperative period (see Chapter 43).[9]

As a general rule, most antihypertensive medications should be continued in the perioperative period.[9] Perhaps no medication has been as extensively studied or widely debated as perioperative β-blockade. Kaplan and colleagues first reported the safety of continuation of β-blockade in the 1970s.[21] Shortly thereafter, Slogoff and coworkers demonstrated an increase in myocardial ischemia in patients on chronic β-blockade when withdrawn before surgery.[22] The preponderance of evidence suggests that patients on chronic β-blockers should be continued on the medication in the perioperative period.[23–26] β-Blockers not should be instituted as new therapy on the day of surgery because of an increased risk of stroke and death.[9,27] It is reasonable to consider β-blockade in high-risk vascular patients prior to surgery, according to the latest ACC/AHA guidelines.[9] This decision should be made in conjunction with the surgical and medical teams caring for the patient.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are generally considered to be beneficial in patients with CVD.[9] They have also been associated with perioperative myocardial and renal protection in adult cardiac surgical patients.[28–30] On the other hand, a large, retrospective observational study in the cardiac surgery population demonstrated that perioperative angiotensin blockade was significantly associated with found vasoplegia, atrial fibrillation, renal failure, and death.[31] Although further randomized controlled trials are warranted, current guidelines suggest it may be reasonable to continue them in the perioperative period.[9,32,33] A reasonable compromise may be to withhold these medications for about 24 hours prior to anesthetic induction to minimize the risk of perioperative vasoplegic hypotension.[34]

The statins have also enjoyed considerable interest because of their known beneficial pleiotropic effects.[35,36] Multiple trials have demonstrated that statins are effective in stroke prevention, independent of their lipid lowering effect.[37–39] Perioperative statin therapy has also been associated with the reduction of perioperative cardiac morbidity and mortality in vascular surgical patients.[40–44] Current guidelines recommend that statin therapy should be continued in the perioperative setting and that it may be reasonable to initiate statin therapy in patients undergoing vascular surgery.[9]

Management of antiplatelet agents must balance the risk of stopping medications versus the risk of bleeding in the perioperative period, particularly in the setting of recent percutaneous coronary intervention with coronary stents.[9] This decision must be made in consultation with the surgical and medical teams managing the patient. In general, it is reasonable to continue aspirin if the risk of adverse cardiac event outweighs the risk of bleeding.[9,45] Management of anticoagulation must be tailored to the individual patient and surgical risks. Patients on anticoagulation deemed high risk may benefit from hospital admission for bridging therapy with heparin and/or antiplatelet therapy before entering the operating room[9] (see Chapters 43 and 44). No guidelines exist to guide management of diabetic medications in the perioperative setting. It may be prudent to hold oral hypoglycemics to prevent unintended hypoglycemic episodes, particularly under general anesthesia. Metformin, in particular, may pose a risk for lactic acidosis in the setting of hypovolemia and iodinated contrast agents frequently used in vascular surgery.[46] Insulin dosing should be adjusted in the setting of preoperative fasting. Blood glucose should be monitored closely in the perioperative setting and covered appropriately with insulin therapy, although recent evidence does not support tight control.[47,48]

Premedication for Anxiolysis and Analgesia

The major goals of premedication for the vascular surgical patient are to reduce anxiety and to provide analgesia for any painful procedures prior to induction of anesthesia. In addition to meeting these basic goals, management of pain and anxiety in the patient with CVD has the distinct benefit of reducing sympathetic stimulation and the risk of myocardial ischemia. Because these patients may also be exquisitely sensitive to narcotics and anxiolytics, these agents should be titrated slowly to clinical effect. When receiving sedation, patients should receive supplemental oxygen and be continuously monitored with pulse oximetry, electrocardiography, and noninvasive blood pressure measurements.

Intraoperative Anesthetic Management

The primary anesthetic used during vascular surgery will depend on factors such as the patient, the surgeon, anatomic considerations, and invasiveness of the surgical procedure. As such, anesthetic techniques are discussed in subsequent sections. On arrival to the operating room, all patients should be placed on standard ASA monitors, including regular noninvasive blood pressure measurement, pulse oximetry, and continuous electrocardiography. Lead V_5 is usually cited as the most sensitive for diagnosing acute myocardial ischemia, although its sensitivity is not perfect, ranging from 66–85%.[49,50] The combination of multiple precordial leads increases the sensitivity to 80–85%, and the addition of lead II increases the sensitivity to higher than 95%.[49,50] It is prudent to place an arterial catheter for invasive blood pressure monitoring for all but the most minor of vascular procedures because of the inherent risk for rapid hemodynamic changes. Patient comorbidities, cross-clamping on major vascular structures, and potential for hemorrhage all contribute to the hemodynamic instability frequently observed during these procedures. Invasive arterial monitoring also allows for frequent blood sampling to assess ventilation and oxygenation, ongoing blood loss and resuscitation needs, and overall metabolic milieu. Because induction of general anesthesia and endotracheal intubation are among the more hemodynamically labile periods, placing the arterial monitoring prior to induction of general anesthesia is wise.

Invasive monitoring with central venous or pulmonary arterial cannulation is not routine for most vascular procedures. Common exceptions include open aortic procedures or when patient comorbidities dictate utility. Large-bore intravenous access, either peripheral or central, is mandatory for any major vascular procedure because of the inherent risk of blood loss and need for resuscitation. Active type and screen and adequate blood product availability should be confirmed before any major vascular procedure is performed.

Although transesophageal echocardiography (TEE) is the most sensitive method for detecting intraoperative myocardial ischemia, it has not supplanted clinical assessment and routine electrocardiography for determination of patients at risk for myocardial ischemia during noncardiac surgery.[9,50–52] The ASA, in conjunction with the SCA, has released practice guidelines for the intraoperative use of TEE.[52] In general, expert opinion has recommended that TEE should be considered in noncardiac surgery in the following circumstances: when the patient has cardiovascular disease that may result in significant clinical compromise, when life-threatening hypotension is anticipated, and when persistent unexplained hypotension and/or hypoxia occurs.[52] Furthermore, these practice guidelines recommend that TEE be strongly considered for major open abdominal aortic procedures and that TEE does not have a routine role during endovascular aortic and distal procedures.[52]

Postoperative Management

In general, patients can undergo tracheal extubation uneventfully in the operating room and recover in the postanesthesia care unit following most vascular surgical procedures. Patients undergoing major abdominal aortic procedures may benefit from close surveillance and management in an intensive care unit setting where mechanical ventilation is frequently continued after initial admission to the unit. In this case, sedation and analgesia should be provided with short-acting agents to facilitate rapid emergence and serial neurologic assessments. Common complications following major vascular surgery include myocardial ischemia, hemodynamic lability, stroke, coagulopathy, renal failure, respiratory failure, coagulopathy, hemorrhage, hypothermia, delirium, and metabolic disturbances.

Carotid Artery and Cerebrovascular Disease

Stroke is important because it is common and clinically serious. An imbalance between blood supply and demand to the brain can result in permanent cerebral infarction (stroke) or transient ischemic attack (TIA), conventionally defined as a focalized neurologic deficit lasting less than 24 hours with no evidence of permanent infarction. Strokes can be defined as ischemic, characterized by disruption of blood flow through a vessel, or hemorrhagic, characterized by bleeding into the brain parenchyma or surrounding spaces.[53] Approximately 87% of strokes in the United States are ischemic in origin.[53] Ischemic strokes can be further subcategorized into five subtypes: cardioembolic strokes, large vessel disease strokes, small vessel disease strokes, strokes related to unusual causes, and strokes of undetermined cause.[54] At least 20% of ischemic strokes are related to extracranial atherosclerotic disease such as carotid stenosis.[55,56]

Clinical Features and Natural History

Stroke is a leading cause of permanent disability and death worldwide.[5,57,58] It is estimated that more than 6 million Americans have suffered a clinical stroke for an overall prevalence of nearly 3% and that the prevalence of clinically silent strokes is 2- to 10-fold higher.[58–61] The global burden of stroke is staggering, accounting for about 10% of deaths worldwide and billions of dollars in stroke-related medical costs.[62,63]

The prevalence of carotid artery disease rises with age, male gender, and racial minorities.[64–69] Although TIAs resolve, they are clinically important because they are a strong predictor of clinical stroke in the near future.[70,71]

Major Milestones in Carotid Artery Intervention

Fisher first described the link between extracranial carotid disease and cerebrovascular disease in 1951.[72,73] Soon thereafter, in 1953, DeBakey described the first successful carotid endarterectomy (CEA) with significant disease-free long-term follow-up.[74] The popularity of CEA has subsequently increased as a result of strong evidence supporting carotid disease as a risk factor for stroke and death.[75–77] Further randomized trials after 1990 repeatedly demonstrated clinical benefit of CEA for both symptomatic and asymptomatic carotid atherosclerosis.[78–84] Mathias first described percutaneous angioplasty of the carotid artery in 1977.[85] Although balloon expandable stents were first introduced in 1989, their use disseminated after the introduction of embolic protection devices that reduced the risk of stroke in the early 1990s.[86,87] Since then, multiple high-quality trials, including meta-analyses, have compared carotid artery stenting (CAS) to CEA.[88–92]

The determination of when and how to intervene to treat carotid atherosclerotic disease is complex. The stroke risk related to the disease itself must be balanced with the stroke risk associated with the chosen intervention. Furthermore, surgical decision making must also take into consideration patient-specific risk factors and risk factors for open (CEA) versus endovascular (CAS) management.

Symptomatic Carotid Atherosclerotic Disease: Indications for Intervention

Symptomatic carotid disease is defined as the onset of sudden and focal neurologic symptoms, either temporary or permanent, that are ipsilateral to the carotid pathology. The most important indicator of future stroke risk is the presence of symptoms within the previous 6 months. Three landmark clinical trials have investigated the benefit of CEA versus medical management for patients with symptomatic carotid disease.[78,80,93]

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was a prospective, multicenter, randomized trial of more than 650 patients with TIA or nondisabling stroke with either moderate (30 to 69%) or severe (70–99%) degree of occlusion of the ipsilateral carotid artery.[78,79] Patients were randomized to either best medical therapy or best medical therapy plus CEA. The study was prematurely terminated in the severe disease group because of overwhelming evidence that surgery was beneficial in this cohort. Although risk of stroke or death was higher at 30 days for the surgical group, longer term outcomes related to stroke and death at 2 years were significantly improved in the surgical cohort. Subsequent study of patients with moderate symptomatic carotid stenosis demonstrated a potential, albeit more modest, degree of benefit in patients with 50–69% stenosis.[79] Patients with stenosis less than 50% did not benefit from surgery. Long-term follow-up in the severe cohort has continued to favor CEA.[94]

The European Carotid Surgery Trial (ECST) was a multicenter, prospective, randomized trial enrolling more than 3000 patients with symptomatic carotid disease to medical management versus medical management plus open surgical intervention.[80] Demonstrable benefit for CEA was found for symptomatic carotid stenosis above 80% for the primary outcome of major ipsilateral stroke or death. Because different methods of measurement of stenosis were used in these two trials, it must be remembered that the carotid stenosis category of 80% in the ECST is approximately equivalent to the 70% category defined by the NASCET criteria.

The Veterans Affairs Cooperative Studies Program (VACSP) trial was a prospective, randomized, multicenter trial of 16 Veterans Affairs Medical Centers. Individuals with angiographically identified carotid stenosis greater than 50% presenting within 120 days of stroke or TIA were randomized to CEA plus best medical therapy versus best medical therapy alone.[93] At a mean follow-up of almost 1 year, a significant reduction in stroke or crescendo TIA was demonstrated in the surgical arm. This benefit was most pronounced in patients with greater than 70% stenosis. An important limitation to this study is that only men were enrolled.

Subsequent pooled analyses of the combined data from the NASCET, ECST, and VACSP trials have been performed.[95,96] A consistent benefit was demonstrated for patients with greater than 70% stenosis, with a number needed to treat (NNT) of 6.3 to prevent one stroke over 5 years. A benefit was also demonstrated in patients with moderate (50–69% stenosis), although less robust. The NNT to prevent one stroke over 5 years in this population was 22. There was no significant benefit of CEA in patients with near total occlusion of the internal carotid artery. CEA also was not beneficial in patients with less than 50% carotid stenosis and was found to be harmful for patients with less than 30% stenosis. Taken together, these studies suggest a clear benefit to CEA for patients with high-grade stenosis.

Asymptomatic Carotid Atherosclerotic Disease: Indications for Intervention

Three major trials have evaluated the utility of CEA in patients with asymptomatic carotid disease.[81–84] The Veterans Affairs Cooperative Studies Program (VASCP) was a prospective, multicenter, randomized

trial of more than 400 men with asymptomatic carotid stenosis of greater than 50% as assessed by angiography, assigned to best medical therapy or best medical therapy plus CEA.[84] A statistically significant reduction in the incidence of ipsilateral neurologic events was noted in the surgical group; however, the combined incidence of 30-day stroke and death showed no benefit from operative intervention.

The Asymptomatic Carotid Atherosclerosis Study (ACAS) was a prospective, multicenter, randomized trial of more than 1600 asymptomatic patients with carotid stenosis greater than 60%, randomized to best medical therapy alone versus best medical therapy and CEA.[81] The primary end point was stroke in the distribution of the study artery or any stroke or death in the perioperative period. After more than 2 years of follow-up, the rate of stroke or death was reduced by more than 50% in the surgical group compared with the medical group.

The Asymptomatic Carotid Surgery Trial (ACST) is the largest prospective, multicenter, randomized trial in the asymptomatic population.[82,83] Asymptomatic patients with greater than 60% stenosis were randomized to immediate CEA versus deferral and medical management until symptoms occurred. All remaining medical management was left to the discretion of the treating physicians. The net 5-year risk for all strokes or perioperative death was reduced in the surgical arm by nearly half. Similar results were found in fatal or disabling stroke. The benefit of CEA was statistically significant for contralateral as well as ipsilateral stroke; improved collateral flow via the circle of Willis is the speculated mechanism for contralateral stroke reduction.

A metaanalysis of these three trials demonstrated a small absolute risk reduction of about 3% for the outcome of any stroke for patients with asymptomatic carotid disease who underwent CEA.[97] The NNT to prevent one stroke at 3 years was approximately 33. The net benefit to CEA in asymptomatic patients is delayed because of perioperative morbidity; the early perioperative morbidity outweighs the modest reduction in stroke risk until 2 years or more after surgery. Thus, asymptomatic patients with between 50% and 70% stenosis must be carefully selected to have at least a 5-year expected survival to benefit from surgical intervention.

Carotid Artery Stenting

Carotid artery angioplasty and stenting (CAS) is an alternative to open surgical intervention for patients with carotid atherosclerotic disease, particularly for patients considered to be poor candidates for surgery or anesthesia. Proponents of this minimally invasive technique cite the apparent ease, speed, and comfort for patients over traditional open repair with CEA. Accumulating evidence suggests similar long-term outcomes between CEA and CAS. Significant differences in short-term morbidity and mortality have been found between the two procedures. Furthermore, the ability to predict which patients may be at high risk for adverse outcomes following open repair has been challenged; although better patient selection has been associated with decreased perioperative complications with CAS, most data were not adequately powered to detect treatment differences between different patient groups.

Endovascular treatment of carotid disease has been extensively studied. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is the largest randomized controlled trial to date comparing CEA with CAS. The physicians enrolled more than 2500 standard-risk patients with either symptomatic or asymptomatic carotid artery disease.[88–92] This study failed to show a difference in composite end point of stroke, MI, or death at 30 days, plus any ipsilateral stroke during long-term follow-up.[88] However, several significant differences were found between CEA and CAS. The rate of adverse events in patients age 70 and older significantly favored CEA over CAS; stenting appears to be more beneficial for younger patients whereas CEA may be more appropriate for older patients.[91] Thirty-day stroke and stroke/death rates were significantly higher in the CAS arm. Thirty-day MI rates were significantly higher in the CEA group. At 1 year after intervention, quality of life was found to be significantly diminished for patients who developed stroke, even minor stroke, compared with those who suffered an MI.[88,90] Stroke complications were associated with poorer long-term survival, with an estimated 4-year mortality after any periprocedural stroke of 21.1% versus 11.6% for patients without stroke.[98] However, the importance of periprocedural MI must not be discounted: subsequent analysis found the mortality rate at 4 years was significantly higher for both patients who developed MI and those with asymptomatic cardiac biomarker increase only, a difference that persisted with adjustment for baseline risk factors.[92]

Multiple metaanalyses have evaluated the use of CAS compared with CEA to treat carotid disease.[99–103] The most recent review was performed by Bonati and associates and included 16 trials involving 7572 patients.[99] In patients with symptomatic carotid stenosis with standard surgical risk, CAS was associated with a greater risk of periprocedural stroke or death, death or any stroke or MI, and any stroke. In subgroup analysis, this difference was significant only in patients aged 70 or older. The end point of death or any stroke up to 30 days after treatment or ipsilateral stroke during long-term follow-up was greater in the CAS group, but the rate of ipsilateral stroke after the initial 30-day perioperative period did not differ between treatments groups, suggesting that beyond the immediate risk, results are similar between the two groups. CAS was favored in terms of risk of MI and cranial nerve palsy. The remainder of recent meta-analyses generally agree that the early risk of stroke or death is increased with CAS versus CEA, whereas long-term outcomes are similar between the two groups. The increased risk is generally noted in patients older than 70 years, suggesting that CAS may be a more reasonable alternative in a younger population. Periprocedural rates of MI are increased following CEA compared to CAS.[100,101] The main caveat of these metaanalyses is that data from early stent trials may introduce bias because of the changes in stent technology and practitioner expertise.

Additional Factors Influencing Surgical Decision Making

Carotid intervention may also depend on factors beyond symptom status and degree of stenosis. Both plaque progression and contralateral carotid disease have been associated with an increased stroke risk.[104–107] The Oxford Plaque Study histologically graded the stability of carotid plaque and noted that inflammatory changes were most commonly seen in symptomatic unstable lesions.[108] Plaque characteristics such as ulceration and echolucency also appear to be unstable and increase stroke risk.[109,110] Unstable carotid plaque has also been associated with clinically silent microembolic strokes that are related to substantial risk of clinically significant stroke.[111]

Patient factors such as age and gender may also influence the decision for carotid intervention.[112] Older patients appear to be at higher risk for adverse events with CAS compared to CEA, as outlined earlier. In both symptomatic and asymptomatic trials of CEA versus medical management, the benefit of CEA appears to be greater for men than for women, particularly in asymptomatic patients.[78–82] Rockman and investigators found that women were at higher risk of stroke following CAS compared to CEA for both symptomatic and asymptomatic patients.[113] This may be due to a greater embolic potential in female carotid plaque.[114] In general, women tend to derive less benefit from carotid intervention than do men, particularly with CAS and in the absence of symptoms. Medical management may be considered for female patients unless symptomatic disease is present.

Adverse factors such as excessive patient comorbidity, scar tissue from previous neck surgery or radiation, and the presence of a tracheal stoma are typically associated with high surgical risk and are indications for CAS. Carotid lesions above the second cervical vertebra or below the clavicle are also less amenable to surgical intervention. Alternatively, severe aortic arch atheroma or significant carotid tortuosity typically increase the rate of complications in patients undergoing CAS and are indications for CEA. The complication rate of the surgeon must also be taken into account when weighing the risk and benefits of carotid intervention for the individual patient.

Finally, the significant advances in best medical therapy for cerebrovascular disease since the early trials of carotid intervention may challenge the role of carotid intervention in patients with asymptomatic disease.[115,116] Further randomized controlled trials are required to define the role of carotid intervention in the modern era of medical management.

Anesthetic Considerations and Management for Carotid Artery Intervention

Preoperative Evaluation and Preparation

Because the risk factors for cerebrovascular and coronary disease overlap significantly, CAD is common and important in patients with carotid artery stenosis.[117] Up to 50% of patients with large vessel cerebrovascular disease have abnormal stress tests despite no known underlying cardiac disease: the underlying CAD is frequently severe.[118] Carotid intimal thickness has also been associated with the clinical extent of CAD.[119] Because CAD is prevalent in patients with carotid arterial disease, it is a primary focus of the preoperative evaluation prior to carotid revascularization.[120] Patients should be risk stratified according to current ACC/AHA guidelines (see Chapter 43).[9]

Intraoperative Anesthetic Technique

Carotid revascularization can be performed under general anesthesia or under local anesthesia. The primary advantage of local anesthesia is the ability to continuously monitor neurologic function in an awake patient, which may more reliably detect cerebral ischemia than the neuromonitoring methods utilized under general anesthesia. Because the need for intraoperative intervention in the awake patient may be detected more promptly and reliably, it can minimize the risks of intervention such as embolic risk of shunt placement. Local anesthetic techniques may also avoid hemodynamic extremes and cardiorespiratory morbidity associated with general anesthesia. General anesthesia, on the other hand, has the benefits of increased patient comfort, decreased patient anxiety, and airway control. It also avoids the need for emergent intraoperative conversion consequent to complications such as seizure and airway compromise.

A recent survey at major academic centers demonstrated a wide divergence in perioperative practice for carotid surgery, indicating a lack of consensus about best practices.[121] Patient outcomes following general versus local anesthesia has been the subject of extensive study.[122–125] The largest and best known study is the General Anaesthesia versus Local Anaesthesia for carotid surgery (GALA) trial that randomized more than 3500 patients undergoing CEA, at 95 medical centers in 24 countries, to either general anesthesia or local anesthesia.[123–125] In this investigation, there were no differences in major adverse events between the two groups with respect to death, stroke, MI, LOS, and quality of life.[123–125] Patients undergoing general anesthesia were more at risk for hemodynamic instability and perioperative cognitive dysfunction. A subsequent study, however, demonstrated that intraoperative shunting was the main risk factor variable associated with perioperative cognitive dysfunction.[126] A recent large meta-analysis ($N = 4596$; 14 randomized clinical trials) demonstrated that anesthetic technique had no effect on death, stroke, MI, postoperative cardiopulmonary complications, hospital LOS, or patient satisfaction after CEA.[122] In this meta-analysis, the use of intraoperative shunting was more common in the general anesthesia group.[122] In summary, the available literature does not support the use of one anesthetic technique over another for carotid surgery. The decision for general versus local anesthesia should consider both patient and surgeon preferences as well as unique patient characteristics that might favor one technique over another. Regardless of technique, the goals of the anesthetic are the same: maintain hemodynamic norms and ensure smooth, rapid recovery from anesthesia to allow for early neurologic assessment.

Local Anesthesia Technique for Carotid Endarterectomy

Local anesthesia is performed with or without a nerve block, usually in conjunction with intravenous sedation to minimize patient discomfort and anxiety. It is important to limit sedation so as to maintain the ability to monitor the neurologic status. Local anesthetic options include cervical epidural injection or superficial cervical plexus block with or without deep cervical plexus block. Superficial cervical plexus block, with or without deep plexus block, is more commonly used because it has demonstrated a significantly lower rate of complications.[127] A superficial cervical plexus block has been found to be as effective as a deep or combined block and can avoid the complications of a deep cervical plexus block such as subarachnoid injection, phrenic nerve blockade, Horner syndrome, and increased risk of conversion to general anesthesia.[128–130]

The ability to rapidly convert to a general anesthetic must be ensured before CEA is performed under local anesthesia. Despite concerns, the rate of conversion to general anesthesia has been reported to be relatively low, occurring in only 4% of patients in the GALA trial.[123] Indications for conversion to general anesthesia include patient intolerance or request, accidental subarachnoid injection with brainstem anesthesia, seizure (related to intravascular injection of local anesthetic), airway compromise (from surgery or oversedation), or other hemodynamic or surgical complication. Patient selection is key to the success of local anesthesia. The patient cannot be claustrophobic (drapes are immediately adjacent to and across the patient's face) and must be able to lay flat and still for the duration (arthritis, chronic obstructive pulmonary disease [COPD], heart failure, and other comorbidities may make this difficult for patients).

General Anesthetic Technique for Carotid Endarterectomy

A major goal during the induction and maintenance of a general anesthetic is to avoid hemodynamic extremes such as the lows (during induction with agents with vasodilatory effects) or the highs (during periods of intense sympathetic stimulation, such as intubation and surgical incision). To this end, a variety of anesthetic agents can and have been used. Typically, a balanced anesthetic technique is employed. Induction of general anesthesia should involve the slow titration of a short-acting hypnotic agent, titrated to effect. The addition of a short-acting opioid may blunt the hemodynamic response to endotracheal intubation. General anesthesia can be maintained effectively with either volatile or intravenous agents.[131] Anesthetics must be titrated to minimize interference with any intraoperative monitoring techniques such as electroencephalography.

In general, endotracheal intubation is preferred because of limited access to the airway during the procedure and the greater ability to manipulate ventilation. The use of a laryngeal mask airway has been described and may avoid some of the complications associated with endotracheal intubation (sympathetic stimulation, coughing with suture line disruption and/or hematoma).[132] Normocapnia should be maintained during the procedure to avoid both a decrease in cerebral blood flow associated with hyperventilation and vasoconstriction, as well as potential intracerebral "steal" during permissive hypercapnia.

Intraoperative Hemodynamic Monitoring

Invasive arterial blood pressure monitoring should be considered because there is potential for sudden hemodynamic changes as a result of anesthesia or surgical manipulation.

Stroke during carotid intervention may result from inadequate cerebral perfusion due to hypotension, thrombosis, embolism, and/or carotid clamping in the setting of insufficient collateral flow from the circle of Willis. Cerebral ischemia can be mitigated if the insult is detected in timely fashion and appropriate interventions are made. An intact neurologic examination in an awake patient remains the gold standard for neurologic monitoring and provides a rationale for carotid intervention under local anesthesia. In this setting, a baseline neurologic assessment is performed before sedative medication is administered. Thereafter, the sedation is titrated to achieve both patient comfort and cooperation with serial neurologic evaluations during the procedure, especially during carotid manipulation and

clamping. A change in neurologic function may require interventions to restore cerebral perfusion; these interventions might include shunt placement and/or permissive systemic hypertension to augment collateral flow via the circle of Willis.

If a general anesthetic technique is chosen, a variety of neuromonitoring techniques are available to monitor for cerebral ischemia during carotid intervention; these techniques include EEG, carotid stump pressure, somatosensory-evoked potentials (SSEPs), transcranial Doppler, and cerebral oximetry[133] (see Chapter 18). Intraoperative EEG is a commonly used neuromonitoring modality. Unprocessed EEG is preferred over processed EEG (eg, bispectral index) because bispectral index monitoring has not been reliably shown to predict cerebral ischemia in this patient population.[134,135] Significant alterations during carotid intervention in the electroencephalographic tracings, such as complete signal loss, a 50% decrease in background activity, and/or an increase in delta wave activity, may indicate intraoperative ischemia and the need for intervention. The clinical studies supporting the utility of routine EEG monitoring during carotid intervention are limited and not conclusive.[136,137] Because both intravenous and volatile anesthetic agents may affect the electroencephalographic tracings, close communication between the anesthesia and neuromonitoring teams remains essential to minimize this anesthetic interference and to maximize both the sensitivity and specificity of EEG to detect cerebral ischemia during the carotid procedure.

Although an intraoperative carotid stump pressure less than 50 mm Hg may predict for stroke after carotid intervention, it has limited utility as the sole method for detecting intraoperative cerebral ischemia and the need for interventions such as shunting.[136,137] A recent meta-analysis ($N = 4557$; 15 prospective and retrospective studies) evaluated the diagnostic value of SSEPs in carotid intervention.[138] A change in SSEPs during carotid intervention had a strong pooled specificity of 91% (95% confidence interval [CI], 86–94), but a weak sensitivity of 58% (95% CI, 49–68).[138] Furthermore, a change in SSEP profiles during carotid intervention significantly raised the risk of perioperative stroke (pooled odds ratio, 14.39; 95% CI, 8.34–24.82).[138]

Transcranial Doppler measures blood velocity in the middle cerebral artery to aid in the detection of significant intraoperative microemboli. This alert may prompt the surgical team to avoid further carotid manipulation that could lead to stroke.[139] Although transcranial Doppler can detect cerebral ischemia, it is not always accurate.[140,141] Cerebral oximetry uses near-infrared spectroscopy to detect cerebral oxygen saturation; however, data to support its use for carotid surgery are mixed.[142–144] Given the current neuromonitoring choices for detection of stroke during carotid intervention under general anesthesia, it is clear that no technique is perfect. Recent meta-analysis has suggested that a combination of stump pressure with EEG or SSEP has the best diagnostic power for detection of cerebral ischemia in this setting.[141] The role for neuromonitoring during CEA with the patient under general anesthesia is prominent when it guides the decision for selective shunting. In the setting of routine shunting for CEA, there is less of a role for these modalities, given that the shunt maintains cerebral perfusion despite the clamped segment of the carotid artery. Ultimately, the choice of neuromonitoring technique, and whether to routinely use neuromonitoring at all, is left to the discretion and expertise of the operative team.

Anesthesia for Carotid Artery Stenting

CAS is a minimally invasive procedure that can usually be performed under local anesthesia or monitored anesthesia care. Sedation is carefully titrated to allow for continuous neurologic examination throughout the procedure. If a general anesthetic technique is employed, short-acting agents are typically administered to allow for a rapid emergence and neurologic evaluation. Because peripheral endovascular access is obtained rather than direct surgical manipulation of the head and neck, a laryngeal mask airway may be chosen rather than endotracheal intubation to attenuate the hemodynamic lability encountered on induction and emergence of general anesthesia.[145] As with any endovascular technique, it may become necessary to convert to open repair. As such, monitoring and vascular access should be planned accordingly.

Intraoperative Challenges

Both CEA and CAS may be associated with hemodynamic lability of both heart rate and blood pressure because of altered baseline carotid baroreceptor sensitivity as well as intraoperative manipulation of the carotid baroreceptors. Carotid baroreceptor manipulation, either directly or endovascularly, may result in a profound parasympathetic response with bradycardia and hypotension. Periods of significant stimulation, such as endotracheal intubation or surgical dissection, can lead to increased sympathetic outflow with resultant hypertension and tachycardia.

Carotid cross-clamping may precipitate ipsilateral cerebral ischemia from decreased carotid blood flow and inadequate collateral flow via the circle of Willis. Blood pressure should be maintained in a normal to slightly higher than baseline range prior to cross-clamping in order to optimize cerebral blood flow. Carotid unclamping may be complicated by impaired autoregulation and disrupted baroreceptor function, resulting in increased cerebral blood flow.[146]

Issues may arise during CAS such as stent kinking, stent thrombosis, carotid dissection, and/or atheroembolism. Technical issues with the stent may often be amenable to observation or additional stent placement, whereas acute thrombosis typically necessitates immediate conversion to open CEA. The incidence of clinically important embolization has significantly decreased with the use of embolic protection devices.[146] In the event of significant distal embolization, management options include catheter-directed thrombolysis, aspiration thrombectomy, and/or aggressive anticoagulation.[146]

Postoperative Complications

Ongoing hemodynamic lability may continue into the postoperative period as a result of continued altered baroreceptor function. Uncontrolled postoperative pain may also contribute to hypertension. Although the risk of MI is substantially lower after CAS compared with CEA, it nevertheless remains a leading cause of perioperative death after carotid intervention.[147,148]

Cerebral hyperperfusion syndrome is a rare but clinically important complication, usually occurring several days following carotid intervention and resulting from impaired cerebral autoregulation after relief of high-grade stenosis.[149] Clinical presentation may progress from severe headache to seizures or, at worst, intracerebral hemorrhage.[149] Management is supportive, with strict control of blood pressure to minimize the risk of intracerebral hemorrhage.[147,149]

Postoperative hematoma following CEA is usually a result of diffuse oozing following heparin administration and concurrent antiplatelet therapy. Although a relatively uncommon occurrence, with reported incidence of approximately 0.5–3%, postoperative hematoma can lead to life-threatening airway compromise.[132] Injury to the recurrent or superior laryngeal nerve may result in paralysis of the ipsilateral vocal cord. Additional complications related to vascular access during CAS are encountered in 3–5% of cases and include infection; bleeding, hematoma, or retroperitoneal hemorrhage requiring transfusion; pseudoaneurysm or arteriovenous fistula formation; and vessel thrombosis or dissection with resultant limb ischemia.[146] The use of iodinated contrast agents may precipitate renal dysfunction, particularly in patients with underlying renal disease.

Abdominal Aortic Disease

The aorta is the major arterial conduit from the heart to the systemic circulation and provides vascular inflow to all of the major abdominal and pelvic organs as it traverses the abdomen.[150] The abdominal aorta is a retroperitoneal structure that begins at the diaphragmatic hiatus and ends at the level of the fourth lumbar vertebra, where it bifurcates into the common iliac arteries.[150]

Abdominal Aortic Aneurysm

An aneurysm is typically defined as a greater than 50% dilation of the expected normal arterial diameter.[150] The aorta tapers gradually from the thorax to the abdomen such that its normal diameter at the level of the renal arteries is approximately 2.0 cm.[151] Although factors such as age, gender, race, and body surface area may influence normal aortic diameter, an abdominal aortic diameter greater than 3.0 cm is considered aneurysmal.[150] Aortic aneurysm occurs most commonly in the abdominal aorta.[152] Aneurysms of the thoracic and thoracoabdominal aortas occur far less commonly (for further details refer to Chapter 23).

Abdominal aortic aneurysms (AAAs) are classified by location as infrarenal (originating below the level of the renal arteries), juxtarenal (originating at the level of the renal arteries), or suprarenal (originating above the renal arteries). This distinction is important because it dictates the complexity of the surgical repair and the potential for hemodynamic derangements, particularly with open intervention and the accompanying aortic cross-clamp. The majority of AAAs are infrarenal, whereas approximately 5–15% involve the suprarenal aorta.[153]

It has recently been recognized that the process of aneurysm formation is a distinct degenerative progression with features such as vessel wall infiltration by macrophages, destruction of elastin and collagen, loss of smooth muscle cells, and neovascularization.[154,155] While inflammation and macrophage infiltration are common to both atherosclerotic and aneurysmal disease, atherosclerosis is primarily noted within the intima and media, whereas aneurysmal disease typically affects the media and adventitia.[154] Although the overwhelming majority of AAAs are caused by degenerative disease, less common causes include infection, inflammatory diseases, trauma, and congenital conditions.

Clinical Features and Natural History

AAAs are typically seen in older adults with an incidence that increases significantly after age 50.[150] The occurrence of AAA is also more common in men and Caucasians.[156,157] Although population-based screening studies estimate an overall AAA prevalence of about 5%, this prevalence is decreasing, perhaps as a result of better risk factor modification.[158,159]

The nonmodifiable risk factors for AAA include age, gender, and family history.[156] Modifiable risk factors include smoking, obesity, hyperlipidemia, hypertension, and atherosclerotic arteriopathy (including CAD).[150,156] Smoking is the modifiable risk factor most strongly associated with AAA.[156,157] Regular exercise and a healthy diet are associated with a decreased risk of AAA.[156] In contrast to most vascular pathophysiology, diabetes mellitus is associated with a reduced risk of AAA.[156] A possible explanation for this protective effect of diabetes against AAA may be the consequent vascular stiffness and calcification, preventing aneurysm formation.[160]

Most AAAs are asymptomatic and are often discovered incidentally.[150] Occasionally, patients may present for vague abdominal pain and/or may note a pulsatile abdominal mass. Rarely, a large AAA may be secondary to a mass effect on related structures, such as vomiting from gastrointestinal compression, urinary symptoms from ureteral compression, or venous complications from iliocaval compression. Most aneurysms eventually become symptomatic secondary to growth or rupture. Rupture of an AAA is most often lethal with a mortality rate of at least 75%. In this setting, of the 50% of patients who reach the hospital alive, about 50% will survive to hospital discharge.[161–163] Given these high mortality rates from rupture and emergency surgery in patients with AAAs, a major management goal is to identify and treat AAAs before they rupture.[150] Current European and North American guidelines recommend ultrasound screening for AAAs in high-risk circumstances, such as for adults older than 64 years and adults with a family history of AAA.[150,164,165] Furthermore, the frequency of surveillance imaging for patients with known AAA is a function of aneurysm size.[164,165]

Indications for Abdominal Aortic Aneurysm Intervention

The single greatest risk factor for aneurysm rupture is size.[150,164,165] Current evidence-based guidelines suggest repair when aneurysm diameter exceeds 5.0–5.5 cm.[150,161,164,165] Rapid aneurysm growth, defined as greater than 10 mm per year, is also an indication for intervention.[150,164] Furthermore, urgent repair is recommended in the setting of symptomatic nonruptured AAA, regardless of size.[150,164,165] Finally, in the setting of excessive perioperative risk, medical rather than surgical management may be considered in patients with multiple significant comorbidities.[150,164,165]

Dubost and colleagues first described open AAA repair in 1951.[166] Although AAA repair is still considered a high-risk surgical procedure, clinical outcomes have steadily improved as a result of ongoing refinements in perioperative management, including advances in anesthetic and surgical techniques.[161] Current estimates of perioperative mortality rates for open AAA repair range from 1.5 to 5.8%.[167–170] A recent meta-analysis demonstrated a perioperative mortality rate of 4.2% for open repair.[171] Endovascular aortic repair (EVAR) for AAA was pioneered by Volodos in 1986 and Parodi in 1991.[172,173] With ongoing improvements in endovascular technology and proceduralist skill, the procedure has become a mainstay of treatment for AAA.[161,164,173,174] Recent epidemiologic studies suggest that more than 50% of AAAs undergo EVAR in the contemporary era.[175,176] High-quality randomized controlled trials comparing endovascular to open abdominal aortic repair have demonstrated a significant perioperative survival benefit due to EVAR with no significant difference in mid- to long-term mortality between AAA repair techniques.[177–184] Whereas open AAA repair has proven long-term durability,[185] EVAR carries a risk of repeat endovascular intervention.[182–184] Ultimately, the decision for open versus endovascular repair for the individual patient depends on multiple factors, such as aortic anatomy, urgency, patient preference, and surgical expertise.

Randomized Trials of Endovascular Versus Open Abdominal Aortic Aneurysm Repair

The UK Endovascular Aneurysm Repair 1 (EVAR 1) trial was a multicenter prospective study ($N = 1252$) of patients with large AAAs who were randomized to either open or endovascular repair.[177,180,182] The 30-day operative mortality rate was reduced by two-thirds in the endovascular cohort, although the need for secondary interventions was also higher in this group.[177] The early survival benefit of EVAR was lost by 2 years.[180] The increased morbidity remained substantial in the EVAR cohort through the long-term follow-up, with new endograft-related complications and reinterventions.[182]

The Dutch Randomized Endovascular Aneurysm Repair (DREAM) trial similarly compared both perioperative and long-term outcomes in patients who underwent endovascular versus open AAA repair.[178,181,182] The DREAM trial was a multicenter trial studying 351 patients with AAA who were randomized to either open or endovascular repair. Trial end points such as perioperative death and a composite of death and major morbidity favored EVAR.[178] At 2-year interim analysis, the survival advantage associated with EVAR was already lost,[181] and at a median of 6 years of follow-up, survival rates remained comparable between cohorts.[182] Similar to the EVAR 1 study, the need for long-term reintervention was significantly higher in the EVAR cohort, most often for graft-related complications such as graft migration or endoleak. The quality of life at 6 months and 1 year was also lower in the EVAR cohort.[186]

The Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative Study Group was a third multicenter prospective trial of 881 patients with AAAs, medically fit for either type of intervention, who were randomized to endovascular or open repair.[179,184] Short-term analysis demonstrated a significant reduction in 30-day mortality and in-hospital mortality in the endovascular group.[179] Consistent with trials such as EVAR 1 and the DREAM, this initial EVAR survival advantage was lost within 3 years of follow-up. The lack of survival benefit beyond the perioperative period held true for high-risk subgroups, including patients with larger aneurysms, older age, higher

surgical risk, or known CAD. No significant difference in device failure, need for reintervention, or 1-year major morbidity was noted between the two groups. In contrast to the DREAM results, no difference in quality of life was noted between the two groups at mid-term analysis. Patients were followed for up to 9 years following intervention with a mean of 5.2 years.[184] Comparable survival rates were again noted between the two groups. Aneurysm rupture after repair, although uncommon, was only associated with EVAR. The rates of secondary procedures and number of postrepair hospitalizations were comparable between cohorts.

The Anévrisme de l'aorte abdominale: Chirurgie versus Endoprothèse (ACE) trial was a multicenter, prospective randomized trial evaluating open versus endovascular AAA repair in patients deemed at low-to-moderate risk for surgery.[187] A total of 299 patients with aneurysms 5.0 cm or greater in diameter were enrolled. In contrast to the aforementioned trials, the ACE trial found no significant difference in perioperative mortality, major morbidity, or reintervention. In long-term follow-up (median 3 years), the endovascular group was more likely to have undergone reintervention with a trend toward higher aneurysm-related mortality.[187] No significant difference was found in overall major or minor morbidity between the two groups, although the open repair group was more likely to have suffered cardiac complications.[187]

Taken together, the results of these trials suggest a short-term survival benefit but no long-term survival benefit with endovascular as compared to open repair. A recent meta-analysis of these four major trials confirmed a significantly lower short-term mortality (1.4% vs 4.2%; $P < .0001$) with EVAR that was not sustained at intermediate or long-term follow-up.[171] There was no difference in either cardiac or aneurysm-related mortality between groups at either intermediate- or long-term follow-up. There was a significantly higher rate of reintervention in the endovascular group, although the majority of these reinterventions were endovascular-based procedures associated with a low mortality rate.

Additional Factors Influencing Surgical Decision Making

In the current era, open repair of AAA tends to be reserved for patients who are not candidates for EVAR. Anatomic constraints pose the greatest barrier to EVAR. A hostile proximal aortic neck is a major indication for open AAA repair.[188,189] A proximal aortic neck may be hostile and compromise adequate endovascular seal because of factors such as short length, excessive angulation, heavy calcification, or high thrombus burden.[150,188,189] Multiple studies have demonstrated an increase in graft-related complications in this setting.[190–192] In a similar fashion, challenging iliac artery anatomy such as calcification, aneurysm, and/or stenosis may be problematic for both adequacy of distal endovascular seal and safety of arterial access. Involvement of the abdominal visceral aortic segment is not necessarily a contraindication to EVAR because current techniques allow for branched, fenestrated, or snorkeled grafts to maintain patency of visceral vessels such as the renal arteries.

Several additional vascular scenarios may mandate open repair. Complications related to previous EVAR (such as endoleak or migration) that are not amenable to further endovascular intervention require open repair. Long-term conversion rates from endovascular to open repair are approximately 1–2%.[193] In general, infection of either the native aorta or aortic graft calls for open intervention. Finally, patients with unique vascular anatomy, such as anomalous renal arteries or in whom the inferior mesenteric artery is paramount for intestinal perfusion, may be better served with open repair.

Anesthetic Considerations and Management for Abdominal Aortic Aneurysm Intervention

Preoperative Evaluation and Preparation

Patients with AAAs are very likely to have high-risk comorbidities.[150] Many risk factors for AAA, such as age, sex, hypertension, hyperlipidemia, and smoking, also increase the risk for CAD, which is the most common cause of both early and late mortality following AAA repair. Both open and endovascular aneurysm repair are associated with an elevated risk for an adverse perioperative cardiac event. In a large study of patients ($N = 1000$) scheduled for peripheral vascular surgery, preoperative coronary angiography demonstrated that only 6% of patients with AAA had normal coronary arteries.[194] In this study, 94% of patients had angiographically identified CAD that was categorized as follows: mild to moderate in 29%, advanced but compensated in 29%, severe but correctable in 31%, and severe yet uncorrectable in 5%.[194]

COPD is also a frequently encountered comorbidity because smoking is a major risk factor for both disease processes. Multiple studies have highlighted that COPD is a significant predictor for increased morbidity and mortality after AAA repair.[195–197] In addition to coronary and pulmonary disease, preoperative renal dysfunction is also an important predictor of perioperative morbidity and mortality.[195,198,199] Therefore, preoperative assessment for AAA repair should delineate the extent of underlying cardiovascular, pulmonary, and renal disease, given their outcome importance. Although EVAR has been associated with lower perioperative morbidity and mortality, the inherent risk of conversion from an endovascular to open aortic approach necessitates a thorough preoperative evaluation for both populations.

Baseline hemoglobin and hematocrit levels are essential because of the risk of major hemorrhage during AAA surgery. Adequate blood product availability must be ensured before any elective repair is performed. Coagulation studies should be considered, particularly in the setting of planned neuraxial instrumentation or drugs that interrupt normal coagulation. A baseline assessment of renal function is essential to evaluate perioperative renal reserve. A baseline ECG is important for diagnosis of new perioperative myocardial injury. Further cardiac testing for this high-risk surgical procedure should be stratified according to current guidelines (see Chapter 43). Although COPD is an important perioperative risk predictor, preoperative pulmonary function testing such as spirometry and arterial blood gases are typically not predictive and are not routinely indicated.[197]

Statin therapy should be continued perioperatively because it may be of particular benefit to patients undergoing AAA repair.[40,200,201] Aggressive attempts to achieve smoking cessation 4–6 weeks before aortic intervention are worthwhile, according to recent trials that have demonstrated consequent significant reductions in perioperative cardiovascular and respiratory complications.[202,203]

Intraoperative Anesthetic Technique

Open Abdominal Aortic Aneurysm Repair

Although regional techniques have been described for high-risk patients, general anesthesia is the most commonly employed technique for open abdominal AAA repair.[204] Surgical exposure is obtained by either a midline transabdominal or lateral retroperitoneal incision. Given the extensive incision and frequency of COPD, epidural analgesia should be considered in this setting to facilitate high-quality pain control, to limit the side effects of parenteral narcotics, and to preserve respiratory function.[205,206] A recent meta-analysis has suggested that this strategy can decrease major complications in AAA repair such as postoperative mechanical ventilation, MI, gastrointestinal morbidity, and renal injury.[207]

Although general anesthesia can be induced by a variety of agents, particular consideration is given to maintaining the patient's baseline hemodynamics in order to maintain adequate end- organ perfusion (typically within 20% of baseline values), while minimizing sympathetic stimulation to noxious events such as endotracheal intubation and placement of invasive monitors. Moderate doses of narcotics and/or intravenous lidocaine on anesthetic induction may prove useful in this regard.[208] Volatile and/or intravenous anesthesia may be utilized for maintenance of general anesthesia. Although recent evidence suggests a cardioprotective effect of volatile agents in cardiac surgery, this benefit is less clear in the context of AAA repair.[209–211]

Invasive blood pressure monitoring is mandatory for tight control of blood pressure during periods of hemodynamic instability and rapid blood loss. Consideration should be given to placement of an arterial catheter before the induction of general anesthesia to guide titration of induction agents to ensure steady hemodynamics during this labile period. Large-bore intravenous access is a necessity and should also be present prior to surgical incision. Adequate blood product availability and assisted means for expeditious transfusion should be available as needed. Cell-saving techniques may decrease the amount of autologous blood needed and mitigate the risks of transfusion.[212] Central venous access should be obtained to facilitate monitoring of overall volume status and to ensure rapid and reliable administration of vasoactive drugs. Invasive monitoring of cardiac output, by PAC or TEE, is reasonable, especially in high-risk patients or patients undergoing complicated surgical repairs requiring high or prolonged aortic cross-clamp times.[52]

Endovascular Abdominal Aortic Aneurysm Repair

EVAR can be successfully performed under local anesthesia, neuraxial anesthesia, or general anesthesia. Although no randomized controlled trials have compared anesthetic techniques, a recent meta-analysis (cumulative $N > 13{,}000$; 10 observational trials) showed no difference in 30-day mortality between techniques but did demonstrate a significantly shorter hospital LOS, lower risk of intensive care unit admission, and reduced perioperative complications in the local group.[213]

Both surgeon and patient preference should also be considered when choosing an anesthetic technique. Certain patient populations are unsuitable candidates for local or neuraxial anesthesia, including patients with significant anxiety, medical comorbidities that preclude their ability to lie flat, and patients with whom communication is limited (such as baseline cognitive dysfunction or language barrier). Currently, EVARs are frequently performed under local anesthesia. The risk of intraoperative conversion from local to general anesthesia (usually precipitated by surgical complication) is less than 1%.[214,215]

Local and Neuraxial Anesthesia Technique for Endovascular Repair

In addition to the postoperative benefits discussed earlier, local or neuraxial anesthesia has several potential intraoperative benefits. Avoiding the myocardial depressant effects of general anesthetic agents and the potentially stimulating periods of induction and emergence may afford better intraoperative hemodynamic stability. Pulmonary outcomes may be improved by avoiding mechanical ventilation and maintaining baseline respiratory mechanics. An awake, conversant patient may also serve as an "early monitor" for complications such as anaphylactic reactions to iodinated contrast agents (eg, pruritus or dyspnea) or arterial rupture (eg, sudden retroperitoneal pain) that may not be immediately evident in an unconscious patient.

Surgical access to the femoral or iliac arteries is obtained either by surgical cutdown or a percutaneous technique. Skin infiltration with local anesthetic, frequently supplemented by ilioinguinal and iliohypogastric nerve blocks, provides adequate anesthesia for arterial access.[216] Neuraxial techniques such as single-dose spinal, continuous spinal, epidural anesthesia, and combined spinal-epidural techniques have all been described as successful.[216–218] Regardless of neuraxial technique, medications should be dosed to obtain an adequate level of regional anesthesia from dermatomal levels T6 through L3 for a period of 3–4 hours. Providers must be prepared to promptly treat hypotension caused by sympathetic blockade that may be encountered with neuraxial anesthesia.

Either local or neuraxial techniques may require supplementation with titrated sedation. Small doses of short-acting agents should be titrated carefully to provide adequate cooperation, sedation, analgesia, and anxiolysis. Care must be taken to avoid oversedation, airway obstruction, and hypoxemia. The ability to convert rapidly and safely to a general anesthetic remains important in the case of either surgical or anesthetic misadventure.

General Anesthesia Technique for Endovascular Repair

General anesthesia eliminates concerns regarding patient comfort, anxiety, and/or the ability to lie immobile and flat for a prolonged duration. It also obviates emergent conversion to general anesthesia. Further advantages of general anesthesia such as dampened bowel peristalsis and precise control of respiration enhance the quality of intraoperative imaging to facilitate accurate stent deployment.

Intraoperative Hemodynamic Monitoring for Endovascular Repair

With the endovascular approach there is typically less hemodynamic instability than with an open aortic intervention because the need for aortic cross-clamping is avoided. Thus, from this perspective, the requirement for invasive arterial blood pressure monitoring is less imperative for EVAR. The ability, however, to place an arterial catheter rapidly in an emergency situation is limited in EVAR because both arms are usually tucked to allow intraoperative fluoroscopy and both groins are usually surgically accessed for the repair. Given these constraints, elective direct arterial blood pressure monitoring is often selected as a precaution in case of arterial rupture and conversion to open repair.

Although EVAR has a lower risk of bleeding and transfusion compared to open aortic intervention, large-bore peripheral intravenous access is still preferred because of the small, but real, risk of conversion to an open approach.[178,179] Central venous access is typically not required unless a significant need for vasoactive medication is anticipated or reliable large-bore peripheral access cannot be established.

Intraoperative Neurologic Monitoring for Abdominal Aortic Aneurysm Repair

Spinal cord ischemia is a feared complication following aortic surgery. Blood flow to the spinal cord is provided by the single anterior and paired posterior spinal arteries, which arise from the vertebral arteries and posterior circulation.[219] The anterior spinal artery typically supplies the anterior two-thirds of the spinal cord and the posterior spinal arteries supply the posterior one-third.[219] Radicular arteries arising from the ascending cervical, deep cervical, intercostal, lumbar, and sacral segmental arteries, as well as hypogastric collaterals, provide additional blood flow to the spinal cord. The thoracolumbar spinal cord is a watershed region with a clinical vulnerability to significant ischemia.[219] The most important segmental artery in this region is the arteria radicularis magna, or artery of Adamkiewicz. This large radicular artery is typically located between T9 and T12 and thus is not at risk of sacrifice for most patients undergoing abdominal aortic repair, although it may originate higher or lower from the aorta.

A major risk factor for spinal cord ischemia during AAA repair is previous thoracic aneurysm repair with exclusion of large high thoracic feeding arteries to the anterior spinal artery, thus making the spinal cord far more dependent on the artery of Adamkiewicz (see Chapter 23),[220,221] Additional risk factors for spinal cord ischemia during AAA repair include prolonged hypotension, anemia, emergency surgery, aortic rupture, and aortic dissection.[219]

Because of the relatively limited length of replacement for isolated AAA repair and the low likelihood of sacrifice of the artery of Adamkiewicz, spinal cord ischemia due to vascular exclusion is a relatively rare occurrence for isolated AAA repair. The incidence of spinal cord ischemia following open AAA repair is generally less than 1%.[198] A recent literature review noted only six reported cases of spinal cord ischemia after EVAR.[222] In patients who have undergone previous descending thoracic aortic injury, the risk of spinal cord ischemia after delayed EVAR does not appear to be increased, despite concerns about a compromised spinal cord arterial network.[223] This lack of increased risk likely reflects the ability of the spinal cord arterial collateral network to adapt over time to loss of segmental arterial supply.[219]

If sufficient concern exists for a risk of spinal cord ischemia, a spinal drain may be prophylactically placed. This scenario is unlikely in AAA repair, given the extremely low risk of spinal cord ischemia. The rationale for spinal drain placement is to augment spinal cord perfusion

pressure, calculated as the difference between the mean arterial pressure (MAP) and the cerebrospinal fluid (CSF) pressure. If CSF drainage is used, it is suggested that no more than 10 mL/h should be drained and CSF pressure should be maintained at 10–12 mm Hg.[219,224] The MAP should be maintained at least 70–80 mm Hg to maintain a spinal cord perfusion pressure higher than 60 mm Hg.[224] Intraoperative CSF drainage and permissive systemic hypertension are typically titrated to results of simultaneous spinal cord monitoring with SSEPs, motor-evoked potentials, or both (see Chapter 23).

Inherent risks exist with spinal drain placement and CSF drainage.[225] Because these risks can outweigh potential benefits in AAA repair, a reasonable approach is to insert a spinal drain only if neurologic insult is apparent postoperatively. Neurologic recovery has been reported with spinal cord rescue in this setting with prompt recognition, permissive hypertension, and timely CSF drainage.[226–228] In this situation, titrated CSF drainage is usually supplemented with systemic blood pressure augmentation to a MAP range of 90–110 mm Hg in order to maximize spinal cord perfusion pressure. In this high-risk setting, the goal hematocrit is greater than 25% to provide adequate oxygen delivery.[219,226]

Intraoperative Challenges

Hemodynamic Management of Aortic Clamping and Unclamping

Hemodynamic perturbations during open AAA repair are influenced by factors such as aortic cross-clamping (AXC), rapid blood loss, significant fluid shifts, and acute cardiac dysfunction. The application of an aortic cross-clamp initiates an array of physiologic derangements governed primarily by the level at which the clamp is applied (Fig. 48.2).[229,230] An increase in MAP and systemic vascular resistance (SVR) caused by impeded arterial flow is the most consistent response to AXC, with an increase in arterial pressure of 10% or more with infrarenal aortic cross-clamping.[230] The potential for a substantially greater increase exists if the aorta is clamped at a higher level such as above the celiac axis where flow to the abdominal viscera is also interrupted.

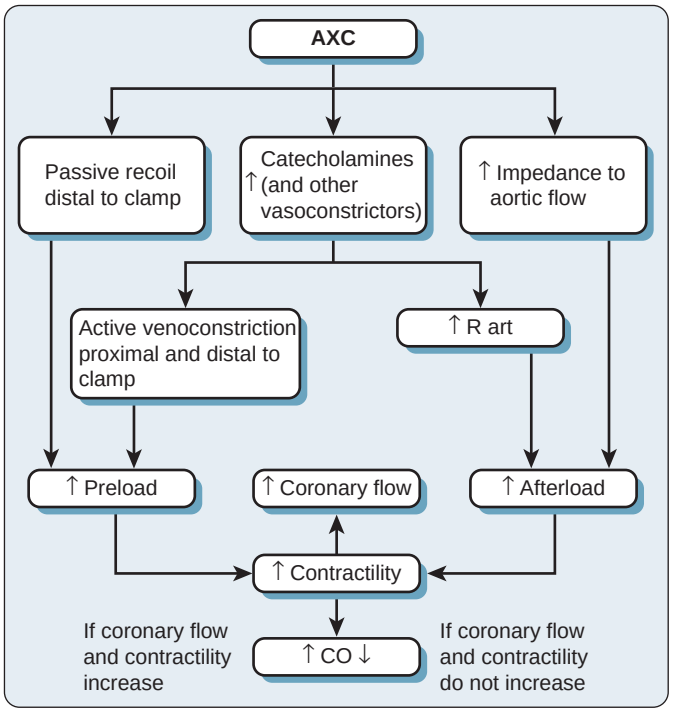


Fig. 48.2 Physiologic changes with aortic cross-clamp placement. Typical hemodynamic response to aortic cross-clamp placement. The level of cross-clamp placement, changes in circulating blood volume, depth of anesthesia and/or anesthetic agents employed, and other physiologic factors may have varying effects. *AXC,* Aortic cross-clamping; *CO,* cardiac output; *R art,* increased arterial resistance. *(Redrawn from Gelman S. The pathophysiology of aortic cross-clamping and unclamping.* Anesthesiology. *1995;82:1026–1060.)*

The hemodynamic effects of an aortic cross-clamp below the level of the celiac axis allows for shifting of blood flow to the splanchnic circulation, which in turn augments its venous capacitance (Fig. 48.3). The typical result of this volume redistribution is little change in venous return and cardiac output, unless major swings in splanchnic venous tone occur. When the clamp is placed above the celiac artery, the splanchnic circulation cannot serve as a reservoir. Rather, venous capacitance below the clamp decreases, expelling blood from the splanchnic system to the central circulation, with resultant increases in filling pressures and venous return. The redistribution of blood volume in this setting is also affected by blood loss, fluid loading, anesthetic depth, and administered vasopressors.[229]

Baseline myocardial contractility reserve may also affect the response to AXC during AAA repair. The increases in preload and afterload acutely increase myocardial work and oxygen demand, particularly with supraceliac clamping. The physiologic response to this increased demand is to increase myocardial perfusion via coronary vasodilation.[229,230] Thus, patients without significant CAD and preserved ventricular function may tolerate these increases in preload and afterload with minimal effect on cardiac output. TEE has demonstrated regional wall motion abnormalities in 33% of patients during suprarenal clamping and in 92% of patients during supraceliac clamping.[231] In the setting of concomitant CAD where the coronary vasculature is already maximally vasodilated and/or there is left ventricular dysfunction, the acute increase in myocardial oxygen demand during AXC may precipitate myocardial ischemia, overt heart failure, or both.

Hemodynamic management during AXC focuses primarily on decreasing afterload and left ventricular wall stress with arteriolar dilators and normalizing preload with venous dilators.[229,230] Typically, short-acting vasoactive agents (such as sodium nitroprusside, nitroglycerin, nicardipine and/or clevidipine) are titrated to achieve these hemodynamic goals in a fashion that adapts rapidly to a changing clinical scenario. Because myocardial ischemia and/or heart failure may present acutely during this critical period, agents to improve myocardial oxygen supply as well as inotropic agents should be available to support ventricular function as necessary. Close communication between the surgical and anesthetic teams is paramount so that pathophysiologic derangements can be anticipated and appropriately managed.

There are several episodes of "aortic clamp release" during open aortic repair (Fig. 48.4). After completion of the proximal aortic anastomosis, the initial superior aortic clamp is then applied lower on the new aortic graft. Even if the initial aortic clamp was supraceliac, the distal aortic anastomosis is commonly infrarenal. The typically brief initial clamp time for the proximal aortic anastomosis results in minor hemodynamic disruption from reperfusion of the celiac and renal vascular territories. In contrast, after completion of the entire AAA repair, release of the distal aortic cross-clamp is frequently associated with dramatic hypotension. The mechanism for hypotension is multifactorial (Fig. 48.5). Distal aortic unclamping results in an immediate and profound (up to 70–80%) decrease in SVR.[232] This distal vasodilation as a result of tissue hypoxia and release of vasoactive mediators promotes sequestration of blood distal to the aortic cross-clamp, resulting in a relative central hypovolemia.[229,230] These vasoactive and inflammatory mediators (such as lactic acid, oxygen free radicals, prostaglandins, endotoxins, and cytokines) promote vasodilation and myocardial depression on release of the aortic cross-clamp. This hypotensive response can be mitigated by surgical techniques such as minimizing ischemic time and releasing the aortic cross-clamp gradually.

Adequate volume loading should be performed during the AXC period in anticipation of the profound vasodilation and relative hypovolemia that accompany clamp removal. Vasodilatory agents during the AXC period may prove useful in this regard. In anticipation of

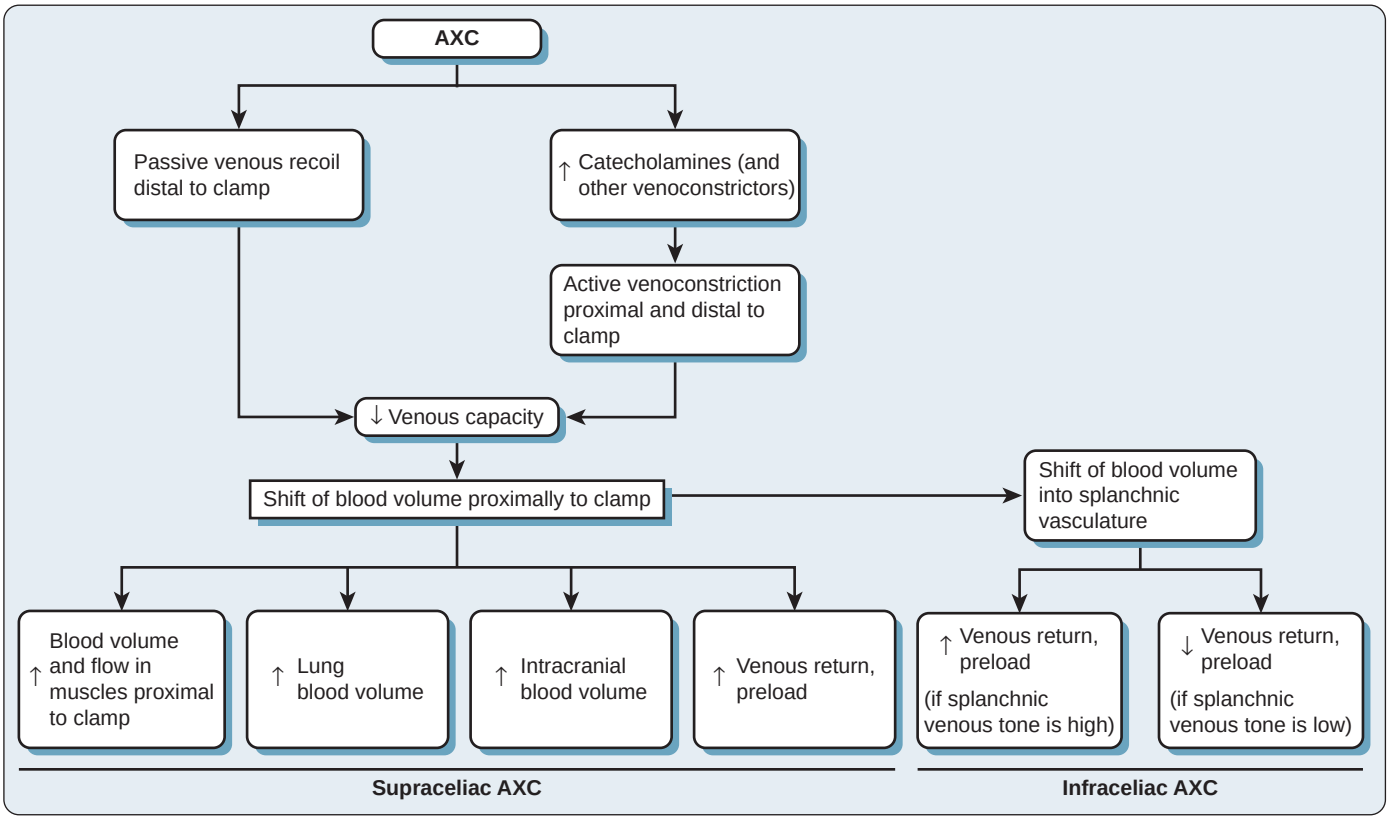


Fig. 48.3 Changes in blood volume distribution during aortic cross-clamping *(AXC)*. The shifting of blood volume with aortic cross-clamping is dependent on the level of cross-clamp placement (supraceliac vs infraceliac), release of catecholamines and administration of vasoactive medications, and overall blood volume. *(Redrawn from Gelman S. The pathophysiology of aortic cross-clamping and unclamping.* Anesthesiology. *1995;82:1026–1060.)*

aortic cross-clamp release, vasodilatory agents should be discontinued and vasopressor agents should be immediately available. A slow release of the aortic cross-clamp and/or opening of iliac artery clamps one at a time may allow for a more gradual metabolic washout with less profound hemodynamic derangements. In case of profound hypotension, the aortic cross-clamp may be reapplied. As with aortic cross-clamp placement, clear communication between the surgical and anesthesia teams is necessary during this critical time.

Hemodynamic Management of Endovascular Stent Deployment

In general, EVAR is associated with fewer extreme hemodynamic perturbations owing to the absence of an aortic cross-clamp. Even though endovascular aortic occlusion during stent deployment may result in transient increases in MAP and afterload similar to those seen with external aortic cross-clamp application, their relative brevity rarely necessitates hemodynamic intervention. Brief deliberate hypotension may be utilized at the time of deployment to position the stent precisely and minimize the risk of distal migration. This can be accomplished by a variety of short-acting vasodilatory agents titrated to effect.[233]

Renal Protection and Function

Postoperative renal dysfunction is a major source of morbidity in AAA repair. During open repair, AXC at all levels reduces renal blood flow. Even infrarenal aortic clamping may decrease renal blood flow by 40%, accompanied by an increase in renal vascular resistance with decreases in renal cortical blood flow and glomerular filtration rate.[230,234] These renal effects are mediated by the renin-angiotensin-aldosterone and sympathetic nervous systems.[229] Renal atheroemboli from AXC may also have a deleterious effect on renal function.

Multiple trials since the 1980s have explored whether agents such as mannitol, furosemide, dopamine, fenoldopam, and *N*-acetyl-L-cysteine are nephroprotective during AAA repair.[235] Although these interventions are still employed, there is inadequate evidence to support this practice.[235] Intraoperative maneuvers such as minimizing AXC time and maintaining adequate hemodynamics are the most prudent measures to limit renal injury during open AAA repair.

Renal dysfunction after EVAR is typically a result of iodinated contrast agents, although atheroemboli and graft impingement of the renal artery ostia may also contribute. In this setting, perioperative maneuvers that minimize the risk of contrast-induced nephropathy include limitation of contrast volume, rehydration with isotonic fluid, and administration of systemic sodium bicarbonate.[236,237]

Postoperative Complications

Despite perioperative advances, complications after AAA repair remain prevalent. The Society for Vascular Surgeons registry has recently reported an 11% perioperative rate of major adverse events after AAA repair, including death, stroke, MI, renal failure, respiratory failure, and paralysis; the overwhelming majority were death and MI.[167] Myocardial injury remains a common and serious complication after AAA repair. A combination of existing risk factors, including CAD and the significant hemodynamic demands discussed earlier, explain the reported perioperative MI rates of 5–10% for open AAA repair, despite careful preoperative assessment (see Chapter 43 for further discussion).[167,238] The relative hemodynamic stability afforded by EVAR likely explains the overall lower rate of perioperative MI, reported at 1.8–5%.[178,238,239]

Pulmonary complications are also common following AAA repair. Mechanical ventilation is commonly continued into the immediate postoperative period for open AAA repair, particularly for more

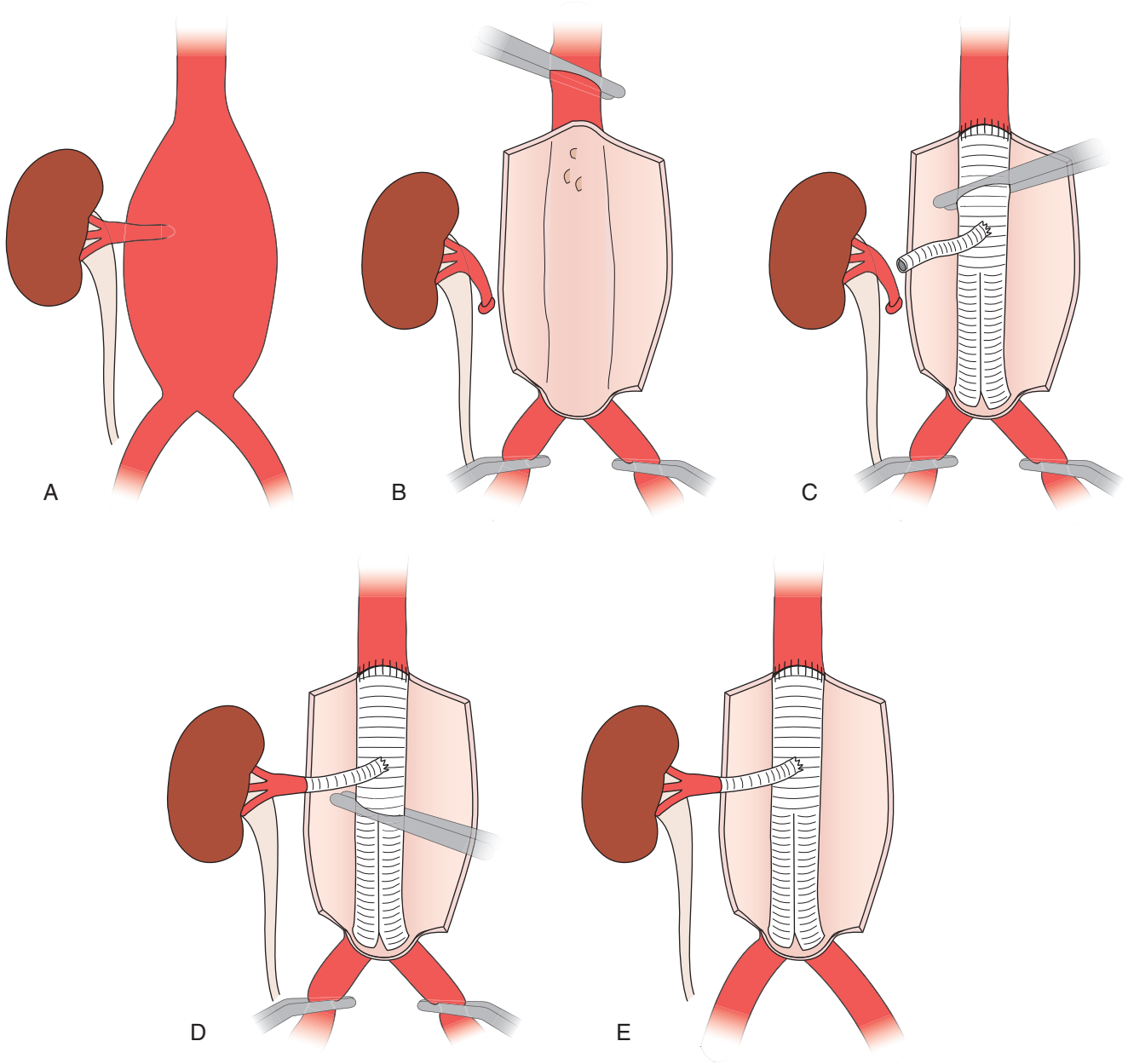


Fig. 48.4 Mobilization of aortic cross-clamp during open abdominal aortic aneurysm repair. To minimize unnecessary ischemic time on visceral organs, the aortic cross-clamp is moved sequentially lower on the graft as each anastomosis is completed. Each cross-clamp release will result in metabolic washout to the previously ischemic organs, although the subsequent quick replacement of the cross-clamp lower on the graft will mitigate some of the hemodynamic alterations. (A) Native aneurysm with right renal artery is shown. (B) Aortal and iliac arteris is clamped. Aneurysm sack is opened and right renal artery is dissected. (C) Aorto-bifemoral graft with separate arterial graft is sewn in. Aortic clamp is moved from native aorta to proximal graft. (D) Right renal artery is anastamosed, with perfusion to right kidney achieve by moving aortic crossclamp distal. (E) Reperfusion of legs: all arterial clamps are removed. *(Redrawn from Woo EY, Damrauer SM. Abdominal aortic aneurysms: open surgical treatment. In: Cronenwett JL, Johnston KW, eds.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Saunders; 2014:2024–2045.)*

complicated procedures. Frequent ongoing resuscitation needs for the first 24–48 hours following repair may make it prudent to "rest" the patient until hemodynamic stability is achieved, particularly in patients with underlying pulmonary compromise such as COPD. Although most patients are liberated from mechanical ventilation thereafter, pulmonary infection still remains a common postoperative complication, occurring in 17% of patients.[238] In contrast, most patients undergoing EVAR either do not require mechanical ventilation or undergo tracheal extubation in the operating room at the end of the procedure. Consequently, pulmonary complications after EVAR are less common with a reported incidence of 3–7%.[178,187,238] Perioperative interventions such as adequate analgesia, aggressive pulmonary toilet, and early ventilator liberation may all help to minimize pulmonary complications after AAA repair.

Perioperative renal dysfunction has an incidence of 10–20% of patients after open AAA repair with a risk of renal replacement therapy

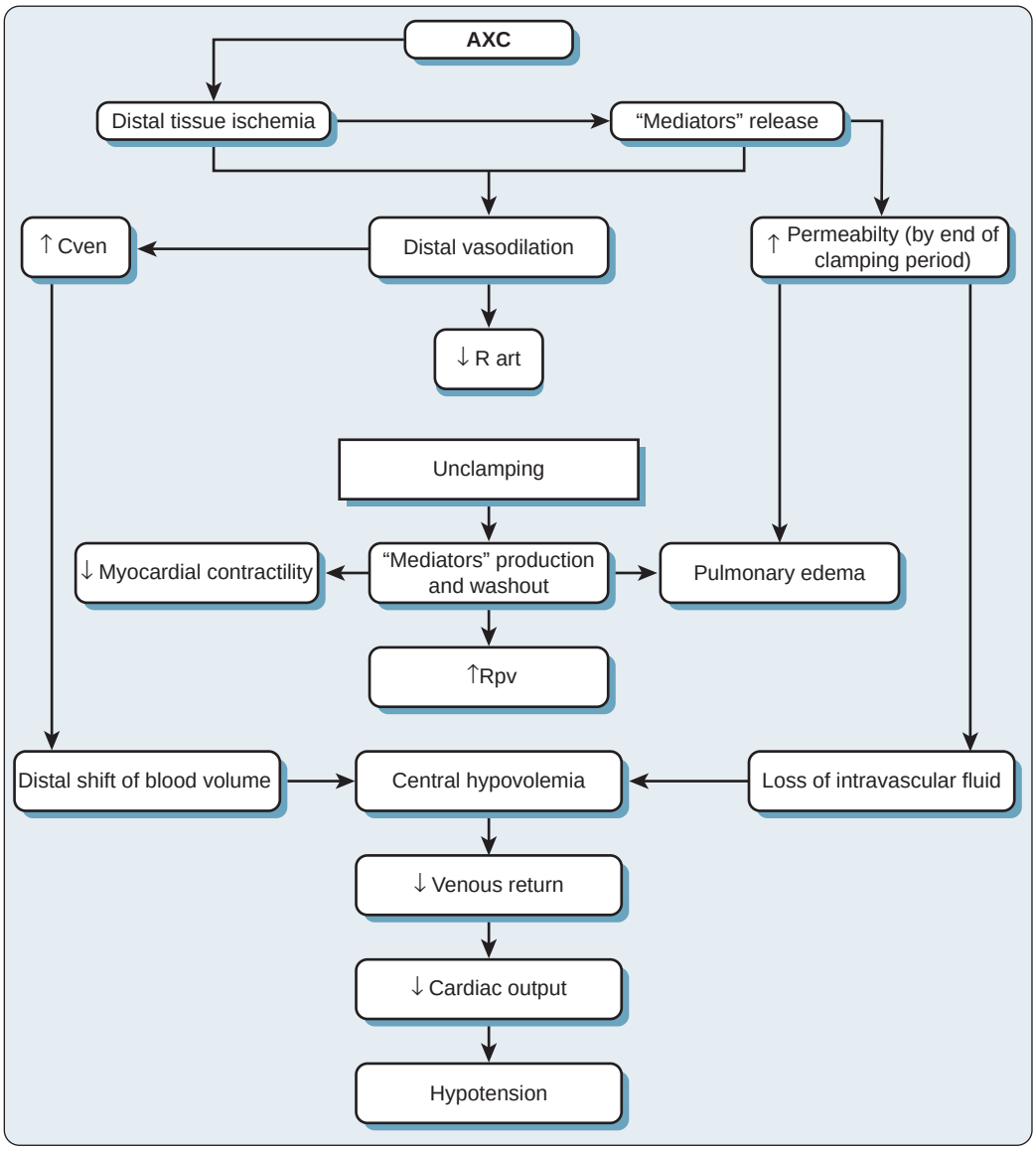


Fig. 48.5 Physiologic changes with aortic cross-clamp release. Typical hemodynamic response to aortic cross-clamp release. *AXC,* Aortic cross-clamping; *Cven,* venous capacitance; *R art,* arterial resistance; *Rpv,* pulmonary vascular resistance. *(Redrawn from Gelman S. The pathophysiology of aortic cross-clamping and unclamping.* Anesthesiology. *1995;82:1026–1060.)*

of 1–3%.[238,240] Although perioperative renal failure after EVAR has a reported incidence of up to 10%, judicious resuscitation with isotonic intravenous fluids, maintenance of normal hemodynamics, and further prophylaxis for contrast-induced nephropathy as previously discussed mitigate the risk for perioperative renal injury.[178,179,238]

Approximately 1% of patients undergoing open AAA repair have complications from bleeding.[238] Bleeding in this setting includes causes such as anastomotic leak, back-bleeding from arterial collaterals, raw-surface oozing, dilutional coagulopathy, hypothermia, and circulating anticoagulants. Meticulous control of surgical bleeding in the operating room and the judicious use of blood product resuscitation, guided by clinical judgment and laboratory values, remain cornerstones of management. Bleeding complications requiring intervention are more common after open as compared with endovascular repair.[238] Vascular events in EVAR include access hematoma, dissection, pseudoaneurysm, arteriovenous fistula, and distal embolization.

Intestinal ischemia remains a serious complication after AAA repair, occurring in about 1–3% of endovascular cases and up to 9% of open cases.[238–243] Despite an extensive collateral arterial network, intestinal ischemia may still result from baseline mesenteric vascular disease, atheroembolization, and/or sacrifice of arterial supply such as the inferior mesenteric artery and hypogastric collaterals.[238,243] Although clinical presentation is variable, early detection remains important; delayed intervention carries a high mortality rate.[244,245] Treatment options range from aggressive resuscitation and broad-spectrum antibiotics for limited disease to emergency bowel resection for full-thickness infarction or evidence of shock.

Spinal cord ischemia is a relatively rare but catastrophic complication of AAA repair. Previous vascular exclusion and length of coverage appear to be the most pertinent factors, although previous aortic surgery, sacrifice of new collateral vessels, aortic cross-clamp duration and location, and perioperative hemodynamic stability are all likely contributors. Spinal rescue in this setting includes permissive systemic hypertension with or without concurrent CSF drainage. Spinal cord ischemia is rare after AAA repair, and these interventions are rarely required.

Lower extremity ischemia is prevalent following both open and endovascular aortic repair. Technical issues with surgical anastomoses,

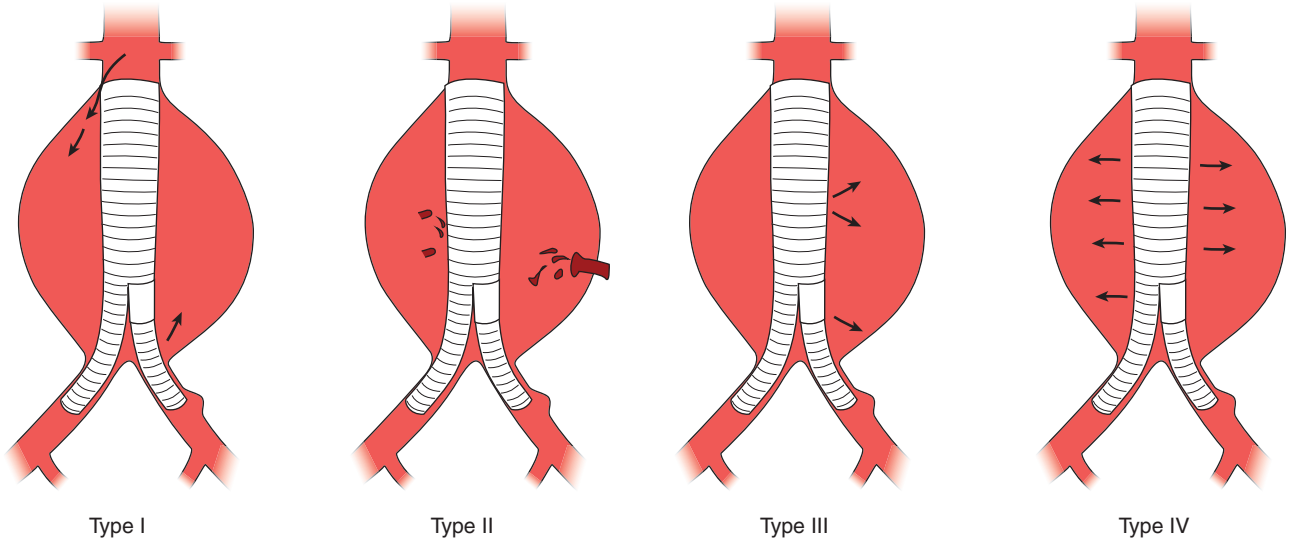


Fig. 48.6 Classification of endoleak. Type I endoleak results from inadequate seal from the proximal or distal end of the endograft. Type II endoleak is caused by inflow from a visceral vessel. Type III endoleak occurs as a result of a defect in the graft, a disconnection of modular graft components, or an inadequate seal. Type IV endoleak occurs as a result of porosity of the graft fabric. Type V endoleak, also known as *endotension*, is an elevation in aneurysm sac pressure without a demonstrable source of endoleak. *(Redrawn from Fairman RM, Wang GJ. Abdominal aortic aneurysms: endovascular treatment. In: Cronenwett JL, Johnston KW, eds.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Saunders; 2014:2046–2061.)*

acute thrombosis, acute embolic disease, and clamp injury may all be a source for lower extremity ischemia. It is important to confirm adequate distal pulses before leaving the operating room and during the early postoperative period. Adequate intraoperative systemic anticoagulation and meticulous surgical technique are important to reduce the likelihood of this complication.

Unique Complications of Endovascular Intervention

Patients undergoing EVAR are at increased risk for subsequent intervention to manage unique complications.[246–248] Endoleak is defined as a failure to exclude the aneurysm from the circulation after device deployment because of a persistent flow of blood into the aneurysm sac. Endoleaks are important because they pressurize the aneurysm sac for a continued risk of expansion and rupture. Five types of endoleak exist, categorized by location and route of blood flow into the space between the graft and the native aneurysm (Fig. 48.6).[150] Meticulous intraoperative imaging will typically identify the presence of an endoleak requiring immediate intervention. Management options include the placement of additional stents, embolization of feeding vessels, or conversion to open repair.

Endovascular graft kinking has been associated with an increased risk for endoleak, stent migration, stent thrombosis, and acute limb ischemia.[249] Graft kinking is more common following endovascular compared with open AAA repair.[249] Surgical options in this setting include additional stent placement, thrombectomy, and open surgical repair. Because stent complications such as separation and migration typically occur after the perioperative period, follow-up remains essential after EVAR.[150]

Abdominal Aortic Dissection

Aortic dissection is an aortic syndrome characterized by a tear in the intima that may subsequently be propagated by pulsatile blood flow with development of a false lumen between the dissected layers of the arterial wall (see Chapter 23).[150,246]

Aortic dissections are classified both temporally and anatomically. Classically, dissections are labeled acute when clinical symptoms have lasted for 14 days or less and chronic if symptom duration exceeds 2 weeks. Recent work, however, suggests four distinct time periods: hyperacute (symptom onset less than 24 hours), acute (2–7 days), subacute (8–30 days), and chronic (>30 days) with risk of mortality that continues to increase significantly even into what is traditionally considered the chronic phase.[250] The majority of late deaths are from rupture of the false lumen, as its long-term patency sets the stage for aneurysmal dilation and rupture.[251]

Anatomically, two classification systems are used to describe aortic dissections (Fig. 48.7). DeBakey first identified variations in aortic dissection based on both the origin of the initial tear as well as the extent of aortic dissection.[252] The Stanford classification system simplifies the schema by entry site only, with Stanford type A dissection originating in the ascending aorta and Stanford type B dissection originating in the descending aorta.[253] In this chapter, discussion of aortic dissection is limited to abdominal aortic dissections. For an in-depth discussion of thoracic and thoracoabdominal aortic dissection, please refer to Chapter 23.

Acute type B dissections are responsible for approximately one-third of all aortic dissections.[247] Isolated dissection of the abdominal aorta is rare; most commonly, the intimal tear originates within a few centimeters of the left subclavian artery. Isolated abdominal aortic dissection is uncommon with an incidence in the International Registry of Acute Aortic Dissection (IRAD) of 1.3%.[254–255] This rare presentation of aortic dissection is frequently associated with hypertension, aortic atheroma, and aortic aneurysm.[254,255]

The clinical presentation of isolated abdominal aortic dissection may vary depending on end- organ compromise: abdominal pain, visceral ischemia, acute renal failure, and limb ischemia have all been reported.[254-257] The initial intimal tear in isolated abdominal aortic dissection is typically infrarenal, although the proximal entry tear site is not always apparent.[254–257]

Medical therapy was employed in two-thirds of patients in the IRAD analysis, while surgery was performed in one-third.[254] Indications for surgery included rupture, visceral or limb ischemia, acute renal failure, refractory pain, and/or uncontrollable hypertension. The majority of surgical repairs were open with better outcomes than in thoracic aortic

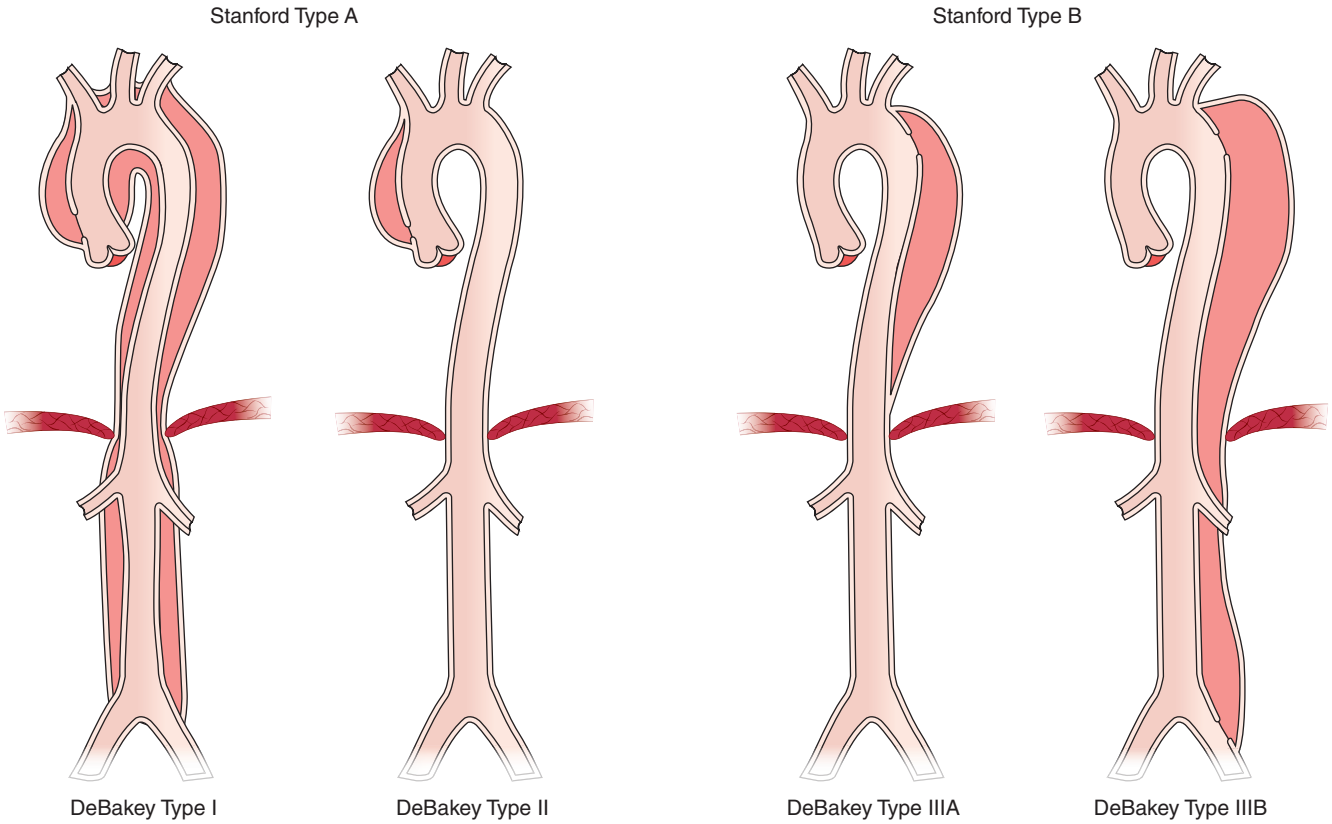


Fig. 48.7 Classification of aortic dissection. Aortic dissections can be classified based on both location of the proximal tear and extent of the dissection (DeBakey) or by the location of the proximal tear alone (Stanford). *(Redrawn from Conrad MF, Cambria RP. Aortic dissections. In: Cronenwett JL, Johnston KW, eds.* Rutherford's Vascular Surgery. *8th ed. Philadelphia: Saunders; 2014:2169–2188.)*

dissection.[254] In this rare abdominal aortic presentation, individual management should be tailored to the clinical situation. Anesthetic considerations in this patient population are similar to those undergoing AAA repair.

Aortoiliac Occlusive Disease

Aortoiliac occlusive disease is a manifestation of PAD that ultimately results in partial or total vascular occlusion. Atherosclerosis is the most common cause of both PAD and aortoiliac occlusive disease; thus, the risk factors are similar and include smoking, age, family history, diabetes, hypertension, hyperlipidemia, as well as more recently identified risk factors such as hyperhomocysteinemia.[165]

Aortoiliac occlusive disease typically begins in the distal aortic segment and the origin of the common iliac arteries and progresses indolently over time.[258] An extensive collateral circulation, primarily from the lumbar and hypogastric arteries, frequently reconstitutes the infrainguinal vessels in disease limited to the aortoiliac segment. Thus, although isolated aortoiliac disease may lead to claudication symptoms (manifested by intermittent thigh, hip, or buttock pain; or impotence from inadequate flow through the internal pudendal artery), it rarely leads to critical limb ischemia. Such patients may tolerate these symptoms for years with expectant medical management. Unfortunately, disease limited to the aortoiliac segment is the exception rather than the rule; more commonly, patients also have extensive infrainguinal disease. Patients with more extensive or multilevel disease are more likely to have more severe claudication symptoms or critical limb ischemia and, not surprisingly, present a more difficult surgical challenge.

Risk factor modification can improve symptoms of claudication and may stabilize disease progression.[259] Most patients, treated appropriately, will not progress to the point of requiring surgical or endovascular treatment. Indications for intervention include disabling or progressive claudication, ischemic rest pain, and tissue loss. The extent to which claudication is disabling is a somewhat subjective decision made jointly by the surgeon and patient based on symptoms and quality-of-life limitations. Current guidelines recommend endovascular or surgical intervention for patients who have significant functional disability that is vocational or lifestyle limiting, who are unresponsive to medical or exercise therapy, and who have a reasonable likelihood of symptomatic improvement.[165,259]

The Trans-Atlantic Inter-Society Consensus (TASC) classifies aortoiliac occlusive disease by location and severity of disease (Fig. 48.8).[260] In general, TASC types A and B represent relatively localized disease of the distal aorta and iliac arteries that is best managed by endovascular intervention.[260] The TASC guidelines further recommend that types C and D disease patterns reflect a more extensive process that is best managed with open repair.[260] Despite these recommendations, recent advances have rendered endovascular treatment as first-line therapy for both localized and extensive aortoiliac disease with comparable outcomes.[259,261] Given this paradigm shift, the Society for Vascular Surgery guidelines now recommend endovascular intervention as a reasonable first-line intervention for both focal and diffuse aortoiliac occlusive disease.[262]

Despite these recent advances in endovascular technology, open surgical reconstruction remains the gold standard for the treatment of aortoiliac occlusive disease, including both bypass and endarterectomy procedures.[259,262]

Extraanatomic bypass procedures such as axillofemoral bypass are typically reserved for high-risk patients with aortoiliac occlusive disease, but they are less durable with reported patency rates below 80%.[262] Because extraanatomic bypass, by definition, does not involve the aortic segment, the hemodynamic lability is avoided. Consequently,

Type A lesions

- Unilateral or bilateral stenoses of CIA
- Unilateral or bilateral single short (≤3 cm) stenosis of EIA

Type B lesions

- Short (≤3 cm) stenosis of infrarenal aorta
- Unilateral CIA occlusion
- Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA
- Unilateral EIA occlusion not involving the origins of internal iliac or CFA

Type C lesions

- Bilateral CIA occlusions
- Bilateral EIA stenoses 3–10 cm long not extending into the CFA
- Unilateral EIA stenosis extending into the CFA
- Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA
- Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA

Type D lesions

- Intrarenal aortoiliac occlusioin
- Diffuse disease involving the aorta and both iliac arteries requiring treatment
- Diffuse multiple stenoses involving the unilateral CIA, EIA, and CFA
- Unilateral occlusions of both CIA and EIA
- Bilateral occlusions of EIA
- Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery

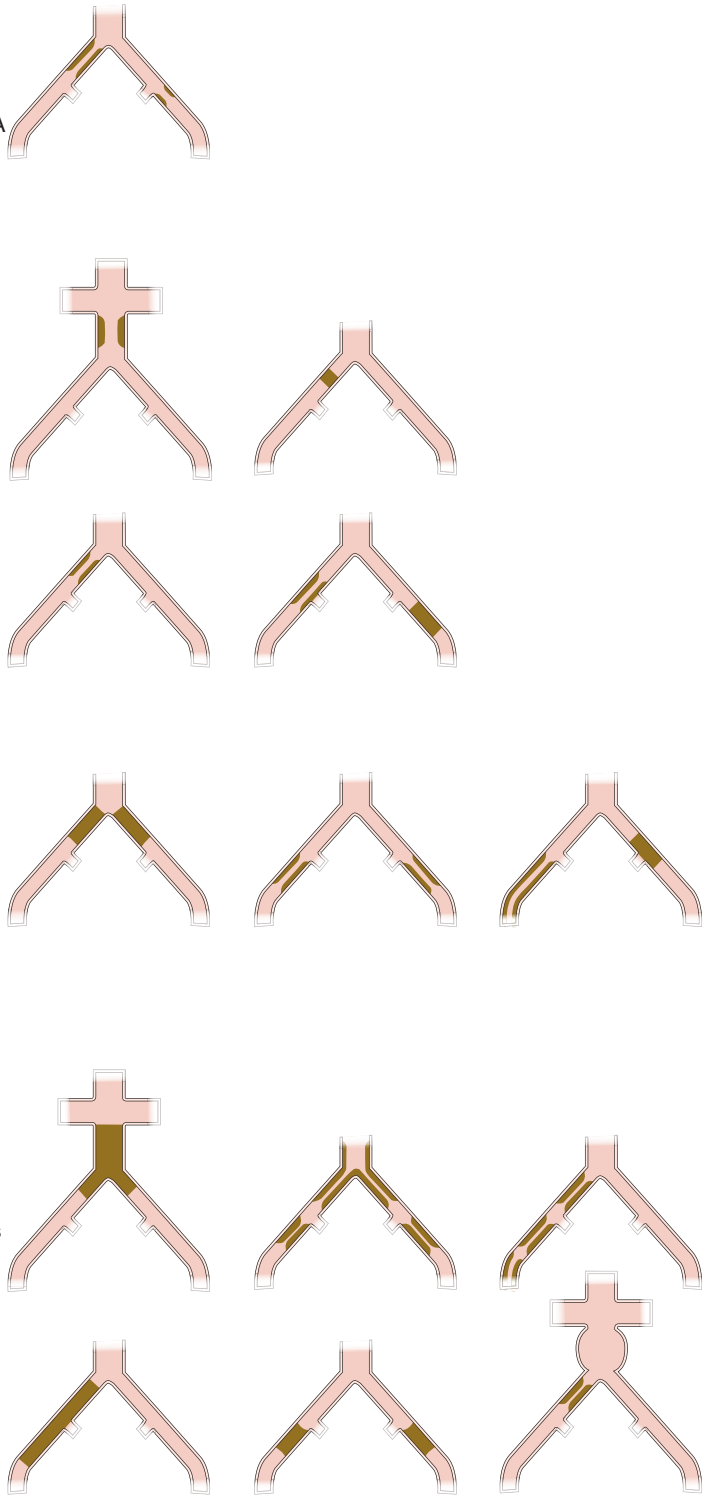


Fig. 48.8 TASC II classifications of aortoiliac disease. Classification of aortoiliac disease based on location, laterality, and disease severity. *AAA,* Abdominal aortic aneurysm; *CFA,* common femoral artery; *CIA,* common iliac artery; *EIA,* external iliac artery. *(Redrawn from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease [TASC II].* J Vasc Surg. *2007;45(suppl S):S5–S67.)*

extensive invasive monitoring is typically not required in this setting, unless patient-specific factors suggest benefit. An arterial catheter and large-bore intravenous access are typically still warranted because of excessive comorbidity, risk for hemorrhage, and risk of hemodynamic changes (albeit less severe) with peripheral vascular clamping.

Lower Extremity Arterial Disease

Lower extremity ischemia has a spectrum of clinical presentations, ranging from exertional muscle pain to gangrene and tissue loss. The clinical manifestations of lower extremity arterial disease (LEAD) depend on the location and severity of arterial occlusion as well as the extent of collateral vessels. Because atherosclerosis is the leading cause of LEAD, it is the focus of discussion in this section about the anesthetic considerations for infrainguinal PAD.

Clinical Features and Natural History

Recent metaanalysis has estimated that more than 200 million people worldwide have clinical LEAD and that its prevalence increased by 23.5% in the first decade of the new millennium alone.[263] An estimated 8 to 12 million Americans are affected by LEAD with an economic healthcare burden measured in billions of dollars.[264] The risk factors for LEAD include advanced age, tobacco abuse, hypertension, hyperlipidemia, and diabetes. In addition, race, genetics, chronic renal disease, and homocysteine[262] have also been associated.[262,265]

Although LEAD may be asymptomatic in up to 50% of patients, it remains a sentinel marker for adverse cardiovascular outcomes because it is frequently associated with atherosclerotic CAD.[262,266–268] The annual incidence of an adverse cardiovascular event in patients with LEAD has been estimated at 5–7%.[260] Although management of known asymptomatic LEAD has been aimed at risk factor modification for atherosclerotic disease, the benefits of this approach have not been clearly demonstrated in the asymptomatic patient subgroup.[262] As such, controversy exists in the appropriateness of screening for asymptomatic LEAD. The 2011 ACCF/AHA guidelines recommend screening in patients older than 65 years, or in patients older than 50 years with a history of diabetes or smoking.[269] In contrast, the Society for Vascular Surgery recommendations suggest that no clear benefit is derived from screening for LEAD in asymptomatic patients, unless it may improve risk stratification and medical management.[262] The U.S. Preventative Services Task Force has also recently concluded that there is insufficient evidence to determine the risk and benefit of routine screening for asymptomatic LEAD.[270]

Claudication is the presenting feature of LEAD in up to 35% of patients.[266] Intermittent claudication is defined as a reproducible discomfort in a defined muscle group that is induced by exercise and relieved with rest. In general, claudication in the buttock and hip typically results from aortoiliac occlusion, whereas claudication in the thigh or lower leg results from progressively distal arterial disease.[266] Intermittent claudication is the first and most common symptom associated with PAD.[266] The natural history of PAD is usually a slow, progressive decline in function. With aggressive medical management, lifestyle adjustment, and exercise therapy, the vast majority of patients do not progress to more advanced disease.[260,266]

In a minority of patients, the disease will progress to critical limb ischemia when existing arterial blood flow is insufficient to meet the basic metabolic demands of resting tissue. The clinical presentation in this setting ranges from rest pain to tissue loss (nonhealing ulcers or gangrene). Risk factors that increase the risk for accelerated disease progression include age, diabetes, smoking, and hyperlipidemia.[260,262] Unlike claudication, critical limb ischemia includes a high risk of limb loss resulting from a more aggressive LEAD with multisegmental involvement. Within 1 year, it is estimated that 25% of patients will progress to amputation and 25% will die from cardiovascular mortality.[165,260] Approximately 50% of patients with critical limb ischemia will also have advanced coronary and cerebrovascular artery disease with a higher mortality risk from MI and/or stroke.[260,271] The management of critical limb ischemia involves aggressive risk factor reduction, wound care, and a low threshold for revascularization.

Indications for Lower Extremity Arterial Intervention

Although surgical intervention is typical in critical limb ischemia, it requires an individualized assessment in the context of intermittent claudication.[262,266] First-line therapy for intermittent claudication includes education, aggressive management of comorbid conditions, and lifestyle modification, including smoking cessation and exercise therapy.[262,266] Continued smoking is a major risk factor for amputation, intervention failure, MI, and death in this setting.[272,273] Meta-analysis has demonstrated that exercise therapy for claudicants significantly improves ambulation up to 200%.[274] In clinical terms, however, this increase translated to an absolute increase in walking distance of less than 100 feet.[275] This relatively modest impact may have limited benefit on perceived quality of life.

The indication for surgical intervention in claudication also depends on the patient's subjective perception of disease burden, given that patients have different thresholds for tolerability of symptoms. For example, relatively mild claudication may be perceived as intolerably disabling in a very physically active patient, whereas very similar symptoms may be fairly well tolerated in more sedentary individuals.

Additional Factors Influencing Surgical Decision Making

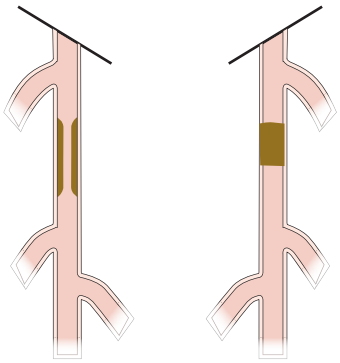
Once the decision has been made for surgical intervention, the selection of open versus endovascular intervention must then also be individualized based on procedural risk, medical comorbidity, overall life expectancy, and expected extent of clinical improvement.[260,262] Open surgical bypass has a long history of success and durability with long-term patency rates greater than 95%.[260,262] Despite this track record, endovascular intervention has become the preferred approach for most patients with LEAD because of low mortality and low morbidity rates. Endovascular procedures, however, have proven less durable in the long term than surgical bypass and have a higher incidence of reintervention.[262]

The TASC II guidelines grade LEAD in four types from type A lesions (relatively short, proximal, and/or localized disease) to type D lesions (long, distal, and/or diffuse or totally occluded disease) (Fig. 48.9).[260] The TASC II guidelines suggest endovascular intervention as the treatment of choice for type A and B lesions and open surgical bypass as the treatment of choice for type C and D lesions, although factors such as operator expertise, patient preference, and patient comorbidities influence the final decision significantly in intermediate lesion types (types B and C).[260] Recent guidelines from the Society of Vascular Surgery recommend endovascular intervention for focal or intermediate length disease of the superficial femoral artery but recommend surgical bypass as an initial strategy for patients with diffuse disease and/or extensive calcification, or for average-risk patients with favorable anatomy for open repair.[260] In general, endovascular intervention for infrapopliteal disease has not been strongly recommended because it has limited benefit.[262]

Because chronic limb ischemia is frequently associated with extensive LEAD, the classic treatment approach has been open repair, which is endorsed by TASC II guidelines.[260] Nevertheless, there is growing support for endovascular intervention because of the higher perioperative morbidity and mortality rates with open repair in this population, although the data are sparse.[276,277] To date, the only randomized, controlled trial to compare open vascular repair to endovascular repair for critical limb ischemia is the Bypass versus Angioplasty in Severe Ischemia of the Limb (BASIL) trial, which enrolled more than 450 patients across 27 centers.[278] Although the perioperative morbidity rate was higher, surgical bypass had a significantly lower immediate failure rate. At 1 year, there was no difference in the primary end point of amputation-free survival, and at 2 years, there was a greater amputation-free survival in the surgical group. Furthermore, patients

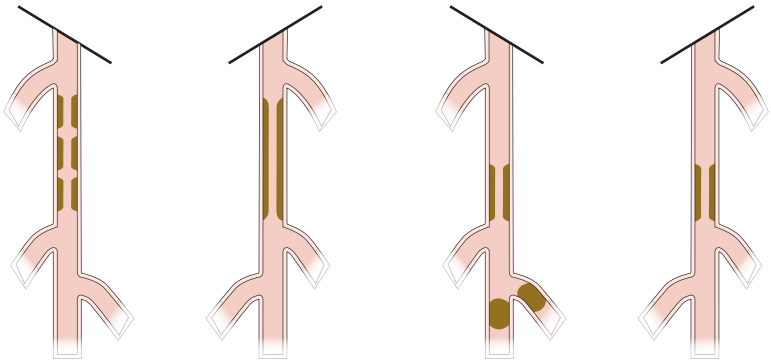
Type A lesions

- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length



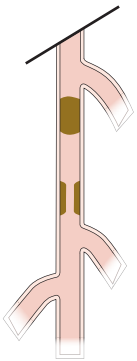
Type B lesions

- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis



Type C lesions

- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions



Type D lesions

- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels

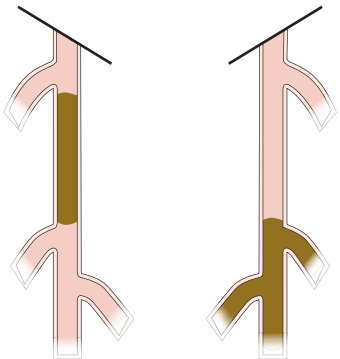


Fig. 48.9 TASC II classifications of femoral popliteal disease. Classification of infrainguinal disease based on location, multiplicity, and disease severity. *CFA,* common femoral artery; SFA, superficial femoral artery. *(Redrawn from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease [TASC II].* J Vasc Surg. *2007;45(suppl S):S5–S67.)*

who underwent open limb salvage after failed endovascular repair did worse than patients who underwent bypass as the primary repair.[279] This landmark trial suggests surgical bypass may benefit patients with chronic limb ischemia and that in the setting of limited life expectancy, endovascular intervention may suffice.[278,279]

Anesthetic Considerations and Management for Peripheral Arterial Intervention

Preoperative Evaluation and Preparation

Patients with LEAD are at high risk for perioperative myocardial ischemia, given the high prevalence of concurrent CAD, as already outlined. The preoperative evaluation should evaluate the extent and severity of underlying concomitant conditions, as per current guidelines (see Chapter 43).[9]

Baseline hemoglobin and hematocrit measurements should be taken, given the possibility for sudden and rapid blood loss. As with any vascular repair, adequate blood product must be available. Because renal dysfunction is highly likely, a basic metabolic panel should be obtained prior to surgery. A baseline ECG is helpful to identify any new myocardial injury that may occur during the perioperative period. Further cardiovascular testing should proceed according to current guidelines.[9]

Patients who have diabetes tend to have more aggressive peripheral vascular disease and amputation rates 5 to 10 times higher than in patients without diabetes.[262] A recent single-center clinical trial demonstrated that tight perioperative glucose control significantly decreases wound infections in diabetics with LEAD undergoing surgical bypass procedures.[280] Aggressive attempts should be made in the perioperative period to formulate a smoking cessation plan, given its significant adverse outcomes in this population.[272,273]

Intraoperative Anesthetic Technique

Open Lower Extremity Arterial Bypass

Open lower extremity revascularization procedures are amenable to anesthetic techniques such as regional blocks, neuraxial anesthesia, and general anesthesia. Although studies have suggested that regional and neuraxial techniques enhance hemodynamic stability and decrease catecholamine responses, these differences likely occur primarily during induction and emergence from general anesthesia.[281–284] Careful management of hemodynamics during these critical periods, therefore, may be just as efficacious. Most clinical trials have failed to demonstrate significant outcome benefit from a particular anesthetic technique in patients with LEAD.[281–287] Although regional and neuraxial anesthetic techniques may enhance lower extremity blood flow due to the concomitant sympathectomy, clinical trials have inconsistently demonstrated higher graft patency rates due to anesthetic technique.[288–290] Given that there is currently no compelling evidence to favor a particular anesthetic technique, the literature suggests at least equivalent outcomes. The final choice of anesthetic technique is left to the discretion of the provider, bearing in mind both patient risks and preferences.

A general anesthetic alleviates concerns of patient anxiety, discomfort, and cooperation. No trials have examined the use of one general anesthetic technique over another. The most important consideration when general anesthesia is employed is careful attention to perioperative hemodynamics, particularly during periods of known lability such as induction, intubation, cross-clamp placement or release, and emergence from anesthesia. A variety of agents can be employed to this end. It is prudent to have a variety of short-acting hemodynamic agents readily available to control changes in hemodynamics, including heart rate and blood pressure.

Neuraxial anesthesia is the most commonly used regional technique. Cutaneous innervation of the lower extremity is provided by the lumbar (primarily above the knee) and lumbosacral (primarily below the knee) plexi.[291] The lumbar plexus is composed of the ventral rami from L1–L4 with variable contribution from T12 (ultimately dividing into the femoral, lateral femoral cutaneous, and obturator nerves), and the lumbosacral plexus is composed of the ventral rami of L4–S3 (ultimately forming the sciatic nerve, which branches to become the tibial and common peroneal nerves). In general, local anesthetics are carefully titrated to slowly bring the anesthetic level to approximately T10 to allow for adequate surgical anesthesia while minimizing hemodynamic compromise. Light sedation with short-acting agents may be considered as supplementation to neuraxial or peripheral anesthesia.

Endovascular Lower Extremity Peripheral Arterial Repair

In general, infrainguinal endovascular interventions are very amenable to monitored anesthesia care or local anesthesia. Arterial access can be obtained percutaneously or via small surgical cutdown, typically under local anesthetic block performed by the surgical team. A variety of short-acting agents have been successfully used for monitored anesthesia care. Most commonly, short-acting opioids (such as fentanyl or remifentanil), benzodiazepines, or low doses of sedative agents such as propofol or dexmedetomidine are used in this regard. In general, hemodynamic perturbations and blood loss during endovascular management are minimal. Invasive monitoring is rarely warranted. As always, the anesthesia team must be prepared for rapid conversion to a general anesthetic should complications occur with either the surgical or the anesthetic management. Some patients may be poor candidates for monitored anesthesia care (eg, cannot lie flat or cannot follow commands); in this case, general anesthesia may be a more prudent strategy.

Intraoperative Challenges

Intraoperative challenges during infrainguinal vascular repair are usually secondary to hemodynamic changes related to peripheral vascular clamping and unclamping. In general, compared with AXC, peripheral vascular clamping is fairly well tolerated with relatively mild changes in afterload, hemodynamics, and myocardial wall stress. Release of the peripheral cross-clamp, as with an aortic cross-clamp, may result in hypotension as a result of a decrease in SVR and release of inflammatory mediators. Adequate volume loading, the availability of vasopressor and inotropic support, and close communication with the surgical team can help prevent profound derangements in hemodynamics during this critical period.

Postoperative Complications

Early complications following open infrainguinal bypass primarily involve graft patency, adverse cardiac events, or wound complications. A large multicenter study of more than 1400 patients undergoing open surgical repair for critical limb ischemia reported early complication rates, including graft occlusion (5.2%), wound complications (4.8%), MI (4.7%), amputation (1.8%), and hemorrhage (0.4%).[292] Perioperative mortality was reported to be 2.7%.[292] Complication rates are likely higher in this population than in those undergoing repair for intermittent claudication because of their greater disease burden and more technically challenging repairs. A large review of more than 5700 patients demonstrated an increase in major adverse events, including MI, heart failure, deterioration in renal function, and respiratory complications in patients with critical limb ischemia compared with patients undergoing elective repair.[293] A review of the National Surgical Quality Improvement Program (NSQIP) database found a higher incidence of death and major graft-related complications (graft failure, wound dehiscence, wound infection, and sepsis) among patients undergoing surgery for critical limb ischemia as opposed to claudication.[294]

Complication rates for endovascular interventions continue to decrease as technical skill improves. A review of more than 3700 patients undergoing endovascular repair for lower extremity PAD found complications related to puncture site in 4.0%, angioplasty site in 3.5%, and vessel site in 2.7%.[295] Surgical reintervention was required in 2% and limb loss occurred in 0.2%. Major systemic complications occurred in 0.4% and mortality in 0.2%. A recent systematic review of 23 studies reported complication rates of 8–17%, with most complications being minor and related to hematoma, arterial perforation, and distal embolization.[296] At 1 year of follow-up, clinical success ranged 50–70% with limb salvage rates of 80–90%.[296]

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49

The Cardiac Patient for Thoracic Noncardiac Surgery

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KEY POINTS

1. Cardiac patients or those who have had previous cardiac surgery often present for intrathoracic diagnostic or therapeutic noncardiac procedures. These patients present unique challenges.
2. Patients with coronary artery disease, valvular heart disease, cardiomyopathies, or pulmonary hypertension may require surgery involving lung isolation and one-lung ventilation (OLV) with its subsequent risk of severe hypoxia.
3. Patients with a low cardiac output tend to desaturate during OLV and often require inotropic support for thoracotomy or thoracoscopy.
4. Double-lumen endobronchial tubes and bronchial blockers are used for OLV during thoracic surgery. Bronchial blockers are a useful option for lung isolation in patients who will remain intubated postoperatively. However, double-lumen tubes are used more often because they are stable during surgery and can be suctioned.
5. It is very important for the anesthesiologist to review the chest imaging before any intrathoracic or airway procedure so that an appropriate airway management strategy can be planned.
6. Management of rigid bronchoscopy is fundamental to anesthesia for a lower airway lesion.

Patients with underlying cardiac disease and patients who have had previous cardiac surgery may subsequently present for intrathoracic diagnostic or therapeutic procedures for noncardiac problems. The reader is directed to other sources for basic thoracic anesthesia information.[1] This chapter presents the essential perioperative management considerations for patients with cardiac diseases who require noncardiac thoracic surgery.

Anesthetic Management for Pulmonary Resection in the Patient With Cardiac Disease

Coronary Artery Disease

Because smoking is prevalent among patients presenting for thoracic surgery, these patients are also at risk for having cardiovascular disease, including coronary and peripheral vascular disease. In particular, patients with coronary artery disease (CAD) need to be optimized medically before proceeding with surgery (see Chapters 1, 20, and 43). These patients may be taking β-blockers and statins, which should be continued through the perioperative period, including the day of surgery. Statin use has been shown to reduce perioperative cardiovascular risk in patients undergoing vascular surgery.[2] Patients with CAD should also be taking aspirin, unless contraindicated. If a coronary stent has been placed, aspirin is generally required for life. Most coronary stents are drug-eluting stents and necessitate taking another antiplatelet drug such as clopidogrel for a year. Typically, clopidogrel is stopped at least 5 days before surgery, and preferably 7 days to allow for placement of neuraxial analgesia. Aspirin should be continued both preoperatively and postoperatively. American College of Cardiology guidelines suggest that, if possible, surgery should be delayed for 1 year following drug-eluting stent placement[3] (see Chapters 43 and 44). This delay is not likely to be feasible in the presence of lung cancer that could spread during a prolonged delay. However, one study suggested that the risks after drug-eluting stents were placed were minimal after 6 months (Fig. 49.1).[4] The risk of the stent thrombosing perioperatively generally outweighs the additional risk of bleeding with continuing aspirin therapy. A recent large prospective study of slightly more than 10,000 patients showed that continuing aspirin perioperatively increased bleeding risk, without impacting cardiovascular risk.[5] However, that study excluded patients with drug-eluting stents placed within 1 year.

Intraoperatively, avoiding excessive myocardial oxygen demand ($M\dot{V}O_2$), which could cause myocardial ischemia, is important. Elevated heart rate can be controlled with β-blockade. The short-acting β-blocker esmolol may be useful to acutely control the tachycardia and hypertension that may result from sympathetic stimulation during laryngoscopy, intrathoracic stimulation, and emergence from general anesthesia. The placement of a double-lumen tube (DLT) may be more difficult than placement of a single-lumen tube (SLT), and a prolonged laryngoscopy is more likely to cause sympathetic stimulation. Nitroglycerin can also be useful to treat hypertension in these situations, especially if the heart rate is low and hypertension persists. Nitroglycerin can provide both venodilation and dilation of coronary arteries (see Chapters 11 and 20).

In addition to demand-related ischemia, adequate supply of oxygen to the myocardium must be maintained. A relatively low hemoglobin oxygen saturation, which may occur during one-lung ventilation (OLV), may not be tolerated in patients at risk for myocardial ischemia. The lowered oxygen blood content could contribute toward the development of myocardial ischemia, and arrhythmias. If the oxygen saturation level drops, it may be necessary to reinstitute two-lung ventilation (TLV), or add continuous positive airway pressure (CPAP). During thoracoscopy, it may only be possible to use a limited amount of CPAP without impairing surgical conditions.

The presence of anemia can impact both myocardial supply and demand. A lowered hemoglobin level reduces the oxygen blood content. In addition, the anemia may lead to a compensatory tachycardia, increasing $M\dot{V}O_2$. Anemia, with tachycardia, is not well tolerated, and these patients should undergo transfusion. Patients who are treated with β-blockers intraoperatively also may not tolerate anemia.[6]

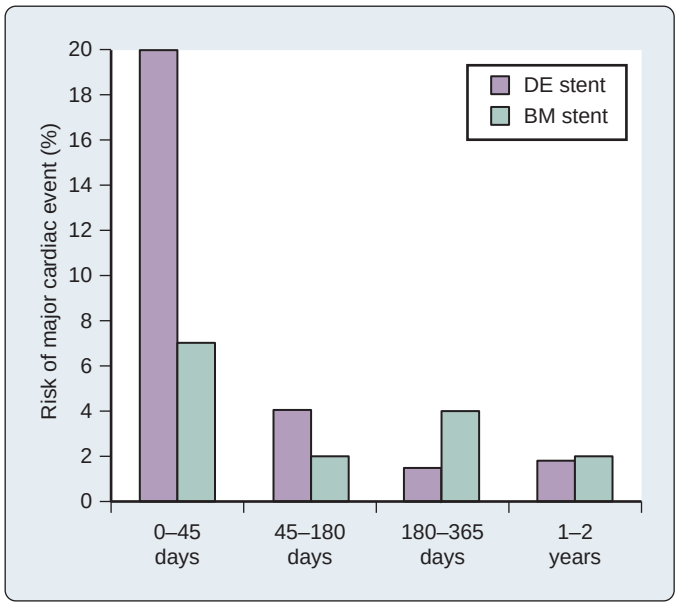
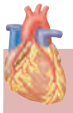


Fig. 49.1 Risk of major 30-day postoperative cardiac events after elective noncardiac surgery in more than 2000 patients after coronary artery stent placement. The risks become minimal after 6 weeks for bare metal *(BM)* stents and after 6 months for drug-eluting *(DE)* stents. *(Based on data from Wijeysundera ND, Wijeysundera HC, Yun L, et al. Risk of elective major noncardiac surgery after coronary stent insertion.* Circulation. *2012;126:1355–1362.)*

Recovery from a thoracotomy incision is accompanied by more pain than recovery from a thoracoscopy. The pain causes sympathetic stimulation and increases $M\dot{V}O_2$. Effective postoperative pain control is especially important in such patients, and an epidural or paravertebral catheter is recommended, if possible. Advanced planning is needed in the case of a patient taking clopidogrel, such that it is discontinued per the guidelines of the American Society of Regional Anesthesia.[7] Otherwise, the surgery either needs to be postponed or needs to be performed without the benefit of an epidural or paravertebral catheter, which might increase the perioperative cardiovascular and pulmonary risk in patients with severe lung disease.

Patients with a smoking history and significant CAD may have experienced a previous myocardial infarction and have a resulting cardiomyopathy. Such patients may have an internal cardioverter-defibrillator, which will require a perioperative management strategy (see Chapters 4, 5, and 45).

A high inspired oxygen concentration is needed to help tolerate OLV without hypoxemia, limiting the ability to use nitrous oxide. Most commonly, potent inhaled agents are used, although the use of greater than 1 minimum alveolar concentration (MAC) may interfere with hypoxic pulmonary vasoconstriction (HPV). Patients with a low left ventricular ejection fraction may not tolerate the myocardial depressant effects of higher doses of the potent inhaled agents. The concomitant intraoperative use of remifentanil can provide analgesia without vasodilation or myocardial depression and will facilitate a rapid emergence following surgery without prolonged respiratory depression. Its use may allow for a reduction in the amount of potent inhaled agent used. Although higher amounts of the potent inhaled agents can inhibit HPV, the use of sevoflurane has been shown to reduce the level of inflammatory mediators during thoracic surgery, compared with propofol and remifentanil.[8] It may be necessary to infuse a vasopressor concomitantly with the anesthetic agents to maintain an adequate perfusion pressure. If the cardiomyopathy is severe, it may be prudent to place a central venous catheter to provide central access for the administration of norepinephrine or phenylephrine. Strategies to manage the patient with CAD are summarized in Box 49.1.



BOX 49.1 STRATEGIES FOR PERIOPERATIVE MANAGEMENT OF PATIENTS WITH CORONARY ARTERY DISEASE UNDERGOING THORACIC SURGERY

- Maintain preoperative aspirin if a coronary stent is present.
- Maintain preoperative β-blocker.
- Hold clopidogrel 7 days preoperatively, if possible, to allow for neuraxial analgesia.
- Avoid hypoxemia during one-lung ventilation.
- Avoid anemia.
- Avoid tachycardia.
- Maintain adequate perfusion pressure.
- Use epidural or paravertebral postoperative analgesia.

Valvular Heart Disease

Patients with coexisting valvular heart disease also need special consideration when presenting for thoracic surgery. Patients with aortic stenosis in particular, will need maintenance of cardiac preload, systemic vascular resistance (SVR), and myocardial contractility. Such patients may not tolerate higher amounts of potent inhaled agents, due to vasodilation and myocardial depression. Patients with aortic stenosis are likely to have compensatory concentric left ventricular hypertrophy and diastolic dysfunction. Patients undergoing thoracic surgery are prone to atrial arrhythmias, especially with a thoracotomy incision. Patients with aortic stenosis and left ventricular hypertrophy are likely to poorly tolerate such arrhythmias, because of an increased dependence on atrial contraction for ventricular filling. The sympathetic block and vasodilation associated with epidural analgesia also may not be well tolerated. A dilute concentration of local anesthesia should be used, such as 0.1% bupivacaine, and the epidural should be activated gradually. In addition to maintaining adequate hydration and avoiding excessive myocardial depression and vasodilation, it may be necessary to also infuse a vasoconstrictor during the general anesthetic. The addition of intravenous remifentanil may be a beneficial adjunct to provide analgesia without myocardial depression or vasodilation (see Chapters 21, 24, and 27).

In the past, the placement of a pulmonary artery catheter (PAC) would have been indicated in the presence of significant ventricular dysfunction and/or valvular heart disease for monitoring pulmonary artery pressures (PAPs) and measurement of cardiac output (CO). Currently, the vast majority of thoracic operations are done without the use of this monitoring technique, which has not been shown to improve outcome.[9] PACs are also prone to being misused as a result of misinterpretation of data.[10] However, the presence of severe pulmonary hypertension (PH) may be an indication for monitoring with a PAC to guide the administration of nitric oxide or other pulmonary vasodilators.

The use of the arterial tracing for evaluation of systolic pressure or pulse pressure variation is predictive of fluid responsiveness[11] (see Chapters 13 and 47). A respiratory-related decrease less than 13% suggests that the patient would be fluid responsive. A change of 9–13% has been shown to reflect an intermediate range of predictability, a gray zone, in which the patient may be fluid responsive. If the systolic pressure or pulse pressure variation is less than 9%, it is unlikely that the patient would be fluid responsive.[12] There has been some question about the usefulness of central venous pressure to predict fluid responsiveness during anesthesia.[13] However, in the open-chest context of a thoracotomy, central venous pressure may be more useful than other monitors to predict fluid responsiveness.[14] A general goal of fluid management for thoracic surgery is to avoid excessive fluid administration and possible pulmonary edema that is more likely to occur following larger lung resections, particularly a right pneumonectomy.

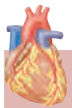
Cardiomyopathies

During OLV for thoracotomy or thoracoscopy, there is an obligate 20–30% shunt through the nonventilated lung. If the CO is decreased, the fall in mixed venous oxygen saturation will lead to a fall in arterial oxygen saturation. Thus, patients with cardiomyopathies may poorly tolerate OLV. They need monitoring of venous saturation and inotropes to support CO. This is particularly a concern in patients having video-assisted thoracoscopic cardiac sympathectomy procedures to treat refractory ventricular arrhythmias.[15] These procedures are being done with increasing frequency to treat ventricular tachyarrhythmias refractory to medical or ablative therapies and also for long QT syndrome.[16] The approach is by left or bilateral video-assisted thoracoscopic surgery (VATS). Intraoperative considerations include reprogramming of implanted electronic antitachycardia devices, percutaneous defibrillator pads, and provisions to optimize CO and oxygenation during OLV. These patients recover slowly from episodes of desaturation during OLV so it is best to avoid desaturation with prophylactic measures discussed later.

Pulmonary Hypertension

Patients with PH (mean PAP > 25 mm Hg by catheterization or systolic PAP > 50 on echocardiography)[17] may present for a variety of noncardiac thoracic surgical procedures, including pulmonary resections for malignant or benign lesions, esophageal surgery, or vascular surgery.[18] Compared to patients with normal PAPs, patients with PH are at increased risk of respiratory complications and the need for prolonged intubation after noncardiac surgery.[19] The classification of PH is discussed in Chapter 26, and it includes primary and secondary causes, including pulmonary arterial hypertension, pulmonary veno-occlusive disease, left-sided heart disease, lung disease and chronic hypoxemia, pulmonary thromboembolic disease, and a variety of autoimmune, metabolic, and systemic disorders.[20] Anesthesiologists often encounter two main types of PH: PH caused by left-sided heart disease and PH caused by lung disease (Box 49.2). Most of the anesthesia literature has focused on patients with underlying cardiac disease.[21] However, patients who present for noncardiac surgery are more likely to have PH secondary to lung disease and the anesthetic management is very different for these two types of PH. This section focuses on patients with PH due to lung disease. Much of what has been learned about anesthesia for patients with this type of PH has come from clinical experience with pulmonary endarterectomies[22] and lung transplantation (see Chapters 25 and 26).

Although estimates vary widely, depending on disease severity and the method of measurement, the prevalence of PH in patients with severe chronic lung disease ranges from 40–50%.[23] As PAPs rise, evidence of cor pulmonale develops as increased strain causes the right ventricle to become hypertrophic and dysfunctional. In the United States, cor pulmonale accounts for 10–30% of all hospital admissions of patients with heart failure, of which 84% are secondary to chronic obstructive pulmonary disease (COPD). The risk of right ventricular (RV) ischemia is also increased. The right ventricle is normally perfused throughout the cardiac cycle. However, the increased RV transmural and intracavitary pressures associated with PH may restrict perfusion of the right coronary artery during systole, especially as PAPs approach systemic levels. Avoiding hypotension is key to managing these patients.



BOX 49.2 MODIFIED CLASSIFICATION OF PULMONARY HYPERTENSION FOR THORACIC ANESTHESIA

Left Heart Disease
- Systolic dysfunction
- Diastolic dysfunction
- Mitral valvular disease: stenosis, regurgitation
- Congenital cardiac disease

Lung Disease
- Pulmonary vascular disease
- Chronic lung diseases, hypoxemia, sleep apnea
- Thromboembolic pulmonary hypertension
- Miscellaneous: autoimmune, metabolic, etc.

The impact of PH on RV dysfunction has several anesthetic implications. The hemodynamic goals are similar to other conditions in which CO is relatively fixed. Care should be taken to avoid physiologic states that will increase pulmonary vascular resistance (PVR), such as hypoxemia, hypercarbia, acidosis, and hypothermia. Conditions that impair RV filling, such as tachycardia and arrhythmias, are not well tolerated. Ideally, under anesthesia, RV contractility and SVR are maintained or increased, whereas PVR is decreased. This would ensure forward flow and minimize the risk of RV ischemia. In practice, these goals can be a challenge to achieve because anesthetics are commonly associated with a decrease in SVR and a variable effect on PVR. An animal study has suggested that desflurane may offer a better hemodynamic profile than sevoflurane or isoflurane with better maintenance of systemic arterial pressure and a more favorable pulmonary-to-systemic pressure ratio.[24]

Ketamine is a useful anesthetic agent in PH due to lung disease.[25] Ketamine is well known for its sympathomimetic effects, increasing cardiac contractility and SVR. However, its effect on PVR is controversial. Although concern is often raised over ketamine's potential to worsen PH, animal and human clinical studies have suggested that in some contexts it may decrease PVR.[26] Anecdotally, ketamine is commonly and safely used for anesthetic induction of patients with severe PH. Inodilators such as dobutamine and milrinone may improve hemodynamics in patients with PH secondary to left-sided heart disease. However, they tend to cause tachycardia and decreased SVR, potentially leading to hemodynamic deterioration of patients with PH due to lung disease. To maintain a systemic blood pressure (SBP) that is greater than the PAP, vasopressors such as phenylephrine or norepinephrine are commonly used. Of the two, norepinephrine is preferable because it maintains CO and decreases the PAP/SBP ratio. In contrast, phenylephrine causes the CO to drop while the PAP/SBP ratio remains unchanged.[27] Increasingly, vasopressin is also used to maintain systemic pressures. Vasopressin appears to significantly increase SBP without affecting PAP in patients with PH (Fig. 49.2).[28,29] In patients with severe PH, selective inhaled pulmonary vasodilators including nitric oxide (10–40 ppm)[30] or nebulized prostaglandins (prostacyclin, 50 ng/kg per min) (Fig. 49.3) [31] should be considered. A useful pharmacologic management strategy for the failing right ventricle in patients with PH secondary to lung disease is the combination of a potent intravenous vasoconstrictor and an inhaled pulmonary vasodilator (Box 49.3). Patients requiring inhaled nitric oxide can be weaned with oral sildenafil postoperatively.[32]

The extremes of tidal volumes (high and low) can cause compression of the extraalveolar or interalveolar blood vessels, both of which contribute to an increased PVR. As a result, a ventilation strategy that avoids atelectasis as well as lung hyperinflation should be employed.

Echocardiography is useful for diagnosis and management of patients with PH. However, it should be appreciated that transthoracic echocardiographic assessments of RV systolic pressure may be plus or minus 10 mm Hg compared to catheterization measurements in more than 40% of patients[33] with a tendency toward underestimation. Transesophageal echocardiography (TEE) is commonly recommended for intraoperative monitoring of RV function in patients with PH.[34] Although echocardiography is extremely useful for differentiating between a normally functioning right ventricle and a dilated hypokinetic right ventricle (and this correlates with outcome in cardiac surgery),[35] for minute-to-minute continuous objective monitoring of RV function, TEE is not yet the ideal monitor. This is because the right ventricle is a very complex nongeometric structure in three dimensions. At present, continuous monitoring of minor changes in regional RV function with standard two-dimensional TEE is, at best, difficult.

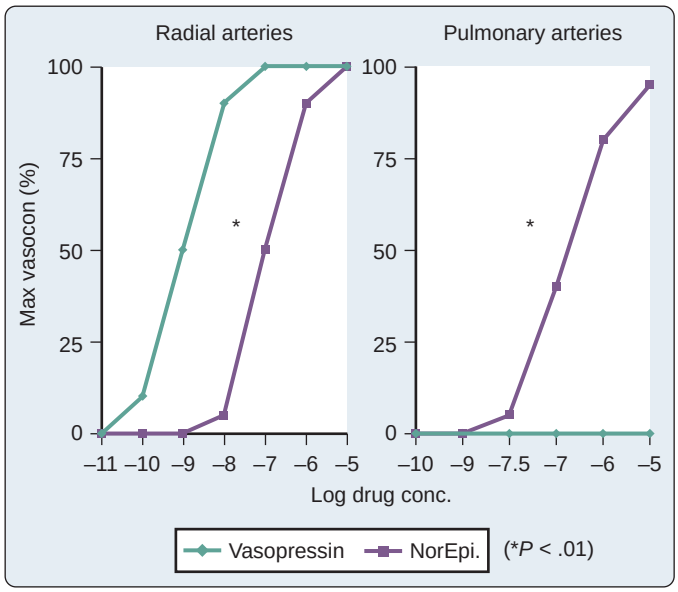


Fig. 49.2 In vitro maximal vasoconstriction *(max vasocon.)* dose-response curves of human radial *(left)* and pulmonary *(right)* arteries to vasopressin and norepinephrine. All vasoconstrictors studied (including phenylephrine and metaraminol) showed similar dose-response patterns in both types of arteries except vasopressin, which showed no constriction of pulmonary arteries. *(Based on data from Currigan DA, Hughes RJA, Wright CE, et al. Vasoconstrictor responses to vasopressor agents in human pulmonary and radial arteries.* Anesthesiology. *2014;121:930–936.)*

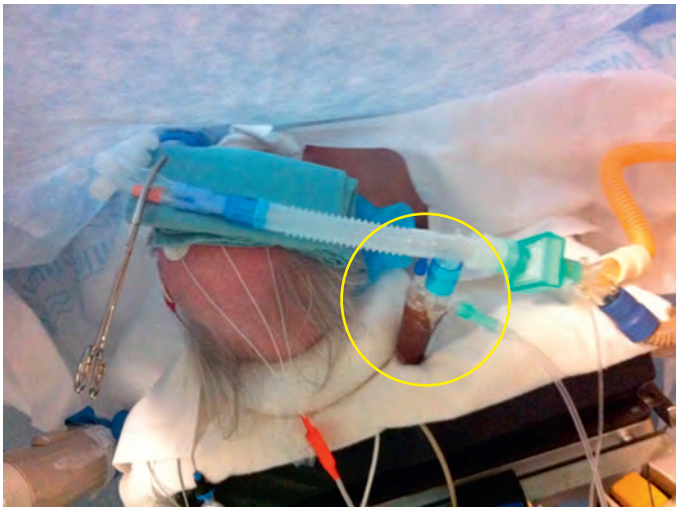


Fig. 49.3 Prostacyclin can be delivered continuously into a standard anesthetic circuit and the dose titrated as needed. In the photograph, prostacyclin is delivered by nebulization to the ventilated lung via a double-lumen tube during thoracic surgery and one-lung ventilation in a patient with pulmonary hypertension.

Advances in echocardiography technology may make continuous objective monitoring of RV function possible in the near future[36] (see Chapters 14–16 and 46).

At present, the basis of intraoperative monitoring for patients with PH who are undergoing noncardiac thoracic surgical procedures remains the PAC. However, it must be understood that PA data alone can be misleading in these patients. Rising PAPs are almost always a bad sign. Falling PAPs may be a good sign, indicating pulmonary vasodilation, or may be a very bad sign, indicating impending RV

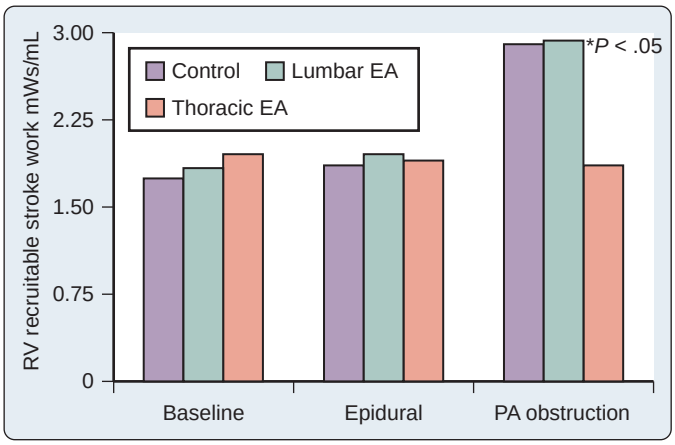
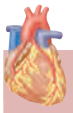


Fig. 49.4 Right ventricular *(RV)* recruitable stroke work, a measure of RV contractility, measured in three groups of anesthetized pigs: *Control* (no epidural) group, *Lumbar EA* (lumbar epidural anesthesia) group, and *Thoracic EA* (thoracic epidural anesthesia) group. Epidural bupivacaine injection had no effect on RV function in either of the study groups. Subsequent inflation of a balloon in the main pulmonary artery *(PA obstruction),* increasing RV afterload, resulted in a compensatory increase in RV contractility in the control and lumbar EA groups but not in the thoracic EA group. *(Based on data from Missant C, Claus P, Rex S, Wouters PF. Differential effects of lumbar and thoracic epidural anesthesia on the haemodynamic response to acute right ventricular pressure overload.* Br J Anaesth. *2009;104:143–149.)*



BOX 49.3 MANAGEMENT PRINCIPLES FOR PULMONARY HYPERTENSION SECONDARY TO LUNG DISEASE

- Avoid hypotensive and vasodilating anesthetic agents whenever possible.
- Ketamine does not exacerbate pulmonary hypertension.
- Support mean systolic pressure with vasopressors: norepinephrine, phenylephrine, vasopressin.
- Use inhaled pulmonary vasodilators (nitric oxide, prostacyclin) in preference to intravenous vasodilators.
- Use thoracic epidural local anesthetics cautiously and with inotropes.
- Monitor cardiac output.

decompensation. Thus, PAP data must be followed in concert with CO, mixed venous saturation, and/or central venous pressure data.

Although there have been multiple case reports of the successful use of lumbar epidural analgesia and anesthesia in obstetric patients with PH,[37] there are very few reports of the use of thoracic epidural analgesia (TEA) in patients with PH. Patients with PH secondary to lung disease seem to be extremely dependent on tonic cardiac sympathetic innervation for normal hemodynamic stability. Animal studies suggest that the hemodynamic response to an increase in RV afterload is very different with thoracic versus lumbar epidural anesthesia. In one study, RV contractility increased as afterload increased in animals with a lumbar epidural, similar to the response in animals without neuraxial block. The cardiac sympathectomy of TEA abolished this increase in contractility[38] (Fig. 49.4). Because of the increased risk of postoperative respiratory complications in these patients, the use of postoperative TEA is often desirable. However, it must be appreciated that these patients will often require a low-dose infusion of inotropes or vasopressors during TEA. This may necessitate continued central venous catheterization and intensive care unit admission. Paravertebral analgesia has been associated with better hemodynamic stability after thoracotomy compared with TEA in patients with normal cardiac

function,[39] but this has not been specifically studied in patients who have PH.

Lung Isolation for Cardiac Patients Having Thoracic Procedures

Procedures in the thoracic cavity are greatly facilitated by the use of OLV. Procedures on the lung, esophagus, or thoracic aorta, or resection of mediastinal masses, frequently require a collapsed lung for a motionless surgical field and optimal surgical exposure.

The Robertshaw-type DLTs have been used in clinical practice for over half a century and are considered the gold standard to achieve lung separation.[40] The Univent tube (Fuji Corp, Tokyo, Japan) and other independent endobronchial blockers were introduced to clinical practice as an alternative to the DLT. These 9-Fr blockers have a steering mechanism to direct them into the selected bronchus. The EZ-Blocker (Teleflex Medical Inc, Research Triangle Park, NC), recently introduced into clinical practice, is a 7-Fr catheter designed with a Y shape and two distal extensions that ride over the carina, and each lung can be selectively deflated. Whether a DLT or blocker is used to provide lung separation, proper position should be confirmed by fiberoptic bronchoscopy (FOB).

Double-Lumen Tubes

Advantages of Double-Lumen Tubes

1. In cases in which the nondiseased lung is exposed to contamination by blood or pus from the diseased lung, the lungs must be isolated. When lung isolation is required, DLTs are preferable to endobronchial blockers because they provide a superior protective seal to prevent contamination of the unaffected lung.
2. DLTs are preferred for bilateral procedures such as bilateral lung transplantation, bilateral sympathectomy, and bilateral lung wedge resection. Once in place, they minimize the manipulation and resulting hemodynamic response.
3. DLTs are more stable once positioned and have less tendency to dislocate during surgical manipulation and patient positioning. This is important in patients with cardiac disease in whom any irritation of the tracheobronchial tree can induce tachycardia, hypertension, and ischemia.
4. It is easier to suction thick secretions or blood clots through the lumen of the DLT. Aggressive pulmonary toilet is particularly crucial in cardiac patients.

Disadvantages of Double-Lumen Tubes

1. DLTs are somewhat bulky and may be more difficult to insert and position compared with SLTs. It may be challenging to switch from a DLT to an SLT if the patient requires postoperative ventilatory support. The use of tube exchange catheters may trigger a cardiovascular response that can be detrimental to the patient with cardiac disease. Tracheal intubation causes a stress response, resulting in increased sympathetic activity that may result in hypertension, tachycardia, and arrhythmias. These changes in hemodynamics can be harmful to patients with hypertension and myocardial ischemia due to inadequate perfusion of the coronary arteries.
2. Previous studies have found a higher incidence of sore throat, hoarseness, and pharyngeal or bronchial tree laceration (Fig. 49.5) associated with DLT use. Knoll and colleagues evaluated the incidence of airway injury after lung surgery and compared techniques.[41] They concluded that the incidence of postoperative hoarseness and number of days with hoarseness and sore throat were significantly decreased in the blocker group compared with the DLT group. Moreover, the blocker technique was associated with a decreased incidence of vocal cord injuries (44% vs 17%, respectively). Any added injury to patients with cardiac disease, who are often on anticoagulant therapy for cardiac stents or arrhythmia, can add a significant increased risk of complications and prolong recovery.

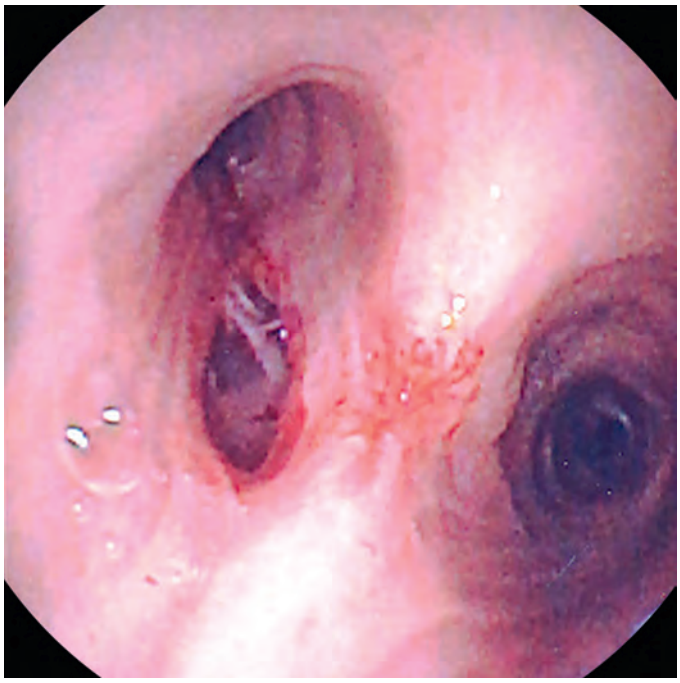


Fig. 49.5 Photograph taken through a fiberoptic bronchoscope of a laceration of the posterior membranous portion of the left mainstem bronchus just dustal to the carina caused by a left-sided double-lumen tube.

Endobronchial Blockers for Lung Separation

Endobronchial blockers can be placed to achieve lung separation and may offer several advantages to patients with cardiac disease.[42] The most significant advantage is the decrease in hemodynamic stress. Because the blocker is inserted through an SLT, it is less stimulating than the insertion and manipulation of a DLT. Some patients arrive from the intensive care unit to the operating room with endotracheal tubes in place; insertion of a blocker would be the best option to avoid changing the existing SLT.

Lung Separation in Thoracic Aortic Aneurysm Surgery

Because of the close anatomic relationship, a thoracic aortic aneurysm can potentially compress the airway at the level of the trachea or, more often, left mainstem bronchus. Patients with a descending thoracic aortic aneurysm and left mainstem bronchus compression who require lung isolation should be managed with a right-sided DLT (Fig. 49.6). Placement of a left-sided DLT is both difficult and dangerous in these patients, presenting the risk of airway trauma and rupture of the aneurysm. A DLT in a descending thoracic aortic aneurysm repair improves surgical exposure and makes it easier to remove blood and secretions. The use of blockers for thoracic aneurysm repair should be limited to situations in which intubation is difficult.

Management of One-Lung Ventilation

During OLV the anesthesiologist has the unique and often conflicting goals of trying to maximize atelectasis in the nonventilated lung to improve surgical access while trying to avoid atelectasis in the ventilated lung (usually the dependent lung) to optimize gas exchange.[43] This can be particularly challenging in the patient with underlying cardiac disease. The gas mixture in the nonventilated lung immediately before OLV has a significant effect on the speed of collapse of this lung. Because of its low blood-gas solubility, nitrogen (or an air-oxygen mixture) will

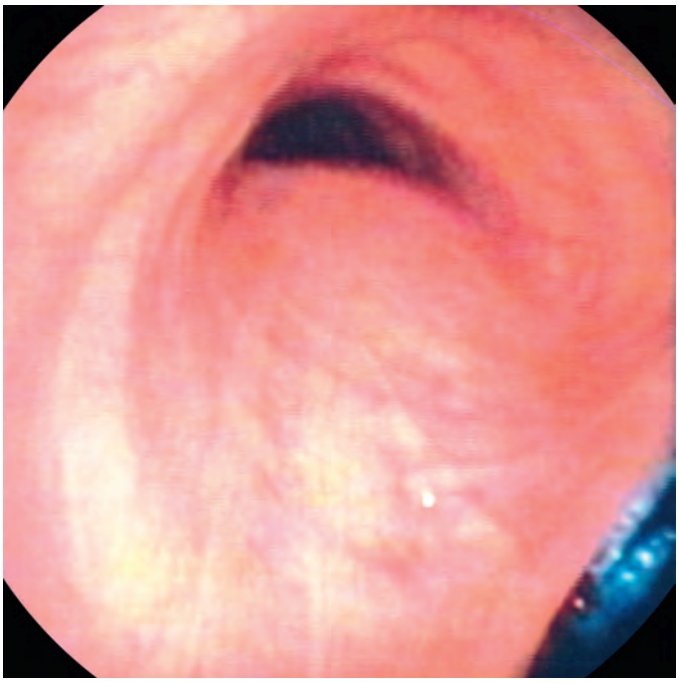


Fig. 49.6 Photograph taken through a fiberoptic bronchoscope of a posterior compression of the left mainstem bronchus caused by an aneurysm of the descending thoracic aorta.

delay collapse of this lung.[44] This is a problem at the start of minimally invasive surgery when surgical visualization in the operative hemithorax is limited. It is important to thoroughly denitrogenate the operative lung, by ventilating with oxygen, immediately before it is allowed to collapse.

During the period of two-lung anesthesia before the start of OLV, atelectasis will develop in the dependent lung. It is useful to perform a recruitment maneuver of the dependent lung immediately after the start of OLV to decrease this atelectasis. Recruitment is important to maintain Pa_{O_2} levels during subsequent OLV.[45]

Hypoxemia

A major concern that influences anesthetic management of patients undergoing thoracic surgical procedures is the occurrence of hypoxemia during OLV. There is no universally acceptable value for the safest lower limit of oxygen saturation during OLV. An arterial oxygen saturation of 90% ($Pa_{O_2} \approx 60$ mm Hg) is commonly seen as the lowest acceptable limit. However, the lowest acceptable saturation will be higher in patients with organs at risk of hypoxia due to limited regional blood flow (eg, coronary or cerebrovascular disease) and in patients with limited oxygen transport (eg, anemia or decreased cardiopulmonary reserve). It has been shown that during OLV, patients with COPD desaturate more quickly during isovolemic hemodilution than do patients without COPD.[46]

Previously, hypoxemia occurred frequently during OLV. Reports for the period 1950–1980 describe an incidence of hypoxemia (arterial saturation <90%) of 20% to 25%.[47] Current reports describe an incidence of less than 5%.[48] This improvement is most likely due to several factors: improved lung isolation techniques, such as routine FOB to prevent lobar obstruction from DLTs; improved anesthetic agents, which cause less inhibition of HPV; and better understanding of the pathophysiology of OLV. The pathophysiology of OLV involves the body's ability to redistribute pulmonary blood flow to the ventilated lung. The anesthesiologist's goal during OLV is to maximize PVR in the nonventilated lung while minimizing PVR in the ventilated lung. Key to understanding this physiologic goal is the appreciation that PVR is correlated with lung volume in a hyperbolic fashion. PVR is lowest at functional residual capacity (FRC) and increases as lung volume rises or falls above or below FRC.[49] The anesthesiologist's aim, to optimize pulmonary blood flow redistribution during OLV, is to maintain the ventilated lung as close as possible to its FRC while facilitating collapse of the nonventilated lung to increase its PVR.

Most thoracic surgery is performed while the patient is in the lateral position. Patients having OLV in the lateral position have significantly better Pa_{O_2} levels than patients during OLV in the supine position because of gravitational enhancement of blood flow to the dependent, ventilated lung.[50] This applies both to patients with normal lung function and to those with COPD.[51]

Hypoxic Pulmonary Vasoconstriction

HPV can decrease the blood flow to the nonventilated lung by as much as 50%.[52] The stimulus for HPV is primarily the alveolar oxygen tension ($P_{A_{O_2}}$), which stimulates precapillary vasoconstriction redistributing pulmonary blood flow away from hypoxemic lung regions via a pathway involving nitric oxide and/or cyclooxygenase synthesis inhibition.[53] The mixed venous P_{O_2} is also a stimulus although considerably weaker than $P_{A_{O_2}}$. HPV has a biphasic temporal response to alveolar hypoxia. The rapid-onset phase begins immediately and reaches a plateau by 20 to 30 minutes. The second (delayed) phase begins after 40 minutes and plateaus after several hours.[54] The offset of HPV is also biphasic, and PVR may not return to baseline for several hours after a prolonged period of OLV. This may contribute to increased desaturation during the collapse of the second lung during bilateral thoracic procedures. HPV also has a preconditioning effect, and the response to a second hypoxic challenge will be greater than to the first challenge.[55]

The surgical trauma to the lung can affect pulmonary blood flow redistribution. Surgery may oppose HPV by release of vasoactive metabolites locally in the lung. Conversely, surgery can dramatically decrease blood flow to the nonventilated lung by deliberately or accidentally mechanically interfering with the unilateral pulmonary arterial or venous blood flow.[56] HPV is decreased by vasodilators such as nitroglycerin and nitroprusside. In general, vasodilators can be expected to cause a deterioration in Pa_{O_2} during OLV. Thoracic epidural sympathetic blockade probably has little or no direct effect on HPV, which is a localized chemical response in the lung.[57] However, thoracic epidural anesthesia can have an indirect effect on oxygenation during OLV if it is allowed to cause hypotension and a fall in CO.

Choice of Anesthetic

All the volatile anesthetics inhibit HPV in a dose-dependent fashion. Animal studies suggest that this inhibition is dependent on the agent: halothane > enflurane > isoflurane.[58] In doses of 1 MAC or less, the modern volatile anesthetics (isoflurane, sevoflurane,[59] and desflurane[60]) are weak and equipotent inhibitors of HPV. The inhibition of the HPV response by 1 MAC of a volatile agent such as isoflurane is approximately 20% of the total HPV response, and this could account for only a net 4% increase in total arteriovenous shunt during OLV.[61] In addition, volatile anesthetics cause less inhibition of HPV when delivered to the active site of vasoconstriction via the pulmonary arterial blood than via the alveolus. During established OLV, the volatile agent only reaches the hypoxic lung pulmonary capillaries via the mixed venous blood. No clinical benefit in oxygenation during OLV has been shown for total intravenous anesthesia above that seen with 1 MAC of the modern volatile anesthetics.[62]

The use of nitrous oxide/oxygen (N_2O/O_2) mixtures is associated with a higher incidence of postthoracotomy radiographic atelectasis (51%) in the dependent lung than when air/oxygen mixtures are used (24%). Nitrous oxide also tends to increase pulmonary artery pressures in patients who have PH, and N_2O inhibits HPV. For these reasons N_2O is usually avoided during thoracic anesthesia.

Cardiac Output

The effects of alterations of CO during OLV are complex. Increasing CO tends to cause increased PAPs and passive dilation of the pulmonary vascular bed, which in turn opposes HPV and has been shown to be associated with increased arteriovenous shunt (Qs/Qt) during OLV.[63] However, in patients with a relatively fixed oxygen consumption, as is seen during stable anesthesia, the effect of an increase in CO is to increase the mixed venous oxygen saturation ($S\bar{v}o_2$). Thus, increasing CO during OLV tends to increase both shunt and $S\bar{v}o_2$, which have opposing effects on PaO_2. There is a ceiling effect to the amount that $S\bar{v}o_2$ can be increased. Increasing the CO to supranormal levels by administering inotropes such as dopamine tends to have an overall negative effect on PaO_2.[64] Conversely, allowing the CO to fall will lead to falls in both shunt and $S\bar{v}o_2$ with a net effect of decreasing PaO_2. It is very important to maintain CO in patients with limited cardiac reserve.

Ventilation Strategies During One-Lung Ventilation

The strategy used to manage the ventilated lung during OLV plays an important part in the distribution of pulmonary blood flow between the lungs. It has been the practice of many anesthesiologists to use the same large tidal volume (eg, 10 mL/kg ideal body weight) during OLV as during TLV. This strategy decreases hypoxemia probably by recurrently recruiting atelectatic regions in the dependent lung and may result in higher PaO_2 values during OLV than compared with smaller tidal volumes.[65] However, there is a trend to use smaller tidal volumes with positive end-expiratory pressure (PEEP) during OLV for several reasons. First, the incidence of hypoxemia during OLV is much lower than it was 20 to 30 years ago. Second, there is a risk of causing acute injury to the ventilated lung with prolonged use of large tidal volumes. Third, a ventilation pattern that allows cyclic atelectasis and recruitment of lung parenchyma seems to be injurious.[66]

Respiratory Acid-Base Status

The efficacy of HPV in a hypoxic lung region is increased in the presence of respiratory acidosis and is inhibited by respiratory alkalosis. However, there is no net benefit to gas exchange during OLV from hypoventilation because the respiratory acidosis preferentially increases the PVR of the well-oxygenated lung and this opposes any clinically useful pulmonary blood flow redistribution.[67] Overall, the effects of hyperventilation usually tend to decrease PAPs.

Positive End-Expiratory Pressure

Resistance to blood flow through the lung is related to lung volume in a biphasic pattern and is lowest when the lung is at its FRC. Keeping the ventilated lung as close as possible to its normal FRC using modest amounts of PEEP favorably encourages pulmonary blood flow to this lung. Several intraoperative factors that are known to alter FRC tend to cause the FRC of the ventilated lung to fall below its normal level; these factors include lateral position of the patient, paralysis, and opening the nondependent hemithorax, which allows the weight of the mediastinum to compress the dependent lung. Attempts to measure FRC in human patients during OLV have been complicated by the presence of a persistent end-expiratory airflow in patients who have COPD.[68] Many patients do not reach their end-expiratory equilibrium FRC lung volume as they try to exhale a relatively large tidal volume through one lumen of a DLT. These patients develop dynamic hyperinflation and an occult PEEP (auto-PEEP).[41]

Auto-PEEP

Auto-PEEP (also called *intrinsic PEEP*) is most prone to occur in patients with decreased lung elastic recoil, such as older adult patients or patients with emphysema.[69] Auto-PEEP increases as the inspiratory-to-expiratory (I:E) ratio increases (ie, as the time of expiration decreases). This auto-PEEP, which averages 4 to 6 cm H_2O in most series of lung cancer patients studied, opposes the previously mentioned factors, which tend to diminish dependent-lung FRC during OLV. The effects of applying external PEEP through the ventilator circuit to the lung in the presence of auto-PEEP are complex. Patients with a very low auto-PEEP (<2 cm H_2O) will experience a greater increase in total PEEP from a moderate (5 cm H_2O) external PEEP than those with a high level of auto-PEEP (>10 cm H_2O). Whether the application of PEEP during OLV improves a patient's gas exchange depends on the individual's lung mechanics. If the application of PEEP tends to shift the expiratory equilibration position on the compliance curve toward the lower inflection point of the curve (ie, toward the FRC) then external PEEP is of benefit (Fig. 49.7). However, if the application of PEEP raises the equilibration point such that it is further from the lower inflection point of the curve, then gas exchange deteriorates.

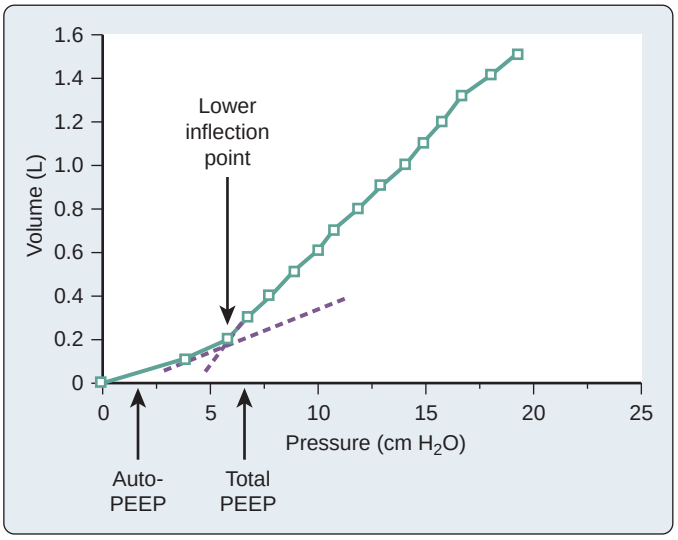


Fig. 49.7 Inspiratory static compliance curve of a young patient with normal pulmonary function during one-lung ventilation (OLV), in this case for removal of a mediastinal tumor. The lower inflection point of the curve (functional residual capacity) was at 6 cm H_2O. The patient had 2 cm H_2O auto–positive end-expiratory pressure (PEEP) during OLV. Adding 5 cm H_2O PEEP to the ventilator raised the total PEEP to 7 cm H_2O and improved arterial partial pressure of oxygen (PaO_2). Young patients and patients with increased lung elastic recoil (eg, as caused by restrictive lung diseases) have an increase in PaO_2 from PEEP during OLV. *(Based on data from Slinger P, Kruger M, McRae K, Winton T. Relation of the static compliance curve and positive end-expiratory pressure to oxygenation during one-lung ventilation.* Anesthesiology. *2001;95:1096–1102.)*

Auto-PEEP is difficult to detect and measure using currently available anesthetic ventilators. To detect auto-PEEP, the respiratory circuit must be held closed at the end of a normal expiration until an equilibrium appears in the airway pressure.[70] Most current intensive care ventilators can be used to accurately measure auto-PEEP, but most anesthesia ventilators cannot.

Tidal Volume

There is an optimal combination of tidal volume, respiratory rate, I:E ratio, pressure- or volume-control ventilation for each patient undergoing OLV. However, to try to assess each of these parameters while still providing anesthesia with the available anesthetic ventilators is not practical and the clinician must initially rely on a simplified strategy (Table 49.1). The results of alterations in tidal volume are unpredictable, in part, because of the interaction of tidal volume with auto-PEEP. The use of 5 to 6 mL/kg tidal volume plus 5 cm H_2O PEEP initially for most patients (except those with COPD) seems a logical starting point during OLV. Tidal volume should be managed so that peak airway pressures do not exceed 35 cm H_2O. This will correspond to a plateau airway pressure of approximately 25 cm H_2O.[71] Peak airway pressures exceeding 40 cm H_2O may contribute to hyperinflation injury of the

TABLE 49.1 Suggested Ventilation Parameters for One-Lung Ventilation

Parameter	*Suggested*	*Guidelines/Exceptions*
Tidal volume	5–6 mL/kg	Maintain: Peak airway pressure <35 cm H_2O Plateau airway pressure <25 cm H_2O
Positive end-expiratory pressure	5 cm H_2O	Patients with COPD: no added PEEP
Respiratory rate	12/min	Tolerate mild hypercapnia $PaCO_2$ (<60 mm Hg), Pa-$ETCO_2$ will usually increase 1–3 mm Hg during OLV
Mode	Volume or pressure controlled	Pressure control for patients at risk of lung injury (bullae, pneumonectomy, post lung transplantation, etc)
FIO_2	Initially 1.0	Decrease as tolerated with air to maintain acceptable SpO_2

COPD, Chronic obstructive pulmonary disease; *FIO_2,* fraction of inspired oxygen; *OLV,* one-lung ventilation; *$PaCO_2$,* arterial pressure of carbon dioxide; *Pa-$ETCO_2$,* arterial-to-end-tidal CO_2 tension gradient; *PEEP,* positive end-expiratory pressure; *SpO_2,* pulse oximetric oxygen saturation.

ventilated lung during OLV.[72] Turning the patient to the lateral position will increase respiratory dead space and the arterial-to-end-tidal CO_2 tension gradient (Pa-$ETCO_2$). This will usually require a 20% increase in minute ventilation to maintain the same $PaCO_2$. Individual variations in Pa-$ETCO_2$ gradient become much larger and $PETCO_2$ is less reliable as a monitor of $PaCO_2$ during OLV. This effect is possibly due to the fact that there are differences in the excretion of CO_2 between the dependent and nondependent lungs.

Volume-Controlled Versus Pressure-Controlled Ventilation

Traditionally, volume-controlled ventilation has been used in the operating room for all types of surgery. The recent availability of anesthesia ventilators with pressure-control modes has made it possible to study and use this form of ventilation during thoracic surgery. Pressure-controlled ventilation has not been shown to improve oxygenation compared with volume-controlled ventilation for most patients, although the peak airway pressures are lower.[73] The decrease in peak pressure with pressure control ventilation may be largely in the anesthetic circuit and not at the distal airway.[74] Pressure control ventilation diminishes the possibility of sudden increases in peak airway pressures that may result from surgical manipulation in the chest. This is of benefit to patients at increased risk for lung injury from high volumes or pressures such as after lung transplantation or during a pneumonectomy.[75] Because of the rapid changes of lung compliance that occur during pulmonary surgery, when pressure-control ventilation is used the delivered tidal volume needs to be closely monitored as this may change suddenly.

Prediction of Hypoxemia During One-Lung Ventilation

The problem of hypoxemia during OLV has prompted much research in thoracic anesthesia. Hypoxemia during OLV is predictable (Box 49.4), preventable, and treatable in most cases.[76]

Preoperative Ventilation-Perfusion Scan

The shunt and PaO_2 during intraoperative OLV are highly correlated with the fractional perfusion of the ventilated lung as determined by a preoperative ventilation/perfusion scan.[77] Patients with long-standing unilateral disease on the operative side develop a unilateral decrease of ventilation and perfusion and tolerate OLV very well. Similarly, patients who intraoperatively have a higher proportion of gas exchange in the dependent lung during OLV tend to have better oxygenation during OLV.

Side of Operation

Patients having right-sided thoracotomies tend to have a larger shunt and lower PaO_2 during OLV because the right lung is larger and normally receives10% more blood flow than the left. The overall mean PaO_2 difference between left and right thoracotomies during stable OLV is approximately 100 mm Hg.[78]

BOX 49.4 FACTORS THAT CORRELATE WITH AN INCREASED RISK OF DESATURATION DURING ONE-LUNG VENTILATION

- High percentage of ventilation or perfusion to the operative lung on preoperative ventilation/perfusion scanning
- Poor PaO_2 during two-lung ventilation, particularly in the lateral position intraoperatively
- Right-sided thoracotomy
- Normal preoperative spirometry (FEV_1 or FVC) or restrictive lung disease
- Supine position during one-lung ventilation

FEV_1, Forced expiratory volume in 1 second; FVC, forced vital capacity; PaO_2, arterial partial pressure of oxygen.

Two-Lung Oxygenation

Patients who have better PaO_2 levels during TLV in the lateral position tend to have better oxygenation during OLV. These patients may have better abilities to match ventilation and perfusion (individual variability of HPV response) and/or they may have less atelectasis in the dependent lung.

Preoperative Spirometry

Studies consistently show that when the previous mentioned factors are controlled, patients with better spirometric lung function preoperatively are more likely to desaturate and have lower PaO_2 values during OLV. Clinically this is evident because emphysematous lung volume reduction patients generally tolerate OLV very well. The explanation is not clear, but it may be related to maintenance of a more favorable FRC in patients with obstructive airway disease during OLV with an open hemithorax due to the development of auto-PEEP.[53]

Treatment of Hypoxemia During One-Lung Ventilation

During OLV there is a fall in arterial oxygenation that usually reaches its nadir 20 to 30 minutes after the initiation of OLV. The oxygen saturation will then stabilize or rise slightly as HPV increases over the next 2 hours. Most patients who desaturate do so quickly and within the first 10 minutes of OLV. Hypoxemia during OLV responds to treatment in the majority of cases. Potential therapies are outlined in Box 49.5.

1. Resume TLV. Reinflate the nonventilated lung and deflate the bronchial cuff of the DLT or the bronchial blocker. This necessitates interruption of surgery, but it is necessary in case of severe or precipitate desaturation, especially in the cardiac patient. After an adequate level of oxygenation is obtained, the diagnosis of the cause of desaturation can be made and prophylactic measures instituted before another trial of OLV is attempted.
2. Increase fraction of inspired oxygen (FIO_2). Ensure that the delivered FIO_2 is 1.0. This is an option in essentially all patients except those who have received bleomycin or similar therapies that potentiate pulmonary oxygen toxicity.
3. Recheck the position of the DLT or bronchial blocker with FOB. Ensure that there is no lobar obstruction in the ventilated lung.
4. Check the patient's hemodynamics to ensure that there has been no decrease in CO. It is very common for the surgeon to accidentally compress the inferior vena cava during pulmonary resections, and the fall in blood pressure and CO that this causes leads to rapid desaturation during OLV. Treat the fall in CO as indicated (eg, inotropes or vasopressors if due to thoracic epidural sympathetic blockade). Stop administration of vasodilators and decrease MAC of volatile anesthetics to less than 1 MAC.
5. Perform a recruitment maneuver of the ventilated lung. To eliminate any atelectasis, inflate the lung to 20 cm H_2O or more for 15

BOX 49.5 THERAPIES FOR DESATURATION DURING ONE-LUNG VENTILATION

Severe or precipitous desaturation: resume two-lung ventilation (if possible).

Gradual desaturation:

- Ensure that delivered F_{IO_2} is 1.0.
- Check position of double-lumen tube or blocker with fiberoptic bronchoscopy.
- Ensure that cardiac output is optimal; decrease volatile anesthetics to <1 MAC.
- Apply a recruitment maneuver to the ventilated lung (this will transiently make the hypoxemia worse).
- Apply PEEP 5 cm H_2O to the ventilated lung (except in patients with emphysematous disease).
- Apply CPAP 1–2 cm H_2O to the nonventilated lung (apply a recruitment maneuver to this lung immediately before CPAP).
- Apply intermittent reinflation of the nonventilated lung.
- Partial ventilation techniques of the nonventilated lung include:
  - Lung oxygen insufflation
  - Lobar insufflation
  - Lobar collapse (using a bronchial blocker)
- Apply mechanical restriction of the blood flow to the nonventilated lung.

CPAP, Continuous positive airway pressure; F_{IO_2}, fraction of expired oxygen; MAC, minimum alveolar concentration; PEEP, positive end-expiratory pressure.

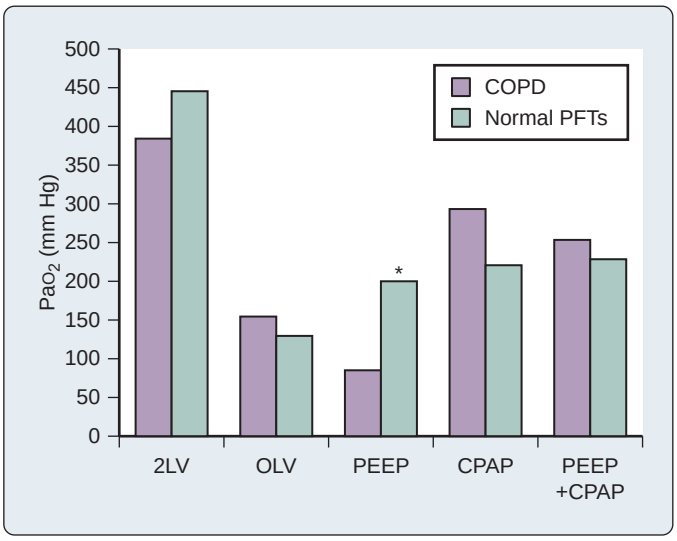


Fig. 49.8 A comparison of the effects of positive end-expiratory pressure *(PEEP)* to the ventilated lung and continuous positive airway pressure *(CPAP)* to the nonventilated lung on mean arterial partial pressure of oxygen *(PaO_2)* levels during one-lung ventilation *(OLV). 2LV,* Two-lung ventilation; *COPD,* group of lung cancer surgery patients; *Normal PFTs,* group of esophageal surgery patients with normal preoperative pulmonary function tests. (*, signif. $P < .05$ vs OLV.) *(Based on data from Fujiwara M, Abe K, Mashimo T. The effect of positive end-expiratory pressure and continuous positive airway pressure on the oxygenation and shunt fraction during one-lung ventilation with propofol anesthesia.* J Clin Anesth. *2001;13:473–477. Capan LM, Turndorf H, Patel C, et al. Optimization of arterial oxygenation during one-lung anesthesia.* Anesth Analg. *1980;59:847–851.)*

to 20 seconds. This may cause transient hypotension and will also cause a transient further fall in the PaO_2 as the blood flow is temporarily redistributed to the nonventilated lung.

6. Apply PEEP to the ventilated lung. It is necessary to perform a recruitment maneuver before applying PEEP to get the maximal benefit. PEEP will raise the end-expiratory volume of the ventilated lung toward the FRC in patients with normal lung mechanics and in those with increased elastic recoil due to restrictive disease. It is not possible to predict the optimal PEEP for individual patients; a level of 5 cm H_2O is a useful starting point. PEEP will increase the end-expiratory lung volume of patients with significant levels of auto-PEEP (eg, patients with emphysema). Unlike CPAP, application of PEEP does not require reinflation of the nonventilated lung and interruption of surgery. PEEP has been shown to be as effective for increasing PaO_2 levels during OLV in patients with normal lung function as CPAP to the nonventilated lung (Fig. 49.8).[79] For patients with normal pulmonary function, it is logical to routinely apply a recruitment maneuver and PEEP from the start of OLV.
7. CPAP with oxygen to the nonventilated lung is the next line of therapy after application of PEEP.[80] An important caveat to be observed when CPAP is applied to the nonventilated lung is that CPAP must be applied to an inflated (recruited) lung to be completely effective. The opening pressure of atelectatic lung regions is greater than 20 cm H_2O,[81] and these units will not be recruited by simple application of CPAP levels of 5 to 10 cm H_2O. Even a period as short as 5 minutes of collapse prior to CPAP application can have deleterious effects on oxygenation during OLV.[82] When CPAP is applied to a fully inflated lung, levels of CPAP as low as 1 to 2 cm H_2O can be used.[83] Because the normal transpulmonary pressure of the lung at FRC is approximately 5 cm H_2O, levels of 5 to 10 cm H_2O CPAP applied to a fully recruited lung result in a large-volume lung that impedes surgery, particularly during minimally invasive procedures.

CPAP levels less than 10 cm H_2O do not interfere with hemodynamics. The beneficial effects of low levels of CPAP are due primarily to oxygen uptake from the nonventilated lung and not to blood flow diversion to the ventilated lung. CPAP is most effective when oxygen (F_{IO_2} 1.0) is applied to the nonventilated lung. Lower F_{IO_2} levels of CPAP are of clinical benefit and can be used along with decreased F_{IO_2} to the ventilated lung in patients at risk of oxygen toxicity.

CPAP, even when properly administered, is not completely reliable to improve oxygenation during OLV. When the bronchus of the operative lung is obstructed, or open to atmosphere (as in a bronchopleural fistula or during endobronchial surgery) CPAP will not improve oxygenation. Also in certain situations, particularly during thoracoscopic surgery where access to the operative hemithorax is limited, CPAP can interfere significantly with surgery.[84]

Pharmacologic Manipulations

Eliminating known potent vasodilators such as nitroglycerin, halothane, and large doses of other volatile anesthetics improves oxygenation during OLV.[85] The selective administration of the vasodilator prostaglandin E_1 to the ventilated lung[86] or a nitric oxide synthase inhibitor (L-NAME)[87] to a hypoxic lobe results in improved redistribution of pulmonary blood flow in animal models. This is not applicable to humans at present. Selective administration of nitric oxide alone to the ventilated lung was not shown to be of benefit in humans.[88] The combination of inhaled nitric oxide (20 ppm) and an intravenous infusion of almitrine, which enhances HPV, has been shown to restore PaO_2 values during OLV in humans to essentially the same levels as during TLV.[89] However, this may have been due primarily to the augmentation of HPV by almitrene.[90] It is unlikely that almitrine, which was previously available in North America as a respiratory stimulant, will be reintroduced to this market because of side effects such as hepatic enzyme changes and lactic acidosis. However, the combination of nitric oxide and other pulmonary vasoconstrictors such as phenylephrine has been shown to improve oxygenation in ventilated intensive care unit patients with adult respiratory distress syndrome,[91] and this may have applications in OLV.

Intermittent Reinflation of the Nonventilated Lung

HPV becomes more effective during repeated hypoxic exposure. Often after reinflation, the oxygen saturation will be more acceptable during a second period of lung collapse. Reexpansion can be performed by regular reexpansion of the operative lung via an attached CPAP circuit.

Partial Ventilation Methods

Several alternative methods of OLV, all involving partial ventilation of the nonventilated lung, have been described and improve oxygenation during OLV. These techniques are useful in patients who are particularly at risk of desaturation, such as those who have had previous pulmonary resections of the contralateral lung or low CO states. These alternatives include the following:

1. Intermittent positive airway pressure to the nonventilated lung. This can be performed by a variety of methods. Russell described attaching a standard bacteriostatic filter to the nonventilated lumen of the DLT with a 2-L oxygen inflow attached to the CO_2 port of the filter.[92] Manual occlusion of the filter for 2 seconds gives an insufflation of approximately 66 mL of oxygen to the nonventilated lung. This could be repeated at 10-second intervals with minimal interference with surgical exposure.
2. Selective insufflation of oxygen to recruit lung segments on the side of surgery but remote from the site of surgery (Fig. 49.9).[93] A useful technique in minimally invasive surgery is intermittent insufflation of oxygen using a fiberoptic bronchoscope. A 5-L oxygen flow is attached to the suction port of a fiberoptic bronchoscope, which is passed under direct vision into a segment of the lung remote from the site of surgery which is then reinflated by triggering the suction on the fiberoptic bronchoscope. The surgeon aids this technique by observing the lung inflation with the thoracoscope to avoid overdistention of the recruited segment(s).
3. Selective lobar collapse of only the operative lobe in the open hemithorax.[94] This is accomplished by placement of a blocker in the appropriate lobar bronchus of the ipsilateral operative lung.

Mechanical Restriction of Pulmonary Blood Flow

It is possible for the surgeon to directly compress or clamp the blood flow to the nonventilated lung.[95] This can be done temporarily in emergency desaturation situations or definitively in cases of pneumonectomy or lung transplantation. Another technique of mechanical limitation of blood flow to the nonventilated lung is the inflation of a pulmonary artery catheter balloon in the main pulmonary artery of the operative lung. The pulmonary artery catheter can be positioned at induction with fluoroscopic or TEE guidance and inflated as needed intraoperatively. This has been shown to be a useful technique for resection of large pulmonary arteriovenous fistulas.[96]

Hypoxemia Prophylaxis

Most treatments outlined as therapies for hypoxemia can be used prophylactically to prevent hypoxemia in patients who are at high risk of desaturation during OLV. The advantage of prophylactic therapy of hypoxemia, in addition to the obvious patient safety benefit, is that maneuvers involving CPAP or alternative ventilation patterns of the operative lung can be instituted at the onset of OLV in a controlled fashion and will not require interruption of surgery and emergent reinflation of the nonventilated lung at a time that may be extremely disadvantageous.

Bilateral Pulmonary Surgery

Because of mechanical trauma to the operative lung, the gas exchange in this lung will always be temporarily impaired after OLV. Also HPV offset may be delayed after reinflation of the first lung collapsed.

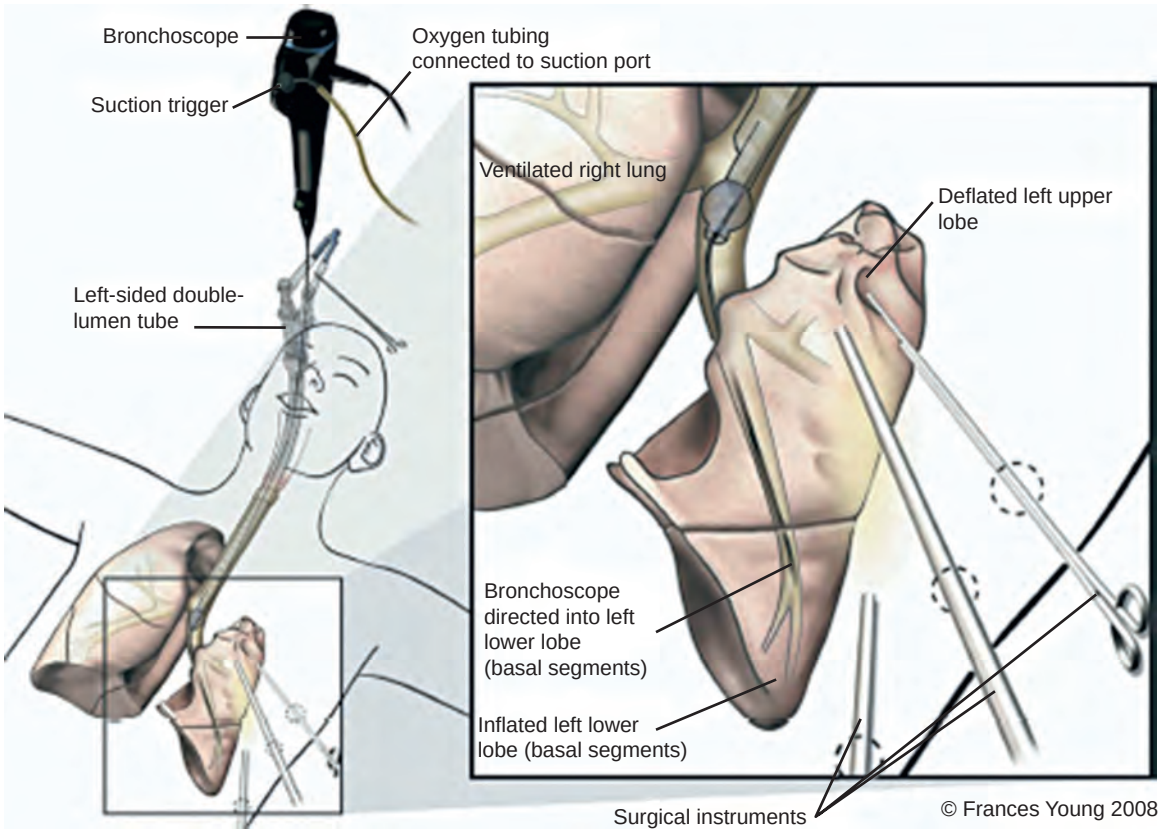


Fig. 49.9 Intermittent oxygen insufflation during thoracoscopic surgery to segments of the nonventilated lung on the side of surgery using a fiberoptic bronchoscope; see text for details. *(Reproduced with permission from Slinger P.* Principles and Practice of Anesthesia for Thoracic Surgery. *New York: Springer; 2011.)*

Desaturation during bilateral lung procedures is particularly a problem during the second period of OLV.[97] Thus, for bilateral procedures it is advisable to operate first on the lung that has better gas exchange and less propensity to desaturate during OLV. For most patients this means operating on the right lung first.

Transesophageal Echocardiography for Noncardiac Thoracic Surgery

TEE is recommended as a category I indication for noncardiac surgery in the circumstances of life-threatening unexplained hypoxemia and/or hypotension[98] (see Chapters 14–16 and 46). It is also recommended when patients have known or suspected cardiovascular disease that may impact outcomes.[99] In clinical practice, TEE is used in a wide variety of circumstances in noncardiac thoracic surgery, including to assess cardiac or great vessel compression from intrathoracic masses, hemodynamic instability, and RV and left ventricular preload and contractility. TEE can be useful in assessing the existence or extent of cardiac involvement from benign or malignant tumors of the lung or mediastinum (Figs. 49.10–49.12). It is often difficult for the surgeon to assess this during thoracotomy or sternotomy. TEE can also be useful in assessing the extent of compression of the superior vena cava, which can occur with lung tumors of the right upper lobe. In addition, TEE can be useful for evaluating hemodynamic instability in patients having noncardiac thoracic surgery. Pericardial tamponade, pulmonary embolism, hypovolemia, and left- or right-sided heart failure may be diagnosed by TEE when other clinical signs or monitors are misleading (Fig. 49.13).

Airway Surgery

Anesthetic Management for Diagnostic or Therapeutic Airway Procedures

Patients with underlying cardiac disease may present for a variety of surgical procedures involving the airways. Flexible FOB is a diagnostic and therapeutic procedure of great value. In many centers, it is common practice to perform flexible FOB before airway or other thoracic surgeries, to reconfirm the diagnosis (if a tumor compresses the airway), or to determine the invasion and obstruction of the distal airway. There are multiple techniques for flexible FOB. Options include awake versus general anesthesia and oral versus nasal approaches. Options for local anesthesia include topical anesthesia via a nebulizer, handheld aerosol, or soaked pledgets; nerve blocks (laryngeal and/or glossopharyngeal nerves); direct administration of local anesthetic through the bronchoscope (spray-as-you-go technique),[100] with or without sedation or opioid or antisialagogues. Options during general anesthesia include spontaneous versus positive pressure ventilation with or without muscle relaxation. Airway management during general anesthesia can be done with an endotracheal tube (ETT) or a laryngeal mask airway (LMA). A swivel bronchoscopy connector with a self-sealing valve is used to facilitate the ventilation and manipulation of the bronchoscope at the same time inhalation and/or intravenous agents can be used for anesthesia. Patients who have copious secretions in the preoperative period should receive anticholinergic medication to ensure a dry field, which provides optimal visualization.

The advantages of an LMA technique include that it allows visualization of the vocal cords and subglottic structures and there is a lower airway resistance, compared with an ETT, when the bronchoscope is inserted (Fig. 49.14). This is particularly useful in the patient with a difficult airway when maintaining spontaneous respiration may be the safest method of anesthetic management.[101] Self-expanding

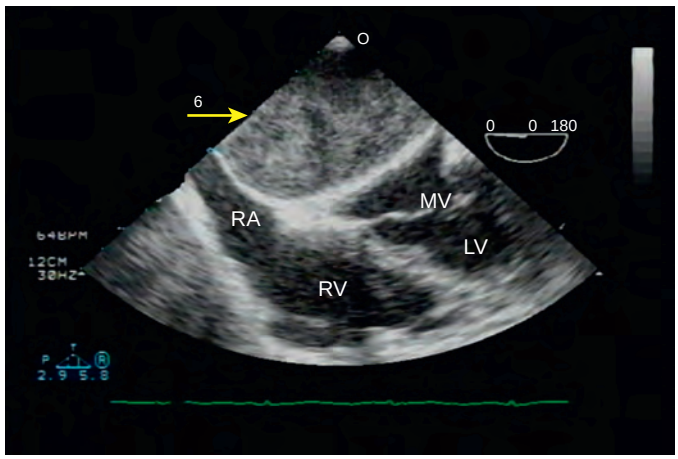


Fig. 49.10 Initial intraoperative midesophageal four-chamber transesophageal echocardiographic view at 0 degrees of the heart. Patient with a posterior mediastinal tumor that was compressing the left atrium, showing near complete compression of left atrium by the tumor *(yellow arrow)* posteriorly and also compression of the right atrium *(RA)*. Although the left atrium was severely compressed by the tumor (a mediastinal Schwannoma), there is no clear evidence that the tumor extends through the wall of the atrium. *MV,* mitral valve; *LV,* left ventricle; *RV,* right ventricle.

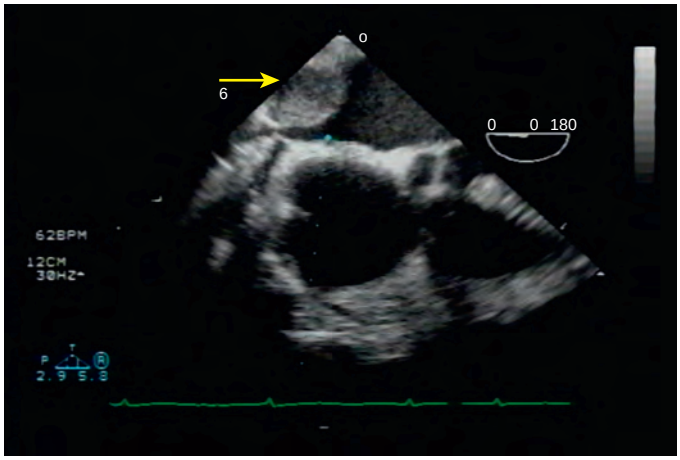


Fig. 49.11 Modified four-chamber transesophageal echocardiographic (TEE) view at 0 degrees after surgical resection of the posterior mediastinal tumor. TEE shows that one lobe of the tumor *(yellow arrow)* remains adherent to the posterior left atrial wall. This was not initially evident to the surgeon.

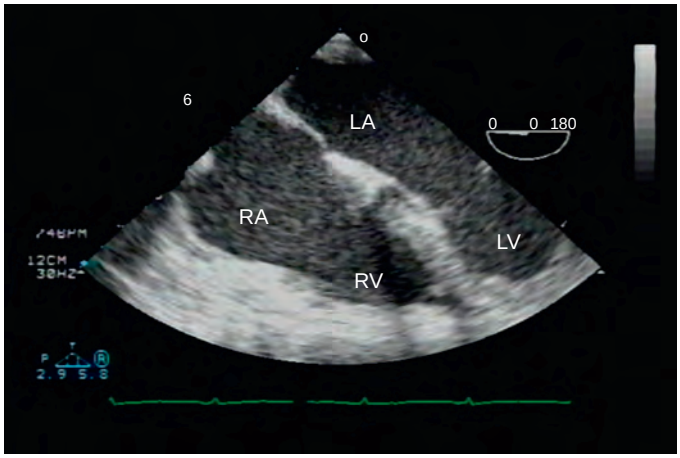


Fig. 49.12 Midesophageal four-chamber transesophageal echocardiographic view after excision of the remaining portion of the mediastinal tumor. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

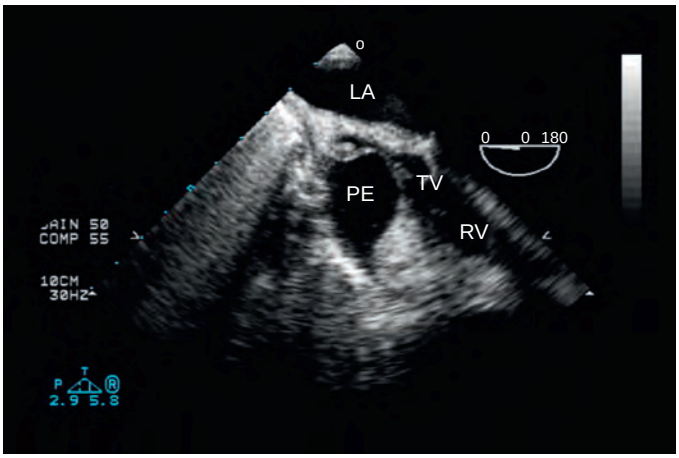


Fig. 49.13 Intraoperative midesophageal four-chamber transesophageal echocardiographic (TEE) view of a patient with bilateral pleural effusions, thought to be secondary to metastatic breast cancer, performed for the diagnosis of severe refractory hypotension after induction of anesthesia. A loculated pericardial effusion *(PE)* is nearly completely obliterating the right atrium and causing a cardiac tamponade. Based on the TEE diagnosis it was possible to add a video-assisted thoracoscopic surgery pericardial window to the originally planned surgery. *LA,* Left atrium, *RV,* right ventricle; *TV,* tricuspid valve.

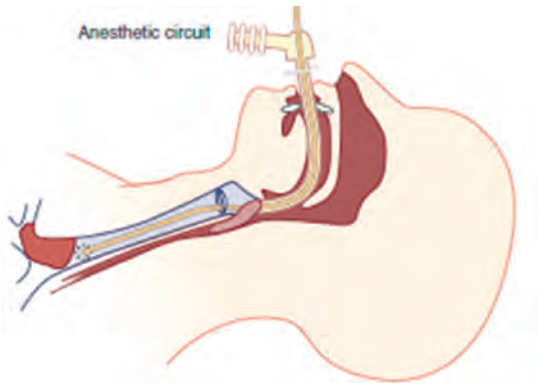


Fig. 49.14 Diagram of fiberoptic bronchoscopy performed via a laryngeal mask airway (LMA) during general anesthesia in a spontaneously breathing patient with a carinal tumor, in this case for diagnosis and Nd:YAG laser tumor excision. The LMA permits visualization of the vocal cords and subglottic structures with the bronchoscope, which is not possible when fiberoptic bronchoscopy is performed via an endotracheal tube. *(Reproduced with permission from Slinger PD, Campos JH. Anesthesia for thoracic surgery. In: Miller RD, ed.* Miller's Anesthesia. *8th Ed. Philadelphia: Saunders; 2015:1942–2006.)*

flexometallic tracheal and bronchial stents can be placed with fiberoptic or rigid bronchoscopy. However, Silastic airway stents require rigid bronchoscopy for placement.

Rigid bronchoscopy has traditionally been considered the technique of choice for the preoperative diagnostic assessment of an airway obstruction involving the trachea and in the therapy of massive hemoptysis and foreign bodies in the airway. The role of interventional bronchoscopy with laser, bronchial dilation, or stent insertion is well established for the treatment of malignant and benign central airway and endobronchial lesions.[102] Rigid bronchoscopy is the procedure of choice for operative procedures such as dilation of tracheal stenosis.

Patients undergoing rigid bronchoscopy should have a complete preoperative evaluation, including radiologic studies. Chest radiographs and chest computed tomographic (CT) scans should be reviewed in the preoperative evaluation. If time permits, it is recommended that patients with severe stridor receive pharmacologic interventions for temporary stabilization of the condition. Treatments may include inspired cool saline mist, nebulized racemic epinephrine, and the use of systemic steroids.[103]

There are four basic methods of ventilation management for rigid bronchoscopy.

1. Spontaneous ventilation. The addition of topical anesthesia or nerve blocks to the airway decreases the tendency to breath-hold and cough when volatile anesthetics are used.
2. Apneic oxygenation (with or without insufflation of oxygen). This requires thorough preoxygenation, and the anesthesiologist will have to interrupt surgery to ventilate the patient before desaturation occurs. This should allow the surgeon working intervals of 3 minutes or longer, depending on the underlying condition of the patient.
3. Positive pressure ventilation via a ventilating bronchoscope. This allows the use of a standard anesthetic circuit but may cause significant air leaks if there is a discrepancy between the size of a smaller bronchoscope and a larger airway.
4. Jet ventilation. This can be performed with a handheld injector such as the Sanders injector[104] or with a high-frequency ventilator. These techniques are most useful with intravenous anesthesia because they entrain gas from either the room air or an attached anesthetic circuit, and the dose of any volatile agent delivered will not be known.

The use of anticholinergic agents before manipulation of the airway will decrease secretions during the bronchoscopic examination. For a patient undergoing rigid bronchoscopy, the surgeon must be at the bedside for the induction of anesthesia and be prepared to establish airway control with the rigid bronchoscope. In adults, intravenous anesthesia and the use of muscle relaxants is more common with ventilation by a combination of methods 3 and 4.

For cases in which the use of muscle relaxants is not contraindicated, a short-acting agent (succinylcholine) can be used initially to facilitate intubation with either a small SLT or the rigid bronchoscope. Non-depolarizing relaxants may be needed for prolonged procedures such as stent placement or tumor resection. Remifentanil and propofol infusions can be administered if an intravenous regimen is the planned anesthetic.[105] This is a useful technique if the surgeon needs repeated access (for suction or instrumentation) to the open airway, because it maintains the level of anesthesia and avoids contaminating the operating room with anesthetic vapors.

In cases where a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser is used, the F_{IO_2} should be maintained in the lowest acceptable range (ie, <30% if possible) according to patient oxygen saturation, to avoid the potential for fire in the airway. Because any common material (including porcelain and metal) can be perforated by the Nd:YAG laser, it is best to avoid any potentially combustible substance in the airway when the Nd:YAG laser is used.[106] Because of its high energy and short wavelength, the Nd:YAG laser has several advantages for distal airway surgery over the CO_2 laser, which is used in upper airway surgery. The Nd:YAG laser penetrates tissue more deeply so it causes more coagulation in vascular tumors, and it can be refracted and passed in fibers through a flexible or rigid bronchoscope. However, there is a higher potential for accidental reflected laser strikes and there is more delayed airway edema.

Rigid bronchoscopes have different sizes, commonly from 3.5 to 9 mm in diameter, with a ventilating side-port to facilitate ventilation when the bronchoscope is placed into the airway. If excessive leak of tidal volume occurs around the bronchoscope with positive pressure ventilation, it may be necessary to place throat packs to facilitate ventilation. Continuous communication with the surgeon or pulmonologist is necessary in case desaturation occurs. If desaturation does occur, it must be corrected by stopping surgery and allowing the anesthesiologist to ventilate and oxygenate the patient, either via the rigid bronchoscope or by removing the bronchoscope and ventilating with a mask, LMA, or ETT.

Pulse oximetry is vital during rigid bronchoscopy because there is a high risk of desaturation. There is no simple way to monitor end-tidal CO_2 or volatile anesthetics because the airway remains essentially open to atmosphere. For patients with underlying cardiac disease, an arterial catheter is usually placed for rigid bronchoscopy to facilitate rapid hemodynamic control. For prolonged procedures, it is useful to perform repeated arterial blood gas analysis to confirm the adequacy of ventilation. An alternative is to interrupt surgery and ventilate the patient with a standard circuit and a mask or ETT to assess the end-tidal CO_2.

Unlike during FOB via an ETT, with rigid bronchoscopy the airway is never completely secure and there is always the potential for aspiration in patients at increased risk, such as those with a full stomach, hiatus hernia, or morbid obesity. It is always best to defer rigid bronchoscopy to decrease the aspiration risk, if possible, in these patients. When there is no benefit to be gained by deferring and/or the airway risk is acute (eg, aspiration of an obstructing foreign body), each case must be managed on an individual basis depending on the context and competing risks.

Other rigid bronchoscopic procedures that require anesthesia include dilation for benign airway stenosis, core-out of malignant lesions in the trachea, laser ablation of endobronchial and carinal tumors, and therapeutic bronchoscopic interventions before surgical resection of lung cancer. In addition, interventional bronchoscopy is often used for the management of airway complications following lung transplantation. Rigid bronchoscopy can be performed in combination with extracorporeal membranous oxygenation or cardiopulmonary bypass (CPB) in high-risk patients.[107]

Complications of rigid bronchoscopy include airway perforation, mucosal damage, hemorrhage, postmanipulation airway edema, and potential airway loss at the end of the procedure. In some situations, it may be necessary to keep the patient intubated with a small (ie, 6.0 mm internal diameter) SLT after a rigid bronchoscopy if an edematous airway is suspected or the patient is not able to be extubated. These patients may require the use of steroids, nebulized racemic epinephrine, or helium/oxygen mixtures to treat stridor in the postoperative period.

Anesthesia for Tracheal Resection

Tracheal resection and reconstruction is indicated in patients who have a tracheal obstruction as a result of a tracheal tumor, previous tracheal trauma (most commonly, postintubation stenosis), congenital anomalies, vascular lesions, and tracheomalacia. For patients who have operable tumors, approximately 80% undergo segmental resection with primary anastomosis, 10% undergo segmental resection with prosthetic reconstruction, and the remaining 10% undergo placement of a Montgomery T-tube stent.

Diagnostic studies are reviewed as part of the preoperative evaluation. The CT scan is a useful diagnostic tool to evaluate the degree, level, and length of the lesion. Bronchoscopy is one of the definitive diagnostic tests for tracheal obstruction. Bronchoscopy for a patient with tracheal stenosis should be carried out in the operating room where the surgical and anesthesia teams are present and ready to intervene should loss of airway occur. An advantage of rigid bronchoscopy over flexible bronchoscopy is that it can bypass the obstruction and provide a ventilation pathway if complete obstruction occurs. During surgery, all patients should have an invasive arterial catheter placed to facilitate measurement of arterial blood gases, as well as measure arterial blood pressure. Central venous pressure catheters are only used if the patient requires CPB.

Various methods for providing adequate oxygenation and elimination of CO_2 have been used during tracheal resection. The alternatives include (1) standard orotracheal intubation, (2) insertion of a sterile SLT into the opened trachea or bronchus distal to the area of resection, (3) high-frequency jet ventilation through the stenotic area, (4) high-frequency positive pressure ventilation, and (5) the use of CPB or extracorporeal membranous oxygenation.

Induction of anesthesia in patients with a compromised airway requires good communication between the surgical team and the anesthesiologist. The surgeon should always be in the operating room during induction and available to manage a surgical airway if this becomes necessary.[108] A rigid bronchoscope must be immediately available. The patient should be thoroughly preoxygenated with 100% oxygen before induction. The airways of patients with congenital or acquired tracheal stenosis are unlikely to collapse during induction of anesthesia. However, intratracheal masses may lead to airway obstruction with induction of anesthesia and should be managed similarly to anterior mediastinal masses (see "Mediastinal Masses"). One airway management technique is to begin the case with rigid bronchoscopy and tracheal dilation and then to pass an SLT through the stenosis. This tube is withdrawn into the proximal trachea once the distal trachea is opened and a second sterile SLT is placed into the distal trachea by the surgeon. Ventilation is via a sterile anesthetic circuit passed across the drapes into the surgical field. With a low tracheal lesion, a right thoracotomy provides the optimal surgical exposure. A sterile SLT is used to provide ventilation to the lung distal to the resection. After the posterior anastomosis is completed, the endobronchial tube is removed and the original SLT is advanced past the site of resection. This technique can also be used for carinal resections.

A third technique for airway management during tracheal resection includes high-frequency jet ventilation through a small-bore ETT or catheter.[109] With this technique, a small-bore uncuffed catheter is placed through the stenotic area, and ventilation is accomplished by intermittently exposing the lung to a high flow of fresh gas through the catheter. Other techniques that have been used for oxygenation during distal airway resections include high-frequency positive pressure ventilation, helium-oxygen mixtures, and CPB.

After the tracheal resection is completed, most patients are kept in a position of neck flexion to reduce tension on the suture line. Replacement of the SLT by an LMA for emergence facilitates bronchoscopy if required. A thick chin-sternum suture may be placed for several days to maintain neck flexion, or a cervical splint may be used.[110] A T-tube with upper limb 0.5 to 1 cm above the vocal cords may be inserted at the end of surgery in cases when glottic edema is a concern, or for patients requiring ventilatory support. If a tracheostomy is performed, it will be done distal to the anastomosis. Early extubation is highly desirable. If a patient requires reintubation, it should be performed with a flexible fiberoptic bronchoscope by advancing an SLT under direct vision over the bronchoscope and then placing it in the patient's trachea. The patient is kept in a head-up position to diminish swelling. Steroids may be useful in these cases to decrease airway edema.

One of the complications in the postoperative period is tetraplegia, with hyperflexion of the neck having been implicated as a potential cause. In these cases, it is necessary to cut the chin stitch. An infusion of propofol and remifentanil, with FOB guidance and full patient cooperation, can aid extubation.[111]

Pulmonary Hemorrhage

Massive hemoptysis can be caused by carcinoma, bronchiectasis, pulmonary vascular disease, and trauma (blunt, penetrating, or secondary to a PAC). Death can occur quickly due to asphyxia. Management requires four sequential steps: lung isolation, resuscitation, diagnosis, and definitive treatment (see Chapters 24 and 26 for detailed discussions) (Fig. 49.15, Box 49.6).

Posttracheostomy Hemorrhage

Hemorrhage in the immediate postoperative period following a tracheostomy is usually from local vessels in the incision such as the anterior jugular or inferior thyroid veins. Massive hemorrhage 1 to 6 weeks postoperatively is most commonly due to trachea-innominate artery fistula.[112] A small sentinel bleed occurs in most patients before

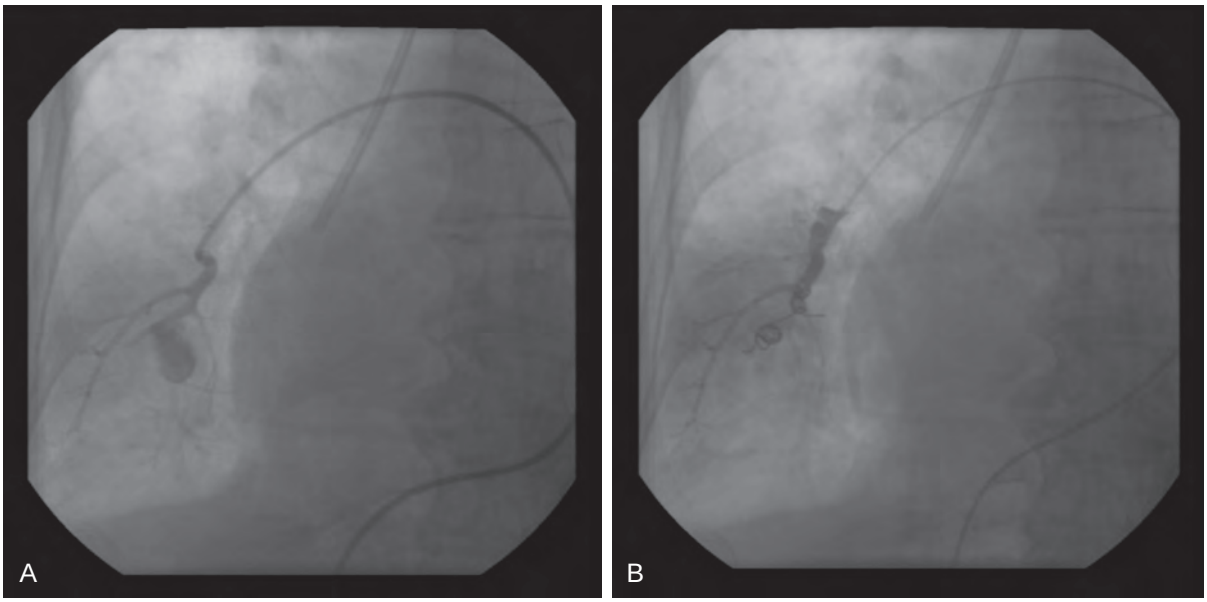


Fig. 49.15 (A) Radiographic dye injection showing a false aneurysm of the pulmonary artery of the right lower lobe following massive hemoptysis induced by a pulmonary artery catheter rupture. (B) A coil has been placed by interventional radiology in the false aneurysm of the right lower pulmonary artery in the same patient. Dye injection shows that the aneurysm has embolized with no further leakage.

BOX 49.6 MANAGEMENT OF THE PATIENT WITH PULMONARY ARTERY CATHETER–INDUCED PULMONARY HEMORRHAGE

- Initially position the patient with the bleeding lung dependent.
- Perform endotracheal intubation, oxygenation, and airway toilet.
- Isolate the lung with an endobronchial double- or single-lumen tube or bronchial blocker.
- Withdraw the pulmonary artery catheter several centimeters, leaving it in the main pulmonary artery. Do not inflate the balloon (except with fluoroscopic guidance).
- Position the patient with the isolated bleeding lung nondependent. Apply positive end-expiratory pressure (PEEP) to the bleeding lung if possible.
- Transport to medical imaging for diagnosis and embolization if feasible.

BOX 49.7 MANAGEMENT OF TRACHEOINNOMINATE ARTERY FISTULA HEMORRHAGE

- Overinflate the tracheostomy cuff to tamponade the hemorrhage. If this fails,
  - Replace the tracheostomy tube with an oral endotracheal tube. Position the cuff with fiberoptic bronchoscopic guidance just above the carina.
- Apply digital compression of the innominate artery against the posterior sternum using a finger passed through the tracheostomy stoma. If this fails,
  - Slowly withdraw the endotracheal tube and overinflate the cuff to tamponade.
  - Then proceed with definitive therapy: sternotomy and ligation of the innominate artery.

a massive bleed. The management protocol for trachea-innominate artery fistula is outlined in Box 49.7.

Mediastinal Masses

Patients with mediastinal masses, particularly masses in the anterior and/or superior mediastinum, present unique problems for the anesthesiologist. Patients may require anesthesia for biopsy of these masses by mediastinoscopy or VATS, or they may require definitive resection via sternotomy or thoracotomy. Tumors of the mediastinum include thymoma, teratoma, lymphoma, cystic hygroma, bronchogenic cyst, and thyroid tumors. Mediastinal masses may cause obstruction of major airways, pulmonary arteries, atria, and/or the superior vena cava. During induction of general anesthesia in patients with an anterior or superior mediastinal mass, airway obstruction is the most common and feared complication. It is important to note that the point of tracheobronchial compression usually occurs distal to an ETT and it is not possible to forcibly pass an ETT through the airway once it has collapsed. A history of supine dyspnea or cough should alert the clinician to the possibility of airway obstruction upon induction of anesthesia. The other major complication is cardiovascular collapse secondary to compression of the heart or major vessels. Symptoms of supine presyncope suggest vascular compression.

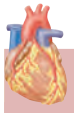
Anesthetic deaths reported have been mainly in children. These deaths may be the result of the more compressible cartilaginous structure of the airway in children or because of the difficulty in obtaining a history of positional symptoms. The most important diagnostic test in the patient with a mediastinal mass is the CT scan of the trachea and chest. Children with tracheobronchial compression greater than 50% on CT scan cannot be safely given general anesthesia.[112] Flow-volume loops, specifically the exacerbation of a variable intrathoracic obstructive pattern (expiratory plateau) when supine, are unreliable[113] for predicting which patients will have intraoperative airway collapse.[114] Preoperative transthoracic echocardiography is indicated for patients with vascular compression symptoms.

General anesthesia will exacerbate extrinsic intrathoracic airway compression in three ways. First, reduced lung volume occurs during general anesthesia, and tracheobronchial diameters decrease according to lung volume. Second, bronchial smooth muscle relaxes during general anesthesia, allowing greater compressibility of large airways. Third, paralysis eliminates the caudal movement of the diaphragm seen during spontaneous ventilation. This eliminates the normal transpleural pressure gradient that dilates the airways during inspiration and minimizes the effects of extrinsic intrathoracic airway compression.

Management of patients with mediastinal masses is guided by their symptoms and the CT scan. Patients with uncertain distal airways should have diagnostic procedures performed under local or regional anesthesia whenever possible. Patients with uncertain airways requiring general anesthesia need a step-by-step induction of anesthesia with continuous monitoring of gas exchange and hemodynamics. This NPIC (*noli pontes ignii consumere*; ie, "don't burn your bridges") anesthetic induction can be an inhalation induction with a volatile anesthetic such as sevoflurane or intravenous titration of propofol with or without ketamine, maintaining spontaneous ventilation until either the airway is definitively secured or the procedure is completed.[115] Awake intubation of the trachea before induction is a possibility in some adult patients if the CT scan shows an area of noncompressed distal trachea to which the ETT can be advanced before induction. If muscle relaxants are required, ventilation should first be gradually taken over manually to ensure that positive-pressure ventilation is possible and only then can a short-acting muscle relaxant be administered (Box 49.8).

Development of airway or vascular compression upon anesthetic induction requires that the patient be awakened as rapidly as possible and then other options for the procedure be explored. Intraoperative life-threatening airway compression usually has responded to one of two therapies: either repositioning of the patient (it must be determined before induction if there is a position that causes less compression and fewer symptoms) or rigid bronchoscopy and ventilation distal to the obstruction (this means that an experienced bronchoscopist and equipment must be immediately available in the operating room). The rigid bronchoscope, even if passed into only one mainstem bronchus, can be used for oxygenation during resuscitation.[115] Once adequate oxygenation has been restored, the rigid bronchoscope can be used to position an airway exchange catheter over which an ETT is passed after the bronchoscope is withdrawn. An alternative technique to secure the airway with rigid bronchoscopy is to first mount an ETT over a small rigid bronchoscope (eg, 6 mm) and then perform rigid bronchoscopy using the bronchoscope to deliver the ETT distal to the obstruction.[116]

Institution of femoral-femoral CPB before induction of anesthesia is a possibility for some adult patients who are unsafe for NPIC general anesthesia (Fig. 49.16). However, the concept of CPB "standby" during attempted induction of anesthesia is fraught with danger[117] because there is not enough time after a sudden airway collapse to establish CPB before hypoxic cerebral injury occurs.[118] The salient points in



BOX 49.8 MANAGEMENT FOR ALL PATIENTS WITH A MEDIASTINAL MASS AND AN UNCERTAIN AIRWAY FOR GENERAL ANESTHESIA

- Determine optimal positioning of patient preoperatively.
- Secure airway beyond stenosis with the patient awake if feasible.
- Have a rigid bronchoscope and surgeon available at induction.
- Maintain spontaneous ventilation if possible (NPIC; see "Mediastinal Masses").
- Monitor for airway compromise postoperatively.

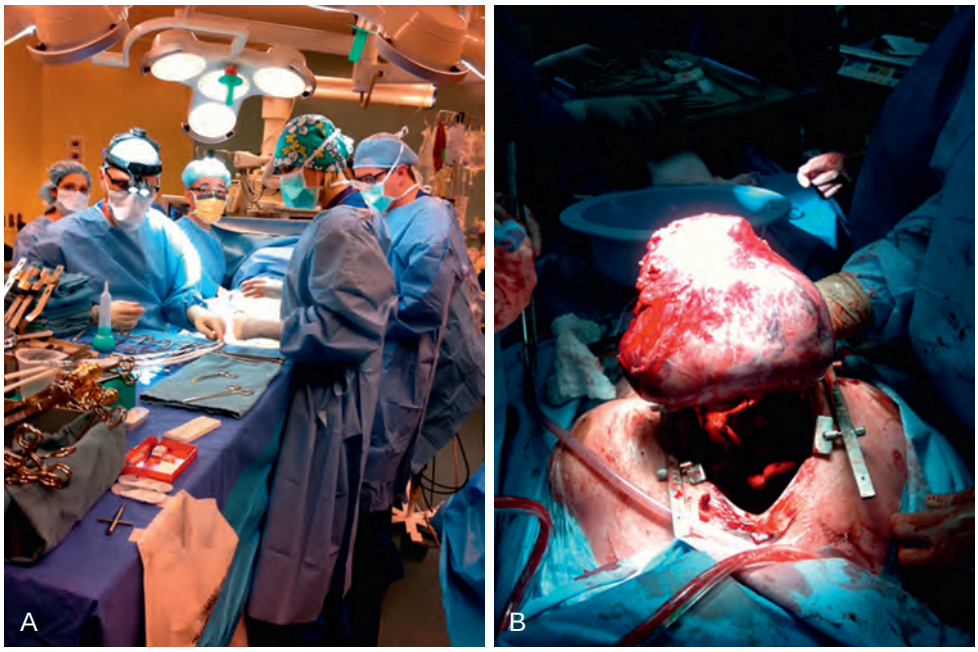


Fig. 49.16 (A) A patient with a large anterior mediastinal mass is placed on femoral-femoral arterial-venous cardiopulmonary bypass before induction of anesthesia. The perspective is from the foot of the operating room table. The patient was reclined to 45O for cannulation. The patient's head and upper body is concealed behind the surgical drapes. (B) A large anterior mediastinal sarcoma is removed from the same patient by sternotomy after induction of anesthesia with spontaneous ventilation while on cardiopulmonary bypass. The perspective is from the head of the operating room table over the surgical drapes.

managing a patient with an anterior or superior mediastinal mass include the following:[119]

1. In virtually all adults with a mediastinal mass, diagnostic procedures and imaging can be performed, if necessary, without subjecting the patient to the risks of general anesthesia.[120]
2. An extrathoracic source of tissue for diagnostic biopsy (pleural effusion or extrathoracic lymph node) should be sought as an initial measure in every patient.
3. Regardless of the proposed diagnostic or therapeutic procedure, the flat (supine) position is never mandatory.

With improved awareness of the risk of acute intraoperative airway obstruction in these patients, life-threatening events are now less likely to occur in the operating room. In adults, acute airway obstruction is now more likely to occur postoperatively, in the recovery room.[121] Vigilance must be maintained throughout the entire perioperative period.

Vascular Anomalies With Airway Compression

A spectrum of congenital vascular abnormalities can cause tracheal, bronchial, and/or esophageal compression. These abnormalities include double aortic arch, right aortic arch with anomalous origin of the left subclavian artery, left aortic arch with anomalous right subclavian, and Kommerell diverticulum.[122] Kommerell diverticulum is an aneurysm at the origin of an anomalous subclavian artery that represents an embryologic remnant of the interrupted fourth aortic arch between the carotid and subclavian arteries. In combination with the ligamentum arteriosum or a patent ductus, it may cause a complete vascular ring compressing the trachea. Symptoms involve varying degrees of esophageal or airway obstruction and may present at any age. There is a tendency for airway symptoms to predominate in children and esophageal symptoms to predominate in adults. Respiratory symptoms and simple bronchoscopy can lead to a misdiagnosis of congenital tracheal stenosis. Diagnosis is confirmed by CT scan (Figs. 49.17–49.19), magnetic resonance imaging, and barium swallow. Surgical correction should follow diagnosis because of the tendency for rupture or dissection of these abnormal vessels.[123] Depending on the anatomy, surgical correction may range from thoracoscopic ligation of the ligamentum arteriosum, to sternotomy with vascular and airway reconstruction potentially requiring hypothermic cardiac arrest.

As with all other lower airway abnormalities, airway management requires a flexible plan and full understanding of the anatomy by the

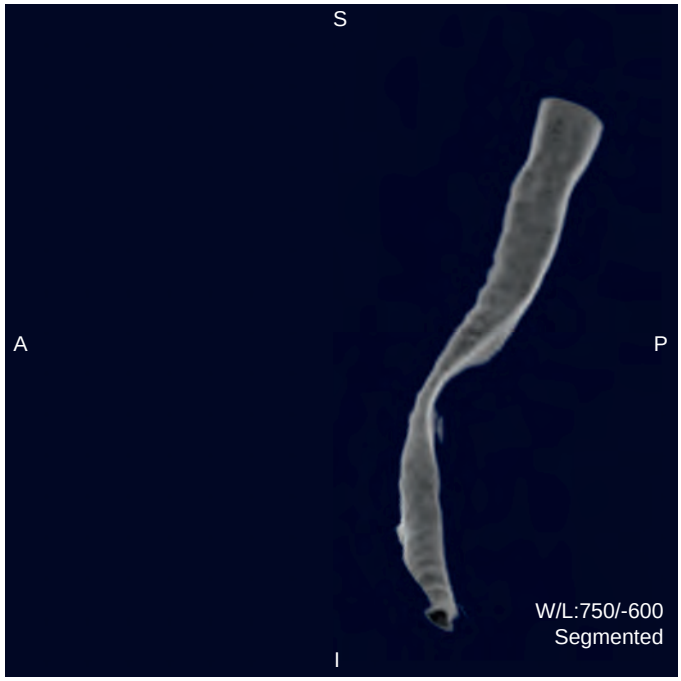


Fig. 49.18 Left lateral computed tomographic reconstruction of the trachea in the same patient showing the posterior compression of the mid-distal trachea.

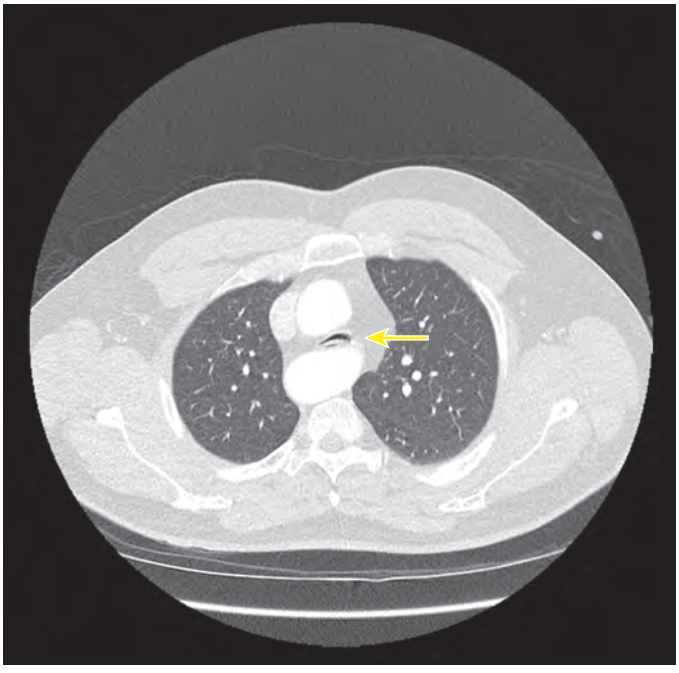


Fig. 49.17 Chest computed tomographic scan of an adult with a Kommerell diverticulum showing mid-distal tracheal compression *(yellow arrow)*. The anterior-posterior tracheal diameter was 3 mm at its narrowest point.

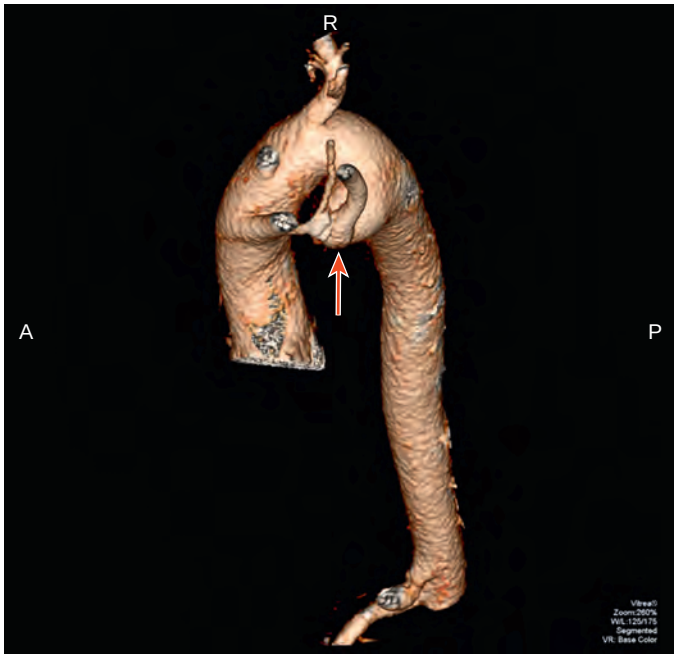


Fig. 49.19 Three-dimensional computed tomographic angiogram from the left lateral perspective of the same patient. The patient has a right-sided aortic arch. The trachea is compressed by the ring formed by the aberrant take-off of the left subclavian artery and the Kommerell diverticulum, which forms the origin of the left common carotid *(arrow)*.

anesthesiologist, based on the preoperative imaging. After induction of anesthesia, a complete FOB via an LMA is usually performed to guide further airway management. Lung isolation when needed may then require placement of a DLT or SLT with bronchial blocker. A rigid bronchoscope should be available in the operating room during induction and emergence from anesthesia in case of distal airway collapse. Consideration should be given to the use of corticosteroids to potentially decrease airway edema postoperatively.

There is the potential for postoperative tracheomalacia in patients who have had severe airway compression. Extubation should be approached in a cautious controlled fashion with the patient alert, sitting, and after a leak test of the ETT. It must be understood that the ETT cuff leak test is not infallible.[124] Another option to consider is extubation during general anesthesia with spontaneous ventilation and observation of the airway via a FOB through an LMA during emergence.

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The Pregnant Patient With Cardiac Disease

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KEY POINTS

1. Maternal heart disease is increasing and complicates up to 4% of pregnancies. It is a leading cause of maternal, fetal, and neonatal morbidity and death.
2. The diagnosis of new cardiovascular disease during pregnancy may be challenging because symptoms and physical signs often overlap with those of a normal, healthy pregnancy.
3. The preferred test during pregnancy to screen for structural cardiac abnormalities and to monitor ventricular and valvular functions and pulmonary pressures is transthoracic echocardiography.
4. A woman with known preexisting cardiac disease should receive preconception assessment and counseling with a rigorous, standardized risk assessment to make informed decisions regarding pregnancy. Several risk assessment tools have been developed.
5. The normal physiologic hemodynamic changes of pregnancy increase myocardial oxygen demand as a result of an increase in heart rate and preload and decrease myocardial oxygen supply secondary to reduced coronary perfusion pressure, dilutional anemia, and shortening of diastole.
6. The severity of valvular heart disease and the prepregnancy New York Heart Association functional class have been found to be the main predictors of adverse maternal and fetal outcomes.
7. Because of the enormous risk of maternal morbidity and mortality, women with pulmonary hypertension should be advised against pregnancy.
8. During labor, uterine contractions, pain, anxiety, and exertion from pushing during the second stage further increase heart rate, arterial blood pressure, and left atrial pressure. This increase adds further stress to a cardiovascular system already strained by the hemodynamic changes of pregnancy and can lead to heart failure.
9. When a pregnant woman with significant cardiac disease requires a nonobstetric operation, both mother and fetus are at a greater risk. The extent of the risk depends on the specific cardiac disease, its interaction with the hemodynamic changes of pregnancy, and its interaction with the hemodynamic changes caused by the surgical procedure and anesthesia.
10. The primary anesthetic goals in peripartum cardiomyopathy are avoidance of drug-induced myocardial depression, maintenance of normovolemia, prevention of increased or rapidly decreased ventricular afterload, and blunting of the sympathetic stimulation induced by pain and anxiety.
11. Resuscitation of the pregnant patient is a rare event that contributes to a lack of knowledge about the unique modifications to the advanced cardiac life support (ACLS) guidelines that are applicable in pregnancy.
12. Modifications to ACLS in pregnancy include performing chest compressions higher on the sternum and with left-sided uterine displacement. Intravenous access sites should be placed above the diaphragm.
13. Voltage for defibrillation and doses of medications during ACLS should not be altered.

Maternal heart disease complicates up to 4% of pregnancies and is a leading cause of maternal, fetal, and neonatal morbidity and death.[1] The prevalence of cardiovascular (CV) diseases (CVDs) in women of childbearing age is increasing for several reasons.[2] As the management and treatment of congenital heart disease (CHD) has improved, growing numbers of women with palliated or corrected CHD who survive into adulthood may become pregnant.[3] Advanced maternal age along with other risk factors, such as obesity, has led to an increase in women presenting with ischemic heart disease.[4] Furthermore, although the incidence of rheumatic heart disease has decreased in developed countries, it remains significant in developing countries and in immigrants from these countries.[5] Cardiomyopathy, manifesting during pregnancy or in the first few months after delivery, is uncommon but accounts for approximately 10% of maternal deaths.[6]

The anesthesiologist involved in the perioperative care of these patients must be well versed in the physiology of pregnancy, the pathophysiology of CVD, and their interactions, to optimize anesthetic management and improve patient outcome. Successful management requires early diagnosis and advanced planning by a multidisciplinary team of obstetricians, cardiologists, anesthesiologists, intensivists, and nurses to optimize outcome. Cardiac surgical procedures during pregnancy carry additional significant maternal and fetal risk and require modification of cardiopulmonary bypass.[7] This topic is covered in Chapters 24 and 31.

This chapter provides a review of the expected hemodynamic changes of pregnancy and the etiologic factors, underlying pathophysiologic features, and peripartum risk of obstetric patients with CVD. It also discusses the management issues faced by the anesthesiologist caring for these patients who present for noncardiac operations during pregnancy and for labor and delivery.

Diagnosis of Heart Disease During Pregnancy

Diagnosis Including Cardiovascular Imaging

The diagnosis of CVD during pregnancy may be challenging because symptoms and physical signs often overlap with the physiologic changes of pregnancy. Pregnant women frequently complain of dyspnea and fatigue, and exercise tolerance is often decreased. Tachypnea, peripheral edema, and lower extremity venous stasis also may occur during pregnancy in women without cardiac disease. Even in women with known preexisting CVD, it is important to differentiate expected pregnancy changes from pathologic exacerbations of underlying disease. The distinction is extremely important because it may trigger either unnecessary modifications in management or a failure to change management.[8]

A pregnant woman who presents with symptoms consistent with possible CVD or exacerbation of known CVD requires a careful medical history, family history, and physical examination (Box 50.1), all interpreted in the context of the physiologic changes of pregnancy. Many disorders, such as cardiomyopathy, Marfan syndrome, CHD, or Brugada syndrome, can be identified by taking a careful personal and family history.[9] In women who are already in the second trimester of pregnancy, blood pressure should be measured with the patient either upright or in the left lateral position to prevent compression of the inferior vena cava and aorta.[10] The pulse often has a rapid upstroke and collapse (a "bounding" character) secondary to the reduced systemic vascular resistance (SVR) and increased cardiac output (CO).[11] Resting heart rate (HR) is generally increased in pregnancy, but rates greater than 100 beats/minute (bpm) or bradycardia require further evaluation for an underlying cause.[8] Jugular venous pressure should be normal, so elevated jugular venous pressure and pulmonary rales are the most reliable signs of heart failure (HF). A loud and widely split S_1 heart sound, caused by the early closure of the mitral valve, and the presence of a third heart sound (S_3) are normal in pregnancy. Soft ejection systolic murmurs are heard in more than 90% of pregnant women, usually over the upper sternal border and the right side of the heart, as a result of increased CO and increased flow through cardiac valves.[12] These murmurs generally disappear at approximately 6 weeks post partum. Very loud systolic murmurs or a palpable thrill, however, suggest underlying disease. Diastolic murmurs are almost always caused by a pathologic process.[10] The murmurs of aortic and mitral regurgitation commonly decrease during pregnancy in response to the decrease in SVR, but the murmurs of mitral or aortic stenosis increase as a result of increased flow through the valves. Auscultation of new or changed murmurs is a reason for further investigation.

BOX 50.1 ABNORMAL PHYSICAL EXAMINATION FINDINGS DURING PREGNANCY

- Heart rate >100 bpm or <50 bpm at rest
- Pulmonary rales
- Systolic murmur louder than 3/6, especially with palpable thrill
- Any diastolic murmur
- Murmur that persists >6 weeks post partum
- Asymmetric lower extremity edema

Oximetry is an important diagnostic tool in patients with cyanotic CHD or shunt lesions.[9] Many pregnant women show some degree of peripheral edema and lower extremity venous stasis secondary to uterine compression of the inferior vena cava impeding venous return. The edema or stasis, however, should be symmetric and decrease with leg elevation and the left lateral decubitus position.

A woman with suggestive findings in the history and physical examination often requires CV testing during pregnancy. Additionally, pregnant women with known CVD may need testing to judge how CV function has been affected by the added stress imposed by pregnancy. Pregnancy may affect the safety, application, and interpretation of several diagnostic cardiac procedures. Additionally, choosing the optimal diagnostic procedure requires consideration of safety for the mother and the fetus.[10] Imaging modalities that do not require ionizing radiation are preferred so long as the required diagnostic information can be obtained. If the necessary information requires a study that uses ionizing radiation, the radiation dose to the fetus should be kept as low as possible.[9]

The electrocardiogram (ECG) often changes during pregnancy. These changes may include a 15- to 20-degree left-axis deviation resulting from diaphragmatic elevation, nonspecific ST-segment and T-wave changes (eg, T-wave inversion in leads III and aVF and ST-segment depression), supraventricular and ventricular ectopic beats, and the presence of small Q waves in lead AVF.[9,11] Ambulatory (Holter) monitoring is noninvasive and safe to use in pregnant patients with suspected arrhythmias that are not captured on an ECG or in patients with previous documented symptomatic arrhythmias and with palpitations. It is important, however, to correlate symptoms with any arrhythmias, so as not to expose the mother and fetus to potentially detrimental treatments.[9,11] Exercise testing may be useful in early pregnancy to establish functional capacity and assess HR, blood pressure, and ischemic changes to exercise. Exercise testing should be used with caution in women with an incompetent cervix, bulging membranes, recent vaginal bleeding, placenta previa or abruption, or preeclampsia. Women with symphyseal-pubic dysfunction, common during pregnancy, may be unable to perform the test because of limited movement. The procedure must be stopped if hypotension develops because this can lead to fetal distress. The European Society of Cardiology recommends performing submaximal exercise tests to reach 80% of predicted maximal HR in asymptomatic pregnant patients with suspected CVD because no evidence indicates that performing exercise testing up to that level increases the risk of spontaneous abortion.[9] Dobutamine stress tests should be avoided in pregnant women because of limited data on dobutamine safety in pregnancy.[9]

The preferred test during pregnancy to screen for structural cardiac abnormalities and to monitor ventricular and valvular function and pulmonary artery pressures (PAP) is transthoracic echocardiography.[9] Many echocardiographic measurements require adjustment for pregnancy, including measurement of chamber dimensions and left ventricular (LV) mass and quantifying velocities across valves, because these values all are increased in pregnancy.[9,12] The use of transesophageal echocardiography (TEE) allows for more detailed examination but is more invasive than transthoracic echocardiography and may be associated with pulmonary aspiration, which is a greater risk during pregnancy as compared with the nonpregnant state. TEE may still be indicated in the diagnosis of endocarditis, mechanical valve thrombosis, and complex CHD. The use of general anesthesia with tracheal intubation, however, may be necessary to protect the airway.[9]

Although it is preferable not to perform chest radiography during pregnancy because of the ionizing radiation exposure, if other tests fail to diagnose the cause of dyspnea or cough, it may be necessary. The chest radiographic findings in pregnancy may show several seemingly pathologic changes, including prominent vascular markings, a horizontal position of the heart, a flattened left heart border, and a raised diaphragm as a result of the gravid uterus. Pulmonary edema, however, should not be seen.[9]

In the setting of suspected acute pulmonary embolus, a computed tomography pulmonary angiogram should be performed because the

risk to the fetus is outweighed by the danger of missed pulmonary emboli and can be minimized by lead shielding. Although echocardiography may aid in the diagnosis by identifying elevated PAPs and impairment and dilatation of the right ventricle, it is less specific.[9]

Cardiac magnetic resonance imaging can provide information on cardiac anatomy and function without the use of ionizing radiation. It is generally used only if other investigations, such as echocardiography, cannot provide the relevant information because the safety of magnetic resonance imaging in the early stages of pregnancy has not been determined. The safety of gadolinium use during pregnancy has not been demonstrated, and this agent should be avoided if possible.[9]

Cardiac catheterization for visualization of coronary arteries and measurement of intracardiac pressures gives high radiation exposure to the fetus and should only be used if absolutely clinically required. It is the diagnostic tool of choice, however, in the management and treatment for ST-segment elevation myocardial infarction (MI) in pregnancy. To reduce fetal radiation exposure, catheterization through the radial artery is preferred to the femoral artery approach, and lead shielding of the uterus should be used. Although heparin is required for the procedure, an activated coagulation time not exceeding 300 seconds is preferable to minimize risk of placental bleeding.[9]

Ionizing Radiation Risk to the Fetus

Pregnant women with suspected or known CVD may require medical procedures for either diagnostic or therapeutic purposes that involve the use of ionizing radiation, such as fluoroscopy for right-sided heart catheterization or mitral balloon valvuloplasty. The effects of ionizing radiation on an embryo and fetus can include pregnancy loss, congenital malformations (eg, microcephaly and microphthalmia), neurobehavioral or intellectual abnormalities, fetal growth retardation, and cancer.[13] The type and magnitude of the potential effects of the radiation on the fetus vary depending on the gestational age at which exposure occurs and the dose of radiation.[9,14] If possible, procedures should be delayed until at least the completion of the period of major organogenesis (>8 weeks of gestational age) because this is when the risks are most significant. The risk is somewhat less in the second trimester, and least in the third trimester, although the central nervous system continues to develop after delivery.[14] The risks and benefits of performing or not performing the examination should be communicated to the patient.[9] Common sense dictates that ionizing radiation should only be used when no alternative exists and at the lowest possible dose and the shortest possible duration.[15] Whenever exposure must occur, it is vital to protect the fetus with lead shielding.[14]

It is unclear what dose of radiation constitutes a danger to the fetus because only limited knowledge of the effects of radiation on the fetus has been obtained from animal studies, human exposures to diagnostic and therapeutic radiation, and atomic bomb exposure.[14] No evidence indicates an increased risk of congenital malformations, neurobehavioral or intellectual abnormalities, fetal growth restriction, or pregnancy loss at doses of radiation lower than 50 mGy (milligray) (10 mGy = 1 rad).[9] Although the effect on these outcomes at radiation doses between 50 and 100 mGy (5–10 rad) is unclear, evidence suggests that doses higher than 100 mGy are associated with increased risk, particularly to the central nervous system tissues.[9,14] Cancer risk to the child is a well-known feature of intrauterine radiation exposure, and some evidence indicates that even very small doses (10–20 mGy) increase the risk by a factor of 1.5 to 2 (1:2000 vs 1:3000).[15] Based on the available information, the International Commission on Radiological Protection stated that radiation exposure of less than 100 mGy (10 rad) during pregnancy should not constitute medical grounds for termination of a pregnancy.[13] However, the American College of Obstetricians and Gynecologists designated that the threshold for medical concern, particularly regarding congenital malformations, should be lowered to 50 mGy (5 rad).[13]

Fortunately, most medical procedures do not expose the fetus to such high levels of radiation. For example, the fetal exposure from a chest radiograph is less than 0.01 mGy, and although the maternal exposure from a percutaneous coronary intervention or radiofrequency catheter ablation is 15 mGy, the fetal exposure is only approximately 3 mGy.[9,14]

Cardiac Risk Stratification During Pregnancy

Ideally, a woman with known preexisting CVD should undergo a preconception evaluation and counseling with a rigorous, standardized risk assessment (see later) to make informed decisions regarding pregnancy, to adjust to the possibility of not having a pregnancy, and to address any correctable lesions before pregnancy.[6,16,17] Evaluation should include assessment of New York Heart Association (NYHA) functional class, a 12-lead ECG, and transthoracic echocardiography. Right-sided heart catheterization may be necessary for women with CHD or pulmonary hypertension (PH).[6] Medications that are contraindicated during pregnancy should be discontinued or changed to acceptable alternatives when possible.[10] Many women present once they are already pregnant and should undergo immediate cardiac evaluation as described earlier.[18] This approach allows for the implementation of safe, guidelines-based care according to the risk assessment.[8] Although women found to be at low risk can often be managed by their primary cardiologist and obstetrician, women who are considered to be at medium or high pregnancy risk should be referred to a tertiary care referral center with expertise in pregnancy and cardiac disease for highly specialized management by a multidisciplinary team.[16]

Several risk assessment tools have been proposed to stratify cardiac risk during pregnancy. By using these risk scores it may be possible to predict whether the woman will tolerate the pregnancy.[16] Three risk assessment tools commonly used to predict maternal CV events during pregnancy are the CARPREG (Cardiac Disease in Pregnancy), the ZAHARA (Zwangerschap bij Vrouwen met een Aangeboren Hartafwijking-II, translated as Pregnancy in Women With CHD II), and one developed by the World Health Organization (WHO).[16] The CARPREG score is based on a prospective study of 562 consecutive pregnant women with known cardiac disease (74% had CHD) in which 13% of the pregnancies had maternal cardiac complications including pulmonary edema, arrhythmia, stroke, and cardiac death. This study identified several independent predictors for the occurrence of an adverse maternal cardiac event during pregnancy and incorporated them to formulate a risk index (Table 50.1).[19] The CARPREG score was modified for patients with CHD with the addition to the risk index of subpulmonary ventricular systolic dysfunction and severe

TABLE 50.1 CARPREG (Cardiac Disease in Pregnancy) System for Predicting Maternal Cardiovascular Events[a]

1. Previous cardiac event (1 point)
   a. Heart failure
   b. Transient ischemic attack
   c. Cerebrovascular accident
   d. Arrhythmia
2. NYHA >functional class II or cyanosis (1 point)
3. Mitral valve area <2 cm^2 (1 point)
4. Aortic valve area <1.5 cm^2 (1 point)
5. Left ventricular outflow tract gradient >30 mm Hg (1 point)
6. Ejection fraction <40% (1 point)

CARPREG Points	*Cardiac Complication Rate*
0	5%
1	27%
2	75%

[a]Points are added, and the total score reflects the predicted cardiac event rate.

NYHA, New York Heart Association.

Modified from Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001;104:515–521; in Chestnut DH, Wong CA, Tsen LC, et al., eds. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelphia: Saunders; 2014.

TABLE 50.2 ZAHARA (Zwangerschap bij Brouwen met een Aangeboren Hartafwijking) for Predicting Maternal Cardiovascular Events[a]

1. History of arrhythmia (1.5 points)
2. Use of cardiac medications before pregnancy (1.5 points)
3. NYHA functional class >II (0.75 point)
4. Left-sided heart obstruction (peak gradient >50 mm Hg or aortic valve area <1.0 cm^2) (2.5 points)
5. Systemic atrioventricular valve regurgitation (moderate/severe) (0.75 point)
6. Pulmonic atrioventricular valve regurgitation (moderate/severe) (0.75 point)
7. Mechanical valve prosthesis (4.25 points)
8. Repaired or unrepaired cyanotic heart disease (1.0 point)

ZAHARA Points	*Cardiac Complication Rate*
0–0.5	2.9%
0.51–1.50	7.5%
1.51–2.50	17.5%
2.51–3.50	43.1%
≥3.51	70.0%

[a]Points are added, and the total score reflects the predicted cardiac event rate.

NYHA, New York Heart Association.

Modified from Drenthen W, Boersma E, Balci A, et al. Predictors of pregnancy complications in women with congenital heart disease. *Eur Heart J.* 2010;31:2124–2132; *in* Chestnut DH, Wong CA, Tsen LC, et al., eds. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelhia: Saunders; 2014.

pulmonic regurgitation.[20] This study, however, was limited by an overrepresentation of complex CHD that explained its very high rate of complications. The ZAHARA investigators constructed a weighted scoring system for women with CHD based on a study of 1802 women in which cardiac complications occurred in 7.6% of completed pregnancies incorporating several additional variables (Table 50.2).[21]

High-risk lesions were underrepresented in the study populations used to generate both the CARPREG and ZAHARA assessment tools, and this underrepresentation led to inaccurate pregnancy risk prediction for the sicker patients.[8] Measurement of serum levels of the biomarker brain natriuretic peptide (BNP) early in pregnancy has also been used to stratify risk. In a study of 87 pregnant women with structural heart disease, BNP levels up to 100 pg/mL had a 33% positive predictive value and a negative predictive value of 100% for identifying adverse maternal cardiac events including HF and arrhythmias during pregnancy, thus making it particularly useful to rule out a cardiac problem.[22]

It is important to stratify risk based on specific lesions because the risks of pregnancy depend on the specific cardiac condition. Predicted risks range from as high as a 50% mortality rate for women with severe PH to a risk that is indistinguishable from that in the general population for some minor lesions.[17]

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology recommends that maternal risk assessment be carried out according to the WHO risk classification.[9] The WHO classification of cardiac risk during pregnancy depend on the specific underlying heart disease and on the presence and severity of ventricular and valvular dysfunction (Table 50.3).[10,17] In addition, in this system pregnancy-related risks are additive, meaning that a patient with a cardiac condition that is considered low risk (WHO 1 or 2) may move up a risk category if other cardiac or noncardiac risk factors (eg, poor ventricular function or diabetes) are present.[17]

Because maternal cardiac disease is associated with an increased incidence of neonatal complications (eg, prematurity, intrauterine growth retardation, and fetal death), it is necessary also to determine the fetal risk of the pregnancy (Box 50.2). Neonatal complications occur in 20% to 28% of pregnant women with heart disease. Neonatal risks increase with NYHA functional class greater than II, the presence of a mechanical valve prosthesis, cyanosis, anticoagulation use during pregnancy, multiple gestations, smoking during pregnancy, aortic stenosis (AS) or mitral stenosis (MS), and the use of cardiac medications before pregnancy.[19,21]

TABLE 50.3 Modified World Health Organization Cardiac Risk Assessment

Class I (No Increase or a Mild Increase in Morbidity From the General Population)

Follow-up during pregnancy may usually be limited to 1 or 2 visits.

- Mild pulmonic valve stenosis
- PDA
- Mitral valve prolapse with minimal mitral regurgitation
- Repaired ASD, VSD, PDA, anomalous pulmonary venous return
- Atrial or ventricular ectopic beats, isolated

Class II (Small Increase in Maternal Mortality, Moderate Increase in Maternal Morbidity)

Follow-up every trimester is indicated.

- Unrepaired ASD or VSD
- Repaired tetralogy of Fallot
- Most arrhythmias
- Mild left ventricular dysfunction
- Hypertrophic cardiomyopathy
- Marfan syndrome without aortic dilation
- Bicuspid aortic valve with aortic diameter <45 mm
- Repaired coarctation
- Heart transplantation

Class III (Significant Increase in Maternal Mortality and Severe Increase in Maternal Morbidity)

Expert cardiac and obstetric care is required before pregnancy, antenatally, and postnatally. Women need frequent (monthly or bimonthly) follow-up during pregnancy, both by a cardiologist and an obstetrician.

- Mechanical valve(s)
- Systemic right ventricle
- Fontan circulation
- Unrepaired cyanotic heart disease
- Complex congenital heart disease
- Marfan syndrome with aortic dilation 40–45 mm
- Bicuspid aortic valve with aortic dilation 45–50 mm

Class IV (Pregnancy Is Not Recommended or Is Contraindicated Because of an Extremely High Risk of Maternal Morbidity and Mortality)

Pregnancy termination should be discussed if women are already pregnant, but when they choose to carry on with the pregnancy, their follow-up is similar to that in women with WHO class III.

- Pulmonary artery hypertension of any cause
- Severe left ventricular dysfunction
- Previous peripartum cardiomyopathy with residual left ventricular dysfunction
- Severe mitral stenosis
- Severe aortic stenosis
- Marfan syndrome with aortic dilation >45 mm
- Bicuspid aortic valve with aortic dilation >50 mm
- Severe unrepaired aortic coarctation
- Severe systemic ventricular dysfunction (LVEF <30%)

ASD, Atrial septal defect; *LVEF,* left ventricular ejection fraction; *PDA,* patent ductus arteriosus; *VSD,* ventricular septal defect; *WHO,* World Health Organization.

Modified from Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart.* 2006;92:1520–1525; Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, et al. European Society of Cardiology guidelines on the management of cardiovascular diseases during pregnancy. *Eur Heart J.* 2011; 32:3147–197; and Regitz-Zagrosek V, Gohlke-Bärwolf C, Iung B, Pieper PG. Management of cardiovascular diseases during pregnancy. *Curr Probl Cardiol.* 2014;39:85–151; in Chestnut DH, Wong CA, Tsen LC, et al., eds. *Chestnut's Obstetric Anesthesia: Principles and Practice.* 5th ed. Philadelhia: Saunders; 2014.

Pregnancy and Cardiac Disease

Cardiovascular Physiologic Changes of Pregnancy, Labor, and Delivery

Cardiovascular physiologic changes of pregnancy are summarized in Table 50.4.

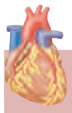
Coronary Artery Disease

The management and treatment goals of coronary artery disease (CAD) in the nonpregnant woman are discussed in Chapter 20. Although the incidence of significant CAD in pregnancy is not known, James and

TABLE 50.4 Cardiovascular Changes in Pregnancy

Variable	*Change-Peaks in the Early Third Trimester (at ≈32 Weeks)*
Blood volume	+35–50%
Plasma volume	+40–45%
Heart rate	+15–20%
Stroke volume	+30%
Cardiac output	+30–50%
Contractility	Variable
Central venous pressure	Unchanged
Pulmonary vascular resistance	−15%
Pulmonary arterial pressure	Unchanged
Pulmonary capillary wedge pressure	Unchanged
Systemic vascular resistance	−15–20%
Systemic blood pressure	−5%
Myocardial oxygen demand	↑
Systolic flow murmur	2/6

Data from Weiner MM, Vahl TP, Kahn RA. Case scenario: cesarean section complicated by rheumatic mitral stenosis. *Anesthesiology.* 2011;114:949–957; and Reimold SC, Rutherford JD. Clinical practice: valvular heart disease in pregnancy. *N Engl J Med.* 2003;349:52–59.



BOX 50.2 FACTORS ASSOCIATED WITH SIGNIFICANTLY INCREASED FETAL MORBIDITY IN WOMEN WITH CARDIAC DISEASE

- NYHA functional class greater than II
- Presence of a mechanical valve prosthesis
- Cyanosis (oxygen saturation < 85%)
- Anticoagulation use during pregnancy
- Multiple gestation
- Smoking during pregnancy
- Aortic or mitral stenosis
- Use of cardiac medications before pregnancy

NYHA, New York Heart Association.

colleagues[23] reported that the incidence of acute MI (AMI) during pregnancy or the postpartum period is 6.2 in 100,000 deliveries, with a 5.1% mortality rate. In that study, the most common time frame for development of AMI was in the third trimester or the immediate postpartum period. Other investigators have reported an incidence of AMI ranging from 3 to 6 in 100,000 deliveries, with a mortality rate of 5% to 37 %.[4,10,24] The rate of fetal death following maternal AMI is approximately 12% to 34%.[24,25]

Myocardial oxygen demand is increased during pregnancy as a result of an increase in HR and preload, whereas myocardial oxygen supply is decreased secondary to a decrease in coronary perfusion pressure, dilutional anemia, and shortening of diastole.[26] This situation presents a challenge to women with known or previously undiagnosed CAD. This challenge becomes greater during labor and delivery and especially immediately after delivery because of further increases in CO. Although CAD in pregnancy is relatively uncommon, the incidence has risen with increasing maternal age and increased risk factors, such as hypertension, diabetes, obesity, and smoking among women of reproductive age.[23,25]

Factors unique to pregnancy may also increase the possibility of MI in women without previous CAD.[27] Investigators have hypothesized that a postpartum degeneration of coronary arterial intima and media leads to an increase in the incidence of coronary artery dissection.[28] Pregnancy-related hypertensive diseases are also associated with an increased incidence of AMI.[27] Additionally, the hypercoagulable state of pregnancy may lead to coronary thrombosis or embolism in women without underlying CAD. Severe postpartum hemorrhage may result in myocardial ischemia,[10] and the use of methylergonovine for postpartum bleeding can cause coronary vasospasm.[9]

The diagnostic principles for myocardial ischemia during pregnancy are the same as for the nonpregnant patient and are based on angina symptoms, changes on the ECG, and increases in cardiac biomarkers (eg, troponin).[9] Creatinine phosphokinase and its MB isoenzyme may not be helpful in the diagnosis of myocardial ischemia during pregnancy because levels of these enzymes are often elevated during pregnancy, especially during labor.[29] The differential diagnosis of chest pain includes common pregnancy symptoms (eg, gastroesophageal reflux disease, nausea and vomiting) musculoskeletal pain, aortic dissection, and preeclampsia.[30]

The hemodynamic goal during an acute coronary syndrome in a gravid patient is to prevent further ischemia by avoiding increases in myocardial oxygen demand or decreases in supply. Medical management is similar to that in nonpregnant patients, with medical therapy consisting of β-blockers for tight HR control and low-dose aspirin, both of which have been found safe and effective in pregnancy.[4] However angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and statins are known teratogens and should be avoided in pregnancy. The preferred approach for women with either acute ST-segment elevation MI (class 1 recommendation) or non–ST-segment elevation MI with risk factors (class IIa recommendation) is percutaneous coronary angiography with intervention and reperfusion through stenting if needed.[9] The radiation exposure to the fetus when shielding is used is minimal, and the benefits outweigh the risks. Clopidogrel should be used only for the shortest duration as possible because of the risk of placental bleeding during pregnancy and the peripartum period, and the use of bare-metal stents is thus preferred over drug-eluting stents.[31]

Coronary artery bypass grafting is rarely needed during pregnancy and is associated with a high fetal mortality rate. In women with non–ST-elevation myocardial ischemia without risk factors, conservative management with medical therapy and watchful waiting can be applied (class IIa recommendation).[9] Women with CAD should have the early institution of neuraxial anesthesia during labor to prevent pain and the increased myocardial oxygen demand that accompanies it.[26] In the case of AMI, labor and delivery should be delayed for at least 2 weeks if possible because the risk of maternal death is significantly increased during this time.[24]

Valvular Heart Disease

A complete discussion of valvular heart disease (VHD), along with its management and treatment, can be found in Chapter 21. The most common causes of VHD in women of childbearing age are rheumatic heart disease and CHD (eg, bicuspid aortic valve), with MS the most common lesion encountered.[32] VHD is a significant cause of maternal cardiac disease because rheumatic heart disease accounts for more than 90% of maternal cardiac disease worldwide. Pregnant women with VHD have an increased incidence of adverse maternal and fetal outcomes,[33] and patients with severe MS form a particularly high-risk group with a reported maternal mortality rate of more than 10% and a cardiac event rate of 67% in some series.[34,35] The most commonly encountered maternal cardiac complications are HF and arrhythmias[36] and the most common fetal complications are prematurity and intrauterine growth retardation.[35]

Women with known VHD before pregnancy should undergo preconception counseling. Guidelines advise against pregnancy for women with moderate or severe MS unless the lesion is corrected before pregnancy. The same is true for women with moderate or severe AS who are symptomatic or have LV dysfunction (class I recommendation).[9] Women at high risk who desire to pursue pregnancy should be managed by a multidisciplinary team in centers with expertise in the management of these patients. The hemodynamic changes of pregnancy can exacerbate mild symptoms. Symptoms tend to worsen with increasing gestational age.[37] The severity of VHD and the prepregnancy NYHA functional class have been found to be the main predictors of

adverse maternal and fetal outcomes.[35,38] In many women with VHD, the disease is first diagnosed during pregnancy when the hemodynamic changes of pregnancy precipitate symptoms.

In general, regurgitant lesions are much better tolerated in pregnancy than are stenotic lesions because the decrease in SVR favors forward flow.[5] In the absence of LV dysfunction, these lesions pose only a minor threat. Symptomatic patients may be treated with diuretic agents and afterload reduction with close monitoring for uteroplacental insufficiency (class I recommendation).[9] Afterload reduction should be provided with nitrates and hydralazine because ACE inhibitors and ARBs are contraindicated in pregnancy.[39] The increase in preload, CO, and HR during pregnancy causes a significant increase in the transvalvular gradient across stenotic lesions.[40] MS also compromises LV filling and increases left atrial pressure (LAP), an increase that is then transmitted to the pulmonary veins.[37] Calculation of mitral valve area by using the pressure half-time technique has been found to be less accurate than the continuity equation during pregnancy (see Chapter 21 for calculations).[41] The decrease in LV filling and the increase in pressure in the pulmonary veins lead to deterioration in functional class, with increased dyspnea, decreased exercise tolerance, and possibly pulmonary edema. Atrial arrhythmias (eg, atrial fibrillation) that result in ventricular rate acceleration are a common cause of worsening symptoms and must be treated aggressively with rate control and possibly cardioversion.[16]

In general, MS is more of a management challenge than AS. In AS, the increase in pressure is reflected initially to the hypertrophied left ventricle, whereas in MS, it affects the pulmonary veins.[40] Women with mild or moderate AS generally tolerate pregnancy well.[39] Medical therapy for stenotic lesions in symptomatic women consists of HR control with β-blockers and restriction of physical activity and preload reduction with diuretic agents (class I recommendation).[9,39] Metoprolol is the preferred β-blocker because atenolol has been linked to adverse fetal outcomes, including intrauterine growth retardation and preterm delivery. HR control leads to improved LV filling and lower LAP. Diuretic use, in particular, must be accompanied by monitoring for signs of uteroplacental insufficiency. Patients with MS or AS whose conditions are refractory to medical therapy may be candidates for percutaneous balloon valvuloplasty, which should be performed with abdominal shielding and delayed until after the first trimester if possible to minimize the radiation risks to the fetus (class IIa recommendation).[9,16] No definitive data are available on transcatheter aortic valve replacement in pregnant patients, but it is likely that this technique will emerge as a viable option in patients with severe AS and hemodynamic decompensation.

Women with valve replacements, particularly mechanical prostheses, are at an increased risk for pregnancy complications and pose a particular challenge because of the risk of valve thrombosis and anticoagulation management. Some investigators consider the presence of a mechanical prosthesis, particularly in the mitral position, a contraindication to pregnancy.[40] Anticoagulation guidelines[9] recommend the continuation of warfarin until 36 weeks of gestational age (class I recommendation), with the possible exception of weeks 6 to 12, because warfarin is teratogenic, when a changeover to either unfractionated heparin or low-molecular-weight heparin may be recommended, particularly if the dose of warfarin is greater than 5 mg/day (class IIa recommendation). After 36 weeks, a changeover to heparin is recommended (class I recommendation). Alternatively, these women can be switched from warfarin to low-molecular-weight heparin from the beginning of pregnancy. These women require weekly monitoring of a postdose anti–factor Xa level (class I recommendation).[9] Investigators had also been concerned that accelerated bioprosthetic valve deterioration occurred during pregnancy, but this has not been borne out in studies.[42]

Pulmonary Hypertension

The incidence of PH in pregnancy is approximately 1.1 in 100,000 pregnancies.[43] The hemodynamic changes of pregnancy are not well tolerated by women with PH.[44] A review of outcomes in pregnant women with PH that covered the years 1978 to 1996 and included 125 pregnancies found an overall mortality rate of 38%.[45] A more recent review covering the years 1997 to 2007 that included 73 pregnancies found a mortality rate of 25%.[46] The risk of maternal morbidity and death in women with PH from any cause makes pregnancy particularly dangerous, and these women should be advised against pregnancy (class III recommendation).[9,26] Those patients who present already pregnant should be offered termination of pregnancy.[10] Death generally occurs in late pregnancy or in the first month after delivery and results from right-sided HF, PH crisis, pulmonary thromboembolism, or arrhythmias.[45,46] Although some evidence indicates better outcomes in women with mild PH (systolic PAP <50 mm Hg), no specific cutoff defines safety.[46,47] Furthermore, PH generally is exacerbated by the physiologic and hemodynamic changes of pregnancy, including increased CO and circulating blood volume and decreased SVR. The vascular remodeling present in women with PH prevents them from compensating with the pulmonary vasodilatory mechanisms of pregnancy that occur in healthy patients.[44] This situation results in increased pulmonary vascular resistance (PVR), overload of the right ventricle, and right ventricular (RV) strain. Even mild forms of PH may become severe.[9,26,43]

When termination of pregnancy is refused and the patient chooses to continue pregnancy, care should be managed in a facility with expertise in high-risk pregnancies and PH management under the care of a multidisciplinary team.[48] Treatment advances and the use of a multidisciplinary team are associated with an improvement in survival.[43] Management during pregnancy involves finding a balance between systemic pressures and PAPs because decreased systemic pressures compromise RV perfusion.[26] Therapy for PH should generally be continued, other than the endothelin-1 receptor blocker bosentan, which is teratogenic in animal studies (class IIa recommendation).[9,43,44] Prostacyclin analogues (eg, epoprostenol), inhaled nitric oxide, and phosphodiesterase-5 inhibitors (eg, sildenafil) have not been found to be teratogenic. Initiating targeted therapies at the beginning of the third trimester is recommended.[44] It is also critically important to avoid conditions that will increase PAPs, including hypoxia, hypercarbia, acidosis, and sympathetic stimulation because they may lead to RV failure.[26] Inotropic support may be needed in the setting of RV failure. Maternal hemodynamic decompensation generally occurs in the second or third trimester and shortly after delivery of the fetus.[26] Early planned delivery, usually at 32 to 34 weeks of gestational age, may have helped contribute to improved outcomes in more recent studies.[44]

Congenital Heart Disease

CHD management in the adult patient is discussed in Chapter 22. CHD has become the most prevalent chronic maternal heart disease during pregnancy, and it accounts for 66% to 80% of cases.[3,36] This change has stemmed from an increased number of patients with CHD living into their childbearing years as a result of advances in surgical repair and palliation procedures.[3] Although many women with CHD tolerate the expected hemodynamic changes of pregnancy, maternal CV complications occur in approximately 5% to 25% of such pregnancies.[20,21,49] The most common complications are HF, thromboembolism, and arrhythmias.

Because CHD is known in most women before pregnancy, preconception counseling with a through risk assessment is indicated. CHD encompasses a wide array of diseases from mild to extremely complex, so the risk of pregnancy varies greatly and also depends on whether the congenital defect has been repaired and whether permanent damage occurred before the repair. Risk increases with higher modified WHO class. Pregnancy should not be discouraged in patients who have had successful surgical repair and who have good exercise tolerance and functional status because these women have only a very small increased risk, provided no mechanical valve has been implanted.[9] Patients who have moderate or complex disease and who choose to continue with pregnancy should be managed in a facility

with expertise in high-risk pregnancies and CHD under the care of a multidisciplinary team.[10]

In the absence of PH, women with repaired shunt lesions, including atrial septal defect, ventricular septal defect, atrioventricular canal defect, and patent ductus arteriosus, tolerate pregnancy well without a significant increase in CV risk.[9] They are, however, at increased risk for preeclampsia.[50,51] Patients with unrepaired shunt lesions have a risk of paradoxical embolism, particularly during labor, when a Valsalva maneuver is employed during the second stage of labor.[3] Patients with unrepaired atrioventricular canal defects are at greater CV risk than patients with either atrial septal defects or ventricular septal defects because severe atrioventricular valve regurgitation or ventricular dysfunction may cause HF during pregnancy. Additionally, if Eisenmenger syndrome develops in patients with unrepaired shunt lesions, the maternal mortality rate increases to 28% to 52%, with a fetal mortality rate of 28%.[46,52,53] The reduction in SVR exacerbates the right-to-left shunt and increases cyanosis, whereas the increase in CO leads to HF.[3] Severe cyanosis (oxygen saturation <85%) makes the chance of a live birth extremely unlikely.[9] Management goals include maintenance of SVR and PVR with strict avoidance of hypoxia, acidosis, hypercarbia, and sympathetic stimulation.[3]

Women who have unrepaired cyanotic heart disease, such as tetralogy of Fallot, should be counseled against pregnancy because these pregnancies have a maternal complication rate greater than 30%.[53] Complications include HF, thromboembolism, and arrhythmias. When maternal resting oxygen saturation is less than 85%, the maternal risk is extremely high, and the chance of a live birth is only 12%.[53] Such women should be advised against pregnancy (class III recommendation).[10] Women with corrected tetralogy of Fallot generally tolerate pregnancy fairly well, with cardiac complications (eg, arrhythmias and HF) reported in up to 12% of patients.[54] Risk factors for complications are preexisting RV dysfunction or dilation, PH, severe pulmonic valve regurgitation, and RV outflow tract obstruction.[10]

The presence of a systemic right ventricle is independently associated with adverse maternal and pregnancy outcomes. This phenomenon is present in patients with congenitally corrected transposition of the great arteries, following an atrial switch operation for complete transposition of the great arteries (ie, Mustard or Senning procedures), or in hypoplastic left heart syndrome with Fontan physiology.[3,55] These patients are at increased risk for HF and life-threatening arrhythmias. Women with severe RV dysfunction or severe atrioventricular valve regurgitation, or those who have NYHA functional class III or IV, should be counseled against pregnancy (class III recommendation).[3,10] Women with Fontan physiology may experience deterioration in functional status. Hemodynamic goals include the maintenance of pulmonary blood flow by minimizing PVR and maintaining intravascular volume, SVR, and sinus rhythm.[3]

Management of Labor and Delivery in Women With Cardiac Disease

Importance of Multidisciplinary Planning

The period of labor and delivery is a critical time for women with heart disease because abrupt hemodynamic changes make decompensation more likely.[39] Uterine contractions, pain, anxiety, and exertion from pushing further increase HR, blood pressure, and LAP, thus stressing an already compromised CV system.[40] CO increases steadily from 15% in early labor to 50% to 60% (approximately 11 L/min) during pushing efforts to an 80% increase in the immediate postpartum period because of the relief of inferior vena cava obstruction.[56–58] Furthermore, each uterine contraction increases CO by 20% by autotransfusing blood into the central blood volume.[59] This process can result in HF and acute pulmonary congestion. As a result, the management of labor and delivery requires a skilled collaborative effort that includes a multidisciplinary team of cardiologists, obstetricians, anesthesiologists, and, for the highest-risk patients, a cardiac surgical team with availability of cardiopulmonary bypass[9] (Box 50.3).

BOX 50.3 QUESTIONS FOR THE MULTIDISCIPLINARY TEAM TO ADDRESS

- What is the best timing for delivery?
- What should be the mode of delivery?
- What is the optimal location for delivery (labor and delivery suite, cardiac operating room)?
- Should a cardiac surgeon and cardiopulmonary bypass capabilities be on standby?
- When should the mother be admitted for predelivery optimization and possible antenatal corticosteroid administration?
- Is any further diagnostic testing necessary?
- What type of anesthesia or analgesia should be planned for the patient?
- What type of monitoring should be employed?
- Where will the patient be monitored after delivery? For how long?
- Which oxytocic drugs will be given?
- What is the contingency plan if the mother presents urgently in labor or in acute decompensation?
- Should any other specific needs, precautions, or concerns be addressed?

Delivery should generally be planned so the team can be present, rather than allowing spontaneous labor. The timing of delivery should be individualized because prospective data are lacking and individual patients' characteristics influence the decision.[9] Women with complex cardiac lesions, severe HF, or severe PH often require an early, planned delivery before maternal and fetal decompensation.[11]

Mode of Delivery

The mode of delivery depends on both the obstetric indications and the maternal hemodynamic status.[11] If a decision is made that the delivery must take place significantly before term as a result of deteriorating maternal cardiac status, then a cesarean delivery will be necessary because induction of labor will likely be unsuccessful. For women who are able to continue the pregnancy to term, the guidelines of the European Society of Cardiology[9] favor vaginal delivery because it poses less cardiac risk, given that it is associated with less blood loss and fluid shifts and also has a decreased risk of venous thrombosis.[60] Studies have shown that vaginal delivery is well tolerated by most women with cardiac disease.[11,33,61–63] Vaginal delivery can be assisted by vacuum or forceps to shorten the second stage of labor and minimize maternal pushing efforts and Valsalva maneuvers, thus avoiding further increases in CO in women who will not be able to tolerate the hemodynamic challenge.[61] Cesarean delivery is generally reserved for obstetric indications.[9,63] In certain situations, however, vaginal delivery should be strongly considered (Box 50.4). These include women in severe HF, those taking oral anticoagulants (because of the risk of neonatal intracranial bleeding), and patients in whom the stress of labor and delivery puts them at greater risk for aortic dissection (eg, Marfan syndrome with an aortic diameter >40–45 mm).[9] Furthermore, some clinicians favor cesarean delivery for women with severe stenotic valvular lesions, severe PH, poor functional class, and acute HF.[9] The trend has tilted in favor of cesarean delivery because it is believed to allow greater control of both timing of delivery and hemodynamic status.

The choice of uterotonic agents is also important in these patients. Most women are able to tolerate a slow intravenous infusion of oxytocin post partum to prevent maternal hemorrhage.[11] Studies suggest that small doses of oxytocin are as effective as larger doses.[64] However, oxytocin causes an increase in PVR and tachycardia.[65] Methylergonovine should be avoided in most women with significant cardiac disease

BOX 50.4 CONDITIONS IN WHICH CESAREAN DELIVERY SHOULD BE STRONGLY CONSIDERED

- Planned early delivery in which induction is unlikely to succeed
- Acute or severe heart failure, poor functional class
- Severe mitral or aortic stenosis
- Severe pulmonary hypertension
- Aortic dilation >40–45 mm in Marfan syndrome
- Women receiving anticoagulation secondary to risk of fetal intracranial hemorrhage

because of the risk of coronary vasoconstriction and both systemic hypertension and PH.[66–68] Carboprost can also cause both systemic hypertension and PH and should be avoided.[69] Furthermore, although misoprostol (administered either sublingually or rectally) has no known cardiac side effects, its efficacy as a uterotonic agent is not clear.[70,71] Conversely, the avoidance of these medications is also not without risk because maternal hemorrhage and the concomitant need for rapid infusion of fluid and blood products are also poorly tolerated in these women.

Anesthetic Options and Monitoring

Anesthetic options differ, depending on mode of delivery, the specific cardiac disease, and the patient's functional status. Controlled studies or standards to guide the practitioner regarding the optimal anesthetic techniques for women with heart disease are lacking.[72] An understanding of the specific cardiac disease and its severity, along with knowledge of the hemodynamic goals, guides the optimal choice of individualized anesthetic techniques.[72,73] The use of neuraxial anesthesia techniques for women receiving anticoagulation must conform to guidelines of the American Society of Regional Anesthesia.[74]

For women who will be undergoing labor, the early institution of analgesia is recommended to decrease sympathetic stimulation secondary to pain that would in turn increase HR and CO. Continuous lumbar epidural analgesia with a low dose of local anesthetic along with an opioid (eg, bupivacaine 0.0625% with fentanyl 2 μg/mL) provides excellent analgesia, with attenuation of the increases in HR and CO with minimal changes in SVR. The addition of an opioid to the local anesthetic solutions enhances the quality of the analgesia without increasing the sympathetic blockade.[73] This regimen can be supplemented with the use of a short-acting β-blocker (eg, esmolol), if needed.[37] Careful titration providing a slow onset of sympathetic blockade enables tighter control over hemodynamic changes.[73] Epidural blockade, however, even with the use of low concentrations of local anesthetic, still reduces SVR. The resultant hypotension, decreased cardiac preload, and reflex tachycardia may be poorly tolerated in women with MS or AS, CAD, PH, or severe HF. A decrease in SVR in women with an intracardiac shunt also has the potential to reverse the direction of flow, thus leading to decreased pulmonary blood flow and hypoxemia. Careful titration and close monitoring are necessary to avoid these complications.[72] Hypotension should be aggressively treated with vasopressor, and HF should be aggressively treated with inotropic support.[26] Patients who are particularly at risk for decompensation and HF may benefit from the prophylactic institution of an inotropic infusion (eg, dobutamine 2–3 μg/kg per min) to prevent HF in the presence of autotransfusion and other changes associated with delivery.

Although women who are critically ill generally undergo cesarean delivery, if labor is chosen, the use of neuraxial opioids without local anesthetics will provide analgesia without any decrease in SVR and thus avoid CV effects.[75] This technique can be accomplished with the use of a continuous spinal technique because epidural analgesia typically requires some local anesthetic agent to provide analgesia.[76] Women with uncorrected tetralogy of Fallot, severe PH, and severe hypertrophic cardiomyopathy may be unable to tolerate any decrease in SVR or cardiac preload, so neuraxial blockade should be used with extreme caution.[72] Invasive monitoring of arterial pressure, central venous pressure, and PAP are reserved for women who have poor functional status or who have severe valvular stenosis or other hemodynamically significant lesions.[73] If instituted, invasive hemodynamic monitoring should be continued into the postpartum period because the large intravascular volume shifts may precipitate pulmonary edema following an otherwise uneventful delivery.[40]

Anesthetic options for women undergoing cesarean delivery include neuraxial and general anesthesia. The advantages of regional anesthesia include an attenuation of sympathetic-mediated increases in HR and CO and minimal alteration in hemodynamics when the doses are carefully titrated. It also avoids the abrupt changes in hemodynamics associated with induction of general anesthesia, laryngoscopy, tracheal intubation, and extubation, although these changes can be blunted with suitable pharmacologic agents, such as intravenous opioids or β-blockers.[73]

General anesthesia has the advantage of airway control and the potential to use TEE monitoring for real-time assessment of cardiac function and volume status.[5,26] Care must be taken to avoid situations that will increase PVR, including hypercarbia, hypoxemia, hypothermia, and sympathetic stimulation.[26] Women who are in the highest risk category should be seen ante partum by a cardiac surgeon, and preparation for lifesaving cardiac support (eg, extracorporeal membrane oxygenation or ventricular assist device) should be available during the cesarean delivery in case maternal decompensation occurs.

If general anesthesia is chosen, it is particularly important that an adequate depth of anesthesia be maintained throughout the intraoperative period to avoid tachycardia and hypertension.[5] Large concentrations of volatile anesthetic agents should be avoided, to prevent uterine atony. A high-dose opioid technique is associated with stable hemodynamics, but it can cause fetal respiratory depression. This effect can be minimized with the use of a short-acting opioid, remifentanil, which does cross the placenta, but its effects are short-lived.[5,63] Although standard monitoring according to the American Society of Anesthesiologists (ASA), including noninvasive blood pressure, ECG, and pulse oximetry, is usually adequate for vaginal delivery, cesarean delivery often requires more invasive monitoring for tight hemodynamic control. Most patients require invasive arterial blood pressure monitoring. Central venous and pulmonary artery catheter monitoring is reserved for critically ill patients and for women who are likely to need vasoactive medications.[77] The hemodynamic perturbations of delivery continue into the postpartum period, so monitoring should continue for at least 48 hours in an intensive care unit.[11,63] Cardiac status takes 2 to 6 weeks post partum to gradually return to baseline.[37]An algorithm for the anesthetic care of these patients is presented in Fig. 50.1.

Noncardiac Surgical Procedures During Pregnancy in Women With Cardiac Disease

Nonobstetric operation during pregnancy is one of the few times that the anesthesiologist must care for two patients simultaneously, with sometimes conflicting goals. When the mother has significant cardiac disease, the risks are even greater. Preoperatively, the anesthesiology team should be in close communication with the patient's cardiologist and obstetrician as part of a multidisciplinary perioperative planning team. A multidisciplinary intraoperative team should include the anesthesiologist, primary proceduralist, obstetrician, neonatologists, and two teams of surgeons: one for the mother and another for the baby in case a cesarean delivery is required. It is self-evident that all nonurgent operations should be delayed until after delivery. Furthermore, any patient requiring a procedure should be managed in a specialized

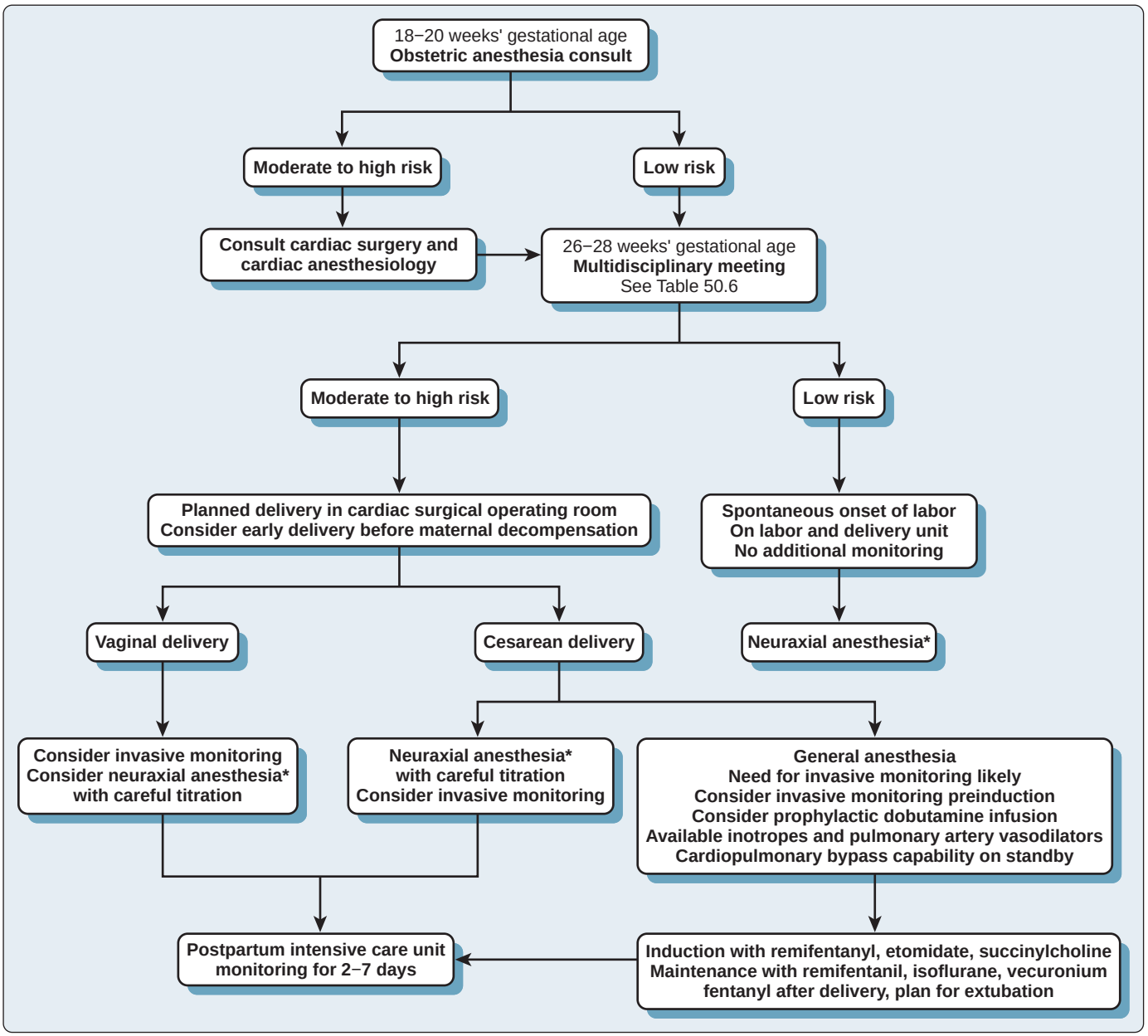


Fig. 50.1 Anesthetic algorithm for the parturient patient with cardiac disease. *Guidelines put forth by the American Society of Regional Anesthesia must be strictly followed.

center with the expertise and capability to care for the mother with cardiac disease and its possible consequences and also to be prepared for urgent delivery and subsequent care of the fetus.

Maternal and Fetal Risks

Between 0.75% and 2% of pregnant woman will require nonobstetric surgical procedures during their pregnancy.[78–80] Appendectomy is the most common operation, with a reported incidence of 1 in 1440 to 1 in 6600 deliveries.[81–83] As the number of pregnant women with heart disease increases, some of these women may also require nonobstetric surgical procedures. In a metaanalysis that included 44 studies of nonobstetric operations during pregnancy from 1966 to 2002, Cohen-Kerem and associates[84] found that perioperative maternal death in healthy women is extremely rare, at 0.006%. The miscarriage rate was 5.8% overall and 10.2% during the first trimester. Third trimester operations were associated with a high rate of preterm delivery.[79] Although it has not been specifically studied, when a pregnant woman with significant cardiac disease requires surgical treatment, both mother and fetus are likely even at a greater risk, the extent of which depends on the specific cardiac disease, its interaction with the hemodynamic changes of pregnancy, and its interaction with the hemodynamic changes caused by the surgical procedure and anesthesia.

Maternal and Fetal Monitoring

Patients with significant cardiac disease require increased monitoring during surgical procedures. This monitoring may include invasive arterial pressure, central venous pressure, or PAP monitoring and TEE, depending on the specific cardiac lesion, operation, and planned anesthetic technique. Patients with poor functional status and operations that involve large fluid shifts require the greatest amount of monitoring. Specific monitoring requirements for different cardiac diseases are found in earlier chapters.

The fetal HR (FHR) should be monitored, if at all possible.[85–87] It is the best way to ensure maintenance of a normal physiologic milieu

for the baby. This is even more important in women with significant cardiac disease because the fetus is at greater risk, given the decreased CO and hypotension leading to uterine hypoperfusion. Monitoring and interpretation should be performed by an obstetrician or someone other than the anesthesiologist, with expertise in FHR interpretation. Regardless of the decision to perform intraoperative FHR monitoring, the FHR and uterine contractions should be monitored before and after the surgical procedure.

Anesthetic Considerations

The anesthetic plan should focus on optimizing the mother's cardiac condition while protecting the developing fetus. A complete discussion of anesthetic considerations for the pregnant woman undergoing nonobstetric surgical procedures is beyond the scope of this chapter. Focused situations with specific considerations for the pregnant woman with cardiac disease are presented.

Organogenesis is complete by week 8, and it is therefore prudent to delay surgical procedures until after this critical period of development. None of the anesthetic agents are known teratogens, and the incidence of congenital defects is not greater following surgical procedures with either general or neuraxial anesthesia.[88] Although the risk of spontaneous abortions in the first and second trimester is increased when mothers undergo surgical procedures, it is not possible to determine which is the cause: the pathophysiologic condition requiring surgical treatment, the surgical procedure itself, or the anesthetic regimen.[80,88,89] The basic principles when anesthetizing the woman are to optimize uteroplacental blood flow by optimizing CO and avoiding hypoxia, hypercarbia, acidosis, and hypotension.

In the healthy parturient patient, uterine blood flow (UBF) is primarily determined by the perfusion pressure, which is directly related to maternal arterial pressure. Conditions that reduce maternal arterial pressure decrease uterine perfusion pressure. These conditions include the following: hypovolemia, which can be relative from sympathetic blockade or actual from hemorrhage; myocardial depressants, such as general anesthetic agents; and mechanical obstruction secondary to aortocaval compression by the gravid uterus. Decreases in UBF from aortocaval compression can be prevented by tilting the mother to the left.

In women with heart disease, uterine perfusion pressure is at risk of being compromised. In low-CO states such as systolic HF or critical AS, the UBF may be compromised by diversion of blood to critical organs. With right-sided HF or PH, the normally low-pressure venous system may become congested so that forward flow to the uterus can be compromised.

An increase in uterine vascular resistance can also decrease UBF. This can occur during anesthesia as a result of catecholamine release or initiation of vasopressors. The most common agents used in healthy parturient patients are phenylephrine and ephedrine. Although earlier studies recommended using a mixed agonist, such as ephedrine, to prevent increased uterine vascular resistance from unopposed α-blockade,[90] later studies indicated that not only is phenylephrine a safe choice, it may be a better choice because ephedrine causes fetal tachycardia that can lead to fetal acidosis.[91,92] The effects of epinephrine and norepinephrine on UBF and outcome have not been fully elucidated. However, the danger of not initiating vasopressor and/or inotropic support in a woman who needs it is great. Therefore, the use of these agents should be instituted as required.

Severe hypoxia and hypercarbia also decrease UBF,[93] whereas even mild hypoxia and hypercarbia directly affect the oxygen tensions and acid-base status of neonatal blood. Supplemental oxygen and end-tidal carbon dioxide monitoring should always be used when sedating this patient population.

The choice of regional or general anesthesia should depend on the type of cardiac disease and the extent of operation. In the patient without heart disease, no evidence indicates that one technique is superior to the other with regard to either maternal or neonatal outcomes.[80,94,95] However, neuraxial techniques may be relatively contraindicated or require very careful titration in some cardiac disease states.

Laparoscopic surgical procedures are safe during pregnancy,[96–98] but patients with cardiac disease may be less able to tolerate the reduced preload or the rise in carbon dioxide partial pressures from insufflation. For healthy patients, the Society of American Gastrointestinal and Endoscopic Surgeons recommends maximizing UBF with left uterine displacement, lowering insufflation pressures to no more than 10 to 15 mm Hg, and monitoring maternal end-tidal carbon dioxide to avoid acidosis.[99] These recommendations help in women with cardiac comorbidities as well.

Glycopyrrolate is commonly given in conjunction with neostigmine for reversal of nondepolarizing neuromuscular agents to prevent anticholinesterase-induced bradycardia or asystole. However, as a quaternary amine, glycopyrrolate does not readily cross the uteroplacental barrier, whereas neostigmine does, and this may lead to iatrogenic fetal bradycardia. Therefore some anesthesiologists prefer to use atropine, which does not cross the placenta. The tachycardic effects of atropine must be considered in women with cardiac disease.

Peripartum Cardiomyopathy

Definition

Although the occurrence of HF in pregnant and postpartum women has been described since the late 1800s, the unique disease entity, peripartum cardiomyopathy (PPCM) (Table 50.5), was first defined in the 1970s by Demakis and Rahimtoola[100] on the basis of three criteria. These criteria are (1) the development of idiopathic life-threatening cardiomyopathy that (2) begins in the last month of pregnancy or within the first 5 months post partum and (3) occurs in patients without recognizable preexisting heart disease.[101] The importance of the timeline provided in the definition was emphasized to exclude other acquired preexisting causes of cardiomyopathy, which may be unmasked earlier in pregnancy (second trimester) in response to CV changes of pregnancy. PPCM is a distinct form of cardiomyopathy resulting from pregnancy, not an exacerbation of underlying idiopathic dilated cardiomyopathy.[102–104]

The Demakis definition was updated, and strict echocardiographic criteria for recognition of LV dysfunction were added by the National Heart, Lung, and Blood Institute and the Office of Rare Diseases (National Institutes of Health) workshop.[105] An LV ejection fraction

TABLE 50.5 Peripartum Cardiomyopathy

Definition	*Echocardiographic Criteria*	*Possible Causes*	*Risk Factors*
Idiopathic	Left ventricular ejection fraction <45% or M-mode fractional shortening <30% or both	Oxidative stress	Multiparity Advanced maternal age Multifetal pregnancy Preeclampsia African American race Prolonged use of tocolysis Family history
No recognizable heart disease	Left ventricular end-diastolic dimension >2.7 cm/m^2	Autoimmunity	
Occurs in the last month of pregnancy or in the first 5 months post partum[a]		Inflammatory conditions	
		Myocarditis	

[a]The Working Group on Peripartum Cardiomyopathy from the Heart Failure Association of the European Society of Cardiology removed time frames from the definition because they believe that they are arbitrary and lead to underdiagnosis.

(LVEF) of less than 0.45 or M-mode fractional shortening of less than 30% (or both) and end-diastolic dimension greater than 2.7 cm/m^2 are required to meet the definition. The Working Group on PPCM from the Heart Failure Association of the European Society of Cardiology redefined PPCM because the investigators believed that the time frames provided in the original definition were arbitrary and led to underdiagnosis.[101] This Working Group defined PPCM as idiopathic cardiomyopathy, manifesting with HF secondary to LV systolic dysfunction toward the end of pregnancy or in the months following delivery, for which no other cause is found and in which LVEF is reduced to less than 45%, but the left ventricle is not always dilated. The Working Group further emphasized that PPCM is a diagnosis of exclusion.

Incidence

PPCM is a relatively rare disease, with an estimated incidence of less than 0.1% of pregnancies,[106] although the incidence varies according to race and geographic region. The actual incidence of PPCM is unknown because most studies have been single-center case series. Estimates of the incidence from case series range from 1 in 1485[107] to 1 in 15,000.[108] The National Hospital Discharge Survey was the first population-based study of PPCM. This survey assessed all births in the United States from 1990 to 2002 and found the incidence of PPCM to be approximately 1 in 3200 (2.5 in 10,000 live births).[109] Therefore, 1000 to 1300 cases occur annually in the United States.[110]

The incidence varies worldwide and is highest in developing countries; the highest incidence of PPCM is in Haiti, with 33 cases in 10,000 (1 in 300) live births, and in South Africa, where 1 case in 1000 live births is reported.[2,111,112] Investigators have speculated that the regional disparities may reflect environmental or genetic factors and different standards of perinatal care.[113] A higher incidence of disease is found among African American woman, even in the United States, who are 3- to 16-fold more likely to be diagnosed with PPCM.[6] No information is available regarding the incidence of PPCM in Europe.[114] A prospective, international, multicenter registry of patients who meet criteria for PPCM is ongoing.[115]

Risk Factors

Risk factors for PPCM include multiparity (parity of four or greater),[102,116,117] advanced maternal age (>30 years old),[117–119] multifetal pregnancy,[119,120] preeclampsia, gestational hypertension,[105,109] HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome,[2] and African American race.[117,121] The prolonged use of tocolysis has also been associated with development of PPCM.[122] Other risk factors include hypertension, diabetes, smoking,[123] and severe anemia.[117] A genetic susceptibility also appears to exist because some cases of PPCM have been found among patients with a family history of dilated cardiomyopathy.[124,125]

Etiology

The pathophysiology of PPCM is not well understood. Several causes have been proposed[126]:

1. Oxidative stress: The most recent hypothesis is that PPCM develops as a result of oxidative stress caused by an imbalance between the production of reactive oxygen species and the biologic system's ability to detoxify them. This oxidative stress enhances activity by the protease cathepsin-D, which leads to increased cleavage of the hormone prolactin, thus resulting in an N-terminal 16-kDa prolactin fragment (also called vasoinhibin), which is a potent antiangiogenic, proapoptotic, and proinflammatory factor. This process leads to massive endothelial damage, capillary dissociation, vasoconstriction, and myocardial dysfunction.[127,128] Consistent with these findings, a novel specific therapeutic approach through inhibition of prolactin secretion by bromocriptine, a dopamine D_2-receptor agonist, prevented the development of PPCM in an animal model of PPCM, and the first human clinical experience yielded promising data for survival and improvement of LV function.[129,130] Multicenter, randomized trials are necessary to confirm these findings and establish bromocriptine's safety profile in pregnancy before broader clinical adoption.[130]
2. Autoimmunity: In a phenomenon called fetal microchimerism, cells from the fetus take up residence in the mother and provoke a cardiotoxic autoimmune component.[131] High titers of autoantibodies against all types of cardiac tissue proteins have been found in most women with PPCM.[132–134] Treatment of PPCM with therapies proven successful in graft versus host disease and organ rejection may be useful.[131]
3. Inflammatory process: Proinflammatory serum markers, such as tumor necrosis factor-α, sFas/Apo1 (a plasma marker of apoptosis), C-reactive protein, interferon-γ, and interleukin-6, have been found to be significantly elevated in women with PPCM.[135,136] This mechanism is supported by the survival benefit observed in a small cohort study of the antiinflammatory agent pentoxifylline in a nonrandomized trial in 58 patients with PPCM.[137]
4. Myocarditis: Myocarditis has been found in the endomyocardial biopsy specimens of the right ventricle of women with PPCM, although the range has been 8.8% to 78% in different studies.[134,138–140] Immunosuppressive drug therapy should be considered when active myocarditis has been confirmed by endomyocardial biopsy.[141]

Clinical Presentation and Diagnosis

Fewer than 10% of cases of PPCM occur at the end of pregnancy,[107] whereas 78% of cases manifest in the first 4 months post partum.[106] The diagnosis of PPCM requires a high index of suspicion because symptoms of PPCM can be confused with the physiologic changes of pregnancy and the early postpartum period. Consequently, women with PPCM generally have a relatively late diagnosis, when they already have NYHA functional class III or IV, which is possibly associated with higher rates of morbidity and death.[2,6,142]

Most patients present with signs and symptoms similar to those of other forms of HF and reflect reduced CO resulting in tissue hypoperfusion and pulmonary edema from congestive HF.[143] These manifestations include dyspnea on exertion, cough, orthopnea, hemoptysis, and paroxysmal nocturnal dyspnea. Additional symptoms include nonspecific fatigue, malaise, palpitations, chest (pleuritic chest pain can be presenting symptoms of pulmonary embolism) and abdominal discomfort (secondary to hepatic congestion), and postural hypotension.[6,102]

On physical examination, signs of HF may be present, including tachycardia, displacement of the apical impulse, presence of an S_3 third heart sound, and evidence of mitral or tricuspid regurgitation. Elevated jugular venous pressure, pulmonary rales, hepatomegaly, and pedal edema may also be present.[2,6,103] Women may have difficulty lying flat.[6]

The differential diagnosis of suspected PPCM includes malignant hypertension, diastolic dysfunction, sepsis, pulmonary embolus, and obstetric complications (eg, preeclampsia, eclampsia, and amniotic fluid embolism).[103]

If PPCM is suspected, a complete blood count, electrolyte determinations, liver function tests, C-reactive protein, arterial blood gases, and troponin levels should be performed.[106] Disease-specific biomarkers include prolactin and factors involved in the prolactin cleavage pathway.[143] Levels of BNP and N-terminal pro-B-type natriuretic peptide can help in confirming the diagnosis.[106,136]

Findings on an ECG may be normal or may show sinus tachycardia and nonspecific ST-segment and T-wave abnormalities, conduction abnormalities such as prolonged PR and QRS intervals, and LV hypertrophy. A chest radiograph often shows cardiomegaly, pulmonary venous congestion, and sometimes pulmonary edema and pleural effusion. An echocardiogram is the key to diagnosis and shows moderate-to-severe LV systolic dysfunction. Doppler evaluation may show moderate-to-severe mitral and tricuspid valve regurgitation and PH.[106,114]

Outcomes and Predictors of Recovery

PPCM is a potentially life-threatening condition,[142] accounting for up to 11% of maternal deaths.[6] It has a highly variable clinical course because rapid progression to end-stage HF may occur within days, and spontaneous and complete recovery may also occur.[102,105] Recovery from PPCM is defined as recovery to an LVEF greater than 50% or improvement by 20%. End-stage HF is seen in 10% to 23% of patients, and recovery to an LVEF greater than 50% is seen in 35% to 50% of patients.[2,144,145]

Several factors have been associated with recovery or nonrecovery. Predictors of recovery include white race, LVEF greater than 30%, LV end-diastolic diameter less than 5.5 cm, and postpartum diagnosis.[146–148] Factors associated with lack of recovery are an LV end-diastolic dimension greater than5.6 cm, LVEF less than 30%, the presence of LV thrombus, and African American race.[126,143,145]

Recovery usually occurs between 2 and 6 months post partum, but it may occur as late as 48 months post partum. Delayed diagnosis, greater NYHA functional class, African American race, LV thrombus, multiparity, and coexisting medical illnesses are associated with delayed recovery.[145,149]

The mortality rate in women with PPCM seems to be decreasing as the treatment for HF has improved. The risk increases with older age, LVEF less than 25%, multiparity, African American ethnicity, and delayed diagnosis.[114] The estimated mortality rate of PPCM in the United States varies significantly in different series, ranging from 0% to 16.5%.[109,126,140,142,145,150]Worldwide, mortality rates range from 1.4% to 32%.[143,151,152] Race, ethnicity, and environmental differences, as well as access to medical care, may be responsible for the varying results in different studies.[153]

Although only a few studies have reported on subsequent pregnancies of women with a history of PPCM, the risk of PPCM in a subsequent pregnancy seems to be elevated, particularly if the LVEF has not recovered to baseline. Almost 50% of such women were reported to have had HF during or following the subsequent pregnancy.[154] In general, the severity of PPCM in a subsequent pregnancy increases.[154,155] Any woman with an LVEF of less than 25% at previous diagnosis or whose LVEF has not normalized should be advised against a subsequent pregnancy (class III recommendation).[9] All patients should be informed that pregnancy can have a negative effect on cardiac function, and development of HF and death may occur.[156]

Management During Pregnancy, Labor and Delivery, and Post Partum

Because of its setting in the peripartum period, PPCM requires a well-coordinated multidisciplinary approach that involves obstetricians, cardiologists, perinatologists, neonatologists, anesthesiologists, and cardiac surgeons to manage a pregnant woman with HF.[6,105,113] Both HF and its treatment in PPCM may result in placental insufficiency, leading to intrauterine fetal death or premature birth.[2] If the patient's condition can be stabilized with medical therapy, continuation of pregnancy to allow for fetal maturity may be possible with close monitoring.[114,143] If the mother's condition deteriorates, however, urgent premature delivery with timely use of corticosteroids for fetal lung maturation should be discussed to rescue both mother and child.[2] Termination of pregnancy often results in improvement of both symptoms and cardiac function and should be considered in patients with worsening symptoms or cardiac function.[114]

The medical management of PPCM is similar to that of other types of HF that focus on reducing preload and afterload and increasing cardiac inotropy (class I recommendation).[9] The treatment varies if the patient is still pregnant or is post partum because the medication safety profiles during pregnancy or lactation must be considered, and medication side effects must be closely monitored and managed.[106] The first aim is to improve symptoms, and the second is to attempt to manage the disease through the administration of targeted therapies.[106] Rapid treatment may be necessary when the patient has pulmonary edema or is hypoxemic. When women with PPCM have hypotension, worsening HF, altered mental status, and increased work of breathing, they should be treated in the hospital.[106] Medications should be continued until LV dysfunction is improved or resolved.[106]

Acute symptomatic management of PPCM should consist of with oxygen and HF medications, mainly β-blockers, afterload-reducing agents such as ACE inhibitors or ARBs, with the addition of loop diuretic agents if necessary.[2,106]

β-Blockers (eg, metoprolol and carvedilol) have been approved for use in PCCM, are considered safe for use during pregnancy, and have been shown to improve survival.[106] These drugs are also crucial for long-term management of systolic dysfunction, if present.[106] β_1-Selective blockers, such as metoprolol or carvedilol, are preferred over nonselective β-blockers, such as propranolol, to avoid the antitocolytic action induced by β_2-receptor blockade.[157] Carvedilol combined with an afterload-reducing agent has been shown effective in PPCM.[105] Newborns born to mothers taking β-blockers are at risk for bradycardia, hypoglycemia, and respiratory depression and these infants should to be monitored for 48 to 72 hours.[6]

ACE inhibitors and ARBs are considered first-line drugs for HF management and have been shown to improve survival.[158–160] These drugs are contraindicated in pregnancy, however, because of their teratogenicity; they may cause oligohydramnios, renal agenesis, and fetal death.[6] These medications are the mainstays of treatment of PPCM after delivery for afterload reduction.[106] They are secreted in breast milk, so breastfeeding must be stopped before commencing therapy.[105] Prenatally, the preferred afterload reduction agent is hydralazine. Patients with more severe cases require intravenous nitroglycerin. Nitroprusside is not recommended because of the potential for cyanide toxicity (see Chapter 11).[113]

Diuretic agents are used to treat symptomatic volume overload, including pulmonary congestion and peripheral edema. Both hydrochlorothiazide and furosemide are safe during pregnancy and lactation. However, the benefit of symptomatic relief must be weighed against the risk of diuretic-induced reduction in intravascular volume that can result in uteroplacental hypoperfusion.[106] For patients taking furosemide, fetal amniotic fluid volume should be measured regularly.[6] Although the potassium-sparing diuretic spironolactone has been used successfully to treat HF, data on its use during pregnancy are insufficient.[106,113]

The use of inotropic agents, such as epinephrine, dobutamine, or milrinone, should be confined to patients severely low CO and those with congestion that persists despite optimal medical therapy with vasodilators and diuretics. The patient should be weaned from these agents as soon as she is hemodynamically stable, adequate organ perfusion is restored, and congestion is reduced.[143]

When inotropes are insufficient to restore CO or in patients who present in cardiogenic shock, temporary circulatory support with an intraaortic balloon pump, extracorporeal membrane oxygenation, or implantation of an LV assist device as a bridge to recovery or even as a bridge to heart transplantation is necessary.[2,143] After clinical and echocardiographic evidence of recovery of cardiac function is observed, weaning from the device may be attempted.[143] Bridging to recovery with an LV assist device has helped to dramatically decrease the percentage of PPCM patients requiring cardiac transplantation (see Chapter 28).[2] However, if attempted weaning from the device is unsuccessful, transplantation should be considered.[143] A large study[161] showed that transplant rejection and graft failure were more likely in patients with PPCM compared with other transplant recipients.

HF[162] and pregnancy[163] are independent risk factors for thromboembolism. Therefore, although the incidence of thromboembolic complications in pregnant women with cardiomyopathy is not known, therapeutic anticoagulation is recommended in patients with PPCM, particularly if the LVEF is less than 35%.[2,6] The administration of heparin or low-molecular-weight heparin during pregnancy and post partum is recommended.[6,164] Warfarin is teratogenic and should

be avoided during pregnancy. Warfarin is considered safe during breastfeeding.[6]

Ventricular arrhythmias have been reported in up to 20% of patients with PPCM. At least one-fourth of deaths in PPCM are presumed to be sudden cardiac deaths caused by malignant ventricular arrhythmias.[135] However, no recommendations exist regarding the need for implantation of an implantable cardioverter-defibrillator for primary prevention. The decision on device implantation is particularly difficult in patients with PPCM because many patients experience an improvement in LV function within the first few months after delivery. Temporary use of a wearable defibrillator should be considered until a final decision is made.[165]

No randomized trials or large cohort studies have addressed the timing and mode of delivery in PPCM or its anesthetic management. It should be a multidisciplinary decision that depends on the clinical status of the mother and the unborn child.[114] A plan for the mode of delivery, type of anesthesia, and need for any invasive hemodynamic monitoring should be identified before the commencement of labor.[6] The use of invasive hemodynamic monitoring before labor and delivery allows for optimization of the hemodynamic status before delivery and for monitoring during and after the delivery.[114,143]

Labor is best accomplished in an institution with experience in managing pregnancies with cardiac disease, and labor should be induced at a time when all necessary medical and surgical teams are present in the hospital.[6] Labor and delivery produce hemodynamic challenges, including increased CO, and blood loss.[143] Women must be carefully monitored during labor, delivery, and the postpartum period. In addition to continuous ECG monitoring, continuous pulse oximetry, and noninvasive blood pressure monitoring, the use of an arterial catheter for continuous blood pressure monitoring and a central venous catheter in anticipation of the need for inotropes and vasopressors should be considered, particularly in women at high-risk for decompensation.[6] In general, medications such as β-blockers should be continued, whereas diuretics and vasodilators should be continued or discontinued on an individual basis. Vaginal delivery is preferred in patients in stable condition. Aggressive pain management is pivotal for controlling HR and SVR.[114,143] Nevertheless, an elective planned cesarean delivery is preferable to better control hemodynamic fluctuations for women who are critically ill and in need of inotropic therapy or mechanical support.[143] Furthermore, a cesarean delivery will be necessary if a preterm delivery is necessary because inducing labor will likely be unsuccessful.

Anesthetic technique must be individualized and depends on an understanding of the physiology of pregnancy and its interaction with the individual patient's pathophysiologic features. Anesthesia during labor and delivery can cause rapid hemodynamic changes, including hypotension from rapid lowering of the SVR, which can be deleterious for the woman with cardiomyopathy.[6] The primary anesthetic goals are avoidance of drug-induced myocardial depression, maintenance of normovolemia, prevention of increased or rapidly decreased ventricular afterload, and blunting of the sympathetic stimulation induced by pain and anxiety.[143] Careful use of general or regional anesthesia can effectively meet these goals.[6] Regional anesthesia may not be possible if the mother is receiving anticoagulation. Furthermore, the use of general anesthesia provides the additional benefit of allowing TEE monitoring. Because alterations in hemodynamic status continue to occur for the first 24 hours after delivery, adequate CV monitoring must be maintained into the postpartum period.[5]

A therapeutic algorithm for patients with acute severe PPCM has been published (Fig. 50.2).[143]

Management During Noncardiac Surgical Procedures

Patients with HF require continuous optimization of cardiac status before, during, and after all surgical procedures. These patients generally do not tolerate any sudden increases or decreases in sympathetic tone leading to increases or decreases in preload and afterload, hypoxia, or hypercarbia that will increase PVR. Patients with severe dysfunction can rapidly decompensate with even small changes in hemodynamic parameters. Anesthetic considerations for patients with HF are discussed in Chapter 28, and anesthetic considerations for pregnant women with other cardiac diseases who are undergoing noncardiac operations are discussed earlier in this chapter. Both require an individualized approach, keeping hemodynamic goals in mind. Pregnant women with HF require even more attention to detail because of the potential for even faster decompensation. Invasive monitoring with an arterial catheter and a CVP catheter for the ability to titrate inotropes and vasopressors rapidly is recommended, particularly in women with severe dysfunction and for procedures with rapid fluid shifts. The use of intraoperative TEE monitoring can be invaluable for early detection of decompensation.

Advanced Cardiac Life Support in the Pregnant Woman

Cardiac arrest in the pregnant woman is challenging to the health care team as they try to resuscitate two patients, the mother and the unborn baby. Maternal cardiac arrest is rare. The 2003 to 2005 Confidential Enquiries into Maternal and Child Health (CEMACH)[166] estimated that cardiac arrest occurs in the United Kingdom in approximately 1 in 20,000 pregnancies. Mhyre and associates[167] estimated that in the United States, between 1998 and 2011, in women hospitalized for delivery, cardiac arrest occurred in 1 in 12,000 admissions, and the most common causes were hemorrhage, HF, amniotic fluid embolism, or sepsis. Because the incidence is rare, most health care professionals will never need to provide advanced cardiac life support (ACLS) to the pregnant women. Furthermore, studies have demonstrated a lack of knowledge among health care providers regarding ACLS for the pregnant woman.[168–170] Cantwell and colleagues[171] identified substandard care in 70% of pregnant women undergoing ACLS for direct deaths (related to an obstetric cause such as preeclampsia) and 55% related to indirect deaths. This lack of knowledge and substandard care led to a worse survival rate in pregnant versus nonpregnant patients.[172]

In 2015, The American Heart Association (AHA) published the most recent ACLS guidelines for pregnant[172] and nonpregnant women.[173] The basic tenets of ACLS are similar between the two groups of patients, with some modifications primarily related to the physiologic and anatomic changes in the pregnant woman. These modifications, however, may mean the difference between a successful and an unsuccessful resuscitation.

In this section, the modifications to ACLS in the pregnant patient and the reasons for the changes are discussed (Table 50.6). These modifications, with practical advice on how to perform them, were published by a group from Toronto,[174] as well as in a consensus statement from the Society for Obstetric Anesthesia and Perinatology.[175]

Activation of Cardiac Arrest Alarm

Most hospitals have a system in place to activate a cardiac arrest alarm, such as "code blue." In addition to the typical resuscitation team, successful resuscitation of the pregnant woman and neonate requires multiple specialty teams that must arrive at the onset of the cardiac arrest. The team includes anesthesiologists, obstetricians, pediatricians or neonatologists, and nurses. Successful resuscitation may require expeditious delivery of the neonate that should be started within 4 minutes of the arrest and completed within 5 minutes (see the later section on perimortem resuscitation).[176] This requires advanced planning and a means of alerting the resuscitation team that a pregnant woman has had a cardiac arrest because the additional personnel (eg, obstetricians, pediatricians, and neonatologists) do not routinely participate in adult resuscitations. This protocol is

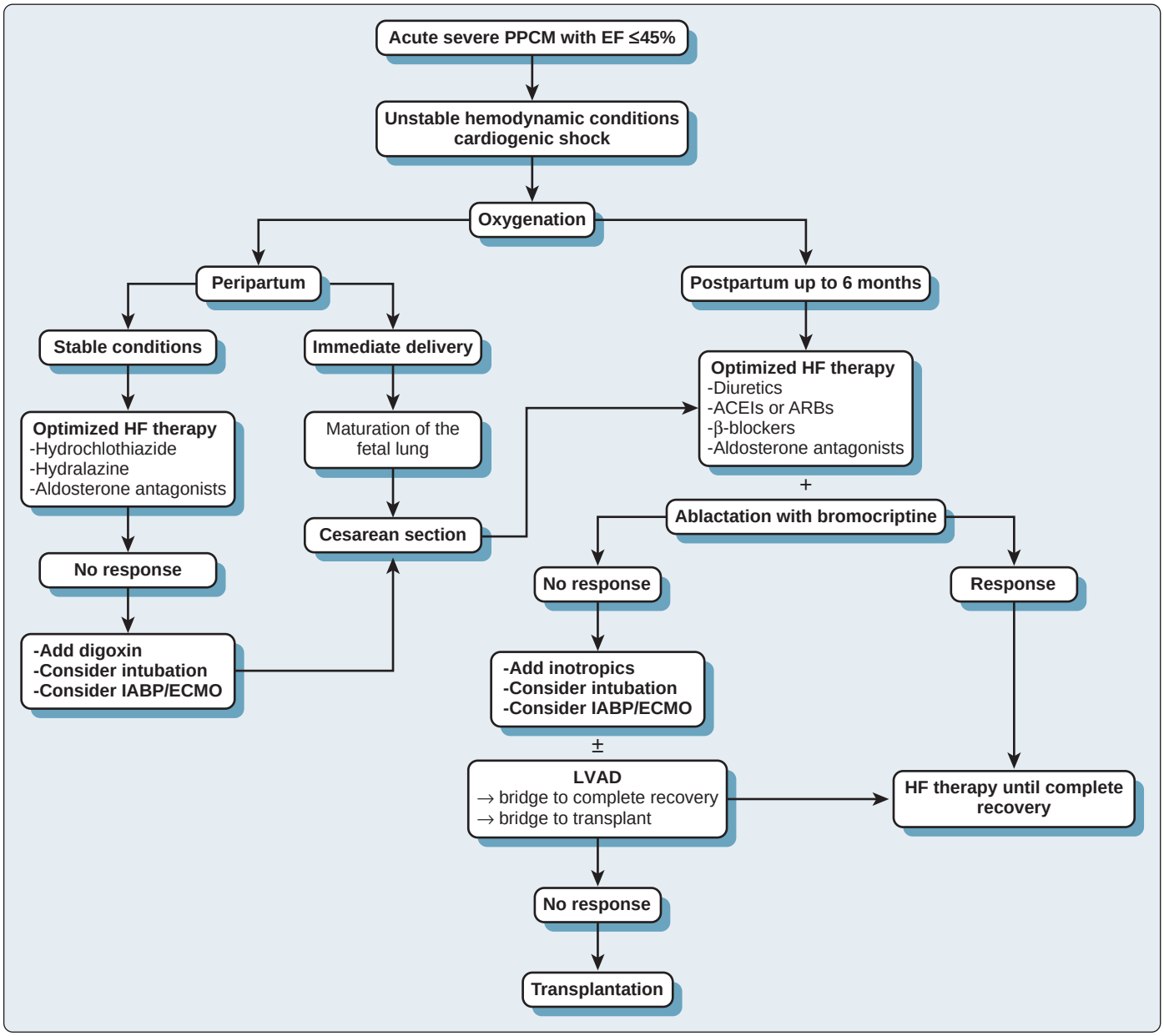


Fig. 50.2 Therapeutic algorithm for acute severe peripartum cardiomyopathy *(PPCM). ACEIs,* Angiotensin-converting enzyme-inhibitors; *ARBs,* angiotensin receptor blockers; *ECMO,* extracorporeal membrane oxygenation; *EF,* ejection fraction; *HF,* heart failure; *IABP,* intraaortic balloon pump; *LVAD,* left ventricular assist device. *(From Bachelier-Walenta K, Hilfiker-Kleiner D, Sliwa K. Peripartum cardiomyopathy: update 2012.* Curr Opin Crit Care. *2013;19:397–403, with permission from Wolters Kluwer Health.)*

TABLE 50.6 Modifications to Advanced Cardiac Life Support Protocol for the Pregnant Woman

ACLS Intervention	*Modifications*
Activation of cardiac arrest:	Notifying multiple specialty teams (eg, anesthesiologists, obstetricians, pediatricians or neonatologists, and nurses)
Patient position	Manual left uterine displacement
Chest compressions	Hand placement higher on the sternum than normal
Airway	Difficult intubation, so laryngoscopy by most experienced person.
	Application of cricoid pressure until airway is secured
Defibrillation	Removal of fetal monitor before defibrillation, if possible
Medications	Intravenous access placed above the diaphragm
Cause of cardiac arrest	BEAUCHOPS: bleeding/DIC, embolism, anesthetic complications, uterine atony, cardiac disease, hypertension/preeclampsia, other (differential diagnosis for standard ACLS guideline), placental issues, and sepsis
PMCD	Cesarean delivery begun within 4 minutes of cardiac arrest, and delivery complete by 5 minutes
Cesarean delivery equipment on crash cart	

ACLS, Advanced cardiac life support; *DIC,* disseminated intravascular coagulation; *PMCD,* perimortem cesarean delivery.

particularly important if the cardiac occurs in a location other than the labor floor.

Patient Position

Aortocaval compression in the supine position occurs by the 20th week of pregnancy and even earlier in some pregnant women.[177] In the supine position, inferior vena cava compression decreases venous return and results in reduced CO during chest compressions. In addition, placental blood flow is reduced in the supine position, thus leading to fetal acidosis. Tilting the patient on her left side improves CO and uteroplacental perfusion.[178] However, tilting the patient to the left may reduce the effectiveness of chest compressions, with greater degrees of tilt decreasing the maximum resuscitative force.[179] Left uterine displacement should be performed with either a human wedge[180] (knees of the resuscitator under the patient's right side) or manual displacement of the uterus, rather than full body tilt, to maximize chest compression force. This maneuver should be performed in anyone with an obvious gravid uterus regardless of gestational age.[167]

Chest Compressions

The 2005 AHA guidelines emphasized the requirement for high-quality chest compressions that included pushing hard and fast at a rate of 100/minute.[181] In the updated guidelines in 2010, high-quality chest compressions were reemphasized, and the sequence of cardiopulmonary resuscitation was changed from starting with rescue breaths in the traditional airway-breathing-circulation (ABC) sequence to starting with chest compressions followed by airway and breathing (CAB).[173] The same applies to the pregnant woman, except that hand placement for chest compressions should be slightly higher on the sternum than normal to account for cephalad movement of the diaphragm from the gravid uterus.[173]

Airway

Anatomic changes to the airway, including laryngeal and pharyngeal edema, can make ventilation and tracheal intubation more difficult. Decreases in functional residual capacity in conjunction with increases in CO, metabolic rate, and oxygen consumption lead to the development of arterial hypoxemia at a faster rate than in the nonpregnant woman.[182] In addition, a decrease in gastric emptying along with a decrease in lower esophageal sphincter tone places the pregnant woman at risk for pulmonary aspiration.[183] Therefore tracheal intubation to maximize oxygen delivery should occur as soon as possible following cardiac arrest and should be performed by the most experienced anesthesiologist. Moreover, a smaller than usual tracheal tube should be used. Although the efficacy of applying cricoid pressure to reduce pulmonary aspiration is controversial,[184,185] cricoid pressure should be applied until tracheal intubation is confirmed, to reduce the risk of pulmonary aspiration. If applying cricoid pressure makes ventilation or tracheal intubation more difficult, however, this pressure should be released.[175,186]

Defibrillation

Nanson and associates[187] measured transthoracic impedance in pregnant women at term and again 6 to 8 weeks after delivery. These investigators found that transthoracic impedance was unchanged. Therefore voltage administered for defibrillation in the pregnant woman should be the same as for the nonpregnant patient.[172] A theoretical concern is that electrical current could induce burns in the fetus or mother if FHR monitors are being used. This is highly unlikely because the electrical current is administered to the maternal thorax. However, it is prudent to remove any fetal monitors before defibrillation if possible.[172] Additionally, a theoretical risk of inducing fetal arrhythmias exists, but the risk is small, and defibrillation should not be delayed or avoided for this reason.[188]

Medications

Aortocaval compression could increase the time for medication to reach the heart or completely impede medications from reaching the heart. Therefore intravenous access should be placed above the diaphragm. Although intravascular volume and volume of distribution increase and protein binding decreases during pregnancy, the timing and doses of medications during ACLS should not be altered from those in the nonpregnant woman.[172]

Etiology of Cardiac Arrest

The maternal mortality rate has been increasing in the United States.[189] Cardiac arrest has direct (obstetric-related) and indirect (not obstetric-related) causes. The nonobstetric causes are not different from those in the nonpregnant woman. The CEMACH found that cardiac disease is the most common indirect cause of cardiac arrest (2.27 in 100,000 pregnancies).[166] This may not be surprising because maternal age is increasing. In addition, women with CHD are surviving into adulthood and becoming pregnant, and they, too, are at greater risk for cardiac arrest.[190]

The AHA has suggested the mnemonic BEAUCHOPS to help remember the possible causes of maternal cardiac arrest. The mnemonic stands for bleeding/disseminated intravascular coagulation, embolism, anesthetic complications, uterine atony, cardiac disease, hypertension/preeclampsia, other (differential diagnosis for standard ACLS guidelines), placental issues, and sepsis.[172] Reversible and treatable causes of cardiac arrest should be sought and include magnesium sulfate toxicity, amniotic fluid embolism, hemorrhage, and anesthetic complications, such as local anesthetic toxicity and total spinal. Magnesium sulfate toxicity should be treated by stopping the infusion and administering calcium.[191] Amniotic fluid embolism had a high fatality rate, but with aggressive treatment survival has increased.[192] Hemorrhage requires aggressive replacement of blood and blood products. Local anesthetic toxicity should be treated with intravenous fat emulsion (Intralipid, Baxter Healthcare, Deerfield, Ill), and total spinal anesthesia should be treated with tracheal intubation and management of hemodynamic instability.

Perimortem Cesarean Delivery

Perimortem cesarean delivery (PMCD) refers to cesarean delivery that is performed after the start of resuscitation and may increase survival for both mother and baby. In 1986, Katz and associates,[176] primarily based on their understanding of the physiology of pregnancy and partially based on existing case reports, recommended that if no return of spontaneous circulation occurs within 4 minutes, cesarean delivery should commence and delivery should occur within 5 minutes. Physiologically, these investigators believed that cardiac compressions are ineffective because of aortocaval compression leading to decreased CO. Katz and colleagues[193] performed a follow-up study in 2005 and reaffirmed the 4-minute rule based on a review of 38 cases in which most mothers and neonates survived when cesarean delivery occurred within this time frame. The AHA included this recommendation in their guidelines.[172] Einav and associates[194] reviewed the literature in 2012 regarding PMCD and found 94 cases of maternal cardiac arrest. These investigators found that most neonates survived if the cesarean delivery occurred within 10 or even 15 minutes of maternal cardiac arrest. Moreover, PMCD was beneficial to the mother in 32% of cases, and none were harmed by the procedure. Furthermore, Einav and colleagues[194] found that performing a cesarean delivery within 4 minutes is challenging. Lipman and colleagues[195] confirmed this finding in a simulation study in which they demonstrated that delivery within 4 minutes cannot be accomplished if the patient is taken from a delivery room to the operating room. Therefore, the recommendation is to perform a PMCD at the location of the cardiac arrest and not attempt to move the patient to the operating room.[175,195] However, even if the decision is made to perform the cesarean delivery in the

room, equipment to perform an emergency cesarean delivery must be present in the delivery room, and some clinicians recommend having equipment for an emergency cesarean delivery present on the labor and delivery resuscitation cart.[196]

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51 Critical Care Medicine in the Operating Room

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KEY POINTS

1. There exists a significant increase in morbidity associated with perioperative complications.
2. Identifying risk factors associated with intensive care unit (ICU) admission in noncardiac surgical patients may help modify these patients' overall perioperative risk.
3. Patients scheduled for ambulatory surgery who have significant risk factors associated with increased morbidity and mortality may require more in-depth perioperative planning.
4. Patients with coronary stents undergoing noncardiac surgery require coordination between perioperative team members.
5. The most common etiology of perioperative stroke is embolic in nature.
6. Identifying patient risk factors for perioperative stroke may aid in reducing the overall perioperative stroke risk.
7. The prompt recognition of acute coronary syndrome in the perioperative period is paramount because therapy should begin immediately to prevent myocardial injury.
8. The mainstays of therapy for perioperative heart failure are diuresis and afterload reduction.
9. In the setting of valvular disease, anesthetic agents should be chosen carefully with hemodynamic goals in mind.
10. Respiratory failure is a heterogeneous syndrome with two major types: hypoxemia and hypercarbia. Each is associated with unique pathophysiology and requires treatment of the underlying disease leading to respiratory failure.
11. A key concept of mechanical ventilation in acute respiratory distress syndrome (ARDS) is avoidance of ventilator-induced lung injury by volutrauma and barotrauma.
12. Noninvasive ventilation should be considered in patients with respiratory failure from COPD or heart failure.
13. The new oral anticoagulants include dabigatran, apixaban, rivaroxaban, and edoxaban. Dabigatran is a direct thrombin inhibitor that can be reversed with idarucizumab (Praxbind) for noncardiac surgery. The other three drugs are factor Xa inhibitors that do not have specific reversal agents at present.
14. Massive hemorrhage remains a common clinical challenge for anesthesiologists. Massive transfusion protocols help facilitate patient care between the bedside physicians and nurses with blood bank and laboratory services.
15. The cornerstone of sepsis therapy is aggressive resuscitation, administration of antibiotics in a timely fashion, and source control of anatomically based infections.

Approximately 230 million surgical procedures are performed worldwide each year.[1] Perioperative mortality is relatively low, but this may be a misleading statistic of surgical safety because postoperative complications continue to be significant.[2] In fact, elderly (>70 years old) high-risk patients may have a postoperative complication rate as high as 50%.[1,3] This subset of patients accounts for only 13% of all surgical procedures but more than 80% of postoperative deaths.[2,4] The management of these high-risk patients presents a unique challenge for the perioperative physician.

This chapter will discuss the perioperative management of critically ill cardiac patients for noncardiac surgery. Given the wide scope of the topic, the authors have addressed several key perioperative complications and issues in the setting of noncardiac surgery and highlight the management of such events. A broad discussion of patient triage is provided initially, followed by a discussion of key diseases presented by organ system.

Perioperative Triage

Although critical care admissions are routine for cardiac surgical patients, they are rare for the noncardiac surgical population. It is vital to determine which patients are appropriate for various perioperative care areas—outpatient surgery, routine inpatient care, or critical care services. Triage can be defined as the process of deciding which patients should be treated first based on degree of sickness or severity of injury.[5] In the present value-based health care system, placing the "right" patients in the "right" location is a difficult but crucial task.

Ambulatory Surgery

A challenging triage decision is identifying which surgical patients are best cared for in inpatient hospital-based versus ambulatory settings. Adequate preoperative patient assessment is important in

determining the appropriate surgical environment. Criteria associated with increased hospital admission after outpatient surgery include age 65 years or older, cardiac diagnoses, peripheral vascular disease (PVD), surgery lasting more than 2 hours, cerebrovascular disease, malignancy, human immunodeficiency virus (HIV), and general anesthesia.[6] However, patients with stable coronary artery disease (CAD) may not be at higher risk for perioperative complications following ambulatory surgery. Nevertheless, a recent National Surgical Quality Improvement Program (NSQIP) database evaluating 5 years of common day case–eligible surgical procedures (244,397 procedures) suggests the following risk factors are associated with an increase in morbidity and mortality: previous cardiac surgical intervention (percutaneous coronary intervention or cardiac surgery), overweight body mass index, obese body mass index, chronic obstructive pulmonary disease (COPD), history of transient ischemic attack/stroke, hypertension, and prolonged surgical time.[7] Patients with cardiac pacemakers or implantable cardioverter-defibrillators can be evaluated for ambulatory surgical cases. However, it is important to determine the type and function of these devices before proceeding with surgery. Similarly, it is appropriate to develop a definitive perioperative plan for the management of these devices in terms of electromagnetic interference and follow-up[8,9] (see Chapters 5 and 45).

Critical Care Services

Roughly 8% of patients undergoing inpatient noncardiac surgery require critical care services.[4] Among approximately 90,000 surgical patients admitted to intensive care units (ICUs) analyzed in an Austrian database, chronic heart failure (HF) and cardiac disease were significant risk factors that led to an increase in mortality.[2] General factors that may contribute to perioperative morbidity and subsequent ICU admissions can be divided into four major groups: (1) significant comorbidities (eg, cardiac disease), (2) increasing age, (3) type and urgency of surgery, and (4) physiologic disturbances that occur during the operation.

Triaging healthy or moribund patients away from critical care services (excluding palliative services and services to those who are brain dead) seems to be relatively straightforward. However, health care providers are challenged by a scarcity of ICU beds and an inherent cost in determining which patients will truly benefit from intensive care.[4,5,10] Improving preoperative evidence-based strategies to identify which patients are at highest risk for postoperative complications may aid in determining patient need. Similarly, reducing hospital variability in managing these patients once they develop postoperative complications is also paramount to reducing morbidity and mortality.[2]

The Society of Critical Care Medicine (SCCM) supports the notion that ICU beds should be given to those patients with a reasonable chance of significant recovery.[11] Before 2012, many studies were published regarding scoring systems for evaluating ICU mortality. However, no large trials addressed the need for an evaluative ICU triage scoring method. Sprung and colleagues performed the first large prospective study (Eldicus) in 11 ICUs among eight European countries developing a triage procedure for the use of critical care services.[12] Factors favoring ICU admission are listed in Table 51.1. Approximately 30% of patients accepted for ICU services had cardiac diseases.[12] The heart was the second most frequent organ involved (second to the lungs) in ICU admissions. The authors further suggested that mortality was reduced with ICU admission, especially in patients with more severe acute illness.[12]

The second question explored in an expansive observational study was the potential benefit of ICU admission for the elderly.[13] Elderly patients are more likely to be rejected for admission to the ICU. Yet analysis suggests a greater mortality reduction in elderly patients admitted to the ICU when compared with younger patients. Based on these findings, the authors recommended intensivists change triage decisions regarding the elderly and consider accepting even those elderly who appear "well."[13]

TABLE 51.1 Factors Associated With Triage Decisions

Factors Associated With ICU Admission	*Factors Associated With Increased Hospital Admission After Outpatient Surgery*	*Factor Associated With Increased Risk of Morbidity/Mortality After Day Case Eligible Procedures*
Surgical patients (vs medical patients)	Age > 65	Previous cardiac surgical intervention (percutaneous coronary intervention or cardiac surgery)
Absence of comorbidities	Cardiac diagnoses	Overweight/obese BMI
Presence of hematologic malignancy	Peripheral vascular disease	COPD
Acute clinical condition	Malignancy	History of TIA/CVA
Need for active intensive care therapies	HIV	Hypertension
Trauma	General anesthesia	Prolonged surgical time
Vascular involvement	Surgery > 2 hours	
Hepatic Involvement		
Acute severity of illness (APS II)		
Lowest surgical Apgar score		

Data from references 6, 7, 12, 14.

Another large retrospective study investigated the utility of the surgical Apgar score (SAS) in determining ICU admission after major abdominal surgery.[14] This scoring system assigns numbers to ranges of estimated blood loss, lowest mean arterial pressure (MAP), and lowest heart rate (HR). After multivariate adjustments, a strong correlation between lowest SAS and decision for ICU admission was noted (odds ratio [OR], 14.41; confidence interval [CI], 95%; 6.-88-30.19; $P < 0.001$). This study suggested that intraoperative hemodynamics and blood loss do indeed influence ICU triage.[14]

Triaging Patients With Coronary Stents and Noncardiac Surgery

Between 5% and 20% of patients with coronary stents may undergo surgical procedures within 2 years following PCI.[15] One of the largest observational studies to date reported an approximately 23% rate of noncardiac surgery 1 year following PCI.[16] Multiple guidelines report that elective surgery should be delayed for at least 4 to 6 weeks after bare metal stent (BMS) placement and 6 to 12 months after drug-eluting stent (DES) placement, depending on the type of stent.[15] The major challenge is determining the risk of perioperative surgical hemorrhage versus dual antiplatelet therapy (DAPT) interruption and its relation to subsequent coronary stent thrombosis (see Chapters 3, 43, and 44).

A safe time period for antiplatelet therapy interruption has yet to be clearly defined. One study suggested that the incidence of coronary stent thrombosis seems to stabilize at approximately 6 months after DES or BMS placement even in the presence of intraoperative cessation of DAPT.[16] However, the three strongest risk factors for a coronary event were recent MI, high cardiovascular (CV) risk and nonelective surgery.[16] Still, the continuation of aspirin is often recommended throughout the perioperative period. In the absence of guidelines supported by strong evidence, it may be important for the care team (primary care doctor, cardiologist, perioperative physicians) to collaborate and develop a definitive perioperative plan regarding continuation of DAPT, type and timing of stent placement, and disposition.[15] Risk factors such as those mentioned earlier may lead the perioperative team to suggest hospital-based surgery with the potential for an overnight stay. Noncardiac surgery that is required in the setting of recent stent placement may be best performed where a 24-hour interventional cardiologist is present and can institute emergent PCI as necessary.[17]

Neurologic System

Perioperative Cerebrovascular Accident

Cerebrovascular accident (CVA) is one of the most significant perioperative complications. The incidence of perioperative CVA in the general surgical population depends on the type of procedure and associated perioperative risk factors but remains low at approximately less than 0.7%.[18] However, CVA is responsible for a substantial increase in long-term disability, length of ICU and hospital stay, and mortality (18%–26%).[18] The etiology is primarily ischemic or embolic. Noncardiac surgery induces a hypercoagulable state. Trauma to tissues enhances formation of thrombus and promotes inflammation. Studies suggest that the perioperative period is marked by decreased levels of tissue plasminogen activator (tPA), increased fibrinogen degradation products, increased thrombin-antithrombin complex, and increased D-dimer. These prothrombotic changes coupled with dehydration, bed rest, general anesthesia, and cessation of anticoagulants increase the risk for postoperative CVA.[19,20]

Embolic perioperative strokes are far more common than those related to hypoperfusion.[21] The majority of embolic perioperative CVAs occur after the second postoperative day and are typically related to the development of atrial fibrillation (AF) or myocardial ischemia. New-onset AF occurs or is present approximately 30% of the time with perioperative stroke.[22]

Perioperative CVA risk factors can be classified as preoperative, intraoperative, and postoperative.[18–20] Common perioperative risk factors are listed in Table 51.2. Modifiable risk factors may be addressed in the preoperative period to reduce morbidity and mortality.[19]

Preventative strategies for perioperative CVA are not well defined. Decreasing surgical time may reduce risk for CVA, but this may be difficult to modify. Patients with symptomatic carotid artery stenosis may benefit from carotid revascularization before undergoing major surgery. However, at least one study of 2000 high-risk patients undergoing noncardiac surgery suggested no association between carotid artery stenosis and perioperative stroke.[23] Poor systolic ejection fraction (EF) may lead to an increased risk in perioperative stroke presumably caused by intracardiac thrombus and atherosclerotic disease. If indicated, transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) may be considered preoperatively to identify intracardiac clots and atherosclerosis, which may increase the risk of an embolic stroke. Preliminary studies suggest a small reduction in perioperative stroke risk with perioperative β-blockers, statins, and glycemic control.[19,20]

TABLE 51.2 Perioperative Risk Factors for Cerebrovascular Accident (CVA)

Preoperative	*Intraoperative*	*Postoperative*
Patient age > 70	Surgery type	Heart failure
Female sex	Type of anesthesia (general vs local)	Low ejection fraction
History of CVA/TIA	Duration of surgery	Myocardial infarction
History of symptomatic carotid artery stenosis	Manipulation of proximal Aortic lesions	Arrhythmias
Atherosclerosis of the ascending aorta	Arrhythmias	Dehydration
History of hypertension	Hyperglycemia	Blood Loss
DM	Hypotension	Hyperglycemia
Creatinine > 2 mg/dl	Hypertension	
History of cardiac disease		
Peripheral vascular disease		
Ejection fraction < 40%		
Smoking		

Data from Macellari F, Paciaroni M, Agnelli G, Caso V. Perioperative stroke risk in nonvascular surgery. *Cerebrovasc Dis.* 2012; 34:175–181; Selim M. Perioperative stroke. *N Engl J Med.* 2007; 356:706–713; and Szeder V, Torbey MT. Prevention and treatment of perioperative stroke. *Neurologist.* 2008; 14:30–36.

Identifying the appropriate timing of elective noncardiac surgery in patients with a prior stroke is important. A large database study (over 400,000 noncardiac surgeries) out of Denmark suggested that a prior stroke is associated with a 1.8-fold increased risk of mortality in patients undergoing noncardiac surgery.[24] More important, this study suggested a very high risk of adverse outcomes in those patients undergoing noncardiac surgery less than 3 months after a stroke. This risk stabilized at approximately 9 months.[24] The risk to patients with prior stroke was similar in those undergoing low- and intermediate-risk surgery when compared with high-risk surgery. Although this study has yet to be replicated in other countries, the perioperative care team should consider delaying elective noncardiac surgery in patients with recent stroke when feasible.[24]

Perioperative anticoagulation should be continued whenever the risk of bleeding is deemed low by the surgical team. Cessation of anticoagulation may result in an increased risk of perioperative CVA.[25] Discontinuing aspirin is likely to exacerbate the already hypercoagulable state of surgery.[25] Studies involving patients undergoing carotid endarterectomies (CEAs) suggested that perioperative continuation of aspirin resulted in a reduction in stroke risk.[26] The 2012 American College of Chest Physicians (ACCP) guidelines suggest continuing aspirin in all perioperative situations except for those with very low cardiac risk or in situations where even minor bleeding may be catastrophic.[27] However, this is a decision best made by the care team in consideration of patient and procedure specific risks and benefits.

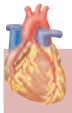
Other anticoagulants such as warfarin and clopidogrel are often stopped several days before surgery. However, cessation of these medications should be based on each unique clinical situation. For instance, one recent study suggested that patients with AF who discontinued warfarin before endoscopy procedures had an approximate threefold increased risk of stroke within 30 days of the procedure.[20] Bridging anticoagulation with heparin or low-molecular-weight heparin (LMWH) may be considered in those patients at high perioperative risk of stroke and where hemorrhage is also a concern.[19,20] If oral anticoagulants must be held prior to surgery, it is prudent for the managing service to restart these drugs as soon as appropriate in the postoperative period.

Currently available therapies for perioperative CVA are sparse. Recent guidelines suggest that early diagnosis and management in a stroke unit with general supportive care (eg, airway protection and mechanical ventilation, if necessary, and avoiding further cerebral damage) are paramount.[21] Administration of intravenous tPA is a proven therapy for ischemic CVA, but relatively contraindicated after major surgery because of the high risk of bleeding.[21,25] Still, the 2013 AHA guidelines recommend against excluding all surgical patients from consideration.[28] Instead, each case should be evaluated by the perioperative team and if possible an expert in the field of CVA. Other modalities such as intraarterial thrombolysis and endovascular mechanical clot disruption may be viable alternatives, with appropriate consultation, for those who have undergone recent major noncardiac surgery. However, two recent trials showed no benefit with these modalities when compared with systemic thrombolysis[29,30] (Box 51.1). Further research may help identify surgical patient populations in which these techniques may be most efficacious.

Cardiovascular System

Cardiac issues remain a significant contributor to perioperative morbidity and mortality.[2] The intraoperative and postoperative management of cardiac complications in noncardiac surgery with specific focus on CAD, HF, valvular disease, and arrhythmias is discussed in Chapters 43 to 51.

Cardiac complications may arise from structural disease of the heart involving coronary arteries, valves, myocardium, or the conduction system. Patients with underlying cardiac disease may require advanced monitoring throughout the perioperative period.[31–34] TEE may serve as an important monitor in the operating room to evaluate cardiac function and fluid status.[35] Smaller "mini-TEE" probes have been described for continuous perioperative monitoring both in the



BOX 51.1 PREVENTATIVE AND THERAPEUTIC STRATEGIES IN CEREBROVASCULAR ACCIDENT (CVA)

Preventative

- Decrease surgical time
- Carotid artery revascularization in symptomatic patient???
- Beta blockers
- Statins
- Glycemic control
- Continuation of anticoagulants when safe
- Consider delaying elective surgery for > 9 months after CVA

Therapeutic

- IV TPA: higher risk of bleeding
- Supportive care: intubation for airway protection and mechanical ventilation
- Intraarterial thrombolysis: questionable efficacy
- Endovascular mechanical clot disruption: questionable efficacy

Data from references 19, 20, 23, 24.

operating room and ICU[36,37] (see Chapters 15 and 46). An understanding of common cardiac diseases will help perioperative clinicians gauge the level of care (monitoring and otherwise) that is appropriate for each unique scenario. For all surgical patients, postoperative disposition may depend on the cardiopulmonary status of the patient, as well as the need for advanced monitoring or critical care.

Acute Coronary Syndrome

Patients with or at risk for CAD present significant challenges to anesthesiologists in the perioperative period. As many as 5% of patients undergoing noncardiac surgery may suffer cardiac complications.[38] Risk factors include a history of ischemic heart disease, HF, stroke, diabetes mellitus, or renal insufficiency.[38] Preoperative risk stratification is discussed in Chapters 1, 43, 44, and 51). Perioperative acute coronary events may range from myocardial ischemia or myocardial injury with and without electrocardiogram (ECG) changes. Myocardial infarction (MI) can be universally defined as an elevation of cardiac biomarkers such as troponin, ECG changes, new regional wall motion abnormalities (RWMAs) seen on echocardiography, or coronary catheterization findings consistent with acute blockages.[39]

The perioperative management of acute coronary syndrome (ACS) or unstable angina presents a unique challenge as patients under anesthesia or those sedated postoperatively may not present with the same signs and symptoms often seen in nonoperative patients. In fact, one large study found that 65% of patients with perioperative MI did not reveal symptoms.[40] In addition, those patients who are diabetic, elderly, or female may present with atypical symptoms or even "silent" MI.[41,42]

The diagnosis is thus often confirmed only when clinical suspicion leads to further laboratory testing or investigation. When patients do complain of symptoms or clinical suspicion exists, clinicians should obtain a 12-lead ECG and serial cardiac biomarkers (troponin, creatine kinase–MB). Cardiology consultation for risk stratification and further testing may be warranted.

The management of ACS in nonoperative patients is well defined, and clinical care pathways are in place to improve patient outcome.[43] Care pathways for the perioperative patient are not well studied. Unique concerns such as bleeding risk, surgical stressors, and perioperative physiologic changes make therapy protocols challenging. Management must be considered in context for each patient and the relative risk/benefit of therapies applied uniquely. Potential therapies are presented broadly in later sections, but these may not be applicable in all situations.

BOX 51.2 MEDICAL THERAPY IN ACUTE CORONARY SYNDROME

- Oxygen to maintain normoxia
- Aspirin 162-325 mg
- $P2Y_{12}$ antiplatelet therapy
- Systemic anticoagulation (if no contraindication)
- Nitroglycerin for pain (if no contraindication)
- Opioid analgesics as needed
- Beta-blockers if stable
- Statin therapy as soon as possible

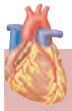
Patients suffering from ACS perioperatively must first be clinically stabilized. Therapies to augment cardiac output (CO) may be needed (Box 51.2). Administration of β-adrenergic agonists (eg, dobutamine [2.5–5 μg/kg/min] or epinephrine [1–2 μg/min]) can be effective. Mechanical augmentation with devices such as intraaortic balloon pump may be considered in severe cases. Arrhythmias may occur and should be managed according to known treatment modalities. Prophylactic lidocaine is not indicated.[42]

Medical therapy with aspirin (162–325 mg) should be initiated if not contraindicated. Additional antiplatelet therapy with a P_2Y_{12} receptor blocker is indicated in ACS, but may not be safe in the perioperative period.[42] In patients with non-ST elevation infarctions, systemic anticoagulation (ie, heparin infusion) may be indicated, but in the perioperative setting the risk of surgical bleeding must be weighed against the risk of advancing ACS. Oxygen should be administered to all hypoxemic patients in concentrations needed to achieve normoxia. There are no data to support the use of oxygen in patients with normal oxygen saturation. Although controversial, some have proposed a harmful effect of hyperoxia owing to direct coronary vasoconstriction.[44–46] Nitroglycerin may be administered to patients with angina symptoms but should be avoided in patients with severe aortic stenosis, RV infarctions, hypotension, or a history of phosphodiesterase inhibitor use in the last 24 hours.[47] Caution should also be used with this medication in patients under neuraxial anesthesia because the combination could precipitate hypotension. Pain control with opioid analgesics may be considered; however, newer evidence suggests that morphine may be detrimental in patients with ACS.[48] Proposed mechanisms include a morphine induced impaired absorption/effectiveness of some antiplatelet therapies.[49] Statin therapy is indicated as soon as possible, because several studies support improved patient outcomes with statin therapy (specifically atorvastatin, 80 mg).[42,50,51] In addition, laboratory evaluation of lipid levels is recommended before discharge.

β-Blocker therapy is perhaps the most controversial perioperative cardiac therapy. Although several studies have shown improved cardiac morbidity and mortality with the administration of perioperative β-blockers, concern for increased stroke risk and all-cause mortality was noted.[40,52] Current guidelines, recommend patients on chronic β-blocker therapy continue this perioperatively.[9] In the setting of perioperative ACS, β-blocker therapy may decrease demand ischemia by improving oxygen supply and demand imbalance and is indicated in stable patients with ACS.[42] The use of β-blockers in unstable patients or patients with acute cocaine intoxication should be cautioned[53,54] (see Chapters 11, 20, 43, and 51).

Angiotensin converting enzyme (ACE) inhibitor therapy should be considered in ACS once patients are stabilized. Indications include all patients with left ventricular ejection fraction (LVEF) of less than 40%, hypertension, diabetes mellitus, or stable chronic kidney disease. Angiotensin receptor blockers may be substituted in patients with HF with an LVEF less than 40% or significant kidney dysfunction (creatinine > 2.5mg/dL for men, > 2.0 mg/dL for women).[42]

The optimum hemoglobin level in patients with perioperative MI is not known. Several studies have evaluated transfusion thresholds in ACS patients, bleeding patients, and critically ill patients.[55,56,57] Routine



BOX 51.3 CARDIAC CONSULTATION TO AID IN RISK STRATIFICATION AND MANAGEMENT IN STEMI AND NSTEMI PATIENTS

- Patients with atherosclerotic heart disease or cerebrovascular disease presenting for noncardiac surgery require extensive communication and collaboration with primary care doctors, cardiologists, and surgeons.
- This communication should be present throughout the perioperative period.
- Presence of coronary stents, use of anticoagulants, and perioperative myocardial ischemia and infarction are examples of scenarios in which such a "team" approach is absolutely essential for good outcome.

red blood cell transfusion in stable, nonbleeding patients is not recommended when the hemoglobin is above 8 g/dL[42] (see Chapters 34, 35, and 51).

More aggressive interventional therapy with cardiac catheterization or fibrinolytics is dependent on the type of myocardial injury and risk of surgical bleeding. ST-elevation myocardial infarctions (STEMIs) present a high mortality if left untreated. In the nonsurgical setting, patient outcome is clearly related to time to reperfusion and a "door to reperfusion time" of less than 90 minutes is recommended.[58] The mainstays of reperfusion therapy include cardiac catheterization and angioplasty/stent placement or fibrinolytic therapy. Multiple studies have shown an improved survival, less bleeding complications, and reduced recurrent MI with catheterization.[59] Both present significant concerns in the perioperative period due to an increased risk of bleeding (see Chapters 3, 20, and 51).

Fibrinolytic therapy is often reserved for centers without percutaneous coronary intervention (PCI) capabilities. It is recommended when symptom onset is less than 12 hours before presentation and PCI would not be available within 120 minutes.[58] However, in the perioperative setting, fibrinolytics will almost universally be contraindicated because of bleeding risk. PCI may be better suited for the treatment of perioperative STEMI. This is not without risk, however, because angioplasty or stent placement often requires dual antiplatelet therapy and anticoagulation. Finally, emergent coronary artery bypass graft (CABG) surgery is an option. This is rarely used for STEMI patients because it is associated with increased mortality when performed in the first 7 days after STEMI.[58] Close consultation with cardiology and surgery is needed to weigh the risks and benefits of therapeutic options in perioperative STEMI patients (Box 51.3).

Patients with non–ST-elevation myocardial infarction (NSTEMI) may be managed more conservatively. However, in patients with low CO or arrhythmias, emergent PCI and reperfusion may be warranted. In stable NSTEMI patients, noninvasive studies may be the first approach. Again, close consultation with cardiology will aid in risk stratification and management (see Box 51.3).

Heart Failure

Heart failure represents a significant perioperative complication presenting in up to 10% of patients after major noncardiac surgery.[60] A preoperative history of HF increases cardiac risk substantially, especially in the presence of risk factors such as CAD and diabetes. HF is broadly defined as a syndrome of impaired cardiac function[61] and is often categorized into two groups: systolic failure associated with depressed left ventricular function (low LVEF) or diastolic failure with a preserved EF.[62]

Like perioperative ACS, care pathways for the perioperative management of HF are ill defined and poorly studied. Retrospective cohort studies using data from large national databases have helped elucidate risk factors, but it remains unclear how specific therapies may affect outcome in the perioperative period.[61] Patients may present with dyspnea, orthopnea, tachypnea, and/or clinical signs such as pulmonary crackles or decreased oxygen saturation. Signs of right-sided heart failure, such as nausea and vomiting, lower extremity edema, and hepatic congestion may also be present. This may result in a confusing clinical picture, because many of the signs and symptoms of HF seen in the perioperative period could also be due to other causes such as surgical insult, pain, and medication side effects.

Clinical suspicion of HF should prompt further investigation, including ECG, chest x-ray, and cardiac biomarkers. Although troponin and creatine kinase may be important in elucidating an etiology, they are not diagnostic of HF. Elevated B-type natriuretic peptide (BNP) is supportive of the diagnosis.[62] Some patients with chronic HF may have a baseline abnormal level of BNP. In such patients an elevation of BNP from baseline may be diagnostic of an acute exacerbation.[63] Echocardiography, either TTE or TEE, can be invaluable in making the diagnosis of HF and monitoring therapeutic effect. Laboratory evaluation should include electrolytes, renal and liver function tests, and hemoglobin.

Therapies are tailored to specific causes and must be directed at managing concomitant respiratory failure. Adequate oxygenation and ventilation is paramount to normalizing cardiac function. Electrolyte imbalances and acid/base disturbances should be corrected to minimize potential detrimental effects on ventricular contractility, pulmonary arterial pressure, and cardiac rhythm. Preload, contractility, and afterload must also be optimized.

In patients with signs of volume overload, diuretic therapy and fluid restriction are mainstays of therapy. Furosemide, a common loop diuretic, may be administered intravenously. Systolic HF with clinical signs and symptoms of low CO may benefit from inotropic therapy.[64,65] In the setting of failed pharmacotherapy, mechanical devices may be used to treat severe HF (eg, intraaortic balloon pump, ventricular assist devices) (see Chapters 11 and 38).

In patients with stable hemodynamics, ACE inhibitor and β-blocker therapy is recommended by the American College of Cardiology (ACC). Additionally, in patients with LVEF less than 35%, aldosterone antagonists are recommended[62] (see Chapter 11).

Valvular Heart Disease

Concomitant valvular disease may be common in the perioperative period. Depending on the severity of valvular disease, surgery and anesthesia may present a significant physiologic challenge. An understanding of the type and severity of valvular disease can help the clinician tailor care appropriately. Preoperative echocardiographic evaluation may help guide perioperative management. A clinical suspicion of undiagnosed valvular disease or recent changes in clinical history should prompt preoperative echocardiographic testing if none has been performed in the last 12 months.[9] A broad overview of specific valvulopathies and management principles in the setting of noncardiac surgery is discussed later. A summary of hemodynamic goals in each valvular disease is presented in Table 51.3 (see Chapter 21).

Aortic Stenosis

Aortic stenosis (AS) is a major predictor of morbidity in noncardiac surgery.[9] In patients 75 years or older, AS is a common finding with an incidence of 3% to 8%. Decreased cardiac reserve blunts the ability to respond to the physiologic stressors of surgery and anesthesia likely accounting for an increased perioperative morbidity and mortality.[66–68] Additionally, AS may be associated with an increased risk of bleeding due to acquired von Willebrand dysfunction.[69] Perioperative management may require invasive monitoring to ensure proper loading conditions and avoid potentially catastrophic decreases in afterload that may lead to ischemia, LV failure, and cardiac demise

Therapeutic goals are similar both intraoperatively and postoperatively. Hypovolemia should be avoided as the LV is often hypertrophied and noncompliant, thus more dependent on elevated filling pressures to maintain preload. Sinus rhythm should be maintained as LV filling

TABLE 51.3 Perioperative Hemodynamic Goals by Type of Valvular Disease

	Heart Rate	*Blood Pressure*
Aortic stenosis	Slow normal	High normal
Aortic regurgitation	Fast normal	Low normal
Mitral regurgitation	Fast normal	Low normal
Mitral stenosis	Slow normal	Normal

is increasingly dependent on atrial contraction in the setting of AS. Tachycardia should be avoided to allow adequate filling time in diastole and ejection time in systole. Systemic vascular resistance (SVR) should be maintained and sudden drops in blood pressure should be avoided because they may cause dangerous reductions in coronary perfusion. Neuraxial anesthesia may cause a decrease in SVR and preload; therefore caution should be used in the setting of AS.[70,71] Phenylephrine and vasopressin are effective medications for maintaining SVR.[72,73]

Aortic Regurgitation

The risk of noncardiac surgery in patients with aortic regurgitation (AR) relates directly to the severity of valvular disease, the cause of AR, and the surgical risk. Moderate to severe AR and intermediate- to high-risk surgery are risk factors for increased pulmonary edema, prolonged intubation, and hospital death.[74] Understanding the degree of AR preoperatively is key when caring for these patients. In patients with severe AR and low LV function (EF <50%), valve repair or replacement should be considered before elective surgery.[75]

Many anesthetic agents cause a decrease in SVR, reducing regurgitant fraction and improving AR. Nevertheless, careful management is necessary. To maintain forward CO, adequate avoidance of bradycardia is important because it may increase regurgitation due to increased diastolic time. Similarly, hypertension and volume overload should be avoided. The use of diuretics and afterload reduction medications may be helpful.

Mitral Stenosis

Patients with moderate to severe mitral stenosis (MS) undergoing noncardiac surgery present a significant challenge to clinicians. LV filling is impaired because of obstructed flow across the stenotic mitral valve. Supraventricular arrhythmias may develop as a result of structural changes in the LA. Pulmonary hypertension can develop because high LA pressures are transmitted backward to the pulmonary vasculature. Eventually, patients with severe MS can develop pulmonary edema and RV failure.

Caring for patients with MS in the perioperative period involves maintaining LV filling pressures and optimizing conditions for RV function. Care must be taken to avoid hypercarbia, hypoxemia, and acidosis, all of which can increase pulmonary vascular resistance and impair RV function. Inotropic support of the RV may be needed. Dobutamine is a reasonable choice with phosphodiesterase inhibitors such as milrinone reserved for more critical scenarios.

Medications that cause tachycardia such as ketamine and anticholinergics may best be avoided. Bradycardia allows for improved LV filling across the stenotic mitral valve. β-Blockers such as esmolol should be available. Anxiolysis to avoid tachycardia is important, but care must be taken to avoid hypercarbia or hypoxemia that may occur with sedation. Avoidance of hypotension may be achieved with "hemodynamically stable medications" such as etomidate. Regional and neuraxial anesthesia may be employed, but clinicians should attempt to avoid hypotension. Epidural anesthesia with gradual dosing of medication may reduce the risk of sudden hypotension.

Mitral Regurgitation

Patients with moderate to severe mitral regurgitation (MR) undergoing surgery are at increased risk of perioperative morbidity and mortality. This is especially true for patients with low EF or AF.[75,76] Patients with chronic MR suffer long-standing volume overload of the LV, which leads to dilation of the ventricle and left atrium. Because of compensatory mechanisms, chronic MR is often well tolerated by patients. Acute MR, on the other hand, is not well tolerated and is often complicated by overt HF, pulmonary hypertension, and pulmonary edema. The most common cause of acute MR is ischemia causing papillary muscle dysfunction although other causes exist. Addressing the underlying cause of acute MR is the mainstay of management.

Key management principles for patients with chronic MR undergoing noncardiac surgery include maintaining sinus rhythm and avoiding bradycardia, hypertension, and volume overload. Sinus rhythm is crucial because atrial contraction may account for 30% to 40% of LV end-diastolic volume. Atrial fibrillation significantly decreases LV filling and can lead to HF and shock. Most anesthetic agents improve MR by decreasing afterload and, thus, decreasing LV systolic pressure. Anesthetic agents that decrease SVR (eg, volatile anesthetics) may be useful; however, those agents associated with bradycardia may worsen MR (eg, remifentanil). Regional or neuraxial anesthesia may be reasonable in the absence of contraindications for placement. Diuretics and afterload reduction should be considered if volume overload or hypertension is encountered.

Arrhythmias

Atrial Fibrillation

Perioperatively, a multitude of factors can precipitate AF, including direct surgical irritation of the atria or pulmonary veins, fluid shifts, electrolyte imbalance, or excess catecholamines related to pain or the physiologic stress of surgery. AF is associated with an increased risk of stroke because slow blood flow through the atria can lead to thrombus formation, particularly in the left atrial appendage.

In patients with AF, the decision of when to stop oral anticoagulants preoperatively is a source of continued concern. Patients at particular risk of stroke may be "bridged" from the time of cessation of oral anticoagulants to surgery with LMWH or unfractionated heparin (UH).[77] The duration of cessation and timing of bridging therapy is decided on an individual basis based on surgical risk of bleeding and patient risk of thromboembolism. At this time, there is limited available evidence for the optimal type and duration of bridging therapy.[78] Those patients in sinus rhythm on chronic warfarin may discontinue it 5 to 7 days before surgery.[77] Higher-risk patients with mechanical valves, a history of stroke, or elevated stroke risk scores may require bridging with LMWH or UH. The management of anticoagulation therapy should be coordinated with the primary care doctor or cardiologist.

Newer oral anticoagulants such as direct thrombin inhibitors and factor Xa inhibitors pose a significant concern in surgical patients.[79] There is far less experience regarding the safe timing of cessation, and standard coagulation studies do not detect the effect level of these newer medications. Furthermore, unlike warfarin, reversal with an antidote is challenging. It is recommended that cessation of these drugs be based on the pharmacologic properties (half-life) of the drug and relative surgical and patient risks. The American Society of Regional Anesthesia has published guidelines on the timing of regional or neuraxial anesthesia in the setting of oral anticoagulants.[80]

Perioperatively, the hemodynamic consequences of AF are of particular concern, especially in the setting of preexisting cardiac conditions. The loss of atrial contraction coupled with beat-to-beat changes in ventricular filling can lead to suboptimal ventricular preload and decreases in CO and blood pressure. Irregular electrical transmission through the atrioventricular (AV) node can lead to rapid ventricular response (RVR) further reducing ventricular filling.

The patient with AF in the operative or critical care setting should initially be evaluated for signs of hemodynamic compromise and categorized as stable or unstable. The unstable patient should undergo immediate cardioversion. It should be recognized that cardioversion might increase the risk of stroke, especially in patients with a history of AF and not on anticoagulation. If possible, evaluation for existing intracardiac thrombus with TEE should be considered. In stable

TABLE 51.4 Rate Control for Perioperative Atrial Fibrillation

Beta-Blockers	*Calcium Channel Blockers*	*Other Agents*
Esmolol 0.5 mg/kg bolus; 50-200 μg/kg/min infusion	Diltiazem 0.25 mg/kg; 5-15 mg/h infusion	Digoxin
Metoprolol 2.5-5 mg up to 15 mg	Verapamil 5-10 mg; 0.125 mg/min infusion	Amiodarone

Data from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014; 130:e199–267.

patients, rate control with medications and anticoagulation are the mainstay of therapy.

Several different classes of medication can be used for rate control. The most common medications are calcium channel blockers, β-blockers, amiodarone and digoxin (Table 51.4). Therapy must be individualized to the patient and clinical scenario (see Chapter 11).

Intravenous β-blocker therapy is useful in the perioperative period where a high catecholamine state may drive RVR. Esmolol has a rapid onset and offset, making it an attractive choice, because patient response to β-blockade can be unpredictable. If hemodynamic instability is precipitated by therapy, the short-acting effect of esmolol is beneficial. Metoprolol is a longer-acting β-blocker available in oral and intravenous form. Side effects of β-blockers include the potential for airway hypersensitivity, hypotension, or worsening HF.

Calcium channel blockers (CCBs) are also a well-known therapy for AF with RVR. Nondihydropyridine CCBs such as diltiazem or verapamil are medications of choice. Diltiazem has a rapid onset and offset. A bolus dose of 0.25 mg/kg followed by an infusion of 5 to 15 mg/hour is an effective method of rate control.[81] Verapamil is less commonly used in the perioperative setting and is associated with more negative inotropy than diltiazem. Caution should be used in HF patients given the negative inotropic properties of CCBs.

Amiodarone is commonly used for rhythm control in AF but can be used for rate control.[82] Its pharmacologic profile (prolonged action) and long-term side effects (thyroid dysfunction, hepatic and pulmonary toxicity) make it less attractive in the perioperative setting. Despite this, some advocate its use in the ICU, citing less hypotension when compared with other regimens.[83]

Supraventricular Tachyarrhythmia

The term *supraventricular tachyarrhythmia (SVT)* refers to any arrhythmia originating above the AV node. It can be subdivided into irregular and regular rhythms with irregular rhythms largely consisting of AF or atrial flutter. Regular SVT includes AV nodal reentry, AV tachycardia in both orthodromic and antidromic forms, AV junctional tachycardia, and other less common types. In the perioperative period, several pathophysiologic mechanisms may precipitate SVT. Common causes include acidosis, hypercarbia, hypoxemia, electrolyte disturbances, hypotension, mechanical irritation of the atria or pulmonary veins, medications, and myocardial ischemia. Investigation into the precipitating factor is a key component in the management of SVT. This includes laboratory analysis and ECG. Resolution of the arrhythmia may be prompt with correction of the underlying disturbance.

Treatment is determined by the stability of the patient. Unstable patients require synchronized cardioversion and should be managed with advanced cardiac life support (ACLS) guidelines. In stable patients, vagal maneuvers (eg, Valsalva maneuver) may be attempted first. Although carotid massage is a known vagal stimulant, caution should be used because inadvertent carotid injury and stroke have been described.[84] Adenosine temporarily slows conduction through the sinoatrial (SA) node and renders the AV node refractory to depolarization. This transient effect makes adenosine a reasonable choice for the treatment of narrow-complex SVT. In the absence of underlying structural heart disease (eg, AS, MS), SVT is often stable and rate control with β-blockade, CCBs, or amiodarone is reasonable.

The treatment of wide-complex SVT and reentrant tachycardia may be more complex. Disorders with accessory pathways such as Wolff-Parkinson-White may respond paradoxically when conduction through the AV node is slowed. This is mediated by increased conduction through the accessory pathway. Every effort to distinguish wide complex SVT from ventricular tachycardia should be made. Amiodarone may be considered in these situations, along with cardiology consultation for use of more advanced antiarrhythmic medications.

Ventricular Arrhythmias

Ventricular arrhythmias arise below the AV node and are typically a wide-complex rhythm. This most commonly originates in scarred or damaged ventricular muscle, creating a conduction pathway outside the normal His-Purkinje system. Wide-complex ventricular rhythms should be differentiated from SVT with aberrancy as the treatment may differ. Baseline ECG characteristics may offer differentiating clues.

Ventricular tachycardia (VT) can be subdivided into nonsustained VT (NSVT) and sustained VT. NSVT is defined as three or more premature ventricular contractions with a rate of 120 beats per minute or more, lasting less than 30 seconds.[85] The incidence may be as high as 50% in patients undergoing major surgery.[86] However, in the absence of underlying disease (MI), aggressive therapy is not indicated. Nevertheless, a search for precipitating causes may be prudent (electrolyte imbalance, ischemia). In patients with myocardial injury and reduced ventricular function, more aggressive therapy with antiarrhythmics or implantable defibrillators may be indicated and consultation with cardiology is recommended.[87–89]

Sustained VT can be subdivided into monomorphic and polymorphic types. Monomorphic VT demonstrates a consistent QRS amplitude and is often related to a reentrant pathway within scarred myocardium.[85] Urgent synchronized cardioversion (50–100 joules, biphasic) is often required. As with other arrhythmias, treatment of the underlying cause should be established. Rate control with medication such as β-blockers and CCBs may be useful, but the risk of hypotension is high, and prompt cardioversion is often preferred. ACLS guidelines provide a framework for management.[90]

Polymorphic VT may be associated with normal or long QT intervals and causes may vary. Normal QT polymorphic VT is often associated with myocardial ischemia. Prolonged QT forms may be related to medications or precipitated by underlying genetic predisposition or both.[91] Treatment includes correction of underlying electrolyte disturbances, intravenous magnesium (2–4 grams), and asynchronous cardioversion. More advanced therapies with antiarrhythmics and, potentially, overdrive pacing may be needed.[91] Consultation with cardiology is warranted.

Pulmonary System

There is a broad spectrum of critical care issues involving the pulmonary system in the perioperative setting. This may arise from primary pulmonary disease, such as COPD, or secondary manifestations, such as cardiogenic pulmonary edema or neuromuscular weakness. This section will focus on key perioperative respiratory diseases, including pulmonary edema, COPD exacerbations, and acute lung injury/acute respiratory distress syndrome, as well as management strategies for these syndromes in the perioperative setting of noncardiac surgery.

Respiratory Failure

Respiratory failure can be categorized into two broad types (Table 51.5).

Type 1: Respiratory Failure—Hypoxemic

Hypoxemic respiratory failure is typically associated with parenchymal lung diseases that affect oxygen exchange at the alveolar level. It is defined as a Pa_{O_2} less than 50 mm Hg on room air. Five pathophysiologic mechanisms can explain hypoxemia, including low oxygen admixture, ventilation and perfusion mismatch, shunting, diffusion

TABLE 51.5 Mechanism and Risk Factors for Respiratory Failure, by Type

	Definition	*Mechanism*	*Common Diseases and Risk Factors*
Type 1	Hypoxemic	Low O_2 admixture	Cardiogenic pulmonary edema
		V/Q mismatch	Acute respiratory distress Syndrome
		Shunting	Pulmonary embolism
		Diffusion impairment	Pneumonia
		Alveolar hypoventilation	Shunts (right to left)
Type 2	Hypercarbic	Central respiratory depression	Neuromuscular disorders Amyotrophic lateral sclerosis Guillain-Barré syndrome
		Respiratory system mechanical failure	
		Respiratory muscle fatigue	Chronic obstructive pulmonary disease

impairment, and alveolar hypoventilation.[92] Shunt physiology is unique because it is nonresponsive to supplemental oxygen. Pulmonary edema and acute respiratory distress syndrome (ARDS) are two examples of hypoxemic respiratory failure and will be discussed later.

Type 2: Respiratory Failure—Hypercarbic With or Without Hypoxemia

Hypercapnic respiratory failure is associated with ventilatory failure and inadequate carbon dioxide elimination. It occurs when the $PaCO_2$ increases above 50 mm Hg in patients without chronic CO_2 retention[93] and may be associated with hypoxemia. There are three main causes of ventilation failure: depression of the respiratory centers in the brainstem, mechanical dysfunction of the respiratory muscles and associated structural tissues (ie, the chest wall and diaphragm), and respiratory muscle fatigue associated with increased work of breathing.[94] Depressed respiratory drive from medication effects (ie, narcotics, inhalation anesthetics) is a classic cause of hypercapnic respiratory failure in the perioperative period. In the ICU, COPD is the most common etiology of type 2 respiratory failure. Rare neuromuscular diseases (ie, amyotrophic lateral sclerosis, muscular dystrophy, and myasthenia gravis) may lead to chronic hypercapnic respiratory failure.[95]

Postoperative Respiratory Failure

Postoperative respiratory failure may be defined as unplanned intubation and mechanical ventilation within 48 hours of surgery.[96] It is a serious complication associated with an 18-fold increased risk of death.[96] Postoperative respiratory failure may be either hypoxemic or hypercarbic depending on the underlying pathophysiology. Patients may also require intubation for impending respiratory failure before hypercarbia or hypoxemia develops. Risk factors for postoperative respiratory failure are either patient related or procedure/anesthesia related. Patient factors include ASA score higher than 3, advanced age, ethanol use, tobacco use, COPD, insulin-dependent diabetes mellitus, HF, hypertension, cancer, liver dysfunction, cachexia and weight loss, and morbid obesity (body mass index [BMI] > 40).[97,98] Surgical and anesthesia factors include emergency surgery, medium- to high-risk surgery, surgery for sepsis, surgical location (upper abdominal or thoracic surgery), and surgery lasting greater than 2 hours.[97–100] General anesthesia may pose a higher risk of postoperative respiratory failure than regional/neuroaxial anesthesia, although this remains controversial.[97–100] Residual neuromuscular blockade is an important risk factor for immediate perioperative respiratory failure.[101]

Respiratory Failure in Circulatory Shock

Circulatory shock–associated respiratory failure develops when an imbalance between respiratory muscle oxygen supply and demand occurs. Respiratory compensation for metabolic acidosis requires an increased minute ventilation to decrease the $PaCO_2$.[102] Increased work of breathing requires greater oxygen supply, which is compromised in shock. Respiratory muscles fatigue and fail when the oxygen supply is insufficient to maintain the higher respiratory workload.[93]

Pulmonary Edema

Starling forces control the net flow of fluid across the alveolar membrane and are proportional to the permeability and surface area of the alveolar membrane, as well as the balance between hydrostatic and oncotic pressures of both the capillaries and alveoli. In the normal lung, the extravasation of fluid from the capillaries into the alveoli is matched by the lymphatic systems ability to drain the lung water. Imbalances in the Starling forces cause pulmonary edema[103] and occur primarily from a high hydrostatic pressure in cardiogenic pulmonary edema or increased alveolar capillary permeability in noncardiogenic pulmonary edema. The endothelial glycocalyx layer normally provides resistance to fluid movement out of the intravascular space. Damage to the glycocalyx layer by ischemia, inflammation, and hypervolemia promotes pulmonary edema.[104] Restoration of the normal ebb and flow of alveolar lung water is often rapid in cardiogenic pulmonary edema as the elevated hydrostatic forces are normalized with diuresis. In contrast, the resolution of noncardiogenic pulmonary edema can be prolonged and requires the restoration of the integrity of the alveolar membrane. In severe cases, the alveolar membrane may not heal and is replaced by fibrotic scar tissue.[105] The patient with pulmonary edema typically presents with tachypnea, dyspnea, and hypoxemia. Differentiating between cardiogenic and noncardiogenic pulmonary edema can be challenging, and the use of echocardiography or other means of evaluating cardiac function may be necessary.

Cardiogenic Pulmonary Edema

Cardiogenic or volume overload pulmonary edema can present with slowly progressive dyspnea or an acute dyspnea referred to as flash pulmonary edema. Slowly progressive edema is caused by a decline in cardiac function and progressive accumulation of intra- and extravascular fluid. Contributing factors include medication effects (noncompliance or inadequate dose), renal dysfunction, and respiratory infection.[106] Flash pulmonary edema is caused by abrupt physiologic derangement, such as a sudden increase in blood pressure, acute myocardial ischemia, acute myocarditis, acute valve dysfunction (ie, mitral regurgitation), or arrhythmia.[106] Elevated filling pressures in the left heart cause an increase in pulmonary venous pressures. Increased hydrostatic pressure in the pulmonary capillary bed forces a transudative edema fluid into the interstitium and the alveoli when the left atrial pressure increases above 18 mm Hg.[103] Alveolar fluid impairs oxygen exchange and results in hypoxemia.

Evaluation of the patient with pulmonary edema should focus on the severity of the respiratory distress and required respiratory support, then shift to an assessment of etiology. Precipitating factors and associated symptoms should be investigated. Patient symptoms such as breathlessness, orthopnea, reduced exercise tolerance, fatigue, and ankle swelling are suggestive of cardiogenic pulmonary edema. Chest radiograph and 12-lead ECG are standard, and laboratory evaluation should include cardiac troponins, complete blood count, complete metabolic panel, and BNP level.[107] An elevated BNP can be useful in the initial diagnosis of cardiogenic versus noncardiogenic pulmonary edema. BNP provides a high sensitivity and specificity for acute HF, and low levels may exclude cardiogenic pulmonary edema.[107–109] BNP trends as a marker of improvement in cardiogenic pulmonary edema, and HF must be used with caution, because it may not correlate with invasive hemodynamic measurements of volume status.[110] Transthoracic echocardiography is recommended for definition of cardiac structure and function (see Chapter 46).

Urgent treatment of pulmonary edema focuses on correction of hypoxemia and stabilization of respiratory distress. Patients with mild to moderate dyspnea and hypoxemia can often be treated with supplemental oxygen via nasal cannula; however, more severe dyspnea may require noninvasive or invasive mechanical ventilation. If not

contraindicated, noninvasive ventilation (NIV) is often attempted before intubation and mechanical ventilation. Compared with patients using a nasal cannula or facemask, those who receive NIV have quicker resolution of their respiratory symptoms and decreased need for intubation.[111] It remains unclear whether there is a mortality benefit from NIV.[112] After respiratory stabilization, diuresis and afterload reduction should be considered. Loop diuretics are the mainstay of therapy for volume overload in cardiogenic pulmonary edema. Hypoxemia and respiratory distress improve as pulmonary edema resolves with a negative fluid balance.[113] Afterload and preload reduction with vasodilators, often nitroglycerin, reduces cardiac workload and may hasten recovery.[114] Inotropes and advanced mechanical heart failure therapies may also be necessary.

Noncardiogenic Pulmonary Edema

The most important cause of noncardiogenic pulmonary edema is ARDS. Less common etiologies of noncardiogenic pulmonary edema include neurogenic, diffuse alveolar hemorrhage, medication-induced (naloxone), and negative-pressure pulmonary edema.[115] Initial treatment of these disorders is similar to the therapy of cardiogenic pulmonary edema and includes stabilization of the respiratory distress with oxygen therapy, NIV, or invasive mechanical ventilation, and loop diuretics are often employed for a negative fluid balance as described earlier.

Negative-Pressure Pulmonary Edema

Negative-pressure pulmonary edema occurs when extreme negative intrathoracic pressure (deep breath) occurs against an obstructed airway. The obstruction can be due to an obstructed endotracheal tube, laryngospasm, or an upper airway obstruction. The large negative inspiratory force against an obstructed airway creates a vacuum effect and draws fluid into the alveoli resulting in pulmonary edema characterized by pink, frothy sputum. The presentation can be immediate or delayed. The incidence may be as high as 11% in patients with complete airway obstruction.[116] The notion that negative-pressure pulmonary edema is typically associated with individuals who are capable of generating significant negative intrathoracic force may be misleading. Many patients who develop this disorder have preexisting cardiac disease (eg, valvular disorders and hypertrophic cardiomyopathy), and the pulmonary edema may be multifactorial.[117]

Acute Respiratory Distress Syndrome

ARDS is a common cause of respiratory failure, affects approximately 200,000 people a year, and is associated with 15% of all ICU admissions.[118] ARDS is characterized by diffuse alveolar damage leading to increased alveolar capillary permeability resulting in pulmonary edema, hypoxemia, and respiratory distress.[119] The most common causes are pneumonia (viral or bacterial), sepsis, trauma, gastric aspiration, transfusion related, medications, and, pancreatitis.[119] The historic diagnosis of ARDS has required three classic criteria: Pa_{O_2}/F_{IO_2} less than 200, bilateral patchy opacities on chest radiograph, and a pulmonary capillary wedge pressure less than 18 mm Hg to exclude cardiogenic pulmonary edema.[120] More recent criteria were established in 2012 by the Berlin Task Force on ARDS because of an increasing awareness that patients with ARDS may have elevated left-heart filling pressures. The diagnosis of ARDS now requires hypoxemia, bilateral opacities on chest radiograph, and the pulmonary edema must be associated with a clinical insult and *not* fully explainable by cardiac function.[121] The Berlin Task Force defined ARDS severity by the degree of hypoxemia with Pa_{O_2}/F_{IO_2}: mild, 200–300; moderate, 100–200; severe, less than 100. These classifications are correlated with increasing mortality rates,[121] which range from 26% to 35%.[122] The cause of death in ARDS is most often related to multisystem organ failure and bacterial sepsis. However, the severity of hypoxemia, dead space fraction, and RV dysfunction are risk factors of poor prognosis.[123]

In contrast to the transudative fluid seen in cardiogenic pulmonary edema, the edema fluid seen in ARDS is exudative and is slower to resolve. Treatment of ARDS is supportive and requires treatment of the underlying condition (eg, antibiotics and source control for sepsis). The mainstay of therapy for ARDS is lung protective ventilation and conservative fluid management. Lung protective ventilation consists of low tidal volume ventilation (6 mL/kg), maintaining plateau pressures less than 30 cm H_2O, and permissive hypercapnia to avoid ventilator-induced lung injury (volume trauma and barotrauma). Lung protective ventilation has been shown to decrease mortality by 22% compared with standard tidal volume ventilation (12 mL/kg).[124] Less iatrogenic injury from mechanical ventilation has led to decreased mortality rates for ARDS.[125]

Conservative fluid therapy in ARDS begins after circulatory shock has resolved (no longer requiring fluid boluses or vasopressors for 12 hours). The goal for conservative fluid therapy is a net negative fluid balance of 500 mL/day achieved through diuresis.[126] This has been shown to decrease ventilator-dependent days and ICU length of stay without increasing the need for renal replacement therapy.[127] Several adjuvant therapies may lead to an additional decrease in mortality from severe ARDS, including short-term muscle relaxation,[128] prone positioning in the ICU,[129] and extracorporeal membrane oxygenation[130] (see Chapters 33 and 39).

Chronic Obstructive Pulmonary Disease

COPD is a very common disorder and is projected to be the third leading cause of death by 2020.[131] Tobacco smoke inhalation continues to be the leading risk factor, and 70% of patients with COPD have a cardiovascular comorbidity requiring medication.[132] COPD is known to cause a constant, low-grade inflammatory response that accelerates atherosclerosis and is associated with a two- to threefold increased risk of cardiovascular death.[133] COPD is a major risk factor for postoperative complications, including pneumonia, respiratory failure, MI, cardiac arrest, sepsis, reoperation, and kidney injury/failure.[134]

COPD is characterized as chronic and progressive airflow limitations from damage to the lung parenchyma or inflammation of the airways. Patients often present with dyspnea, respiratory signs of distress (ie, accessory muscle use), increased sputum production, and chronic cough. Exposure to tobacco smoke is nearly universal, although there are other risk factors such as environmental exposures and rare genetic defects (α_1 antitrypsin deficiency). Common physical findings suggestive of COPD include expiratory wheezing, increased expiratory time, diminished breath sounds, and a barrel chest.[135] The diagnosis of COPD is confirmed with spirometry showing a post-bronchodilator FEV_1/FVC ratio less than 0.7 and FEV_1 less than 80% predicted value.[135] Assessment of COPD severity is important because disease severity directly relates to increased risk of exacerbation.[136] The Global Initiative for Chronic Obstructive Lung Disease has developed a simple disease severity scale based on FEV_1 with the assumption that the patient has an FEV_1/FVC less than 0.7. Patients with an FEV_1 less than 80% predicted value have mild disease; those with FEV_1 50–79, moderate; FEV_1 30–49, severe; and FEV_1 less than 30, very severe.[137] Other risk factors for exacerbation include GERD, asthma, HF, cancer, and respiratory infections.[138]

It is important for the anesthesiologist to recognize the severity of COPD in patients presenting for surgery. Preoperative pulmonary function testing should be considered for those who are at risk for COPD or have an established diagnosis of COPD. A specific level of functional status and spirometric data points have not been established for COPD patients who require an operation; however, information from pulmonary function testing may be beneficial in preoperative medical optimization. The risks/benefits discussion for an operation should include the potential need for postoperative mechanical ventilation. Medical records should be reviewed with a focus on medical management of COPD and propensity for exacerbation. Standard medical therapies for COPD include smoking cessation and inhalers for symptom alleviation. Bronchodilator therapy with a β_2-agonists (ie, albuterol, salmeterol) and/or antimuscarinics (ie, tiotropium) is

commonplace, as is inhaled corticosteroid. Oxygen therapy is added when patients develop resting hypoxemia, pulmonary hypertension, or HF.[137] These medications should be continued in the perioperative period.

COPD exacerbations are characterized by worsening of symptoms ranging from increased wheezing to hypercarbic respiratory failure. Treatment includes respiratory support with oxygen, noninvasive or invasive mechanical ventilation, and medical management. NIV is the mainstay of therapy in severe COPD exacerbations and has been shown to decrease mortality, need for intubation, and hospital length of stay.[139] Common initial settings for NIV are an inspiratory pressure of 12 cm H_2O and expiratory pressure of 5 cm H_2O with F_{IO_2} as needed. In the perioperative period, the anesthesiologist should be cognizant of the relative contraindications to NIV such as diminished mental status, ability to protect the airway/aspiration risk, recent and severe facial surgery or trauma, hemodynamic instability, and upper gastrointestinal surgery. Once NIV is initiated, frequent patient assessment is required. An arterial catheter may be considered for serial blood gas analysis. NIV failure is defined as no improvement or worsening of the respiratory acidosis within one hour of initiation and intubation should be considered.[140] Declining mental status and increased work of breathing are additional signs of NIV failure, suggesting intubation and mechanical ventilation. Similar to ARDS, the goal of mechanical ventilation in respiratory failure from COPD is avoidance of ventilator-induced lung injury from volume trauma and barotrauma. It may be prudent to adjust the inspiratory-to-expiratory ratio to account for a prolonged expiratory phase.[139] Pharmacotherapy for acute COPD exacerbations includes antibiotics for respiratory infection if needed, inhaled β_2-agonists (eg, albuterol), and anticholinergic agents (eg, ipratropium). Systemic corticosteroids are recommended.[137]

Hematology

Many aspects of perioperative medicine and anesthesia critical care involve the hematologic system. In the perioperative period, clinicians are often challenged by perturbations in the hematologic system, which may impair oxygen delivery and/or the coagulation cascade. This section will focus on three clinical challenges that the anesthesiologist may face in all phases of the perioperative period: management of chronic anticoagulation, massive hemorrhage, and venothromboembolism (VTE) prophylaxis and treatment.

Perioperative Management of Anticoagulation

A variety of disorders are treated with long-term anticoagulation; these range from prothrombotic disorders such as factor V Leiden to AF to problems with mechanical heart valves. The perioperative management of these anticoagulants must balance the need for anticoagulation with the increased risk of surgical bleeding. Risk factors for bleeding in chronically anticoagulated patients include mechanical mitral valve prosthesis (requires higher level of anticoagulation), cancer, history of bleeding complications from anticoagulation, restarting heparin anticoagulation within 24 hours of surgery, and heparin bridging.[141] The decision to stop, continue, or bridge anticoagulant therapy must be considered in the context of patient- and procedure-related risk factors such as a high-risk of stroke from AF or low surgical bleeding risk (ie, cataracts). This section will review the anticoagulants, the suggested timing of cessation before elective surgery, and anticoagulation reversal agents for emergent surgery or bleeding complications. Alterations in these medications should be coordinated with the managing physician (see Chapters 34 and 35).

Warfarin

Warfarin impairs the coagulation cascade by interrupting the carboxylation of factors II, VII, IX, and X, as well as the synthesis of protein C and S. The resultant anticoagulated state can be monitored with the prothrombin time (PT) or international normalized ratio (INR). Cessation of warfarin 5 days before surgery is a recognized strategy.[142] After surgery, warfarin can be reinitiated when the risk of thromboembolic disease outweighs the risk of bleeding. Patients may require bridging therapy with LMWH. The continuation of warfarin throughout the perioperative procedure may be acceptable in certain situations (ie, cataract surgery), and warfarin may be beneficial in some procedures such as catheter ablation of AF, in which the perioperative stroke risk is high and surgical bleeding risk is low.[143]

Several modalities of warfarin reversal exist, including vitamin K, fresh-frozen plasma, and prothrombin complex concentrates (PCCs). Activated factor VII may be considered as well. Reversal agents should be chosen based on the relative level of urgency, pharmacologic properties, and their associated side effect profile.

New Oral Anticoagulants (NOACs)

New pharmacologic agents have been developed with more specific inhibition of the coagulation cascade than warfarin. Several potential advantages over warfarin have been reported, including no requirement for serial laboratory testing (no laboratory testing is available), less dietary restrictions, and less potential for drug interaction. These agents include direct thrombin inhibitors (ie, dabigatran) and direct factor Xa inhibitors (ie, rivaroxaban, apixaban, and edoxaban). Notably, these medications have been shown to have a decreased risk of intracranial hemorrhage versus warfarin.[144] However, these agents have a decisive disadvantage to warfarin in the perioperative period because no specific antidotes exist and the treatment of serious and life-threatening bleeding is difficult.[145] Four-factor PCCs are nonspecific, but potentially useful reversal agents for the NOACs should hemorrhagic complications occur.[146,147]

Direct Thrombin Inhibitors

There are several direct thrombin inhibitors (DTIs), including hirudin, argatroban, and bivalirudin.[148] The most commonly used intravenous agent is argatroban, which is often used in patients who develop heparin-induced thrombocytopenia. Argatroban undergoes hepatic metabolism, and its elimination is independent of the kidneys, making it ideal for critically ill patients at risk for kidney injury. The anticoagulation effect can be measured by the PTT with a goal 1.5 to 3 times the patient's baseline. Argatroban infusion should be stopped 2 to 4 hours before an intervention or surgery. Confirmation of normal coagulation can be made by a normalization of PTT.[149] Bivalirudin has been used increasingly for similar indications and has the advantage of a very short half-life.

Dabigatran is an oral direct thrombin inhibitor. Of note, it can be reversed with idarucizumab (Praxbind) in emergency situations. Dabigatran is indicated for treatment of AF and VTE prophylaxis/treatment. Dabigatran use in artificial mechanical valves is unproven.[150] Caution should be used in patients with renal impairment because the half-life may be increased from 12 to 24 hours.[150] Routine coagulation tests such as PT and aPTT may be altered with dabigatran; however, the degree of alteration and the presence of a normal test does not exclude impaired coagulation. A normal dilute thrombin time suggests that the anticoagulation activity of dabigatran has resolved (Table 51.6).[151] The American Heart Association suggests that dabigatran should be held for at least 2 days before surgery and a dilute thrombin time obtained to confirm normalization. It is recommended that patients with renal dysfunction have surgery delayed at least 5 days.[150] The timing of neuraxial anesthesia in patients who have stopped dabigatran is not well defined. Dabigatran should be restarted after surgery when the risk of thrombosis outweighs the risk of bleeding because the onset of anticoagulation is very rapid.[150]

Treatment of serious and life-threatening bleeding is difficult with DTIs because there are no specific antidotes, with the exception of dabigatran. Key measures in the management of bleeding are cessation of DTIs and supportive care. In life-threatening bleeding, dialysis may facilitate faster removal of dabigatran from plasma. Four-factor PCCs and activated factor VII can be considered in life-threatening bleeding from dabigatran but have unproven efficacy.[150] Antifibrinolytics may

TABLE 51.6 New Oral Anticoagulants

	Mechanism of Action	*Half-Life (Hours)*	*Last Dose Before Surgery (Days)*	*Anticoagulant Monitoring*	*Safety of Neuroaxial Anesthesia*	*Reversal Agents in Hemorrhagic Complications (Nonspecific)*
Dabigatran	Direct thrombin inhibitor	12	2 (CKD: 5)	None (Dilute thrombin time[a])	No data	Idarucizumab PCCs Factor VIIa Dialysis
Rivaroxaban	Factor Xa inhibitor	5-13[b]	2 (CKD: unknown)	None	No data	PCCs Factor VIIa
Apixaban	Factor Xa inhibitor	8-15[b]	2 (CKD: unknown)	None	No data	PCCs Factor VIIa

[a]A normalized dilute thrombin time suggests anticoagulation effect of dabigatran has resolved.
[b]Levy JH, Faraoni D, Spring JL, et al. Managing new oral anticoagulants in the perioperative and intensive care unit setting. *Anesthesiology.* 2013; 118:1466–1474.

also be considered. The risk of hemorrhage and thrombosis should be considered before the use of these agents. Consultation with a hematologist is warranted.

Factor Xa Inhibitors

Factor X is produced in the liver by a vitamin K–dependent process, and the activated form converts prothrombin to thrombin. Oral inhibitors of activated factor X, rivaroxaban, apixaban, and edoxaban have been shown to be effective in the prevention of stroke in patients with nonvalvular AF. In addition, a decreased rate of major bleeding is associated with these inhibitors when compared with warfarin.[152,153] Factor Xa inhibitors are indicated for VTE treatment and prophylaxis, including in postsurgical patients after major joint arthroplasty. Factor Xa inhibitors are associated with a decreased incidence of bleeding compared with LMWH.[154–157] As with dabigatran, they are not indicated for treatment of artificial heart valves. No standard or specific laboratory assays of factor Xa inhibitors are available; thus routine monitoring of anticoagulation effects is not required. Factor Xa activity assays are under evaluation.[158] The safety of these drugs with neuroaxial anesthesia is unknown, and no recommendations exist regarding the time from discontinuation to the time of neuroaxial anesthesia. Bridging for procedures is not necessary for oral factor Xa inhibitors because they have short half-lives.

There are no specific reversal agents to oral factor Xa inhibitors in patients with bleeding complications. The mainstay of treatment is cessation of the anticoagulant and supportive care. A normal factor Xa activity assay suggests no anticoagulant effects.[158] Four-factor PCC and activated factor VII can be considered in life-threatening bleeding, but these have unproven efficacy.[159,160] The risk of thrombosis should be considered before the use of these reversal agents, and they should generally be titrated to effect. Antifibrinolytics may be considered. Consultation with a hematologist is strongly suggested.

Massive Hemorrhage

Massive hemorrhage is a significant cause of morbidity and mortality worldwide. The anesthesiologist is confronted by massive hemorrhage in a variety of clinical settings, including trauma, obstetric hemorrhage, gastrointestinal bleeding, and major operations (spine, transplantation).[161] Massive hemorrhage is defined as the need for more than 10 units of packed red blood cells (PRBCs) or approximately a patient's total blood volume in 24 hours, transfusion of more than 4 units of PRBCs in 1 hour, and/or replacement of more than 50% of total blood volume in 3 hours.[161] Coagulopathy of massive transfusion can develop quickly from hypothermia, dilutional coagulopathy, platelet dysfunction, fibrinolysis, and hypofibrinogenemia.[162] The pathophysiologic changes associated with massive transfusion have led to a clinical interest in higher ratios of blood product transfusion (plasma-to-platelets-to-red blood cells such as 1:1:1) and have been shown to be effective in preventing early mortality (within 24 hours) of trauma patients.[163] The exact ratio of plasma-to-platelets-to-red blood cells has not yet been delineated, and a large study of trauma patients that compared a ratio of 1:1:1 with a ratio 1:1:2 showed no difference in mortality at 24 hours or 30 days. However, more patients in the 1:1:1 group achieved hemostasis, and fewer died of exsanguination in the first 24 hours.[164] Furthermore, a systematic review showed no strong evidence to use a precise blood product transfusion ratio.[163,165] Notably, the data on massive transfusion have been geared toward trauma patients. It is unclear if the high platelet-to-plasma-to-red blood cell ratios is generalizable to other patient populations experiencing massive hemorrhage, specifically those with cardiac disease undergoing noncardiac surgery (see Chapters 34 and 35).

The treatment of massive transfusion relies on a multidisciplinary approach fostering excellent communication and efficiency between the care team and supportive services such as the blood bank and laboratory. Massive transfusion protocols have been developed to overcome institutional barriers and help facilitate the care of these critically ill patients. Multiple protocols exist and vary in the ratio of platelets-to-plasma-to-red blood cells but are related in their formula-based approach (no laboratory tests) to coordinate care and improve efficiency.[166] Adherence to formula-driven massive transfusion protocols has been associated with improved survival from massive hemorrhage.[167] Laboratory-driven transfusion protocols have been created, but they are limited by long laboratory turnaround times and subsequent questioning of the relevancy of the laboratory tests. Massive transfusion protocols based on point-of-care testing such as thromboelastography (TEG) or thromboelastometry (TEM) have been shown to be noninferior to formula-driven protocols.[168] TEG- and TEM-based protocols may actually decrease the amount of blood product administration, which may lead to a decrease in transfusion-related morbidity and mortality. TEG and TEM may elucidate a specific pathology of massive transfusion coagulopathy and lead to targeted therapy such as antifibrinolytics, cryoprecipitate, PCCs, or activated factor VII.[169]

One of the main complications of massive hemorrhage is death by exsanguination or inadequate transfusion, which accounts for approximately 40% of associated mortality.[170] The coagulopathy of massive transfusion and the treatment are addressed in the preceding section. Transfusion-related reactions can also account for significant morbidity and include hemolytic and nonhemolytic reactions, immunologic reactions such as transfusion-related acute lung injury (TRALI), circulatory affects such as transfusion-associated circulatory overload (TACO), and metabolic effects including hypocalcemia, hypomagnesemia, hyperkalemia, metabolic acidosis from hypoperfusion, and hypothermia.[161] Complications are more likely in patients with preexisting comorbidities including those with cardiac disease.

Venothromboembolism Prophylaxis and Treatment in the Perioperative Setting

Venothromboembolism is a common and serious complication in the postoperative setting. The overall risk of VTE with appropriate prophylaxis is approximately 1%, but it can be as high as 2.5% in high-risk procedures such as joint replacement.[171] Risk factors include age greater than 60, history of VTE or thrombophilia, cancer, comorbid medical conditions such as HF or infection, bed bound or decreased activity

level for three or more days, obesity, and ICU admission. High-risk patients may have as much as a 6% risk of VTE.[172,173] Guidelines from the American College of Chest Physicians regarding VTE prophylaxis fall into four patient categories: very low, low, moderate, and high-risk with corresponding risk of VTE at less than 0.5%, 1.5%, 3%, and 6% percent, respectively. Very-low-risk patients require no pharmacologic or mechanical VTE prophylaxis. Sequential compression boots are recommended for low risk patients. Moderate-risk patients should receive sequential compression boots and pharmacologic prophylaxis with a heparinoid. The recommendation for high-risk patients is mechanical and pharmacologic prophylaxis that is extended 4 weeks postoperatively.[174] Patients undergoing joint arthroplasty are at especially high risk of VTE complications postoperatively, and it is recommended that chemoprophylaxis of VTE be extended to 35 days with LMWH, warfarin, dabigatran, apixaban, edoxaban, or rivaroxaban.[175] IVC filters may be considered for patients at high-risk of VTE with contraindications to anticoagulation.

Treatment of VTE can be separated into two subsets: isolated deep venous thrombosis (DVT) and pulmonary embolism (PE). Both scenarios require anticoagulation in the absence of contraindication; however, PE with major impact on cardiovascular and pulmonary systems may benefit from thrombolytic therapy. The CHEST guidelines for initial therapy of DVT and PE recommend intravenous anticoagulation (ie, heparin or argatroban in HIT) or oral rivaroxaban. Treatment of initial VTE should be for 3 months with LMWH, fondaparinox, or warfarin.[176] The NOACs also have gained approval for VTE treatment. Patients who have VTE but are unable to be anticoagulated may benefit from an IVC filter.

The presentation of PE consists of dyspnea, chest pain, and occasionally hemoptysis. Massive PE is defined as PE associated with hypotension (SBP < 90) and shock. It occurs in approximately 4.5% of all PEs and is associated with a very high mortality rate (~50%).[177] The gold standard diagnostic tool of PE is pulmonary angiography, but it is typically not required because CT angiography of the chest has high sensitivity and specificity.[178] Ventilation-perfusion nuclear medicine scan is occasionally used for diagnosis of patients with suspected PE who are hemodynamically stable, but have contraindications to CT angiography of the chest. Echocardiography for PE may be useful in hypotensive patients who are unable to have a CT angiography of the chest. Echocardiography is neither sensitive nor specific, but new RV dilation and dysfunction is suggestive of massive PE in the setting of suspected PE. Thrombus may be identified in the right-sided heart structures or in the pulmonary artery. Furthermore, a normal RV in a hypotensive patient makes PE an unlikely etiology.[178]

Hemodynamically stable PE requires no additional treatment beyond anticoagulation . Treatment of massive PE focuses on reperfusion of the lung and dissolution of the thrombus and systemic thrombolytic therapy as recommended by the Chest Guidelines and European Society of Cardiology.[176,178] If contraindications exist to systemic thrombolytic therapy, then catheter-guided thrombolytic therapy, catheter-guided embolectomy, or surgical embolectomy is recommended given the high mortality rate.[176,178] If evidence of thrombus is found in the RV, surgical embolectomy may be preferred to catheter-guided embolectomy.[177] Supportive care includes respiratory support with intubation and mechanical ventilation and hemodynamic therapy with vasopressors and inotropes.

Sepsis

Infection and sepsis account for approximately 21% of all admission to the ICU with approximately 750,000 cases per year.[179,180] The most common sites of infection are respiratory, blood stream, genitourinary, abdominal, and prosthetic device infections.[180] Mortality from severe sepsis has improved significantly but remains approximately 18% to 30%.[181] Anesthesiologists encounter patients with sepsis in several settings, including the operating room for source control of the infection (ie, ureteral stents for pyelonephritis/hydronephrosis, exploratory laparotomy for gastrointestinal derived sepsis), off-site locations (ie, diagnostic radiology, interventional radiology, GI lab for ERCP), and the ICU for supportive procedures and management (ie, intubation, vascular access procedures, arterial catheter placement).

Sepsis is defined along a spectrum that requires suspected or confirmed infection and the systemic inflammatory response syndrome (SIRS). SIRS criteria include temperature dysregulation (>38.3°C or < 36.0°C), tachycardia (HR > 90), tachypnea (RR > 20), and leukocytosis or leukopenia.[181] Severe sepsis includes the criteria for sepsis and objective evidence of organ dysfunction. Septic shock is vasodilatory shock unresponsive to aggressive fluid resuscitation.[182] Sepsis is a syndrome, and its presentation can vary as widely as the infections that cause sepsis. Presentation also depends on associated organ system dysfunction and preexisting medical conditions such as cardiac disease and COPD.

The initial treatment of sepsis revolves around three concepts: source control, antibiotics, and early goal-directed resuscitation. Initial evaluation of the patient with suspected sepsis should focus on anatomic etiology of the infection. A detailed history and physical examination can help guide the diagnostic workup. Intravenous access should be obtained and laboratory inquiries may include blood cultures, CBC, CMP, lipase, coagulation parameters, and lactate. Radiographic workup will likely involve chest radiography and imaging such as computerized tomography. If an anatomic infection is identified, source control by surgery, interventional radiology, or ERCP may be required.[183]

Empiric broad-spectrum antibiotics should be started early for a patient with suspected sepsis.[183] Antiviral and antifungal agents should be considered in patients at risk for such infections. Targeted antibiotic therapy should be delayed until a causative organism is identified and sensitivities to antibiotics are determined.

The Surviving Sepsis Campaign recommends protocolized resuscitation in patients presenting with sepsis-associated hypotension and elevated blood lactate levels.[183] Treatment goals include a central venous pressure of 8 to 12 mm Hg by aggressive crystalloid administration, a mean arterial pressure of 65 mm Hg by vasopressors as needed, urine output greater than 0.5 mL/kg/hr, and a central venous oxygen saturation of 70% by PRBC transfusion to a hematocrit greater than 30%. Inotropic support should be considered as needed.[184] Early GDT improves mortality rates and decreases organ system dysfunction. Norepinephrine is considered the vasopressor of choice in septic shock, and vasopressin is often added as a second-line agent if needed.[185,186] Lactate clearance is also a well-defined goal of sepsis resuscitation.[187]

It must be noted that the resuscitation and recommendations from the Surviving Sepsis Campaign have been questioned with emerging data from large randomized controlled trials. Two large trials were published in 2014 (1600 patient trial in Australia and New Zealand and 1341 patient trial in the United States) comparing nonprotocolized care to protocolized early GDT in early sepsis patients and found no difference in mortality, length of hospital stay, or duration of organ system support.[188,189] In light of this new information, the sepsis guidelines may be modified.

Sepsis presents a major challenge for patients with preexisting cardiac disease because the vasodilatory state places increased workload on the heart. Patients with compromised hearts may have significant difficultly meeting this demand, and mortality of patients with HF in sepsis may be as high as 70%.[190] Furthermore, it is well established that the septic state is a potent myocardial depressant. Advanced hemodynamic monitoring with pulmonary artery catheter (PAC), TEE, transpulmonary thermodilution, or pulse waveform analysis may be useful for hemodynamic optimization.[191]

Perioperative anesthetic management of septic patients includes all of the considerations discussed earlier, including antibiotics and resuscitation with intravenous fluids and vasopressors. The induction and maintenance of anesthesia can be a considerable challenge because most agents are vasodilatory in nature. Consideration can be given to ketamine and etomidate, although concern about adrenal suppression after single-dose etomidate exists.[192] If propofol is used, dose reduction should be strongly considered. The minimum alveolar concentration (MAC) of anesthetic gases is decreased in sepsis.[193] Hemodynamic

monitoring with an arterial catheter, CVP and PAC pulse pressure variation, and/or TEE should be considered. Recovery in the ICU and postoperative intubation should also be considered.

In patients with preexisting cardiac disease, infections of cardiac implantable electronic devices (CIEDs) may cause sepsis. Infections of CIEDs are relatively common with an infection rate of 4%.[194] CIED infections consist of pocket infections, bloodstream infections, or CIED-related endocarditis. The majority of infections are from gram-positive skin flora; however, gram-negative bacteria may account for 20% of infections, and broad-spectrum antibiotic coverage should be strongly considered. Survival is improved in patients who have their device explanted.[194] Supportive treatment for sepsis in these patients should consider that there is coexisting cardiac disease, and advance monitoring should be strongly considered.

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Perioperative Care to Reduce Major Adverse Cardiac Events and Mortality in Noncardiac Surgical Procedures

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KEY POINTS

1. Major adverse cardiac events (MACE) are relatively common in patients undergoing noncardiac surgical procedures. The incidence of perioperative myocardial infarction (PMI) is 1% to 5%, whereas approximately 8% of patients experience a perioperative increase in cardiac troponins without other criteria for MI (myocardial injury after noncardiac surgery [MINS]).
2. Preventive and therapeutic strategies for acute coronary syndromes are well established in the nonsurgical setting, but clear evidence about the impact of such strategies on both incidence and outcomes of perioperative myocardial injury or PMI is lacking. Many therapeutic interventions that have cardioprotective properties may be difficult to apply, or even harmful, in the perioperative period.
3. Factors associated with an increased risk of MACE are patient specific (advanced age, high American Society of Anesthesiologists class, renal failure, anemia) and surgery specific (type of procedure, urgency, complexity, intraoperative complications). Several scoring systems allow clinicians to predict, both preoperatively (Revised Cardiac Risk Index, National Surgical Quality Improvement Program) and intraoperatively (ANESCARDIOCAT), the risk of cardiac adverse events and to identify patients who need preventive measures and strict intraoperative and postoperative monitoring.
4. Risk stratification is pivotal in patients with PMI or MINS because therapeutic options also depend on a careful balance between the risk of mortality associated with the cardiac complications and the risks (primarily bleeding) of therapeutic strategies (dual antiplatelet therapy, percutaneous coronary interventions).
5. Thrombolysis in Myocardial Infarction and Global Registry of Acute Cardiac Events scores allow reliable prediction of 30-day, 6-month, and 12-month mortality rates in patients with ST-segment elevation MI (STEMI) and non–ST-segment elevation MI (NSTEMI), respectively. Conversely, the risk of bleeding may be predicted according to the type of surgical procedure and patient-related factors (CRUSADE [Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines] score).
6. NSTEMI is the most common type of PMI. Unlike STEMI, it is often caused by an impaired balance between myocardial oxygen supply and demand in the absence of complete occlusion of a coronary vessel. Accordingly, the need for urgent revascularization is less stringent as compared with STEMI, whereas prevention or prompt treatment of conditions such as anemia, hypotension, hypoxia, pain, and tachycardia is of primary importance.
7. Percutaneous coronary intervention should always be considered in patients with perioperative STEMI, especially in patients with good life expectancy and moderate-to-large infarctions. Probably, only patients at low risk of death and at high risk of bleeding should be treated with medical therapy alone.
8. High-dose statins, aspirin, and low-dose oral β-blockers should be initiated within 24 hours in all patients with MINS, unless contraindicated. A platelet receptor P_2Y_{12} inhibitor (clopidogrel, prasugrel, ticagrelor) may be added when bleeding risk is decreased sufficiently. Angiotensin-converting enzyme inhibitors should be started in patients with an ejection fraction of less than 40%, hypertension, diabetes, and stable chronic kidney disease.
9. A novel Web-enabled, "democracy-based" approach to consensus building has been used to summarize the best-quality and most widely agreed-on evidence about mortality reduction in different settings, including the noncardiac surgical perioperative period.
10. Hemodynamic optimization, noninvasive ventilation, neuraxial anesthesia, selective decontamination of the digestive tract, and avoidance of β-blocker initiation shortly before surgical procedures may improve survival in patients undergoing noncardiac operations. Statins, tranexamic acid, and liberal transfusion strategies may also be considered to reduce mortality rates, but further investigations are needed.
11. Levosimendan, intraaortic balloon pump, volatile anesthetic agents, remote ischemic preconditioning, leukocyte depletion, and protective ventilation have been shown to reduce mortality rates in other settings, especially in cardiac surgical procedures. It is reasonable to suspect that these interventions will have similar beneficial effects in noncardiac surgical patients.

Despite technical improvements, major surgical procedures currently remain associated with high mortality and morbidity rates. In Europe, an overall 30-day mortality rate of 4% has been reported after major noncardiac operations, and the rate can reach 6% in high-risk populations.[1,2]

More than half of these deaths are attributable to *major adverse cardiac events* (MACE) including nonfatal cardiac arrest, acute myocardial infarction (AMI), congestive heart failure (HF), or new cardiac arrhythmias.[3] Cardiac complications are the most common causes of postoperative morbidity and death; they occur in up to 5% of adult patients undergoing surgical procedures, and they have a major impact on both length and costs of hospitalization.[4] Perioperative myocardial infarction (PMI) is the most dangerous cardiac complication, and coronary artery disease (CAD) is a major determinant of both early and late mortality rates.

Perioperative Myocardial Infarction or Injury

According to the third universal definition,[5] *myocardial infarction* (MI) is defined as a rise and fall in cardiac troponin (cTn) with at least one value above the 99th percentile upper reference limit (>0.014 ng/mL), together with at least one of the following:

- Ischemic chest pain
- New and significant electrocardiographic (ECG) changes such as ST-segment or T-wave changes, left bundle branch block, Q waves
- New regional wall motion abnormalities (echocardiography)
- Intracoronary thrombus (angiography or autopsy)

Myocardial injury after noncardiac surgery (MINS) is defined as (1) an elevation of postoperative troponin with an ischemic origin, (2) without other criteria of PMI, (3) that is prognostically relevant.[6] Two different mechanisms lead to PMI:[5] PMI type 1 is caused by spontaneous rupture of a vulnerable coronary plaque or, uncommonly, by severe coronary vasospasm, leading to platelet aggregation, occlusive (ST-segment elevation, STEMI) or nonocclusive (ST-segment depression, NSTEMI) thrombus formation, and prolonged myocardial ischemia resulting in cell death. Plaque disruption is demonstrated in autopsy studies in approximately 50% of patients who died of PMI.[7] PMI type 2 usually results from a sustained imbalance between myocardial oxygen supply (decreased) and demand (increased) combined with the presence of significant, obstructive, but not occlusive, CAD. Most patients with PMI type 2 have ST-segment depression (NSTEMI).

Patients undergoing major operations are particularly prone to ischemic adverse events because of the surgery-associated inflammation and hypercoagulable state, as well as perioperative factors that increase the risk of plaque rupture (pain, hypertension, elevated levels of catecholamines), increase myocardial oxygen demand (hypertension, tachycardia, elevated left ventricular [LV] diastolic pressure), or decrease myocardial oxygen supply (blood loss, anemia, hypotension, hypoxia, tachycardia, coronary vasoconstriction).[4] NSTEMI is the most common type of PMI. Compared with patients with STEMI, patients with NSTEMI are generally older, have multivessel and/or left main CAD more frequently, and often have multiple risk factors and comorbidities.[8]

Epidemiology of Perioperative Myocardial Infarction

In most studies the incidence of PMI is between 1% and 5%, whereas the incidence of MINS is 8%.[9,10] The rather wide variability in the rate of PMI reflects the different populations and type of surgical procedures (major or minor, vascular or nonvascular) considered, as well as the different definitions of PMI or ischemia (ST-segment deviation or troponin elevation) and troponin cutoff values used. Most PMIs (≈80%) occur on the ward, 48 to 72 hours postoperatively, whereas only 20% of PMIs develop in the operating room.[11,12] However, the risk remains elevated during the first 2 postoperative weeks in patients undergoing orthopedic surgical procedures.[11] Patients usually exhibit the strongest stress reaction within 72 hours postoperatively. Several factors may affect the myocardial oxygen delivery (DO_2)/myocardial oxygen consumption ($M\dot{V}O_2$) balance, including discontinuance of medications or decreased doses, preoperative diet, electrolyte disorders, pain, anxiety, stress reactions, bleeding, neuroendocrine changes (increased catecholamine release triggered by postoperative pain and other stresses), and alterations in the coagulation mechanism.

Diagnosis of Myocardial Ischemia and Infarction

The diagnosis of myocardial ischemia may be overlooked in the perioperative period. Indeed, some patients with myocardial injury do not meet the diagnostic criteria for PMI. Typical anginal symptoms occur in less than one-half of patients, and the symptoms are often masked by analgesics, advanced age, and diabetes. Some patients experience vague chest pain, shortness of breath, hemodynamic instability, and palpitations. ST-segment depression is quite common, occurring in approximately 30% of patients, whereas 20% of patients have T-wave inversion, and 10% have ST-segment elevation. Conversely, ECG changes may be only minor or transient in approximately 40% of patients.[4] However, continuous ECG monitoring is not widely used, and its implementation is difficult.

Because neither clinical symptoms nor ECG changes can guarantee early recognition of PMI, the best diagnostic tool is cTn. It is also a strong independent predictor of short-term and intermediate-term mortality rates. However, the interpretation of cTn increase can be troublesome in some cases because of the interference of renal dysfunction, cerebral disease, and inflammation.

Outcome After Perioperative Myocardial Damage

Perioperative myocardial damage has been linked to short-term, midterm, and long-term cardiac morbidity and death.[9] Because perioperative myocardial damage is most often silent, many patients remain untreated. This may also contribute to an increased risk of long-term cardiovascular (CV) death. Accordingly, perioperative cardiac monitoring should be implemented to allow early diagnosis and treatment.

Short-Term Outcome

An 11% to 25% 30-day mortality rate has been reported in patients with PMI.[10,11,13] In the large Perioperative Ischemic Evaluation Study (POISE) trial,[10] the 30-day mortality rate was 11.6% among patients who had a PMI and 2.2% among patients who did not.[14] Nonfatal cardiac arrest (odds ratio [OR], 14.5), HF (OR, 10.3), and coronary revascularization interventions are more common in this population.[6] Sixty percent of patients die within 7 days after MI occurrence, most of them within 48 hours. Acute HF, cardiogenic or septic shock, and multiorgan failure are the most common causes of death.

A simple score including three independent predictors of death—age 75 years or older (1 point), anterior ischemic findings (1 point), ST-segment elevation or new left bundle branch block (2 points)—showed a good correlation with 30-day mortality rates in patients with MINS.[6] According to this scoring system, predicted 30-day mortality ranged from 5.2% if none of the aforementioned predictors were present (0 points) to 49.8% if all of them were present (4 points) (Table 52.1). Patients with MINS have a lower risk of fatal cardiac events than do patients with PMI, but a higher risk of death than patients with no elevated cardiac biomarkers. In a large, international study, the 30-day mortality rate among patients with MINS was 9.8%, as opposed to 1.1% among patients without MINS.[6,11]

Long-Term Outcome

In addition to early adverse events, cTn also predicts late mortality rates. The 1-year mortality rate following vascular surgical procedures was shown to be 20% in patients with pathologic troponin increases, as compared with 4.7% in patients with normal values.[14] Identifiers of outcome included preoperative creatinine level greater than 2.0 mg/dL (OR, 2.55), preoperative history of HF (OR, 1.96), and age older than

TABLE 52.1 A Mortality Score in Patients With Myocardial Injury After Noncardiac Surgery[a]

Predictor	*Points*
Age ≥75 y	1
Anterior ischemic findings	1
ST-segment elevation or new left bundle branch block	2

[a]Expected 30-day mortality rates: 0 points = 5.2%; 1 point = 10.2%; 2 points = 19.0%; 3 points = 32.5%; 4 points = 49.8%.

Modified from Botto F, Alonso-Coello P, Chan MT, et al. Myocardial injury after non cardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors and 30 day outcomes. *Anesthesiology.* 2014;120:564–578.

70 years (OR, 1.62). These data show that in a homogeneous group of patients with documented CAD who undergo elective vascular surgical procedures, a combination of preoperative risk variables, including age, renal function, and previous HF, along with postoperative elevations in cardiac biomarkers in diabetic patients, predicts long-term outcome.

Risk Stratification and Prevention

The treatment of patients who develop a cardiac ischemic complication during or after noncardiac surgical procedures starts with prevention, through the identification of those factors and markers that can predict a complicated course. Variables significantly associated with an increased risk of MACE are as follows: (1) patient-specific: old age, high American Society of Anesthesiologists (ASA) class and cardiac risk indexes, renal failure, and anemia; and (2) surgery-specific: type of procedure (emergency or urgent, major operation, particularly vascular) and intraoperative complications (severe hypotension, serious bleeding, increased heart rate).

Patient's Age

The incidence of PMI and MINS increases significantly in patients more than 70 years old, especially in men with CV risk factors.[11,12] The OR is 1.84 and increases by 1.5 per decile. Mortality and death from CAD are strongly associated with age. As a consequence of the aging population, it is estimated that this problem will increase in future decades. Older patients are more frail, have multiple comorbidities, and exhibit more severe CAD. They also tend to present greater technical challenges during percutaneous coronary intervention (PCI) because of heavier coronary artery calcification, tortuous anatomy in coronary and peripheral arteries, increased risk of procedure-related complications (eg, contrast-induced nephropathy, vascular or neurologic complications), and reduced tolerance to bleeding problems.

Cardiac Risk Indexes

Two clinical indexes have been developed to estimate patients' risk of perioperative cardiac complications. The Revised Cardiac Risk Index (RCRI) incorporates six independent variables that predict the risk of cardiac complications: history of ischemic heart disease, HF, cerebrovascular disease, diabetes mellitus, chronic renal failure (serum creatinine >2 mg/dL), and major operations (suprainguinal vascular, intrathoracic, and intraperitoneal). Perioperative risk of both cardiac complications (eg, nonfatal AMI and nonfatal cardiac arrest) and death increases with index scores.[15–17] For example, in a large cohort study including 782,969 patients,[15] the in-hospital mortality rate was 1.4% for RCRI of 0, 2.2% for RCRI of 1, 3.9% for RCRI of 2, 5.8% for RCRI of 3, and 7.4% for RCRI of 4 and greater.

The RCRI is currently the most widely used cardiac risk stratification tool. However, it has several limitations, including its relatively low discriminative ability. In fact, although the RCRI has a moderately good ability to discriminate patients who develop cardiac events from those who do not after mixed noncardiac surgical procedures (area under the curve [AUC], 0.75), it is less accurate in patients undergoing vascular surgical procedures (AUC, 0.64), and it is less able to predict all-cause mortality (AUC median, 0.62).[18]

To overcome these limitations of RCRI, the National Surgical Quality Improvement Program (NSQIP) score was developed and validated on 211,410 surgical patients.[19] This model includes age, ASA class, functional status, abnormal serum creatinine, and a novel and more appropriate organ-based categorization of surgery. Risk may be quantified by a risk calculator on the Internet. The discriminative or predictive ability of the NSQIP score is significantly better as compared with RCRI (AUC, 0.88 vs 0.75). This risk index works well in vascular surgical patients.

Renal Failure

The most important comorbidity associated with poor postoperative outcome is chronic kidney disease (CKD). The rate of adverse cardiac events and the length of hospital stay increase significantly in patients with impaired renal function. A post hoc analysis of a large, prospective, multicenter investigation revealed that the rate of major adverse CV and cerebrovascular events was increased (OR, 3.9) in patients with CKD from stage 3b onward (estimated glomerular filtration rate <45 mL/min).[20]

Most of the CV disease risk factors, such as older age, diabetes mellitus, systolic hypertension (longer and more severe exposure), and low levels of high-density lipoprotein cholesterol, in addition to an inflammatory and thrombogenic milieu, are highly prevalent in patients with CKD. CAD and valvular disease are more common and severe in these patients, with one-half of all deaths resulting from cardiac causes. CKD-associated anemia also reduces myocardial oxygen supply and is associated with cardiomyopathy. LV hypertrophy increases myocardial demand and evolves toward diastolic dysfunction that impairs subendocardial perfusion and may be complicated by diastolic HF. The stiff ventricle is more vulnerable to preload and afterload changes, tachycardia, and loss of atrial kick during atrial fibrillation or other arrhythmias.

Some precautions may be useful to reduce the risk of perioperative cardiac events in patients with CKD. Stress testing can identify patients with CAD. The use of short-term statins is controversial (see later), but it is part of standard care in many centers. Discontinuation of angiotensin-converting enzyme inhibitor (ACEI) therapy for at least 10 hours before general anesthesia is recommended to reduce the risk of postinduction hypotension. Anemia may require preoperative blood transfusion, supplementation with iron, or administration of erythropoietin. Patients with end-stage renal disease should undergo dialysis the day before the operation.

The main goals during surgical procedures include a mean arterial pressure greater than 65 to 70 mm Hg (or higher for the uncontrolled hypertensive patient) and adequate volume status. Particular attention should be paid to analgesic requirements in the perioperative period. Opioids may accumulate in patients with CKD, with increased risk of respiratory depression, whereas nonsteroidal antiinflammatory drugs are not recommended because of the risk of worsening renal function.[21]

In patients with renal impairment, it is appropriate to measure baseline values of troponin to compare them with the postoperative values. Troponin values may be elevated in the setting of even mild renal failure, probably reflecting microinfarctions or LV hypertrophy.[22] However, patients undergoing dialysis who have elevated troponin levels are more likely to have severe angiographic CAD and high mortality risk.[23]

Anemia and Blood Transfusion

The prevalence of preoperative anemia (hemoglobin [Hb] <13 g/dL for men and <12 g/dL for women) is increasing in the surgical population, especially in older patients. In a large (39,309 patients) European study, anemia was found in 31% of men and 26% of women.[24] Preoperative anemia is commonly associated with comorbidities such as renal failure, CAD, HF, diabetes mellitus, and hepatic cirrhosis and is known to increase mortality rates. In fact, anemia reduces D_{O_2}, increases heart rate, and may be complicated by hypotension.

After adjustment for major confounders including transfusion, preoperative anemia has been shown to be strongly associated with a more

than twofold increase in 90-day mortality rates, as well as increased postoperative intensive care unit (ICU) admission and greater use of ICU resources (hemodynamic monitoring, mechanical ventilation, inotropic and vasoactive agents).[24–26] In particular, in-hospital mortality rates increase linearly with the reduction in hematocrit.[27]

Although anemia increases mortality rates, the consequent need for transfusions also may contribute to increased mortality (according to the "second hit" theory). However, some data suggest that blood transfusions may not necessarily be harmful and, particularly, that more liberal transfusion strategies may even be associated with reduced mortality rates in certain settings.[28–31]

Patients at risk for anemia who are undergoing elective surgical procedures should be screened 4 to 8 weeks preoperatively, and the causes of anemia (eg, blood loss, nutritional deficiencies, renal failure, chronic and/or inflammatory diseases) should be identified and treated. Iron supplementation (oral or intravenous [IV], depending on iron status or tolerance and timing of the operation) is recommended (grade 1C recommendation) in patients with iron deficiency (serum ferritin <30 μg/L). The efficacy of iron supplementation in raising Hb concentration and decreasing perioperative transfusion rate is well demonstrated. If iron deficiency is ruled out, erythropoietin-stimulating agents administered up to an Hb concentration of 12 to 13 g/dL are suggested (grade 2A recommendation). The need for blood transfusions has been shown to be reduced by approximately 50% in patients treated with these drugs (data from pooled studies including mainly orthopedic surgical patients). The risk of thrombotic complications, particularly in patients with CAD, coronary stenting, or risk of venous thrombosis, should be considered.[32,33]

Type of Surgical Procedure

The type of surgical procedure is a strong risk factor for MACE and death. Urgent or emergency operation has been well recognized as the strongest predictor of death, with an increase of more than three times in 30-day mortality rates (OR, 3.5). Unfortunately, it is a largely unmodifiable risk factor.[2,5,34]

Vascular surgical procedures are associated with a twofold to fourfold higher risk of adverse cardiac events (PMI, cardiac death) as compared with other types of noncardiac operations. In fact, CAD is more common among patients undergoing vascular surgical procedures (with a prevalence ranging from 37% to 78%) than in other noncardiac surgical patients.[35] Aortic cross-clamping and declamping, abrupt changes in systemic arterial pressure, fluid shifts, hypoxia induced by one-lung ventilation, acute anemia secondary to major bleeding, and inflammatory or hypercoagulable states induced by both surgical procedures and transfusions can trigger perioperative ischemia and MI, especially in patients with CAD, acute HF, or LV dysfunction.

The vascular procedure with the highest associated mortality rate is operation for abdominal aortic aneurysmal rupture, followed by elective thoracoabdominal aortic replacement, lower extremity arterial bypass, and carotid endoarterectomy.[16,36] Patients requiring lower extremity amputation also have diffuse and severe CAD (up to 92% in a pathologic study).[37] Accordingly, perioperative risk is high in these patients, with reported 30-day mortality rates of up to 17%[38] and PMI as the leading cause of postprocedural death. Conversely, endovascular aortic repair procedures are associated with reduced myocardial stress and, accordingly, with a decreased incidence of perioperative myocardial damage.[39] However, an increase in troponin levels after endovascular aortic repair procedures has been shown to be associated with a higher long-term incidence of adverse cardiac events (49 vs 15% in a follow-up period of 3 years).[40]

Cardiac Biomarkers

Preoperative Troponin

cTn has high sensitivity for detection of small amounts of myocardial necrosis. Increased cTn levels indicate the presence of, but not the underlying reason for, myocardial injury. Besides AMI, troponin release may be associated with many other disorders including HF, sepsis, and end-stage renal disease (Box 52.1). Regardless of the cause of cTn release, elevated cTn levels almost always imply a poor prognosis.

BOX 52.1 CAUSES OF TROPONIN ELEVATION IN THE ABSENCE OF MYOCARDIAL ISCHEMIA

Cardiac Causes
- Heart failure
- Cardiac arrhythmias
- Cardioversion
- ICD shock
- Myocarditis
- Pericarditis
- Cardiac amyloidosis

Noncardiac Causes
- Sepsis and septic shock
- Pulmonary embolism
- Primary pulmonary hypertension
- Pulmonary edema
- Chronic renal failure
- Stroke
- Subarachnoid hemorrhage
- High dose of chemotherapy
- Sympathomimetic drugs

ICD, Implantable cardioverter-defibrillator.

Elevated preoperative cTn values are found in a variable proportion of patients undergoing vascular surgical procedures. In the largest trial available,[41] the preoperative finding of increased cTn (high-sensitive troponin T, hsTnT) was present in up to 24% of patients, and it was independently associated with a significantly higher risk of PMI, cardiac death, and all-cause death. Moreover, hsTnT showed an additive value (AUC, 0.80) in association with cardiac risk index (AUC, 0.65) and natriuretic peptide levels (AUC, 0.76). A combined end point (including all-cause death, PMI, acute HF, and cardiac arrest) occurred in 9.4% of patients with hsTnT levels higher than 0.014 ng/mL, as compared with 1.9% in patients with hsTnT levels of up to 0.014 ng/mL ($P < .001$).

Possible causes of elevated cTn associated with adverse outcomes include silent myocardial ischemia or microinfarction, LV dysfunction, cerebrovascular disease, renal impairment, sepsis, pulmonary hypertension, and pulmonary embolism. The need to add cTn to routine preoperative tests performed in high-risk surgical patients is still debated. According to the 2014 European Society of Cardiology/European Society of Anaesthesiology (ESA/ESC) guidelines,[42] the assessment of cTn in high-risk patients, both before and 48 to 72 hours after major surgical procedures, may be considered (class IIb, level B), even if the suboptimal specificity of this test should be taken into account.

A practical approach in patients with preoperatively increased troponin levels involves a baseline transthoracic echocardiogram (primarily assessing ventricular function and regional wall motion), a cardiologic consultation, and when feasible, deferral of operation until the troponin levels fall (Fig. 52.1). If it is not possible to postpone the procedure, a less invasive surgical approach, targeted perioperative monitoring, and careful cardiac optimization should be recommended. Moreover, patients should be informed about the increased risk.

Postoperative Troponin

Evaluation of peak cTn level during the first 3 days after noncardiac surgical procedures improves the ability to identify patients with myocardial damage, even in the absence of symptoms or ECG changes. This value is also an independent predictor of 30-day mortality rates. In a recent large international cohort study involving 15,065 patients

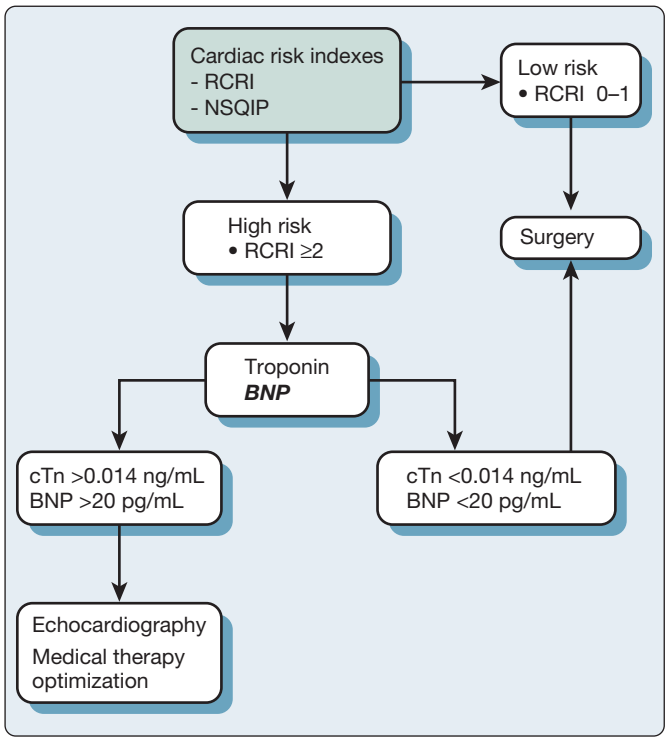


Fig. 52.1 Preoperative risk stratification. *BNP,* Brain natriuretic peptide; *cTn,* cardiac troponin; *NSQIP,* National Surgical Quality Improvement Program; *RCRI,* Revised Cardiac Risk Index.

aged 45 years old or older from five continents, an abnormal value of TnT (≥0.04 ng/mL) was found in 8% of patients within 3 days after noncardiac surgical procedures, and it was an independent predictor of 30-day mortality rates (9.8% vs 1.1%; adjusted ratio 4.82).[6] In another cohort study including 2216 subjects older than 60 years of age who were undergoing medium-risk to high-risk noncardiac surgical procedures, an elevation of cTnI (>0.06 ng/mL) was recorded in 19% of patients. The 30-day mortality rate in these patients was 8.6%, as compared with 2.2% in patients without cTnI elevation ($P < .001$). The relative risk of death was 2.4 for patients with lower increases in cTnI (0.07–0.59 ng/mL) and 4.2 for patients with higher increases (≥0.60 ng/mL). The median time to death was 12 days.[43] Perioperative cTn surveillance thus may be useful for early identification of patients at increased risk of death and may also allow prompt initiation of appropriate therapeutic interventions.

B-Type (Brain) Natriuretic Peptides

B-type (brain) natriuretic peptides (BNPs) are released from myocardium in response to multiple physiologic stimuli, including ischemia, myocardial stretch, inflammation, and other neuroendocrine triggers. Preoperative BNP levels are strong independent predictors of adverse short-term CV outcome. The preoperative addition of BNPs to the widely used risk stratification systems (RCRI and functional capacity assessment) leads to a significantly improved risk discrimination (AUC from 65% to 80%).[18,44] The predictive value of N-terminal pro–brain natriuretic peptide (NT-proBNP) seems to be higher as compared with BNP, probably because it is more indicative of baseline conditions and is less affected by transient fluctuations in concentrations, given its longer half-life.

Although the optimal cutoff of BNPs to predict CV events after surgical procedures is not well defined, converging results from several studies and metaanalyses suggest a cutoff value of approximately 20 to 30 pg/mL for BNP (with 95% sensitivity and 44% specificity), and of approximately 125 pg/mL for NT-proBNP.[44] In a relatively small prospective study in high-risk patients undergoing major noncardiac operations, a preoperative BNP level greater than 40 pg/mL allowed identification of patients with an almost sevenfold increased risk of cardiac events. In particular, each 100 pg/mL increase in BNP levels was associated with a 35% increase in the relative risk of death.[45]

The utility of BNP testing in patients with renal failure is controversial. In fact, the prognostic value of BNPs seems to be reduced as patients' glomerular filtration rate decreases. NT-proBNP has been shown to have no prognostic value when the glomerular filtration rate is less than 30 mL/1.73 m^2 per minute.[46] Conversely, one review suggested that the NT-proBNP cutoff does not require adjustment in patients with renal dysfunction.[47]

Finally, the negative predictive value of normal BNP levels (<20 pg/mL) to indicate a favorable postoperative outcome is as high as 96%,[48] a finding suggesting that patients with normal levels of BNPs may proceed directly to operation with no additional preoperative cardiac testing.[49,50]

Postoperative (days 1 to 3) measurement of BNPs in addition to preoperative values significantly improves the prediction of death or nonfatal MI at both 30 days (OR, 3.7) and more than 180 days.[51] An individual patient data metaanalysis including 2051 patients demonstrated that patients with postoperative BNP values of 0 to 250 pg/mL, greater than 250 to 400 pg/mL, and greater than 400 pg/mL reached a composite end point including 30-day death and nonfatal MI at a rate of 6.6%, 15.7%, and 29.5%, respectively. Similarly, patients with NT-proBNP values of 0 to 300, greater than 300 to 900, and greater than 900 pg/mL reached the same composite end point at a rate of 1.8%, 8.7%, and 27%, respectively.[52]

No prospective randomized controlled trials (RCTs) have investigated the use of BNP-guided management in perioperative medicine. Nevertheless, according to a metaanalysis of RCTs that showed a 48% reduction in all-cause mortality rates with BNP-guided therapy in nonsurgical patients with HF,[53] the following approach seems reasonable.[54] In the presence of clinical risk factors and/or reduced physical capacity, measurement of BNPs should be performed 4 to 5 weeks before a scheduled major operation. If BNP levels are lower than the optimal cutoff (20 pg/mL), the patient can proceed with the surgical procedure without the need for further testing. Conversely, if BNPs levels are higher than this threshold, further testing, primarily echocardiography and (BNP-guided) optimization of medical therapy (eg, fluid restriction, diuretics, ACEIs or nitrates, β-blocking agents, switching atenolol to carvedilol or bisoprolol) may be recommended.

Worsening of renal function and hypotension, sometimes also induced by ACEIs themselves, must be prevented. Specific therapeutic interventions may be considered in selected cases; for example, cardiac resynchronization therapy in patients with symptomatic NYHA functional class III disease with an LV ejection fraction (LVEF) of less than 35% and a large QRS complex (>120 ms) or transcatheter mitral clip implantation in patients with severe functional mitral regurgitation. Repeating assessment of BNPs shortly before the surgical procedure may allow for adjustment of perioperative treatment strategies (eg, choice of surgical and anesthetic techniques, perioperative monitoring, fluid, drugs, and management of devices).

Perioperative Risk Indices

Intraoperative factors identified as independent predictors of adverse postoperative cardiac events are related to surgical type (vascular surgical procedures), complexity (eg, duration of the procedure, need for blood transfusions), and urgency, as well as to physiologic insults (tachycardia, prolonged hypotension or hypertension, hypothermia).[34,55]

A metaanalysis of 14 studies, including mainly nonrandomized evidence, found a strong association between the need for blood transfusions and postoperative cardiac events. Unfortunately, it was not possible to define an accurate point estimate associated with the risk of adverse cardiac events. CV physiologic variables (eg, >20 mm Hg fall in mean arterial pressure lasting >60 min, >30% increase in baseline systolic pressure, tachycardia in the recovery room, and transmitral flow propagation <45 cm/s) were shown to be independently

BOX 52.2 THE SEVEN ANESCARDIOCAT SCORE FACTORS[a]

1. History of coronary artery disease
2. History of chronic congestive heart failure
3. History of cerebrovascular disease
4. Chronic kidney disease
5. Preoperative abnormal ECG (LV hypertrophy, LBBB, ST-T abnormalities)
6. Intraoperative hypotension (≥20 mm Hg or ≥20% fall in MAP for >1 h)
7. Blood transfusion

[a]Risk of major adverse cardiac and cerebrovascular events: 0 factors = 1.5%; 1 factor = 4.5%; 2 factors = 8.9%; ≥3 factors = 20.6%.
ECG, Electrocardiogram; *LBBB*, left bundle branch block; *LV*, left ventricular; *MAP*, mean arterial pressure; *ST-T*, ST-segment and T-wave.
From Sabaté S, Mases A, Guilera N, et al. Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in noncardiac surgery. *Br J Anaesth*. 2011;107:879–890.

associated with adverse outcomes in some of the included studies. In the only investigation that controlled for blood transfusions, the aforementioned association was not observed. This finding suggests that changes in physiologic variables (eg, hypotension, tachycardia, and hypothermia) may jointly contribute with anemia to the increased cardiac risk observed in patients needing blood transfusions; however, these variables become independently predictive only in the absence of the need for blood transfusions.[34]

The ANESCARDIOCAT score stratifies patients undergoing elective or emergency noncardiac interventions of intermediate-to-high surgery-specific risk in four groups with different (very low, low, intermediate, and high) degrees of risk of major adverse cardiac and cerebrovascular events (MACCE). This scoring system is based on the following factors: intraoperative hypotension, defined as 1 hour of a 20 mm Hg or greater decrease or a 20% change in mean arterial pressure; need for blood transfusion; history of CAD, HF, and/or cerebrovascular disease; CKD; baseline ECG abnormalities including LV hypertrophy, left bundle branch block, and ST-segment and T-wave abnormalities (Box 52.2). The predicted rate of MACCE was 1.5% if none of these factors was present (very low risk), 4.5% in the presence of one factor (low risk), 8.9% in the presence of two factors (intermediate risk), and 20.6% when three or more factors were present (high risk).[3] Among the foregoing predictors of postoperative adverse cardiac events, physiologic variables (and, to a certain extent, transfusions) are the main factors potentially modifiable by anesthesiologists and may thus offer an opportunity to improve patients' outcomes.

Postoperative Management

In patients at high risk for PMI, an electrocardiogram and a blood sample for troponin should be obtained at baseline, immediately postoperatively, and after 6 and 12 hours, as well as once a day for the first 3 postoperative days to detect early myocardial damage. As mentioned, ECG abnormalities such as ST-segment depression, transient ST-segment elevation, and/or prominent T-wave inversions may be present, but they are not required for the diagnosis of PMI or perioperative myocardial injury. Consultation with a cardiologist is always appropriate. Echocardiography is helpful for detecting the site and extension of regional wall motion abnormalities and to quantify global cardiac function.

Adequate analgesia and sedation are pivotal to prevent or minimize the deleterious effects of sympathetic stimulation on myocardial ischemia. Of course, hemodynamic stability plays a key role in preventing adverse cardiac events: adequate DO_2 should be maintained by adequate Hb levels (≥8 g/dL at least, although higher Hb values, for example between 9 and 10 g/dL, may be desirable to improve outcome).[28,29,31]

Finally, active prevention of infection may help reduce the incidence of PMI, given both the "hemodynamic" changes induced by sepsis, or simply by fever (eg, tachycardia), and the myocardial dysfunction associated with severe sepsis and septic shock.[56]

Medications and Percutaneous Interventions to Prevent and Treat Perioperative Major Adverse Cardiac Events

Few RCTs have evaluated the efficacy of medical or interventional treatments in reducing in-hospital and long-term outcomes after PMI in noncardiac surgical procedures. Accordingly, the following considerations about drug therapy and PCI for PMI are mainly extrapolated from evidence on management of acute coronary syndromes in the nonsurgical setting,[57–60] by adapting the strategies generally used in the coronary care unit (CCU) to the scenario of perioperative ICU.

Statins

Statins (3-hydroxy-3-methyl-glutaryl–coenzyme A reductase inhibitors) have a strong protective effect against cardiac complications in patients undergoing surgical procedures.[61–69] A large, retrospective cohort study including 77,082 patients showed significantly reduced in-hospital mortality rates following major noncardiac surgical procedures in statin-naïve patients treated with statins (OR, 0.62; 95% confidence interval [CI], 0.58–0.67).[61] These findings were confirmed by a metaanalysis of RCTs that found a significant reduction in both MI rate (relative risk [RR], 0.53; 95% CI, 0.37–0.77; $P = .001$) and 30-day mortality rate (RR, 0.50; 95% CI, 0.27–0.91; $P = .02$) in the subgroup of patients undergoing noncardiac surgical procedures who were treated with statins for longer than 1 week preoperatively.[62] In a retrospective study, symptomatic patients undergoing carotid endarterectomy and taking statin therapy at the time of hospital admission had a significantly lower mortality rate as compared with patients who were not treated with statins (OR, 0.25; 95% CI, 0.07–0.90).[63]

Statins contribute to plaque stability by means of reducing plaque size (through lipid lowering), modifying the physicochemical properties of the lipid core, and decreasing oxidative stress and inflammation (by inhibition of macrophage accumulation and metalloprotease production). Moreover, statins improve endothelial function and inhibit thrombogenic response. High doses of atorvastatin (80 mg daily; 40 mg/day in older adults) seem to be more effective than standard doses in reducing CV mortality rates and rates of recurrence of unstable angina and MI, as well as the need for myocardial revascularization (class 1 recommendation, level of evidence A). A metaanalysis of 4 large trials including a total of 27,548 patients found a significant 16% reduction in both coronary death or MI ($P < .00001$) and any CV event in patients treated with high-dose statin therapy, as compared with patients receiving standard doses.[70] Treatment with high doses should be continued for at least 1 year. However, benefits occur as early as 30 days. Lack of perioperative use of statins was found to be one of the clinical variables, along with peak postoperative troponin levels, associated with 2.5-year death after vascular surgical procedures (OR, 0.19; 95% CI, 0.07–0.49; $P < .001$).[71]

Among the drugs used for the treatment of PMI, statins are the easiest to handle. Indeed, contraindications (ie, pregnancy, acute hepatic injury, porphyria) are uncommon, and high doses are usually safe (rhabdomyolysis and myopathy are infrequent) and well tolerated. Furthermore, statins may exert a protective effect on both the brain (prevention of delirium and stroke) and the kidneys (enhanced recovery of renal function after acute kidney injury) in vascular surgical patients, and they may also have a therapeutic role in sepsis and venous thrombosis.[72,73]

However, critically ill patients with a complicated course should be closely monitored because they represent a population at increased risk of important statin side effects or drug interactions that may go unnoticed. In patients who require treatment with drugs that increase the plasma concentration of statins through interaction with CYP3A4 (eg, calcium channel blockers, antifungal agents, and macrolides), the use of pravastatin or fluvastatin may be preferable because these statins are not primarily metabolized by CYP3A4. Conversely, rifampicin, phenobarbital, carbamazepine, and phenytoin induce both CYP3A4 and CYP2C9, thus leading to increased metabolism of liver-metabolized statins. Accordingly, the lipid-lowering effect of statins can be reduced by concomitant use of these drugs. Finally, when statin therapy is initiated or whenever any change in statin use occurs (except for pravastatin), careful monitoring of the international normalized ratio (INR) is recommended in patients taking warfarin because of the potential risk of bleeding complications. In practice, perioperative initiation of high-dose statins to prevent PMI is reasonable (class IIa, level B) before vascular surgical procedures and may be considered (class IIb, level C) in other high-risk surgical procedures.

β-Blockers

It is generally accepted that patients previously treated with β-blockers should receive these drugs in the perioperative period. β-Blocker therapy can be a double-edged sword, however. β-Blockers exert a cardioprotective effect by reducing $M\dot{V}O_2$, the rate of atrial and ventricular arrhythmias, and mechanical stress on vulnerable plaques. However, they may cause hypotension and hinder an increase in cardiac output (CO) when it is required. Probably because of this ambivalence, in a large trial (POISE) the *intraoperative* use of β-blockers in *unselected patients* was shown to lead to a reduction of PMI, as well as to a dangerous increase in stroke and mortality rates.[10] In patients with intermediate-risk or high-risk myocardial ischemia as documented by preoperative stress testing and who accordingly are *at increased risk of PMI*, the risk/benefit ratio appears to be favorable. Therefore preoperative (2–7 days before the operation) β-blocker therapy is indicated for reduction of PMI in these patients, although the grade of recommendation is weak (class IIb, level C). The rationale for the use of β-blockers *in patients with ongoing MI* is twofold: in the early hours, these drugs reduce infarct size; in the following days, they have an antiremodeling effect. Regarding the use of β-blockers in CCU, the recommendations of American Heart Association (AHA) and those of ESC differ.

AHA guidelines suggest that it is reasonable to administer IV β-blockers at admission, unless they are contraindicated, in patients with MI who are hypertensive or have ongoing ischemia, and that an oral β-blocker should be initiated in any patient, with no contraindications, within the first 24 hours (class 1, level A).[57] The main contraindications to β-blocker therapy include symptomatic HF, low-output states, a PQ interval greater than 0.24 milliseconds, second- or third-degree atrioventricular block without a cardiac pacemaker, active asthma, and the presence of risk factors for cardiogenic shock (ie, late diagnosis [>12 h] of AMI, age >70 years, systolic arterial pressure <120 mm Hg, heart rate <60 bpm, and heart rate >110 bpm).

ESC guidelines are less categorical because most trials were conducted before the advent of modern reperfusion strategies. The role of routine early IV β-blocker administration is less clearly established, and higher IV doses may be associated with early hazard and increased mortality rates.[59]

β-Blocker use has been associated with reduction of adverse events, including death, in patients who do not undergo reperfusion. Conversely, in patients who underwent myocardial revascularization, the benefits are limited to a reduction of MI and angina, but at the price of an increased risk of HF and cardiogenic shock.[74]

Anemia is a cause for concern, particularly in older adults, when using β-blockers. In a large, single-center, propensity-matched cohort study including 4387 patients and focusing on acute surgical anemia, β-blocker therapy was found to be associated with a greater incidence of MACE (RR, 2.38; 95% CI, 1.43–3.96; $P = .0009$) only when Hb levels dropped by more than 35% from baseline.[75] Anemia may worsen the perioperative adverse effects of β-blockade by further limiting $D\dot{O}_2$. Conversely, the ability of the heart to increase stroke volume (SV) at an Hb value between 9 and 10 g/dL is rate dependent. An animal study found that cerebral oxygenation was maintained during hemodilution, but it was reduced after short-term administration of metoprolol because the compensatory increases in both CO and cerebral blood flow were severely attenuated.[76] Given the circulatory abnormalities of older patients, anemia and decreased CO are potential mechanisms for the increased stroke rate found in the POISE trial.[77]

Perioperative β-Blocker Strategy

β-Blockers may be started in ICU patients *with PMI* (without contraindications). However, some precautions should be taken to make the use of these drugs safer.

Oral administration of β-blockers is indicated in all patients not undergoing PCI because of the antiischemic effect of these drugs. Oral β-blocker therapy is also indicated, in association with ACEIs and aldosterone antagonists, in patients who have undergone coronary revascularization with a moderate-to-large MI (LVEF <40%), to achieve an antiremodeling effect. It is advisable to start *2 or 3 days postoperatively* with *low doses* of a β_1-selective antagonist (bisoprolol 1.25 mg daily, metoprolol 25 mg twice daily [bid]) or an α_1/β-antagonist (carvedilol 6.25 mg bid) and gradually titrate doses over time.

Early IV administration should be limited to patients with tachycardia and hypertension (to decrease $M\dot{V}O_2$) and to patients with atrial fibrillation when rate control is needed. The indication for use is more compelling in patients not undergoing PCI. Before IV administration of β-blockers, any risk condition that may underlie (compensatory) tachycardia should be excluded or treated. Patients with acute anemia may need blood transfusion rather than (or before) β-blockers. Echocardiography should be performed to rule out severe impairment of LV function, particularly if associated with functional mitral regurgitation and/or right ventricular dysfunction. An attractive choice, because of its very short half-life, is esmolol (a test dose of 20 mg; bolus injection of 0.5–1 mg/kg over 30 s; followed by continuous infusion of 50 μg/kg per min, up to 300 μg/kg per min).

Oral (2.5–5 mg bid) or IV (5 mg bolus followed by 5 mg infusion over 8 h) ivabradine, a cardiac pacemaker "funny channel" (I_f) inhibitor, could be an attractive alternative to β-blockers for patients at risk of hypotension. The efficacy and safety of IV ivabradine administration in STEMI were demonstrated in a pilot study of 124 patients treated with PCI, in which heart rate was reduced by 22 bpm, on average without hypotension, and LV volumes were lowered (anti–adverse remodeling effect) as compared with patients not receiving ivabradine.[78]

Angiotensin-Converting Enzyme Inhibitors and Aldosterone Antagonists

ACEIs and aldosterone antagonists (spironolactone, eplerenone) are highly recommended (class 1, level A) in patients with a large PMI, reduced LV systolic function (LVEF <40%), or diabetes mellitus. ACEIs can be used safely in patients with stable renal insufficiency (up to a creatinine level of 3 mg/dL). Aldosterone blockade is contraindicated in patients with severe renal dysfunction (creatinine >2.5 mg/dL in men and >2 mg/dL in women; or serum potassium levels >5 mEq/L). In patients who are intolerant of ACEIs (cough), the angiotensin receptor antagonist valsartan (80 mg bid, up to 160 mg bid) is recommended and well tolerated. During the first weeks of treatment, serum potassium and creatinine levels should be monitored closely. The greatest benefits in patients with large MI (antiremodeling effect) are obtained when administration of ACEIs is started within 24 hours. However, the hemodynamic impact of aggressive ACEI (as well as β-blocker) therapy in the early postoperative period remains to be investigated.

Nitrates

Nitrates such as nitroglycerin reduce $M\dot{V}O_2$ by decreasing LV preload and afterload, and they increase coronary blood flow by dilating capacitance vessels. However, the main limitations of nitrate therapy are the reflex increase in heart rate and contractility induced by peripheral vasodilation that reduce the hemodynamic benefits of nitrates on $M\dot{V}O_2$, the early occurrence of tolerance, and the lack of proven benefits on MACE. For these reasons, IV administration of nitrates is indicated for a short period (usually <24 h) and only for the treatment of persistent myocardial ischemia (ST-segment elevation or depression), particularly when complicated by systemic hypertension or HF. Nitroglycerin should not be administered to patients with myocardial ischemia and hypotension unless it is used concomitantly with an arterial vasoconstrictor such as phenylephrine, and it should be used with caution in patients with right ventricular infarction (as a result of the preload dependence of pulmonary output). Because no improvement in outcomes has been shown, long-term (oral or transdermal) administration of nitrates should be restricted to patients with HF who cannot tolerate ACEIs.

Antithrombotic Agents

Antiplatelet drugs comprise the cornerstone of management of acute coronary syndromes in the nonsurgical setting. Early and aggressive treatment with dual antiplatelet therapy (DAPT) is routinely used to prevent complete coronary occlusion or stent thrombosis after revascularization. Adverse cardiac events have been shown to be significantly reduced with DAPT, whereas the absence of antithrombotic therapy is an independent risk factor for death.[58–60] However, this therapeutic strategy has the untoward effect of increasing the risk of bleeding events, especially gastrointestinal (GI) bleeding as a result of direct damage to the gastric mucosa and inhibition of prostaglandin production, and it may be particularly hazardous in the perioperative period. Aspirin is the established first-line therapy (class 1 recommendation, level of evidence A). The initial loading dose is 162 to 325 mg daily, subsequently reduced to a maintenance dose of 81 to 162 mg to minimize the risk of bleeding. A platelet receptor P_2Y_{12} inhibitor (clopidogrel, prasugrel, or ticagrelor) is usually administered in addition to aspirin because DAPT has been shown to be superior to aspirin alone in reducing adverse events.[79] Approved P_2Y_{12} inhibitors (class 1 recommendation) include the following:

- Clopidogrel, 600 mg loading dose, then 75 mg daily (level of evidence B in the United States, C in Europe)
- Prasugrel, 60 mg loading dose, then 10 mg daily (level of evidence B)
- Ticagrelor, 180 mg loading dose, then 90 mg twice daily (level of evidence *B*)

Compared with aspirin alone, clopidogrel was found to reduce the incidence of a composite end point of CV death, nonfatal MI, and stroke at 30 days by 20%.[79] The efficacy of clopidogrel, however, is limited by the delayed onset of its effect (several hours after ingestion), secondary to the slow biotransformation from prodrug to the active metabolite, as well as by the substantial interpatient variability in the response to the drug. Another limitation of clopidogrel is its irreversible platelet inhibition.

Ticagrelor and prasugrel have a faster onset of action and provide greater and more consistent platelet inhibition. These pharmacokinetic and pharmacodynamic advantages translate to greater outcome improvement. In fact, as compared with clopidogrel, ticagrelor and prasugrel were found to reduce the same composite end point by 16% and 24%, respectively.[80,81] Ticagrelor has some advantages over prasugrel. Prasugrel is not recommended (at the dose of 10 mg daily) in patients with a history of transient ischemic attack or stroke because of an increased risk of fatal intracranial bleeding, and it has neither clinical benefit nor greater sensitivity to bleeding in patients with a body weight of less than 60 kg or in patients older than 75 years of age. In patients older than 75 years of age or patients weighing less than 60 kg, a dose of 5 mg daily of prasugrel can be given, but its efficacy and safety have not been prospectively assessed. Moreover, administration of prasugrel before coronary angiography in patients with NSTEMI did not lead to a reduction in the primary end point when compared with the drug's administration at the time of PCI.[58]

Consistent with the more pronounced antiplatelet effects, major bleeding is more common with ticagrelor and prasugrel than with clopidogrel. Nevertheless, the balance between safety (bleeding) and efficacy (reduction of adverse outcomes) favors prasugrel and ticagrelor.

Unfortunately, PMI usually occurs within 3 days after surgical procedures, and this timeline limits the early and widespread use of these drugs in the postoperative ICU setting because they may lead to significant bleeding both at the surgical site and in the GI tract. To date, no specific studies have addressed the risks of surgical bleeding in patients treated with antiplatelet agents for PMI. Available data mostly come from investigations performed in cardiac surgical patients in stable condition and *without PMI* who are treated shortly after surgical procedures with antiplatelet drugs because of previous coronary stents; these investigations showed an increased risk of bleeding, reexploration, and transfusions. In a large study involving 4998 noncardiac surgical patients (65% of whom were undergoing orthopedic or general operations; only 6% vascular operations) without PMI, perioperative aspirin administration increased the risk of major bleeding by approximately 20% (4.6 vs 3.8%; hazard ratio [HR], 1.23; 95% CI, 1.01–1.49; $P = .04$).[82]

The decision to administer DAPT, as well as its timing, in patients with PMI is challenging. Perioperative bleeding itself is an independent predictor of adverse outcome. In-hospital mortality rates are approximately 10% to 20% for major bleeding, as compared with 10% for reinfarction and 3% for stroke.[83] The reason for such high mortality rates is multifactorial and includes the burden of comorbidities, bleeding-related hemodynamic instability, the possible unfavorable impact of blood transfusions on outcome, and the risk of stent thrombosis or reinfarction resulting from discontinuation of antithrombotic agents. Clinical factors that carry additive risk for GI bleeding are advanced age (>70 y), diabetes mellitus, HF, a history of ulcers and previous GI bleeding, alcohol abuse, and renal failure.[84,85] Advanced age predisposes patients to a greater risk of bleeding because of vessel injuries caused by aging, whereas patients with renal failure have advanced and diffuse arterial disease and coagulation abnormalities, and they are more prone to antithrombotic overdose resulting from reduced clearance.

Strategy for Using Antithrombotic Agents While Minimizing the Risk of Bleeding

Several strategies may help prevent bleeding in patients who require antithrombotic therapy, including the following: prophylaxis of GI bleeding with high doses of proton pump inhibitors; tailoring antithrombotic drug doses according to age and renal function; use of fondaparinux or bivalirudin, which are proven to have a lower rate of bleeding complications; and the adoption of radial access, vascular closure devices, and ultrasound-guided femoral access in patients undergoing PCI. In particular, the use of proton pump inhibitors in patients receiving antiplatelet drugs, including clopidogrel, has been associated with a significant reduction in the risk of GI bleeding, erosions, and ulcers.[86–88] The use of point-of-care platelet function monitoring may have the potential to guide antiplatelet therapy in the early perioperative period to optimize the balance between cardiac protection and the risk of bleeding. However, no aggregometry targets have been identified that could be clinically useful for this purpose in the noncardiac surgical perioperative period.

Blood transfusion is reasonable (benefits probably exceed the risks) in patients with hemodynamic instability and hematocrit lower than 25% or Hb lower than 8 g/dL. Controversies still remain for higher Hb concentrations. Restrictive transfusion strategies were formerly thought to be associated with better outcomes, but newer data seem to suggest that more liberal transfusion triggers may reduce mortality rates in certain patients. In patients receiving antiplatelet therapy,

platelet transfusion may be considered even when the platelet count is normal if hemorrhage continues despite the usual hemostatic techniques.

Postoperative patients admitted to the ICU may be intubated and unable to swallow. In these cases, antiplatelet drugs can be administered through a nasogastric tube after crushing the tablets (and mixing the resulting powder with 50 mL of water). In healthy volunteers, the administration of crushed tablets resulted in faster and greater bioavailability as compared with whole tablets.[89] However, careful attention should be paid to those conditions of reduced enteral absorption or impaired hepatic metabolism that may affect both pharmacokinetics and pharmacodynamics of orally administered antiplatelet drugs.

Percutaneous Coronary Intervention

Early primary PCI with stenting, performed by an experienced team, is the preferred therapeutic option for STEMI. Normal anterograde flow is restored in approximately 90% to 95% of patients. DAPT is mandatory to prevent stent thrombosis, but it increases bleeding risk in the perioperative period. Before excluding PCI because of the risk of bleeding, however, the following data coming from CCU cases should be considered. As compared with thrombolysis, primary PCI resulted in a 25% reduction in mortality rate and in a 64% reduction in reinfarction.[90] Conversely, thrombolytic therapy was shown to reduce hospital mortality rates by 18% (10.7% vs 13%; OR, 0.81), as compared with medical therapy (without DAPT).[91] Accordingly, the overall reduction in mortality rates with PCI, as compared with medical therapy, may be estimated to be 50%. Despite the lack of specific evidence, PCI should always at least be considered in patients with perioperative STEMI. Coronary angioplasty without stenting with a medicated balloon (to avoid the immediate need for DAPT) may be an option in patients at high-risk of bleeding.

Treatment of Perioperative Myocardial Infarction

Treatment should be individualized according to the following: (1) age, comorbidity, and life expectancy of the patient; (2) hemodynamic status; (3) type of PMI (STEMI, NSTEMI) or MINS; and (4) the balance between the risks of death and bleeding (Fig. 52.2). Patients with significant ST-segment changes, hemodynamic or electrical instability, recurrence of angina are admitted to the ICU or CCU. High-dose atorvastatin and low-dose aspirin, when the bleeding risk is acceptable, are recommended in all patients.

Age and Comorbidity

Age is one of the most important predictors of risk with a PMI. Patients older than 75 years of age have a mortality rate at least doubled that of younger patients. Moreover, the risk of complications of MI increases with age. Older patients are also at higher risk of side effects of medical treatment, particularly bleeding from antithrombotic agents, hypotension and bradycardia from β-blockers, and renal failure. Accordingly, drugs should be used with caution, generally at lower doses, and adapted to estimated glomerular filtration rate. Nevertheless, older patients have the largest survival benefit from an invasive rather than a conservative strategy, although at the price of an increased risk of major bleeding and need for transfusions. Age therefore should not constitute a contraindication to aggressive treatment. The advice of all of the clinical team about risks and benefits of aggressive versus medical treatment of PMI, as well as the patient's perspective, is important for both frail older patients and patients with serious comorbidities (eg, severe hepatic, pulmonary, or renal failure, active or inoperable cancer).

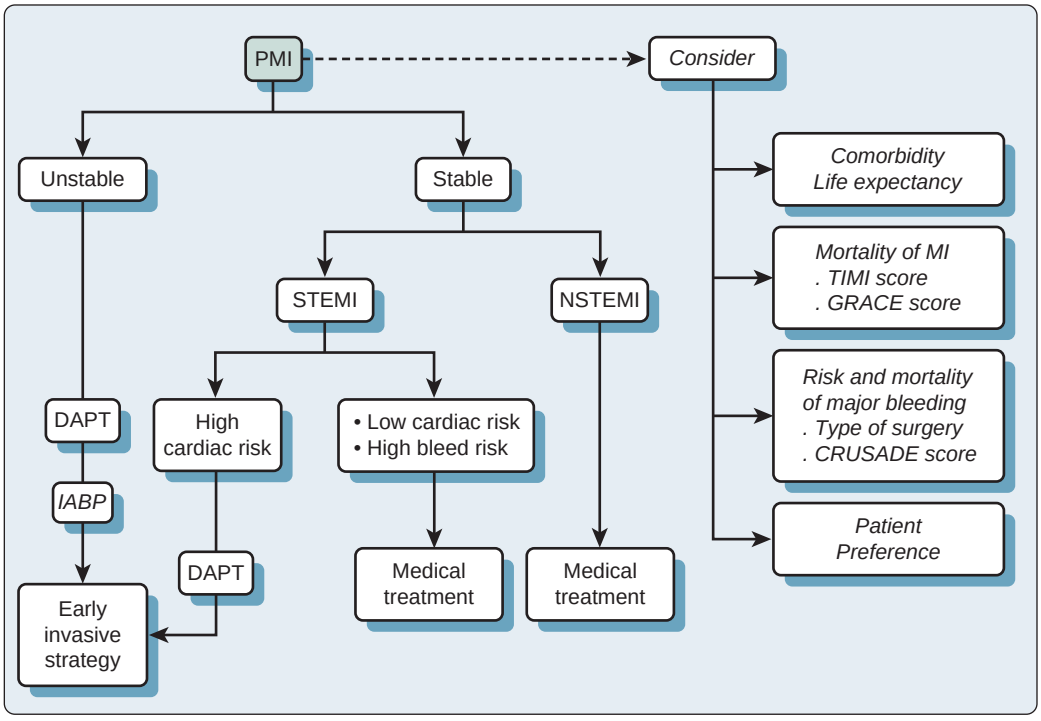


Fig. 52.2 Treatment of perioperative myocardial infarction (PMI): first 24 hours. *CRUSADE,* Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; *DAPT,* dual antiplatelet therapy; *GRACE,* Global Registry of Acute Cardiac Events; *IABP,* intraaortic balloon pump; *MI,* myocardial infarction; *NSTEMI,* non–ST-segment elevation myocardial infarction; *STEMI,* ST-segment elevation myocardial infarction; *TIMI,* Thrombolysis In Myocardial Infarction.

Patients in Unstable Condition

Patients with PMI and hemodynamic instability require a rapid and aggressive diagnostic and therapeutic approach. First, major surgical bleeding leading to MACE must be excluded as the primary cause of instability. Most cases of PMI complicated by hemodynamic instability are caused by severe ischemic LV dysfunction associated with extensive or proximal CAD. Hypotension in the presence of critical coronary artery stenosis dramatically reduces coronary blood flow, whereas tachycardia increases $M\dot{V}O_2$, thus creating a vicious cycle that can lead to cardiogenic shock. In-hospital mortality rates can reach 30% to 50%. In view of the high mortality rates with medical treatment, immediate coronary angiography and PCI are recommended after administration of DAPT. PCI in patients in unstable condition may be limited by the no-reflow phenomenon, as well as by the greater risk of stent thrombosis associated with a low-flow state, although in some cases the improvement in 6-month survival rate, compared with medical therapy, is significant.[92] Patients in cardiogenic shock with multivessel CAD may have the best chance of survival with PCI of all proximal critical stenoses.

The supportive treatment of patients with ongoing ischemia, cardiac dysfunction, and hypotension is particularly difficult because catecholamines may increase infarct size and produce atrial or ventricular arrhythmias, and they are poorly tolerated in patients with right ventricular dysfunction.

Intraaortic balloon pump (IABP) counterpulsation is used in this situation to increase both myocardial perfusion and CO. However, data showing improved survival in noncardiac surgical settings are lacking.[93] The risk/benefit ratio of IABP use should be carefully evaluated in patients with aortic aneurysms or peripheral vascular disease. Particular attention should be paid to patients with peripheral vascular disease who are at risk of ischemia of the lower limb. Finally, if an atrial arrhythmia is present in the patient in unstable condition, synchronized electrical cardioversion is mandatory.

Patients in Stable Condition

In hemodynamically stable patients, the choice of the best therapeutic strategy should take into account the balance between the risk of death from PMI and the risk of major bleeding in the perioperative period. *Risk of death* can be easily calculated at the bedside (also with the aid of specific mobile phone applications) by using TIMI (Thrombolysis in Myocardial Infarction) or GRACE (Global Registry of Acute Cardiac Events) risk scores (Tables 52.2–52.4). These scoring systems, validated in nearly 35,000 patients with both STEMI (TIMI and GRACE) and NSTEMI (GRACE), show a strong predictive ability and an excellent concordance with observed 30-day, 6-month, and 12-month mortality rates.[94–98] Both TIMI and GRACE scores identify a subgroup of patients at high risk of cardiac death who probably need an aggressive invasive therapeutic strategy despite the risk of bleeding, as well as a subgroup of low-risk patients, who may be managed with medical therapy, especially if the bleeding risk is high.

TABLE 52.2 TIMI (Thrombolysis In Myocardial Infarction) Score (ST-Segment Elevation Myocardial Infarction)

Factor	*Points*
Age 65–74 y; ≥75 y	2; 3
Systolic arterial pressure <100 mm Hg	3
Heart rate >100 bpm	2
Killip class 2–4	2
Anterior STEMI or left bundle branch block	1
Diabetes or hypertension or angina	1
Weight <67 kg	1
Time to treatment >4 h	1

STEMI, ST-segment elevation myocardial infarction.

The *risk of bleeding* is related to surgical factors and patient factors. With regard to the hemorrhagic risk, surgical interventions can be classified into low-risk, medium-risk, and high-risk procedures (Table 52.5), according to previous studies and expert opinion. A patient's individual risk may be predicted using the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) bleeding score (Table 52.6, Fig. 52.3), developed in approximately 89,000 patients with STEMI or NSTEMI.[85]

ST-Segment Elevation Myocardial Infarction

Elevation of ST segments usually results from an *acute coronary thrombotic occlusion*. In this setting, urgent coronary angiography and PCI lead to a significant reduction in mortality rates. Accordingly, these procedures should always be considered in patients with perioperative STEMI, especially in those with good life expectancy and moderate-to-large infarctions. In our opinion, only patients at low risk of death (<3%–5%) and, at the same time, at high-risk of bleeding should be treated with medical therapy alone.

Infarction size can be quantified by echocardiography and by both clinical and ECG parameters. Signs of large infarctions include the presence of pulmonary rales, ECG changes involving more than three leads, ST-segment elevation in aVR (which suggests left main or proximal left anterior descending artery stenosis), new onset of bundle branch block or arrhythmias in inferior infarction, a reduction of LVEF (< 40%), or right ventricular involvement.

Before a PCI procedure, a loading dose of aspirin (162–325 mg), together with a loading dose of a P_2Y_{12} inhibitor (clopidogrel 600 mg, prasugrel 60 mg, ticagrelor 180 mg), should be administered as early as possible. Clopidogrel may cause less bleeding, but it is also the least effective. Prasugrel should be avoided in patients with a history of transient ischemic attack or stroke, body weight less than 60 kg, and age older than 75 years.

TABLE 52.3 30-Day Mortality Rates According to TIMI (Thrombolysis In Myocardial Infarction) Score (ST-Segment Elevation Myocardial Infarction)

Score	*30-Day Mortality Rate*
0	<1%
1	1.6%
2	2.2%
3	4.4%
4	7.3%
5	12.4%
6	16.1%
7	23.4%
8	26.8%
>8	35.9%

TABLE 52.4 GRACE (Global Registry of Acute Cardiac Events) Score and Mortality Rates (Non–ST-Segment Elevation Myocardial Infarction)

Risk Category	*GRACE Score*	*Risk of Death*	
Low	≤108	<1%	In-hospital
	≤88	<3%	Discharge to 6 months
Intermediate	109–140	1–3%	In-hospital
	89–118	3–8%	Discharge to 6 months
High	>140	>3%	In-hospital
	>118	>8%	Discharge to 6 months

Modified from Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;35:2383–2431.

TABLE 52.5 Surgical Hemorrhagic Risk

	Low Risk	*Medium Risk*	*High Risk*
Surgical Procedures	Hernioplasty Cholecystectomy Appendectomy Colectomy Gastric resection Intestinal resection Breast surgery Carotid endarterectomy Bypass or endarterectomy of lower extremity EVAR TEVAR Limb amputations Hand surgery Shoulder and knee arthroscopy Minor spine surgery Wedge resection	Haemorrhoidectomy Splenectomy Gastrectomy Obesity surgery Rectal resection Thyroidectomy Open abdominal aorta surgery Prosthetic shoulder surgery Major spine surgery Knee surgery Foot surgery Prostate biopsy Orchiectomy Circumcision Lobectomy Pneumonectomy Mediastinoscopy Sternotomy Mediastinal mass excision	Intracranial surgery Intraspinal surgery Eye posterior chamber surgery Open thoracic and thoracoabdominal aorta surgery Major prosthetic (hip or knee) surgery Major traumatology (pelvis, long bones) Fractures of the proximal femur in older patients Radical and partial nephrectomy Cystectomy and radical prostatectomy TURP TURBT Hepatic resection Duodenocephalopancreatectomy

EVAR, Endovascular aortic repair; *TEVAR,* thoracic endovascular aortic repair; *TURBT,* transurethral resection of bladder tumor; *TURP,* transurethral resection of the prostate.

TABLE 52.6 Calculation of CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Score

Predictor	*Points*	*Predictor*	*Points*
Baseline Hematocrit (%)		**Sex**	
<31	9	Male	0
31–33.9	7	Female	8
34–36.9	3	**Signs of CHF at Presentation**	
37–39.9	2	No	0
≥40	0	Yes	7
Creatinine Clearance (mL/min)		**Previous Vascular Disease**	
≤15	39	No	0
>15–30	35	Yes	6
>30–60	28	**Diabetes Mellitus**	
>60–90	17	No	0
>90–120	7	Yes	6
>120	0	**Systolic Blood Pressure (mm Hg)**	
Heart Rate (bpm)		≤90	10
≤70	0	91–100	8
71–80	1	101–120	5
81–90	3	121–180	1
91–100	6	181–200	3
101–110	8	≥201	5
111–120	10		
≥121	11		

CHF, Congestive heart failure.

Modified from Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;35:2383–2431.

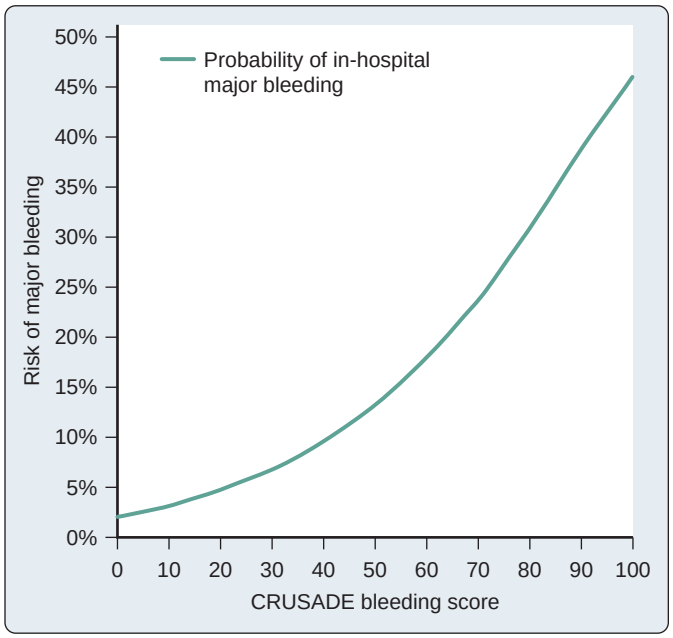


Fig. 52.3 CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) score and risk of major bleeding. *(Modified from Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA).* Eur Heart J. *2014;35:2383–2431.)*

Non–ST-Segment Elevation Myocardial Infarction

Three characteristics distinguish NSTEMI from STEMI. First, NSTEMI may result from a *myocardial oxygen supply/demand mismatch* induced by extracardiac causes. The treatment of these causes may reverse ischemic changes. Second, in most cases *no complete thrombotic occlusion* of a coronary artery is accountable for the infarction, but only a critical stenosis often involving multiple coronary vessels. Accordingly, as compared with STEMI, the need for urgent PCI is less compelling, especially if the hemorrhagic risk is high, as in the perioperative period. Finally, the incidence of adverse events at 1-year follow-up is higher in NSTEMI than in STEMI. As a consequence, a strategy of routine invasive therapy before hospital discharge has been shown to be generally superior to medical therapy alone.

Myocardial oxygen supply/demand mismatch is typically induced by hypotension, acute anemia, or hypertension and tachycardia, usually in patients with CAD, LV hypertrophy, and/or aortic stenosis. Before antiischemic therapy is begun, these causes must be found and treated vigorously. Moreover, anemia from acute bleeding is an absolute contraindication to reperfusion and antiplatelet therapy. After underlying causes are excluded (ie, pain, anemia, hypoxemia), tachycardia should be treated to reduce infarct size. IV β-blockers are then continued orally to control heart rate and hypertension.

Coronary angiography is recommended before hospital discharge in patients at high cardiac risk (diabetes, renal failure, significant ST-segment depression, LVEF <40%, previous PCI or coronary artery bypass graft, GRACE risk score >109).

Myocardial Injury After Noncardiac Surgery

High-dose statins (atorvastatin 80 mg daily), aspirin (325 mg day 1, then 100 mg daily), and low-dose oral β-blockers (eg, bisoprolol 1.25 mg daily) should be initiated within 24 hours in all patients without contraindications. A $P2Y_{12}$ inhibitor (eg, ticagrelor 90 mg bid) may be added to low-dose aspirin in the postoperative period. ACEIs should be started in patients with an LVEF of less than 40%, hypertension, diabetes, and stable CKD.

An invasive strategy (coronary angiography and PCI) before hospital discharge is indicated in patients in whom angina or hemodynamic or electrical instability develops during mobilization. PCI is also reasonable in patients without severe comorbidities who are asymptomatic but who have a high risk of short-term cardiac events (GRACE score >140). In the remaining low-risk patients, an ischemia provocative test during medical therapy is recommended before discharge; coronary angiography is performed if myocardial ischemia is documented unless the patient has extensive comorbidities.

The hypothesis that providing appropriate therapy to patients with MINS may limit long-term mortality was validated in a study in 667 consecutive patients undergoing major vascular surgical procedures. Patients with postoperative elevated troponin levels, but not receiving early evidence-based CV therapy (antiplatelet agents, β-blockers, statins, ACEIs), had a significant increase in MACE (death, AMI, HF, myocardial revascularization) at 12 months (HR, 2.80; 95% CI, 1.05–24.2; $P = .04$).[99]

Perioperative Care to Reduce Mortality Rates in Noncardiac Surgical Procedures

The all-cause mortality rate after noncardiac surgical procedures has been reported to be 0.8% to 1.5%.[42] However, postoperative mortality rates may greatly increase according to patient-related and procedure-related factors, such as age (≥80 y), ASA physical status grade of 3 or greater, cancer, surgical specialty (GI, thoracic, and vascular surgical procedures are those at higher risk), and the severity and urgency (expedited, urgent, immediate) of the procedure.[100] Moreover, large differences in mortality rates exist among different countries,[2] and even among different centers. With more than 230 million major surgical procedures performed annually worldwide,[1] even small reductions in perioperative mortality rates would result in thousands of lives saved each year.[101]

In their daily clinical practice, anesthesiologists make many choices that can affect clinically relevant outcomes in the (1) preoperative period (drug continuation or discontinuation), (2) operating room (anesthetic technique, airway management, type and amount of fluids administered, hemodynamic monitoring and optimization, type and age of blood products administered and transfusion triggers); and (3) postoperative care (cardiocirculatory support, ventilation, drug prescriptions). However, for nonsurgical interventions (drugs, techniques, strategies), evidence from RCTs and consensus on their impact on postoperative mortality rates are limited.[101,102] For example, a systematic review found no evidence derived from high-quality studies even to support routine preoperative testing in unselected adults undergoing noncardiac surgical procedures.[103]

We developed a novel approach to consensus building that made it possible to summarize the best-quality and most widely agreed-on evidence about mortality reduction in different settings, including the noncardiac surgical perioperative period.[101,102,104–108]

"Democracy-Based," Web-Enabled Approach to Consensus on Perioperative Mortality Reduction

Physicians should base their clinical decisions mostly on the best evidence available in the literature. However, must always contend with the challenging issue of understanding the meaning, applicability, robustness, and biologic plausibility of clinical evidence coming from published studies.[109] Moreover, although some topics lack high-quality investigations from which to draw conclusions, at other times a plethora of often contradictory data does not allow clinically useful synthesis. In both cases, guidelines may be inconclusive or even lacking.[108] Consensus conferences are currently considered the best way to assess evidence systematically and to reach agreement among experts, particularly when no definitive conclusions can be drawn from RCTs or metaanalyses. This approach, unfortunately, has some limitations, including the high priority given to expert opinions (with a poor definition of "expertise"), the risk of influences and biases, as well as the possibility that the resulting recommendations may not be widely applicable.[108,110,111]

A "democracy-based" process, feasible thanks to the advent of the Internet, was suggested as a possible alternative to the "traditional" approach to consensus on mortality reduction.[101,102,104–109,111] This method brings together the features of consensus conferences, international surveys, and systematic reviews, thus leading to a rigorous selection of published evidence through an open, dynamic, comprehensive, and easily reproducible process that also provides insightful details on current worldwide clinical practice.[108,111]

The Five Steps of Consensus Building

1. *Literature search and analysis*. One or more search strings, together with contacting experts and authors of collected manuscripts and assessing references of recent reviews and guidelines, are used to identify all interventions with an influence on mortality. From 2010 to 2013, the "democracy-based" consensus method was applied to four different settings: cardiac surgical procedures,[104] the perioperative period of any surgical procedure,[101,102] acute kidney injury,[105] and critically ill patients,[106,107] with small differences in the article collection strategy, mostly related to the type of evidence considered. The identified articles are then reviewed by a trained team of physicians. For postoperative mortality reduction, articles are included in the subsequent step if they fulfill the following criteria: dealing with nonsurgical interventions (drugs, strategies, or techniques), reporting a statistically significant effect on mortality rates, published in a peer-reviewed journal, and including adult patients.
2. *First Internet-based survey*. Many colleagues, including professionals and experts in the field, especially corresponding authors of recently published articles, are asked through a Web-based poll whether they agree or not with the beneficial or unfavorable effect on mortality of the listed interventions. Moreover, they are invited to suggest further topics or articles and to add comments.
3. *Consensus meeting*. A task force of anesthesiologists, intensivists, surgeons, cardiologists, and epidemiologists meets to discuss and, if necessary, to vote on each topic, after it has been presented by previously designated discussants and taking into account the results of the Web polling. Moreover, new articles suggested by participants are evaluated for inclusion. A brief summary statement describing the effects on mortality and the reasons for the inclusion is finally formulated for each topic.
4. *Second Internet-based survey*. Summary statements are listed online, and voters are asked whether they agree with these statements or not. Moreover, participants in the online survey may be asked whether they use the presented interventions in their clinical practice. Topics receiving a low percentage of agreement are excluded.
5. *Publication*. An article describing the results of the consensus process is prepared, reviewed, and approved by the most active participants in the meeting before it is sent to a peer-reviewed journal for publication.

Results of the Web-Based Consensus Conference on Perioperative Mortality

In the first international Web-based consensus conference on mortality reduction in the perioperative period,[101] evidence collection was focused on RCTs and metaanalyses of RCTs (Fig. 52.4). Among the

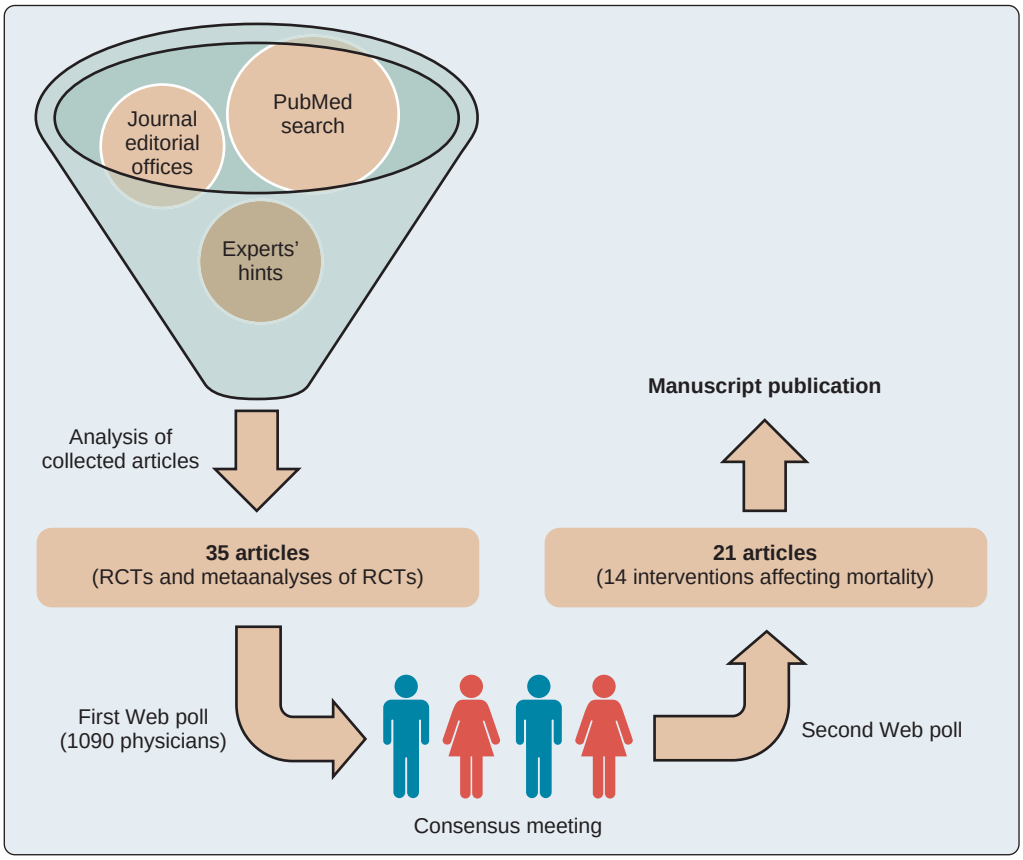


Fig. 52.4 The Web-based consensus process. *RCTs*, Randomized controlled trials.

7742 articles analyzed, only 35 (concerning 24 different interventions) fulfilled all inclusion criteria and were accordingly voted on by 1090 physicians from 77 countries. An additional 14 articles (10 topics) were excluded during the subsequent steps, for the following reasons:

- The study included nonsurgical populations, or the effect on mortality was found only in small subanalyses (antifungal prophylaxis, pexelizumab, avoidance of hyperoncotic colloids, fondaparinux).
- The effect on mortality was lost at later follow-up, was questioned by follow-up investigations, or did not strictly pertained to the perioperative period (hypotensive resuscitation, *N*-acetylcysteine, nesiritide, statins, tranexamic acid).
- The study had a low percentage of agreement at the second Web poll (dopexamine).

Of the 14 interventions that potentially increase or decrease perioperative mortality rates according to the final findings of the consensus process (Fig. 52.5), 7 have been only (or mostly) investigated in the cardiac surgical setting (chlorhexidine oral rinse,[112] insulin,[113,114] IABP,[115] leukocyte depletion,[116] levosimendan,[117] volatile anesthetic agents,[118] avoidance of aprotinin[119]). The remaining topics, concerning noncardiac operations, are discussed in the next sections and are summarized in Box 52.3. However, some of these interventions (eg, perioperative supplemental oxygen) have been questioned by newer studies, whereas some of those excluded interventions could be reevaluated (eg, tranexamic acid, statins). In addition, further strategies, such as more "liberal" transfusion triggers, have been suggested to influence perioperative mortality rates in more recent investigations. Finally, it is reasonable to assume that some of the interventions that conferred survival benefits in cardiac surgical patients may have a beneficial effect in noncardiac surgical patients as well.

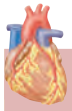
May reduce mortality	*May increase mortality*	
• Chlorhexidine oral rinse • Insulin for glycemic control • Intraaortic balloon pump • Leukocyte depletion • Levosimendan • Volatile anesthetics	• Aprotinin	Cardiac surgery
• Clonidine • Neuraxial anesthesia • Noninvasive ventilation • Perioperative hemodynamic optimization • Selective decontamination of the digestive tract	• Metoprolol	Noncardiac surgery

Fig. 52.5 Interventions influencing perioperative mortality rates (any surgical procedure) according to the first international Web-based consensus conference.

Interventions That May Reduce Mortality Rates in Noncardiac Surgical Procedures

Perioperative Hemodynamic Optimization

Referred to as goal-directed therapy (GDT), hemodynamic optimization involves the proactive administration of fluids (associated or not



BOX 52.3 PRACTICAL (EVIDENCE-BASED) SUGGESTIONS TO REDUCE MORTALITY RATES IN NONCARDIAC SURGICAL PATIENTS

- *Hemodynamic optimization* according to adequate monitoring and flow-related parameters should be pursued in high-risk patients. However, the best monitoring tools, hemodynamic goals, and resuscitation targets are yet to be defined.
- *Noninvasive ventilation* should be promptly started in patients in whom postoperative acute respiratory failure develops. Its intraoperative role, although promising, is less clear.
- *Neuraxial anesthesia*, as well as epidural analgesia in addition to general anesthesia, should be preferred whenever possible, although physicians' skills and a highly individualized choice of the anesthetic technique are probably pivotal.
- *Selective decontamination of the digestive tract* may be considered in postoperative patients in the intensive care unit, but this topic needs further research.
- *β-Blocker* initiation in unselected patients shortly before surgical procedures should be avoided. However, perioperative *continuation* of β-blockers is recommended in patients already receiving these drugs. This topic needs further research.
- *Statins, tranexamic acid,* and *liberal transfusion strategies* may be considered to improve survival. However, these topics merit further research.
- *Levosimendan, intraaortic balloon pump, volatile anesthetic agents, remote ischemic preconditioning, leukocyte depletion, and protective ventilation* have been proven to reduce mortality rates in other settings, but they may also be beneficial in noncardiac surgical patients.

with inotropic drugs) to maintain one or more flow-related hemodynamic parameters within a certain target, to match the imbalance that often occurs in the perioperative period between oxygen supply and demand or to prevent tissue hypoxia and organ injury.

Five metaanalyses of RCTs found reduced mortality rates with GDT protocols in patients undergoing noncardiac surgical procedures.[120–124] The trials included in these metaanalyses were highly heterogeneous in both their quality and design. Furthermore, hemodynamic optimization strategies investigated by different studies were extremely varied, including the following: different hemodynamic goals (ie, CO, D_{O_2}, dynamic parameters such as SV variation or pulse pressure variation, central/mixed venous oxygen saturation [S_{cO_2}/$S\bar{v}O_2$], and flow time corrected [FTc]); different monitoring devices (pulmonary artery catheter, pulse contour analysis, esophageal Doppler imaging, bioreactance); different resuscitation targets (normal or "supranormal" D_{O_2} levels); and different therapeutic interventions to achieve these goals and targets (fluids, inotropes, blood transfusions).

The metaanalyses by Cecconi and colleagues[120] (32 RCTs, 2808 noncardiac surgical patients) and by Hamilton and associates[122] (29 RCTs, 4805 patients undergoing any operation) reported reduced mortality rates with GDT as compared with standard therapy (OR, 0.2; 95% CI, 0.09–0.41; $P < .0001$ and OR, 0.48; 95% CI, 0.33–0.78; $P = .0002$, respectively). However, subgroup analyses revealed that the effect on mortality rates was restricted to studies using pulmonary artery catheters as the monitoring tool, CO or D_{O_2} as hemodynamic goals, fluids and inotropes as therapeutic strategies, and "supranormal" resuscitation targets. Moreover, Cecconi and colleagues (as well as Gurgel and do Nascimento[121]) found that the survival benefit was restricted to patients with an extremely high-risk of death (≥20%), whereas Hamilton and colleagues[122] showed that the survival benefit was lost when considering only the most recent studies (those published since 2000) and only the higher-quality RCTs. Conversely, the effect on mortality rates was not found to be related to trial quality in the metaanalysis by Poeze and associates,[124] whereas Brienza and colleagues[123] suggested that a favorable effect on outcome also may be obtained without "supranormal" resuscitation targets, although no data on mortality rates were reported.

The more recent RTCs investigating the use of GDT protocols based on minimally invasive or noninvasive monitoring devices, which are gradually replacing invasive monitoring in most noncardiac surgical settings, failed to show clinical benefit.[125–128] To conclude, it is not difficult to agree with the concept that hemodynamic status should be promptly "optimized" in the perioperative period to prevent the development of an "oxygen debt" and, probably, to reduce postoperative major complications and mortality rates. However, the best monitoring tools, hemodynamic targets, therapeutic interventions to use (including the *type* of fluids or inotropes), and the most appropriate settings are yet to be clearly defined.

Noninvasive Ventilation

Several articles reported the *intraoperative* use of noninvasive ventilation (NIV) during nearly all types of surgical procedures including abdominal, thoracic, urologic, orthopedic, obstetric, ophthalmic, and neurosurgical, as well as endovascular cardiac procedures.[129] Improved outcomes were found with the *postoperative* use of NIV.[130,131] One multicenter trial including 209 patients from 15 ICUs showed a reduced rate of tracheal intubation and a lower incidence of complications (infections, sepsis, pneumonia, and anastomotic leaks) in patients in whom postoperative hypoxia developed after abdominal surgical procedures and who were treated with 7.5 cm H_2O continuous positive airway pressure through a helmet as compared with standard care.[132]

So far, however, randomized evidence of improved survival with NIV in noncardiac surgical patients comes from only two small RCTs performed in patients undergoing thoracic and solid organ transplantation.[133,134] Auriant and associates[133] randomized 48 patients who developed acute hypoxemic lung failure after pulmonary resection and received either pressure support ventilation through a nasal mask (set to maintain exhaled tidal volumes within 8–10 mL/kg, respiratory rate <25 breaths/min, and arterial oxygen saturation >90%) or standard care. A threefold reduction in 120-day mortality rate was shown in the NIV-treated group (12.5% vs 37.5%; $P = .045$). A similar NIV strategy through a face mask was found by Antonelli and colleagues[134] to reduce ICU mortality rates from 50% to 20% ($P = .05$) in patients in whom acute lung failure developed after liver, kidney, or lung transplantation.

Nevertheless, strong indications that NIV may have a key role in reducing perioperative mortality rates derive from the critical care setting. In fact, with as many as eight multicenter RCTs in support,[135–142] NIV is the therapeutic intervention with the best evidence to have a significant impact on mortality rates in critically ill patients in the history of modern medicine.[106] A metaanalysis of RCTs by Cabrini and associates,[143] including 7365 patients, confirmed that NIV reduced mortality rates in acute care settings (RR, 0.73; 95% CI, 0.66–0.81, $P < .001$) when it was used to treat or prevent acute respiratory failure, but not as a means to allow earlier tracheal extubation. Moreover, the survival benefit is lost when NIV is started too late. Accordingly, NIV should be promptly applied whenever indicated. Most remarkably, the favorable effect of NIV on mortality rate was preserved also when only postoperative patients with acute respiratory failure were considered. This finding indicates that NIV may be pivotal in the treatment of *postoperative* respiratory failure to reduce mortality rates.

Conversely, the role of *intraoperative* NIV in reducing mortality rates is less clear. NIV may be used in the operating room to treat sudden respiratory distress, to allow continuation of the operation without tracheal intubation. More often, it is used as a prophylactic measure in patients with cardiorespiratory diseases who cannot tolerate the supine position or to avoid respiratory failure resulting from deep sedation.[129] Similarly, the use of NIV, through both a face mask and a helmet, has been described in patients undergoing diagnostic procedures (upper digestive endoscopy, fiberoptic bronchoscopy, transesophageal echocardiography) that may induce respiratory

distress and/or require deep sedation.[144–148] A full-face mask that can be opened is available (Janus, Biomedical, Florence, Italy); it can be positioned and provides NIV without stopping the ongoing endoscopic procedure.[149] Large, randomized trials are needed to assess the impact on mortality rates of intraoperative or intraprocedural use of NIV, both as a prophylactic measure and as a rescue treatment.

Neuraxial Anesthesia

Both spinal anesthesia and epidural anesthesia used alone, as well as epidural anesthesia or analgesia in association with general anesthesia, have been reported to have favorable effects (eg, antiinflammatory effects, reduction of stress response biomarkers, better functional recovery, lower cancer recurrence) and to reduce the incidence of postoperative major complications (particularly pulmonary complications and venous thromboembolism) in patients undergoing noncardiac surgical procedures.[150–157] It is reasonable to assume that the use of neuraxial anesthesia techniques in these settings may improve survival, although this is a matter of long-standing debate. In fact, no RCT has been able to show any difference in mortality rates between regional anesthesia and general anesthesia. Moreover, despite several large, observational or retrospective studies, mostly involving orthopedic surgical patients, that suggested a mortality reduction with neuraxial anesthesia,[158,159] data coming from more recent similar investigations are conflicting.[160,161]

The results of four metaanalyses, two of them more recent, suggest postoperative mortality reduction when using neuraxial anesthesia.[151,152,162–164] Rodgers and associates[151] analyzed 141 RCTs in which patients (a total of 9559) undergoing all types of surgical procedures (mainly general, gynecologic, obstetric, orthopedic, urologic, and vascular operations) were randomized to receive neuraxial anesthesia or general anesthesia. These investigators found a reduction in 30-day mortality rate of approximately one-third with neuraxial anesthesia (OR, 0.70; 95% CI, 0.54–0.90; $P = .006$), without significant differences among the different types of surgical procedures. The survival benefit observed reflected a trend toward reduction in deaths from several complications including pulmonary embolism, cardiac events, stroke, and infection. In the same year, Urwin and colleagues[152] performed a metaanalysis limited to trials involving patients with hip fracture and found a similar reduction in 1-month mortality rate in patients receiving regional anesthesia (OR, 0.66; 95% CI, 0.47–0.96). Other metaanalyses conducted thereafter had conflicting results. However, Guay and associates[162,163] performed an overview of nine Cochrane systematic reviews including RCTs that compared neuraxial anesthesia with general anesthesia alone, or combined neuraxial and general anesthesia with general anesthesia alone, in patients of any age undergoing any surgical procedures. These investigators confirmed with a moderate level of evidence that neuraxial anesthesia, as compared with general anesthesia, was associated with a reduction in up-to-30-day mortality rates (RR, 0.71; 95% CI, 0.53–0.94; heterogeneity index [I^2], 0%) in patients undergoing surgical procedures at intermediate-to-high cardiac risk. Moreover, neuraxial anesthesia was associated with a lower risk of pneumonia (RR, 0.45; 95% CI, 0.26–0.79; I^2, 0%), whereas the rate of MI was similar with the two techniques.

Finally, the metaanalysis by Pöpping and colleagues[164] focused on epidural analgesia in addition to general anesthesia, as compared with general anesthesia alone, and showed a reduction in mortality rate from 4.9% to 3.1% (OR, 0.60; 95% CI, 0.39–0.93), without significant heterogeneity among data ($P = 0.44$; I^2, 0%). Moreover, the risk of arrhythmias (atrial fibrillation and supraventricular tachycardia), respiratory depression, deep vein thrombosis, atelectasis, pneumonia, ileus, and postoperative nausea and vomiting was significantly reduced with epidural analgesia, although an increased risk of arterial hypotension, itch, urinary retention, and motor blockade was found. A metaanalysis by Landoni and associates[165] reported a reduced mortality rate with epidural analgesia in cardiac surgical patients (RR, 0.65; 95% CI, 0.48–0.86; $P = .003$), with a risk of epidural hematoma of 1 in 3552.

Unfortunately, in addition to the well-known limitations of metaanalyses, none of these investigations was able to consider the individual skills of anesthesiologists, which probably have a key role in this context.[157]

In our opinion, regional anesthesia should be the anesthetic technique of choice in noncardiac surgical procedures whenever possible. However, key factors to improve outcomes and probably to reduce mortality rates are careful and comprehensive risk assessment, anesthesiologists' skills, and a highly individualized choice of anesthetic technique. For example, especially in patients with cardiac diseases, even the degree of patients' anxiety or fear, which may increase the risk of MACE and death, should be taken into account when choosing between general anesthesia and regional anesthesia. Conversely, the indiscriminate use of a technique only because it has been shown to reduce mortality rates, with all the limitations of evidence-based medicine, may be harmful for the single patient.

Selective Decontamination of the Digestive Tract

Selective decontamination of the digestive tract (SDD) involves the use of topical and oral nonabsorbable antimicrobial agents (polymyxin E, tobramycin, amphotericin B, and vancomycin in case of endemic methicillin-resistant *Staphylococcus aureus*), possibly in conjunction with parenteral antibiotics (usually cephalosporins) to control the overgrowth of potentially pathogenic microorganisms, as often occurs in critically ill patients.[166] This prophylactic measure has been largely proven to reduce bloodstream and pulmonary infections and mortality rates in ICU patients.[167–170] The effectiveness of SDD also has been investigated in surgical ICU patients. However, the metaanalysis performed by Nathens and Marshall[171] in 1999 including 11 randomized trials is the only study showing a survival benefit with SDD in the postoperative setting.[101] Those investigators found that SDD significantly reduced mortality rates among critically ill surgical patients (OR, 0.70; 95% CI, 0.52–0.93) because of a reduced rate of bacteremia and pneumonia. Furthermore, the survival benefit was greater with the use of SDD regimens that included both oral and parenteral antimicrobial agents (OR, 0.60; 95% CI, 0.41–0.88).

Conversely, the *perioperative* use of SDD protocols outside the ICU setting has not been shown to reduce mortality rates, although it seemed to be a promising prophylactic measure, especially in patients undergoing upper GI tract surgical procedures.[171]

The use of SDD is not widespread, nor is it generally suggested, even in the critical care setting. The reason is probably multifactorial and mainly reflects concern about development of bacterial resistance to antibiotics, even if SDD seems to be safe from this point of view.[166,172] A large, multicenter RCT in patients undergoing elective colorectal cancer operations that is evaluating the role of SDD in addition to standard antibiotic prophylaxis and that includes death among its end points is currently ongoing.[173] Meanwhile, the role of SDD, both in the perioperative period and in postsurgical ICU patients, as a strategy to improve survival remains uncertain.

Interventions That May Increase *Mortality Rates in Noncardiac Surgical Procedures*

Perioperative β-Blockers

Preoperative prescription of β-blockers was formerly thought to be an effective and safe strategy to reduce cardiac risk in patients undergoing noncardiac surgical procedures.[174,175] However, the evidence about safety of perioperative β-blockade was mainly based on a set of investigations (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography [DECREASE]) that were accused of serious scientific misconduct.[176] Conversely, β-blockers started shortly before noncardiac surgical procedures have been shown to increase mortality rates significantly in patients with, or at risk for, ischemic heart disease, according to the large multicenter trial POISE,[10] as well as three metaanalyses.[176–179] In the POISE study,[10] 8351 patients with CV disease, or who were scheduled for major vascular operations, or with at least three of seven risk factors (intrathoracic or intraperitoneal operations, emergency or urgent procedures, previous HF, transient ischemic attack, diabetes, serum creatinine >175 μmol/L, age >70 y) were

randomized to receive oral extended-release metoprolol or placebo for 30 days starting 2 to 4 hours preoperatively. Although the rate of MI was reduced by approximately 27% (4.2% vs 5.7%; $P < .0017$), a 33% increase in the overall mortality rate (3.1% vs 2.3%; $P = .0317$) and a 100% increase in the rate of stroke (1.0% vs 0.5%; $P = .0053$) were found, mainly the result of hypotension.

The metaanalysis by Bouri and associates[176] included 11 trials in which bisoprolol (3 studies), metoprolol (5 studies), atenolol (2 studies), or propranolol (1 study) was started between 37 days and 30 minutes preoperatively and was continued for 5 to 30 days postoperatively. After excluding the DECREASE trials, these investigators found a significant increase in all-cause mortality rates with perioperative β-blockers (RR, 1.27; 95% CI, 1.01–1.60; $P = .04$), and they strongly argued for a change in guidelines.

In the revised 2014 ESC/ESA guidelines on noncardiac surgical procedures, the recommendations on perioperative β-blockers were substantially downgraded.[42,180] Although perioperative *continuation* of β-blockers is still recommended in patients already receiving these drugs, it is suggested that their *initiation* may be considered in patients with recognized ischemic heart disease and in patients undergoing high-risk surgical procedures with ASA grade 3 or higher or with two or more RCRI risk factors (class II, level of evidence B). Atenolol or bisoprolol may be preferred to metoprolol, and careful dose titration according to individualized heart rate targets is advisable. Conversely, perioperative initiation of β-blockers is not recommended in patients undergoing low-risk procedures.

Two other metaanalyses were published shortly after the 2014 update of the ESC/ESA guidelines. A Cochrane systematic review of 89 RCTs (19,211 patients) investigating the perioperative use of β-blockers in both cardiac and noncardiac surgical procedures showed, despite a significant reduction in the rate of AMI, myocardial ischemia and supraventricular arrhythmias, a potential increase in all-cause mortality rates and in cerebrovascular complications with the use of β-blockers in patients undergoing noncardiac surgical procedures that became significant (RR, 1.27; 95% CI, 1.01–1.59; and RR, 2.09; 95% CI, 1.14–3.82, respectively) after restricting the analysis to trials with a low risk of bias.[177] Hypotension and bradycardia were significantly more common in patients receiving β-blockers. Finally, Wijeysundera and colleagues[178,179] also found increased risks of hypotension, bradycardia, and nonfatal stroke with perioperative β-blockade, regardless of the inclusion or exclusion of both the POISE and the DECREASE trials. Moreover, this metaanalysis showed a significantly increased overall mortality rate (RR, 1.30; 95% CI, 1.03–1.64), after exclusion of the DECREASE studies, in patients in whom β-blockers were started within 1 day before the surgical procedure.

It is likely that the proper β-blocking agent, started early enough preoperatively (to allow adequate dose titration) and administered to the appropriate subset of patients, would effectively and safely prevent adverse cardiac events in noncardiac surgical patients. This approach may not be easy to apply, however, in several clinical contexts.

Further Strategies to Possibly Reduce Mortality Rates in Noncardiac Surgical Procedures: Evidence From Updates and Other Clinical Settings

Statins

At the time of the first international Web-based consensus conference on perioperative mortality, two relatively small RCTs suggested an improvement in survival with statins administered perioperatively in noncardiac surgical patients.[65,181] The study by Schouten and associates (DECREASE III),[65] including 250 patients who were randomized to receive 80 mg of fluvastatin or placebo for 30 days before vascular surgical procedures, reported a reduction in the composite outcome of death or MI, whereas in the investigation by Kobashigawa and colleagues,[181] conducted in 97 cardiac transplant recipients, statins were started 1 or 2 weeks postoperatively, and the survival benefit was shown only at 1-year follow-up. For these reasons, statins were excluded from the list of interventions believed to reduce perioperative mortality rates.[101,102] Moreover, the former trial belongs to the controversial group of the DECREASE investigations, whereas the latter does not include noncardiac surgical procedures.

As mentioned, a subsequent metaanalysis including 16 RCTs (2275 patients) investigated the perioperative use of statins in statin-naïve patients 18 years old or older who were undergoing cardiac, vascular, and other noncardiac surgical procedures.[67] A reduction in both MI rate and mortality rate was found in the subgroup analysis restricted to noncardiac surgical patients (RR, 0.53; 95% CI, 0.37–0.77; $P = .001$; and RR, 0.50; 95% CI, 0.27–0.91; $P = .02$, respectively), with no heterogeneity among the trials (I^2, 0%). However, only 3 of 16 studies involved noncardiac surgical patients (2 of which included vascular surgical patients). Those investigators concluded that current data were insufficient to recommend perioperative statin therapy definitively in patients scheduled for noncardiac surgical procedures. This is a promising topic that deserves further research.

Antifibrinolytic Drugs

Tranexamic acid is the only antifibrinolytic drug that seems to have a favorable effect on perioperative mortality rates. According to a metaanalysis of 129 RCTs including 10,488 patients, strong evidence indicates that tranexamic acid reduces the need for transfusions in surgical patients by more than one-third (RR, 0.62; 95% CI, 0.58–0.65; $P < .001$).[182] However, uncertainty remains about its impact on MI, stroke, deep vein thrombosis, pulmonary embolism, and mortality rates. Although a reduced mortality rate with the use of tranexamic acid was found (RR, 0.61; 95% CI, 0.38–0.98; $P = .04$), statistical significance was lost after restriction of analysis to studies with adequate concealment. Additionally, a network metaanalysis, including both randomized and observational studies aimed at investigating the effects of aprotinin on survival in patients undergoing cardiac surgical procedures, showed that tranexamic acid was associated with reduced mortality rates only when compared with aprotinin, but not when compared with ε-aminocaproic acid or no antifibrinolytic drugs.[183] Moreover, no differences in mortality rates were found among aprotinin, ε-aminocaproic acid, or no treatment. This finding confirms the results of previous investigations showing that aprotinin can be harmful in patients undergoing cardiac surgical procedures.[119] However, it also suggests that the perioperative use of tranexamic acid may reduce mortality rates, or at least is safe. Finally, indirect evidence about a possible beneficial effect of tranexamic acid on mortality rates in the perioperative period comes from the trauma setting, which is similar to that of surgery.

The large, multicenter RCT, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2), included 20,211 patients from 274 hospitals and found that a short course of tranexamic acid (1 g over 10 min, followed by continuous infusion of 1 g over 8 h, starting within 8 h from injury) significantly reduced all-cause mortality rates in bleeding trauma patients (RR, 0.91; 95% CI, 0.85–0.97; $P = .0035$), with a greater effect when tranexamic acid was started earlier.[184]

Liberal Transfusion Strategy

A growing body of evidence indicating detrimental effects of red blood cell (RBC) transfusions, including increased mortality rates,[185,186] led to the widespread adoption of restrictive transfusion policies (eg, the use of an Hb transfusion trigger ≤7–7.5 g/dL), which were not inferior to more liberal strategies.[187–190] However, a large, multicenter RCT[28] and two single-center RCTs,[29,30] all published in 2015, found improved survival with the use of more liberal transfusion triggers in patients who underwent cardiac, cancer, and orthopedic surgical procedures.

In the Transfusion Indication Threshold Reduction (TITRe2) study,[28] 2003 patients with postoperative Hb levels lower than 9 g/dL after elective cardiac surgical procedures were randomized to receive RBC transfusions when Hb was lower than 9 or 7 g/dL. Despite the significantly reduced rate of transfusion (53.4% vs 92.2%), more deaths

were observed in the restrictive group (HR, 1.64; 95% CI, 1.00–2.67; P = .045). De Almeida and associates[29] investigated the same transfusion triggers (Hb <9 g/dL vs Hb <7 g/dL) in 198 patients admitted to ICUs after major operations for abdominal cancer. Both 30-day and 60-day mortality rates were lower in the group receiving the liberal strategy as compared with the restrictive group (8.2 vs 22.8%, P = .005; and 11.3 vs 23.8%, P = .022, respectively). Finally, Gregersen and colleagues[30] enrolled 284 patients who had undergone surgical procedures for hip fracture and found an increased per-protocol 30-day mortality rate (HR, 2.40; 95% CI, 1.1–5.2; P = .03) among patients who received RBC transfusions according to a lower Hb threshold (9.7 g/dL), as compared with those who were transfused more liberally (Hb <11.3 g/dL). In addition, both per-intention-to-treat and per-protocol 90-day mortality rates were higher in the restrictive group in a subgroup analysis including only nursing home residents.

This is doubtless a very controversial topic, but a metaanalysis of RCTs confirmed a beneficial effect on survival of the liberal approach by pooling together the 17 perioperative RCTs performed.[31] RBC transfusions do have the potential to do harm even if their quality, purification, and storage is improving. However, avoiding transfusions *when they are needed* may be even more dangerous. The key point may be to assess carefully whether transfusions are really necessary in the single patient. Several factors (age, comorbidities, hemodynamic status, clinical setting) should be taken into account or used as triggers (blood lactate, D_{O_2}, $S\bar{v}O_2$, regional oxygen saturation).

Perioperative Supplemental Oxygen

One line of research has aimed to investigate the hypothesis that a deliberate increase in the perioperative fraction of inspired oxygen (F_{IO_2}) would reduce the rate of surgical site infections, based on the well-known effects of hyperoxia on both bactericidal activity of neutrophils and wound healing.[191] A metaanalysis of five RCTs that compared an F_{IO_2} of 0.8 with an F_{IO_2} of 0.3 in patients undergoing colorectal surgical procedures showed a reduced mortality rate (but not a reduction in surgical site infections) with supplemental oxygen.[192] Accordingly, this intervention was included in the consensus paper as a potential strategy to improve survival in patients undergoing noncardiac surgical procedures.[101] The design of these and other subsequent similar trials was criticized, however.[193] Moreover, the large Supplemental Oxygen and Complications After Abdominal Surgery (PROXI) trial[194] did not find any difference in the rates of surgical site infections and 30-day mortality in patients undergoing abdominal surgical procedures who were receiving 80% or 30% oxygen, but the 2-year follow-up showed an unexpected increased mortality rate in the supplemental oxygen group (HR, 1.3; 95% CI 1.03–1.64; P = .03).[195] Accordingly, a deliberately high perioperative F_{IO_2}, whose effectiveness in reducing surgical site infections is not proven, is not advised.

Levosimendan

Patients who develop postoperative low-CO syndrome may need supportive therapy with inotropes to maintain an adequate hemodynamic status. However, inotropic drugs (especially catecholamines) lead to increased $M\dot{V}O_2$ and may consequently precipitate myocardial ischemia or increase the extent of an ongoing AMI. Moreover, most inotropic drugs can cause arrhythmias. Levosimendan, an inodilating (and antiinflammatory) calcium sensitizer,[196,197] showed cardioprotective properties in patients with HF and in cardiac surgical patients.[198–200] Most remarkably, levosimendan has been shown to reduce mortality rates in patients undergoing cardiac surgical procedures, according to a small RCT[201] and five metaanalyses.[198,202–205] A Bayesian network metaanalysis found that levosimendan was the only inodilator drug associated with a reduction in mortality rates, as compared with placebo, in patients undergoing cardiac surgical procedures.[205] Finally, a large multicenter RCT (Levosimendan in High Risk Patients Undergoing Cardiac Surgery [CHEETA]) aimed at confirming these findings is currently ongoing.[206] Even if levosimendan, with more than 100 performed RCTs, is the best studied inotropic drug[207] and the only one with survival benefits,[205] no evidence exists in patients undergoing noncardiac surgical procedures. It is only presumed that a similar favorable effect may apply in this setting, especially in patients with perioperative low-CO syndrome.

Preoperative Intraaortic Balloon Pump Counterpulsation

In high-risk patients undergoing coronary artery bypass graft operations, preoperative mechanical cardiocirculatory support with IABP can reduce perioperative and 30-day mortality rates, as shown by a small RCT[208] and four metaanalyses of RCTs.[115,209–211] Although IABP placement may potentially lead to serious complications, especially vascular or infectious, the rates of lower limb ischemia and local infection were shown to be relatively low (0.94% and 0.47%, respectively) in a retrospective study including 423 cardiac surgical patients receiving perioperative IABP.[212] Whether this strategy may confer a survival advantage in carefully selected patients with high-risk CAD who are undergoing noncardiac surgical procedures should be investigated.

Volatile Anesthetic Agents

According to two metaanalyses of RCTs,[118,213] the use of modern halogenated anesthetic agents (isoflurane, desflurane, or sevoflurane) as compared with totally IV anesthesia, may reduce mortality rates in patients undergoing cardiac surgical procedures, seemingly because of a cardioprotective action whose mechanism is similar to that of ischemic preconditioning. However, some investigations failed to show any beneficial effect of volatile anesthetic agents on troponin release or mortality rates after cardiac surgical procedures.[214] Moreover, a cardioprotective action was not observed in patients undergoing coronary stenting procedures.[215]

The largest multicenter RCT comparing the use of volatile anesthetic agents with totally IV anesthesia in patients undergoing cardiac surgical procedures is currently ongoing (http://clinicaltrials.gov/show/NCT02105610: Volatile Anesthetics to Reduce Mortality in Cardiac Surgery [MYRIAD]), and it will probably make a significant contribution to the definition of the role of volatile anesthetic agents in reducing myocardial injury and mortality rates. It would be important to know whether such an effect could be used to prevent MACE and to reduce mortality rates in noncardiac surgical patients. So far, however, the available evidence in this setting is scarce and somewhat conflicting.[216–218] Large, multicenter investigations are needed to assess the potential advantages of volatile anesthetic agents in patients at risk for perioperative myocardial injury or MI, although this type of trial may be difficult to perform.[219] Moreover, the pleiotropic pharmacologic effects of anesthetic agents are unpredictable. For example, a large multicenter RCT is ongoing to investigate the beneficial effect of a propofol-based anesthetic and the detrimental effect of a volatile-based anesthetic agent in cancer surgical procedures (http://clinicaltrials.gov/show/NCT01975064: Cancer and Anesthesia: Survival After Radical Surgery—A Comparison Between Propofol and Sevoflurane Anesthesia [CAN]).

Remote Ischemic Preconditioning

Repeated short episodes of ischemia and reperfusion in a remote vascular territory (eg, by applying a blood pressure cuff on an upper limb and inflating or deflating it every 5 minutes for three cycles) may protect the heart from ischemia or reperfusion injury. This effect is possibly caused by the release of one or more substances that reach the heart and activate cell-signaling pathways, probably involving mitochondria, this resulting in greater resistance to ischemic insults.[220] Thielmann and associates[221] randomized 329 patients who were undergoing coronary artery bypass graft operations to receive remote ischemic preconditioning or not. These investigators found reduced postoperative release of cTn (cTnI:AUC, 0.83; 95% CI 0.70–0.97; P = .022) and a reduced all-cause mortality rate (HR, 0.27; 95% CI 0.08–0.98; P = .046) in the preconditioning group. The topic has possible applications in noncardiac surgical patients at risk for perioperative myocardial ischemia. However, further research is needed in both settings.

Leukocyte Depletion of Transfused Blood

Removing leukocytes from blood to be transfused is thought to prevent transfusion-related immunomodulation, probably leading to a reduced risk of infections.[222] In cardiac surgical patients, cardiopulmonary bypass may magnify the inflammatory mechanisms through which blood transfusions may lead to increased susceptibility to infections and/or to multiorgan dysfunction. Two large RCTs found a reduced mortality rate with transfusion of leukodepleted RBCs as compared with standard buffy coat–depleted RBCs.[116,223] Whether this favorable effect is restricted to the cardiac surgical population or whether it may also occur in other surgical settings is not clear. However, leukodepletion of blood products is regarded as best practice in most Western countries.

Insulin for Tight Glycemic Control

In the landmark investigation by Van den Berghe and colleagues,[113] maintaining blood glucose levels between 80 and 110 mg/dL through continuous infusion of insulin was found to reduce mortality in patients admitted to the ICU significantly after cardiac or noncardiac surgical procedures. Improved survival with intensive glycemic control also was shown in a subsequent metaanalysis of RCTs,[114] as well as in an RCT[224] in patients undergoing cardiac surgical procedures, although with less "tight" targets of blood glucose control (<180 mg/dL and 120–160 mg/dL, respectively). However, a metaanalysis including 29 RCTs performed in both medical and surgical ICU patients failed to show any survival benefit with intensive glucose control. Conversely, a higher risk of hypoglycemia was found.[225] The large Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicenter investigation[226] also raised important concerns about tight glycemic control. An increase in mortality rates was found in ICU patients in whom blood glucose was maintained between 81 and 108 mg/dL, as compared with a higher blood glucose target (<180 mg/dL). Accordingly, caution should be used when adjusting glycemic levels in ICU patients, to avoid dangerous hypoglycemic episodes. Further studies are desirable in the perioperative setting.

Lung-Protective Ventilation

Protective ventilation, involving the use of low tidal volumes and moderate-to-high levels of positive end-expiratory pressure (with or without recruitment maneuvers), is one of the interventions shown to improve survival in critically ill patients.[106] Three multicenter RCTs found a reduction in mortality rates with protective ventilation in patients with acute respiratory distress syndrome.[227–229] Data are accumulating to support the *prophylactic* use of protective ventilation to prevent acute respiratory distress syndrome in patients without lung injury, including the *intraoperative* use of low tidal volumes in noncardiac surgical patients.[230,231] This topic is very attractive and deserves further large investigations.

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